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# INVESTIGATION OF POTENTIAL ETIOLOGICAL CONTRIBUTORS TO PATHOMORPHOLOGICAL ASPECTS OF RENAL DAMAGE IN COVID-19 PATIENTS: A CROSS-SECTIONAL STUDY.

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## ABSTRACT

### Background:
The COVID-19 pandemic extends beyond respiratory issues. It impacts various organs, including the kidneys, leading to complications such as acute kidney injury.
*Objectives:* This study aimed to examine the histological characteristics of kidney damage among individuals who succumbed to COVID-19 and to elucidate underlying factors contributing to renal pathology in individuals with COVID-19.

### Methods:
Utilizing a cross-sectional design, data were extracted from the medical records of 301 patients at Darbhanga Medical College and Hospital in Bihar, India. The primary focus was on individuals concurrently afflicted with SARS-CoV-2 infection and various kidney conditions, encompassing acute kidney injury (AKI), chronic kidney disease (CKD), nephritic syndrome, nephrotic syndrome, etc. Diverse data elements, including demographics, clinical outcomes, treatment durations, diagnoses, and laboratory test results, were collected.

### Results:
Key findings from this investigation revealed a positive correlation between elevated creatinine levels and older age, as well as an association between higher initial creatinine levels and shorter treatment duration. Notably, patients who did not survive exhibited significantly higher initial creatinine levels compared to discharged patients. Patients diagnosed with COVID-19 and AKI experienced an extended hospital stay compared to those without AKI. Moreover, individuals with AKI complicating CKD experienced a significantly extended hospitalization period compared to those without AKI. Importantly, individuals with AKI faced a substantially higher risk of mortality compared to subjects who were diagnosed with CKD only. Furthermore, individuals suffering from AKI had a considerably elevated risk of mortality when compared to individuals without CKD or AKI.

### Conclusion:
This study highlights its impact on clinical outcomes, the importance of early creatinine measurement, and the risk associated with advanced age and AKI complications.

### Recommendation:
Consider closely monitoring elderly individuals with COVID-19, as advanced age is identified as a significant risk factor for the development of AKI as a complication of CKD.

***Keywords:*** *Kidney diseases, COVID-19, Acute kidney injury, Chronic kidney disease, Hemodialysis*
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## INTRODUCTION

The COVID-19 has posed an unprecedented global health challenge. While primarily characterized as a respiratory illness, it has become increasingly clear that this disease's impact extends beyond the lungs. In addition to respiratory symptoms, the virus has been linked to a wide range of extrapulmonary complications, including cardiovascular issues, neurological symptoms, and renal dysfunction.[1]
The kidneys, essential for maintaining homeostasis in the human body, are vulnerable to various diseases and insults, including viral infections. Emerging clinical and pathological data have indicated a heightened incidence of AKI and kidney dysfunction in COVID-19 patients. Several studies have provided valuable insights into the pathomorphological changes observed in the kidneys of COVID-19 patients.[1-3]
Histopathological analyses of kidney tissue from COVID-19 patients have revealed a spectrum of renal lesions. A study performed by Su et al.[1] demonstrated that acute tubular injury, characterized by tubular dilation, epithelial cell necrosis, and cast formation, was a predominant feature in these patients' kidney biopsies. In addition, the authors noted the presence of viral particles within the renal tubules, suggesting that the virus may directly affect renal cells. The study by Diao et al.[2] corroborated these findings, emphasizing the role of endothelial injury and microvascular thrombosis in the renal pathology of COVID-19 patients.
While the presence of viral particles in renal tissue has been documented, it remains a topic of debate whether direct viral invasion is the primary cause of kidney damage.
Recent research has highlighted the potential role of immune-mediated mechanisms in renal injury during COVID-19.[3] In their study, Wu et al.[4] observed a pronounced lymphocytic infiltrate in the renal interstitium, indicative of an immune response. This suggests that the immune system's reaction to the virus may contribute to kidney damage. Furthermore, the release of proinflammatory cytokines, commonly referred to as the "cytokine storm," may exacerbate renal pathology, as documented in the work of Mehta et al.[5]
In addition to the immune response, there is growing evidence that COVID-19-associated coagulopathy and endothelial dysfunction play crucial roles in kidney injury.[5] The endothelial damage observed in COVID-19 patients may lead to microthrombi formation, impairing renal blood flow and function. Ackermann et al.[6] provided a

comprehensive histological analysis of COVID-19 autopsies, identifying severe endothelial injury throughout various organs, including the kidneys. This underscores the systemic nature of endothelial dysfunction in COVID-19 and its potential contribution to renal pathomorphology.

Hypoxia, often associated with severe COVID-19 cases, may also be a contributing factor in kidney injury. It is a key regulator of the body's response to low oxygen levels, can influence kidney function and inflammation. Recent work by Perico et al.[7] suggests that hypoxia-inducible factor stabilization may be involved in the evolution of AKI in patients with COVID-19.

In the subsequent sections, we will delve deeper into each of these etiological factors, exploring their interplay and potential therapeutic implications, offering a holistic perspective on the pathomorphology of kidney damage in COVID-19. In this context, we conducted a study with an aim to examine the histological characteristics of damaged kidneys in patients who died from COVID-19, and to identify the underlying factors responsible for renal pathology in patients with COVID-19.

## METHODOLOGY

### Study design, setting and population

This cross-sectional study was conducted at Darbhanga Medical College and Hospital, located in Bihar, India. The study setting involved a detailed explanation, encompassing the location, infrastructure, and facilities of the hospital. Data collection occurred over specific dates, and follow-up was conducted to ensure a comprehensive analysis of the study outcomes. The dataset comprised a total of 301 patients whose medical records were scrutinized as part of this investigation.

### Study Size

The research initially enrolled a cohort of 450 participants who underwent eligibility assessment. Eligibility criteria included being at least 18 years old, confirmation of SARS-CoV-2 infection through molecular testing, and a diagnosis of kidney diseases such as AKI, CKD, nephritic syndrome, nephrotic syndrome, glomerulonephritis, or other conditions related to impaired renal tubule function, including individuals who had undergone kidney transplantation. From this initial pool, 310 individuals were identified as potentially eligible, and following confirmation, 301 participants ultimately participated in the study.

### Inclusion Criteria

Individuals aged 18 or older, verified to be infected with SARS-CoV-2 through a molecular test, and experiencing kidney-related conditions such as AKI, CKD, nephritic syndrome, nephrotic syndrome, glomerulonephritis, other alterations associated with impaired renal tubular function, or individuals who have undergone kidney transplantation.

### Exclusion criteria

Various data elements were extracted, encompassing demographic information, clinical outcomes, treatment duration, diagnoses, and laboratory test results.

### Data Collection

Serum samples were used to assess biochemical parameters such as creatinine, urea, and C-reactive protein, while potassium levels were measured in plasma samples using readily available biochemical kits. The testing procedures adhered to the manufacturer's instructions. Notably, all patient data underwent anonymization to safeguard their privacy and confidentiality.

### Variables

The collected data underwent statistical analysis using the R Commander software package. To assess the distribution of quantitative variables, the Kolmogorov–Smirnov test was employed. Correlation between variables was examined using Spearman, Kendall, and Pearson tests. Comparison of means for similar variables utilized Student's t-test, while the Mann–Whitney test was applied for unequal variables. Qualitative variables (categorical variables) were scrutinized using the chi-square test, and for the analysis of multiple estimates for categorical variables, ANOVA was employed.

### Bias:

To address potential bias, various statistical tests were employed, including the Kolmogorov–Smirnov test for distribution analysis, Spearman, Kendall, and Pearson tests for correlation analysis, and the chi-square test for categorical variable analysis. These tests were chosen based on the nature of the data and variables, ensuring a comprehensive and unbiased analysis.

### Statistical methods

Regarding the application of statistical methods, the analysis was executed employing the R Commander software package. A range of statistical tests were employed for specific purposes:

1. Distribution Analysis: To understand the distribution of quantitative variables, a Kolmogorov-Smirnov test was employed. This test is instrumental in assessing whether the data follows a normal distribution, a pivotal aspect in the selection of appropriate statistical methods.
2. Correlation Analysis: To investigate relationships and correlations between variables, Spearman, Kendall, and Pearson tests were utilized. These tests provided insights into the associations among various factors.
3. Comparison of Averages: In order to compare means of similar variables, the study employed the student's t-test. For unequal variables, the "Mann-Whitney test" was applied. These tests were instrumental in identifying significant differences among groups or conditions.
4. Categorical Variable Analysis: Qualitative variables (categorical variables) were scrutinized using the chi-square test. This test played a crucial role in exploring associations between categorical variables and assessing the significance of these associations.
5. Multiple Estimates for Categorical Variables: To assess differences in multiple estimates of categorical variables, the analysis of variance (ANOVA) was employed. This method is essential for comprehending variations within and between different categories.
6. A significance level (α) was predefined at 0.05. Consequently, differences between indicators were deemed statistically significant if the p-value resulting from the statistical tests was less than 0.05.

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## RESULTS

The study recruited a total of 450 participants, subject to eligibility assessment, meeting the following criteria: being at least 18 years old, having a confirmed SARS-CoV-2 infection through molecular testing, and being diagnosed with kidney diseases such as AKI, CKD, nephritic syndrome, nephrotic syndrome, glomerulonephritis, or other conditions related to impaired renal tubule function, including individuals who had undergone kidney transplantation. Among them, 310 were identified as potentially eligible, and after confirmation, 301 participants ultimately participated in the study.

In addition to the observed correlations, the study also examined various characteristics of the participants, including demographics, clinical outcomes, treatment durations, diagnosis, and laboratory test results. These characteristics provided a comprehensive overview of the study population.

A positive correlation was observed between higher creatinine concentration and older age. Additionally, it was noted that a short-term treatment duration correlated with elevated creatinine levels on the initial day of hospitalization. Significantly elevated 1st day creatinine levels were observed among patients who did not survive their hospitalization (92.50 ± 96.87 vs. 155.585 µmol/L). Subjects with a diagnosis of AKI during their COVID-19 course experienced a considerably prolonged hospitalization period (11.79 ± 12.76 days) compared to the patients without AKI (8.25 ± 9.13 days) (Figure 1).

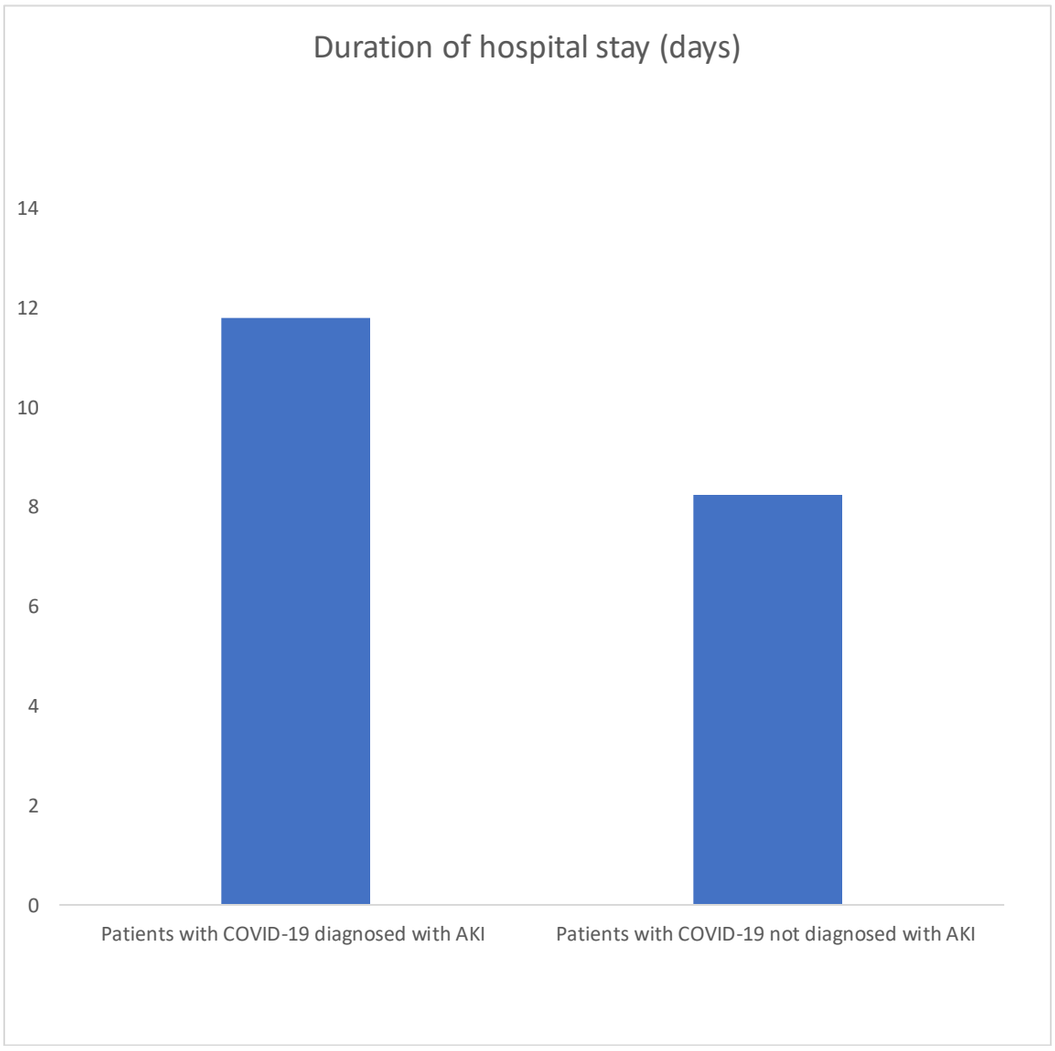

*Figure 1: Evaluating hospitalization duration in patients with COVID-19 diagnosed with and without AKI*

Significantly prolonged hospitalization was observed in patients with CKD complicated by AKI in comparison to individuals without AKI (16.84±14.62 vs. 9.62±16.42 days, $p < 0.001$). Additionally, in comparison to the subjects with CKD alone, patients with AKI exhibited a 7.81 times higher likelihood of mortality (95% CI 2.59; 5.89, $p < 0.001$).
Furthermore, individuals had a 7.81-fold increased risk of mortality compared to those with CKD alone, as shown in Table 1. This underscores the substantially elevated mortality risk associated with AK



| | **Outcomes** | | **95% CI** | **p-Value** |
|---|---|---|---|---|
| | **Death** | **Survival** | | |
| **CKD complicated by AKI** | 12 | 16 | 0.98; 3.42 | < 0.001 |
| **CKD without AKI** | 21 | 93 | | |
| **Only AKI** | 93 | 53 | 2.59; 5.89 | < 0.001 |
| **Only CKD** | 21 | 94 | | |
| **Only AKI** | 93 | 53 | 1.43; 10.59 | < 0.001 |
| **No CKD or AKI** | 3 | 11 | | |

**Table 1: Impact of kidney disease on patient outcomes**

The hospitalization duration significantly exceeded in patients receiving hemodialysis (HD) compared to those without HD treatment (15.17 ± 14.52 vs. 8.55 ± 9.63 days, $p < 0.001$). In the subgroup of AKI patients, those undergoing HD had a more extended hospital stay than CKD patients receiving HD (16.24 ± 14.1 vs. 11.00 ± 12.47days, $p = 0.022$). However, patients with CKD complicated by AKI experienced a shorter hospitalization duration (25.30 ± 16.76 days, $p = 0.010$), as detailed in Table 2.

**Table 2: Duration of treatment in patients with AKI and CKD treated with HD and without HD**

| | **Duration of hospital stay (days)** | **p-Value** |
|---|---|---|
| **Overall patients treated with HD** | 15.17 ± 14.5 | <0.001 |
| **Overall patients treated without HD** | 8.55 ± 9.63 | 0.022 |
| **AKI patients treated with HD** | 16.24 ± 14.1 | 0.010 |
| **CKD patients treated with HD** | 11.00 ± 12.47 | <0.001 |
| **Patients with CKD complicated by AKI** | 25.30 ± 16.76 | |

Patients with CKD, undergoing HD had significantly less duration of treatment than patients with CKD than for those with CKD complicated by AKI, as reflected in Table 2 (11.00 ± 12.42 vs. 25.30 ± 16.76 days, $p < 0.001$).

Out of the total patient population, 26.3% received HD treatment, and their hospitalization duration was nearly double that of patients who did not undergo HD treatment (15.17 ± 14.5 vs. 8.55 ± 9.63 days). The utilization of HD was 0.77 times more prevalent in CKD patients in comparison to individuals with AKI (95% CI (0.52; 1.015).

## DISCUSSION

The histological assessment of kidney damage consistently reveals a common pattern across various pathological processes. This pattern is characterized by several key features, notably damage to the renal tubular apparatus, which can manifest in various varieties and categories of dystrophic alterations, encompassing protein, lipid, and vacuole-related modifications. In many instances, it also involves the necrosis of the epithelium in the cortical segment of the nephron.[8-11]

Most commonly, these histological alterations are identified within the renal proximal tubules, including the coiled and linear subtypes. Remarkably, this histological pattern remains relatively consistent, irrespective of the underlying cause of damage, except for cases of direct trauma. This pattern is consistently observed in various conditions, including those involving direct toxic harm, immune-related damage (including autoimmune reactions and toxic-allergic responses), ischemia, systemic conditions such as acute respiratory distress syndrome, systemic inflammatory response syndrome, disseminated intravascular coagulation, multiple organ failure syndrome, and even cases involving direct viral damage to renal cells. Strikingly, throughout these diverse aetiologies, the glomerular apparatus of the kidneys remains largely unaffected. [8-11]

Turning to the context of COVID-19, a detailed examination of kidney micrographs reveals distinct features. The primary pathological alterations observed in kidney cells entail vacuole degeneration, cell swelling, presence of SARS-CoV-2 viral inclusion bodies in renal tubular epithelial cells and their detachment.[12,13] Furthermore, the virus can induce tubule damage through the action of the membrane attack complex. The epithelial cells appear non-nucleated and are often seen as small or granular clusters, yet they retain their cellular structure.[14,15]

In the case of COVID-19-related kidney damage, a notable departure from the norm is observed. Unlike other aetiologies, COVID-19-related kidney damage affects both the tubular and glomerular apparatuses. Kidney cortical changes in COVID-19 are characterized by venous congestion. The most pronounced alterations occur in the proximal and, to a lesser extent, distal convoluted tubules, marked by expansion and focal necrosis of the tubular epithelium.[10-12]

Furthermore, patients who died from COVID-19 display distinctive features in their acute renal tubular injuries, particularly the formation of granular casts within the proximal tubules. Notably, these granular casts are rarely found in the linear tubules, including loops of Henle within the kidney's medulla. These histological changes are further highlighted by the significant expansion and deformation of renal glomerular cavities containing deteriorating glomerular epithelial cells.[9-12]

Notably, in a study conducted by Yin and Zhang[16], renal histopathological samples from individuals with COVID-19 revealed that the most prevalent observation was the disruption of malpighian tuft capillaries, accompanied by the hyperplasia of glomerular epithelial cells and the presence of abundant "eosinophilic intracytoplasmic protein" aggregates. This strongly suggests that the SARS-CoV-2 virus has a direct impact on and causes damage to nephrons. SARS-CoV-2 has the potential to trigger a cytokine storm, characterized by heightened levels of inflammatory factors and "granulocyte colony-stimulating factor", resulting in ischemia, hypoxia, fibrosis, rhabdomyolysis, intrarenal inflammation etc.

In accordance, a study done by Chan L. and colleagues[17,18] revealed a significant association between AKI and elevated mortality rates among patients with COVID-19. Furthermore, it was noted that patients at more advanced stages of AKI experienced poorer survival outcomes.[17,18] Another study by Sindhu et al.[19] found that among patients who developed AKI, 29.5% required intensive care unit (ICU) treatment, and 22.6% needed mechanical ventilation. The study also reported an overall mortality rate of 22.1% for patients with AKI, which significantly rose to 74.5% for those who required ICU care. Importantly, findings of the study highlighted that advanced age, the presence of stage 3 AKI, and the necessity for mechanical ventilation were factors associated with increased mortality among patients with AKI.[19] In contrast, our study revealed significantly prolonged hospitalization in patients with CKD complicated by AKI compared to individuals without AKI (16.84±14.62 vs. 9.62±16.42 days, $p < 0.001$). Additionally, when compared to subjects with CKD alone, patients with AKI exhibited a 7.81 times higher likelihood of mortality (95% CI 2.59; 5.89, $p < 0.001$).

Furthermore, our study emphasized that the duration of hospitalization significantly exceeded in patients receiving HD compared to those without HD treatment (15.17 ± 14.52 vs. 8.55 ± 9.63 days, $p < 0.001$). Within the subgroup of patients with AKI, those undergoing HD had a more extended hospital stay than CKD patients receiving HD (16.24 ± 14.1 vs. 11.00 ± 12.47 days, $p = 0.022$).

## CONCLUSION

Kidney damage in COVID-19 is an emerging and complex clinical challenge. The pathomorphology of renal injury in COVID-19 patients involves a combination of direct viral effects, immune-mediated responses, endothelial dysfunction, and hypoxia. Understanding the etiological factors underlying this complication is crucial for developing effective therapeutic strategies. The study underscores the significance of assessing creatinine concentrations on the initial day of admission to the hospital, as it aids in predicting hospital stay length and the likelihood of mortality.

This study further establishes that advanced age is a significant risk factor for the development of AKI as a complication of CKD in individuals suffering from COVID-19, and it is associated with prolonged hospitalization. Notably, patients who experience AKI and those with CKD complicated by AKI face more risk of extended hospitalization and a high risk of mortality. Importantly, gender differences did not appear to influence these outcomes.

## LIMITATIONS

The study is constrained by a limited sample size, which may impact the generalizability of its findings to a larger population. Consequently, the applicability of these findings to broader populations or real-world scenarios may be restricted.

## RECOMMENDATION

Consider closely monitoring elderly individuals with COVID-19, as advanced age is identified as a significant risk factor for the development of AKI as a complication of CKD.

## List of abbreviations

AKI- Acute kidney injury
CKD- Chronic kidney disease
ANOVA- Analysis of variance
HD- Hemodialysis
ICU- Intensive care unit

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