Review

The Renal Manifestations of SARS-CoV-2: A Guide for Family Physicians

Austin P. Morrissey [1,†], Nagla Elzinad [1,†], Chris El Hayek [1], Saran Lotfollahzadeh [1] and Vipul C. Chitalia [1,2,3,*] (iD)

1 Renal Section, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, MA 02118, USA
2 Veterans Affairs Boston Healthcare System, Boston, MA 02118, USA
3 Institute of Medical Engineering and Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
* Correspondence: vichital@bu.edu; Tel.: +1-617-638-7330; Fax: +1-617-638-7326
† Shared first authorship.

Abstract: COVID-19 is a devastating systemic disease characterized by multisystem involvement driven by exuberant hyperinflammatory and dysregulations in coagulation. In COVID-19 patients, renal failure contributes to morbidity and mortality, and its early detection and timely management are critical to minimize such untoward and irreversible complications. In the healthcare system, family physicians constitute the first node in the management of patients, yet there is a dearth of reports and guidelines focusing on them for specific organ affection. This review provides an overview of recent studies examining the renal manifestations following SARS-CoV-2 infection. We focus on the tell-tale signs and laboratory findings of renal affection in the pediatric and adult populations with COVID-19, specifically for family practitioners to assist in their appropriate triage. Among different manifestations, urinary abnormalities and a modest increase in creatinine are the early indicators of renal affection in COVID-19 patients. Although renal transplant patients are conventionally managed by specialized teams, they may present to family physicians during a pandemic. This review provides a framework for family physicians to promptly detect early indicators of renal involvement in patients infected with SARS-CoV-2, including providing triage guidance for kidney transplant recipients.

Keywords: COVID-19; SARS-CoV-2; renal involvement; kidney disease; urinary abnormalities

1. Introduction

In 2019, a series of viral pneumonia cases in Wuhan, China, foreshadowed a global and deadly pandemic [1]. The virus central to the pandemic was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 12 December 2022, the World Health Organization reported 646,266,987 confirmed cases of COVID-19 and 6,636,278 deaths globally [2]. The Centers for Disease Control (CDC) reports 1,080,472 COVID-19-related deaths in the US [3]. According to the European Renal Association- European Dialysis Transplant Association (ERA-EDTA) Registry, during a cross-section of three months in 2020, a total of 4298 renal transplant patients were diagnosed with COVID-19 and 76.4% of patients with chronic kidney disease on at least one type of dialysis (hemodialysis and peritoneal dialysis) had a COVID-19 infection [4].

COVID-19 is essentially a multiple-organ disease; evidence suggests that renal involvement can be common and particularly severe [5]. Renal manifestations such as acute kidney injury (AKI) have been shown to predict mortality in COVID-19 patients [5]. SARS-CoV-2 enters human cells through the angiotensin-converting enzyme 2 (ACE-2) receptor and orchestrates a host of changes that produce a hyper-inflammatory prothrombotic milieu [6]. Interestingly, ACE-2 expression is ~100-fold higher in renal tissue than in pulmonary tissue [7].

The CDC estimated that 74% of adult COVID-19 cases do not require hospitalization (18–65 years old) [8]. Therefore, most cases are mild and managed in the outpatient setting by the family practitioner, who serves as the first node of healthcare. There is a risk of renal involvement and damage even in mild or asymptomatic COVID-19 patients that might be underestimated [9]. Since renal affection augurs poor prognosis in COVID-19 patients, this review aims to assist in their early recognition by family practitioners. Lastly, in this review, we summarize the renal manifestations of SARS-CoV-2 in the adult, pediatric and geriatric populations separately. We also provide a framework for early detection strategies and testing regimens to aid in timely clinical decision-making.

2. Materials and Methods

The literature search was conducted using the Ovid MEDLINE and PUBMED databases from 1 January 2019 to 30 November 2022. Search terms included "COVID-19", SARS-CoV-2", "renal manifestations," "AKI", "CKD", "glomerulonephritis" and "kidney transplantation". The included studies had to have patients with SARS-CoV-2 infection with renal manifestations. Studies in languages other than English or with COVID-19 patients without kidney manifestations were excluded. We included case series, case reports, cross-sectional studies and retrospective cohort studies for this review. Our search resulted in 6000 articles, and after screening titles and abstracts, 600 of those had kidney involvement, which we further summarized using 40 studies for this review. A narrative synthesis was performed to summarize the findings of the included studies.

3. Results

Primary evidence of the renal manifestations of SARS-CoV-2 is summarized in Table 1 [5,7,9–24]. Furthermore, the table contains pertinent details from each study including patients' characteristics, comorbidities and clinical outcomes. These aspects are detailed in the following section.

Table 1. Renal manifestations in patients with COVID-19.

Patient Population	Authors/Year of Publication	Study Design	Sample Size—Test Result/Site of the Study	Sex	Mean Age	Presenting Signs and Symptoms	Comorbidities	Clinical Course
Adult	Zhou et al. 2020 [5]	Retrospective cohort	191 + *, MC	F38%–M62%	56 years	Fever 94%, Cough 79%	HTN 30%, DM 19%, CVD 8%, COPD 3%, CKD 1%, Other 23%	Respiratory failure 54%, Acute cardiac injury 17%, AKI 15%, RRT 10%
Adult	Li et al. 2020 [7]	Retrospective cohort	193 +, MC	F49%–M51%	57 years	Fever 89%, Cough 69%	CVD 36%, Endocrine20%, Respiratory14%, GI 10%	ARDS 28%, AKI 28%, Acute cardiac injury 12%, RRT 7%
Adult	Hirsch et al. 2020 [9]	Retrospective cohort	5449 +, MC	F39.9%–M60.1%	64 years	N/A	HTN 55.7%, DM 33.0%, Obesity 27.1%, CVD 11%	AKI 36.6%, 90% of patients with AKI required mechanical ventilation
Adult	Flythe et al. 2021 [10]	Retrospective cohort	4264 +, MC	F 46%–M54%	65 years	Shortness of breath 69%, Cough 62%, Fever 56%	HTN 87%, DM 63%, CVD 28%, Asthma 23%	Mortality in underlying renal disease 50%
Adult	Chan et al. 2021 [11]	Retrospective cohort	3993 +, SC	F43%–M57%	64 years	N/A	HTN 38%, DM 26%, CKD 11%, CHF 13%	AKI 46%, RRT 19%, Proteinuria 84%, Hematuria 81%, Leukocytoria 60%
Adult	Fisher et al. 2020 [12]	Retrospective cohort	3345 +/1265 - **, MC	F46%–M54%	64 years	Higher respiratory and pulse rates AKI.	DM 27%, CKD 12%, Obesity 20%	AKI 56.9%
Adult	Akilesh et al. 2020 [13]	Case series	17 +, MC	F50%–M50%	54 years	N/A	N/A	ATI 82%, RRT 47%
Adult	Shetty et al. 2020 [14]	Case series	6 +, SC	F50%–M50%	56 years	Fever (66%)	N/A	N/A
Adult	Charoenngam et al. 2022 [15]	Retrospective cohort study	1424 +, SC	F44%–M56%	56 years	N/A	DM 32.3%, HTN 53%, Dyslipidemia 35%	AKI in Black patients 39.4%, in white patients 23.1%

Table 1. *Cont.*

Patient Population	Authors/Year of Publication	Study Design	Sample Size—Test Result/Site of the Study	Sex	Mean Age	Presenting Signs and Symptoms	Comorbidities	Clinical Course
Pediatric	Stewart et al. 2020 [16]	Retrospective cohort	56 +, SC	F33%–M67%	9 years	Fever 88%, Abdominal pain 46%, Diarrhea 73%	Underlying comorbidities 56%	AKI 35%
Pediatric	Gonzalez et al. 2020 [17]	Observational study	101 +, MC	F43%–M57%	9 years	Fever 61.86%, GI 14%	Oncologic 6%, Psychiatric 4%, Hematologic 4%, Cardiac 3%	Those with GI symptoms had higher risk of PICU admission
Pediatric	Basalely et al. 2021 [18]	Retrospective cohort	152 +, MC	F49%–M51%	8 years	GI 70%, Fever 78%, Rash 35%	Asthma 10%, Congenital heart disease 6.7%, Cancer 5%	AKI 11.8% of the entire cohort, AKI 18.2% in MIS-C cohort
Pediatric	Raina et al. 2022 [19]	Retrospective cohort	2546 +, MC	F49%–M51%	5 years	Respiratory 49%, Circulatory 33%, GI 21%, Hematologic 17.6%, Renal 11.7%	CVD 58.8%, Hematology 45.3%	AKI 10.8%
Geriatric	Xu et al. 2021 [20]	Retrospective cohort	1191, + and -, MC	F57%–M43%	83 years	N/A	HTN 40%, DM 37%, Dementia 30%	AKI 29% in +, 18% in -
Geriatric	Yuasa 2022 [21]	Retrospective cohort	181 +, SC	F44%–M56%	72 years	N/A	HTN73%, DM 45%, CVD 26%, Obesity 20.99%	AKI 56.9%
Kidney transplants	Elias et al. 2020 [22]	Prospective cohort	1216, + and -, MC	F44%–M56%	56 years	N/A	N/A	AKI 42%, RRT 7%
Kidney transplants	Mohan et al. 2021 [23]	Retrospective cohort	190481 + and -, MC	F36%–M64%	65 years	N/A	Obesity 52%, DM 69%	Mortality 16%
Kidney transplants	Monfared et al. 2021 [24]	Case–control	64 +,SC	F29%–M71%	51 years	Fever 73.9%, Cough 73.9%	HTN 87%, DM 47%, IHD 17.4%	N/A

F = Female; M = Male; *: COVID-19 Positive; **: COVID-19 Negative. HTN: Hypertension; DM: Diabetes mellitus; CVD: Cardiovascular disease; IHD: Ischemic heart disease; RRT: Renal replacement therapy; AKI: Acute kidney injury; PICU: Pediatric intensive care unit; ATI: Acute tubular injury; MC: Multicenter; SC: Single center. Patient group is coded by color. Beige: Adult; Yellow: Pediatric; Blue: Geriatric, Green: Kidney transplant recipients.

3.1. Chronic Kidney Disease and COVID-19

Chronic kidney disease (CKD) is a global public health problem that affects around 10% of the general population [25]. Previous studies have shown that patients with underlying kidney disease who contract COVID-19 have an increased risk of severe illness and death [10,26,27]. For example, Mohamed et al. evaluated the mortality risk of CKD patients infected with COVID-19 using data from 7624 hospitalized patients diagnosed with COVID-19 at the Mount Sinai Health System in New York, with 7.8% of the cohort having CKD at hospital admission [26].The COVID-19 mortality rate was significantly higher in CKD patients (23.1% vs. 10.2%), with 1.51 greater likelihood of dying.

Additionally, Flythe et al. examined the clinical courses and outcomes of critically ill COVID-19 patients with and without pre-existing CKD in the United States [10]. The study included 4264 critically ill patients with COVID-19 admitted to intensive care units at 68 hospitals across the country. The authors categorized the patients into three groups: those without CKD, those with CKD and those with CKD who were receiving dialysis. They considered CKD as a baseline estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2. Their equations for estimated glomerular filtration rate were based on the Chronic Kidney Disease Epidemiology Collaboration formula and the Modification of Diet in Renal Disease formula.

The study found that 50% of patients with CKD had expired by the 28th day of admission, compared to 35% of patients without CKD. Death rates on the 28th day of admission were similar between dialysis and non-dialysis CKD groups (51% vs. 50%). Patients on dialysis were admitted to the ICU faster on average (4 days vs. 7 days). Additionally, 5% of patients with non-dialysis-dependent CKD had to begin dialysis, compared to 2% of patients without pre-existing CKD. These findings suggest that patients with compromised renal function may be at greater risk of severe kidney damage from COVID-19, which can lead to poor prognosis and an increased risk of in-hospital mortality.

Furthermore, Jdiaa et al. conducted a systematic review of 69 systematic reviews and 66 primary studies that examined the impact of chronic kidney disease (CKD) on COVID-19 mortality, hospitalization and clinical course [27]. The results showed that patients with CKD were at increased risk of hospitalization and mortality from COVID-19. The pooled estimates from primary studies for mortality in patients with CKD and COVID-19 showed a hazard ratio of 1.48 (95% CI 1.33–1.65) (moderate certainty).

Taken together, the findings of these studies suggest that CKD is a significant predictor of mortality from COVID-19, independent of other patient characteristics. This indicates that patients with CKD should be promptly referred to specialty care when SARS-CoV-2 infection is suspected to improve their outcomes.

3.2. Adult COVID-19 Patients with Acute Kidney Injury (AKI)

Moderate to severe renal complications, such as acute kidney injury (AKI), have been observed in patients diagnosed with COVID-19. A single episode of AKI increases the risk of end-stage renal disease by 13-fold [28]. Therefore, early detection and timely management of AKI in COVID-19 patients is crucial to minimize the risk of irreversible damage and improve outcomes. The signs of AKI may be subtle in otherwise healthy or asymptomatic patients, and urine abnormalities such as hematuria and proteinuria may be easily missed if urinalysis is not performed.

The prevalence of AKI amongst COVID-19 patients is well illustrated by Hirsch et al., who conducted a retrospective cohort study of 5499 adults hospitalized with COVID-19. Overall, 37% *(n = 1993)* of patients developed acute kidney injury (AKI) according to Kidney Disease Improving Global Outcomes (KDIGO) guideline criteria [9]. Of these patients, half required mechanical ventilation and vasopressor medication, and 14% required renal replacement therapy (RRT). The most common comorbidities among AKI patients were hypertension (64.8%), diabetes (41.6%) and obesity (28%). Urine studies were available for a portion of the AKI patients (N = 646/1993), and revealed that 64% had hematuria and 74% had proteinuria. Among patients who developed AKI during hospitalization, 35%

died as inpatients, and 40% were still hospitalized a month later. Patients who required RRT had increased mortality, with 55% expiring by the 28th day of admission. These findings highlight the need for further research on the prevalence of asymptomatic urinary abnormalities in COVID-19 patients and their implications for AKI.

While it has been observed that patients with AKI have a higher prevalence of SARS-CoV-2 RNA in their kidneys compared to those without AKI (72% vs. 43%), determining whether the renal dysfunction observed in COVID-19 patients is a direct effect of the virus or secondary to other systemic damage is challenging, due to the complex interactions between organ systems [29]. In pulmonary–renal interactions, for example, acute respiratory distress syndrome (ARDS) can lead to the development of AKI through systemic processes such as decreased cardiac output and increased renal interstitial pressure [30]. AKI, on the other hand, has been shown to promote lung injury through regional inflammation and fluid overload. In addition, AKI can lead to cardiorenal syndrome (CRS), where primary dysfunction of one organ often results in secondary dysfunction of the other organ, leading to cardiovascular failure in up to 60% of AKI patients in intensive care units [31].

3.3. Adult Kidney Transplant Recipients

Kidney transplant recipients face unique health concerns with COVID-19, such as having a higher mortality risk, with some estimates as high as 20% [22,23]. Although we understand that family physicians may not routinely manage kidney transplant recipients, understanding the relevant risks will broaden practitioners' clinical expertise during specific circumstances, including pandemics. Therefore, we succinctly summarize the renal manifestation in kidney transplant patients to assist family physicians.

In a study comparing the COVID-19 clinical course between non-renal transplant recipients and renal transplant recipients, the latter had lower platelet and lymphocyte counts [24]. All kidney transplant patients take immunosuppressive medications to reduce the transplant rejection. Hence, these immunocompromised patients may have a blunted immune response to SARS-CoV-2 infection. Accordingly, the lymphocyte count in transplant recipients may not reflect the severity of a SARS-CoV-2 infection. Given the higher risk of rapid progression and mortality, kidney transplant recipients should be promptly referred to tertiary care centers due to their immunosuppressive status.

3.4. Glomerulonephritis in COVID-19 Patients

The glomerular disease with SARS-CoV-2 infection can present with proteinuria and hematuria on urine dipstick tests with or without increase in creatinine. Recent biopsy studies in such patients revealed a wide variety of glomerular pathologies such as collapsing glomerulopathy (hypertrophy of podocytes compressing on glomerular tufts), and endothelial injury/thrombotic microangiopathy [13,14]. Therefore, the development of proteinuria, irrespective of other organ dysfunction, should raise the suspicion of glomerulonephritis, warranting a specialty referral. Lastly, there have been a few reports of glomerulonephritis following Pfizer and Moderna COVID-19 vaccination [32]. These patients presented with evidence of AKI, edema and microscopic hematuria. However, these reports are exceedingly rare, and the renal safety profile of both vaccines is well established. Family physicians should still be aware of these rare complications—especially during their follow-up with recently vaccinated CKD patients.

3.5. Pediatric COVID-19

The Canadian Pediatric Society reported that children account for 21% of all COVID-19 cases but have a lower proportion of hospitalizations (2.5%) and death (0.08%) [33]. While severe manifestations of COVID-19 are rare in the pediatric population, serious complications are still a concern, especially in unvaccinated children or those with comorbidities. Herein, we describe renal manifestations of COVID-19 in the pediatric population. Notably, we present evidence associating severe COVID-19 with AKI in children.

Stewart et al. examined 52 pediatric patients who were positive for SARS-CoV-2 infection and were admitted to an academic hospital [16]. All patients were younger than 16 years old, with a median age of 9 years. The most common symptom at presentation was fever (88%). Hematuria was found in 30% of patients screened for it (N = 40), and proteinuria in 23% (N = 22). Approximately half of the cohort had elevated creatinine levels beyond the upper limit reference interval for the age group—a highly significant event and a marker of renal dysfunction. Additionally, 30% of the cohort fit the author's diagnostic criteria for AKI, which Stewart et al. defined as serum creatinine values 50% above the upper limit reference interval (0.96 mg/dl for a 9-year-old patient) (Table 2).

Table 2. Pediatric reference intervals used to diagnose AKI, as diagnosed as 1.5x upper limit reference interval for the patient's age [25].

Age Group	[Creatinine] mg/dl	
	Lower (LLRI) #	Upper (ULRI) ##
0–<14 days	0.3051	0.9153
14 days–<1 year	0.1582	0.3842
1–<3 years	0.1695	0.3503
3–<5 years	0.2599	0.4181
5–<7 years	0.2825	0.4746
7–<9 years	0.3390	0.5424
9–<11 years	0.3164	0.6641
11 years	0.4068	0.7232
12 years	0.4068	0.7571

The table has been adapted by converting micromole/liter to milligrams/deciliter. Note that reference intervals do not vary with gender until after 13 years old. # LLRI: Lower limit reference interval. ## ULRI: Upper limit reference interval.

Interestingly, Stewart et al. noted a stark difference in the presentation between patients who developed AKI and patients who did not. The children who developed AKI presented with higher rates of diarrhea (73% vs. 42%) and vomiting (67% vs. 47%) than those who did not, which suggests a possible greater volume depletion resulting in pre-renal AKI. The increased rates of gastrointestinal symptoms amongst children who developed AKI is an important clinical indicator, as other studies have associated gastrointestinal symptoms as a predictor of pediatric COVID-19 severity and pediatric intensive care unit admission (PICU) [17]. Notably, the diagnostic criteria used by Stewart et al. are liberal and may not capture the entire incidence of AKI in this cohort. The diagnostic criteria of serum creatinine 50% above the upper reference limit interval excludes patients who have a subtle increase in serum creatinine but a baseline that is closer to the lower limit reference interval. Nonetheless, the clinical course for these children was mild. The elevations in creatinine resolved in all patients by discharge—apart from one patient who had an underlying metabolic condition and a previous history of AKI. No patients required renal replacement therapy.

3.6. Multisystem-Inflammatory Syndrome in Children (MIS-C) and AKI

Multi-system inflammatory syndrome in children (MIS-C) is a severe post-infection complication of pediatric COVID-19 categorized by an abnormal hyperimmune response [34]. MIS-C can manifest in otherwise healthy children and can be life-threatening. A study performed by Basalely et al. examined the incidence of AKI in 140 hospitalized children who were diagnosed with either acute COVID-19 (n = 97) or MIS-C (n = 55) [18]. All patients were under 18 years old, and the median age was ~8 years old. The authors found that 12% of the entire cohort developed AKI, which Basalely et al. defined using serum creatinine levels. The prevalence of AKI varied between groups and was 18% in the MIS-C group and

8% in the COVID-19 group. Similarly, in children who developed AKI, the most common symptoms at presentation were gastrointestinal. Two children with COVID-19 required continuous kidney replacement therapy, but, otherwise, AKI resolved by discharge as estimated. Elevated serum creatinine is a helpful surrogate marker of the filtration function of the kidney. However, the kidney has several other functions. Therefore, the return of creatinine to baseline level does not indicate a normalization of all other kidney functions such as synthetic function, etc.

The long-term consequences of AKI in COVID-19 pediatric patients remain unknown. However, it is crucial not to conceptualize a patient's first episode of AKI as a transient or isolated event. Instead, AKI is a significant risk factor for developing CKD and renal fibrosis [22]. Therefore, children who sustain AKI following COVID-19 should be closely monitored over time by primary care providers and nephrology services. The above studies collectively show an imminent need for further investigation of renal dysfunction and COVID-19 in children.

It should be noted that renal dysfunction can be found incidentally in hospitalized patients. Therefore, it is unknown if renal dysfunction may also occur in children with mild or asymptomatic COVID-19 who are not admitted to tertiary care centers. Ideally, future studies on pediatric COVID-19 should include outpatient cohorts and have longer follow-up periods. Additional studies should also be carried out on pediatric transplant patients due to their high risk of complications [35]. These studies may help create a streamlined diagnostic criterion for AKI in children.

3.7. Renal Histopathology and COVID-19

Current evidence suggests COVID-19 deleteriously impacts kidneys in glomerular and tubular compartments [36–38]. This is supported by three studies that evaluated kidney biopsy samples from patients with severe COVID-19 and clinical features of acute kidney injury. The first study, conducted by Sharma et al., involved ten hospitalized patients with severe COVID-19 and clinical features of acute kidney injury [36]. All of the biopsy samples taken from these patients showed varying degrees of acute tubular necrosis. This can result in impaired kidney function and may lead to more serious complications, such as kidney failure.

The second study, conducted by Kudose et al., involved a cohort of 17 patients with COVID-19 [37]. The most common finding in the kidney biopsy samples from these patients was collapsing glomerularopathy, which was observed in 30% of the cohort. Collapsing glomerulopathy is a type of focal segmental glomerulosclerosis characterized by the collapse of glomerular capillaries, hypertrophy and hyperplasia of podocytes and severe tubulointerstitial damage [39]. This severe loss of glomerular structural integrity is typically associated with a marked reduction in glomerular filtration rate and proteinuria and can progress to end-stage renal disease.

Additionally, Su et al. examined 26 postmortem biopsies of patients with COVID-19 in China, 9 of which showed clinical signs of kidney injury [38]. Histopathological analysis revealed significant damage to the proximal tubules, characterized by dilatation of the tubular lumen with cellular debris and loss of the apical brush border. Electron microscopy showed clusters of coronavirus-like particles with distinctive spikes in the tubular epithelium and podocytes. ACE-2 was upregulated in these patients and showed prominent expression in proximal tubular cells. The upregulation of ACE-2 may explain the pattern of damage observed in the proximal tubules.

Taken together, these studies suggest that COVID-19 can lead to significant changes in kidneys, such as acute tubular necrosis and collapsing glomerulopathy. This may have significant long-term implications for patients with COVID-19, potentially resulting in end-stage renal disease. It is, therefore, essential for medical practitioners to be aware of the potential for renal injury in COVID-19 patients and to monitor them closely for signs of kidney damage. In addition, further research is needed to better understand the

mechanisms by which the virus affects the kidneys and to develop strategies for prevention and treatment.

3.8. Geriatric Patients and AKI

COVID-19 has disproportionately impacted elderly patients, with age being the most significant risk factor for death. Patients aged 65 and over account for 80% of all COVID-19 hospitalizations, and this group has a 23-fold higher risk of death compared to younger adults [40]. Elderly patients are at a particularly high risk of complications from COVID-19, including AKI. AKI is associated with worse outcomes in these patients, and elderly individuals account for an even higher percentage of cases in which AKI develops. It is, therefore, important for family physicians to be aware of the risk of AKI among elderly patients with COVID-19 and the associated factors so that prompt action can be taken to identify and manage them.

To better understand this phenomenon, several studies have investigated the incidence, risk factors and outcomes of AKI in elderly patients with COVID-19. Yuasa et al. conducted a study involving 182 elderly patients admitted to a Public Tertiary Referral Hospital in São Paulo state from March to December 2020 [21]. The overall incidence of AKI in the elderly population was 56.91%, and higher levels of baseline creatinine and the need for mechanical ventilation were independently associated with AKI development. Moreover, mortality was higher among those who developed AKI than those who did not (46.41% vs. 24.70%). Urinalysis revealed proteinuria in ~50% of elderly patients, and hematuria in 46%.

Xu et al. evaluated the incidence, risk factors and outcomes for AKI in patients hospitalized with COVID-19 at two large geriatric clinics in Stockholm and compared them to patients treated for non-COVID-19 diagnoses during the same period [20]. The results showed that 29% of older adults with COVID-19 developed AKI during hospitalization, whereas the incidence of AKI in non-COVID cases was 18%. AKI in COVID-19 patients was associated with an eightfold higher in-hospital mortality rate than those who did not develop AKI but still had COVID-19. After adjusting for age, gender, lab values, initial vital signs and medications, the mortality risk was 80 times higher for those with COVID-19 and AKI, and 10 times higher for those without COVID-19 and with AKI compared to patients without COVID-19 and without AKI.

Bowe et al. investigated AKI incidence amongst a national cohort of 5216 US veterans hospitalized with COVID-19 and a median age of 70 years [41]. Overall, 32% of patients developed AKI, with 12% of those requiring renal replacement therapy. Older age, male gender, Black race, obesity, hypertension, diabetes and lower estimated glomerular filtration rate (eGFR) were all significant predictors of AKI during hospitalization with COVID-19. Compared to those without AKI, those with AKI exhibited greater need for mechanical ventilation, had longer hospital stays and had higher mortality. Black race was a strong predictor for AKI and associated with an increased risk of death. This study highlights the importance of closely monitoring and providing post-AKI care to reduce the risk of recurrence and long-term adverse consequences.

The exact reason why older adults are more susceptible to AKI during COVID-19 is unknown. Aging is accompanied by a dysregulated immune system marked by thymic atrophy, immunosenescence and inflammaging—a state of chronic increase in systemic inflammation [40]. Inflammaging may predispose elderly patients to cytokine storms, leading to vascular inflammation and organ dysfunction. Cytokine storms are present in 50% of fatal COVID-19 cases, with 82% of those cases occurring in people over 60 years old [40]

Family physicians should be aware of the increased risk of developing AKI among elderly individuals with COVID-19, as well as the clinical markers that suggest it—such as proteinuria or hematuria on urinalysis—and should prompt further testing and evaluation. Early diagnosis followed by timely interventions may help reduce mortality rates and improve patient outcomes in this population.

3.9. Race and Risk of AKI

The coronavirus pandemic has had a particularly pronounced effect on communities of color in the U.S. Racial disparities in the incidence of COVID-19 have been extensively documented and, according to the Centers for Disease Control and Prevention, Black and Hispanic people are being infected and dying at almost twice the rate of white people [42]. These health disparities have resulted in poorer health outcomes among people of color, including higher rates of chronic diseases such as hypertension and diabetes, which put Black and Hispanic individuals at higher risk for complications from COVID-19 [43,44]

In order to better understand the increased risk posed to Black patients affected by COVID-19, Wiley et al. conducted a retrospective cohort study of 831 adult COVID-19 patients (68.5% Black) from four academic hospitals to compare risks of hospitalization between Black and non-Black patients presenting to the emergency department (E.D.) [45]. After adjusting for age, Black patients were found to have 55% higher likelihood of hospitalization compared to non-Black patients. Moreover, once hospitalized, Black patients had a 67% higher incidence of acute kidney injury (AKI) when adjusted for age.

Charoenngam et al. similarly sought to evaluate racial differences in hospital outcomes amongst hospitalized COVID-19 patients [15]. Using data collected from the Boston Medical Center (BMC), they observed that after adjusting for potential confounders, Black race was associated with an increased likelihood ratio of 2.2 times for both AKI and pulmonary embolism. In addition to these findings, they also noted higher levels of inflammatory markers (ESR, D-dimer, ferritin and LDH) in Black patients compared with white patients, suggesting a racial difference in the inflammatory burden from COVID-19. The authors noted several biological variables that may contribute to the increased incidence of AKI in Black patients with COVID-19. For example, genetic polymorphisms in the ACE2, IL-6 and AChE genes have been associated with a higher COVID-19 disease burden and have been shown to be more prevalent in the Black population. Furthermore, the Apolipoprotein L1 (APOL1) high-risk allele, which is known to be strongly associated with focal segmental glomerulosclerosis and HIV-associated nephropathy, is present in approximately 14% of the Black population. It is thought that the systemic inflammatory response in COVID-19 interacts with the APOL1 variant gene, leading to impairment of glomerular epithelial cell autophagy, mitochondrial function and cell injury, thereby causing collapsing glomerulopathy and AKI with nephrotic-range proteinuria.

4. Triaging and Monitoring Suspected Renal Involvement

Family physicians should advise patients who have symptoms consistent with COVID-19 to be tested without delay, per current CDC guidelines (December 2022) [46]. Likewise, asymptomatic patients who have had close contact with individuals with confirmed or probable SARS-CoV-2 infections in the past 10 days should be tested at least five days after the exposure occurred. If the patient has not had a confirmed diagnosis of COVID-19 in the past 90 days, either nucleic acid amplification tests (NAATs) or antigen tests can be used. A positive result on either test indicates SARS-CoV-2 infection. If a patient has a negative antigen test result, the test should be repeated at 48 h for a total of two tests. This is due to the fact that antigen tests are generally less sensitive than NAATs and, therefore, may produce false negative results [47]
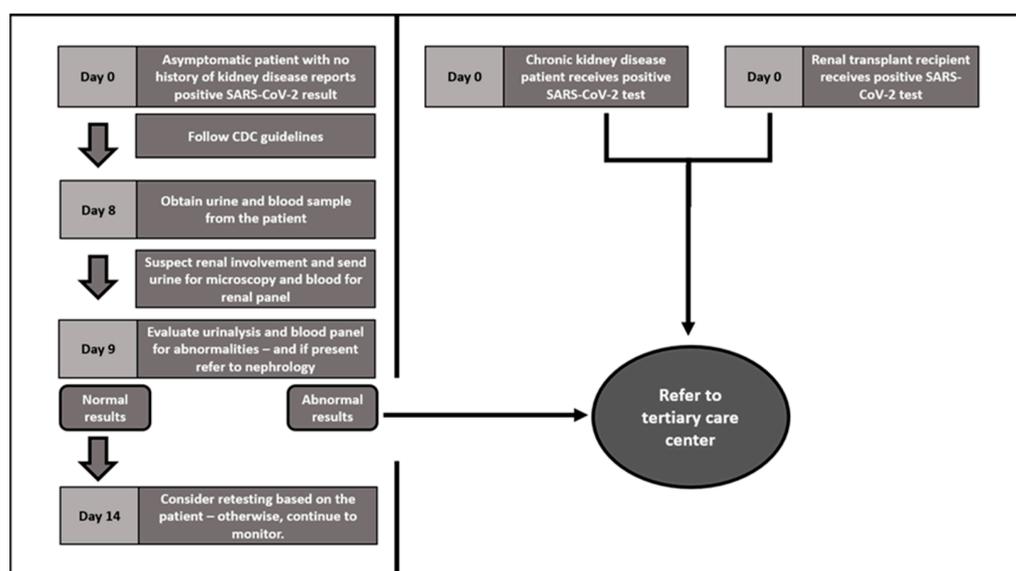
4.1. Management

Most patients with COVID-19 experience either asymptomatic or mild illness that does not warrant medical interventions, or mild to moderate illness that can be managed in an outpatient setting [48]. However, some patients may progress to a severe form of the infection around one week after the onset of symptoms [49]. In this regard, family physicians should refer to the NIH COVID-19 treatment guidelines for up-to-date recommendations concerning general management, effectiveness of therapeutics, rationale for treatment of sub-populations and therapeutic management [50–52]. An analysis of

patient-level data and a detailed review of COVID-19 treatment guidelines are beyond the scope of this review.

4.2. Renal Function Monitoring

Family physicians can monitor patients with COVID-19 for renal involvement using a multifaceted approach that incorporates clinical assessment, laboratory testing and follow-up with nephrologists when needed. The American Association for Clinical Chemistry recommends routine measurement of blood creatinine in patients at risk for AKI [53]. Additionally, urine dipstick testing can be performed to check for proteinuria and hematuria, which may indicate more severe cases of AKI [54]. If an evaluation suggests acute kidney injury is present, the patient should be referred to a nephrologist. Once the patient has been seen by a nephrologist, primary care providers must closely follow-up with the patient to assess any changes in condition as well as therapeutic interventions being utilized (Figure 1).

Figure 1. A flowchart for triaging patients with SARS-CoV-2 infection and potential renal involvement.

5. Conclusions

COVID-19 has created unprecedented management challenges for healthcare providers. Family practitioners are the first line of defense in the management of these cases. Renal dysfunction augurs poor prognosis in COVID-19 patients who exhibit signs of urine abnormalities and elevated creatinine. Patients who exhibit these signs represent a cohort of patients who may develop worse renal manifestations and may require advanced therapeutics. Therefore, it is imperative that family practitioners closely collaborate with nephrologists in the management of these patients.

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