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OPINION REVIEW

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

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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

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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.

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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

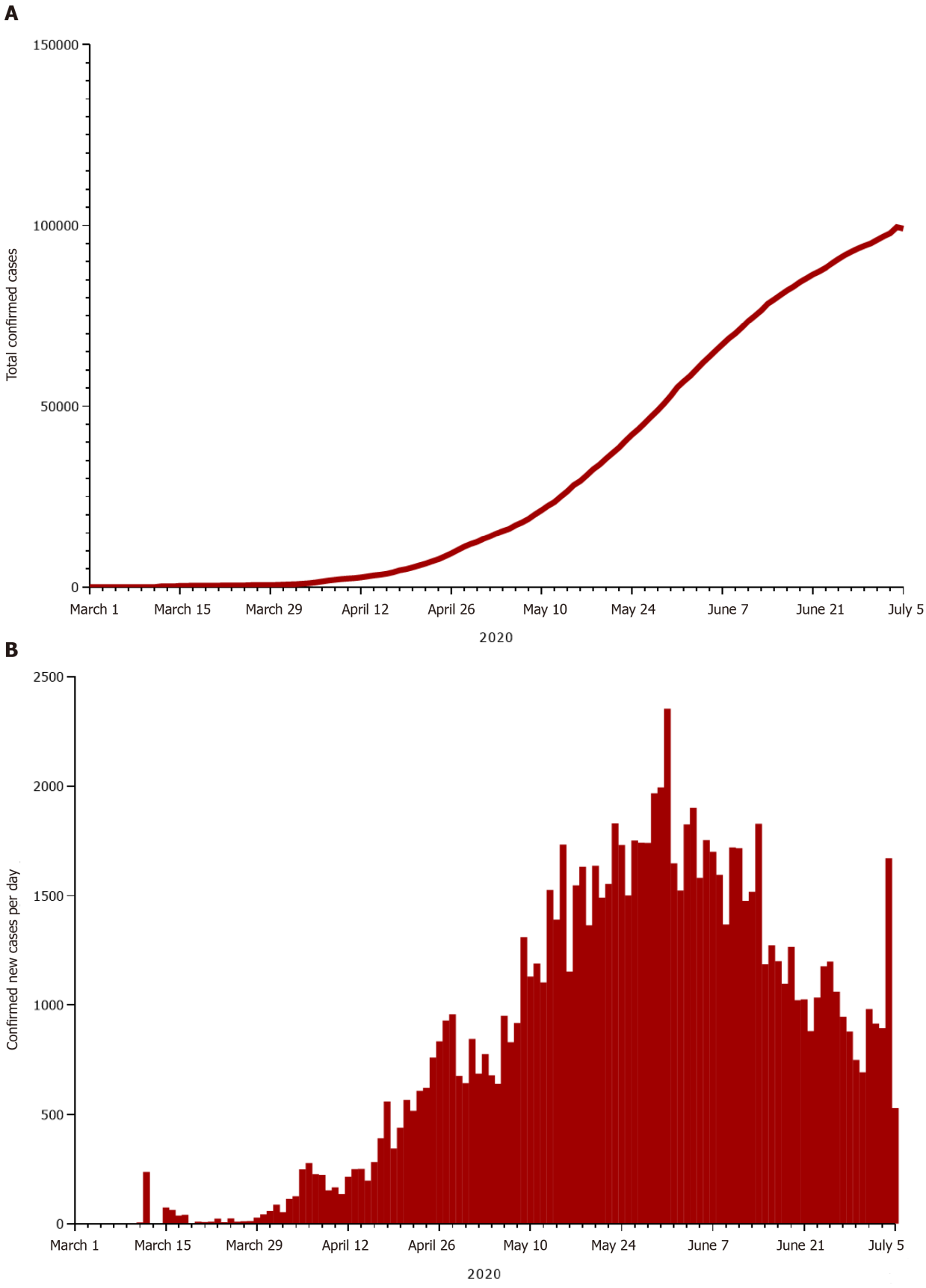


Figure 1 Total confirmed cases[1] and daily confirmed cases of COVID-19 in Qatar[8]. A: Total confirmed cases; B: Daily confirmed cases. A: Citation: Worldometer. Covid-19 coronavirus pandemic. [cited July 6, 2020]. Available from: https://www.worldometers.info/coronavirus/#countries; B: Citation: World 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.

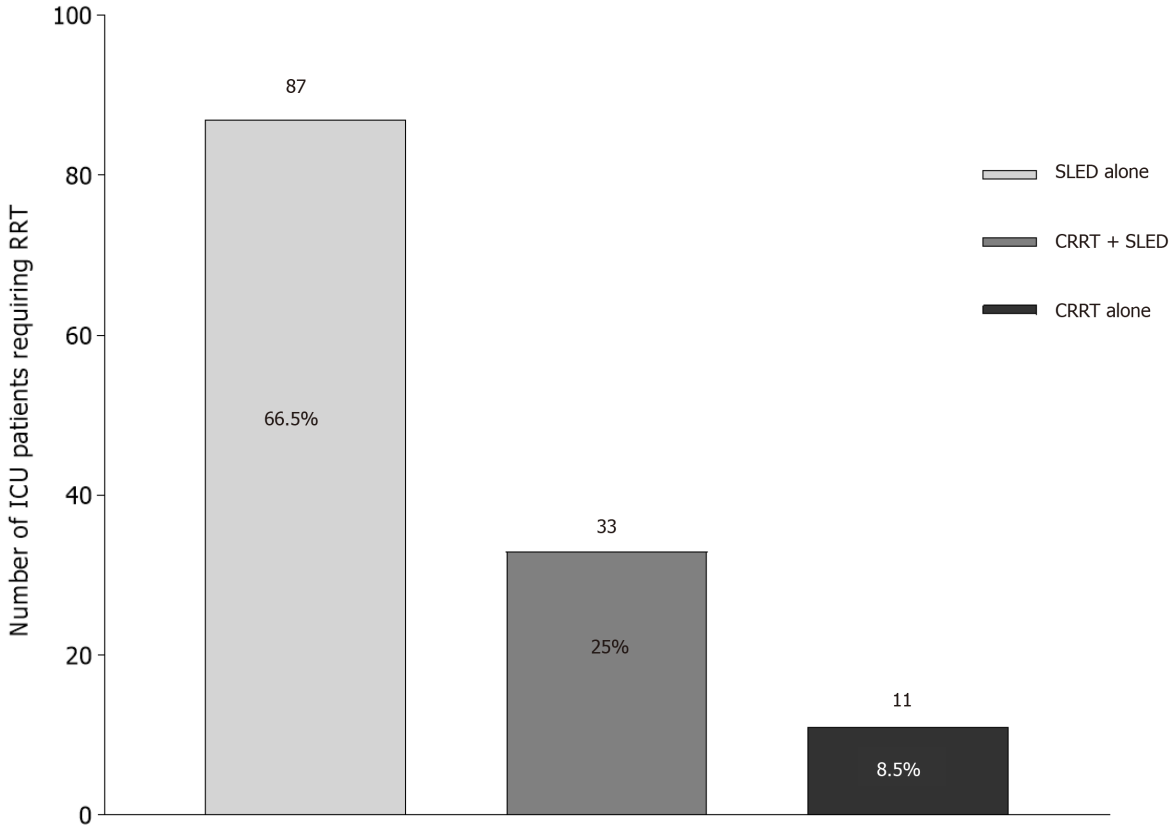


Figure 2 Renal replacement therapy modalities used in 131 cases of coronavirus disease 2019-related acute kidney injury in the intensive care unit between March 1 and July 3. CRRT: Continuous renal replacement therapy; ICU: Intensive care unit; RRT: Renal replacement therapy; SLED: Sustained low-efficiency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

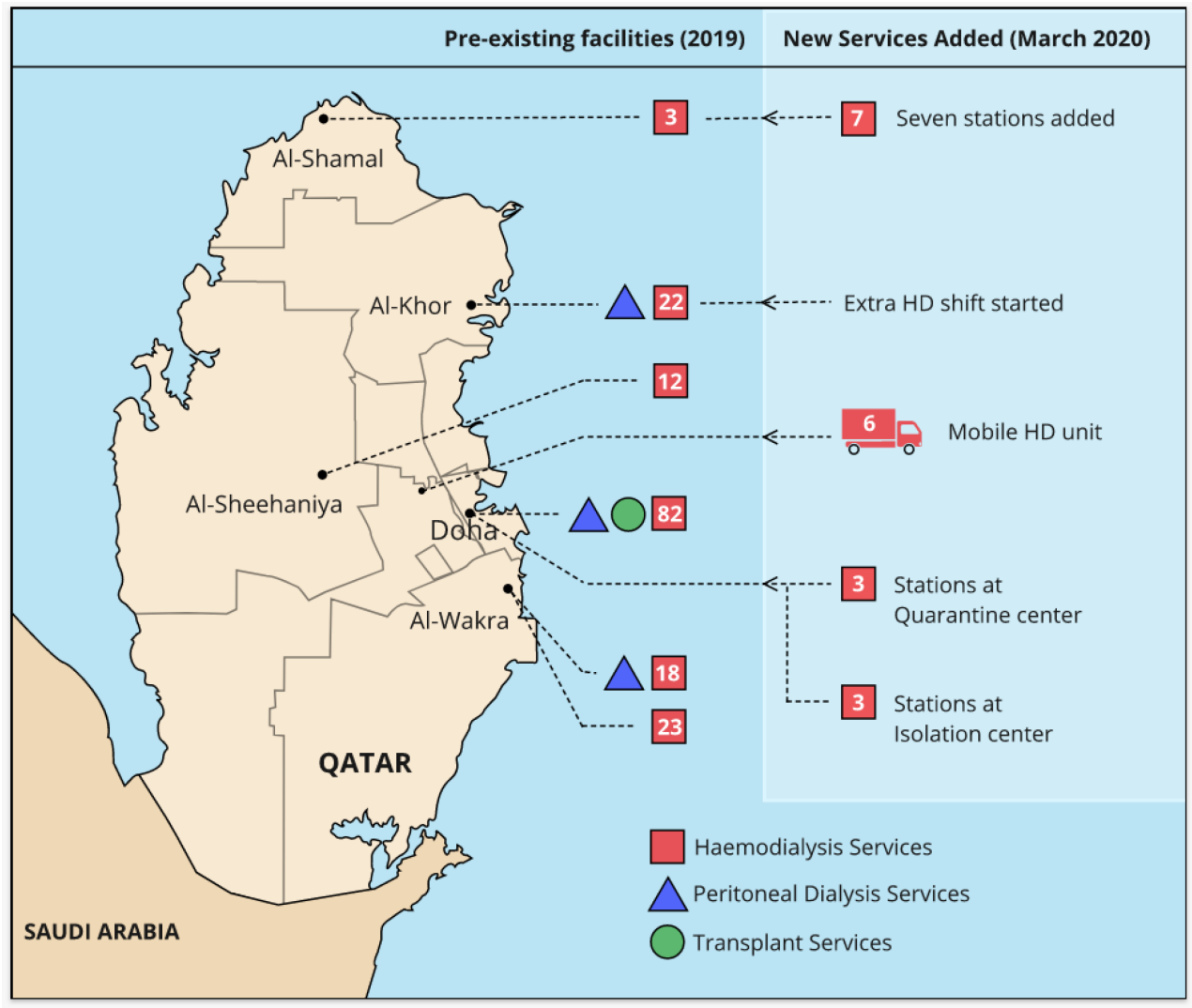


Figure 3 Geographical distribution of renal replacement therapy facilities in Qatar before and during the coronavirus disease 2019 pandemic. The values in red squares represent the number of haemodialysis stations at that centre (adapted from reference[5] with permission). Citation: Al-Malki H, Rashed 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].

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REVIEW

Kidney injury in COVID-19

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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

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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

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

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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.

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ORIGINAL ARTICLE

Retrospective Study

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

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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.

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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

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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.

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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

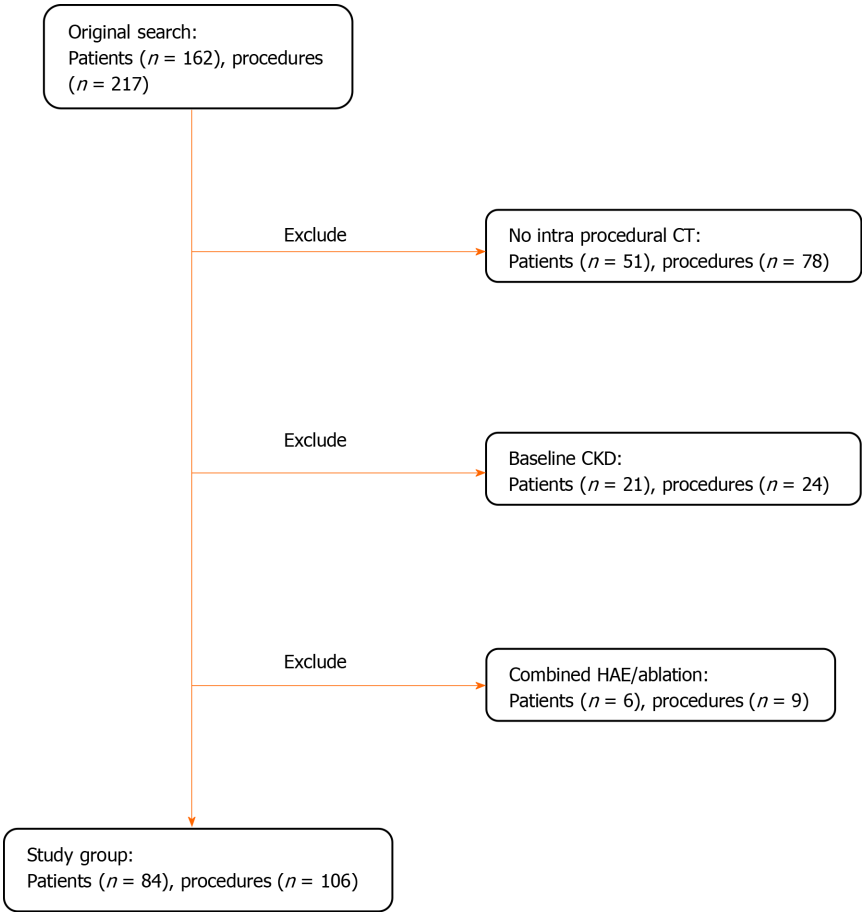


Figure 1 Flow chart of study. CT: Computed tomography.

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

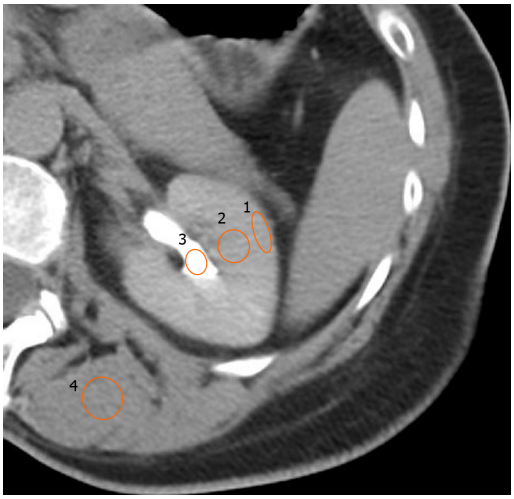


Figure 2 Example of Regions-of-interest drawn on the post-embolization non-contrast enhanced computed tomographic to determine the phase of renal enhancement. ROI 1 measures the Hounsfield units (HU) of the renal cortex. ROI 2 measures the HU of the renal medulla. ROI 3 measures the HU of the renal pelvis.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

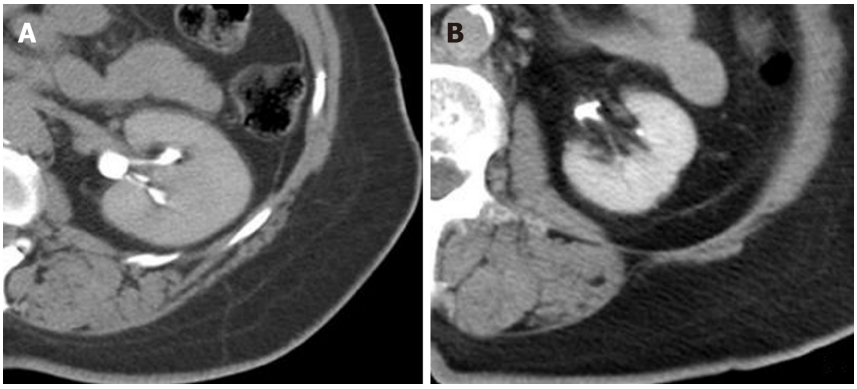


Figure 3 Computed tomographic. A: Immediate post-embolization non-contrast computed tomographic demonstrating homogenous renal parenchymal enhancement (renal cortex and medulla) with Hounsfield units of 172 and incomplete opacification of renal collecting system, consistent with Early Excretory renal 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).

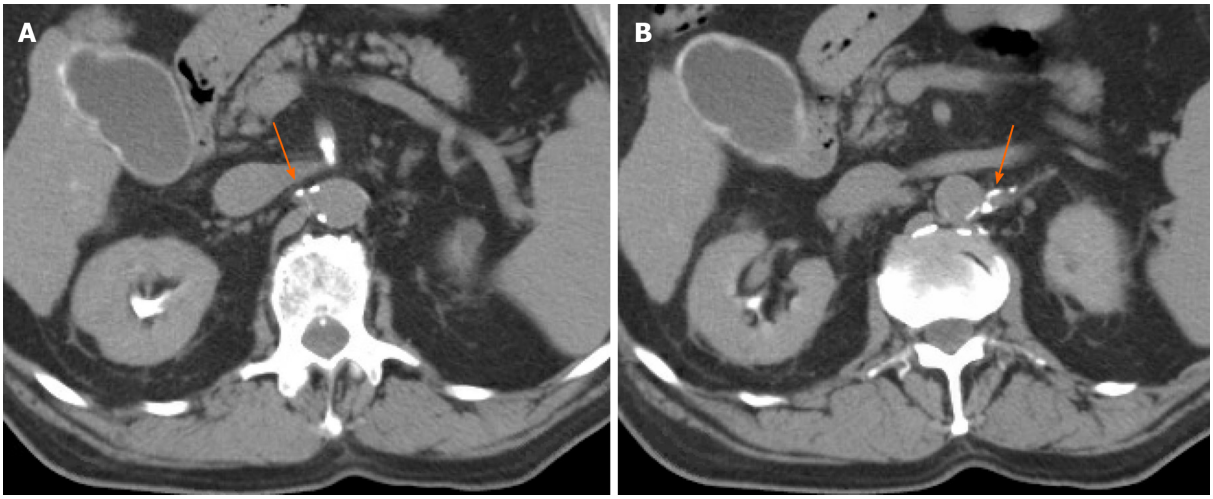


Figure 4 Any discernible plaque along the renal arteries with more than 130 Hounsfield units were considered calcifications. Immediate post-embolization non-contrast computed tomographic demonstrating renal artery calcifications in the right (arrow) (A) and left (arrow) (B) renal arteries.

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.

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