The value of some biochemical parameters in the prediction of kidneys severity in COVID-19 patients

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Abstract

Severe infection with the novel coronavirus (COVID-19) is currently associated with long hospital stay and high mortality; COVID-19 infection has pneumonia as one of its symptoms but can quickly progress to acute renal complication. It is, therefore, justifiable to determine the level of some potential biomarkers that could help in, early, rapid and effective identification of severe cases. Among the biomarkers that could aid in early diagnosis of mild and severe COVID-19 infections include the serum urea & creatinine levels, as well as serum conjugated bilirubin level. These serum biomarkers, especially serum urea and creatinine levels, reflect the glomerular filtration rate (GFR), which is a direct measure of kidneys function; hence, they could serve as early indicator renal complications during severe COVID-19 infection. Therefore, it is imperative to highlight the early monitoring of patients with AKI and carefully control kidney function during severe/acute coronavirus infection; impaired GFR should be monitored closely by clinicians in severe COVID-19 patients.

Keywords: *Covid-19, glomerular filtration rate, kidney biomarkers.*

قيمة بعض المتغيرات البيوكيميائية في توقع شدة الكلى في مرضى كوفيد -19

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الخلاصة

ترتبط الاصابات الشديدة بفيروس كورونا المستجد (COVID-19) بطول فترة الاقامة في المستشفى بالاضافة الى ارتفاع معدل الوفيات في المصابين. تعتبر عدوى (COVID-19)التهاب رئوي ولكن يمكن ان تتطور بسرعة الى مضاعفات كلوية حادة ؛ لذلك من المبرر تحديد مستوى بعض المؤشرات الحيوية المحتملة التي يمكن ان تساعد في التشخيص المبكر للعدوى الخفيفة والشديدة لمرضى الكلى والذين تم اصابتهم بمرض كورونا المستجد ويشمل مستويات اليوريا والكرياتنين في الدوالدم , كذلك مستوى البيلروبين المترافق في الدم. حيث يمكن أن تعكس تلك المؤشرات الحيوية مدى تأثير كوفيد المستجد على حالة مرضى الفشل الكلوي ومن بين تلك المؤشرات الحيوية هو معدل الترشيح الكبيبي (GFR) الذي يمثل مقياس مباشر لوظيفة الكلى ؛ وبالتالي ، يمكن أن تكون بمثابة مؤشر مبكر لمضاعفات كلوية أثناء الاصابة الشديدة بمرض كورونا المستجد . لذلك ، من الضروري تسليط الضوء على المراقبة المبكرة لمرضى القصور الكلوي الحاد والتحكم بعناية في وظائف الكلى أثناء الإصابة بفيروس كورونا الحاد. كما يجب مراقبة (GFR) عن كثب من قبل الاطباء الاختصاص للمصابين ب كوفيد-19 الحاد.

P-ISSN: 2664-0562
E-ISSN:2664-0554

الكلمات المفتاحية: فيروس كورونا المستجد-19 , معدل الترشيح الكبيبي .

Introduction

Coronavirus is an enveloped RNA virus that causes human respiratory infections, such as severe acute respiratory syndrome (SARS), and acute exacerbation of chronic bronchitis (AECB). SARS-CoV epidemic is one of the notable coronavirus-related human infection that caused great social panic in 2003 [1]. Currently, the world is battling with the containment of another novel coronavirus called SARS-CoV-2 which was first reported in Wuhan, China in 2019 [2]. SARS-CoV-2 is a novel human virus that can infect numerous host species [3], including young and old people. Data from three large case series suggests that adults infected with SARS-CoV-2 mostly present symptoms such as fever, myalgia, headache, cough, dyspnoea, sore throat, diarrhoea, rhinorrhoea, expectoration and pharyngalgia. Other symptoms such as dyspnoea, cyanosis, malaise, restlessness, bad appetite, poor feeding, and reduced activity also presents as the disease progresses [4,5]. Respiratory failure may also be encountered in most severe cases, especially in the younger patients, causing unresponsiveness to oxygen therapy, septic shock, metabolic acidosis, impaired renal function, and other health complications [6].

1.1. Renal anatomy

The kidneys are delicately located within the upper part of the abdominal cavity on either side of the vertebral column. The glomeruli are the filtration unit of the kidneys; they are embedded within the cortex beneath the fibrous tissue that encloses each kidney. The collecting ducts are housed in the medulla of the kidneys and the pelvis is a cavity in the upper part of the ureter through which waste products such as urine passes through. The ureter connects he kidneys and the urinary bladder which serves as a temporary reservoir for urine. There are almost 1 million nephrons per kidney; these are tube-like structures that converges into a larger bowel called the Bowman’s capsule. The other segments of the nephron are the glomerulus, proximal convoluted tubule (PCT), the loop of Henle, the distal convoluted tubule (DCT), and the collecting tubule [7]. The DCT empties into the collecting duct that carries urine from the renal cortex to the papilla. The distal end of the renal papilla is made of numerous collecting ducts that converge into the papillary duct that later empties into the calyx.

The kidneys help in regulating body processes (homeostasis) through blood filtration, acid balance regulation, water & electrolyte balance, blood hormone levels regulation, as well as waste products elimination. The health status of the kidneys is assessed through series of kidney function tests. Reliance on physical examination for evaluating kidney function is both imprecise and unreliable; hence, the plasma and urine levels of various biomarkers are evaluated for accurate

P-ISSN: 2664-0562
E-ISSN:2664-0554

kidney function assessment. Some of the biomarkers of interest for kidneys function assessment are the urine protein levels, glomerular filtration rate (GFR), electrolytes balance, and serum urea, creatinine, and uric acid levels [8]. CKD patients are evaluated mainly to establish the diagnosis, comorbid conditions, disease severity, kidney function-related complications, risk of CVD, and risk of kidney function loss [9].

1.2. Diagnosis & differential diagnosis

The diagnosis of COVID-19 infection requires assessment of its clinical symptoms following the guidelines provided by the WHO and USCDC for clinical and epidemiological identification of symptoms suggestive of COVID-19 infection [10, 11]. Radiological studies could also aid the diagnosis of pneumonia in virally-infected patients. Adult patients have been reported to commonly exhibit bilateral (75%) and multi lobe (71%) lung involvement [4,5]. Confirmation of COVID -19 infection is mainly dependent on extensive laboratory tests, such as RT-PCR on the throat swabs, stool, blood, and sputum samples collected from suspected patients. Laboratory findings suggestive of COVID -19 infection include leucocytosis / leucopenia, neutrophilia, lymphocytosis, thrombocytosis/ thromcytopenia, and anaemia. Hepatic findings that are suggestive of COVID-19 infection are elevated level of liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), high level of serum C-reactive protein level, high creatinine kinase activity, elevated lactate dehydrogenase, serum creatinine, and blood urea nitrogen levels. Regarding the infection index, the level of pro-calcitonin may be elevated as well [12].

1.3. Renal function test

Even though COVID-19 infection is mainly associated with acute respiratory failure and diffuse alveolar damage, it is important to explore the involvement of other body organs as well [13] as the virus may find its way into the blood after infecting the lungs, thereby localizing in the kidney and give rise to renal cells damage. Evidence suggests that COVID-19 RNA has been found in the plasma sample of about 15% COVID-19 patients via real-time polymerase-chain-reaction (RT-PCR) [4]. Furthermore, 6.7% of COVID-19 patients with SARS have been reported to develop acute kidney injury (AKI) and the mortality rate is about 91.7% in patients with AKI. As per the KDIGO criteria, AKI refers to a condition where the serum creatinine level has increased by 0.3 mg/dl within 48 h or when there is a 50% increase in serum creatinine level from the baseline within 7 days [15]. It is, therefore, necessary to investigate the route of kidney infection in SARS-CoV-2 patients [14]. The high rate of morbidity and mortality associated with COVID-19 infection, coupled with the presentation of a wide range of other non-respiratory symptoms, are suggestive of the involvement of other organs, such as the liver, kidneys, and GIT during active COVID-19 infection [16-18].

P-ISSN: 2664-0562
E-ISSN:2664-0554

Except a few cases of chronic dialysis complicated by COVID-19 [19 -21], most SARS patients do not show impaired kidneys function with elevated levels of plasma creatinine upon admission [21]. However, COVID-19 patients present inflammation related indicators such as increased interleukin-6, increased erythrocyte sedimentation rate (ESR), and increased C-reactive protein (CRP). The relationship between the biochemical/clinical features and disease severities in COVID-19 patients is yet to be fully understood [22].

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, baseline serum creatinine refers to the level of serum creatinine on admission while hypocalcemia is a serum calcium level < 2.2 mmol/L. Sepsis was defined as organ dysfunction (life-threatening) due to a poor host response to an infection; septic shock is a form of sepsis that is complicated by cellular/metabolic and circulatory dysfunction which is often associated with high mortality [24]. Acute respiratory distress syndrome (ARDS) is normally diagnosed following the Berlin definitions [25] while AKI is mainly defined based on the KDIGO guidelines [18]. The date of AKI onset refers to the earliest day of observing changes in serum creatinine level that meet the KDIGO criteria. The determination of the stage of AKI is based on the peak level of serum creatinine post-AKI detection; the stages are graded thus: 1.5 - 1.9 folds increase (stage 1), 2.0-2.9 folds increase (stage 2), and ≥ 3 folds increase (stage 3) [26].

2.1. Mechanism of renal involvement and AKI in COVID-19 infection

COVID-19 infection could have a range of impacts on the kidney, including AKI due to acute tubular necrosis caused by hydration, sepsis, storm syndrome, rhabdomyolysis, cytokine & hypoxia. With the establishment of the direct cytopathic effect of viruses on some renal cells, it is possible that viruses can directly invade renal tubular cells or the glomerulus. As per previous studies, coronavirus can enter cells via a mechanism mediated by the angiotensin-converting enzyme II receptors which are predominant in kidney cells. AKI is also a strong cause of COVID-19-related deaths and is considered an indicator for surviving COVID-19 infection. Overall, COVID-19 patients should be closely monitored in terms of controlling the risk factors associated with renal injury [27]. Renal disorder has been identified as a common observation in coronavirus patients [28, 29]. A study by Li et al [29] on the renal function in 59 COVID-19 patients reported that 63% of the patients had proteinuria while 19% of the patients showed elevated level of serum creatinine and 27% had high urea nitrogen level. Furthermore, CT scan of the kidneys of the 27 patients showed that all the patients presented evidence of inflammation and renal parenchyma edema [30].

A serial investigation of 710 COVID-19 patients in Wuhan, China showed that 44% of the patients had proteinuria while hematuria was found in 26.9% of the patients. Furthermore, 15.5 % of

P-ISSN: 2664-0562
E-ISSN:2664-0554

the patients showed high plasma creatinine levels while the blood urea nitrogen level was high in 14.1% of their subjects. The investigation also observed acute kidney injury in 3.2% of the sampled patients. It was also observed through Kaplan-Meier analysis-based survival curves that kidney failure accounts for the greater risk of hospital deaths. The Cox regression model identified AKI, hematuria, increased plasma creatinine, proteinuria, and increased urea nitrogen as the independent risk factors for COVID-19-related hospital deaths prediction [31]. Renal disturbances in COVID-19 infection was found to be caused by dehydration due to fever and reduced fluids in the aged patients. Dehydration impacts the kidneys in many negative manners, such as reducing the GFR and increasing the chances of AKI. Although mild volume depletion can be reversed with hydration, acute tubular necrosis may occur in severe volume depletion due to persistent ischemia. Other possible causes of renal impairment in COVID-19 infection are sepsis, cytokine storm syndrome, hypoxia, and rhabdomyolysis [31].

Furthermore, viruses can directly invade renal tubular cells, glomeruli, or interstitium as previous studies have already reported direct cytopathic effect of virus on renal cells [32, 33]. The invasion of renal cells, as per previous studies, is mediated by the ACE2 receptors which are predominant in renal cells and serves as a viral receptor. The level of ACE2 expression in renal cells and various parts of the GIT (such as the small intestine and duodenum) is almost 100 folds higher compared to its expression in the cells of the pulmonary tract. This finding explains the reason for the invasion of renal cells by COVID-19. Previous studies have reported low rate of coronavirus-induced glomerulopathy; however, there is possibility for virus-induced specific immunological abnormalities and immune complexes deposition of viral particles [29-34]. Renal failure could also result from complication with uncontrolled hypertension or diabetes, as well as use of non-steroidal anti-inflammatory drugs (NSAIDS) [33, 34].

2.2. Blood urea and plasma creatinine concentration

Acute renal impairment is a clinical finding of at least 30% increase in plasma creatinine level from the baseline value upon admission (based on the result of three consecutive blood analysis) or a plasma creatinine value of 160 µmol/L following a normal value upon admission [35]. COVID-19 patients have been shown to present serial median plasma creatinine levels that progresses to ARF within 20 days of viral infection (ranges from 5 to 48 days). The plasma creatinine level of patients that died from COVID-19 infection normally increases progressively, with a doubling time of 18.3 days upon admission. Contrarily, those that survived COVID-19 infection presents progressive decline in plasma creatinine level from the 10^{th} day post-admission [36-38]. Those that succumb early to the infection usually presents rapid increase in plasma creatinine level; those that survived

P-ISSN: 2664-0562
E-ISSN:2664-0554

show an average plasma creatinine value doubling time of < 15 days after admission. Patients with ARF that succumbed to COVID-19 within 15 days of admission had elevated plasma LDH and lower plasma albumin [37]. Blood urea nitrogen level is also mildly increased in COVID-19 patients (< 26 μmol/L within 48 h) and about 7.2% of those without CKD show trace or 1+ albuminuria [38].

3.1. COVID-19 and dialysis patients

Patients on haemodialysis (HD) are prone to several changes upon infection with COVID-19. However, patients with uraemia are more susceptible to the infection and may present greater changes in infectivity and clinical symptoms. Workers in HD centres (such as medical staff and facility staff, even the patients themselves and their relatives) are at a greater risk of infection transmission [38].

Although HD patients often present higher level of inflammatory cytokines in comparison to non-HD patients, COVID-19 patients on HD have been reported to present lower levels of serum inflammatory cytokines when compared to COVID-19 patients that are not on HD. Furthermore, COVID-19 patients on HD show lower frequency of lymphocytes in peripheral blood mononuclear cells than other COVID-19 patients [39]. Currently, the risk of SARS-CoV-2 infection transmission to HD patients and their families, medical staff, workers, and others is significantly high in HD centres [40].

Therefore, the Taiwan Society of Nephrology [41], the Chinese Society of Nephrology [42], and the Centres for Disease Control and Prevention [43] have published guidelines for HD centres for the COVID-19 pandemic. As the screening, isolation, prevention, protection, and distribution are basic principles in the reduction and containment of the COVID-19 in HD centres, the management of dialysis patients with COVID-19 must be conducted based on standard protocols [44].

3.2. COVID-19 and renal impairment

The incidence of early renal injury in COVID-19 patients demonstrated the presence of abnormalities in levels of estimated glomerular filtration rate (66.7%), creatinine clearance (41.7%), and increased microalbuminuria (41.7%), without significant abnormalities in blood urea nitrogen and plasma creatinine. They sound that the measurement of urine micro-albumin, urine immunoglobulin -G, urine transferrin, and α1-microglobulin could help in early diagnosis of renal impairment in COVID-19 patients [45]. Available data suggests that SARS-CoV-2 infection can have a direct cytotoxic effect on renal tubules and cause acute renal failure. Retrospective analysis of 85 patients with COVID-19 demonstrated that 27.06% of patients developed acute renal failure, especially in elder patients. Furthermore, kidney tissue examinations of post-mortem specimens confirmed lymphocyte infiltration, severe acute tubular necrosis, and accumulation of viral

P-ISSN: 2664-0562
E-ISSN:2664-0554

nucleocapsid protein antigen in kidney tubules [46]. The presence of SARS-CoV-2 virus particles in urine of COVID-19 patients might be due to penetration of viral particles through the glomerular barrier [47]. It is also reported that 51.67 % of COVID-19 patients with pneumonia had proteinuria since the severity of pneumonia is directly associated with levels of urine protein [48].

4. Conclusion

COVID-19 is a global health emergency; even though viruses are known to mainly target respiratory cells, the invasion of other organs (such as the kidneys) during active viral infection, may also be a possibility. The increased mortality and morbidity rates of COVID-19 infection can be substantially minimized by aiming at interventions that reduce potential harm to the kidneys, as well as by close monitoring of patients renal biomarkers (such as serum level of creatinine, proteinuria, blood urea nitrogen (BUN), and hematuria) owing to the greater risk of mortality in patients with elevated creatinine levels compared to patients with normal serum creatinine level.

The kidneys have been recently identified as one of the organs with high vulnerability to impairment during COVID-19 infection based on the high levels of some kidney biomarkers (such as urea, creatinine, & low level of Vit. D) during COVID-19 infection. Vitamin D deficiency could also cause hypocalcaemia and low PTH levels; this could explain why patients that exhibit low serum calcium levels ($\leq$2.0 mmol/L) normally present the worse clinical findings, such as having higher MODS incidence, greater risk to septic shock, as well as higher chance of 28^{th}-day mortality. COVID-19 patients with no organ complication have a mortality rate of 4.1% while those with organ complication have a mortality rate of up to 40.0%. Hence, early detection kidney impairment and proper intervention could save COVID-19 patients from death. Clinicians should be more considerate about renal injuries and should follow the protocols provided by the WHO.

P-ISSN: 2664-0562
E-ISSN:2664-0554

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P-ISSN: 2664-0562

E-ISSN:2664-0554