ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2020 June 30; 9(1): 1-8

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Irregular Volume 9 Number 1 June 30, 2020

MINIREVIEWS

Contents

World Journal of Nephrology

Volume 9 Number 1 June 30, 2020

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology* , Li Zuo, MD, PhD, Doctor, Professor, Department of Nephrology, Peking University People's Hospital, Beijing 100044, China

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

Responsible Electronic Editor: *Li-Li Wang*

Proofing Production Department Director: *Xiang Li*

Responsible Editorial Office Director: *Jia-Ping Yan*

NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
Xiang-Mei Chen, Li Zuo

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

PUBLICATION DATE
June 30, 2020

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 2020 June 30; 9(1): 1-8

DOI: 10.5527/wjn.v9.i1.1

ISSN 2220-6124 (online)

MINIREVIEWS

Renal transplant recipient seizure practical management

Harpreet Sawhney, Simon S Gill

ORCID number: Harpreet Sawhney (0000-0003-3192-4073); Simon S Gill (0000-0001-8883-6942).

Author contributions: Sawhney H was involved in writing the original draft, read and approved the final manuscript; and Gill SS was involved in writing the original draft, read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Manuscript source: Invited manuscript

Received: December 2, 2019
Peer-review started: December 2, 2019
First decision: December 11, 2019
Revised: May 23, 2020
Accepted: June 10, 2020
Article in press: June 10, 2020
Published online: June 30, 2020

P-Reviewer: Al-Haggar M, Gonzalez FM, Kakaei F
S-Editor: Ma YJ
L-Editor: A

Harpreet Sawhney, Department of Nephrology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London W12 0HS, United Kingdom

Simon S Gill, Department of Radiology, Frimley Health NHS Foundation Trust, Slough, Berkshire SL2 4HL, United Kingdom

Corresponding author: Harpreet Sawhney, MA(Cantab) MBBS, MRCP, Doctor, Department of Nephrology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du Cane Road, London W12 0HS, United Kingdom. harpreet.sawhney@doctors.org.uk

Abstract

Seizures are not uncommon in renal transplant patients. The common aetiologies are metabolic disturbance associated with renal failure, immunosuppression and associated complications and infections. Their management can be challenging because of altered pharmacokinetics of antiepileptic drugs (AEDs) and their removal by dialysis. A practical approach to the management of seizure in renal transplant patients is discussed. This review highlights the guidelines for use of various AEDs in renal transplants.

Key words: Seizures; Renal transplant; Haemodialysis; Uraemia; Antiepileptic drugs

Core tip: For selection of an antiepileptic drug (AED) in renal transplant patients: it should be a non-enzyme inducer; its metabolism and excretion should not be affected by renal failure; there are minimal dose adjustments with haemodialysis; the loading dose of most AED remain the same in renal impairment; and, sodium valproate is a good choice for an antiepileptic drug in renal transplant patients.

Citation: Sawhney H, Gill SS. Renal transplant recipient seizure practical management. *World J Nephrol* 2020; 9(1): 1-8
URL: https://www.wjgnet.com/2220-6124/full/v9/i1/1.htm
DOI: https://dx.doi.org/10.5527/wjn.v9.i1.1

INTRODUCTION

Seizures occur in 6%-36% of transplant patients[1]. Renal transplant patients may suffer

E-Editor: Wu YXJ

from seizures because of immunosuppression, infections or pre-existing epilepsy. With deteriorating renal transplant function renal failure and dialysis disequilibrium can also cause seizures. Seizures may be a reflection of metabolic derangement, drug toxicity or associated with life threatening central nervous system pathology. Though generalised tonic clonic seizures are easily recognised in these patients, confirming the diagnosis can be a challenge because of motor symptoms mimicking seizures in uraemic patients and non-convulsive status epilepticus.

The experience of using anti-epileptic drugs (AEDs) along with immunosuppression in transplant patients is quite rich in renal transplants; it being the oldest and most common transplant procedure. However, there are no double blind, controlled randomised clinical trials for the use of AEDs in this cohort. The literature for the use of newer AEDs is scarce.

This review gives a practical approach to manage seizures in renal transplant patients based on review of literature and current guidelines.

Pre-renal transplantation phase

Patients intending to be a recipient of a renal transplant are well evaluated. When they are on the waiting list to receive the transplant, they are in steady state. Any convulsive crisis cannot be attributed to uremic encephalopathy or dialysis disequilibrium syndrome that affect acute new patients requiring renal replacement therapy.

Co-existing epilepsy: It is not uncommon to see patients with renal failure with co-existing unrelated cerebral pathology resulting in epileptic seizures. There are uncommon syndromes, which may present with renal failure and neurological dysfunction. "Action myoclonus – renal failure syndrome" is a distinctive form of progressive myoclonus epilepsy associated with renal failure. Before the dialysis and renal transplant era, it was not recognised, as patients succumbed to rapidly progressive renal failure. It is an autosomal recessive disorder and may present with renal or neurological features. The neurological presentation includes progressive action myoclonus, tremors, cerebellar ataxia and infrequent generalised tonic clonic seizures. Proteinuria is detected in all cases at an early stage, progressing to renal failure. Renal biopsies demonstrate a severe variant form of focal glomerulosclerosis, a collapsing glomerulopathy. Renal dialysis and transplantation are effective for renal function only, the neurological features continue to progress in spite of normal renal function[2].

Peri-renal transplantation phases

Renal transplant patients require sedatives, anaesthetics and narcotics for surgery and pre-surgical evaluation. Many drugs used for this may cause seizures. Central anticholinergic syndrome is associated with blockage of the central cholinergic transmission and presents with seizures, agitation, hallucinations, stupor and respiratory depression.

Seizures can be a side effect of immunosuppressive therapy. High dose methyl-prednisolone given concurrently with cyclosporine can trigger seizures[3]. Calcineurin inhibitors such as tacrolimus and cyclosporine have been associated with posterior reversible encephalopathy syndrome (PRES). PRES is a syndrome which is associated with headaches, confusion, seizures and visual loss. Adverse neurological effects after mycophenolate mofetil (MMF) are uncommon. However, concomitant use of MMF with corticosteroids and cyclosporine may cause encephalopathy and seizures . Also, a case report of a generalised tonic-clonic seizure has been noted when aciclovir was used while the patient was on MMF[4].

Immunosuppression increases the risk of opportunistic infections, which may present with symptomatic seizures. The treatment of these infections may be associated with seizures because of its toxicity. Imipenem, a commonly used drug for bacterial infections in immunosuppressed patients, has been associated with seizures[5,6].

Post-renal transplantation phase

In the post renal transplantation phase, in the context of a failing graft, with acutely worsening renal function, seizures are commonly associated with uraemic encephalopathy or disequilibrium syndrome caused by haemodialysis (Table 1). Aluminium encephalopathy in children and dialysis encephalopathy are not seen with modern dialysis procedures.

Seizures in renal insufficiency can be due to electrolyte imbalance (hyponatraemia, hypocalcemia, hypomagnesemia), hypertensive encephalopathy, intracranial haemorrhage (particularly subdural haematoma) or drug intoxication[7].

Seizures are common in acute renal transplant failure. These usually occur in the

Table 1 Causes of seizures in renal transplant

Encephalopathy
Uraemic encephalopathy
Dialysis disequilibrium syndrome
Aluminium encephalopathy
Reversible posterior encephalopathy syndrome
Metabolic derangement
Hyponatremia
Hypocalcemia
Hypomagnesemia
Immunosuppression neurotoxicity
Tacrolimus (FK-506)
Cyclosporin
High dose corticosteroids
CNS infections
Meningitis
Encephalitis
Abscess
Drug toxicity
Quinolone antibiotics (*e.g.*, Ciprofloxacin)
Beta Lactams (*e.g.*, Penicillin, Mezlocillin, Cephalosporins)
Antidepressants
Bupropion HCL
Cerebrovascular disease
Subdural haematoma
Cerebral infarct
Intracerebral haemorrhage
Co-existing epilepsy
Primary CNS lymphoma
Action myoclonus – renal failure syndrome

early couple of weeks of renal failure when patient is oliguric or anuric. Seizures are relatively uncommon in chronic renal transplant failure and are seen at a pre-terminal state when significant uraemic encephalopathy is present.

Uraemic encephalopathy: It is characterised by altered mental status, sluggishness, seizures, movement disorders and ataxia. The coexistence of features of neural depression commonly seen in a metabolic encephalopathy along with neural excitation are typical of uraemic encephalopathy. Early movement disorders include muscle cramps, tremors and asterixis. A culmination of asterixis and myoclonus has been labelled as uraemic twitching and seen in severe uraemic encephalopathy[8]. Chorea and athetosis are seen rarely. These movement disorders can be confused with seizures. Video electroencephalography (EEG) is helpful in differentiating these movement disorders from epileptic seizures as there is no corresponding epileptic activity in for former.

Dialysis disequilibrium syndrome: It is an increasingly rare syndrome characterised by headache, nausea, restlessness, hypertension, blurred vision, seizures, muscular twitching, asterixis and confusion. It usually presents during or immediately after haemodialysis or during the initiation of continuous renal replacement therapy[9,10]. Rapid clearance of urea from plasma than brain leads to cerebral oedema.

Co-existing epilepsy: It is not uncommon to see patients with renal failure with co-existing unrelated cerebral pathology resulting in epileptic seizures. There are uncommon syndromes, which may present with renal failure and neurological dysfunction. Action myoclonus – renal failure syndrome is a distinctive form of progressive myoclonus epilepsy associated with renal failure. It was not recognised prior to dialysis and renal transplant era as patients succumbed to rapidly progressive renal failure. It is an autosomal recessive disorder and may present with renal or neurological features. The neurological presentation includes progressive action

myoclonus, tremors, cerebellar ataxia and infrequent generalised tonic clonic seizures. Proteinuria is detected in all cases at an early stage, progressing to renal failure. Renal biopsies show collapsing glomerulopathy, a severe variant of focal glomerulosclerosis. Dialysis and renal transplantation are effective for renal function only, the neurological features continue to progress in spite of normal renal function[11]. In other rare multisystemic conditions such as Tuberous Sclerosis patients also develop renal impairment and neurological dysfunction.

A PRACTICAL APPROACH TO SEIZURE MANAGEMENT

The seizures in a renal transplant recipient patient can be acute symptomatic seizures. These seizures are triggered by metabolic disturbance and do not reoccur if the provocative factor is eliminated or adequately treated. Patients need a fast acting anti-epileptic for short duration and long-term prophylactic anti-epileptic treatment is not required. The underlying provocative factor, for example, metabolic disturbance should be rectified. In case of dialysis disequilibrium syndrome, dialysis should be immediately stopped if patient develops seizures or obtundation. Some studies suggest that severe dialysis disequilibrium syndrome can be reversed by more rapidly with either 5 mL of 23% saline or 12.5 mg of Mannitol. However both measures may remain ineffective[12].

On the contrary, symptomatic seizures relate to structural brain lesions, for example, infective focus or an infarct, carry a high risk of recurrence and need long-term prophylactic treatment. Long standing epileptic seizures not associated with renal disease should be treated on their own merit.

Pharmacokinetics of AEDS in renal disease

It is important to understand the pharmacokinetics of AED in the setting of renal disease. The plasma drug levels of AEDs can be affected by renal failure, haemodialysis and peritoneal dialysis. The 2002 Renal-Disease-Outcome-Quality-Initiative developed guidelines which classify chronic renal disease (CKD) into five stages. CKD stage 5 is defined as a "glomerular filtration rate (GFR) of < 15 mL/min per 1.73 m²" and in this stage renal replacement therapy in the form of dialysis or transplantation has to be considered to sustain life[13].

Protein binding, GFR and drug solubility, determine AEDs renal clearance. Unlike lipid soluble drugs, water-soluble drugs are excreted in urine. Most drug metabolites (for example, epoxides) are more water-soluble than the parent drug. Hence most drug metabolites are excreted in the urine. A number of patients with CKD and nephrotic syndrome are hypoalbuminemic. This affects the pharmacokinetics of protein bound AEDs. As protein binding is decreased due to low albumin, a larger amount of free drug is available for clinical effect. Patients may have side effects of the drug even though total plasma levels of the drug are in the therapeutic range because of increased free drug levels. It is worth emphasising that loading dose of AEDs is independent of renal clearance. Therefore this usually does not require adjustment in renal failure. It is the amount of drug available in the body compared to plasma concentration. The loading dose is used to achieve faster steady state and therapeutic effects.

Haemodialysis: AEDs are cleared from blood circulation by haemodialysis into the dialysate through the filter membrane. This depends upon the molecular size of the drug, water solubility protein binding, volume distribution and dialysis condition. The haemodialysis related factors, which affect AED clearances include type of membrane, surface area, blood flow rates, dialysis frequency and duration. Modern high efficiency dialysis with larger surface area of dialysis membrane and large pore size can dialyze more drugs compared to low efficiency dialysis of the past. A number of recommendations made in literature are based on old studies.

Some AEDs are readily removed by haemodialysis. These are ones that have a combination of having a small volume distribution, not highly protein bound and are water soluble. On the other hand, AEDs with high lipid solubility and protein binding as well as high volume distribution are difficult to remove by haemodialysis.

Peritoneal dialysis: It utilises peritoneal membrane as the dialyzing membrane, which is less effective for AED clearance compared to haemodialysis. However, in the setting of associated peritonitis, significant amount of drug binds to proteins and is removed in the peritoneal effluent, increased drug clearance may occur.

Home haemodialysis: This involves short daily treatments for 2-3 h, 5-6 times per week or night time dialysis when the patient sleeps with longer hours 3-6 nights per

week. The longer dialysis time in these patients may increase the AED clearance.

Continuous renal replacement therapy: This modality is often used in critically ill patients. Membranes used are usually of larger pore size, which allow larger drug molecules to be filtered. There is continuous ultrafiltration of plasma water. These factors may lead to an increase in drug clearance compared to haemodialysis.

Choice of anti-epileptic drugs

Treating seizures in renal transplant patients is a challenge. The drug should be effective for particular seizure type. For example, phenytoin, carbamazepine and levetiracetam are effective for generalised tonic clonic or focal seizures. Sodium valproate is a good choice for myoclonic seizures. Carbamazepine can make myoclonic seizures worse and should be avoided in such a setting. AED should be fast acting in acute symptomatic seizures to avoid further recurrences. Benzodiazepines are first line drug for terminating such a seizure. We recommend Lorazepam 2-4 mg IV in such a setting. In the absence of an IV line as in a community based setting, buccal midazolam is an alternative. An algorithm for the management of acute onset generalised tonic clonic seizure is given in Table 2[14].

Renal transplant patients are treated with immunosuppressive agents, which are metabolised in the liver. The AEDs, which induce hepatic enzyme system CYP450 *e.g.*, carbamazepine and phenytoin, should be avoided. These drugs increase the metabolism of immunosuppressive drugs metabolised in the liver and make them ineffective with their standard dose.

AEDs may need dose adjustment in patients with renal failure, especially if these patients are dialysed. The dose adjustment for various AEDs in various stages of renal failure and haemodialysis is summarised in Table 3[15,16]. The commonly used drugs in renal transplant patients are:

Sodium valproate: Renal disease has little effect on valproate metabolism as it is almost entirely eliminated by hepatic metabolism. It is 85%–95% protein bound and protein binding is affected by renal disease. The total plasma concentration falls, but free Valproate levels remain unchanged. Valproate is poorly soluble in water and has a small volume of distribution. It is highly protein bound. Less than 20% of Valproate is removed by haemodialysis[17]. No dose adjustment is necessary in renal failure, and there may be a need for small supplement dose in high flux haemodialysis. It is hepatic enzyme inhibitor and may enhance immunosuppression. It also is effective for almost all seizure types, including myoclonic seizures and can be given intravenous to treat acute symptomatic seizures. These characteristics make it a drug of choice in renal transplant patients.

Phenytoin: Renal failure has a significant effect on phenytoin's pharmacokinetics. Although kidneys only clear upto 5% of phenytoin. There is an increase in the free fraction of phenytoin because of decreased protein binding in renal failure. If dosing is based on total Phenytoin plasma concentration, it can lead to over-dosing and toxicity. Phenytoin's water solubility is poor. Phenytoin has a volume of distribution that is modest, being 90% bound to protein. There is very minor loss in haemodialysis or peritoneal dialysis[18,19]. In plasmapheresis, 10% of total phenytoin is removed with each treatment. Though it is a commonly used drug in renal transplants with acute onset of recurrent seizures, it should be avoided as it is a hepatic enzyme inducer and decreases plasma levels of immunosuppressive drugs.

Levetiracetam: Approximately two-thirds of levetiracetam is cleared by the renal. Its clearance decreases in proportion to decrease in GFR and its dose decreases accordingly (Table 3). It is water soluble, has low volume distribution and protein binding. This makes it highly dialyzable. Approximately, half of drug body pool is removed during a four hour session of haemodialysis. Levetiracetam can be used as an intravenous loading dose in acute onset seizures, as it has a fast mechanism of action. It is a non-enzyme inducer and does not interact with drugs used for immunosuppression. However, there is a need to adjust the dose in renal failure and dialysis.

Newer anti-epileptic drugs: There has been a rapid growth of new AEDs in the last 10 to 15 years. For many of these drugs specific data for use in renal disease is lacking. However, a good understanding of AED and its pharmacokinetics in renal disease can allow its rational use in renal transplant patients. Brivaracetam appears to be promising drug in patients with renal disease. It is a non-enzyme inducer, broad spectrum AED, which crosses the blood brain barrier fast and effective in acute onset recurrent seizures. Its pharmacokinetic is unaltered in renal failure and no dose adjustment is required in haemodialysis[20].

Table 2 A practical approach to generalised tonic clonic seizure in renal transplant patients (modified from Chabolla *et al*[14], 2006)

Acute onset generalised tonic clonic seizure	
Monitor ABC	
IV Lorazepam 2 mg	
Post seizure	Persistent seizure or recurrent seizures without regaining consciousness follow status epilepticus protocol
Eliminate or correct identified provocative factors	
Neurologic examination, EEG, MRI brain	
If all negative, monitor without AED	
If any positive (Neurologic examination abnormal or EEG – Epileptic activity or MR structural lesion) OR spontaneous recurrence when monitoring without AED -> then Initiate AED	

EEG: Electroencephalography; MRI: Magnetic resonance imaging; AED: Antiepileptic drug.

CONCLUSION

Key points for selection of an AED in renal transplant patients: (1) It should be a non-enzyme inducer; (2) Its metabolism and excretion should not be affected by renal failure; (3) There are minimal dose adjustments with haemodialysis; (4) The loading dose of most AED remain the same in renal impairment; and (5) Sodium valproate is a good choice for an antiepileptic drug in renal transplant patients.

Table 3 Dose adjustment for antiepileptic drugs in patients with renal impairment

GFR (mL/min)	60-90	30-60	15-30	< 15	Haemodialysis
Levetiracetam	500-1000 mg BD	250-750 mg BD	250-500 mg BD	500-1000 mg OD	Plus 250-500 mg/d
Toparimate	50% decrease	50% decrease	50% decrease		50-100 mg after HD
Zonisamide	100-400 mg	100-400 mg			
Oxcarbazepine	300-600 mg BD	300-600 mg BD	300 mg/d starting dose	NA	NA
Esclicarbazepine	None	400-600 mg OD	400-600 mg OD		
Clobazam	None	None	None	NA	None
Pregabalin	None	50% decrease	25-125 mg/d	25-75 mg /d	25-150 mg after HD
Lacosamide	None	None	300 mg/d		Plus < 50% after HD
Rufinamide	None	None	None	NA	Plus 30% after HD
Vigabatrin	25% decrease	50% decrease	75% decrease	NA	NA
Tiagabine	None	None	None	None	None
Lamotrigine	None	None	None	None	NA
Phenytoin	None	None	None	None	May need in high flux HD
Carbamazepine	None	NA	NA	75% dose	Plus 75% after HD
Valproate	None	None	None	None	May need in high flux HD
Perampanel	None	None	NA	NA	NA
Brivaracetam	None	None	NA	NA	None

This table is modified from Glynn *et al*[9], Diaz *et al*[15] Lexicomp online drug information[16]. NA: Not available.

REFERENCES

1 **Patchell RA**. Neurological complications of organ transplantation. *Ann Neurol* 1994; **36**: 688-703 [PMID: 7979215 DOI: 10.1002/ana.410360503]
2 **De Deyn PP**, Saxena VK, Abts H, Borggreve F, D'Hooge R, Marescau B, Crols R. Clinical and pathophysiological aspects of neurological complications in renal failure. *Acta Neurol Belg* 1992; **92**: 191-206 [PMID: 1332359 DOI: 10.1007/BF01400606]
3 **el-Dahr S**, Chevalier RL, Gomez RA, Campbell FG. Seizures and blindness following intravenous pulse methylprednisolone in a renal transplant patient. *Int J Pediatr Nephrol* 1987; **8**: 87-90 [PMID: 3308730 DOI: 10.1111/j.1464-410X.1987.tb04661.x]
4 **Pellerin D**, Singh K, Maniatis T, Chalk CH, Green L. Mycophenolate Mofetil-Induced Status Epilepticus. *Can J Neurol Sci* 2018; **45**: 585-587 [PMID: 30234475 DOI: 10.1017/cjn.2018.326]
5 **Koppel BS**, Hauser WA, Politis C, van Duin D, Daras M. Seizures in the critically ill: the role of imipenem. *Epilepsia* 2001; **42**: 1590-1593 [PMID: 11879372 DOI: 10.1046/j.1528-1157.2001.34701.x]
6 **Sutter R**, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs: A systematic review. *Neurology* 2015; **85**: 1332-1341 [PMID: 26400582 DOI: 10.1212/WNL.0000000000002023]
7 **Brouns R**, De Deyn PP. Neurological complications in renal failure: a review. *Clin Neurol Neurosurg* 2004; **107**: 1-16 [PMID: 15567546 DOI: 10.1016/j.clineuro.2004.07.012]
8 **Gobbi G**, Bertani G, Pini A. Electrolyte Sporadic, Metabolic and Endocrine Disorders. In: Engel IJ, Pedley TA. Epilepsy: A Comprehensive Textbook. Philadelphia: Lipponcott-Raven, 1998: 2605-2627
9 **Glynn SM**, Parent JM, Aminoff MJ. Seizures and General Medical Disorders. In: Josephson SA, Aminoff MJ. Aminoff's Neurology and General Medicine: 5th ed. Amsterdam: Elsevier, 2014: 1159-1177 [DOI: 10.1016/B978-0-12-407710-2.00057-6]
10 **RENAL Replacement Therapy Study Investigators**; Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; **361**: 1627-1638 [PMID: 19846848 DOI: 10.1056/NEJMoa0902413]
11 **Badhwar A**, Berkovic SF, Dowling JP, Gonzales M, Narayanan S, Brodtmann A, Berzen L, Caviness J, Trenkwalder C, Winkelmann J, Rivest J, Lambert M, Hernandez-Cossio O, Carpenter S, Andermann F, Andermann E. Action myoclonus-renal failure syndrome: characterization of a unique cerebro-renal disorder. *Brain* 2004; **127**: 2173-2182 [PMID: 15364701 DOI: 10.1093/brain/awh263]
12 **Zepeda-Orozco D**, Quigley R. Dialysis disequilibrium syndrome. *Pediatr Nephrol* 2012; **27**: 2205-2211 [PMID: 22710692 DOI: 10.1007/s00467-012-2199-4]
13 **National Kidney Foundation**. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1-266 [PMID: 11904577 DOI: 10.1111/j.1745-7599.2002.tb00119.x]
14 **Chabolla DR**, Wszolek ZK. Pharmacologic management of seizures in organ transplant. *Neurology* 2006; **67**: S34-S38 [PMID: 17190920 DOI: 10.1212/WNL.67.12_suppl_4.S34]
15 **Diaz A**, Deliz B, Benbadis SR. The use of newer antiepileptic drugs in patients with renal failure. *Expert Rev Neurother* 2012; **12**: 99-105 [PMID: 22149658 DOI: 10.1586/ern.11.181]
16 **Lexicomp online drug information**. UpToDate Electronic website. [updated 2017]. Available from: https://www.wolterskluwercdi.com/lexicomp-online/
17 **Bruni J**, Wang LH, Marbury TC, Lee CS, Wilder BJ. Protein binding of valproic acid in uremic patients. *Neurology* 1980; **30**: 557-559 [PMID: 6768007 DOI: 10.1212/wnl.30.5.557-a]
18 **Martin E**, Gambertoglio JG, Adler DS, Tozer TN, Roman LA, Grausz H. Removal of phenytoin by

hemodialysis in uremic patients. *JAMA* 1977; **238**: 1750-1753 [PMID: 578272 DOI: 10.1001/jama.238.16.1750]

19 **Czajka PA**, Anderson WH, Christoph RA, Banner W. A pharmacokinetic evaluation of peritoneal dialysis for phenytoin intoxication. *J Clin Pharmacol* 1980; **20**: 565-569 [PMID: 7440764 DOI: 10.1002/j.1552-4604.1980.tb01671.x]

20 **Sargentini-Maier ML**, Rolan P, Connell J, Tytgat D, Jacobs T, Pigeolet E, Riethuisen JM, Stockis A. The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. *Br J Clin Pharmacol* 2007; **63**: 680-688 [PMID: 17223857 DOI: 10.1111/j.1365-2125.2006.02829.x]

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

ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2020 November 29; 9(2): 9-42

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Continuous Publication Volume 9 Number 2 November 29, 2020

OPINION REVIEW

REVIEW

ORIGINAL ARTICLE

Retrospective Study

World Journal of Nephrology

Continuous Publication Volume 9 Number 2 November 29, 2020

Contents

ABOUT COVER

Associate editor of *World Journal of Nephrology*, Dr. Juan F Navarro-González is Chair of the Research Division, with a joint appointment as Staff Nephrologist, at the University Hospital Nuestra Señora de Candelaria (Santa Cruz de Tenerife, Spain), Assistant Professor of Nephrology at the University of La Laguna (Santa Cruz de Tenerife, Spain), National Coordinator of the GEENDIAB (Spanish Study Group for the Study of Diabetic Nephropathy), and member of the Steering Committee of the Spanish Renal Research Network (Spanish Ministry of Science and Innovation). He earned his MD degree from the University of La Laguna in 1989, where he subsequently obtained his PhD degree in 2007, along with award of the Extraordinary Doctorate Prize. He has over 150 peer-reviewed publications and has authored more than 20 book chapters. His articles have garnered more than 8,000 citations and his H-index is 48. (L-Editor: Filipodia)

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
Continuous Publication

EDITORS-IN-CHIEF
Li Zuo

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

PUBLICATION DATE
November 29, 2020

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

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Nephrology

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

World J Nephrol 2020 November 29; 9(2): 9-17

DOI: 10.5527/wjn.v9.i2.9

ISSN 2220-6124 (online)

OPINION REVIEW

Restructuring nephrology services to combat COVID-19 pandemic: Report from a Middle Eastern country

Muhammad Asim, Mohamad Alkadi, Abdullah Hamad, Muftah Othman, Essa Abuhelaiqa, Omar Fituri, Ihab El-Madhoun, Hassan Al-Malki

ORCID number: Muhammad Asim 0000-0003-3180-1671; Mohamad Alkadi 0000-0003-0009-5823; Abdullah Hamad 0000-0003-4677-7686; Muftah Othman 0000-0002-1114-9893; Essa Abuhelaiqa 0000-0001-6389-9234; Omar Fituri 0000-0003-4654-4137; Ihab El-Madhoun 0000-0001-9115-0693; Hassan Al-Malki 0000-0001-6859-4253.

Author contributions: Asim M conceived the presented idea, structured the manuscript, and designed the figures; All authors were involved in acquisition of data, drafting the manuscript and revising it critically for important intellectual content.

Conflict-of-interest statement: The authors declare no potential conflicts of interest in relation to this article.

Muhammad Asim, Mohamad Alkadi, Abdullah Hamad, Muftah Othman, Essa Abuhelaiqa, Omar Fituri, Ihab El-Madhoun, Hassan Al-Malki, Nephrology Division, Department of Medicine, Hamad Medical Corporation, Doha 3050, Qatar

Corresponding author: Muhammad Asim, BSc, FRCP, MBBS, Associate Professor, Nephrology Division, Department of Medicine, Hamad Medical Corporation, Al-Rayan Street, Doha 3050, Qatar. masim@hamad.qa

Abstract

Coronavirus disease 2019 has spread across the world and has been classified as a pandemic. It has overwhelmed the healthcare systems. Specifically, it has overstretched the intensive care units and renal replacement therapy services in many countries. In this paper, we discuss the reconfiguration of nephrology services in the State of Qatar during the current pandemic. We highlight the key strategies that have been implemented to ensure that renal replacement therapy capacity is not constrained in either the intensive care or ambulatory setting. Some innovative approaches for the safe delivery of ambulatory care to dialysis and kidney transplant patients are also discussed.

Key Words: Coronavirus; COVID-19; Nephrology; Pandemic; Renal replacement therapy; Infection control

Core Tip: Although the impact of the pandemic and the healthcare models differ across countries, pandemic preparedness planning is vital to improve the effectiveness of a country's response to the pandemic. Renal replacement therapy is a lifesaving treatment, and it is imperative that healthcare systems invest in technical infrastructure, staff, and supplies to provide efficient critical care nephrology services in the setting of a pandemic.

Citation: Asim M, Alkadi M, Hamad A, Othman M, Abuhelaiqa E, Fituri O, El-Madhoun I, Al-Malki H. Restructuring nephrology services to combat COVID-19 pandemic: Report from a Middle Eastern country. *World J Nephrol* 2020; 9(2): 9-17

Manuscript source: Unsolicited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: Qatar

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: July 23, 2020
Peer-review started: July 23, 2020
First decision: October 21, 2020
Revised: October 26, 2020
Accepted: November 4, 2020
Article in press: November 4, 2020
Published online: November 29, 2020

P-Reviewer: Abboud OI
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Wang LL

URL: https://www.wjgnet.com/2220-6124/full/v9/i2/9.htm
DOI: https://dx.doi.org/10.5527/wjn.v9.i2.9

INTRODUCTION

An epidemiological shift in public health priorities from communicable diseases to noncommunicable diseases has been observed in the last two decades. However, humankind continues to grapple with infectious diseases, including Ebola, dengue, middle east respiratory syndrome, and severe acute respiratory syndrome. The novel coronavirus disease (COVID-19) was first identified in the Chinese city of Wuhan in December 2019, and it has spread across the world, causing widespread increases in morbidity and mortality, economic collapses, and social fragmentation. It was classified as a pandemic on March 11, 2020. Qatar recorded its first confirmed case of COVID-19 on February 29, 2020. As of July 6, the total number of tests performed in Qatar stands at 135848 per million population, and there are 99799 confirmed cases (Figure 1A)[1]. Patients with kidney disease, especially those requiring renal replacement therapy (RRT), are at an increased risk for COVID-19 infection and have worse clinical outcomes owing to their underlying immunocompromised state and high frequency of comorbid risk factors such as cardiovascular disease, hypertension, diabetes mellitus, and pulmonary disease. This paper discusses the restructuring of nephrology services to combat COVID-19 in the State of Qatar, the country with the highest number of confirmed cases per million population in the world[1].

CHRONIC KIDNEY DISEASE IN QATAR

Occupying a peninsula on the western coast of the Arabian Gulf, Qatar is an independent state in the Middle East. It has a land area of approximately 11600 km^2 and a population of 2.8 million. Qatar's healthcare expenditure per capita is highest among all countries in the Middle East[2]. More than 85% of the population are noncitizens as a result of international migration of workers from developing countries. There is a high prevalence of risk factors for chronic kidney disease (CKD) such as obesity, diabetes mellitus, and hypertension among citizens and South Asian migrants, which has translated into an increased burden of CKD as well as end-stage renal disease (ESRD)[3,4].

Qatar's noncitizen population is transient because of the contractual nature of their employment. Many expatriates choose to return to their home countries if a serious illness such as ESRD is diagnosed[5]. Conversely, some patients avail the subsidized RRT in Qatar as they cannot afford such therapy in their native countries. A study of Qatar's annual data on RRT revealed that the unadjusted prevalence of RRT-treated ESRD was 666 per million population as of 31 December 2019. Forty-two percent of all patients on RRT had a functioning kidney transplant, 47.5% were receiving haemodialysis (HD) therapy, and 10.5% were being treated with peritoneal dialysis (PD).

DEVELOPMENT OF A NEPHROLOGY OPERATIONS COMMITTEE FOR PANDEMIC PREPAREDNESS PLANNING AND RESPONSE

General nephrology services and renal replacement therapies in Qatar are largely provided by the Ministry of Public Health (MoPH) government hospitals (Hamad Medical Corporation's network of hospitals); there are no private dialysis/organ transplantation services. Each hospital in the network works as an independent unit with its own budget and staffing arrangements. During the pandemic, the organizational structure has been reformulated such that planning, coordination, and resource management have been centralized. For instance, the Chief of Nephrology Division at Hamad General Hospital, the principal hospital in the capital city of Doha, has been given the responsibility of reconfiguring and expanding nephrology services to meet needs.

A multidisciplinary nephrology operations committee for pandemic preparedness planning and response was formed in February 2020. The committee, which has

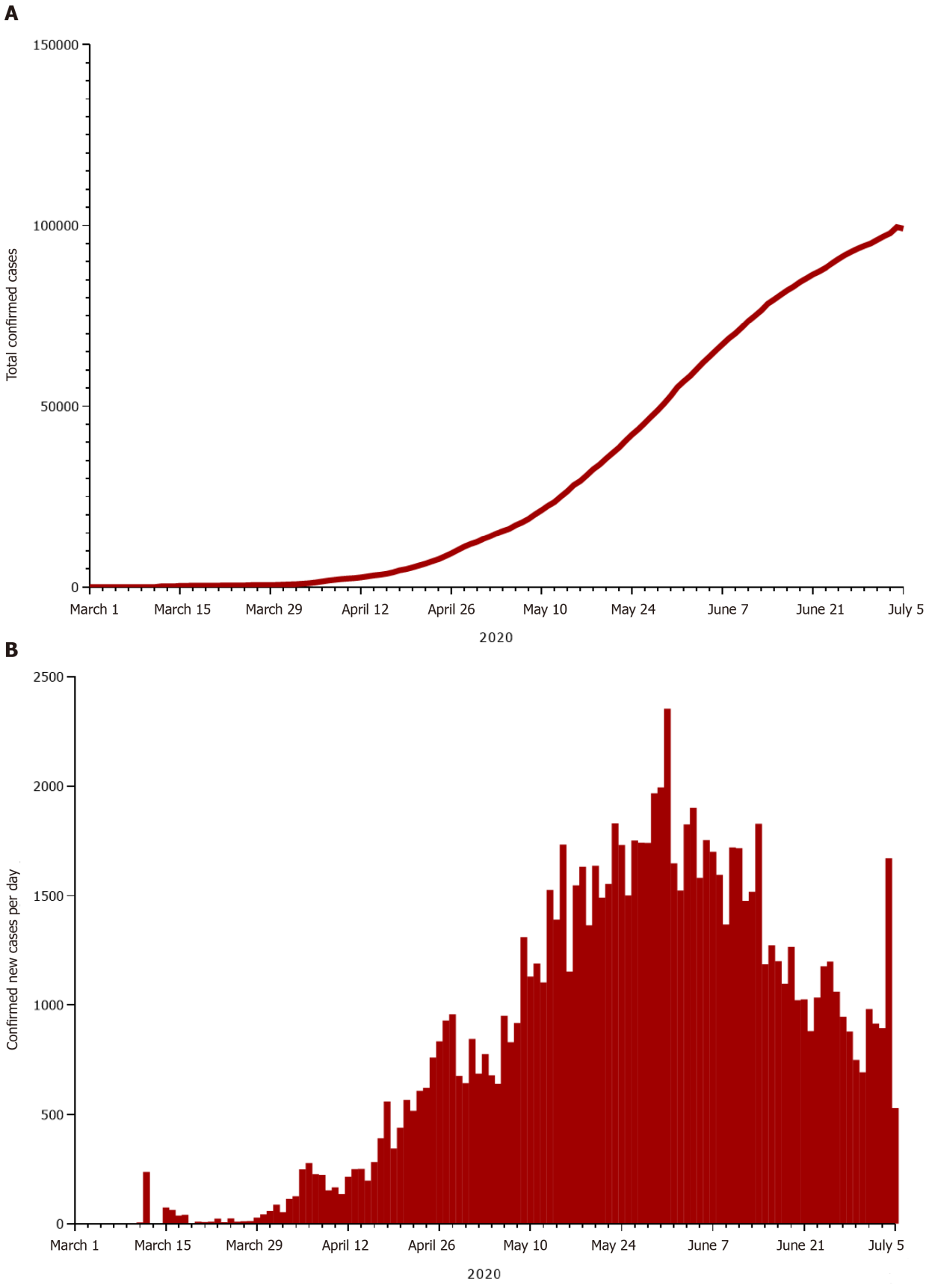

Figure 1 Total confirmed cases[1] and daily confirmed cases of COVID-19 in Qatar[8]. A: Total confirmed cases; B: Daily confirmed cases. A: Citation: Worldometer. Covid-19 coronavirus pandemic. [cited July 6, 2020]. Available from: https://www.worldometers.info/coronavirus/#countries; B: Citation: World Health Organization. Coronavirus disease (COVID-2019) situation reports. [cited July 6, 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/.

representation from the nephrology division, administration, nursing staff, technicians, and infection control team, meets regularly to devise and refine action plans based on the evolving COVID-19 situation. It continuously reviews the dialysis treatment capacity of all healthcare facilities in the country and the distribution of the nephrology workforce. It also implements policies and protocols to limit cross infection and clinical care pathways to cope with patient volume during different phases of the pandemic.

In February, when COVID-19 had not yet peaked in most parts of the world, there was a paucity of epidemiological data regarding the impact of COVID-19 on the kidneys. Hence, it was difficult to accurately predict the effect of the pandemic on nephrology health services. Nevertheless, it was anticipated that despite the higher mortality rates associated with previous coronavirus infections, COVID-19 will place a heavier burden on critical care units and create a larger demand for RRT due to its contagiousness. Based on the local prediction models and data from China and the United States, it was estimated that approximately 30%-40% of hospitalized COVID-19 positive patients will require intensive care unit (ICU) admission, and 25% of ICU patients will require RRT[6,7].

Succession and workforce planning are critical because healthcare services often face periods of illness, self-isolation, or quarantine for healthcare professionals during pandemics. Hence, back-up strategies for each key personnel were made. In Qatar, all types of renal replacement therapies are carried out by dialysis nurses, including continuous renal replacement therapy (CRRT). There was a concern that increased demands for RRT during the pandemic will be compounded by the shortage of trained staff thus adversely affecting the staff-to-patient ratio. Hence, a training programme was developed to provide 225 ICU nurses with essential knowledge and skills for performing CRRT procedures.

Advance purchase agreements and stockpiling arrangements were made to acquire HD and CRRT machines as well as portable reverse osmosis units to boost the RRT capacity.

Steps were also taken to ensure that dialysis fluid and consumable dialysis supplies matched the requirements. Anticipating the increased risk of infection in kidney transplant and dialysis patients, policies were implemented to protect this vulnerable group of patients. Focus was placed on measures to mitigate the risk of cross-infection among patients and staff at dialysis centres. A key strategic decision was made by the MoPH to geographically separate and treat COVID-19 patients in designated facilities. Meanwhile, other facilities, including those that usually operate at near-surge capacity, have continued to provide uninterrupted acute health care to patients without COVID-19.

CONFRONTING THE PANDEMIC

National lockdown and social distancing measures were imposed in March 2020 to curb the spread of the virus and 'flatten the curve' (a public health strategy to spread healthcare needs over time). Qatar approached the peak phase of the pandemic in late May 2020, when there were approximately 2300 cases per day (Figure 1B)[8]. Nephrology services were refigured to mitigate the risk of COVID-19 while providing optimized care not only to the vulnerable CKD population but also to the critically ill patients in ICUs, which hinges largely on the provision of RRT. The following are some of the critical changes that have been implemented.

Minimizing risk of exposure in the outpatient setting

To minimize the risk of viral transmission to healthcare professionals and patients in the outpatient department, in-person patient visits have been eliminated or severely curtailed since March 2020; telemedicine clinics have become a primary mechanism for routine outpatient care. Patients are notified about their upcoming telemedicine appointment *via* a phone call or text-message a couple of days prior to their appointment. On the day of appointment, the nephrologist calls each patient on the clinic list and addresses their medical needs. If deemed necessary, an in-person visit is arranged by the physician. The patients are screened for fever and symptoms of COVID-19 before entering the clinic area. Although this approach has its limitations, most patients find telemedicine visits more convenient than in-person visits. In our experience, no-show rates have been effectively reduced by telemedicine.

Frequent monitoring of renal function or drug levels is often required for many high-risk and vulnerable patients, such as patients on immunosuppression. Many

patients refrained from attending the main hospital laboratory for their blood work in fear of COVID-19. Consequently, a special laboratory service has been created in an isolated area of the hospital, only accessible to kidney disease patients. This has minimized waiting time, given confidence to patients, and improved their compliance with laboratory tests. A home phlebotomy service has also been organized for the elderly or mobility-constrained high-risk individuals.

Since early April, hospital outpatient pharmacies have been closed, and a medication home delivery service has been provided to all patients through a collaborative project with Q-Post, the national postal service. Considering the high demand for this service, which requires up to 3 business days for delivery, a back-up pharmacy has been established in a convenient but secluded area of the hospital to cater only to transplant patients in need of an urgent supply of medication.

Managing critically ill patients requiring RRT

Although all acute care hospitals are equipped with ICU facilities to treat COVID-19 patients, the majority of such patients are treated in two of Hamad Medical Corporation's COVID-19 designated acute care hospitals. The main buildings of these hospitals have been gradually transformed into mega intensive care units that offer advanced respiratory support in a modern ICU environment. A few critically ill COVID-19 patients have been managed in non-COVID-19 hospitals because they were too ill to be transferred; each COVID-19 patient is treated in a dedicated wing of the ICU by dedicated nursing staff to avoid transmission of infection within the facility.

Table 1 compares the baseline and current (6 July 2020) RRT capacities for critically ill patients with acute kidney injury in acute care hospitals. When the projected COVID-19 peak approached, 100 ICU nurses had completed their CRRT training and proved to be an important resource for managing CRRT. Several ICU physicians, nephrologists, and nurses from other hospitals have been redeployed to these facilities to strengthen the workforce. Staying ahead of the curve has been a key strategy, one involving close monitoring of the evolving situation, conducting forward-looking assessments of the adequacy and efficacy of the nephrology services, and expanding the system capacity, erring on the side of overestimation. As a result of these measures, ICUs have never reached maximum occupancy, and RRT capacity has never been constrained despite staff absences due to illness/quarantine.

RRT is prescribed and supervised by nephrology physicians, although a collaborative goal-oriented approach agreed upon by nephrology and ICU teams is followed. This team-based approach is particularly helpful in COVID-19 positive patients with coexisting shock and acute respiratory distress syndrome to ensure alignment of critical care fluid interventions and RRT prescription. Sustained low-efficiency dialysis (also known as prolonged intermittent renal replacement therapy, if a CRRT machine is used) using the haemodialysis machine is the main modality of RRT for haemodynamically unstable ICU patients, although all forms of RRT are in use. An informal survey of the largest ICU at a COVID-19 designated facility revealed that sustained low-efficiency dialysis, either alone or in combination with CRRT, was prescribed in more than 90% of the cases of acute kidney injury related to COVID-19 from March 1 to July 3 (Figure 2). High-flow CRRT has not been used although some patients with cytokine storms have been treated with adsorptive membranes to remove inflammatory mediators as a part of a clinical trial. One ICU nurse was able to simultaneously manage two patients on CRRT in double/multiple-occupancy rooms, thereby decreasing organizational costs, conserving personnel protective equipment, and alleviating staffing shortage issues. Interdisciplinary collaboration continues so that experienced dialysis nurses are always around to serve as core-experts and provide guidance.

ICU patients on maintenance PD are managed by PD nurse specialists. To decrease staff exposure and fatigue due to frequent alarms, all patients on cycler-assisted PD are switched to manual PD using three exchanges per day unless the fluid status or biochemical parameters warrant a more intensified regimen. Fluid overload has been successfully managed with hypertonic solutions; to date, none of the patients have required a switch to HD. Used dialysate is disposed of in the dirty utility room and plastic waste in yellow biohazard bags.

Mitigating the risk of COVID-19 in ambulatory dialysis centres

Dialysis centres can become a source of viral transmission unless proper infection prevention and control practices are followed. The country's largest dialysis facility in Doha accommodates 480 HD patients and provides outpatient facilities to 170 PD patients and 350 CKD stage 5 non-dialysis patients. It also has diabetes and podiatry clinics and a pharmacy unit. Preparing a dialysis facility as large as this and training

Table 1 Baseline and current renal replacement therapy capacities for critically ill patients with acute kidney injury

Resources	Baseline capacity (December 2019)	Current capacity (July 6, 2020)	Reserve capacity
ICU beds	130	529	171
Haemodialysis machines	268	347	-
CRRT machines	8	30	14
Portable reverse osmosis units	50	95	-
Trained ICU nurses for CRRT	0	100	125

CRRT: Continuous renal replacement therapy; ICU: Intensive care unit.

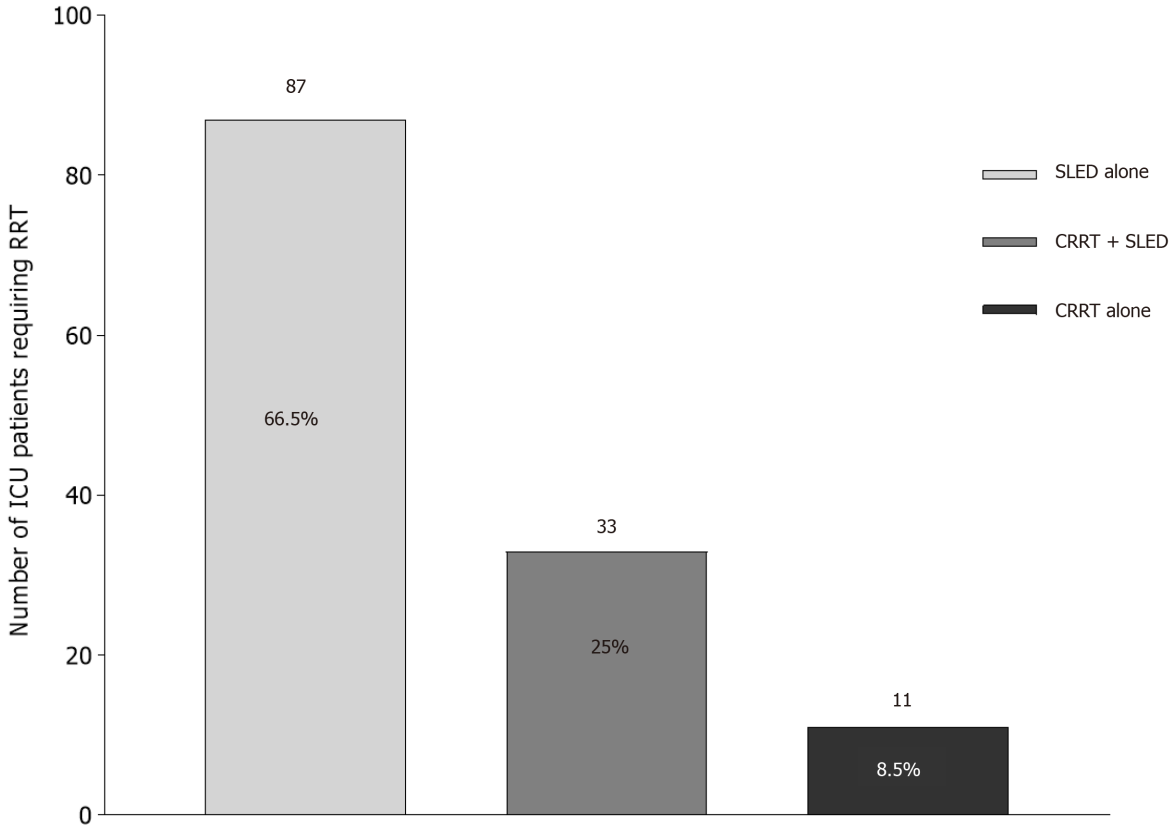

Figure 2 Renal replacement therapy modalities used in 131 cases of coronavirus disease 2019-related acute kidney injury in the intensive care unit between March 1 and July 3. CRRT: Continuous renal replacement therapy; ICU: Intensive care unit; RRT: Renal replacement therapy; SLED: Sustained low-efficiency dialysis.

the healthcare professionals to safely manage the patients has been a critical task.

A clinical protocol has been formulated in conjunction with the infection control team and Communicable Disease Centre, taking into consideration the recommendations of international societies and the World Health Organization to prevent, mitigate, and contain transmission to staff, patients, and visitors in the dialysis facilities[9,10]. Staff and patients are educated on hand and respiratory-related hygiene. Staff are fit-tested for N95 respirator masks, trained on proper donning and doffing of personnel protective equipment, and screened fortnightly using COVID-19 PCR. Dialysis centres have adequate signage, and hand sanitizer dispensers are installed at multiple places. All personnel entering the dialysis centre are required to have mandatory body temperature checks using infrared thermal devices. Patients are advised to call ahead if they have fever or symptoms of respiratory tract infection.

Another key strategy is to triage patients upon arrival at the dialysis facility using a questionnaire. Patients with no signs of infection are issued a screening ticket authorizing their entry to the treatment areas. Any patient suspected to be infected is dialyzed in a negative-pressure isolation room or a room with portable HEPA filter. A

nasopharyngeal swab is taken and the MoPH notified. The dialysis machine is meticulously disinfected before and after each use.

Confirmed COVID-19 patients are dialyzed at the designated centres (and are red flagged on the Cerner electronic record system). The discharge criteria for patients have been updated by the MoPH during the pandemic.

Providing maintenance HD for COVID-19 patients and patients in quarantine centres

A six-bay mobile modern dialysis truck has been stationed next to one of the main COVID-19 designated acute care hospitals and is currently being used to dialyze stable COVID-19 patients on maintenance HD at field hospitals (Figure 3).

Special treatment rooms have also been set up to provide treatment to maintenance HD patients at quarantine centres (incoming travellers to Qatar and for locally exposed patients) and isolation centres (COVID-19 patients who are stable). Patients at these facilities are dialyzed using NxStage System haemodialysis machines and portable reverse osmosis units and supervised by the home-haemodialysis nephrology team.

Accommodating the excess number of non-COVID-19 patients undergoing maintenance HD

An unusual increase in the prevalence of non-COVID-19 patients undergoing maintenance HD has been observed during the pandemic. Expatriates with newly diagnosed ESRD, many of whom would normally opt to return to their home-countries, as well as visitors on maintenance HD are stranded in Qatar due to the air travel disruptions and entry restrictions imposed by several countries. These factors, coupled with a marked decrease in transplant activity, have led to an increased demand for maintenance haemodialysis therapy. To accommodate these patients, extra stations have been added to an existing ambulatory dialysis facility, and an extra shift has been introduced at units that would normally run two shifts of patients per day (Figure 3). Available slots at inpatient HD units are also being utilized to accommodate these additional patients. All these measures have significantly enhanced the capacity to offer maintenance HD to additional patients without compromising the dialysis prescription of pre-existing HD patients.

Providing safe transportation to dialysis patients

The lack of public transport during the pandemic has been a significant barrier to commuting for many haemodialysis patients who do not have individual transport. Hamad Medical Corporation's ambulance service has played a vital role in providing safe transportation to these patients to and from dialysis facilities while following safety guidelines provided by the Communicable Disease Centre. Some of the ambulances are assigned exclusively to transport confirmed or suspected COVID-19 patients between the health facilities. The staff wears the recommended personnel protective equipment, and the ambulance undergoes a deep-clean disinfection after each trip. The ambulance service has seen a 30% increase in the daily activity from COVID-19-related missions during the peak phase.

Modifying nephrology fellowship programme

The COVID-19 pandemic has imposed new challenges and opened new learning opportunities for the Nephrology fellows in the training programme. The weekly fellows' seminar has been put on hold, and some of the fellowship rotations have been modified. The fellows have received brief training in critical care medicine and have been assigned to work in intensive care units under the supervision of intensivists and nephrologists. These changes in their rotation have broadened their learning experience. They have become more confident in managing critically ill patients and in prescribing different modalities of RRT in the ICU setting.

FUTURE DIRECTIONS

Although the COVID-19 surge appears to be abating in Qatar, the complete eradication of COVID-19 is unlikely to occur anytime soon. It is probable that we will continue to see critically ill COVID-19 patients who require acute nephrology care for the next several months. There is also the possibility of a second wave of the infection. Hence, it would be wise to retain the expanded ICU and RRT treatment capabilities.

Given the pitfalls in the COVID-19 PCR diagnostics, the potential for donor

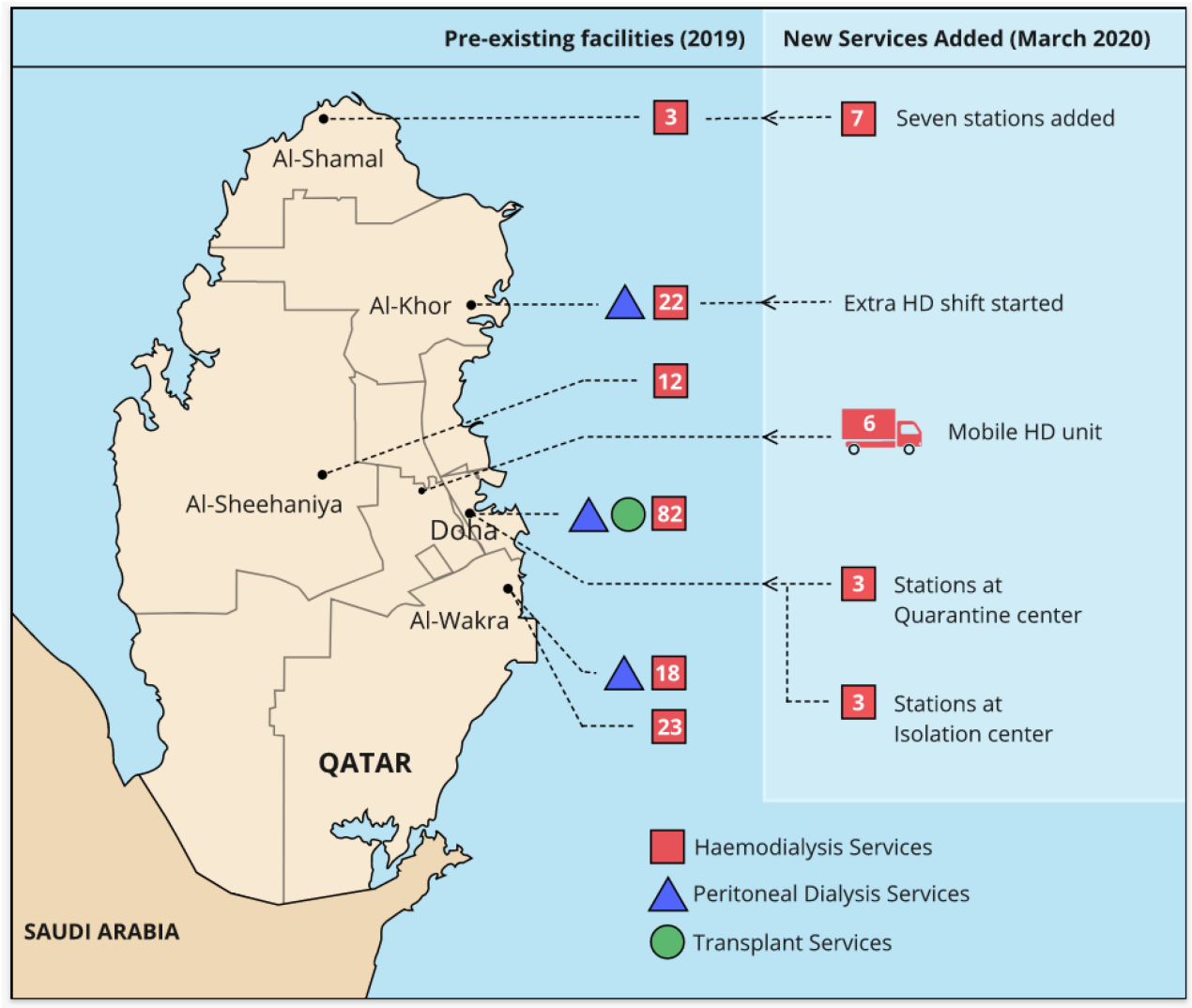

Figure 3 Geographical distribution of renal replacement therapy facilities in Qatar before and during the coronavirus disease 2019 pandemic. The values in red squares represent the number of haemodialysis stations at that centre (adapted from reference[5] with permission). Citation: Al-Malki H, Rashed AH, Asim M. Renal replacement therapy in Qatar—Past, present and future. *Open J Nephrol* 2018; 8: 42-55. Copyright© The Authors 2018. Published by Scientific Research Publishing.

derived/hospital-acquired infection and concerns over the severity of illness in heavily immunosuppressed transplant recipients, organ procurement and transplantation activities have been unfavourably influenced by the COVID-19 pandemic. Methods for reinvigorating the transplant programme are now being considered. Transplant pathways and algorithms have been developed to guide donor and recipient screening and management. In the initial phase, transplantation will be restricted to highly sensitized patients and those with urgent clinical indications, if COVID-19-free pathways can be ensured.

Follow-ups for patients who had COVID-19-related kidney disease, the backlog of postponed living kidney donor and transplant recipient workup, and other nonurgent nephrology services will create a surge in outpatient activity once people overcome the fear of hospitals. Outpatient nephrology services will need to be enhanced to cope with the accumulated elective volumes.

CONCLUSION

Outbreaks of infectious diseases are likely to pose an ongoing threat to humankind. It is also expected that we will encounter recurrence of COVID-19 outbreaks in the future. Before effective vaccines and medical treatments become available, we need to remain vigilant to detect cases early, devise innovative approaches to protect the vulnerable, and implement infection control strategies to prevent major outbreaks that

overwhelm the health services. RRT is a lifesaving treatment, and it is imperative that healthcare systems invest in technical infrastructure, staff, and supplies to provide efficient critical care nephrology services in the setting of a pandemic. We are struck by the reports of physicians working under tremendous pressure and making difficult decisions of ventilator/ICU bed rationing as well as the heroic efforts of nephrologists working with the RRT capacity that has been stretched to the breaking point in regions where the magnitude of the pandemic and healthcare capacity deficits could not have been foreseen[11,12].

ACKNOWLEDGEMENTS

We thank Dham T, Abdulla A, Joseph J, Joseph S, and all the Hamad Medical Corporation staff for their excellence in patient care in these extremely difficult times. We also thank Hamza Asim for his assistance with computer graphics.

REFERENCES

1 **Worldometer**. Covid-19 coronavirus pandemic. [cited July 6, 2020]. Available from: https://www.worldometers.info/coronavirus/#countries
2 **Macrotrends**. Qatar healthcare spending 2000-2020. [cited July 4, 2020]. Available from: https://www.macrotrends.net/countries/QAT/qatar/healthcare-spending
3 **World Health Organization**. STEPwise approach to chronic disease risk factor surveillance. [cited July 4, 2020]. Available from: https://www.who.int/ncds/surveillance/steps/qatar/en/
4 **Ramachandran A**, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 2012; **3**: 110-117 [PMID: 22737281 DOI: 10.4239/wjd.v3.i6.110]
5 **Al-Malki H**, Rashed AH, Asim M. Renal replacement therapy in Qatar—Past, present and future. *Open J Nephrol* 2018; **8**: 42-55 [DOI: 10.4236/ojneph.2018.82006]
6 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]
7 **Lewnard JA**, Liu VX, Jackson ML, Schmidt MA, Jewell BL, Flores JP, Jentz C, Northrup GR, Mahmud A, Reingold AL, Petersen M, Jewell NP, Young S, Bellows J. Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study. *BMJ* 2020; **369**: m1923 [PMID: 32444358 DOI: 10.1136/bmj.m1923]
8 **World Health Organization**. Coronavirus disease (COVID-2019) situation reports. [cited July 6, 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
9 **Centers for Disease Control and Prevention**. Interim additional guidance for infection prevention and control recommendations for patients with suspected or confirmed COVID-19 in outpatient hemodialysis facilities. [cited July 4, 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhealthcare-facilities%2Fdialysis.html
10 **World Health Organization**. Rational use of personal protective equipment for coronavirus disease (COVID-19): Interim guidance, 27 February 2020. [cited July 4, 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCov-IPCPPE_use-2020.1-eng.pdf?Sequence=1&isAllowed=y
11 **Rosenbaum L**. Facing Covid-19 in Italy - Ethics, Logistics, and Therapeutics on the Epidemic's Front Line. *N Engl J Med* 2020; **382**: 1873-1875 [PMID: 32187459 DOI: 10.1056/NEJMp2005492]
12 **Goldfarb DS**, Benstein JA, Zhdanova O, Hammer E, Block CA, Caplin NJ, Thompson N, Charytan DM. Impending Shortages of Kidney Replacement Therapy for COVID-19 Patients. *Clin J Am Soc Nephrol* 2020; **15**: 880-882 [PMID: 32345750 DOI: 10.2215/CJN.05180420]

World Journal of Nephrology

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

World J Nephrol 2020 November 29; 9(2): 18-32

DOI: 10.5527/wjn.v9.i2.18

ISSN 2220-6124 (online)

REVIEW

Kidney injury in COVID-19

Adeel Rafi Ahmed, Chaudhry Adeel Ebad, Sinead Stoneman, Muniza Manshad Satti, Peter J Conlon

ORCID number: Adeel Rafi Ahmed 0000-0002-5910-6980; Chaudhry Adeel Ebad 0000-0003-1552-5371; Sinead Stoneman 0000-0003-0941-6507; Muniza Manshad Satti 0000-0001-5630-2153; Peter J Conlon 0000-0001-6772-9531.

Author contributions: Ahmed AR conceived and designed the study, performed literature review and analysis, drafted and critically revised and edited the manuscript and approved the final version; Ebad CA contributed to the section on management of renal transplant recipients in coronavirus disease 2019, final editing and critical analysis of the article; Stoneman S contributed to the section on direct viral invasion of renal parenchyma, final editing and critical analysis of the article; Satti MM contributed to the literature review for the pathophysiology of acute kidney injury in acute respiratory distress syndrome, final editing and critical analysis; Conlon PJ contributed and supervised with conception and design of the study, literature review and analysis, drafting and critical revision and editing and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest.

Adeel Rafi Ahmed, Chaudhry Adeel Ebad, Sinead Stoneman, Department of Nephrology, Beaumont Hospital, Dublin D09 V2N0, Ireland

Muniza Manshad Satti, Department of Medicine, Connolly Hospital, Dublin D15X40D, Ireland

Peter J Conlon, Department of Nephrology, Beaumont Hospital and Royal College of Surgeons in Ireland, Dublin D09 V2N0, Ireland

Corresponding author: Adeel Rafi Ahmed, MBChB, MRCP, Staff Physician, Department of Nephrology, Beaumont Hospital, Dublin 9, Dublin D09 V2N0, Ireland.
adeel.r.ahmed@gmail.com

Abstract

Coronavirus disease 2019 (COVID-19) continues to affect millions of people around the globe. As data emerge, it is becoming more evident that extrapulmonary organ involvement, particularly the kidneys, highly influence mortality. The incidence of acute kidney injury has been estimated to be 30% in COVID-19 non-survivors. Current evidence suggests four broad mechanisms of renal injury: Hypovolaemia, acute respiratory distress syndrome related, cytokine storm and direct viral invasion as seen on renal autopsy findings. We look to critically assess the epidemiology, pathophysiology and management of kidney injury in COVID-19.

Key Words: COVID-19; SARS-CoV-2; Acute kidney injury; Cytokine storm; Acute respiratory distress syndrome; Renal replacement therapy

Core Tip: Kidney injury in coronavirus disease 2019 (COVID-19) is associated with increased mortality with hypovolaemia, acute respiratory distress syndrome (ARDS), cytokine storm and direct viral invasion having a prominent pathophysiological role. Haematuria and proteinuria are present in a high proportion of cases reflecting possible glomerular involvement, and collapsing glomerulopathy has also been reported in genetically predisposed patients. This is further supported by autopsy findings showing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in proximal tubules and podocytes. Evidence supports a conservative fluid management strategy in COVID-19 associated ARDS with standard indications for renal replacement therapy. Hypercoagulation is a prominent feature leading to filter clotting, thus regional citrate

Manuscript source: Unsolicited manuscript

Specialty type: Urology and Nephrology

Country/Territory of origin: Ireland

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: June 25, 2020
Peer-review started: June 25, 2020
First decision: August 22, 2020
Revised: October 3, 2020
Accepted: October 20, 2020
Article in press: October 20, 2020
Published online: November 29, 2020

P-Reviewer: Omar AS
S-Editor: Zhang L
L-Editor: Filipodia
P-Editor: Wang LL

anticoagulation should be used. Kidney transplant recipients with COVID-19 should have immunosuppression reduced.

Citation: Ahmed AR, Ebad CA, Stoneman S, Satti MM, Conlon PJ. Kidney injury in COVID-19. *World J Nephrol* 2020; 9(2): 18-32
URL: https://www.wjgnet.com/2220-6124/full/v9/i2/18.htm
DOI: https://dx.doi.org/10.5527/wjn.v9.i2.18

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to the coronavirus disease 2019 (COVID-19) is affecting millions of people worldwide, carrying a case fatality rate between 0.9% to 7.2% depending on the demographics, implementation of preventative measures, testing strategies and availability of health care resources[1-3]. Severe disease is seen in approximately 20% of cases, of which around 6% represents the critically ill COVID-19 patients[4,5]. Amongst the critically ill, 65% to 95% have acute respiratory distress syndrome (ARDS), followed by acute kidney injury (AKI) and acute cardiac injury/cardiomyopathy[6-8]. AKI is common among critically ill patients with COVID-19 and is an independent marker of mortality[9,10]. Prompt recognition and management of AKI in COVID-19 can limit its progression and contribute to reducing morbidity and mortality[9]. Multiple mechanisms of kidney injury have emerged as we learn more about SARS-CoV-2[11]. In this review, we look to answer the many pertinent questions regarding the epidemiology, pathophysiology and management of AKI in COVID-19 patients.

MAIN BODY

Epidemiology

AKI, in general, has an incidence of around 3%-18% in hospitalised patients and is associated with 10%-20% mortality in the non-intensive care hospital setting, with up to 50% mortality in the intensive care setting[12-14]. There is a paucity of evidence identifying the role AKI plays in COVID-19. Majority of studies use Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI in COVID-19[15]. Assessment of data from major published cohorts on COVID-19, combining results from intensive care unit (ICU) admissions with non-ICU admission, reveals an overall AKI incidence of around 4.2% (Table 1)[2,4,6-8,10,16]. Amongst the non-survivors (NS), the incidence of AKI is approximately 30% and renal replacement therapy (RRT) is required in 19.5% (Table 1). Comparatively in the severe acute respiratory syndrome (SARS) outbreak in 2003, the incidence of AKI was around 6.7%, and multivariate analysis showed AKI as a significant independent risk factor for predicting mortality (relative risk: 4.057; 99% confidence interval: 1.461-11.27; $P < 0.001$)[17].

What is the mechanism of AKI in COVID-19? Four possible key mechanisms are becoming evident in the COVID-19 pandemic (Table 2): Hypovolaemia[9,18], ARDS related AKI[19,20], cytokine storm syndrome (CSS) associated AKI[21-23], and direct viral tropism for proximal tubular cells and podocytes *via* the angiotensin-converting enzyme 2 (ACE2) carboxypeptidase[24,25].

Hypovolaemia

A majority of patients have significant insensible water losses due to high-grade pyrexia and tachypnoea on presentation[26]. A subgroup of patients has substantial gastrointestinal symptoms leading to extrarenal volume loss[18]. These patients are particularly prone to developing pre-renal AKI.

ARDS related AKI

AKI is seen in around 35%-50% of patients who develop ARDS and substantially increases mortality by nearly two-fold in the ICU[27-30]. ARDS and its associated mechanical ventilation strategies can cause or aggravate renal injury *via* multiple pathways[31]. There are broadly five categories; haemodynamic effects, gas exchange

Table 1 Summary of acute kidney injury incidence in coronavirus disease 2019 patients

Ref.	Zhou *et al*[2]	Yang *et al*[8]	Guan *et al*[4]	Wan *et al*[16]	Arentz *et al*[6]	Cheng *et al*[10]	Italian data March 20, 2020 [7]	Combined results without Italian data	Combined results with Italian data
Total patients	191	52	1099	135	21	701	47021	2199	49220
Critically Ill[1]	50	52	55	40	21	73	N/A	291	
ARDS	59 (30.1%)	35 (67%)	37 (3.4%)	20 (14.8%)	20 (95.2%)	97[4] (13%)	N/A	268 (12.2%)	
AKI	28 (14.7%)	15 (28.8%)	6 (0.5%)	5 (3.7%)	4 (19%)	36 (5.1%)	N/A	94 (4.2%)	
RRT	10 (5%)	9 (17.3%)	9 (0.85)	5 (3.7%)	N/A	N/A	N/A	33 (1.5%)	
Non survivors (NS)[2]	54 (28.3%)	32 (61.5%)	67[2] (6.1%)	1 (0.7%)	11 (52.4%)	113 (16.1%)	3200 (6.8%)	278 (154)[5] (12.6%)	3478 (3354) (7%)
AKI in NS[2,3]	27 (50%)	12 (37.5%)	4[2] (6%)	4[3] (10%)	N/A	N/A	944 (29.5%)	47 (30.5%)	991 (29.5%)
RRT in NS[2,3]	10 (18.5%)	8 (25%)	8[2] (11.9%)	4[3] (10%)	N/A	N/A	N/A	30(19.5%)	

[1]Critically ill is defined as intensive care unit (ICU) admitted or categorised as a severe case where separate ICU data are not provided by the primary authors.
[2]The study by Guan *et al*[4] (NEJM) includes patients in ICU admission, on mechanical ventilation and non-survivors.
[3]The study by Wan *et al*[16] includes patients with critical illness.
[4]Patients on mechanical ventilation.
[5]Excluding data from Arentz *et al*[6] and Cheng *et al*[10] as acute kidney injury incidence was not provided in non-survivors. AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; RRT: Renal replacement therapy.

Table 2 Summary of the mechanism of kidney injury in coronavirus disease 2019

Mechanism of kidney injury	Hypovolaemia	ARDS related AKI	Cytokine storm syndrome associated AKI	Direct viral invasion
Pre-renal	Fever causing insensible losses; Gastrointestinal volume losses	Haemodynamic instability; High positive end expiratory pressure /intrathoracic pressure; Right heart failure	Haemodynamic instability	
Renal[1]		Inflammation; Hypoxia/hypercapnia; Acid-base dysregulation; Tubular injury	Inflammation; Possible glomerulopathy and TMA (hypercoagulability)	Inflammation; Possible Tubulopathy; Podocytopathy; Interstitial inflammation
Post renal				

[1]The most common intrinsic renal lesion observed is acute tubular necrosis. AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; TMA: Thrombotic microangiopathy.

impairment (hypoxemia/hypercapnia), acid-base dysregulation, hyper inflammation and neurohormonal effects[32]. In COVID-19, significant AKI generally develops after the onset of ARDS, suggesting lung- kidney crosstalk as the dominant mechanism of kidney injury[2,33].

The haemodynamic effects of acute pulmonary disease result in increased pulmonary artery pressures, right ventricular failure, venous congestion and increased intra-abdominal/intrathoracic pressures[34-38].

Impaired gaseous exchange with hypercapnia leads to a reduction of renal vasodilatory response and renal blood flow with altered diuresis and increased oxygen utilisation in the proximal tubule[39-41]. Severe hypoxemia also causes a reduction in renal blood flow with possible activation of the hypoxia-inducible factor system, influencing lung and kidney outcomes[42]. There is the activation of renin-angiotensin-aldosterone system, with increased aldosterone secretion with resultant activation of the sympathetic nervous system and release of non-osmotic vasopressin[31,43]. An immune-mediated/inflammatory response is noted in ARDS with

the release of interleukin (IL)-6, tumour necrosis factor (TNF alpha), IL-1, transforming growth factor and substance P[44-47].

Mechanical ventilation can worsen the haemodynamic effects and cause ventilator-induced lung injury leading to further cytokine release and multi-organ dysfunction syndrome[48]. The effects of excessive positive end-expiratory pressure (and high tidal volumes) on kidney function include a further increase in intrathoracic pressures, which causes increased right ventricular dysfunction, reduced venous return and reduced cardiac output[34-36].

AKI independently worsens ARDS. AKI leads to increased production, decreased clearance of inflammatory cytokines and down-regulation of lung aquaporin and ion channels[49,50]. The rise in circulatory cytokines, particularly IL-6, leads to increased infiltration of lungs with neutrophils and macrophages, and increased pulmonary vasculature permeability worsens ARDS[51,52]. In the later phase of inflammation, IL-6 promotes IL-10 production, which has anti-inflammatory and organ protective effects[53]. Limited data suggest AKI promotes neutrophil dysfunction, causing reduced clearance of infection and increasing lung permeability[54,55]. Haemodynamically, the inflammatory state and increased alveolar-capillary permeability combined with decreased urine output in AKI worsens pulmonary oedema[56,57]. Most immunological studies are based on animal models, however, observational data support the negative impact of AKI on pulmonary outcomes in critically ill patients, with two times more requiring invasive mechanical ventilation[58,59].

The incidence of shock is variable in COVID-19 based on the reported cohort studies; in the ICU setting it may be as high as 35%[2,8]. This vasopressor dependent state causes renal blood flow dysregulation, including ischaemia-reperfusion injury, metabolic reprogramming and inflammation resulting in AKI[60]. Preliminary reports suggest rhabdomyolysis is not a major component of COVID-19, but data vary in each centre with some case reports showing a significant rise in creatine kinase and other viral infections (H1N1 and SARS) have reported this complication[4,61-63].

Cardio-renal syndrome can play a significant role in critically ill COVID-19 patients[64,65]. In cardio-renal syndrome, excessive inflammation and rise in cytokines seem central to the pathophysiological process[64,66]. The high levels of IL-6, TNF and IL-1 have a direct cardio-depressant effect and may promote myocardial cell injury[67,68]. Acidaemia promotes pulmonary vasoconstriction, increases right ventricular afterload and exacerbates negative inotropic effect[69,70]. Myocarditis may also occur in COVID-19[71].

The overall combined effect of this entire process is an inflammatory, cardio-depressant, acidotic, volume retaining state with high intrathoracic and intraabdominal pressures resulting in high renal back pressures, decreased and dysregulated renal blood flow and severe renal tubular injury.

Cytokine storm syndrome associated AKI

Observational data from a subgroup of patients with COVID-19 suggest the development of features consistent with CSS triggered by SARS-CoV-2 virus characterised by high serum ferritin, D-dimer, lactate dehydrogenase, cytopenia, ARDS, acute cardiac injury, abnormal liver function test, raised IL-6 and coagulation abnormalities[72-75]. Viral infections have been reported as one of the most common triggers for cytokine storms[76]. One study demonstrated similar or lower levels of cytokines in COVID-19 pneumonia when compared to other critically ill patients, questioning the hypothesis of CSS[77]. However, the use of dexamethasone, a potent anti-inflammatory steroid, has demonstrated a significant reduction in mortality amongst critically ill COVID-19 patients, highlighting the major role of hyperinflammation[78].

Can this hyperinflammatory state cause AKI? Various case series have indicated significant renal involvement, particularly in CSS associated with secondary haemophagocytic lymphohistiocytosis (sHLH)[22,79-82]. The majority present with AKI with or without nephrotic range proteinuria[79]. Histological and observational findings indicate polymorphic renal lesions with acute tubular necrosis (ATN) being the most common, followed by tubulointerstitial nephritis (TIN), collapsing glomerulopathy (with podocytopathies) and thrombotic microangiopathy (TMA)[22,79,82]. ATN and TIN are most likely due to sepsis-related haemodynamic changes, coagulopathy (disseminated intravascular coagulopathy) and perhaps the direct toxic effect of raised cytokines (IL-6 and TNF) on renal epithelial cells[83]. Nephrotic syndrome with collapsing glomerulopathy and podocytopathies are generally seen in severe cases of sHLH with African ethnic predisposition[80]. It is hypothesised a circulating cytokine during CSS phase of sHLH may cause podocytopathy[82]. Hyperinflammation, as seen in COVID-19, also leads to a hypercoagulable state that can cause fibrin thrombi

occlusions in renal capillaries (TMA pattern of renal injury)[84-86].

Renal biopsy histology of patients of black ethnicity who had AKI and were subsequently SARS-CoV-2 positive showed collapsing glomerulopathy, severe podocyte effacement with acute tubular injury (ATI)[87,88]. The APOL1 genotyping on the biopsy material was performed, and the patients were found to be homozygous for the G1 risk allele. Genetic predisposition with CSS may lead to collapsing glomerulopathy in COVID-19[89].

The hyperinflammatory state can cause renal injury *via* multiple mechanisms as highlighted, however, the discussion is incomplete without further assessing the role of direct viral tropism for renal parenchyma and renal autopsy findings.

Direct viral invasion

Viruses must gain entry into a cell and use the host cell machinery to replicate. The ACE2 is the coreceptor used by SARS-CoV-2 to gain entry to the cells[90]. ACE2 forms part of the renin-angiotensin-aldosterone system, a cascading peptide-pathway that regulates vascular tone and salt and water balance. The ACE2 degrades angiotensin II to angiotensin, resulting in vasodilation and countering the effects of ACE[91-94].

The ACE2 is expressed in the kidney, staining abundantly in the brush border of tubular epithelial cells, moderately in parietal epithelial cells and absent in glomerular or mesangial endothelial cells[92]. Although hypertension may be a risk factor for poor prognosis with SARS-CoV-2 infection, inferences that this is due to effects on ACE2 expression as a consequence of ACE inhibitor or angiotensin receptor blocker (ARB) use are not supported by data[91,95]. Previous studies have not shown that there is upregulation of plasma ACE2 activity in patients taking ACE inhibitors or ARBs compared to patients not on these agents[94,96,97].

There is currently no data to suggest that even if ACE inhibitors or ARBs did upregulate ACE2 expression that this would facilitate faster or greater viral entry of SARS-CoV-2 into cells[91].

SARS-CoV-2 shares 79.6% sequence identity to SARS-CoV; therefore, the mechanism of COVID-19 associated AKI may share some similarities with SARS[93].

The data on whether SARS-CoV-2 caused direct kidney injury through viral entry are conflicting. In an autopsy series of 18 patients who died of SARS infection, viral sequences were located in the epithelial cells of the renal distal tubules[98]. Similarly, using a murine monoclonal antibody specific for SARS-CoV-2 nucleoprotein in four patients who died of SARS, SARS-CoV-2 antigen and RNA was found in the epithelial cells of distal convoluted renal tubules[99]. However, in a smaller case series in which autopsy findings from kidney specimens of seven SARS patients were presented, there was no virus or viral-like particles in the tubular epithelial or glomerular cells. Similarly, SARS-CoV-2 was not detected in these seven kidney samples using *in situ* hybridization[17]. Data from the Middle East respiratory syndrome (MERS) suggested the presence of the virus in the proximal tubular epithelial cells[100].

Observational and histopathological studies on COVID-19 have suggested renal parenchymal involvement[10,25,87,101-104]. A retrospective study from Tongji Hospital in Wuhan, China showed the prevalence of haematuria and proteinuria at presentation among NS was significantly more compared to recovered patients (86% and 82% *vs* 50% and 38%)[101]. This coincided with significantly higher levels of inflammatory markers on presentation. A prospective analysis of 701 patients with COVID-19 from the same hospital showed a prevalence of 43.9% with proteinuria and 26.7% with haematuria[10]. This study further demonstrated haematuria and proteinuria were independent markers of in-hospital mortality in COVID-19, suggesting more aggressive disease and early features of possible direct viral invasion and hyperinflammation.

Early histopathological analysis from autopsies conducted on COVID-19 patients demonstrated on light microscopy primarily proximal ATI and ATN with vacuolar degeneration, TIN, endothelial injury, diffuse red blood cell aggregation in peritubular capillaries and glomerular capillary loops, rarely with focal fibrin thrombi[25,102]. Electron microscopy showed SARS-CoV-2 viral particles in the cytoplasm of the proximal tubule, distal tubule and podocytes. The ACE2 expression was prominent in proximal tubular cells, particularly in areas with severe ATI. Furthermore, focal strong parietal epithelial cells staining was present as well as occasional weaker podocyte staining of ACE2. Six autopsy cases showed the presence of CD68+ macrophages and membrane attack complex, C5b-C9, in the tubulointerstitium[25].

Based on limited evidence, it is plausible that during severe infection and high viral loads, SARS-CoV-2 infection and replication in renal tubular cells and podocytes causes ATI and ATN with subsequent TIN, which is further exacerbated by CSS. Fibrin thrombi and a TMA pattern of renal injury may be present due to

hypercoagulable state. This entire process of kidney injury with the presence of SARS-CoV-2 in the renal parenchyma can be described as COVID-19 nephropathy. Patients with dysregulation or a genetic variant of ACE2, allowing rapid SARS-CoV-2 infiltration, may show early signs of intrinsic renal injury by new-onset proteinuria and haematuria[103-105]. Larger studies looking into renal histology in COVID-19 are required to elucidate the detailed mechanism of renal injury.

Renal management of COVID-19

The COVID-19 can be divided into three phases with the first phase being mild symptoms, characterised by fever and cough, continuing for approximately 5 d, progressing to the second phase with new-onset or worsening of dyspnoea and or hypoxia (silent hypoxia), which lasts 2 to 5 d, and the final phase demonstrating severe viral pneumonitis and ARDS requiring ICU management[2,8,106]. Majority of the patients (81%) remain in the first phase and do not require significant hospitalisation[1]. As mentioned previously, AKI significantly increases in-hospital mortality, particularly in the ICU setting, which also holds in case of COVID-19[10,27,29,103].

Risk factors

A majority of the patients that present to the hospital with COVID-19 are 60 years or older with a high proportion having diabetes, hypertension and ischaemic heart disease[1,2,4]. These co-morbidities are associated with micro and macrovascular complications, all affecting renal blood flow. Any minor haemodynamic or nephrotoxic insult can lead to a substantial AKI in these patients[66,107].

All patients presenting with symptoms of COVID-19 should have urinalysis (urine dipstick, midstream urine and spot urine protein to creatinine ratio) and should be possibly repeated at each phase of the disease[108,109]. Identification of haematuria and proteinuria may allow early recognition of patients with a high risk of disease progression to ARDS, AKI and increased mortality[10,103,104,109-111]. Active urinary sediments are seen in a much larger proportion of COVID-19 patients than those with only diabetes and hypertension[10,25,102-104]. Urinalysis should be considered in conjunction with other baseline investigations such as FBC, renal profile, liver function tests, D-dimer, fibrinogen, ferritin, procalcitonin, lactate dehydrogenase, IL-6, C-reactive protein, troponins, creatine kinase and Sequential Organ Failure Assessment (SOFA) score[72].

Data extrapolated from research looking at risk factors for AKI in ARDS highlights age, presence of diabetes and heart failure, worsening acidosis on day 1 of ARDS, higher severity of illness score (SOFA and APACHE III) and obesity as strongly associated with the development of AKI[20]. Similar risk factors for AKI, with the inclusion of black race, have been identified in data specific to COVID-19[33].

Drug dosing needs to be adjusted as per creatinine clearance and potential nephrotoxic treatment options need to be assessed for risk-benefit[111]. All drugs can cause acute interstitial nephritis, and a high diagnostic suspicion is of paramount importance. Remdesivir, an antiviral drug, has shown some evidence of quicker recovery and trend towards lower mortality amongst patient with severe COVID-19[112]. However, the drug is primarily renally excreted and is currently not recommended in patients with an estimated glomerular filtration rate below 30 mL/min/1.73 m^2[113]. Animal models at high doses showed it can potentially cause AKI[113].

Volume management

The primary management of severe COVID-19 revolves around oxygenation and achieving an appropriate volume status. From a volume perspective, patients that present early during the disease can be hypovolaemic with gastrointestinal symptoms, fever and/or have an exacerbation of heart failure; therefore, volume management should aim to achieve euvolemia and stabilisation of blood pressure, which may be achieved through diuretics or intravenous fluids[4,114,115]. The minimum required volume should be used to achieve effective arterial volume.

Choice of fluids remains a matter of literature debate, however, current data suggest large volume resuscitation should be through balanced crystalloids rather than isotonic saline due to lower incidence of AKI[116,117]. Isotonic saline can lead to the development of hyperchloremic acidosis, which harms organ perfusion[118,119]. Acidosis is also an independent risk factor for developing AKI in ARDS[20]. Isotonic bicarbonate can be considered in hypovolemic patients with significant metabolic acidosis (particularly in pH < 7.20) and AKI[120].

Once initial volume resuscitation is accomplished, the next aim should be to achieve

and maintain cumulative net even balance[121-124]. The most well-established data comes from the comparison of Two Fluid-Management Strategies in the Acute Lung Injury (FACTT) trial, consisting of 1000 patients with ARDS, where the conservative fluid strategy (cumulative 7-d fluid balance -136 ± 491 mL) compared liberal fluid strategy (cumulative 7-d fluid balance 6992 ± 502 mL) had significantly more ventilator-free days and ICU-free days. A post-hoc analysis showed a non-statistically significant higher incidence of AKI in the liberal fluid strategy group[124]. A large retrospective study comparing conservative fluid strategy (FACTT) with semi-conservative fluid strategy (FACTT lite: Cumulative 7-d fluid balance 1918 ± 323 mL) in ARDS showed similar ventilator-free days and incidence of AKI and lower incidence of new-onset shock[122]. Both FACTT and FACTT lite protocols contained instructions to withhold furosemide until patients achieved a mean arterial pressure of greater than 60 mmHg for 12 h. However, specific fluid management in new-onset shock was not defined in both protocols. Despite its inaccuracies, targeting a central venous pressure of around 8 mmHg and pulmonary artery occlusion pressure of around 12 mmHg with monitoring of urine output provided the best outcomes in both protocols[121,122]. Volumes assessment is based on many other factors including passive leg raise response, inferior vena cava diameter, lung ultrasound, ejection fraction, capillary refill time and blood pressure (vasopressor requirements). It is important to note volume management strategies need to be individualised and various other factors such as ethnicity may impact decision making[125].

Until more robust evidence is available in volume management of COVID-19 induced ARDS, we continue to support a relatively conservative fluid management strategy.

Role of continuous renal replacement therapy in COVID-19

Around 20% of NS in COVID-19 required RRT, which was primarily continuous renal replacement therapy (CRRT) (Table 1)[2,4]. Many of these patients required it due to AKI with severe electrolyte derangements and/or volume overload intending to achieve net even or negative fluid balance. The timing of initiating CRRT varies amongst centres, however, two major randomised control trials over the last decade showed a delayed strategy of either absolute indications developing or AKI KDIGO stage 3 for more than 48 h compared to an early strategy of RRT within 6-12 h of AKI KDIGO stage 3 that had no difference in mortality, ICU-free days, ventilator-free days and vasopressor-free days[126-129]. Many patients did not require CRRT in the delayed group due to recovery of native renal function. However, a large proportion of COVID-19 patients are in ARDS at the time of AKI and some small randomised control trials have suggested early initiation of CRRT in ARDS improved oxygenation and mechanical ventilation-free days[130-132]. A post-hoc analysis of Artificial Kidney Initiation in Kidney Injury trial assessing subgroup of patients with ARDS (n = 207) showed no difference in ventilator-free days between the two RRT strategies and quicker renal function recovery with delayed strategy once AKI KDIGO 3 had occurred[126]. Some observational data are suggesting a higher incidence of circuit clotting in COVID-19, thus regional citrate anticoagulation should be first-line based on the availability of trained staff and centre experience[9,133].

CRRT timing should be based on an individual patient's physiological reserve. This depends on age, cardiovascular risk factors, pulmonary comorbidities, baseline renal function and the trend of inflammatory and renal injury markers[129]. A delayed strategy of waiting for 48–72 h after progressing to AKI KDIGO 3 or until an absolute indication that arises may apply to most COVID-19 patients with septic shock[129]. CRRT can be applied earlier in ARDS patients, who despite optimum volume management with diuretics are not able to attain an early cumulative net even or negative fluid balance.

Some authors have suggested using extracorporeal blood purification technologies particularly in the context of CSS seen in COVID-19 patients[134,135]. These technologies are primarily direct haemoperfusion, plasma adsorption on a resin, CRRT with hollow fibre filters with adsorptive properties and high-dose CRRT with medium cut-off or high cut-off membranes[134]. Extracorporeal cytokine adsorption and removal can be potentially beneficial in patients with CSS[136-138]. Yet, no conclusive data exist regarding its benefits, particularly when managing COVID-19. Previous studies involving these technologies have been either too small to reach a conclusion or showed no benefit[139-143]. Some data are emerging from Italy and Germany where cytokine adsorption technology was applied in managing COVID-19. We cannot currently recommend the use of extracorporeal blood purification outside the standard use of CRRT in COVID-19 due to inconclusive evidence but look forward to future studies.

Management of COVID-19 in renal transplant recipients

Renal transplant recipients with COVID-19 have a higher incidence of AKI and mortality compared to the general population[144-150]. Data from case series show AKI in 30%-57% of presentations with a mortality of up to 28%[144-146]. A relatively high percentage present with gastrointestinal symptoms, particularly diarrhoea, causing hypoperfusion of renal parenchyma and loss of bicarbonate ion[144,145,149]. Appropriate volume resuscitation in the early phase, stabilisation of blood pressure and withholding nephrotoxic medication including ACE-inhibitors and ARBs remain the principles of treatment. Diarrhoea can also cause supra-therapeutic calcineurin inhibitor (CNI) levels causing AKI.

Viral infection can be severe in patients on immunosuppression as immune system response, particularly T cell-mediated, is diminished. Transplant recipients with suspected or confirmed COVID-19 should have immunosuppression adjusted immediately based on case to case and severity of disease[151].

In general, antimetabolites (mycophenolate mofetil, azathioprine) should be stopped completely. CNI (tacrolimus, cyclosporin) dose should be reduced by up to 50% or stopped completely in severe cases[148,150]. The aim is target trough tacrolimus 3-5 ng/mL and cyclosporine 25-50 ng/mL. The mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) should be stopped or switched to CNI. The mTOR inhibitors have a well-known side effect of pneumonitis, which may worsen pneumonia associated with COVID-19 disease. Steroids dose should be increased to stress dose strengths during this initial phase[151].

The time frame to restart immunosuppression is not clear and can be considered based on improvement in clinical parameters and negative results of SARS-CoV-2 swab polymerase chain reaction. Each case needs to be evaluated in-depth merited on risks and benefit to recommence immunosuppressive therapy with a multi-disciplinary team approach, especially infectious disease and transplant physicians.

A suggested approach is to restart CNI at a half dose of usual maintenance dose with aim of trough level at a lower threshold in cases where CNI was stopped, with aim of up-titration of dose in further 2 wk. Steroids dose should be continued at a stress dose level during this titration period. Anti-metabolites and mTOR inhibitor recommencement can be considered after 2-4 wk based on case outcome[151].

Drug interactions need to be considered in transplant recipients with new potential therapies in the management of the disease. Risk of rejection will persist when off immunosuppression, which may need to be balanced on an individual case severity basis.

CONCLUSION

AKI leads to worse outcomes in COVID-19. Multiple mechanisms of renal injury are involved but can broadly be categorised into hypovolaemic, ARDS related, CSS associated and direct viral invasion of the renal parenchyma. Haematuria and proteinuria are associated with higher mortality and may signify aggressive disease early, thus all patients should have a baseline urinalysis. SARS-CoV-2 has an affinity towards the renal parenchyma and is seen in renal autopsies with associated intrinsic renal damage, collectively termed as COVID-19 nephropathy. Volume assessment is key in managing COVID-19; patients can present hypovolaemic during the early phase, particularly transplant recipients due to a high incidence of gastrointestinal symptoms, and aim should be to achieve euvolemia. Current evidence supports a conservative fluid management strategy during ARDS. Standard indications for CRRT apply, however, early initiation can be considered in ARDS if diuretics fail to support a conservative fluid management strategy. Renal transplant recipients have a higher case fatality rate, and immunosuppression needs to be reduced in COVID-19.

REFERENCES

1 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

2 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076

DOI: 10.1016/S0140-6736(20)30566-3]
3 **Onder G**, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* 2020; **323**: 1775-1776 [PMID: 32203977 DOI: 10.1001/jama.2020.4683]
4 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
5 **Grasselli G**, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA* 2020; **323**: 1545-1546 [PMID: 32167538 DOI: 10.1001/jama.2020.4031]
6 **Arentz M**, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA* 2020; **323**: 1612-1614 [PMID: 32191259 DOI: 10.1001/jama.2020.4326]
7 **Luigi Palmieri XA**, Antonino Bella, Stefania Bellino, Stefano Boros, Marco Canevelli, Maria. Characteristics of COVID-19 patients dying in Italy Report based on available data on March 20th, 2020 Epidemiology for public health. Higher Institute of Health 2020. Available from: https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf
8 **Yang X**, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475-481 [PMID: 32105632 DOI: 10.1016/S2213-2600(20)30079-5]
9 **Ronco C**, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med* 2020; **8**: 738-742 [PMID: 32416769 DOI: 10.1016/S2213-2600(20)30229-0]
10 **Cheng Y**, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; **97**: 829-838 [PMID: 32247631 DOI: 10.1016/j.kint.2020.03.005]
11 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]
12 **Bedford M**, Stevens PE, Wheeler TW, Farmer CK. What is the real impact of acute kidney injury? *BMC Nephrol* 2014; **15**: 95 [PMID: 24952580 DOI: 10.1186/1471-2369-15-95]
13 **Hoste EAJ**, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, Goldstein SL, Cerdá J, Chawla LS. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018; **14**: 607-625 [PMID: 30135570 DOI: 10.1038/s41581-018-0052-0]
14 **Sawhney S**, Marks A, Fluck N, Levin A, Prescott G, Black C. Intermediate and Long-term Outcomes of Survivors of Acute Kidney Injury Episodes: A Large Population-Based Cohort Study. *Am J Kidney Dis* 2017; **69**: 18-28 [PMID: 27555107 DOI: 10.1053/j.ajkd.2016.05.018]
15 **Robbins-Juarez SY**, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, Mohan S. Outcomes for Patients with COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. *Kidney Int Rep* 2020; **5**: 1149-1160 [PMID: 32775814 DOI: 10.1016/j.ekir.2020.06.013]
16 **Wan S**, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, Lang C, Huang D, Sun Q, Xiong Y, Huang X, Lv J, Luo Y, Shen L, Yang H, Huang G, Yang R. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol* 2020; **92**: 797-806 [PMID: 32198776 DOI: 10.1002/jmv.25783]
17 **Chu KH**, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, Fung KS, Tang HL, Yan WW, Chan HW, Lai TS, Tong KL, Lai KN. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int* 2005; **67**: 698-705 [PMID: 15673319 DOI: 10.1111/j.1523-1755.2005.67130.x]
18 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]
19 **Bautista E**, Arcos M, Jimenez-Alvarez L, García-Sancho MC, Vázquez ME, Peña E, Higuera A, Ramírez G, Fernández-Plata R, Cruz-Lagunas A, García-Moreno SA, Urrea F, Ramírez R, Correa-Rotter R, Pérez-Padilla JR, Zúñiga J. Angiogenic and inflammatory markers in acute respiratory distress syndrome and renal injury associated to A/H1N1 virus infection. *Exp Mol Pathol* 2013; **94**: 486-492 [PMID: 23542734 DOI: 10.1016/j.yexmp.2013.03.007]
20 **Panitchote A**, Mehkri O, Hastings A, Hanane T, Demirjian S, Torbic H, Mireles-Cabodevila E, Krishnan S, Duggal A. Factors associated with acute kidney injury in acute respiratory distress syndrome. *Ann Intensive Care* 2019; **9**: 74 [PMID: 31264042 DOI: 10.1186/s13613-019-0552-5]
21 **Tisoncik JR**, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. *Microbiol Mol Biol Rev* 2012; **76**: 16-32 [PMID: 22390970 DOI: 10.1128/MMBR.05015-11]
22 **Ramos-Casals M**, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; **383**: 1503-1516 [PMID: 24290661 DOI: 10.1016/S0140-6736(13)61048-X]
23 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration; UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]
24 **Ye M**, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of Angiotensin-converting enzyme 2 and Angiotensin-converting enzyme: implications for albuminuria in diabetes. *J Am Soc Nephrol* 2006; **17**: 3067-3075 [PMID: 17021266 DOI: 10.1681/ASN.2006050423]
25 **Diao B**, Wang C, Wang R, Feng Z, Tan Y, Wang H, Wang C, Liu L, Liu Y, Liu Y, Wang G, Yuan Z, Ren

L, Wu Y, Chen Y. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. medRxiv. 2020: 2020.03.04.20031120 [DOI: 10.1101/2020.03.04.20031120]

26 **Selby NM**, Forni LG, Laing CM, Horne KL, Evans RD, Lucas BJ, Fluck RJ. Covid-19 and acute kidney injury in hospital: summary of NICE guidelines. *BMJ* 2020; **369**: m1963 [PMID: 32457068 DOI: 10.1136/bmj.m1963]

27 **Cooke CR**, Kahn JM, Caldwell E, Okamoto VN, Heckbert SR, Hudson LD, Rubenfeld GD. Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. *Crit Care Med* 2008; **36**: 1412-1420 [PMID: 18434894 DOI: 10.1097/CCM.0b013e318170a375]

28 **Liu KD**, Matthay MA. Advances in critical care for the nephrologist: acute lung injury/ARDS. *Clin J Am Soc Nephrol* 2008; **3**: 578-586 [PMID: 18199848 DOI: 10.2215/CJN.01630407]

29 **McNicholas BA**, Rezoagli E, Pham T, Madotto F, Guiard E, Fanelli V, Bellani G, Griffin MD, Ranieri M, Laffey JG; ESICM Trials Group and the Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE (LUNG SAFE) Investigators. Impact of Early Acute Kidney Injury on Management and Outcome in Patients with Acute Respiratory Distress Syndrome: A Secondary Analysis of a Multicenter Observational Study. *Crit Care Med* 2019; **47**: 1216-1225 [PMID: 31162201 DOI: 10.1097/CCM.0000000000003832]

30 **Darmon M**, Clec'h C, Adrie C, Argaud L, Allaouchiche B, Azoulay E, Bouadma L, Garrouste-Orgeas M, Haouache H, Schwebel C, Goldgran-Toledano D, Khallel H, Dumenil AS, Jamali S, Souweine B, Zeni F, Cohen Y, Timsit JF. Acute respiratory distress syndrome and risk of AKI among critically ill patients. *Clin J Am Soc Nephrol* 2014; **9**: 1347-1353 [PMID: 24875195 DOI: 10.2215/CJN.08300813]

31 **Husain-Syed F**, Slutsky AS, Ronco C. Lung-Kidney Cross-Talk in the Critically Ill Patient. *Am J Respir Crit Care Med* 2016; **194**: 402-414 [PMID: 27337068 DOI: 10.1164/rccm.201602-0420CP]

32 **Joannidis M**, Forni LG, Klein SJ, Honore PM, Kashani K, Ostermann M, Prowle J, Bagshaw SM, Cantaluppi V, Darmon M, Ding X, Fuhrmann V, Hoste E, Husain-Syed F, Lubnow M, Maggiorini M, Meersch M, Murray PT, Ricci Z, Singbartl K, Staudinger T, Welte T, Ronco C, Kellum JA. Lung-kidney interactions in critically ill patients: consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup. *Intensive Care Med* 2020; **46**: 654-672 [PMID: 31820034 DOI: 10.1007/s00134-019-05869-7]

33 **Hirsch JS**, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; **98**: 209-218 [PMID: 32416116 DOI: 10.1016/j.kint.2020.05.006]

34 **Mitaka C**, Nagura T, Sakanishi N, Tsunoda Y, Amaha K. Two-dimensional echocardiographic evaluation of inferior vena cava, right ventricle, and left ventricle during positive-pressure ventilation with varying levels of positive end-expiratory pressure. *Crit Care Med* 1989; **17**: 205-210 [PMID: 2646069 DOI: 10.1097/00003246-198903000-00001]

35 **Pinsky MR**, Desmet JM, Vincent JL. Effect of positive end-expiratory pressure on right ventricular function in humans. *Am Rev Respir Dis* 1992; **146**: 681-687 [PMID: 1519848 DOI: 10.1164/ajrccm/146.3.681]

36 **Husain-Syed F**, McCullough PA, Birk HW, Renker M, Brocca A, Seeger W, Ronco C. Cardio-Pulmonary-Renal Interactions: A Multidisciplinary Approach. *J Am Coll Cardiol* 2015; **65**: 2433-2448 [PMID: 26046738 DOI: 10.1016/j.jacc.2015.04.024]

37 **Hering R**, Wrigge H, Vorwerk R, Brensing KA, Schröder S, Zinserling J, Hoeft A, Spiegel TV, Putensen C. The effects of prone positioning on intraabdominal pressure and cardiovascular and renal function in patients with acute lung injury. *Anesth Analg* 2001; **92**: 1226-1231 [PMID: 11323351 DOI: 10.1097/00000539-200105000-00027]

38 **Narendra DK**, Hess DR, Sessler CN, Belete HM, Guntupalli KK, Khusid F, Carpati CM, Astiz ME, Raoof S. Update in Management of Severe Hypoxemic Respiratory Failure. *Chest* 2017; **152**: 867-879 [PMID: 28716645 DOI: 10.1016/j.chest.2017.06.039]

39 **Sharkey RA**, Mulloy EM, Kilgallen IA, O'Neill SJ. Renal functional reserve in patients with severe chronic obstructive pulmonary disease. *Thorax* 1997; **52**: 411-415 [PMID: 9176530 DOI: 10.1136/thx.52.5.411]

40 **Howes TQ**, Deane CR, Levin GE, Baudouin SV, Moxham J. The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. *Am J Respir Crit Care Med* 1995; **151**: 378-383 [PMID: 7842195 DOI: 10.1164/ajrccm.151.2.7842195]

41 **Barnes T**, Zochios V, Parhar K. Re-examining Permissive Hypercapnia in ARDS: A Narrative Review. *Chest* 2018; **154**: 185-195 [PMID: 29175086 DOI: 10.1016/j.chest.2017.11.010]

42 **Del Vecchio L**, Locatelli F. Hypoxia response and acute lung and kidney injury: possible implications for therapy of COVID-19. *Clin Kidney J* 2020; **13**: 494-499 [PMID: 32905208 DOI: 10.1093/ckj/sfaa149]

43 **Pannu N**, Mehta RL. Effect of mechanical ventilation on the kidney. *Best Pract Res Clin Anaesthesiol* 2004; **18**: 189-203 [PMID: 14760882 DOI: 10.1016/j.bpa.2003.08.002]

44 **Hassoun HT**, Grigoryev DN, Lie ML, Liu M, Cheadle C, Tuder RM, Rabb H. Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. *Am J Physiol Renal Physiol* 2007; **293**: F30-F40 [PMID: 17327501 DOI: 10.1152/ajprenal.00023.2007]

45 **Rabb H**, Wang Z, Nemoto T, Hotchkiss J, Yokota N, Soleimani M. Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int* 2003; **63**: 600-606 [PMID: 12631124 DOI: 10.1046/j.1523-1755.2003.00753.x]

46 **Hassoun HT**, Lie ML, Grigoryev DN, Liu M, Tuder RM, Rabb H. Kidney ischemia-reperfusion injury induces caspase-dependent pulmonary apoptosis. *Am J Physiol Renal Physiol* 2009; **297**: F125-F137 [PMID: 19403643 DOI: 10.1152/ajprenal.90666.2008]

47 **Singbartl K**, Bishop JV, Wen X, Murugan R, Chandra S, Filippi MD, Kellum JA. Differential effects of kidney-lung cross-talk during acute kidney injury and bacterial pneumonia. *Kidney Int* 2011; **80**: 633-644 [PMID: 21734638 DOI: 10.1038/ki.2011.201]

48 **Hepokoski M**, Englert JA, Baron RM, Crotty-Alexander LE, Fuster MM, Beitler JR, Malhotra A, Singh P. Ventilator-induced lung injury increases expression of endothelial inflammatory mediators in the kidney.

Am J Physiol Renal Physiol 2017; **312**: F654-F660 [PMID: 28365585 DOI: 10.1152/ajprenal.00523.2016]
49 **Yap SC**, Lee HT. Acute kidney injury and extrarenal organ dysfunction: new concepts and experimental evidence. *Anesthesiology* 2012; **116**: 1139-1148 [PMID: 22415388 DOI: 10.1097/ALN.0b013e31824f951b]
50 **Andres-Hernando A**, Dursun B, Altmann C, Ahuja N, He Z, Bhargava R, Edelstein CE, Jani A, Hoke TS, Klein C, Faubel S. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. *Nephrol Dial Transplant* 2012; **27**: 4339-4347 [PMID: 22778179 DOI: 10.1093/ndt/gfs256]
51 **Klein CL**, Hoke TS, Fang WF, Altmann CJ, Douglas IS, Faubel S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. *Kidney Int* 2008; **74**: 901-909 [PMID: 18596724 DOI: 10.1038/ki.2008.314]
52 **Hoke TS**, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, Tao Y, Dursun B, Voelkel NF, Edelstein CL, Faubel S. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. *J Am Soc Nephrol* 2007; **18**: 155-164 [PMID: 17167117 DOI: 10.1681/ASN.2006050494]
53 **Andres-Hernando A**, Okamura K, Bhargava R, Kiekhaefer CM, Soranno D, Kirkbride-Romeo LA, Gil HW, Altmann C, Faubel S. Circulating IL-6 upregulates IL-10 production in splenic $CD4^+$ T cells and limits acute kidney injury-induced lung inflammation. *Kidney Int* 2017; **91**: 1057-1069 [PMID: 28214022 DOI: 10.1016/j.kint.2016.12.014]
54 **Bentzer P**, Fisher J, Kong HJ, Mörgelin M, Boyd JH, Walley KR, Russell JA, Linder A. Heparin-binding protein is important for vascular leak in sepsis. *Intensive Care Med Exp* 2016; **4**: 33 [PMID: 27704481 DOI: 10.1186/s40635-016-0104-3]
55 **Miller L**, Singbartl K, Chroneos ZC, Ruiz-Velasco V, Lang CH, Bonavia A. Resistin directly inhibits bacterial killing in neutrophils. *Intensive Care Med Exp* 2019; **7**: 30 [PMID: 31147868 DOI: 10.1186/s40635-019-0257-y]
56 **Siddall E**, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. *Kidney Int* 2017; **92**: 37-46 [PMID: 28318633 DOI: 10.1016/j.kint.2016.11.029]
57 **Klein SJ**, Lehner GF, Forni LG, Joannidis M. Oliguria in critically ill patients: a narrative review. *J Nephrol* 2018; **31**: 855-862 [PMID: 30298272 DOI: 10.1007/s40620-018-0539-6]
58 **Hoste EA**, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015; **41**: 1411-1423 [PMID: 26162677 DOI: 10.1007/s00134-015-3934-7]
59 **Ostermann M**, Chang RW. Impact of different types of organ failure on outcome in intensive care unit patients with acute kidney injury. *J Crit Care* 2011; **26**: 635.e1-635. e10 [PMID: 21798703 DOI: 10.1016/j.jcrc.2011.05.014]
60 **Peerapornratana S**, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019; **96**: 1083-1099 [PMID: 31443997 DOI: 10.1016/j.kint.2019.05.026]
61 **Wu VC**, Hsueh PR, Lin WC, Huang JW, Tsai HB, Chen YM, Wu KD; SARS Research Group of the National Taiwan University College of Medicine and National University Hospital. Acute renal failure in SARS patients: more than rhabdomyolysis. *Nephrol Dial Transplant* 2004; **19**: 3180-3182 [PMID: 15575009 DOI: 10.1093/ndt/gfh436]
62 **Chen LL**, Hsu CW, Tian YC, Fang JT. Rhabdomyolysis associated with acute renal failure in patients with severe acute respiratory syndrome. *Int J Clin Pract* 2005; **59**: 1162-1166 [PMID: 16178983 DOI: 10.1111/j.1368-5031.2005.00540.x]
63 **Meegada S**, Muppidi V, Wilkinson DC 3rd, Siddamreddy S, Katta SK. Coronavirus Disease 2019-Induced Rhabdomyolysis. *Cureus* 2020; **12**: e10123 [PMID: 32879836 DOI: 10.7759/cureus.10123]
64 **Yang C**, Jin Z. An Acute Respiratory Infection Runs Into the Most Common Noncommunicable Epidemic-COVID-19 and Cardiovascular Diseases. *JAMA Cardiol* 2020; **5**: 743-744 [PMID: 32211809 DOI: 10.1001/jamacardio.2020.0934]
65 **Apetrii M**, Enache S, Siriopol D, Burlacu A, Kanbay A, Kanbay M, Scripcariu D, Covic A. A brand-new cardiorenal syndrome in the COVID-19 setting. *Clin Kidney J* 2020; **13**: 291-296 [PMID: 32695320 DOI: 10.1093/ckj/sfaa082]
66 **Ronco C**, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52**: 1527-1539 [PMID: 19007588 DOI: 10.1016/j.jacc.2008.07.051]
67 **Krishnagopalan S**, Kumar A, Parrillo JE, Kumar A. Myocardial dysfunction in the patient with sepsis. *Curr Opin Crit Care* 2002; **8**: 376-388 [PMID: 12357104 DOI: 10.1097/00075198-200210000-00003]
68 **Chen D**, Assad-Kottner C, Orrego C, Torre-Amione G. Cytokines and acute heart failure. *Crit Care Med* 2008; **36**: S9-16 [PMID: 18158483 DOI: 10.1097/01.CCM.0000297160.48694.90]
69 **Figueras J**, Stein L, Diez V, Weil MH, Shubin H. Relationship between pulmonary hemodynamics and arterial pH and carbon dioxide tension in critically ill patients. *Chest* 1976; **70**: 466-472 [PMID: 10136 DOI: 10.1378/chest.70.4.466]
70 **Brady JP**, Hasbargen JA. A review of the effects of correction of acidosis on nutrition in dialysis patients. *Semin Dial* 2000; **13**: 252-255 [PMID: 10923354 DOI: 10.1046/j.1525-139x.2000.00068.x]
71 **Madjid M**, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol* 2020; **5**: 831-840 [PMID: 32219363 DOI: 10.1001/jamacardio.2020.1286]
72 **Ruan Q**, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; **46**: 846-848 [PMID: 32125452 DOI: 10.1007/s00134-020-05991-x]
73 **Mo P**, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, Xiong Y, Cheng Z, Gao S, Liang K, Luo M, Chen T, Song S, Ma Z, Chen X, Zheng R, Cao Q, Wang F, Zhang Y. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis* 2020 [PMID: 32173725 DOI: 10.1093/cid/ciaa270]
74 **Zhang W**, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S. The

use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. *Clin Immunol* 2020; **214**: 108393 [PMID: 32222466 DOI: 10.1016/j.clim.2020.108393]

75 **Cao X**. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol* 2020; **20**: 269-270 [PMID: 32273594 DOI: 10.1038/s41577-020-0308-3]

76 **Rouphael NG**, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007; **7**: 814-822 [PMID: 18045564 DOI: 10.1016/S1473-3099(07)70290-6]

77 **Kox M**, Waalders NJB, Kooistra EJ, Gerretsen J, Pickkers P. Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions. *JAMA*2020 [PMID: 32880615 DOI: 10.1001/jama.2020.17052]

78 **RECOVERY Collaborative Group**, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

79 **Aulagnon F**, Lapidus N, Canet E, Galicier L, Boutboul D, Peraldi MN, Reuter D, Bernard R, Schlemmer B, Azoulay E, Zafrani L. Acute kidney injury in adults with hemophagocytic lymphohistiocytosis. *Am J Kidney Dis* 2015; **65**: 851-859 [PMID: 25480521 DOI: 10.1053/j.ajkd.2014.10.012]

80 **Thaunat O**, Delahousse M, Fakhouri F, Martinez F, Stephan JL, Noël LH, Karras A. Nephrotic syndrome associated with hemophagocytic syndrome. *Kidney Int* 2006; **69**: 1892-1898 [PMID: 16557222 DOI: 10.1038/sj.ki.5000352]

81 **Kapoor S**, Morgan CK, Siddique MA, Guntupalli KK. Intensive care unit complications and outcomes of adult patients with hemophagocytic lymphohistiocytosis: A retrospective study of 16 cases. *World J Crit Care Med* 2018; **7**: 73-83 [PMID: 30596029 DOI: 10.5492/wjccm.v7.i6.73]

82 **Karras A**. What nephrologists need to know about hemophagocytic syndrome. *Nat Rev Nephrol* 2009; **5**: 329-336 [PMID: 19424103 DOI: 10.1038/nrneph.2009.73]

83 **Nahum E**, Ben-Ari J, Stain J, Schonfeld T. Hemophagocytic lymphohistiocytic syndrome: Unrecognized cause of multiple organ failure. *Pediatr Crit Care Med* 2000; **1**: 51-54 [PMID: 12813287 DOI: 10.1097/00130478-200007000-00010]

84 **Panigada M**, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost* 2020; **18**: 1738-1742 [PMID: 32302438 DOI: 10.1111/jth.14850]

85 **Spiezia L**, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P, Simioni P. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thromb Haemost* 2020; **120**: 998-1000 [PMID: 32316063 DOI: 10.1055/s-0040-1710018]

86 **Zhang Y**, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, Wang C, Zhao J, Sun X, Tian R, Wu W, Wu D, Ma J, Chen Y, Zhang D, Xie J, Yan X, Zhou X, Liu Z, Wang J, Du B, Qin Y, Gao P, Qin X, Xu Y, Zhang W, Li T, Zhang F, Zhao Y, Li Y, Zhang S. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med* 2020; **382**: e38 [PMID: 32268022 DOI: 10.1056/NEJMc2007575]

87 **Larsen CP**, Bourne TD, Wilson JD, Saqqa O, Sharshir MA. Collapsing Glomerulopathy in a Patient with COVID-19. *Kidney Int Rep* 2020; **5**: 935-939 [PMID: 32292867 DOI: 10.1016/j.ekir.2020.04.002]

88 **Kissling S**, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, Lhopitallier L, Sadallah S, Fakhouri F. Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int* 2020; **98**: 228-231 [PMID: 32471639 DOI: 10.1016/j.kint.2020.04.006]

89 **Wu H**, Larsen CP, Hernandez-Arroyo CF, Mohamed MMB, Caza T, Sharshir M, Chughtai A, Xie L, Gimenez JM, Sandow TA, Lusco MA, Yang H, Acheampong E, Rosales IA, Colvin RB, Fogo AB, Velez JCQ. AKI and Collapsing Glomerulopathy Associated with COVID-19 and *APOL 1* High-Risk Genotype. *J Am Soc Nephrol* 2020; **31**: 1688-1695 [PMID: 32561682 DOI: 10.1681/ASN.2020050558]

90 **Wan Y**, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J Virol* 2020; **94** [PMID: 31996437 DOI: 10.1128/JVI.00127-20]

91 **Vaduganathan M**, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med* 2020; **382**: 1653-1659 [PMID: 32227760 DOI: 10.1056/NEJMsr2005760]

92 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

93 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

94 **Ramchand J**, Patel SK, Kearney LG, Matalanis G, Farouque O, Srivastava PM, Burrell LM. Plasma ACE2 Activity Predicts Mortality in Aortic Stenosis and Is Associated With Severe Myocardial Fibrosis. *JACC Cardiovasc Imaging* 2020; **13**: 655-664 [PMID: 31607667 DOI: 10.1016/j.jcmg.2019.09.005]

95 **Shibata S**, Arima H, Asayama K, Hoshide S, Ichihara A, Ishimitsu T, Kario K, Kishi T, Mogi M, Nishiyama A, Ohishi M, Ohkubo T, Tamura K, Tanaka M, Yamamoto E, Yamamoto K, Itoh H. Hypertension and related diseases in the era of COVID-19: a report from the Japanese Society of Hypertension Task Force on COVID-19. *Hypertens Res* 2020; **43**: 1028-1046 [PMID: 32737423 DOI: 10.1038/s41440-020-0515-0]

96 **Epelman S**, Shrestha K, Troughton RW, Francis GS, Sen S, Klein AL, Tang WH. Soluble angiotensin-converting enzyme 2 in human heart failure: relation with myocardial function and clinical outcomes. *J*

Card Fail 2009; **15**: 565-571 [PMID: 19700132 DOI: 10.1016/j.cardfail.2009.01.014]

97 **Ramchand J**, Patel SK, Srivastava PM, Farouque O, Burrell LM. Elevated plasma angiotensin converting enzyme 2 activity is an independent predictor of major adverse cardiac events in patients with obstructive coronary artery disease. *PLoS One* 2018; **13**: e0198144 [PMID: 29897923 DOI: 10.1371/journal.pone.0198144]

98 **Gu J**, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, Zou W, Zhan J, Wang S, Xie Z, Zhuang H, Wu B, Zhong H, Shao H, Fang W, Gao D, Pei F, Li X, He Z, Xu D, Shi X, Anderson VM, Leong AS. Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 2005; **202**: 415-424 [PMID: 16043521 DOI: 10.1084/jem.20050828]

99 **Ding Y**, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, Shen H, Qiu L, Li Z, Geng J, Cai J, Han H, Li X, Kang W, Weng D, Liang P, Jiang S. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol* 2004; **203**: 622-630 [PMID: 15141376 DOI: 10.1002/path.1560]

100 **Alsaad KO**, Hajeer AH, Al Balwi M, Al Moaiqel M, Al Oudah N, Al Ajlan A, AlJohani S, Alsolamy S, Gmati GE, Balkhy H, Al-Jahdali HH, Baharoon SA, Arabi YM. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection - clinicopathological and ultrastructural study. *Histopathology* 2018; **72**: 516-524 [PMID: 28858401 DOI: 10.1111/his.13379]

101 **Chen T**, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020; **368**: m1091 [PMID: 32217556 DOI: 10.1136/bmj.m1091]

102 **Su H**, Yang M, Wan C, Yi LX, Tang F, Zhu HY, Yi F, Yang HC, Fogo AB, Nie X, Zhang C. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; **98**: 219-227 [PMID: 32327202 DOI: 10.1016/j.kint.2020.04.003]

103 **Li Z**, Wu M, Yao J, Guo J, Liao X, Song S, Li J, Duan G, Zhou Y, Wu X, Zhou Z, Wang T, Hu M, Chen X, Fu Y, Lei C, Dong H, Xu C, Hu Y, Han M, Zhou Y, Jia H, Chen X, Yan J. Caution on Kidney Dysfunctions of COVID-19 Patients. medRxiv. 2020: 2020.02.08.20021212 [DOI: 10.2139/ssrn.3559601]

104 **Zhou H**, Zhang Z, Fan H, Li J, Li M, Dong Y, Guo W, Lin L, Kang Z, Yu T, Tian C, Gui Y, Qin R, Wang H, Luo S, Hu D. Urinalysis, but not blood biochemistry, detects the early renal-impairment in patients with COVID-19. 2020 [DOI: 10.1101/2020.04.03.20051722]

105 **Hussain M**, Jabeen N, Raza F, Shabbir S, Baig AA, Amanullah A, Aziz B. Structural variations in human ACE2 may influence its binding with SARS-CoV-2 spike protein. *J Med Virol*2020 [PMID: 32249956 DOI: 10.1002/jmv.25832]

106 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

107 **Khwaja A**. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**: c179-c184 [PMID: 22890468 DOI: 10.1159/000339789]

108 **Ostermann M**, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care* 2016; **20**: 299 [PMID: 27670788 DOI: 10.1186/s13054-016-1478-z]

109 **Hsu RK**, Hsu CY. Proteinuria and reduced glomerular filtration rate as risk factors for acute kidney injury. *Curr Opin Nephrol Hypertens* 2011; **20**: 211-217 [PMID: 21455065 DOI: 10.1097/MNH.0b013e3283454f8d]

110 **Patschan D**, Müller GA. Acute Kidney Injury in Diabetes Mellitus. *Int J Nephrol* 2016; **2016**: 6232909 [PMID: 27974972 DOI: 10.1155/2016/6232909]

111 **Izzedine H**, Jhaveri KD, Perazella MA. COVID-19 therapeutic options for patients with kidney disease. *Kidney Int* 2020; **97**: 1297-1298 [PMID: 32317113 DOI: 10.1016/j.kint.2020.03.015]

112 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]

113 **Adamsick ML**, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, Nigwekar S, Rhee EP, Sise ME. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. *J Am Soc Nephrol* 2020; **31**: 1384-1386 [PMID: 32513665 DOI: 10.1681/ASN.2020050589]

114 **De Backer D**, Dorman T. Surviving Sepsis Guidelines: A Continuous Move toward Better Care of Patients with Sepsis. *JAMA* 2017; **317**: 807-808 [PMID: 28114630 DOI: 10.1001/jama.2017.0059]

115 **Lee SJ**, Ramar K, Park JG, Gajic O, Li G, Kashyap R. Increased fluid administration in the first three hours of sepsis resuscitation is associated with reduced mortality: a retrospective cohort study. *Chest* 2014; **146**: 908-915 [PMID: 24853382 DOI: 10.1378/chest.13-2702]

116 **Semler MW**, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Critically Ill Adults. *N Engl J Med* 2018; **378**: 829-839 [PMID: 29485925 DOI: 10.1056/NEJMoa1711584]

117 **Self WH**, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW; SALT-ED Investigators. Balanced Crystalloids versus Saline in Noncritically Ill Adults. *N Engl J Med* 2018; **378**: 819-828 [PMID: 29485926 DOI: 10.1056/NEJMoa1711586]

118 **Eisenhut M**. Adverse effects of rapid isotonic saline infusion. *Arch Dis Child* 2006; **91**: 797 [PMID: 16923868 DOI: 10.1136/adc.2006.100123]

119 **Lobo DN**, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury? *Kidney Int* 2014; **86**: 1096-1105 [PMID: 24717302 DOI: 10.1038/ki.2014.105]

120 **Jaber S**, Paugam C, Futier E, Lefrant JY, Lasocki S, Lescot T, Pottecher J, Demoule A, Ferrandière M, Asehnoune K, Dellamonica J, Velly L, Abback PS, de Jong A, Brunot V, Belafia F, Roquilly A, Chanques G, Muller L, Constantin JM, Bertet H, Klouche K, Molinari N, Jung B; BICAR-ICU Study Group. Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet* 2018; **392**: 31-40 [PMID: 29910040 DOI: 10.1016/S0140-6736(18)31080-8]

121 **National Heart**, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564-2575 [PMID: 16714767 DOI: 10.1056/NEJMoa062200]

122 **Grissom CK**, Hirshberg EL, Dickerson JB, Brown SM, Lanspa MJ, Liu KD, Schoenfeld D, Tidswell M, Hite RD, Rock P, Miller RR 3rd, Morris AH; National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome*. *Crit Care Med* 2015; **43**: 288-295 [PMID: 25599463 DOI: 10.1097/CCM.0000000000000715]

123 **Grams ME**, Estrella MM, Coresh J, Brower RG, Liu KD; National Heart; Lung; and Blood Institute Acute Respiratory Distress Syndrome Network. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clin J Am Soc Nephrol* 2011; **6**: 966-973 [PMID: 21393482 DOI: 10.2215/CJN.08781010]

124 **Liu KD**, Thompson BT, Ancukiewicz M, Steingrub JS, Douglas IS, Matthay MA, Wright P, Peterson MW, Rock P, Hyzy RC, Anzueto A, Truwit JD; National Institutes of Health National Heart; Lung; and Blood Institute Acute Respiratory Distress Syndrome Network. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med* 2011; **39**: 2665-2671 [PMID: 21785346 DOI: 10.1097/CCM.0b013e318228234b]

125 **Marts LT**, Kempker JA, Martin GS. Fluid Management in Acute Respiratory Distress Syndrome: Do We Have All the FACTTs to Determine the Effect of Race? *Ann Am Thorac Soc* 2017; **14**: 1391-1392 [PMID: 28862495 DOI: 10.1513/AnnalsATS.201706-501ED]

126 **Gaudry S**, Hajage D, Schortgen F, Martin-Lefevre L, Verney C, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, de Prost N, Lautrette A, Bretagnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel JM, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard JD, Dreyfuss D. Timing of Renal Support and Outcome of Septic Shock and Acute Respiratory Distress Syndrome. A Post Hoc Analysis of the AKIKI Randomized Clinical Trial. *Am J Respir Crit Care Med* 2018; **198**: 58-66 [PMID: 29351007 DOI: 10.1164/rccm.201706-1255OC]

127 **Gaudry S**, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, de Prost N, Lautrette A, Bretagnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel JM, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard JD, Dreyfuss D; AKIKI Study Group. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N Engl J Med* 2016; **375**: 122-133 [PMID: 27181456 DOI: 10.1056/NEJMoa1603017]

128 **Barbar SD**, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, Lebert C, Bohé J, Badie J, Eraldi JP, Rigaud JP, Levy B, Siami S, Louis G, Bouadma L, Constantin JM, Mercier E, Klouche K, du Cheyron D, Piton G, Annane D, Jaber S, van der Linden T, Blasco G, Mira JP, Schwebel C, Chimot L, Guiot P, Nay MA, Meziani F, Helms J, Roger C, Louart B, Trusson R, Dargent A, Binquet C, Quenot JP; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. *N Engl J Med* 2018; **379**: 1431-1442 [PMID: 30304656 DOI: 10.1056/NEJMoa1803213]

129 **Ahmed AR**, Obilana A, Lappin D. Renal Replacement Therapy in the Critical Care Setting. *Crit Care Res Pract* 2019; **2019**: 6948710 [PMID: 31396416 DOI: 10.1155/2019/6948710]

130 **Han F**, Sun R, Ni Y, Hu X, Chen X, Jiang L, Wu A, Ma L, Chen M, Xv Y, Tu Y. Early initiation of continuous renal replacement therapy improves clinical outcomes in patients with acute respiratory distress syndrome. *Am J Med Sci* 2015; **349**: 199-205 [PMID: 25494217 DOI: 10.1097/MAJ.0000000000000379]

131 **Garzia F**, Todor R, Scalea T. Continuous arteriovenous hemofiltration countercurrent dialysis (CAVH-D) in acute respiratory failure (ARDS). *J Trauma* 1991; **31**: 1277-84; discussion 1284 [PMID: 1920560 DOI: 10.1097/00005373-199109000-00013]

132 **Jin ZC**, Yu ZX, Ji MS, Zhou H. [Application of continuous veno-venous hemofiltration in patients with acute respiratory distress syndrome]. *Zhonghua Yi Xue Za Zhi* 2008; **88**: 2274-2277 [PMID: 19087678]

133 **Helms J**, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; **46**: 1089-1098 [PMID: 32367170 DOI: 10.1007/s00134-020-06062-x]

134 **Ronco C**, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol* 2020; **16**: 308-310 [PMID: 32273593 DOI: 10.1038/s41581-020-0284-7]

135 **Ronco C**, Reis T, De Rosa S. Coronavirus Epidemic and Extracorporeal Therapies in Intensive Care: si vis pacem para bellum. *Blood Purif* 2020; **49**: 255-258 [PMID: 32172242 DOI: 10.1159/000507039]

136 **Bottari G**, Guzzo I, Marano M, Stoppa F, Ravà L, Di Nardo M, Cecchetti C. Hemoperfusion with Cytosorb in pediatric patients with septic shock: A retrospective observational study. *Int J Artif Organs* 2020; **43**: 587-593 [PMID: 32003289 DOI: 10.1177/0391398820902469]

137 **Kellum JA**, Song M, Venkataraman R. Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. *Crit Care Med* 2004; **32**: 801-805 [PMID: 15090965 DOI: 10.1097/01.ccm.0000114997.39857.69]

138 **Houschyar KS**, Pyles MN, Rein S, Nietzschmann I, Duscher D, Maan ZN, Weissenberg K, Philipps HM, Strauss C, Reichelt B, Siemers F. Continuous hemoadsorption with a cytokine adsorber during sepsis - a review of the literature. *Int J Artif Organs* 2017; **40**: 205-211 [PMID: 28525674 DOI: 10.5301/ijao.5000591]

139 **Monard C**, Rimmelé T, Ronco C. Extracorporeal Blood Purification Therapies for Sepsis. *Blood Purif* 2019; **47** Suppl 3: 1-14 [PMID: 30974444 DOI: 10.1159/000499520]

140 **Schädler D**, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jörres A, Quintel M, Engel C, Kellum JA, Kuhlmann MK. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial. *PLoS One* 2017; **12**: e0187015 [PMID: 29084247 DOI: 10.1371/journal.pone.0187015]

141 **Borthwick EM**, Hill CJ, Rabindranath KS, Maxwell AP, McAuley DF, Blackwood B. High-volume haemofiltration for sepsis in adults. *Cochrane Database Syst Rev* 2017; **1**: CD008075 [PMID: 28141912 DOI: 10.1002/14651858.CD008075.pub3]

142 **Klein DJ**, Foster D, Schorr CA, Kazempour K, Walker PM, Dellinger RP. The EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock): study protocol for a randomized controlled trial. *Trials* 2014; **15**: 218 [PMID: 24916483 DOI: 10.1186/1745-6215-15-218]

143 **Klein DJ**, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. *Intensive Care Med* 2018; **44**: 2205-2212 [PMID: 30470853 DOI: 10.1007/s00134-018-5463-7]

144 **Alberici F**, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N, Scolari F. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int* 2020; **97**: 1083-1088 [PMID: 32354634 DOI: 10.1016/j.kint.2020.04.002]

145 **Akalin E**, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, Ross M, Forest S, Goldstein YD, Ajaimy M, Liriano-Ward L, Pynadath C, Loarte-Campos P, Nandigam PB, Graham J, Le M, Rocca J, Kinkhabwala M. Covid-19 and Kidney Transplantation. *N Engl J Med* 2020; **382**: 2475-2477 [PMID: 32329975 DOI: 10.1056/NEJMc2011117]

146 **Banerjee D**, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. *Kidney Int* 2020; **97**: 1076-1082 [PMID: 32354637 DOI: 10.1016/j.kint.2020.03.018]

147 **Columbia University Kidney Transplant Program**. Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York. *J Am Soc Nephrol* 2020; **31**: 1150-1156 [PMID: 32317402 DOI: 10.1681/ASN.2020030375]

148 **Guillen E**, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, Campistol JM, Diekmann F, Ventura-Aguiar P. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? *Am J Transplant* 2020; **20**: 1875-1878 [PMID: 32198834 DOI: 10.1111/ajt.15874]

149 **Fernández-Ruiz M**, Andrés A, Loinaz C, Delgado JF, López-Medrano F, San Juan R, González E, Polanco N, Folgueira MD, Lalueza A, Lumbreras C, Aguado JM. COVID-19 in solid organ transplant recipients: A single-center case series from Spain. *Am J Transplant* 2020; **20**: 1849-1858 [PMID: 32301155 DOI: 10.1111/ajt.15929]

150 **Zhu L**, Xu X, Ma K, Yang J, Guan H, Chen S, Chen Z, Chen G. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. *Am J Transplant* 2020; **20**: 1859-1863 [PMID: 32181990 DOI: 10.1111/ajt.15869]

151 **Alberici F**, Del Barba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Gaggia P, Movilli E, Bove S, Malberti F, Farina M, Bracchi M, Costantino EM, Bossini N, Gaggiotti M, Scolari F; Brescia Renal Covid Task Force. [Managing patients in dialysis and with kidney transplant infected with Covid-19]. *G Ital Nefrol* 2020; **37** [PMID: 32281754]

World Journal of Nephrology

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

World J Nephrol 2020 November 29; 9(2): 33-42

DOI: 10.5527/wjn.v9.i2.33

ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Retrospective Study

Findings on intraprocedural non-contrast computed tomographic imaging following hepatic artery embolization are associated with development of contrast-induced nephropathy

Mohamed M Soliman, Debkumar Sarkar, Ilya Glezerman, Majid Maybody

ORCID number: Mohamed M Soliman 0000-0001-6445-9791; Debkumar Sarkar 0000-0002-4647-8339; Ilya Glezerman 0000-0002-2212-9097; Majid Maybody 0000-0003-4650-6640.

Author contributions: Soliman MM contributed to analysis and interpretation of data, drafting of manuscript, critical revision; Sarkar D contributed to acquisition of data, analysis and interpretation of data, critical revision; Glezerman I contributed to study conception and design, analysis and interpretation of data, critical revision; Maybody M contributed to study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision.

Supported by the NIH/NCI Cancer Center, No. P30 CA008748.

Institutional review board statement: The local Institutional Review Board approved this retrospective review (Protocol 16-402) of all patients who underwent hepatic artery embolization (HAE) between January 2010 and January 2011.

Conflict-of-interest statement: All authors declare no conflicts of

Mohamed M Soliman, Debkumar Sarkar, Majid Maybody, Interventional Radiology Service, Memorial Sloan Kettering Cancer Center, New York, NY 10065, United States

Ilya Glezerman, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, United States

Corresponding author: Majid Maybody, MD, Associate Professor, Interventional Radiology Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, M276C, New York, NY 10065, United States. maybodym@mskcc.org

Abstract

BACKGROUND

Contrast-induced nephropathy (CIN) is a reversible form of acute kidney injury that occurs within 48-72 h of exposure to intravascular contrast material. CIN is the third leading cause of hospital-acquired acute kidney injury and accounts for 12% of such cases. Risk factors for CIN development can be divided into patient- and procedure-related. The former includes pre-existing chronic renal insufficiency and diabetes mellitus. The latter includes high contrast volume and repeated exposure over 72 h. The incidence of CIN is relatively low (up to 5%) in patients with intact renal function. However, in patients with known chronic renal insufficiency, the incidence can reach up to 27%.

AIM

To examine the association between renal enhancement pattern on non-contrast enhanced computed tomographic (CT) images obtained immediately following hepatic artery embolization with development of CIN.

METHODS

Retrospective review of all patients who underwent hepatic artery embolization between 01/2010 and 01/2011 (n = 162) was performed. Patients without intraprocedural CT imaging (n = 51), combined embolization/ablation (n = 6) and those with chronic kidney disease (n = 21) were excluded. The study group comprised of 84 patients with 106 procedures. CIN was defined as 25% increase above baseline serum creatinine or absolute increase ≥ 0.5 mg/dL within 72 h post-embolization. Post-embolization CT was reviewed for renal enhancement patterns and presence of renal artery calcifications. The association between non-

interest related to this article.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: United States

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: May 27, 2020
Peer-review started: May 27, 2020
First decision: June 5, 2020
Revised: August 19, 2020
Accepted: September 14, 2020
Article in press: September 14, 2020
Published online: November 29, 2020

P-Reviewer: El-Serafy AS
S-Editor: Zhang L
L-Editor: A
P-Editor: Wang LL

contrast CT findings and CIN development was examined by Fisher's Exact Test.

RESULTS

CIN occurred in 11/106 (10.3%) procedures (Group A, n = 10). The renal enhancement pattern in patients who did not experience CIN (Group B, n = 74 with 95/106 procedures) was late excretory in 93/95 (98%) and early excretory (EE) in 2/95 (2%). However, in Group A, there was a significantly higher rate of EE pattern (6/11, 55%) compared to late excretory pattern (5/11) (P < 0.001). A significantly higher percentage of patients that developed CIN had renal artery calcifications (6/11 *vs* 20/95, 55% *vs* 21%, P = 0.02).

CONCLUSION

A hyperdense renal parenchyma relative to surrounding skeletal muscle (EE pattern) and presence of renal artery calcifications on immediate post-HAE non-contrast CT images in patients with low risk for CIN are independently associated with CIN development.

Key Words: Hepatic artery embolization; Non-contrast computed tomographic; Contrast-induced nephropathy; Renal enhancement pattern; Intra-arterial; Renal artery calcification

Core Tip: Contrast-induced nephropathy (CIN) is a reversible form of acute kidney injury that occurs within 48-72 h of exposure to intravascular contrast material. CIN is the third leading cause of hospital-acquired acute kidney injury and accounts for 12% of such cases. Identification of early indicators of CIN development is important in taking timely management strategies. There is no known mechanism for early identification and timely initiation of preventive measures in patients otherwise considered low risk for development of CIN after transarterial hepatic artery embolization. This work helps clinicians identify patients at risk of CIN at the time of hepatic artery embolization.

Citation: Soliman MM, Sarkar D, Glezerman I, Maybody M. Findings on intraprocedural non-contrast computed tomographic imaging following hepatic artery embolization are associated with development of contrast-induced nephropathy. *World J Nephrol* 2020; 9(2): 33-42
URL: https://www.wjgnet.com/2220-6124/full/v9/i2/33.htm
DOI: https://dx.doi.org/10.5527/wjn.v9.i2.33

INTRODUCTION

Contrast-induced nephropathy (CIN) is a reversible form of acute kidney injury (AKI) that occurs within 48-72 h of exposure to intravascular contrast material[1]. The most widely accepted definition of CIN is a 25% increase in serum creatinine (sCr) concentration from baseline sCr, or an absolute increase of at least 0.5 mg/dL which appears within 48-72 h after contrast media exposure, is maintained for 3-5 d and returns to baseline over 7-10 d, after excluding other causes[2,3].

CIN is the third leading cause of hospital-acquired AKI and accounts for 12% of such cases[4]. Risk factors for CIN development can be divided into patient- and procedure-related. The former includes pre-existing chronic renal insufficiency and diabetes mellitus. The latter includes high contrast volume and repeated exposure over 72 h[4-7]. The incidence of CIN is relatively low (up to 5%) in patients with intact renal function[8]. However, in patients with known chronic renal insufficiency, the incidence can reach up to 27%[8]. CIN more commonly develops following intraarterial contrast exposure (*e.g.*, diagnostic arteriograms, coronary interventions, transarterial therapies) than with peripheral intravenous administration (*e.g.*, computed tomography)[9,10]. Although the acute decline of renal function in CIN is reversible within 1-2 wk, a higher 1-mo and 1-year mortality rates have been reported in those patients, particularly following arterial angiography[11,12].

Identification of early indicators of CIN development is important in taking timely

management strategies. The elevation in sCr occurs 2-3 d following contrast exposure, and is a poorly-timed indicator[13,14]. Persistent renal enhancement after intravenous or intraarterial contrast administration on non-contrast enhanced computed tomographic (CT) images obtained within 7 d post-contrast exposure has been associated with development of CIN[15]. There is no known mechanism for early identification and timely initiation of preventive measures in patients otherwise considered low risk for development of CIN after transarterial hepatic artery embolization[16-18].

When available, a non-contrast CT or cone beam CT imaging of upper abdomen is routinely performed at the end of hepatic artery embolization (HAE) to assess contrast retention pattern in embolized tumors as a surrogate for treatment response[19-21]. This volume of imaging also covers the kidneys. The aim of this study is to identify early predictors for CIN by examining the appearance of kidneys on non-contrast intraprocedural CT images.

MATERIALS AND METHODS

Patient selection

The local Institutional Review Board approved this retrospective review (Protocol 16-402) of all patients who underwent HAE between January 2010 and January 2011. Informed consent from individual patients for the retrospective review was waived.

For the hepatic artery embolization procedure for treatment of primary or secondary hepatic malignancies, all patients were chosen based on multidisciplinary consensus and were seen in a dedicated outpatient interventional radiology clinic, where history, laboratory tests and imaging were reviewed. Eligibility for transarterial HAE was based on clinical status and laboratory test results (Child-Pugh A or B, Total serum bilirubin < 2 mg/dL, Eastern Coorpative Oncology Group performance status < 3). The type of embolization (bland *vs* chemoembolization) was based on multidisciplinary consensus. Informed consent was obtained for HAE from all patients prior to the procedure.

Inclusion and exclusion criteria

All patients who underwent HAE for treatment of primary or secondary hepatic malignancies within the defined time period were included in the study (n = 162). A total of 217 procedures were performed. Based on the procedure suite, post-embolization non-contrast CT images were available in 139/217 (64%) procedures. Patients with known chronic kidney disease (CKD) stage 3 or higher [GFR < 60 mL/min/1.72 m^2 using the CKD-EPI formula] were excluded (n = 21) since they are typically admitted for IV fluid hydration prior to the procedure and are at high risk for CIN. Patients who underwent percutaneous ablation in combination to embolization were excluded due to delay in post embolization non-contrast CT acquisition (n = 6). A total of 84 patients (106 procedures) were included in the final analysis (Figure 1).

Data collection

Patient electronic records were reviewed for age, gender, ethnicity, type of liver malignancy, presence and etiology of cirrhosis, presence of medical comorbidities related to chronic kidney disease (diabetes mellitus, hypertension, coronary artery disease, prior history of contrast allergies, and number of embolization procedures performed. Laboratory test results were reviewed for sCr prior to embolization, and post-embolization peak sCr in the first 72 h following embolization. Procedural details including type of embolization (bland *vs* chemoembolization), total contrast volume administered, and total procedure duration (defined by total sedation or anesthesia time) were recorded. CIN was defined as 25% increase in sCr above baseline or an absolute increase of ≥ 0.5 mg/dL in sCr within 72 h of embolization. Patients were divided into two groups based on the change in post-embolization sCr: Group A developed CIN and Group B did not develop CIN. Immediate post-embolization non-contrast CT images was reviewed for renal enhancement pattern and presence of renal artery calcifications. All data was compiled in a Health Insurance Portability and Accountability Act-compliant database.

Patient demographics are recorded in Table 1. A total of 84 patients (53 males, 31 females; mean age 63 years, range: 29-87 years) with 106 procedures were included in the final analysis.

Table 1 Patient demographics and baseline characteristics (*n* = 84), patient demographics and baseline characteristics and comorbidities

Clinical characteristics	Value
Sex	
Male	53
Female	31
Age (Yr, average, range)	63 (29-87)
Ethnicity	
Caucasian	62
African American	8
Hispanic	4
Asian	10
Medical comorbidities	
Diabetes mellitus	17
CAD/HTN	29
Cirrhotic?	
Yes	38
No	46
Etiology of cirrhosis	
HCV	16
HBV	6
EtOH	4
NASH	3
Hemochromatosis	1
Unknown	8
Type of liver malignancy	
Primary	
HCC	40
Other	5
Secondary	
NET	20
GIST	4
Other	15
Number of treatments (*n* = 106)	
1	66
2	14
3	4

CAD: Coronary artery disease; HTN: Hypertension; HCV: Hepatitis C virus; HBV: Hepatitis B virus; EtOH: Alcoholic cirrhosis; NASH: Non Alcoholic Steato Hepatitis; HCC: Hepatocellular carcinoma; NET: Neuroendocrine tumor; GIST: Gastrointestinal stromal tumor.

Hepatic artery embolization and CT acquisition

Pre-procedural imaging was reviewed prior to the procedure. General endotracheal anesthesia (*n* = 85) or conscious sedation (*n* = 21) were used. Patients were prepped and draped in a standard sterile fashion. Following ultrasound (US)-guided common femoral artery access and utilizing Seldinger technique, a 5 French guide catheter was

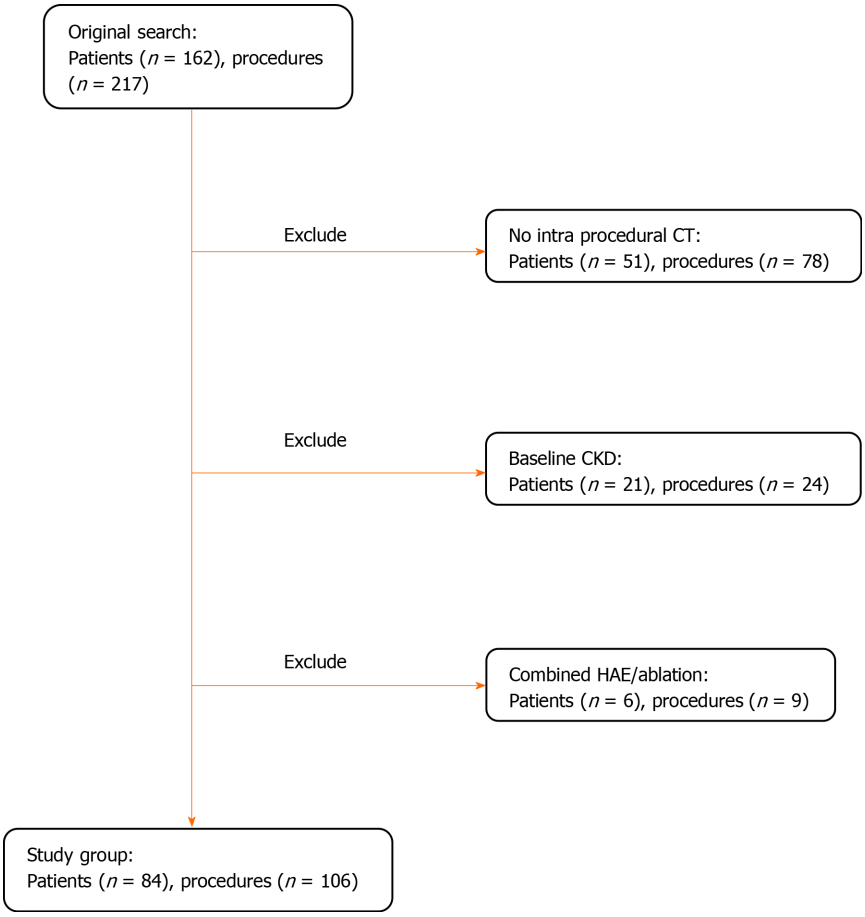

Figure 1 Flow chart of study. CT: Computed tomography.

advanced through a 6 French vascular sheath into the origin of the celiac axis or superior mesenteric artery. Angiograms were obtained using Iohexol (Omnipaque 300; GE Healthcare, Marlborough, MA, United States). A 2.4-2.8 French microcatheter was advanced over a micro guidewire co-axially through the guide catheter for superselective catherization of target branches based on angiographic findings and predetermined area of treatment. Treatment was done with either Embospheres (Merit Medical, South Jordan, UT, United States), Embozene (Boston Scientific, Burlington, MA, United States) and Poly-Vinyl Alcohol particles under continuous angiographic monitoring until complete arterial stasis was achieved. Hemostasis was obtained with a femoral closure device. All patients underwent bland HAE with an average procedural duration of 111.8 min, and average total administered contrast volume of 174.3 mL (average, median, range; Group A: 155, 152.5, 50-320 mL. Group B: 161, 150, 58-350 mL). Post-embolization non-contrast CT was obtained immediately after achieving hemostasis (10-20 min after embolization completion) in all study patients. Patients were transferred to the post-anesthesia care unit and were subsequently admitted for symptomatic management of post-embolization syndrome.

Non-contrast CT analysis

The assessment of renal enhancement pattern and presence of renal artery calcifications was performed by two independent readers. In the case of disagreement, a third reader was involved to assess the CT findings. Regions-of-interest were drawn on the renal cortex, medulla and pelvis to accurately determine the phase or pattern of renal enhancement and categorize them based on predetermined thresholds as either: Corticomedullary, nephrographic, early excretory (EE) or late excretory (LE) (Figures 2 and 3)[22,23]. Corticomedullary pattern occurs 25-80 s after contrast injection and is defined by intense enhancement of the renal cortex relative to the renal medulla, with a difference in Hounsfield units (HU) approaching 100 HU. Nephrographic pattern occurs 85-120 s after contrast injection and is defined by homogenous enhancement of the renal parenchyma (cortex and medulla) with HU range of 120-170. The excretory patterns occur 3-5 min after contrast injection. EE pattern is defined by the opacification of the renal calyces/pelvis, with hyperdense renal parenchyma relative

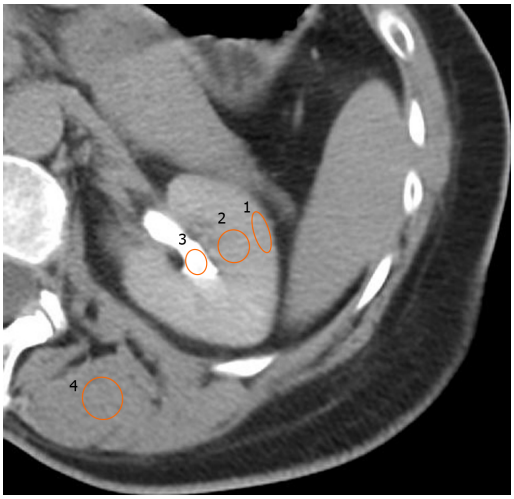

Figure 2 Example of Regions-of-interest drawn on the post-embolization non-contrast enhanced computed tomographic to determine the phase of renal enhancement. ROI 1 measures the Hounsfield units (HU) of the renal cortex. ROI 2 measures the HU of the renal medulla. ROI 3 measures the HU of the renal pelvis. ROI 4 measures the HU of surrounding skeletal muscle. In this example, the renal enhancement phase is late excretory.

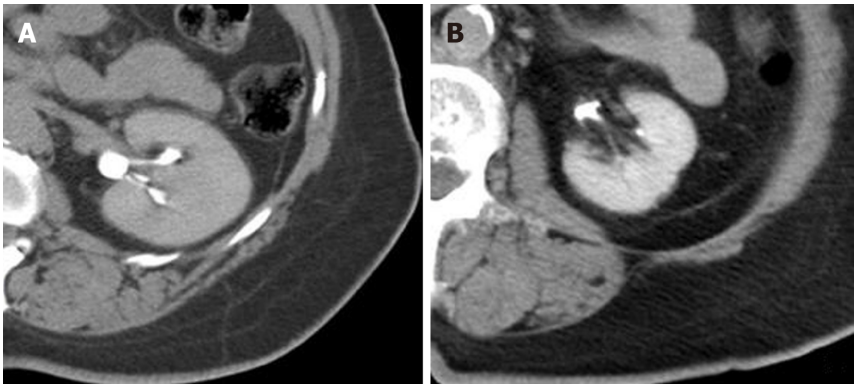

Figure 3 Computed tomographic. A: Immediate post-embolization non-contrast computed tomographic demonstrating homogenous renal parenchymal enhancement (renal cortex and medulla) with Hounsfield units of 172 and incomplete opacification of renal collecting system, consistent with Early Excretory renal enhancement phase. Hyper enhancement of renal parenchyma compared to adjacent paraspinal skeletal muscle is evident; B: Immediate post-embolization non-contrast computed tomographic demonstrating complete opacification of the renal collecting system with renal parenchyma iso-dense to surrounding skeletal muscle, consistent with late excretory renal enhancement phase.

to surrounding skeletal muscle. LE pattern is defined by a renal parenchyma iso-dense to skeletal muscle, with contrast fully opacifying the renal pelvis and ureter. Due to timing of post HAE intraprocedural CT imaging (10-20 min after completion of embolization), the corticomedullary and nephrographic patterns were not seen in our patient cohort. Renal enhancement pattern was divided into only 2 later patterns of EE or LE. Any discernible plaque along the renal arteries with more than 130 Hounsfield units were considered calcifications (Figure 4).

Statistical analysis

Descriptive statistics (mean, standard deviation) were used to describe the patient demographics and procedural details. Continuous data are reported as the mean value ± SD. A Mann-Whitney U Test was performed to examine difference in baseline serum creatinine, and total contrast volume and procedure duration between the two patient groups. A Fisher's Exact Test was utilized to compare the prevalence of diabetes mellitus amongst the two patient groups. The association between renal enhancement pattern, presence of renal artery calcifications and the development of CIN (Group A *vs* B) were analyzed by Chi-Square test of Independence. *P* value 0.05 was considered to indicate statistical significance. All analyses were performed with SPSS statistical software version 12.0 (SPSS, Inc., Chicago, IL, United States).

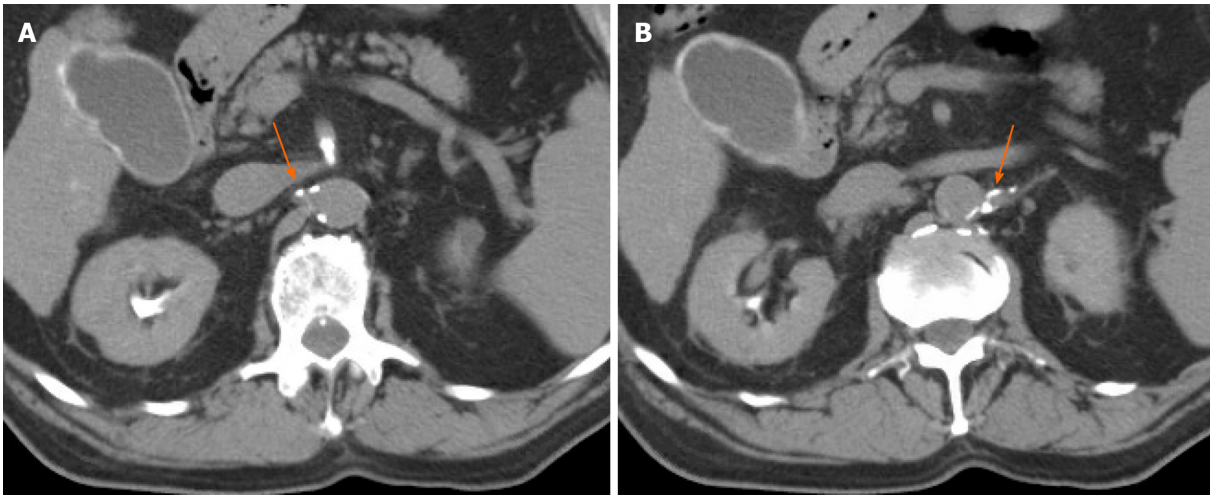

Figure 4 Any discernible plaque along the renal arteries with more than 130 Hounsfield units were considered calcifications. Immediate post-embolization non-contrast computed tomographic demonstrating renal artery calcifications in the right (arrow) (A) and left (arrow) (B) renal arteries.

RESULTS

There was no significant difference between the baseline sCr (P = 0.46), total contrast volume administered (P = 0.61), total procedure duration (P = 0.25), or prevalence of diabetes mellitus (P = 0.38) amongst the two groups.

The renal enhancement patterns are recorded in Table 2. In patients who did not experience CIN (Group B, n = 74 with 95 procedures) the renal enhancement pattern was late excretory in 93/95 procedures (98%) and early excretory in 2/95 procedures (2%). CIN occurred following 11/106 (11.2%) procedures in 10 distinct patients (Group A). In this group, there was a significantly higher rate of early excretory renal enhancement (6/11 procedures, 55%) compared to late excretory pattern (5/11 procedures, 45%) (P < 0.001). Renal artery calcifications were detected in 26 post-embolization non-contrast CT scans. A significantly higher percentage of patients that developed CIN had detectable renal artery calcifications (6/11 *vs* 20/95, 55% *vs* 21% respectively, P = 0.01).

Patients in Group A were hospitalized for a median of 4 d post-embolization (IQR: 3-10 d). Peak sCr was reached in a median of 2 d post-embolization (IQR: 1-2.5 d). Those who stayed in the hospital for 2 d or longer (n = 9) demonstrated complete normalization of sCr prior to discharge. No patient required hemodialysis or hemofiltration. One patient required a nephrology consultation due to oliguria despite Foley catheter placement.

DISCUSSION

The findings of this study suggest an association between the renal enhancement pattern on the immediate post-HAE non-contrast enhanced CT imaging and the development of CIN in low-risk patients. It also suggests an association between renal artery calcifications and development of CIN.

The cornerstone of CIN management is prevention. Risk stratification, IV fluid administration and avoidance of nephrotoxic medications are all essential in prevention[24]. Randomized clinical trials have consistently shown the efficacy of IV fluid hydration in the prevention of CIN in high-risk patient populations[25-28]. All investigated fluid regimens included a pre-procedural component and a post-procedural component (*e.g.*, IV 0.9% normal saline 12 h pre-HAE and 12- h post-HAE). The consensus is that both components contribute to volume expansion and prevention of CIN development[24]. No head-to-head study was performed investigating the efficacy of pre-procedural hydration compared to post-procedural hydration.

High-risk patients are followed by nephrologists in the outpatient setting, are typically admitted the day before an interventional procedure for IV fluid administration and are followed by nephrologists during their admission and after discharge. Conversely, low-risk patients typically arrive on the day of the procedure

Table 2 Non-contrast computed tomographic findings and their association with contrast-induced nephropathy development

Association between non-contrast CT findings and CIN (*n* = 106)			
Renal enhancement pattern	Group A (*n* = 11) (%)	Group B (*n* = 95) (%)	*P* value
Early excretory	6 (55%)	2 (2%)	< 0.001
Late excretory	5 (45%)	93 (98%)	
Renal artery calcifications	Group A	Group B	
Yes	6 (55%)	20 (21%)	0.01
No	5 (45%)	75 (79%)	

CT: Computed tomography; CIN: Contrast-induced nephropathy.

and no special renal protective precautions are taken.

Currently there is no mechanism for early identification and timely initiation of preventive measures for patients who do not have risk factors for development of CIN after transarterial hepatic artery embolization[16-18]. In this study, we propose that risk stratification could be initiated within the interventional radiology procedure room. The proposed method is simple with no need for any calculations or image processing. If in a patient low risk for development of CIN, the renal parenchyma is hyperdense compared to adjacent skeletal muscle at the end of hepatic artery embolization, preventive measures should be initiated immediately. In this group of low-risk patients with no history of CKD, CIN or contrast-allergies, an early excretory pattern on the post-embolization CT imaging was associated with the development of CIN. In addition, the presence of renal artery calcifications was found to be independently associated with CIN development. This is in agreement with prior studies showing the association of renal artery calcification with renal function[29,30]. Renal artery calcification can be identified prior to embolization intervention by reviewing CT scan of abdomen. These patients should be treated like those at risk for CIN with pre and post procedural hydration. For those patients stratified based on immediate post procedural CT imaging renal enhancement patterns, a nephrology consultation should be initiated, along with rapid initiation of IV fluid hydration to prevent CIN development. These patients should also be marked for preventive measures for their future angiographic interventions.

This study has several limitations. Inherent to its retrospective design and small sample size, extensive multivariable logistic regression and analysis of potential confounders are limited. The method used to determine renal enhancement patterns is not free of subjectivity despite utilization of multiple readers. Furthermore, the exact timing of non-contrast CT acquisition was variable and could be a potential confounder.

Larger, prospective studies should be conducted with standardized post-HAE CT acquisition timing to investigate this association.

Hyperdense renal parenchyma relative to surrounding skeletal muscle (Early excretory renal enhancement pattern) on immediate post HAE non-contrast CT images and also the presence of renal artery calcification are associated with the development of CIN.

CONCLUSION

Hyperdense renal parenchyma relative to surrounding skeletal muscle (Early excretory renal enhancement pattern) on immediate post HAE non-contrast CT images and also the presence of renal artery calcification are associated with the development of CIN.

ARTICLE HIGHLIGHTS

Research background

Contrast-induced nephropathy (CIN) is a reversible form of acute kidney injury that

occurs within 48-72 h of exposure to intravascular contrast material. A higher 1-mo and 1-year mortality rates have been reported in these patients, particularly following arterial angiography.

Research motivation

The cornerstone of CIN management is prevention.

Research objectives

To help with early identification and timely initiation of preventive measures in patients otherwise considered low risk for development of CIN after transarterial hepatic artery embolization.

Research methods

Retrospective review of all patients who underwent hepatic artery embolization between 2010 and 2011 (n = 162) was performed. After removing exclusions, the study group comprised of 84 patients with 106 procedures. CIN was defined as 25% increase above baseline serum creatinine or absolute increase ≥ 0.5 mg/dL within 72 h post-embolization. Post-embolization computed tomographic (CT) was reviewed for renal enhancement patterns and presence of renal artery calcifications. The association between non-contrast CT findings and CIN development was examined by Fisher's Exact Test.

Research results

CIN occurred in 11/106 (10.3%) procedures (Group A, n = 10). The renal enhancement pattern in patients who did not experience CIN (Group B, n = 74 with 95/106 procedures) was late excretory in 93/95 (98%) and early excretory (EE) in 2/95 (2%). However, in Group A, there was a significantly higher rate of EE pattern (6/11, 55%) compared to late excretory pattern (5/11) (P < 0.001). A significantly higher percentage of patients that developed CIN had renal artery calcifications (6/11 *vs* 20/95, 55% *vs* 21%, P = 0.02).

Research conclusions

A hyperdense renal parenchyma relative to surrounding skeletal muscle (EE pattern) and presence of renal artery calcifications on immediate post-HAE non-contrast CT images in patients with low risk for CIN are independently associated with CIN development.

Research perspectives

Prospective studies are required to further assess the findings of this study.

REFERENCES

1 **Parfrey PS**, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon PJ. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med* 1989; **320**: 143-149 [PMID: 2643041 DOI: 10.1056/NEJM198901193200303]

2 **Goldenberg I**, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. *CMAJ* 2005; **172**: 1461-1471 [PMID: 15911862 DOI: 10.1503/cmaj.1040847]

3 **Gleeson TG**, Bulugahapitiya S. Contrast-induced nephropathy. *AJR Am J Roentgenol* 2004; **183**: 1673-1689 [PMID: 15547209 DOI: 10.2214/ajr.183.6.01831673]

4 **Hou SH**, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; **74**: 243-248 [PMID: 6824004 DOI: 10.1016/0002-9343(83)90618-6]

5 **Mehran R**, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl* 2006; S11-S15 [PMID: 16612394 DOI: 10.1038/sj.ki.5000368]

6 **McCullough PA**, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, Tumlin J; CIN Consensus Working Panel. Risk prediction of contrast-induced nephropathy. *Am J Cardiol* 2006; **98**: 27K-36K [PMID: 16949378 DOI: 10.1016/j.amjcard.2006.01.022]

7 **Mehran R**, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; **44**: 1393-1399 [PMID: 15464318 DOI: 10.1016/j.jacc.2004.06.068]

8 **Morcos SK**, Thomsen HS, Webb JA. Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol* 1999; **9**: 1602-1613 [PMID: 10525875 DOI: 10.1007/s003300050894]

9 **Kooiman J**, Pasha SM, Zondag W, Sijpkens YW, van der Molen AJ, Huisman MV, Dekkers OM. Meta-analysis: serum creatinine changes following contrast enhanced CT imaging. *Eur J Radiol* 2012; **81**: 2554-

2561 [PMID: 22177326 DOI: 10.1016/j.ejrad.2011.11.020]
10 **Karlsberg RP**, Dohad SY, Sheng R; Iodixanol Peripheral CTA Study Investigator Panel. Contrast-induced acute kidney injury (CI-AKI) following intra-arterial administration of iodinated contrast media. *J Nephrol* 2010; **23**: 658-666 [PMID: 20540038]
11 **Coca SG**, Peixoto AJ, Garg AX, Krumholz HM, Parikh CR. The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis. *Am J Kidney Dis* 2007; **50**: 712-720 [PMID: 17954284 DOI: 10.1053/j.ajkd.2007.07.018]
12 **Lindsay J**, Canos DA, Apple S, Pinnow E, Aggrey GK, Pichard AD. Causes of acute renal dysfunction after percutaneous coronary intervention and comparison of late mortality rates with postprocedure rise of creatine kinase-MB *vs* rise of serum creatinine. *Am J Cardiol* 2004; **94**: 786-789 [PMID: 15374790 DOI: 10.1016/j.amjcard.2004.06.007]
13 **Tublin ME**, Murphy ME, Tessler FN. Current concepts in contrast media-induced nephropathy. *AJR Am J Roentgenol* 1998; **171**: 933-939 [PMID: 9762972 DOI: 10.2214/ajr.171.4.9762972]
14 **Mohammed NM**, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced Nephropathy. *Heart Views* 2013; **14**: 106-116 [PMID: 24696755 DOI: 10.4103/1995-705X.125926]
15 **Chou SH**, Wang ZJ, Kuo J, Cabarrus M, Fu Y, Aslam R, Yee J, Zimmet JM, Shunk K, Elicker B, Yeh BM. Persistent renal enhancement after intra-arterial *vs* intravenous iodixanol administration. *Eur J Radiol* 2011; **80**: 378-386 [PMID: 21470810 DOI: 10.1016/j.ejrad.2011.02.044]
16 **Huo TI**, Wu JC, Lee PC, Chang FY, Lee SD. Incidence and risk factors for acute renal failure in patients with hepatocellular carcinoma undergoing transarterial chemoembolization: a prospective study. *Liver Int* 2004; **24**: 210-215 [PMID: 15189271 DOI: 10.1111/j.1478-3231.2004.00911.x]
17 **Cho HS**, Seo JW, Kang Y, Bae EJ, Kim HJ, Chang SH, Park DJ. Incidence and risk factors for radiocontrast-induced nephropathy in patients with hepatocellular carcinoma undergoing transcatheter arterial chemoembolization. *Clin Exp Nephrol* 2011; **15**: 714-719 [PMID: 21695415 DOI: 10.1007/s10157-011-0470-9]
18 **Hayakawa K**, Tanikake M, Kirishima T, Yoshinami N, Shintani H, Yamamoto E, Morimoto T. The incidence of contrast-induced nephropathy (CIN) following transarterial chemoembolisation (TACE) in patients with hepatocellular carcinoma (HCC). *Eur Radiol* 2014; **24**: 1105-1111 [PMID: 24526284 DOI: 10.1007/s00330-014-3099-8]
19 **Wang X**, Erinjeri JP, Jia X, Gonen M, Brown KT, Sofocleous CT, Getrajdman GI, Brody LA, Thornton RH, Maybody M, Covey AM, Siegelbaum RH, Alago W, Solomon SB. Pattern of retained contrast on immediate postprocedure computed tomography (CT) after particle embolization of liver tumors predicts subsequent treatment response. *Cardiovasc Intervent Radiol* 2013; **36**: 1030-1038 [PMID: 23152036 DOI: 10.1007/s00270-012-0506-x]
20 **Herber S**, Biesterfeld S, Franz U, Schneider J, Thies J, Schuchmann M, Düber C, Pitton MB, Otto G. Correlation of multislice CT and histomorphology in HCC following TACE: predictors of outcome. *Cardiovasc Intervent Radiol* 2008; **31**: 768-777 [PMID: 18196335 DOI: 10.1007/s00270-007-9270-8]
21 **Hu J**, Maybody M, Cao G, Wang X, Chen H, Zhu X, Yang R, Wang X. Lipiodol retention pattern assessed by cone beam computed tomography during conventional transarterial chemoembolization of hepatocellular carcinoma: accuracy and correlation with response. *Cancer Imaging* 2016; **16**: 32 [PMID: 27716376 DOI: 10.1186/s40644-016-0090-4]
22 **Yuh BI**, Cohan RH. Different phases of renal enhancement: role in detecting and characterizing renal masses during helical CT. *AJR Am J Roentgenol* 1999; **173**: 747-755 [PMID: 10470916 DOI: 10.2214/ajr.173.3.10470916]
23 **Sheth S**, Fishman EK. Multi-detector row CT of the kidneys and urinary tract: techniques and applications in the diagnosis of benign diseases. *Radiographics* 2004; **24**: e20 [PMID: 14730056 DOI: 10.1148/rg.e20]
24 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: 19414839 DOI: 10.7326/0003-4819-150-9-200905050-00006]
25 **Gupta RK**, Bang TJ. Prevention of Contrast-Induced Nephropathy (CIN) in Interventional Radiology Practice. *Semin Intervent Radiol* 2010; **27**: 348-359 [PMID: 22550376 DOI: 10.1055/s-0030-1267860]
26 **Briguori C**, Visconti G, Focaccio A, Airoldi F, Valgimigli M, Sangiorgi GM, Golia B, Ricciardelli B, Condorelli G; REMEDIAL II Investigators. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury. *Circulation* 2011; **124**: 1260-1269 [PMID: 21844075 DOI: 10.1161/CIRCULATIONAHA.111.030759]
27 **Solomon R**, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994; **331**: 1416-1420 [PMID: 7969280 DOI: 10.1056/NEJM199411243312104]
28 **Mueller C**, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, Roskamm H. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002; **162**: 329-336 [PMID: 11822926 DOI: 10.1001/archinte.162.3.329]
29 **Vashishtha D**, McClelland RL, Ix JH, Rifkin DE, Jenny N, Allison M. Relation Between Calcified Atherosclerosis in the Renal Arteries and Kidney Function (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol* 2017; **120**: 1434-1439 [PMID: 28826901 DOI: 10.1016/j.amjcard.2017.07.020]
30 **Roseman DA**, Hwang SJ, Manders ES, O'Donnell CJ, Upadhyay A, Hoffmann U, Fox CS. Renal artery calcium, cardiovascular risk factors, and indexes of renal function. *Am J Cardiol* 2014; **113**: 156-161 [PMID: 24210678 DOI: 10.1016/j.amjcard.2013.09.036]

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