THE KIDNEY AND SKIN DUO IN SARS-COV-2/COVID-19

ABSTRACT
SARS-CoV-2 infection has spread to a huge number of countries. After viral exposure, 80% of the cases will behave as mild or asymptomatic, around 15% will require a hospital facility and 5% will require Intensive-Care-Unit (ICU) management and the use of mechanical ventilation. Although SARS-CoV-2 is not as lethal as other severe acute respiratory syndromes (SARS) viruses, it has caused more infections, deaths and economic impact than any other worldwide infectious disease. According to initial pandemic reports, acute kidney injury (AKI) has occurred in around 3-9% of COVID-19 patients, however, not only those numbers have increased up to 20-42% in critically-ill cases and in deceased people, but also, patients with renal involvement seem to have an increased risk of mortality. Similarly, cutaneous manifestations in COVID-19 have appeared in around 8-20% of patients and are also subtle at the beginning, but later on they can progress to more severe skin disease. Common COVID-19 pathogenic features seem to be shared by the kidney and the skin and such cutaneous manifestations might be an alert for the need of early kidney function monitoring in order to initiate supportive interventions that may protect such organ from severe renal dysfunction and end stage disease.

KEYWORDS
Skin; Kidney; Sars-CoV-2; COVID-19

INTRODUCTION
By December 12th 2020, SARS-CoV-2 infection has spread to 213 countries, 71,780,957 confirmed cases of infection have been reported, 1,607,304 deaths and 50,308,949 patients recovered. For this same date, of the 19,864,704 actively infected, 19,758,129 (99.5%) are found with mild symptoms and 106,575 (0.5%) in serious or critical condition (source: worldometers.info). After viral exposure, 80% of the cases will behave as mild or asymptomatic, around 15% will require a hospital facility and 5% will require Intensive-Care-Unit (ICU) management and the use of mechanical ventilation. The need for hospital-based healthcare in those patients with severe or critical illness is responsible for the collapse of the majority of health systems in the world.

Although SARS-CoV-2 is not as lethal as other severe acute respiratory syndromes (SARS) viruses, it has caused more infections, deaths and economic impact than any other worldwide infectious disease. The entry of SARS-CoV-2 viruses into host cells is mediated by a virus-surface spike protein that contains a receptor-binding-domain (RBD) that recognizes the angiotensin-converting enzyme 2 (ACE2) as its receptor. However, an important structural difference in the conformation of the loops in the ACE2-binding ridge between the RBMs of SARS-CoV-2 and SARS-CoV has been recently reported. Other coronavirus receptors involved in viral entry and known to be expressed by endothelial cells include sialic acid receptors (CD147 or basigin), transmembrane serine protease 2 (TMPRSS2) receptor, CD209L and extracellular matrix metalloproteinase inducer (CD147 or basigin), and cathepsin B and L. These virological features not only define particular virus-host interactions at the molecular level, but also contribute to its efficient transmission and to its wide spectrum of clinical presentations that range from asymptomatic to severe or even fatal cases.

According to initial pandemic reports, acute kidney injury (AKI) has occurred in around 3-9% of COVID-19 patients, however, not only those numbers have increased up to 20-42% in critically-ill cases and in deceased people, but also, patients with renal involvement seem to have an increased risk of mortality. Interestingly, mild renal abnormalities occur at the beginning of Sars-CoV2 infection but could last for many months. Up to now, pathological findings in COVID-19 have presented in around 8-20% of patients and are also subtle at the beginning, but later on they can progress to more severe skin disease. Common potential pathogenic features of kidney and skin manifestations in severe and critically-ill COVID-19 patients are: an excess of expression of the angiotensin II receptor, an elevation of pro-inflammatory cytokines, a vasotropism towards blood-vessels endothelial cells within both organs. Such abnormalities contribute to organ/tissue injury, vessel dysfunction and alterations in vascular permeability, a dysregulation of coagulation homeostasis, vasodilation, and endothelial dysfunction with potential development of disseminated intravascular coagulation (DIC). In fact, it seems that viral injured endothelial cells trigger the release of pro-inflammatory mediators and a cascade of events that occur during the coagulation process leading to the production of blood-vessels microthrombi that in turn cause organ/tissue ischemia. The resultant hypoxic state not only affects different organs but also contributes to injury in patients with advanced age or with underlying comorbidities causing a multi organ dysfunction which further increases the mortality risk of those population.

The Kidney in COVID-19
Previous studies have demonstrated that ACE2 is expressed in renal mesangial cells, podocytes, proximal cell brush border, the parietal epithelium of Bowman’s capsule, and the collecting ducts. COVID-19-related nephropathy seems to occur due to a higher expression of ACE2 that leads to urine abnormalities such as albuminuria, proteinuria, and haematuria in 60-65%, and 26-48% of patients, respectively. Haematuria and proteinuria usually present at the first day of hospital admission and can alert physicians for starting renal protective measures. In addition, blood-urea-nitrogen (BUN) seems to start to increase from day 0 to day 16 (Median 2 days), whereas plasma creatinine uric acid(UA) and D-Dimer start to increase at 0 to day 20 (median: 5 days), day 0 to day 20 (median: 7 days) and at day 0 to day 22, respectively. Interestingly, described renal dysfunctions in non-severe COVID-19 patients, have been reported to be mild and are not usually diagnosed as AKI, whereas in severe patients, AKI has been very frequent (66% of severe-ill patients). In fact, the mortality risk of COVID-19 patients with AKI was reported to be 5.3 times higher than those patients without AKI.

Once AKI occurs, it is usually accompanied not only by severe metabolic acidosis in severe Covid-19 infection, but also by mitochondrial dysfunction, acute tubular necrosis, collapsing glomerulopathy, and protein leakage in Bowman’s capsule. Such
The Skin in COVID-19

A high expression of ACE2/CD147, TMPRSS2-2, and CD26-related genes was found in the skin, however, it is not yet known if COVID-19-related skin manifestations are explained only by a reaction to the systemic infection or due to viral replication in keratinocytes, or both, as viral particles have been reported in the cutaneous blood vessels in patients with COVID-19 infection. Nevertheless, and in line with the presence of a cytokine storm, that affect the lungs, the heart, and the kidney, the spectrum of cutaneous manifestations of COVID-19, seem to be a resultant of an interplay of the humoral and cellular immune response, and possibly due to the formation of reactive oxygen species, the interference of vasodilatory signals, vascularity of small blood vessels, embolic occlusion of the vessels and/or due to complement activation. In this respect, papulopurulent or perifollicular lesions and viral exanthem like rashes have been suggested to be related with an initial cell mediated response. On the other hand, chicken pox like and zosteriform blisters might be secondary to viremia and a cytopathic effect in keratinocytes. In addition, livenoid and/or pseudo-chilblain lesions seem to be the resultant of small to medium vessel occlusion either due to hypoxia, microthrombi formation or immune complex deposition. Figures 1, 2A, 2B. In fact, pernio-like lesions have been reported to appear either concurrently with or after COVID-19 symptoms, and interestingly, in a very large worldwide registry, 174 out of 318 patients with suspected or confirmed COVID-19 more than half of the population (55%), presented only with pernio-like cutaneous lesions. In addition, and according to the results of a prospective nationwide consensus study in Spain that included 375 cases, 5 COVID-19 clinical cutaneous patterns have been seen: 1) Maculopapular eruptions in 47% patients; 2) Acral areas of erythema with vesicles or pustules (pseudo-chilblains) in 19% patients; 3) Acral areas of erythema with vesicular or pustular (pseudo-chilblain) lesions in 19% patients; 4) Virucular eruptions (9%); 5) Livedo reticularis (6%). Interestingly, maculopapular and vesicular eruptions seem to appear early in the course of the disease and chilblain-like lesions frequently appear late whereas the other patterns tend to develop in between the aforementioned skin manifestations.

Given these findings, skin manifestations in the COVID-19 pandemic can be an early sign of viral infection and could assist clinicians either to suspect or recognize the disease which could be particularly useful in asymptomatic patients. Also, as renal and skin lesions share some pathogenic and vessel dysfunction features, skin manifestations could alert for the need of early kidney function monitoring regardless of the presence of chronic comorbidities. In turn, supportive interventions at the early stage of COVID-19 illness could potentially protect the kidney from severe renal dysfunction and end stage disease.

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Conflicts Of Interests:
The authors have no conflict of interest to declare

Figure Legends:
Figure 1: Low power viewing highlighting dermal oedema, minimal perivascular inflammation and dilated thrombosed small blood vessels.
Figures 2 A & B. Higher magnification showing the thrombi (A) and highlighted by PAS (B)

REFERENCES
21. Post A, de Haam L, Bakker SJL et al. Kidney Infarction in Patients With COVID-19 symptoms , and interestingly, in a very large worldwide registry, 174 out of 318 patients with suspected or confirmed COVID-19 more than half of the population (55%), presented only with pernio-like cutaneous lesions. In addition, and according to the results of a prospective nationwide consensus study in Spain that included 375 cases, 5 COVID-19 clinical cutaneous patterns have been seen: 1) Maculopapular eruptions in 47% patients; 2) Acral areas of erythema with vesicles or pustules (pseudo-chilblains) in 19% patients; 3) Urticarial lesions (19%); 4) Vesicular eruptions (9%); 5) Livedo reticularis (6%). Interestingly, maculopapular and vesicular eruptions seem to appear early in the course of the disease and chilblain-like lesions frequently appear late whereas the other patterns tend to develop in between the aforementioned skin manifestations.

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