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# COVID-19 and lupus nephritis: Biomarkers

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**Abstract**
Background: Globally, coronavirus disease 2019 (Cov-19) has resulted in the confinement of nearly three billion people and its management considered the trend topic. Lupus nephritis (LN) is the most common and serious manifestation of systemic lupus erythematousus (SLE). Clinical picture of Cov-19 in LN patients is often complicated by bacterial infections or thrombotic events, unless the prognosis of lupus nephritis remains unsatisfactory. Conventional clinical parameters including creatinine clearance, proteinuria, urine sediments, anti-dsDNA and complement levels are not sensitive or specific enough for detecting ongoing Cov-19 infection activity in lupus kidneys and early relapse of nephritis. Thus, novel biomarkers are necessary to enhance diagnostic accuracy and sensitivity of renal disease, prognostic stratification, monitoring of treatment response and detection of early renal flares.

**Keywords:** lupus nephritis, COVID-19, biomarker

## Introduction

### Background

Since December 2019, COVID-19 has infected nearly five millions worldwide resulted in around 300 thousands` deaths. Lethality and deadly nature of this virus was initially underestimated [1]. It is now well established that outcomes of COVID-19 vary considerably among individuals with some populations at higher risk than the others. Therefore, individuals with systemic lupus Erythematosus (SLE) are a unique population with protective and predisposing factors to develop severe COVID-19 [2]. Fortunately, COVID-19 can be classified as asymptomatic, mild, moderate, severe or critical based on infection` severity that could require prolonged intubation have already been described, which are the determinant of intensive care unit (ICU) admission and have resulted in a consecutive risk of ICU saturation [3].

After several revisions of WHO classification of lupus nephritis aims to enhance the quality of communication among renal pathologists and clinical nephrologists regarding pathologic findings in lupus nephritis (LN) [4]. Commonly, frequent clinical manifestations were arthralgia, edema (61.1%) and skin rash. Where, Cov-19 associated LN might have aggravated anemia, where could believed that haematocrit less than 20% was a strong clinical predictor of poor prognosis [5].

Renal involvement is common in SLE and often determines the course of the disease. Nearly 70-80% of all cases of SLE have some clinical manifestation of lupus nephritis, mostly glomerulonephritis; [6]. WHO classifications were incorporates new information regarding behavior of specific types of lupus nephritis, standardizes definitions and encourages uniformity and reproducibility of reported pathological findings. Furthermore, it eliminates category I that includes normal glomeruli, clarifies status of class III, defines more precisely class IV, simplifies class V and proposes strict definition for class VI [7].

Clinically, viral-induced kidney injury can occur acutely or chronically as a consequence of both a direct impact on the infected cell, also from subsequent systemic and local responses of the innate and adaptive immune system [8]. Current review article topic could be related to the severity of the disease by an increase in the initial renal viral charge and/or severe systemic inflammation. Moreover, the exhaustive collection of basal serum creatinine of ICU patients could contribute to this higher incidence, providing a more realistic spectrum of COVID-19-associated renal injury [8].

Immune complexes formed by binding of autoantibodies to antigen are thought to be a major mediator of SLE. In particular, anti-double-stranded DNA (anti-dsDNA) antibodies are found in the sera of up to 70% of SLE patients, and their presence is 95% specific for SLE, [9] making them an important disease hallmark. Correlations between anti-ds DNA antibodies titers and SLE disease activity further suggest that these autoantibodies play a pathogenic role in SLE. Although current treatments for SLE have dramatically improved survival, a cure, or even long-term relief of symptoms, remain elusive for most patients [10].

Like all chronic disorders, B cells are considered to be overactive and defective regulation of B cell activation has been demonstrated in several animal models of SLE. Lupus nephritis, which correlates with anti-dsDNA titers, is one of the most common symptoms of SLE. Notably, treatment of SLE patients with drugs targeting B cells has achieved some success [10].

While Cov-19 infection, hypertension is associated with development of ESRD in lupus nephritis patients with a relative risk of 1.67, but there is no correlation between survival and hypertension at the time of diagnosis of lupus or at the time of incipient nephritic syndrome [12]. More and above, while others suggested that the presence of nephritic

syndrome at Cov-19 affection, thus, while time of initial biopsy was associated with increased probability of developing renal failure. However, the patients who had remission of the nephritic syndrome had significantly lower probability of renal failure or death than did the patients without remission, based on prior reports ensuring that at the onset of lupus nephritis was a poor prognostic sign [13].

Recently published clinical studies from various regions of the world have reported COVID-19 mortality rates between 0-33percent among the hospitalized patients [3]. None of the medications used to treat SLE/ lupus nephritis were associated with the severity of the COVID-19 infection. Hydroxychloroquine, which was earlier on used to treat COVID-19 had a higher frequency of pre-exposure use among those with mild to moderate disease [6]. Recently published data have consistently and convincingly concluded that there is no significant difference in standardized cumulative COVID-19 mortality between hydroxychloroquine users and nonusers.

According to published guidelines, the direct role of the virus is debated, whereas the cytokine storm and the hypoxic and thrombotic complications seem more important. The long-term outcome of the renal damage appears to be quite good. Long-term follow-up will allow us to say whether the renal damage is part of the long COVID [3].

Experimental evidence ensured that SARS-CoV-2 uses the receptor ACE2 for cell entry and podocytes express ACE2 [9]. Glomerular changes and nephritis like histology have been described in postmortem samples from patients with COVID-19. Other zoonoses, such as some hantaviruses cause nephrotic syndrome, which in turn induces cardiopulmonary syndrome. Complications of nephrotic syndrome are known to be similar to capillary leak syndrome and preventive therapies are available [12].

Moreover, possibility of a viral-specific acute tubular injury. SARS-CoV-2 (the virus causing COVID-19) penetrates the cells via two receptors [Angiotensin-converting enzyme 2 (ACE2) and Transmembrane protease, serine 2 (TMPRSS2)], [13]. While ACE2 is highly expressed in proximal tubular epithelial cells and in podocytes, TMPRSS2 is only detectable in the proximal tubule S3 segment. By infiltrating the renal tubular cell, SARS-CoV-2 might induce acute tubular injury. This could explain why 9 out of 26 autopsied patients in China with COVID-19-associated LN had primarily diffused proximal tubular injury with some frank necrosis and no glomerular injury. Severe acute tubular injury with interstitial nephritis (CD68 macrophage infiltration of the tubulointerstitial) [12-13]. Patients had less severe renal involvement and may not be representative of more severe patients. Pulmonary damages have been reported as an inflammatory pattern integrated into a cytokine storm syndrome. Between renal and pulmonary injuries might have several explanations, co-occurrence does not necessarily mean a common pathway. However, one is left to wonder if infection with SARS-CoV-2 might result in inflammation or direct viral injury of both organs. Renal biopsies in patients with severe COVID-19-associated LN might thus be considered and lead to specific anti-inflammatory therapies for interstitial nephritis predominant LN [13].

**Unmet Needs: Novel Biomarkers**

Current laboratory markers for lupus nephritis such as proteinuria, urine protein-to-creatinine ratio, creatinine clearance, anti-dsDNA and complement levels are unsatisfactory. They lack sensitivity and specificity for differentiating renal activity and damage in lupus nephritis. Significant kidney damage can occur before renal function is impaired and first detection by laboratory parameters. Persistent proteinuria may not necessarily indicate ongoing inflammation in the kidneys and may be contributed by pre-existing chronic lesions or recent damage in the kidneys during the course of the disease. Flares of nephritis can occur without any observable and recent increase in the degree of proteinuria.

Renal biopsy is the gold standard for providing information on the histological classes of lupus nephritis and the relative degree of activity and chronicity in the glomeruli. However, it is invasive and serial biopsies that are impractical in the monitoring of lupus nephritis. Thus, novel biomarkers that are able to discriminate lupus renal activity and its severity, predict renal flares, and monitor treatment response and disease progress are clearly necessary.

A biomarker refers to a biologic, biochemical, or molecular event that can be assayed qualitatively and quantitatively by laboratory techniques. The levels of biomarkers should correlate with disease pathogenesis or activity in different organ systems. An ideal biomarker for lupus nephritis should possess the following properties: a) good correlation with renal activity as reflected by the degree of proteinuria and urine sediments, b) sensitive to change so that it can be used for serial monitoring of disease activity in the kidneys and defining treatment response and clinical remission, c) ability to predict renal activity/flares before an obvious change in conventional clinical parameters occurs so that early treatment/preventive strategies can be considered, d) specific to nephritis among patients with SLE and e) specific to SLE for aiding early diagnosis of lupus nephritis.

In addition, a useful biomarker should be easy to assay, simple to interpret, and readily available in most laboratories with a reasonable cost. Hitherto, quite a number of serum and urine biomarkers have been studied in lupus nephritis. Most of these markers have only been tested in cross-sectional studies and only a few have been evaluated in longitudinal studies. The number of patients having been tested is relatively small and the results have not been confirmed by independent groups of investigators. Even for biomarkers that have been prospectively evaluated, further validation has to be performed in larger groups of patients with lupus nephritis.

In this paper, biomarkers that have been recently studied in lupus nephritis are systematically reviewed. Information is grouped under three subheadings; a) biomarkers that correlate with SLE renal activity in longitudinal studies, b) biomarkers that correlate with lupus nephritis activity in cross-sectional studies and c) biomarkers that correlate with renal histology or prognosis of lupus nephritis.

**Biomarkers correlate with LN Prognosis**

Chemokines. Monocyte chemoattractant protein-1 (MCP-1) is a leukocyte chemotactic factor that is involved in mediating inflammation and injury in lupus nephritis. In human lupus nephritis, increased expression of MCP-1 on endothelial cells, renal epithelial cells, and infiltrating mononuclear cells in the tubulointerstitial regions can be demonstrated by immunohistochemical staining and in situ hybridization [14].

Level of MCP-1 in urine is increased in patients with a variety of glomerulonephritis and correlates with the extent of proteinuria and the severity of glomerular lesions. Recent cross-sectional studies have confirmed that levels of urine MCP-1 are elevated in patients with active lupus nephritis compared to those with inactive renal disease or healthy controls [15].

Neutrophil Gelatinase-Associated Lipocalin (NGAL). Lipocalin-2 is a small glycosylated protein produced in many tissues and organs. Lipocalin-2 was first described in human neutrophil granules as neutrophil gelatinaseassociated lipocalin (NGAL). NGAL belongs to a family of carrier proteins that are important for cellular iron transport, apoptosis, bacteriostasis, and tissue differentiation. NGAL is constitutively expressed at low levels in the kidneys, but upregulated following acute renal injury and various insults such as inflammation, ischemia and infection [16].

Urine NGAL level was a significant predictor of renal disease activity in SLE patients and a significant predictor for flares in patients with a history of biopsy-proven nephritis. The specificity and sensitivity of urine NGAL level in predicting renal flares was higher than that of anti-dsDNA titer [17].

Tumor Necrosis Factor-Like Inducer of Apoptosis (TWEAK). Tumor necrosis factor- (TNF-) like inducer of apoptosis (TWEAK) is a multifunctional cytokine that belongs to the TNF-ligand superfamily. The main source of soluble TWEAK is believed to be the macrophages. TWEAK binds to its cognate receptor, Fn14, in various tissues and mediates a number of physiological processes such as cellular proliferation, survival, differentiation, migration, and angiogenesis. TWEAK/Fn14 interaction has also been found to be involved in upregulation of proinflammatory mediators and induction of cell death and apoptosis (weak effect). While TWEAK expression is low in normal tissues, it is dramatically increased in the context of inflammation and injury. Thus, it is thought that TWEAK is important in the physiological processes of tissue repair and regeneration but its expression is dysregulated in chronic inflammatory states [18].

Overall, although uTWEAK is a promising biomarker for lupus nephritis because of its high specificity for lupus renal disease and good correlation with renal disease activity, it may not be sensitive enough to predict a renal flare early and cannot replace the need for a renal biopsy [19].

**Urine Proteomics:** Hepcidin is a low-molecular-weight peptide hormone mainly produced by the liver. Hepcidin has antimicrobial activity, regulates iron metabolism, and is thought to be involved in the pathogenesis of anemia of chronic illness including chronic kidney disease. Urinary excretion of hepcidin is greatly enhanced in patients with iron overload, infections or inflammatory diseases [20].

**Autoantibodies:** Anti-C1q Antibodies. C1q is the first component of the classical pathway of the complement system. C1q plays a crucial role in the clearance of immune complexes and apoptotic bodies. Both humans and mice with C1q deficiency are at risk of developing lupus-like syndromes and immunemediated glomerulonephritis because of defective clearance of apoptotic cells, autoantigens and immune complexes. Although an elevation of anti-C1q titer is shown to predict the development of lupus nephritis or renal flares in these studies, its performance is not significantly better than that of anti-dsDNA and complement levels. The high negative predictive value of anti-C1q for severe renal disease may be helpful for prognostic stratification of SLE patients. The usefulness of anti-C1q level in monitoring of lupus activity in patients with negative anti-dsDNA antibodies has to be further explored [15].

Antinucleosome Antibodies. Nucleosomes released by apoptotic cells are major T and B cell autoantigens in SLE. Nucleosomes may act as bridging molecules that recognize heparin sulphate/collagen components of the glomerular basement membrane for the binding of antinucleosome and other nephritogenic antibodies [22].

Although newer autoantibodies are available and useful for the monitoring of lupus nephritis activity, they are generally not more sensitive than conventional markers such as anti-dsDNA and complements in predicting renal flares.The usefulness of these autoantibodies in the monitoring of disease activity in subsets of SLE patients in whom conventional markers are negative has yet to be studied. The performance of a panel of conventional and novel autoantibodies in the diagnosis, monitoring, and prognostic stratification of lupus nephritis has to be evaluated in the future [23].

Physicians aware of the likely existence of a frequent, severe and specific COVID-19-associated LN, also a tubulointerstitial injury without glycosuria. Further work should be carried out promptly in order to identify and assess specific therapeutic options.

## Conclusion

Among all admitted patients, early detection of COVID-19-associated nephritis and to assess risk of respiratory decompensation by capillary leak syndrome, plus could advice carefully monitored for pulmonary interstitial oedema due to severe fluid overload similar to nephrotic syndrome; immune incompetence due to renal loss of immunoglobulins; circulatory insufficiency due to hypalbuminaemia; poor drug response because of impaired plasma protein binding and thromboembolic events due to antithrombin deficiency.

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## Conflict of Interest

The authors declare no conflicts of interest. None of the authors has any other financial or personal relationships could inappropriately influence or bias content of current article.

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