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Anthony Kodzo-Grey Venyo *

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Review Article

Corona Virus (Covid-19) Infection and the Kidney: A Review and Update

Anthony Kodzo-Grey Venyo

[1] North Manchester General Hospital, Department of Urology, Manchester, United Kingdom.

Corresponding author: Anthony Kodzo-Grey Venyo, North Manchester General Hospital, Department of Urology, Manchester, United Kingdom.

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Abstract

The new coronavirus infection / disease 2019 (COVID-19) has become a global world health pandemic disease which has been regarded a health emergency in every country. COVID-19 infection has predominantly affected individuals whose ages have ranged between 30 years and 79 years old and out of these infections it has been documented that about 81% of the COVID-19 infection cases had been considered to be mild disease. Even though majority of individuals who develop COVID-19 infection do manifest with symptoms and signs that simulate the common cold, COVID-19 infection has also emanated in the development of alveolar damage which has been ensued by the development of alveolar damage which has resulted in the development of progressive respiratory failure in which fatalities had resulted in in 6.4% of the COVID-19 infection cases. The COVID-19 infection cases. It has been iterated that direct viral injury, uncontrolled inflammation, activation of coagulation, as well as complement cascades are conjectured to form part of the pathogenesis of COVID-19 infection. COVID-19 infection does affect not only the respiratory tract but it does also affect various organs of the body including the kidney. Individual patients who have been affected by COVID-19 infection have developed features of kidney damage through acute kidney injury, and they tend to manifest with mild proteinuria, haematuria, or slightly raised serum levels of creatinine which has been considered to have ensued from kidney tropism of the virus as well as from multi-organ failure. The impact of COVID-19 infection upon patients who have already pre-existing renal impairment, with the inclusion of individuals who already have chronic kidney disease (CKD), renal transplant recipients, as well as individuals who are undergoing haemodialysis (HD) have not yet been fully studied. Nevertheless, it could be envisaged that individuals have already been having some form of kidney disease could have more severe impairment of renal function and they would need renal support. There is no consensus opinion most effective specific treatment options for COVID-19 infection in general and infection of the kidney yet to be ratified. Results of research studies had documented many agents which might be potential efficacious against COVID-19 infection, and many of these molecules have depicted preliminary efficacy against COVID-19 infection and they are at the moment being tested in clinical trials. It is important to check the renal function of all COVID-19 infected patients who do not have pre-existing renal disease as well as those who already have known renal disease so that based upon the results of the initial renal function test results and follow-up renal function results, clinicians can plan effective renal support management for all patients including rehydration and avoidance of renal toxic medicaments.

Key Words: COVID-19 infection; kidney function; haemodialysis, chronic kidney disease; estimated glomerular filtration rate; acute kidney injury

Introduction

It has been iterated that the coronavirus disease (COVID-19) outbreak had resulted in swift efforts to learn about the clinical course, prognostic markers, and complications of coronavirus disease and that as a consequence there has been a lot of scattered information available relating to severe acute respiratory syndrome coronavirus-2 infection; nevertheless, its pathophysiology has been poorly understood virus [1]. It has also been stated that macroscopic and microscopic findings of COVID-19 infected organs are pertinent for the understanding of any disease, including COVID-19 infection [1]. It has been documented that in the large number of original studies that are available to be read and studied on COVID-19 infection, it could be difficult to ascertain a full picture of the effect of COVID-19 infection has upon the body as a whole, in view of the fact that many studies had reported conflicting results [1]. The ensuing article on COVID-19 infection in general and in association with acute kidney injury (AKI) which has been divided into two parts: (A) Overview of COVID-19 infection generally and (B) Miscellaneous

narrations and discussions related to some case reports, case series and studies related to COVID-19 infection kidney injury.

Methods

Internet data bases were searched including: Google, Google Scholar, Yahoo, and PUBMED. Search words that were used included: COVID-19 infection, Coronavirus infection, and COVID-19 infection of kidney, COVID-19 Renal infection, Acute Kidney Injury in COVID-19 infection, renal failure in covid-19 infection, and kidney failure in coronavirus infection. Two hundred and thirty nine (239) references were identified which were used in writing the review and update of the literature on COVID-19 infection in general and in association with acute kidney injury (AKI) which has been divided into two parts: (A) Overview of COVID-19 infection generally and (B) Miscellaneous narrations and discussions related to some case reports, case series and studies related to COVID-19 infection kidney injury.

[(A)] Overview

Definition / general statements

Some of the summations made related to the definition and some general aspects of COVID-19 infection include the following: [2]

- Coronavirus disease 2019 (COVID-19) is a terminology that is utilized for an infectious respiratory disease which is caused by novel coronavirus SARS-CoV-2 which had emerged in Wuhan, China at the end of 2019, emanating in a global pandemic
- Infection control guidance for healthcare professionals have been made related to COVI-19 infection and could be found as follows:
    - CDC [3]
    - Personal protective equipment (PPE) basics [4]
- COVID-19 represents a viral infection which is caused by coronavirus SARS-CoV-2 which can progress to severe acute respiratory syndrome with pneumonia and acute respiratory distress syndrome [2]
- COVID-19 infection did spread rapidly and became a pandemic with more than 100 million confirmed cases of CIVID-19 infection and over 2 million deaths related to COVID-19 infection globally by end of January 2021 [2]
- Histologically, COVID-19 does show upon microscopy examination of the infected tissue of the lung in cases of COVID-19 infection of the lung diffuse alveolar damage corresponding to the phase of the disease ranging from the acute to the fibrotic phase that is, divided into 3 main injury patterns: epithelial, vascular and fibrotic [2]
- A definite diagnosis of CIVID-19 infection tends to be based upon the detection of viral RNA by RT-PCR [2]

Terminology

- It has been iterated that COVID-19 is also referred to as novel coronavirus pneumonia [2]
- It has additionally been iterated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is also referred to as 2019 novel coronavirus (2019-nCoV) [2] [pathologyoutlines.co]
- It is important to know that COVID-19 infection does affect various organs of the body and not the lung alone. [2]

Epidemiology of COVID-19 in General

- COVID-19 pandemic [2]
    - It has been iterated that in December 2019, cases of pneumonia that were associated with unknown aetiology had been reported from Wuhan, Hubei Province, China to WHO [2] [5]
    - It has also been documented that in January 2020, the Chinese authorities had identified a novel type of coronavirus, which was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]
    - It has been reported that at the beginning of February 2020, almost 10,000 cases of COVID-19 were confirmed in China and more than 100 cases of COVID-19 infection had been identified outside of China [2, 6]
    - It has been iterated that the COIVID-19 disease did spread rapidly and that it became a pandemic with more than 100 million confirmed cases and over 2 million deaths globally by end of January 2021 [2]
    - It has been iterated that the United States of America now has the most confirmed cases of COVID-19 infection with more than 25 million reported cases and confirmed deaths that amounted to more than 400,000 throughout the world. [2, 7]
- Person to person transmission of COVID-19 infection is suspected to occur through respiratory droplets including coughing and sneezing. [2]
- The key to slowing the spread of COVID-19 infection is through widespread testing for COVID-19 infection so that patients could be quickly identified and isolated from the public. [2]
- More than 120 SARS-CoV-2 vaccines are under development [8]

Sites affected by COVID-19 infection

- It has been iterated that the upper respiratory tract tends to be affected by COVID-19 infection in mild disease of the respiratory tract [2]
- It has also been iterated that bilateral lobes of the lung tend to be affected in more severe COVID-19 disease [2]
- It is important to note that COVID-19 infection does affect various organs of the body including the kidney and the urinary tract [2].

Pathophysiology

- It has been iterated that with regard to the pathophysiology of COVID-19 infection a spike surface glycoprotein of the virus does bind onto the host through receptor binding domains of the angiotensin converting enzyme 2 (ACE2), that is most abundant in type II alveolar cells [2] [9]
    - In COVID-19 infection there tends to be10 times to 20 times higher binding affinity in comparison with the SARS-CoV-1 virus [2] [10]
- It has been explained that after a SARS-CoV-2 has attached to a target cell, the virion does release RNA into the cell, that initiates replication of the virus which then further disseminates to infect more cells [2] [11]
- It has been documented that SARS-CoV-2 does produce many virulence factors which promote shedding of new virions from host cells as well as inhibit immune response [2]
- It has been iterated that there tends to be virus independent immunopathology in fatal COVID-19 [2] [12]
    - It has been documented that organ injury and death in COVID-19 tends to be immune mediated rather than pathogen mediated [2]
    - It has also been stated that tissue inflammation as well as organ dysfunction in fatal COVID-19 do not correlate with the tissue and cellular distribution of SARS-CoV-2 [2]

Aetiology

- It has been iterated that in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive sense, single stranded RNA virus having close genetic similarity to bat coronaviruses tends to be found. [2] [13]

Clinical features of COVID-19 in general

- It has been iterated that the average time from exposure COVID-19 to the onset of symptom is 5 days [2] [14]
    - It has also been stated that 97.5% of people who develop symptoms related to COVID-19 infection do so within 11.5 days [2] [8]
- It has been iterated that the asymptomatic COVID-19 infection rate 46% [2] [15]
- It has been documented that COVID-19 infection is rare in children, and this does amount to about 2% to 5% of confirmed cases of COVID-19 infection and children tend to have milder symptoms and very low hospitalization rate of less than 7% [2] [8]
- It has been iterated that the common symptoms of COVID-19 infection in hospitalized patients do include the following: [2] [8]
    - Fever in 70% to 90% of cases
    - Dry cough in 60% to 86% of cases
    - Shortness of breath in 53% to 80% of cases
    - Fatigue in 38% of cases
    - Myalgias in15% to 44% of cases
    - Nausea / vomiting or diarrhoea in15% to 39% of cases
    - Headache, weakness in 25% of cases
- It has been iterated that patients who have COVID-19 infection could manifest with nonclassical symptoms [2] [8] which could include:
    - Isolated gastrointestinal symptoms
    - Isolated anosmia or ageusia in 3% of cases
- It has been iterated that COVID-19 infection could emanate in progress to severe acute respiratory syndrome as well as its major clinicopathological phenotypes that include pneumonia and acute respiratory syndrome. [2]
    - The distribution of severity of COVID-19 infection has been summated as follows: [2] [16] :
        - Mild or no disease in 81% of cases
        - Severe disease in 14% of cases
        - Critical disease in 5% of cases
        - Overall case fatality rate in 2.3% of cases
    - It has been documented that 20% to 42% of hospitalized patients who had COVID-19 infection developed acute respiratory distress syndrome [2] [17] [18]
- It has been reported that patients who required intensive care support (ICU) supportive care had manifested with acute respiratory distress syndrome, acute cardiac injury, acute kidney injury and shock as well as up to 15% of them had fatal outcomes [2] [19]
- The documented common complications that ensued COVID-19 infection among hospitalized patients were summarized as follows: [2] [8]
    - Pneumonia in 75% of cases
    - Acute respiratory distress syndrome in15% of cases
    - Acute liver injury in19% of cases
    - Cardiac injury in 7% to 17% of cases with troponin elevation, acute heart failure, dysrhythmias, myocarditis [2] [8]
    - Prothrombotic coagulopathy resulting in venous and arterial thromboembolic events in10% to 25% of cases
    - Acute kidney injury in 9% of cases
    - Acute cerebrovascular disease in 3% of cases

- Shock in 6% of cases

- It has additionally been iterated that a rare multi-system inflammatory syndrome which is similar to Kawasaki disease has recently been described in children which amounted to 2 cases per 100,000 persons aged who were less 21 years old. [2] [8]

Diagnosis

Summations related to diagnostic testing of SARS-CoV-2 (COVID-19) that have been documented include: [2]

It has been iterated that nasopharyngeal swab has been recommended for the specimen; oropharyngeal swab, sputum and bronchoalveolar lavage could be utilized alternatively [2] [20]

- It was stated that positive rates of SARS-CoV-2 PCR testing by specimen types were reported as follows: bronchoalveolar lavage fluid 93%, sputum 72%, nasal swabs 63%, pharyngeal swabs 32% [8]

- Definite diagnosis of COVID-19 infection is based upon the detection of viral RNA by real time RT-PCR through many available laboratory tests. [21] [22]

- False negative COVID-19 test results could occur in up to 20% to 67% of patients depending upon the quality and timing of testing

  - A modelling study had estimated sensitivity at 33% 4 days pursuant to exposure, 62% on the day of the onset of the symptom and 80% 3 days pursuant to the onset of symptom [23]

Laboratory test results in COVID-19 infection

- Summations related to routine haematology and biochemistry blood test meta-analysis data of patients who have COVID-19 infection do include: [2] [19]

  - Evidence of decreased albumin
  - Evidence of high C reactive protein level
  - Evidence of high lactate dehydrogenase (LDH) level
  - Evidence of lymphopenia
  - Evidence of high erythrocyte sedimentation rate (ESR)

- D dimer elevation was also reported in COVID-19 infection [2] [10]

Radiology imaging description of chest imaging in COVID 19 pulmonary infected patients [2]

- It has been iterated that chest radiographs of individuals who have COVID-19 infection of the lungs do demonstrate Ground glass opacities, crazy paving pattern and consolidation in bilateral lobes which tend to be common findings [2] [24]

- It has been documented that in individuals who have COVID-19 infection of the lungs,15% of computed tomography (CT) scans of the thorax and 40% of chest radiograph findings tend to demonstrate normal features early in the disease [2] [8]

- It has been iterated that evolution of abnormalities within the pulmonary system does occur within the first 2 weeks pursuant to the onset of COVID-19 infection. [2]

Factors of prognostication in COVID-19 pulmonary infection

Some of the risk-factors associated with COVID-19 pulmonary infections have been summated as follows; [2]

- Risks for the development of acute respiratory syndrome do include an age greater than 65 years, underlying diseases including diabetes mellitus, as well as secondary infection. [2] [17], [25]

- Risk factors for progression of COVID-19 infection / disease do include: male sex, old age of being older than 65 years of age, as well as smoking [2] [26]

- Risk factors for critical / mortal states of COVID-19 infection, in order of strength of association have been summated to include: [2] [27]

  - Cardiovascular disease
  - Respiratory disease
  - Diabetes mellitus
  - Hypertension

Treatment of COVID-19 pulmonary infection [2]

- It has been iterated that home management is recommended for patients who have mild COVID-19 infection symptoms

  - It has been stated that the optimal duration of home isolation is under investigation but the COVID-19 virus is shed for an average of about 20 days after the commencement of the COVID-19 infection in hospitalized patients [2] [27].

- It has been advised that patients who have severe COVID-19 disease should require hospital care

  - It has been iterated that patients who have severe COVID-19 disease may need oxygenation support, ranging from low dose oxygen supplement to invasive ventilation as well as extracorporeal membrane oxygenation (ECMO) [2].

- It has been iterated that among antiviral medicaments including ribavirin, favipiravir, and remdesivir which are undergoing clinical testing, remdesivir does seem to be most promising [2, 8].

It has been iterated that NIH COVID-19 Treatment Guidelines Panel has recommended utilization of dexamethasone in patients on ventilators and in those who do require supplemental oxygen but not in other COVID-19 infected patients [27-29]

Macroscopic examination features of COVID-19 pulmonary infected lung.

It has been iterated that gross examination of the lung of individuals who are infected with pulmonary COVID-19 tend to demonstrate the ensuing features: [2]

- Gross examination of the lung of individuals who have pulmonary COVID-19 infection does various features from pulmonary oedema to consolidation of the lung [2] [30]
- Gross examination of COVID-19 infected lung does demonstrate increased lung weight [2]
- Macroscopic examination of the lung of patients who have COVID-19 pulmonary infection does show haemorrhagic changes within the lung [2] [31]
- Gross examination of the lung of individuals who have COVID-19 pulmonary infection does demonstrate evidence of macroscopic pulmonary emboli [2] [31]
- Macroscopy examination of lungs of individuals who have pulmonary COVID-12 infection may demonstrate evidence of pleurisy in which features of pleural inflammation may be seen [2]
- In cases of COVID-19 infection of the lung that is associated with superimposed secondary infection, there would be evidence of purulent inflammation. [2]

Microscopy examination features of COVID-19 infected lung

It has been iterated that **p**ulmonary changes tend to be the most significant finding in COVID-19 pulmonary disease, even though the features are nonspecific [2, 32-35]

- It has been documented that the findings of diffuse alveolar damage (DAD) that correspond to the phase of COVID-19 infection disease tend to be seen upon microscopy examination as follows:
  - In the exudative phase of COVID-19 pulmonary disease, microscopy examination of the lung does demonstrate hyaline membrane formation, desquamation of pneumocytes, cellular or proteinaceous exudates, alveolar haemorrhage, fibrinoid necrosis of small vessels [34] [35]
  - In the organizing phase of COVID-19 pulmonary infection, microscopy examination of the lung does demonstrate interstitial and intra-alveolar proliferation of fibroblasts, lymphocytic infiltration, type II pneumocyte hyperplasia, as well as fibrin deposition
  - In the fibrotic phase of COVID-19 pulmonary infection, microscopy examination of the lung does show dense collagenous fibrosis, and architectural remodelling [34, 35]
- Lung injury patterns in COVID-19 disease [2] [31] [36]:

  Lung injury patterns of COVID-19 disease include:
  - Epithelial pattern in 85% of cases in which DAD with varying degrees of organization, denudation, hyperplasia of pneumocytes are seen
  - Vascular pattern of COVID-19 disease in 59% of cases in which can be found diffuse intra-alveolar fibrin, microvascular damage, (micro) thrombi, acute fibrinous as well as organizing pneumonia
  - Fibrotic pattern of COVID-19 disease in 22% of cases in which can be found: fibrotic DAD, and interstitial fibrosis
- Viral infection changes:
  - Multinucleated enlarged pneumocytes with large nuclei, amphophilic cytoplasm and prominent nucleoli in alveolar spaces
  - Intranuclear inclusions
- Bacterial pneumonia may be superimposed upon the COVID-19 pulmonary disease

- Extra-pulmonary COVID-19 infection changes [2] [31]
  - Cardiovascular COVID-19 infection changes that tend to be visualized upon microscopy examination does include: mild pericardial oedema, some serosanguinous pericardial effusion, mild myocardial oedema, low grade interstitial infiltration of mononuclear cells, as well as endotheliitis
    - It has been iterated that widespread systemic vasculitis that is with associated thrombo-emboli tends not to bet as common as was initially thought [2] [37]
  - Hepatobiliary COVID-19 infection changes that tend to be visualized include: hepatic congestion, mild steatosis, patchy hepatic necrosis, Kupffer cell hyperplasia, increased number of lymphocyte predominant inflammatory cells in the portal tracts and sinusoids, as well as endotheliitis [2]

- Renal COVID-19 infection changes that tend to be visualized do include: various degrees of acute tubular injury, lymphocytic tubule interstitial infiltration, fibrin or hyaline thrombi in blood vessel, glomerular capillary dilatation, as well as lymphocytic endotheliitis [2] [38]
- Gastrointestinal COVID-19 changes that tend to be visualized include: epithelial damage, prominent endotheliitis, as well as ischemic enterocolitis [2]
- Spleen COVID-19 changes that tend to be seen include: reduced number of lymphocytes with necrosis, atrophy, congestion, haemorrhage, as well as infarction [2]
- Bone marrow COVID-19 infection changes that tend to be seen include: histiocytic hyperplasia, as well as hemophagocytosis [2] [39]
- Other COVID-19 infection changes that tend to be found include: cutaneous manifestations, prostatic manifestations, inflammation as well as clots in placenta with funisitis [2]

Cytology examination features of COVID-19 infection of the lung

- It has been iterated that cytology examination of bronchoalveolar lavage (BAL) in COVID-19 infection of the lung does show the following: [2]
  - Abundant activated plasma cells, as per a single case report [2] [40]
  - Alveolar macrophages could feature nuclear clearing or intranuclear cytopathic inclusions [2]

Immunohistochemistry Positive stains

- It has been iterated that immunohistochemistry (IHC) positive staining for SARS-CoV-2 antigen was detected in pneumocytes, ciliated airway cells as well as upper airway epithelium in the acute phase [2] [41]

Electron microscopy examination features of COVID-19 pulmonary disease specimen.

It has been iterated that electron microscopy examination of COVID-19 infection pulmonary tissue does demonstrate the following: [2]

- Spherical particles that are sized 60 mm to 140 nm [2]
- Distinctive spikes upon the surface that measure 9 nm to 12 nm which give virions the appearance of a solar corona, that is consistent with the Coronaviridae family [2]
- Inclusion bodies that are filled with virus particles in membrane bound vesicles in cytoplasm of the respiratory epithelium [2] [42]

Molecular / cytogenetics description features of COVID-19 infection patients

- It has been iterated that ISH, including RISH and FISH positive testing for SARS-CoV-2 antigen tend to be detected in pneumocytes, ciliated airway cells as well as upper airway epithelium in the acute phase [2] [43] [44]
- It has been iterated that sample post-mortem examination pathology reports of COVID-19 infection usually tend to reveal the following: [2]
  - Diffuse alveolar damage due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
  - Diffuse alveolar damage with changes that are compatible with viral infection

Differential diagnoses

Some of the documented differential diagnoses of COVID-19 pulmonary disease include the following: [2]

- Diffuse alveolar damage due to COVID-19 is stated to be morphologically indistinguishable from other DAD causes [45], including other viral pneumonias: cytomegalovirus, respiratory syncytial virus as well as herpes simplex virus.
- Severe acute respiration distress syndrome in which detection of SARS virus needs to be undertaken to confirm the diagnosis.[2]
- Acute respiratory distress syndrome of other aetiological causes [2]
- Idiopathic acute interstitial pneumonia. [2]

Epidemiology of Acute Kidney Injury in COVID-19 Infection

- It has been iterated that there is increasing evidence to demonstrate that there is a high prevalence of acute kidney injury (AKI) in COVID-19 patients [46] [47] [48]
- It has been documented that the presentations of acute kidney injury are many and they do tend to include: proteinuria, haematuria, raised serum levels of serum creatinine (SCR), or blood urea nitrogen (BUN), to acute renal failure. [46]
- It has been intimated that a metanalysis of data related to COVID-19 infected patients had shown that more than half of the patients that constituted fifty seven percent (57%) of the patients who had COVID-19 infection had developed proteinuria, which was followed by raised serum levels of serum creatinine (Scr) that ranged between 9.6% and 15.5% and blood urea nitrogen (BUN) levels that ranged between 13.7% and 14.1% [46] [47] [49]
- It has been stated that computed tomography (CT) that is undertaken in cases of cases of COVID-19 infection with kidney injury also demonstrates inflammation of kidney as well as oedema of kidney. [46] [50]
- It has been documented that pathology examination of specimens of kidney of patients who have COVID-19 infection associated with acute kidney injury (AKI) does tend to show diffuse proximal convoluted tubule injury with loss of brush border as well as frank necrosis. [38] [46]. [51].

- It has been iterated that in comparison with patients who have Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), the incidence of acute kidney injury (AKI) was 6.7% and 42% respectively. [46] [52] [53].
- It has been documented that the incidence of acute kidney injury (AKI) related to COVID-19 infected patients was highly variable and that in the early cases that had been reported from China, COVID-19 patients who had acute kidney injury (AKI) was uncommon [46] [54-56], and the incidence subsequently more severe with incidence rates that had varied from 25% to 29% in patients who had been admitted to the intensive care unit (ICU) [46, 56, 57] .
- It has been stated that large cohort studies related to COVID-19 infection that had been undertaken within the western countries did reveal that the incidence of acute kidney injury (AKI) had ranged between 27% and 37% [46] [58] [59], as well as the incidence subsequently became more severe which had amounted to 68% with regard to critically ill COVID-19 patients who had been admitted into the intensive care unit (ICU) within the New York city [60]. However, it is now clearly understood that the incidence of acute kidney injury (AKI) related to COVID-19 infected patients tends to be associated with the age of the patient, the smoking status of the patient, the cytokine storm, the severity of the COVID-19 disease, the ethnicity of the patient, and the history of diabetes mellitus, as well as hypertension, and cardiovascular disease of the patient [46] [48].
- It has also been iterated that acute kidney injury (AKI) is an independent risk factor for the poor long-term renal outcome and mortality in critically ill COVID-19 infected patients [46] [60] [61].
- It has been stated that during a follow-up study acute kidney injury (AKI) was found to be a major cause of in-hospital mortality. Furthermore, the complete kidney recovery rate of AKI in COVID-19 infection patients was found to be only about 30% to 4 [46]
- 5% based upon some recent reports [46] [62-64].
- Acute kidney injury is stated to be one of severe complications that emanate in COVID-19 infected patients and the mortality of in-hospital COVID-19 infected patients; nevertheless, the mechanisms of COVID-19-associated acute kidney injury (AKI) has remained largely unclear and this would to the undertaking of additional studies. [46]

Inflammation could be a mechanism of Acute Kidney Injury (AKI) in COVID-19 Patients

It has been iterated that many factors including: direct virus infection, cytokine storm, hypoxia, sepsis shock, hemodynamic instability as well as rhabdomyolysis, hypertension, and diabetes could be associated with the development of acute kidney injury (AKI) patients who have in COVID-19 infection. [46] It has additionally been iterated that out of the aforementioned factors for the development of acute kidney injury (AKI) inflammation stress could be a mechanism for the development of acute kidney injury in patients who have COVID-19 infection as has been elaborated upon in a subsequent section of this article. [46]

Angiotensin II (Ang II) and hypertension stress.

- Some authors have iterated that the kidney has tended to be a target organ for the development of SARS-COV-2 virus infection in view of the high expression levels angiotensin-converting enzyme 2 (ACE2), which is a receptor for the development of SARS-COV-2 virus [65] within the kidney tissues, especially within renal tubular epithelial cells (TECs) [46] [66] [67] [68].
- It has also been documented that SARS-COV-2 could be able to directly bind to ACE2 and infect kidney cells, that is supported by high levels of SARS-COV-2 spike (S) and nucleoprotein (N protein) in patients who have been afflicted by COVID-19 infection with acute kidney injury [46, 38, 51, 69].
- It has been intimated that within the kidney, renin-angiotensin-aldosterone system (RAAS) does maintain renal hemodynamic and regulates renal sodium transport within both normal physiological states and pathological conditions. [46]
- It has furthermore been stated that Ang II and Ang 1-7 are the two major effectors of RAAS and that they tend to be tightly controlled by two major enzymes of ACE and ACE2 [46] [70], and that Ang II does act through its receptor-1 (AT1) in order to mediate renal inflammation and fibrosis by activating NF-kB and Smad signalling crosstalk pathways, whilst Ang 1-7 does tend to bind receptor Mas to counter-regulate these pathological effects of Ang II [46] [70]
- It has been explained that the principal primary function of ACE2 is to covert Ang II into Ang 1-7 in order to exert its anti-inflammatory, vasodilatory and natriuretic properties [46] [71]
- It has been iterated that pursuant to binding to ACE2, SARS-COV-2 does significantly downregulate ACE2 expression [46] [72] [73] and this does emanate in an inhibition or loss of Ang 1-7 whilst enhancing Ang II-AT1-dependent kidney inflammation, vasoconstriction, thrombosis as well as anti-diuresis effects [46] [74].
- A number of authors had iterated that Ang II is a key mediator of AKI [46] [75] [76] [77]; however; it has been iterated that the ACE2-Ang-1-7-Mas axis tends to be reno-protective [46], [78].
- It has additionally been stated that SARS-COV-2 viral infection to the kidney might downregulate ACE2-Ang1-7-Mas signalling while promoting the Ang II-AT1 signalling to mediate inflammation of the kidney and acute kidney injury (AKI). [46]
- It has also been iterated that a simulating mechanism had also been ascertained in patients who had ARDS [46] [79].
- Hence, the interaction between SARS-COV-2 virus and ACE2 might eventually impair the ACE2-Ang 1-7 while enhancing Ang II signalling, emanating in hypertension as well as inflammatory stress both systemically and locally within the kidney. It has been stated that the aforementioned postulate could well explain that hypertension is an independent risk factor in patients who have COVID-19 [46] [80]
- Nevertheless, it has been iterated that the role of Ang II signalling in COVID-19 infection patients who develop progressive kidney injury has remained yet to be determined or fully explained. [46]

Diabetes mellitus and metabolic stress

- It has been iterated that diabetes mellitus is a factor for the development of acute kidney injury [81] and that patients who

have diabetes mellitus tend to be associated with severity as well as death in cases of pandemic influenza (HINI) [82], SARS-COV. [83] as well as in MERS-COV [84].

- It has also been iterated that recent studies that had been undertaken had also found that COVID-19 patients who had diabetes mellitus have tended to have higher acute kidney in jury (AKI) rate as well as mortality rate in comparison with those individuals who were non-diabetic [55] [85].
- It has been additionally stated that the aforementioned findings had also been confirmed in a recent meta-analysis in 5497 COVID-19 patients [86].
- It has been iterated that it has been now well accepted that metabolic stress with the inclusion of hyperglycaemia, obesity, insulin resistance and high levels of glycosylation end products (AGEs) in patients who have diabetes mellitus could trigger the production of pro-inflammatory cytokines and does promote the oxidative stress [46] [87]
- Hyperglycaemia has also been stated to be a risk factor for the development of acute kidney injury (AKI) with regard to patients who have diabetes mellitus [46] [60] .
- It has been documented that the IκB kinase-β (IKKβ)/NF-κB axis does represent a key inflammatory pathway in diabetes mellitus in response to hyperglycaemia and insulin resistance [46] [88]
- It has additionally been intimated that AGEs could also induce activation of NF-κB, which does result in the production of pro-inflammatory cytokines [46] [89].
- It has been documented that by comparing with non-diabetic COVID-19 patients, COVID-19 patients who have diabetes mellitus do have significantly higher levels of IL-6 and CRP [46] [90].
- Furthermore, it has been stated that patients who have diabetes mellitus also do develop hypertension, which is associated with activation of Ang II-AT1 while inhibiting ACE2-Ang 1-7 signalling [46] [91].
- Additionally it has been iterated that in view of the fact that ACE2 is also expressed within the pancreas, infection of SARS-COV-2 might also damage pancreatic islet β-cells as well as aggravate hyperglycaemia [46] [92].
- Hence it has been deduced that enhanced metabolic inflammation within the diabetic kidney could represent another mechanism that is contributory to the development of acute kidney injury (AKI) with regard to COVID-19 patients. [46] Nevertheless, it has also been iterated that the mechanisms that are responsible for the development of metabolic stress in acute kidney injury (AKI) pursuant to COVID-19 infection has remained yet to be explored. [46]

Cytokine storm

- Some authors had iterated that inflammatory cytokines had been recognized as a critical factor related to the progression of COVID-19 infection. [46] [93] [[new 94]] [94].
- It has been stipulated that the inflammatory response that is triggered by SARS-COV, MERS-COV or SARS-COV-2 could recruit as well as activate monocytes, macrophage and dendritic cells to produce inflammatory cytokines [46] [95] [96], which might be essential in the control of the viral replication and cleaning of the infected cells [46] [97]. Nevertheless, it has also been iterated that overactive immune responses could cause excessive and persistent cytokine production which does lead to cytokine storm and which does result in multiple organ dysfunction as is seen in patients who have SARS [46] [98], MERS [46] [99], and COVID-19 infection [46] [100].
- It has been stipulated that in these patients, a number of proinflammatory cytokines including interleukin (IL)-1β, IL-6, IL-12, interferon γ (IFN-γ) as well as monocyte chemoattractant peptide (MCP-1) tend to be associated with extensive lung damage in SARS patients [46] [101].
- It has also been stated that the blood levels of IL-10, IL-15 as well as TGF-β1 tend to be also positively correlated with the severity of the disease with regard to patients who have MERS [46] [102].
- Other authors had intimated that with regard to COVID-19 patients, the levels of IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte colony stimulating factor (G-CSF), IFN-γ, interferon γ inducible protein (IP)-10, tumour necrosis factor-alpha (TNF-α) as well as MCP-1 also tend to be increased over the healthy controls and they become worsened in those patients who are admitted into the intensive care unit (ICU) with severe acute lung injury [46] [103] [104].
- Some authors had iterated that Cytokine storm could also trigger acute kidney injury (AKI) under various clinical conditions with the inclusion of secondary hemophagocytic lympho-histiocytosis (sHLH) [46] [105]. [106]. [107] [108] [109].
- sHLH is also documented to be found in patients who have SARS and COVID-19 [46] [110] [111].
- It has additionally been iterated that cytokine storm could also emanate in the development of antiphospholipid syndrome in acute kidney injury (AKI) patients who have COVID-19 [46] [112] [113] and that out of these aforementioned inflammatory cytokines, IL-6 had been identified as a key mediator in COVID-19 patients, and this has been further described in the later part of the ensuing document.

IL-6

- It has been reported that a number of studies had illustrated that among the inflammatory cytokines, IL-6, does represent the strongest as well as important mediator in COVID-19 infected patients. [46] [114] [115].
- It has been documented that meta-analysis which had involved 12681 COVID-19 infected patients had confirmed that IL-6 was significantly higher in those individuals who had severe disease conditions. [46] [116] [117].
- It had also been iterated that serum levels of IL-6 had positively correlated with the severity of COVID-19 infections. [46] [117-119], as well as it additionally predicted the mechanical ventilation need for COVID-19 infection patients [46] [120].
- It has been iterated that with regard to COVID-19 infected patients of the older age group, IL-6 does represent an independent risk factor for mortality within the hospital [46] [121].
- It has been pointed out that IL-6 also does represent a predictor for the development of acute kidney injury (AKI) with regard

to patients who are under various clinical conditions with the inclusion of cardiovascular disease, kidney diseases, as well as liver transplantation [46] [122-124].

- It has also been stated that IL-6 was also found in ischaemic acute kidney injury (AKI) animal model. [46] [125].
- It has also been iterated that in response to injury, IL-6 tends to be upregulated and released from kidney TECS as well as it does play a pivotal role in the pathophysiology of acute kidney injury. [46] [125].
- It has been stated that there is increasing evidence which had shown that IL-6 does represent not only a biomarker but it is also a mediator for the development of acute kidney injury (AKI) in view of the fact that mice that lack IL-6 tend to be resistant to $HgCL_2$-induced acute kidney injury (AKI) [46] [125] [126] [127].
- It has additionally been iterated that with regard to patients who have COVID-19 infection, the serum levels of IL6 tend to be elevated in those patients who have acute kidney injury (AKI), [46] [128], as well as the serum levels of IL-6 do tend to increase further in patients who are critically ill. [46] [112] [129].
- It has furthermore been iterated that serum levels of IL-6 could also predict clinical outcomes of acute kidney injury (AKI) in view of the fact that the serum levels of IL-6 tend to be significantly reduced in those individual patients when acute kidney injury (AKI) is recovered pursuant to effective therapy. [46] [130].
- It has been explained that mechanically, JAK-STAT3 is a downstream signal transduction of IL-6-membrane-bound-IL-6 receptor (MIL-6R)/soluble-bound-IL-6 receptor (sIL-6R). [46] It has also been further explained that the IL-6-mIL-6R/sIL-6R-JAK-STAT3 signing pathways tend to be activated during cytokine storm in severe COVID-19 patients [46] [95].

- Mechanistically, JAK-STAT3 is a downstream signal transduction of IL-6-membrane-bound-IL-6 receptor (mIL-6R)/soluble-bound-IL-6 receptor (sIL-6R). The IL-6-mIL-6R/sIL-6R-JAK-STAT3 signing pathways are activated during cytokine storm in severe COVID-19 patients [46]. [95].
- Nevertheless, it has additionally been documented that the functional role as well as the molecular mechanisms of IL-6 with regard to the pathogenesis of COVID-19 associated acute kidney injury (AKI) has remained not clarified. [46]

C-reactive protein (CRP)

- It has been iterated that C-reactive protein (CRP) tends to be produced by the liver as well as many inflammatory cells as well CRP is an acute phase protein. [46]
- It has been documented that CRP is widely utilized in clinical settings as an acute inflammatory biomarker [46]
- It has been iterated that CRP has been proven to be a predictor for the development of post-operative acute kidney injury (AKI) in patients who undergo Coronary Artery Bypass Graft (CABG) operation. [46] [131].
- Some authors have stated that CRP which is highly sensitive tends to be associated with the development of acute kidney injury (AKI) in individual patients who develop acute myocardial infarction [46] [132] [133].
- It has additionally been stated that CRP does represent an independent predictor for the development of acute kidney injury (AKI) among myocardial infarction patients who have ST segment elevation on their ECG tracings who undergo percutaneous interventional procedures. [46] [134].
- It has ben iterated that there is evidence which has indicated that serum CRP level also represents a pathogenic factor that is contributory to the development of inflammatory diseases with the inclusion of atherosclerosis [46] [135]. as well as acute kidney injury [46], [136]. [137]. [138]. [139] [140].
- It has been iterated that the mechanisms of CRP associated with the progression of acute kidney injury (AKI) do include stimulation of macrophage activation [46] [136], induction of cell death by causing GI cell cycle arrest as well as autophagy [46] [138] and promotion of inflammation [46] [140].
- Some authors had stipulated that the activation of NF-κB/p65 as well as TGF-β/Smad3 signalling pathways represent the major mechanisms through which CRP does mediate the development of acute kidney injury (AKI) [46] [137] [139] [140].
- It has been iterated that COVID-19 infected patients who have developed acute kidney injury (AKI) had been documented to demonstrate higher levels of serum CRP in comparison COVID-19 infected patients who did not develop acute kidney injury (AKI) [46] [141]. and that serum levels of CRP also represent a risk factor for the development of acute kidney injury (AKI) in COVID-19 infected patients [46] [142]
- Tan et al. had reported that serum CRP levels tend to be significantly elevated pursuant to SARS-CoV-2 infection, which does become further increased when the disease is progressive but the CRP level does decline dramatically when COVID-19 is recovered [46] [143].
- It has been stated that serum levels of CRP are significantly elevated after SARS-CoV-2 infection, which becomes further increased when the disease is progressive but declines dramatically when COVID-19 is recovered [46] [143] [[new 144]], and based upon this it would be deduced that the levels of serum CRP could be a predictor for the clinical outcomes of COVID-19 infected patients [46].
- It has been documented that meta-analysis had confirmed this postulate that in contrast to mild and survival subgroup of COVID-19 patients, high levels of CRP tend to be associated with severe and death subgroup of COVID-19 patients [46] [116] [117] [144].
- It has additionally been iterated that CRP is also understood to be an indicator for renal replacement therapy and the need for mechanical ventilation in COVID-19 infected patients [46] [145].
- Based upon the aforementioned, it had been deduced that raised lever of serum CRP is independently associated with poor clinical outcomes in COVID-19 infected patients [46] [107] [147].
- Additionally, it has been iterated that the pathogenic role as well as mechanisms of CRP in COVID-19-associated AKI has remained largely not known. [46]

TGF-ß

- TGF-β has been defined as a pleiotropic cytokine which does signal through its downstream canonical and non-canonical pathways in order to diversely regulate renal inflammation and fibrosis [46] [144] [148].
- It has been iterated that SARS-COV nucleocapsid protein could interact with Smad3 in order to activate the canonical pathway [46] [149].
- on the other hand, the non-canonical TGF-β signalling pathway also does tend to be activated by the papain-like protease of SARS-COV by inducing the expression of TGF-β1 [46] [150].
- It has been stated that with regard to COVID-19 patients, plasma levels of TGF-β tend to be significantly raised as well as associated with the severity of the disease as well as poor clinical outcomes [46] [151] [152]
- It has been iterated that elevated TGF-β2 mRNA had also been identified in the bronchoalveolar lavage (BAL) fluid of COVID-19 infected patients [46] [153] which could be contributory to the development of lung inflammation as well as fibrosis in view of the fact that TGF-β1 is also a growth factor that is associated with fibrosis [46] [144] [148].
- It has been stipulated that that SARS-COV-2 encoded microRNAs have the ability to target TGF-β signalling pathway in order to induce TGF-β-dominated adaptive immune response [46] [154]
- It has been iterated that the upregulation of TGF-β1 in COVID-19 infected patients tends to be responsible for the recruitment of neutrophils into the site of inflammation [46] [155].
- It has also been documented that TGF-β could also induce MCP-1 to activate macrophage-dependent inflammation within the diabetic kidney through a Smad3-dependent LRNA9884 [46] [156].
- Additionally, it has been stated that induction of IL-6 production by TGF-β1 also does lead to systemic inflammation as well as "cytokine storm" [46] [157].
- It has been iterated that TGF-β could induce IgA class switching, which could contribute to vasculitis in critically ill patients who have COVID-19 infection [46] [158]. Based upon this it had been concluded that TGF-β could significantly contribute to the immediate and long-term effects of COVID-19 infection [46].
- Even though the role of TGF-β in COVID-19 infection associated acute kidney (AKI) does remain not-clear, recent findings had been reported which had documented that conditional deletion of TGF-β receptor II from renal proximal tubules does protect against mercuric chloride and cisplatin-induced AKI does reveal a critical role of TGF-β signalling in acute kidney injury (AKI) [46] [159, 160] .
- It has been iterated that mice which specifically lack bronchial epithelial TGF-β1 (epTGFβKO) tend to be protected against influenza-induced weight loss, airway inflammation, as well as viral replication [46] [161]. Which does suggest the impact of TGF-β in viral infection.
- It has been stated that mechanistically, TGF-β1 might act through Smad3 to cause acute kidney injury (AKI) as genetic deletion or pharmacological inhibition of Smad3 could block acute kidney injury (AKI) in ischemic mice with or without high human CRP conditions [46] [162].
- It has been iterated that, Smad3 could be activated by both TGF-β-dependent as well as independent mechanisms which include: Ang II, advanced end products (AGE), as well as CRP under various disease conditions including hypertension and diabetes mellitus [46] [163-165].
- It has also been stated that activation of Smad3 signalling could account for the clinical notion which is held that patients who have diabetes mellitus as well as hypertension have a high risk for the development of COVID-19 [46] [48].
- It has been iterated that mechanistically, Smad3 does promote acute kidney injury (AKI) by directly binding to p21/p27 in order to suppress CDKs/cyclin E to cause the G1 cell cycle arrest [46] [166-167].
- It has been inferred from the aforementioned iterations that it is highly possible that TGF-β/Smad3 signalling could contribute to COVID-19-associated acute kidney injury (AKI), which does warrant further investigation studies. [46]

Complement activation

- It has been iterated that the complement system is the first response of host immune system which does recognize as well as does eliminate virus, such as SARS-COV or SARS-COV-2 [46] [48] [130]. [168
- It has been stated that there are many pathways that are involved in the in the systemic complement activation that include the lectin pathway, classical pathway, and alternative pathway [46] [168]. [169].
- It has been iterated that the lectin pathway tends to be triggered by the binding of mannose-binding lectin (MBL) with SARS-COV spike (S) protein [46] [170] which does lead to the activation of mannan-binding lectin-associated serine protease 2 (MASP-2).
- It has been stated that the N protein of coronavirus also tends to be associated with the severity of lung injury according to MASP-2-mediated complement overactivation. Hence, alteration of MASP-2-binding motif or blocking the MASP-2-N protein interaction does attenuate lung injury [46] [171].
- The classical pathway is activated by the binding of antibodies, which forms the immune complexes with viral antigens to complement C1 complex [46] [168] [169].
- It has been iterated that the classical, lectin and alternative pathways resulting in the formation of C3 convertase to activate the complement system, which tends to be observed in the lung pursuant to SARS-COV infection [46] [168] [169] [172
- It has been intimated that the role of C3 in SARS-COV-induced lung injury is confirmed in C3 deficient mice in which deletion of C3 protects against ARDS with lower levels of cytokine and inflammatory monocytes infiltration [46] [172]
- The complement system is activated during the progression of COVID-19 infection [136]. It has been stated that the activation of complement system tends to be related to the disease severity and the respiratory failure in COVID-19 infection patients [46] [172] [173] [174]

- It has been shown that the C5a-C5aR1 axis does play an important role in the development of ARDS in COVID-19 infected patients [46] [175]. on the other hand, C4d and C5-9 are colocalized with the SARS-COV-2 S protein in the lung and skin vasculature [46] [176].
- It has been iterated that the activation of alternative pathway of complement also does participate in the pathogenesis of acute kidney injury (AKI), [46] [177] [178].
- It had been reported that local synthesis or deposition as well as activation of complement by renal epithelium is an important cause of acute kidney injury (AKI) [46] [179] [180]
- It has also been stated that strong C5b-9 staining had been demonstrated on the apical brush border of TECs of the kidney with SARS-COV-2 infection [46] [51]
- It has been iterated that activation of the classical complement pathway was also found in the acute kidney injury (AKI) kidney in critically ill children with COVID-19 infection [46] [129]. Nevertheless, the functional role and mechanisms of complement activation in COVID-19-assicated AKI do largely remain not clarified. [46]

The Lung-Kidney Crosstalk Pathway.

- It has been iterated that the crosstalk between the lung and the kidney had been observed in patients who had acute kidney injury (AKI) and ARDS [46] [181]
- It has been noted that clinically, acute lung injury (ALI) and acute kidney injury (AKI) are complications which often tend to be encountered in patients who have critical illness [46] [145] [182]
- It has been iterated that mechanical ventilation could improve upon lung function; nevertheless, mechanical ventilation is a risk factor for the development of acute kidney injury (AKI) in patients who are critically. [46] [183] [184]
- It has been iterated that positive pressure of mechanical ventilation could increase the risk for the development of acute kidney injury (AKI) by almost 8-fold [46] [145], which tends to be associated with systemic hemodynamic and neurohormonal changes as well as biotrauma [46] [106]. [185] [186]
- It has also been iterated that ARDS could trigger acute kidney injury (AKI) through mechanisms that are associated with systemic hypoxia, hypercapnia, systemic inflammatory response syndrome (SIRS), as well as mechanical ventilation. [46]
- It has also been stated that patients who had severe hypoxemia in the intensive care unit (ICU) that was associated with acute kidney injury (AKI) had required renal replacement therapy [46] [182]
- It has been explained that the kidney is susceptible to the development of hypoxic injury in view of the high rate of oxygen consumption [46] [106] [187]. Hence, it was iterated that hypoxia could induce acute kidney injury (AKI) as well as tubular necrosis or apoptosis [46] [186].
- It has been iterated that hypercapnia in COVID-19 patients could also affect the renal blood flow by stimulating renal vasoconstriction [46] [188]
- It had additionally been iterated that the lung-kidney cross-talk also has tended to be associated with the cytokine storm [46] [189]
- It has been stated that the inflammatory reaction which is caused by the lung injury could damage the kidney in order to release abundant inflammatory cytokines, which, in turn, does promote the damage within the lung [46] [38]. Based upon this evidence, Chen et al., [46] are of the opinion that the approaches to limit ventilator-induced lung injury and decrease the duration of mechanical ventilatory support to protect against the development of acute kidney injury (AKI) in critically ill patients had been proposed for the treatment of critically ill COVID-19 who have acute lung and kidney injury.

Therapeutic Potential For COVID-19 Associated Acute Kidney Injury (AKI).

Continuous renal replacement therapy (CRRTT)

- It has been iterated that continuous renal replacement therapy (CRRT) is a terminology that is utilized for an advanced approach to the treatment of who have acute kidney injury (AKI) by improving overload water status as well as removing inflammatory factors, [46], [190] especially, with regard to those patients who have septic AKI [46] [191]
- It has been documented that CRRT has been used in AKI patients who had severe MERS as well as in critically ill COVID-19 [46]] [192]
- Nevertheless, it has also been stated that whether the early initiation or high intensity of CRRT could improve upon the progression of acute kidney injury (AKI) COVID-19 patients has remained to be ascertained. [46]

Tocilizumab (TCZ)

- TCZ is a terminology that is utilized for a recombinant humanized monoclonal antibody against the human membrane and soluble IL-6 receptors and it is widely utilized for the therapy of immunoinflammatory rheumatic diseases [193, 194]
- It has been iterated that TCZ had been demonstrated to block the IL-6/NF-κB/JNK pathway to have a protective effect against sepsis-induced acute lung injury and AKI [46] 195]
- It has been iterated that considering that IL-6 is important in COVID-19, TCZ has been utilized to treat COVID-19 patients clinically [46].
- It has also been iterated that the early therapy with TCZ had been demonstrated to effectively improve upon the oxygen status in COVID-19 patients [46] [193].
- It has been documented that a meta-analysis of TCZ studies that had been undertaken in a total of 1675 patients as well as 6279 COVID-19 patients with who were critically ill showed that TCZ treatment could significantly reduce the in-hospital mortality rate, although patients do remain to need for haemodialysis as well as ventilation [46] [196]

- It has been recommended that the therapeutic efficacy of TCZ on COVID-19-associated AKI does need to be further studied [46].

Complement Inhibitor

A C3 inhibitor AMY-101

- It has been iterated that AMY-101 is a terminology that is utilized for a highly selective as well as potent C3 inhibitor and it is currently being tested in a Phase II clinical trials in patients who have sepsis, haemodialysis-induced inflammation or malaria anaemia [46] [197], [198], [199] [200]
- It has been reported that treatment with utilization of AMY-101 is safe and it could significantly improve upon the clinical manifestations in severe COVID-19 patients [201]

Chen et al. [46] had iterated that further Phase II and III clinical trials are still going on.

An anti-C5 antibody

- It has been stated that an anti-C5 antibody had been clinically utilized in patients who had C3 glomerulopathy and in many types of acute kidney injury (AKI) with the inclusion of atypical haemolytic uremic syndrome as well as paroxysmal nocturnal haemoglobinuria. [46] [202]
- It has been documented that treatment with the anti-C5 antibody had been demonstrated to improve upon the kidney function as well as ameliorate the intra-renal complement activation as well as systemic inflammation in ischaemic reperfusion-induced acute kidney injury (AKI) mouse model [46] [202]
- It has also been stated that the first result of anti-C5 therapy had also demonstrated a rapid as well as promising effect upon COVID-19 patients. [46] [203]
- Nevertheless, Chen et al. [46] had recommended that more clinical trials would be needed in order to ascertain conclusive results of the anti-C5 antibody therapy on COVID-19 patients who have acute kidney injury (AKI) [46].

Anti-TGF-ß treatment

- It has been iterated that in view of the fact that SARS coronavirus could upregulate TGF-ß as SARS coronavirus can upregulate TGF-β [46] [151, 152]. It has been postulated that TGF-β might be a valid target for the treatment of COVID-19 infection [46] [204, 205].
- It has been documented that with regard to a recent Phase II clinical trial, inhibition of TGF-β expression by OT-101, an anti-sense to TGF-β1, had been demonstrated to suppress SARS-COV and SARS-COV-2 replication and this allowed patients to recover without going into respiratory crisis [46] [206], which had indicated COVID-19 could be treated with TGF-β inhibition. Nevertheless, it should be realised that TGF-β does have diverse roles with regard to inflammation of the kidney as well as in fibrosis [46] [144] [148] and targeting the upstream of TGF-β might also cause adverse effects.
- Chen et al. [46] iterated that their recent studies had demonstrated that TGF-ß could trigger acute kidney injury (AKI) through the Smad3-dependent mechanism as well as therapy with Smad3 inhibitors including SIS3 or a natural product of Traditional Medicament Quercetin could effectively suppress acute kidney injury (AKI) even under high human CRP conditions. [46] [144, 207]
- Chen et al. [46] stated that the aforementioned findings do indicate that targeting Smad3 does specifically rather than the entire TGF-ß signalling could represent as a novel as well as effective treatment for acute kidney injury (AKI) in COVID-19 patients clinically. [46]

Chen et al. [46] made the ensuing conclusions:

- Acute kidney injury (AKI) tends to be a common compilation with regard to critically ill COVID19 infected patients.
- Inflammation could represent a key mechanism that triggers the process of acute kidney injury in COVI-19 infected patient.
- Many inflammatory stress molecules and pathways with the inclusion of Ang II-associated hypertensive stress, diabetes-related metabolic stress, cytokine storm, high CRP, overreactive TGF-β signalling, complement activation, as well as lung-kidney crosstalk might promote the development of acute kidney injury (AKI) in COVID-19 infected patients.
- Hence provision of treatments by the targeting of these molecules and pathways could represent a novel and specific treatment option for acute kidney injury (AKI) in COVID-19 infected patients.

[(B)] Miscellaneous Narrations and Discussions Related to Coronavirus (COVID 19) Infection and the Kidney

Alvarez-Belon et al. [208] made the ensuing summations related to coronavirus (COVID 19) infection and the kidney:

- Despite earlier on reports, kidney involvement, which does include acute renal injury, has been found as a serious sequel of COVID-19 disease, especially with regard to ill patients.
- The reported prevalence of kidney injury in association with Coronavirus (COVID 19) infection does vary considerably, and this variation could be a reflection of reporting practices, even though the differences in the pre-existing comorbidities and socioeconomic factors, as well as the differences between ethnic groups, almost certainly are contributory.
- Kidney involvement in cases of Coronavirus (COVID 19) infection could manifest an active urinary sediment or as changes within the levels of serum creatinine as well as in urine output that tends to emanate in acute kidney injury.
- Together with acute kidney injury that complicates critical illness, the cause of acute kidney injury in association with Coronavirus (COVID 19) infection often tends to be multifactorial and it often does manifest as part of a multi-organ dysfunction syndrome.
- The treatment of acute kidney injury in association with Coronavirus (COVID 19) often tends to be mainly supportive, with utilization of kidney replacement therapy that tends to be required in approximately 25% of reported cases of acute kidney injury in association with Coronavirus (COVID 19 infection).
- Very little data currently exists as to the long-term burden of COVID-19-associated acute kidney injury; nevertheless, there is evidence which does suggest that only about one-third of patients are discharged who have recovered kidney function.

Askari et al. [209] made the ensuing summaries related to Coronavirus (Covid-19) infection and kidney disease:

- Recently, the novel coronavirus disease 2019 (COVID-19) has led to the attraction of the attention of scientists due to the fact that it does tend to be associated with a high mortality rate among older adults as well as individuals who have been suffering from chronic disease for example chronic kidney diseases (CKDs).
- It is important to ascertain the molecular mechanisms through which COVID-19 infection does affect the kidneys so that they could accordingly develop appropriate nutritional as well as pharmacological strategies to combat the problem.
- Even though many studies had recently recommended many approaches for the treatment of COVID-19 in chronic kidney disease (CKD), its impact upon patients who have kidney diseases does remain the biggest challenge globally.
- They had reviewed the most recent evidence relating to the cause, potential nutritional supplements, treatment options, and management of COVID-19 infection among vulnerable individuals as well as individual patients who have chronic kidney disease (CKD).
- To date, no effective therapy does exist for the management of COVID-19 induced renal dysfunction based upon their review of the literature, and treatments that currently being utilized have yet been limited to utilization of anti-inflammatory medications including for example ibuprofen, and antiviral medicaments for examples Remdesivir, as well as Chloroquine / hydrochloride which could increase the chance of treatment.

Askari et al. [209] concluded that knowledge regarding kidney damage in COVID-19 infection is very limited.

Lin et al. [210] iterated that information related to coronavirus disease (COVID-19) in patients who have chronic disease (CKD) has remained limited. In order to ascertain the influence of COVID-19 infection upon patients who already have pre-existing CKD, Lin et al. [210] had undertaken a systematic review as well as meta-analysis to evaluate and to compare the risks of all-cause mortality, hospitalization, as well as progression between patients who have and those patients who do not have CKD. Lin et al. [210] had selected randomized controlled trials (RCTS), prospective or retrospective, observational, case control, cross-sectional, as well as case studies that had analysed the outcomes of COVID-19 infection with regard to patients who had pre-existing CKD from PUBMED, Embase, as well as Cochrane Central Register of Controlled Trials databases that had been published on the internet preceding 16th July 2020. Lin et al. [210] summarized the results as follows:

- A total of 27 studies which had comprised of 77,856 patients who had COVID-19 infection had been identified, and 3922 patients with COVID-19 infection who had pre-existing CKD were assigned to the CKD group, and 73,934 patients were assigned to the non-CKD group.
- The pooled analysis of their study did show that patients who had CKD did have significantly higher risk for the development of all-cause mortality, and hospitalization in comparison with those patients who did not have CKD [odds ratio (OR) 2.25, 95% confidence interval (CI) 1.91-2.66, $p < 0.001$; OR 4.29, 95% CI 2.93 – 6.28, $p < 0.001$, respectively].
- Patients who had CKD did have a higher risk for the development of critically ill conditions in comparison with patients who did not have CKD in the pooled analysis of studies with utilization of multi-variable adjustment (adjusted OR 2.12, 95% CI 0.95 – 4.77, $p = 0.07$) as well as in the analysis of all included studies (OR 1.27, 95% CI 0.71 – 2.26, $p = 0.41$); nevertheless, both analyses had not attained statistical significance.

Lin et al. [210] concluded that COVID-19 infected patients who had CKD did have significantly increased risks for the development of all-cause mortality as well as hospitalization in comparison with patients who did not have CKD.

Zhang and Liang. [211] made the ensuing summations related to some of the general aspects of Coronavirus infection and its association with miscellaneous aspects of kidney function as follows:

- In December 2019, an outbreak of acute respiratory illness had developed and the disease had subsequently been referred to as coronavirus disease 2019 (COVID-19) by the World Health Organization, which had emerged within Wuhan, Hubei in China.
- Up to the 28th of March 2020, there had been 512,701 confirmed cases of COVID-19 infection as well as 23,495 deaths which had been related to COVID-19 infection that had been document globally [212].
- After December 2019, COVID-19 has constituted a global health threat.
- Based upon efforts that had been made by experts as well as scientists globally, the understanding of COVID-19 infection has greatly increased.
- Researchers had undertaken deep sequencing analysis of samples that had been obtained from the lower respiratory tract from which they had identified a novel coronavirus which had since then been referred to as novel coronavirus 2019 [2019-nCoV, which thee days has tended to be referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- The virus has been confirmed as the cause of COVID-19 infection. [213]
- COVID-19 infection is the third epidemic which had been caused by coronavirus within the 21st century, ensuing SARS which is caused by SARS-CoV, and Middle East respiratory syndrome (MERS).
- Studies had demonstrated that 2019-nCOV as well as SARS-CoV do share the same cell entry receptor, angiotensin-converting enzyme 2 (ACE2). [214] [215]
- It has been iterated that the expression of ACE" patterns within different organs, tissues, as well as cell types might uncover the potential risk for the development of 2019-nCoV infection.
- It has been documented that ACE2 does get expressed within human being epithelial tissues of the lung, the small intestine, the heart, the liver, as well as within the kidney. [216]
- It had been reported that immunohistochemistry staining studies of samples that had been obtained from autopsy specimens from patients who had been afflicted by SARS had demonstrated SARS-CoV virions, RNA, and antigen within the lung, as well as other organs with the inclusion of the kidney [217]
- One in vitro study which had been undertaken [218] did confirm that SARS-CoV with proximal tubular epithelial cells had demonstrated persistent and productive infection that had partly correlated with the immunohistochemistry expression of ACE2 expression.
- With the utilization of state-of-the-art single cell techniques, Zou et al. [219] (did stratify organs into high and low risk based upon the immunohistochemistry expression level of ACE2. Within their analysis, they had observed that the kidney should be listed as high risk. These immunohistochemistry staining

findings did suggest the possibility of 2019-nCoV infection of kidney cells.

- The clinical presentations of COVID-19 within some areas of China had been recently reported by some authors [220] [221] [222]
- Based upon the immunohistochemistry expression of ACE2 within organs, besides respiratory symptoms, non-respiratory symptomatology including: fatigue, myalgia, as well as diarrhoea had also been reported.
- Acute kidney injury (AKI) had been reported as one of the complications which do occur during the period of progression of COVID-19 in both patients who have comorbid with kidney disease and those who do did not have co-morbid kidney disease [221] [222]
- One study which had comprised of 138 patients who had COVID-19 infection, [222] of 138 patients did report that nearly 4% of patients who had COVID-19 had developed AKI.
- Huang et al. [221] had reported upon 41 patients who had COVID-19 infection and among them 10% of the patients did have elevated levels of serum creatinine (>133 micro-mol per litre upon their admission and 7% of the patients AKI. Laboratory tests did show that the level of serum urea and creatine had increased progressively with the progression of the COVID-19 infection.
- It has been iterated that the incidence of AKI in patients who have COVID-19 is similar to the incidence of AKI which is found in patients who are affected by SARS and that one retrospective study had reported that 6% of the patients who had SARS had developed AKI [223].
- With regard to a study of 536 patients who had SARS, 6.7% had developed acute renal impairment, and the involvement of the kidney in cases of SARS had been associated with a high mortality rate of 91.7% [224]
- Similarly, patients who had been afflicted by COVID-19 infection who had received care in intensive care units were found to be more likely to develop AKI in comparison with patients who had not received care within intensive care units [222]. All the aforementioned findings had suggested that AKI might be one of the risk factors for the emanation of mortality in patients who have COVID-19 infection.
- The pathophysiology mechanisms that are responsible for the development of AKI in COVID-19 infection, might be multi-factorial with the inclusion of direct infection with the 2019-nCoV, immune as well as inflammatory responses that are induced by viral infection, as well as systemic toxic reaction that emanate from respiratory failure. The aforementioned mechanisms could be closely associated with death of patients who have severe COVID-19 infection.
- It has been advised that considering the fact that the routes of transmission of COVID-19 infection had contributed greatly to the rapid spread of 2019-nCoV infection, this does remind clinicians that urine samples should be tested to exclude a potential alternative route of transmission of the disease except respiratory droplets and direct contact [225] [226] .
- They would advise that with regard to treating patients who have COVID-19 infection, special care of renal function should be taken into account .Based upon the aforementioned reasons, such information does call for care of patients related to their renal function who are currently under emergency as well as their potential post-cure management for kidney recovery.

Zhang and Liang. [211] had suggested that epidemiology studies should be undertaken to analyse kidney impairment and its characteristics in cases of 2019-nCoV infection and that this study could shed light upon further investigations of the pathogenesis, route of 2019-nCoV infection, as well as production of effective antiviral agents and vaccines.

Lynch and Tang [227] made the ensuing iterations:

- Acute kidney injury (AKI) has been reported as a complication of COVID-19.
- Nevertheless, the epidemiology, management, and associated outcomes have varied greatly between studies. The pathophysiology remains unclear.
- The aetiology of AKI in the setting of COVID-19 does appear to be multifactorial.
- Systemic effects of sepsis, inflammation, as well as vascular injury do likely play some role.
- Additionally, SARS-CoV-2 does bind to the angiotensin-converting enzyme 2 receptor, which is highly expressed within the kidney, which does provide a route for direct infection. Older age, baseline comorbidities, as well as respiratory failure represent strong risk factors for the development of AKI.
- Regardless of the aetiology, acute kidney (AKI) does carry a significantly increased risk for in-hospital mortality, especially with regards to those with critical illness.
- Currently, the management of acute kidney injury (AKI) in patients who have COVID-19 infection does remain supportive.
- The key messages that need to be learnt include: (a) Acute Kidney Injury (AKI) is common in patients who have COVID-19 infection; (b) future studies are needed in order to examine the response to anti-viral treatment as well as long-term renal outcomes in patients who have acute kidney injury (AKI).

Benedetti et al. [228] made ensuing summating iterations related to COVID-19 infections and the kidney:

- The new coronavirus disease 2019 (COVID-19) has developed into a world health emergency.
- COVID-19 infection predominantly does affect individuals whose ages have tended to be between 30 years and 79 years and 81% of cases of COVID-19 infection have been classified as mild. Despite the fact that majority of the general population do tend to manifest with symptoms that simulate the common cold, COVID-19 has also induced alveolar damage which has emanated in the development of progressive respiratory failure which has resulted in noted fatalities in 6.4% of COVID-19 infection cases.
- Direct viral injury, uncontrolled inflammation, activation of coagulation, as well as complement cascades are conjectured to participate within the pathogenesis of COVID-19 infection.
- Patients who have been affected by COVID-19 infection have demonstrated features of kidney damage via the process of acute kidney injury, mild proteinuria, haematuria, or slight elevation in creatinine possibly as a sequel of kidney tropism of the virus and multiorgan failure.
- The impact of COVID-19 upon patients who have pre-existing impairment of kidney function, including those who have chronic kidney disease, recipients of kidney transplantation, as well as individuals who are undergoing haemodialysis (HD) has not yet been clearly established.
- No specific treatments for COVID-19 infection have been ascertained yet.
- Research has demonstrated several agents which may have potential efficacy against COVID-19 infection, as well as many of these molecules have illustrated preliminary efficacy against

COVID-19 infection and they are currently undergoing testing in clinical trials.

George and Khoza [229] made the ensuing iterations about COVID-19 infection:

- Since December 2019, a novel coronavirus which is referred to as Severe Acute Respiratory Virus 2 (SARS-CoV-2) has caused an outbreak of a respiratory illness throughout the world.
- Although SARS-CoV-2 does primarily affect the respiratory system, other organs including the heart and kidneys tend to be implicated.
- The pathophysiology of Acute Kidney Injury (AKI) related to coronavirus 2019 (COVID-19) patients has not been clearly defined.
- Direct kidney injury does emanate from the entry of virus through angiotensin-converting enzyme-2 (ACE2) receptors which tend to be highly expressed by the podocytes and proximal convoluted tubules, as suggested by "viral-like" particles the are seen upon electron microscopy.
- Nevertheless, the link between the presence of viral particles within kidney tissue and kidney injury has not been fully explained.
- Additionally, it has also been postulated that collapsing focal segmental glomerulosclerosis (FSGS), myoglobin toxicity, sepsis-linked, and glomeruli fibrin thrombi is part of the mechanism for the development of AKI.
- Reported cases of COVID-19 infection link FSGS and high-risk apolipoprotein 1 (APOL1) alleles in patients of African ancestry.
- Typically, these patients do manifest with AKI and nephrotic-range proteinuria.
- The rate of development of AKI among hospitalized patients is high and associated with a higher mortality rate in older patients who have comorbidities.
- Furthermore, even higher mortality is currently being reported among patients who have chronic kidney disease and kidney transplant recipients as a result their immune system dysfunction.

Amann et al. [230] made ensuing general statements related to COVID-19 infection:

- With the exclusion of pulmonary disease which is very common in COVID-19 infection, acute kidney injury (AKI) is one of the most frequently encountered as well as most severe organ complications in severe coronavirus disease 2019 (COVID-19).
- The SARS-CoV-2 virus has been detected in renal tissue.
- Patients who have been having chronic kidney disease (CKD) before developing COVID-19 infection and patients who are on dialysis and specifically kidney transplant patients do represent a particularly vulnerable population.
- The increasing number of COVID-19 infected patients who have renal involvement has led to an evolving interest in the analysis of its pathophysiology, morphology and modes of Coronavirus detection within the kidney.
- Meanwhile, there are ample data from several autopsy and kidney biopsy studies which do differ with regard to the quantity of cases as well as with regard to their quality.
- While the detection of SARS-CoV-2 RNA in the kidney does lead to reproducible results, the utilization of electron microscopy for visualisation of the virus tends to be difficult and is currently critically discussed in view of various artefacts.
- The exact contribution of indirect or direct effects on the kidney in COVID-19 are not yet known or clearly understood and these currently do remain the focus of intensive research

Li et al. [231] stated that the causative virus of coronavirus disease 2019 (COVID-19), could cause severe fatal pneumonia and that the clinical manifestations of COVID-19 infection do include asymptomatic infection, severe pneumonia, as well as acute respiratory failure. They additionally iterated that data relating to acute kidney injury due to COVID-19 infection in patients who had undergone renal replacement therapy have been scarce. They reported two cases COVID-19 infection contemporaneously with acute kidney injury pursuant to renal transplantation. They reported that two patients who had COVID-19 infection did undergo kidney transplantation and they were subsequently diagnosed as having acute kidney injury. The first patient had manifested with progressive respiratory symptoms as well as acute renal injury. He was treated with utilization of diuretics as well as a suspension of immunosuppressive treatment; nevertheless, the patient died. The second patient had manifested with respiratory symptoms, hypoxemia, as well as progressive deterioration kidney function which was ensued by improvement. Her mycophenolate mofetil was discontinued pursuant to her admission, and tacrolimus was stopped 10 days subsequently. Moxifloxacin as well as methylprednisolone were continued in addition to albumin as well as globulin infusion. A diuretic treatment was given, and the dose of prednisolone was gradually reduced along with tacrolimus. The patient clinically recovered satisfactorily. Li et al. [231] concluded that patients who do develop COVID-19 pursuant to kidney transplantation are at risk for the development of acute kidney injury, and their prednisolone, immunosuppressant, as well as gamma globulin therapy should be adjusted based upon their condition.

Enghard et al. [232] stated the following:

- Investigators had reported that 107 patients out of 822 patients who had participated in the study that amounted to 13% of the participants who had an estimated glomerular filtration rate (eGFR) which was calculated based upon the Chronic Kidney Disease Epidemiology Collaboration Equation. [234] of 90 mL/min per 1·73 m^2 or more and no acute kidney injury during the acute phase did have an eGFR of less than 90 mL/min per 1·73 m^2 during their follow-up assessments.
- Huang and associates had interpreted this observation as related to persistent renal dysfunction.
- A persistent and potentially progressive reduction in eGFR with absence of acute kidney injury at the time of acute infection would certainly have important implications for the follow-up surveillance of COVID-19 infection. Nevertheless, they would like to point out that an alternative explanation is possible.
- eGFR is calculated upon the basis of serum creatinine values, which do undergo small fluctuations over a period of time as a result of shifts within hydration and other factors. [235] Such fluctuations would stochastically place some individuals who have normal GFR within the eGFR group of 90 mL/min per 1·73 m^2 or more during acute phase of the COVID-19 disease and in the eGFR group of less than 90 mL/min per 1·73 m^2 during their follow-up assessment, which would not necessarily represent a sign of worsening kidney function.
- Huang and associates did demonstrate an opposite seeming improvement of kidney function with an eGFR of 90 mL/min per 1·73 m^2 or more in 142 (29·7%) of 478 patients during their follow-up assessments with an eGFR of less than 90 mL/min per 1·73 m^2 and no evidence of acute kidney injury during the acute disease.
- They do encourage the investigators to illustrate eGFR trajectories between the acute phase and follow-up independent from their cut-offs in order to substantiate the robustness of their findings.

Srivastava et al. [236] made the ensuing summations related to COVID-19 infection:

Coronavirus disease 2019 is a pandemic disease, which had affected millions of people throughout the world in the year 2020.

- COVID-19 infection is caused by a virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the family of coronaviruses and which primarily does affect the respiratory system.
- COVID-19 infection does have a wide spectrum of clinical presentations which do range from asymptomatic form to mild, moderate and severe forms of the disease depending upon the age, comorbidity and immunity of an affected individual.
- Hyper-inflammatory response due to SARS-CoV-2 does adversely affect several internal organs. Besides lung injury, which tends to be the main outcome of SARS-CoV-2 infection, COVID-19 infection has been reported to adversely affect other organs that include the liver and kidneys.
- SARS-CoV-2 virus can also have a direct adverse effect upon and the kidneys due to systemic inflammatory response or drug toxicity, which does lead to elevated levels of liver injury markers and acute kidney injury.
- The clinical sequelae of SARS-CoV-2 infection could be worse with regard to patients who are suffering from pre-existing liver and kidney disease.
- To date, there have been many reports related to the mechanism of liver and kidney injury during SARS-CoV-2 viral attack. Nevertheless, the long-term effect of this infection upon these organs is yet to be clearly understood.

Oto et al. [237] undertook a multi-centre, retrospective study in which they utilized data of patients who had been hospitalized for COVID-19 that were collected from 34 centres in Turkey. Oto et al. [237] reviewed demographic characteristics, clinical findings, laboratory parameters (hemogram, CRP, AST, ALT, LDH, and ferritin) at admission and follow-up, and treatment strategies were reviewed. Oto et al. [237] analysed predictors of poor clinical outcomes. The primary outcomes of the study included in-hospital mortality and the need for intensive care unit (ICU) admission. Their secondary outcome was composite in-hospital mortality and/or intensive care unit (ICU) admission. Oto et al. [237] summarized the results as follows:

- One hundred nine (109) patients that comprised of 63 males and 46 females whose mean age was 48.4 ± 12.4 years were included in the study.
- Acute kidney injury (AKI) did develop in 46 patients that amounted to 42.2% of the patients, and 4 of the patients that amounted to 3.7% of the patients did require renal replacement therapy (RRT).
- A total of 22 patients that amounted to 20.2% of the patients were admitted into the intensive care unit (ICU), and 19 patients that amounted to 17.4% of the patients had required invasive mechanical ventilation.
- Fourteen (14) patients that amounted to 12.8% of the patients died.
- The patients who had been admitted into the intensive care unit (ICU) were significantly older with an age of over 60 years that amounted to 38.1% vs 14.9%, $p = 0.016$.
- Twenty three (23) of the patients that amounted to 21.1% of the patients reached to composite outcome and these patients were significantly older with an age of over 60 years of 39.1% versus. 13.9%; $p = 0.004$, and they had lower serum albumin of 3.4 g/dl [2.9–3.8] versus. 3.8 g/dl [3.5–4.1], $p = 0.002$), higher serum ferritin level of 679 µg/L [184–2260] versus. 331 µg/L [128–839], $p = 0.048$), and lower lymphocyte counts of 700/µl [460–950] versus. 860 /µl [545–1385], $p = 0.018$.
- Multivariable analysis did identify presence of ischemic heart disease and initial serum creatinine levels as independent risk factors for the development of mortality, whereas age over 60 years and initial serum creatinine levels were independently associated with intensive care unit (ICU admission).
- Upon analysis for the prediction of secondary outcome, age above 60 years and initial lymphocyte count were found to be independent variables in multivariable analysis.

Oto et al. [237] made the ensuing conclusions:

- Over the age of 60 years, ischemic heart disease, lymphopenia, poor graft function were independent risk factors for the development of severe COVID-19 in their group of patients.
- The presence of ischemic heart disease and poor graft function were found to be independently associated with mortality.

Le Stang et al. [238] made the ensuing summations related to COVID-19 infection of the kidney:

- The involvement of the kidney is a common complication during SARS-CoV-2 infection.
- Its association with poor outcomes of the patients, particularly in critically ill patients, does raise issues whether kidney involvement in COVID-19 infection does reflect multi-organ damage or if it is a specific feature of the COVID-19 infection.
- Virus entry route through ACE2 ligation and TMPRSS2 colligation does allow the identification of potential viral targets in the kidney, including tubules, endothelial cells, and glomerulus.
- Reports had described damages of all these structures and virus kidney tropism had been identified in renal extracts in autopsy series, no direct viral infection had been found in the latter structures so far on kidney biopsies.
- Notwithstanding the technical challenge of disclosing viral invasion within tissues and cells, viral direct cytopathogenic effect generally did not appear to be the cause of the observed kidney damage.
- Inflammation and altered haemodynamic which has been referred to as “viral sepsis,” could rather be responsible for organ dysfunction, including kidneys.
- As SARS-CoV-2 inexorably continues its rampant spread, understanding the sequence of events in the kidneys could help inform improved therapeutic strategies, including antiviral drugs and immunomodulators.

Singh and Singh [239] made the ensuing summations related to COVID-19 infection and the contemporary development of the corona:

- The contemporary evolution of the coronavirus disease 2019 (COVID-19) outbreak from the Wuhan, China, with a high rate of transmission will act the global medical emergency with immense morbidity and mortality rate across the world. The cell entry of COVID-19 via angiotensin-converting enzyme 2 receptor (ACE-2 receptor) will damage the respiratory system by the cytopathic effect induced by replication of the virus genome in the host and respond respiratory failure with an elevation of cytokine factor-like interleukin (IL) IL-6, IL-8, tumour necrosis factor-alpha (TNF-alpha), etc. However, the lung-kidney cross talk will evidence the activation of molecular mechanisms from pro-inflammatory cytokines and concerned with kidney damage, though the elevated rate of ACE-2 receptor in the kidney will enhance the possibility of mortality with consideration of acute kidney injury.

Singh and Singh [239] made the following conclusions:

- Patients with COVID-19 with acute kidney injury exhibit the lung as the primary site of involvement which subsequently leads to kidney-lung cross talk. The COVID-19 angiotensin-converting enzyme-2 receptor not solely presents in the

respiratory system, although expression of angiotensin-converting enzyme 2 receptor elevated in the kidney; thus, it represents renal tubular damage. Therefore, mortality rate is slightly higher in COVID-19 patients associated with acute kidney injury and defines a negative marker for survival. In addition, proteinuria, haematuria, as well as blood urea nitrogen and creatinine are considered for the extant of kidney activity in COVID-19 patients. The emphasis should be on very close observation of kidney functions with the involvement of potential cytokine inhibitor to evade the enforcement of inflammatory cytokine from lung damage to alleviate the mortality of COVID-19–associated acute kidney injury patients.

Conclusion

- Even though majority of individuals who have been afflicted by COVID-19 have manifested with symptoms that simulate common cold, COVID-19 infections has also induced alveolar damages which have which has emanated in the production of progressive respiratory failure and fatalities in 6.4% of COVID-19 infection cases.
- It is believed that direct viral injury, uncontrolled inflammation of coagulation, as well as complement cascades are postulated to participate in the pathogenesis of COVID-19 infection.
- Some patients who have been afflicted by COVID-19 infection have depicted kidney damage through the process of acute kidney injury (AKI), development of mild proteinuria, visible and non-visible haematuria, or slight elevation in their serum creatinine levels, possibly as an emanation of kidney tropism of the COVID-19 VIRUS as well as multi-organ failure.
- There reports of increasing clinical evidence which have indicated that acute kidney injury (AKI) does represent a common as well as severe complication which tends to develop with regard to patients with COVID-19 infection who are critically ill.
- Some of the risk factors in COVID-19 infected patients that have tended to be linked with the development of acute kidney injury (AKI) do include: the older age group, the severity of the COVID-19 infection, the ethnicity of the patient, the history of diabetes mellitus, hypertension, as well cardiovascular disease. Out of the aforementioned factors, inflammation could represent a key player in the pathogenesis of acute kidney injury (AKI) in patients who have been afflicted with COVID-19 infection.
- There is a postulated highly probability that SARS-COV-2 infection could trigger the activation of many inflammatory pathways that include: angiotensin II, cytokine storm such as interleukin-6, (IL-6), C-reactive protein (CRP), TGF-ß signaling, complement activation, as well as lung-kidney crosstalk to induce acute kidney injury (AKI).
- It would hence be considered that therapies that target the aforementioned inflammatory molecules as well as pathways with utilization of a monoclonal antibody against IL-6 (Tacilizumab), C3 inhibitor AMY-101, anti-C5 antibody, anti-TGF-ß OT-101, as well as utilization of CRRT in patients with COVID-19 infection who are critically ill, could represent novel as well as specific treatment options for acute kidney injury (AKI) with regard to COVID-19 infected patients.
- There is so far no consensus global opinion regarding any specific treatments for COVID-19 infection.
- The results of some research studies related to COVID-19 infection have reported many agents which might have potential efficacy against COVID-19 infection, and many of these molecules have depicted preliminary efficacy against COVID-19 infection and these are currently being tested in some clinical trials.
- Clinicians globally should be encouraged to report their experiences related to cases and case series of COVID-19 infections they managed so that more lessons would be learnt about COVID-19 infections and the biological behavior of COVID19.

Conflict Of Interest

None

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