

## Correlation between Acute Kidney Injury and Inflammatory markers in Coronavirus Disease 2019

Muhammad Anees<sup>1</sup>, Muhammad Raza<sup>2</sup>, Omair Farooq<sup>2</sup>, Asim Mumtaz<sup>3</sup>

<sup>1</sup> Department of Nephrology, Farooq Hospital, Westwood Branch, Lahore, Pakistan

<sup>2</sup> Department of Medicine, Farooq Hospital, Westwood Branch, Lahore, Pakistan

<sup>3</sup> Department of Pathology, Farooq Hospital, Westwood Branch, Lahore, Pakistan

### Abstract:

**Background and Objectives:** Coronavirus Disease 2019 (COVID-19) particularly when severe may commonly present with Acute Kidney Injury and may show elevated blood levels of inflammatory markers. Current study aims at determining the correlation between AKI and raised inflammatory markers in COVID-19.

**Materials and Methods:** Medical records of 250 patients admitted in COVID-19 isolation intensive care unit of Farooq Hospital, Westwood Branch, Lahore between 1<sup>st</sup> July 2021 and 30<sup>th</sup> September 2021 were retrospectively reviewed and data comprising of demographic, clinical and laboratory parameters was collected. Patients with confirmed diagnosis of COVID-19 from Real Time Polymerase Chain Reaction (RT-PCR) were included in the study while those with incomplete medical records or known history of chronic kidney disease (CKD) were excluded. Statistical analysis of collected data was then made and  $p$  value  $< 0.05$  was considered statistically significant.

**Results:** Among 176 patients who fulfilled the inclusion criteria, most  $n=138$  (78.4%) were males with mean age of  $51.26 \pm 15.20$  years. Diabetes Mellitus was most common comorbidity observed in 70 (39.8%) patients and mean length of hospital stay was  $8.46 \pm 4.12$  days. AKI was found in 91 (51.7%) patients. All four inflammatory markers: C-Reactive Protein (CRP), D-dimers, ferritin and procalcitonin (PCT) were found significantly raised in COVID-19 patients having AKI ( $p < 0.05$ ).

**Conclusions:** Raised inflammatory markers in patients having severe COVID-19 are associated with increased risk of AKI.

**Keywords:** COVID-19, AKI, Inflammatory markers, CRP, Ferritin, D-dimers, Procalcitonin.

### Corresponding Author:

Professor Muhammad Anees  
Consultant Nephrologist  
Farooq Hospital, West Wood Branch,  
Lahore, Pakistan  
Email: [dranees109@hotmail.com](mailto:dranees109@hotmail.com)

DOI: 10.53778/pjkd61190

Received: 08 February, 2022

PJKD 2022;6(1):6-12

### Introduction:

The world has been facing recurrent outbreaks of Coronavirus Disease 2019 (COVID-19) since December 2019 affecting 305 million people and causing 5.5 million deaths globally.<sup>1</sup> The total number of COVID-19 cases in Pakistan have now crossed 1.3 million with fatalities reaching up to 29000.<sup>2</sup> COVID-19 is a multi-systemic disease caused by Severe Acute Respiratory Syndrome Coronavirus type-2 (SARS-CoV-2) that primarily affects lungs but other organs particularly kidneys may be secondarily involved.<sup>3</sup> Renal manifestations of COVID-19 can be in form of proteinuria, hematuria, glomerulonephritis but Acute Kidney Injury (AKI) is also quite common.<sup>4</sup> Renal insult

in COVID-19 can be from hypoxia, ischemia, sepsis or drugs and is more likely to occur when the disease is severe and complicated.<sup>4</sup> Elevated blood levels of inflammatory markers like C-Reactive Protein (CRP), D-dimers, ferritin, procalcitonin (PCT) and interleukin-6 (IL-6) in COVID-19 may indicate severe disease thus putting patients at high risk of developing AKI.<sup>5</sup> The mechanism probably involved is hyper-inflammatory response to massive SARS-COV-2 invasion resulting in to severe renal tubular injury.<sup>6</sup> As AKI is preventable, a comprehensive understanding of association between these raised inflammatory markers and risk of AKI development can be helpful in preventing AKI in these patients and may also improve their overall management. Till now, limited data regarding this aspect of COVID-19 is available both locally and internationally. Current study aims at determining the correlation between risk of developing AKI and raised inflammatory markers in COVID-19 patients.

### Materials and Methods:

The study was conducted at COVID-19 isolation intensive care unit of Farooq Hospital Westwood Branch Lahore from October 1<sup>st</sup>, 2020, to December 31<sup>st</sup>, 2020. Medical records of 250 patients admitted there during specified period were retrospectively reviewed. All patients with confirmed diagnosis of COVID-19 from Real Time Polymerase Chain Reaction (RT-PCR) through nasopharyngeal swab were included in the study while those with incomplete medical records or known history of chronic kidney disease (CKD) were excluded from the study. The data comprising of demographics (age and gender), clinical (comorbidities, length of hospital stay, symptoms and vital signs at presentation) and laboratory (hematological and biochemical) parameters was extracted from medical records and collected. Among the biochemical laboratory parameters, in addition to serum urea and creatinine, four known inflammatory markers being CRP, D-dimers, ferritin and PCT were specially considered and classified as normal or high level according to the standard cut limits: CRP: 10 mg/L, D-dimers: 0.5 mcg/ml, ferritin: 300 ng/ml and PCT: 0.25 ng/ml. AKI was defined as a change  $\geq 0.3$  mg/dl in serum creatinine concentration from its baseline value throughout the length of hospital stay. Baseline creatinine value was defined as lowest observed serum creatinine concentration during the entire hospital stay. Based upon the definition of AKI, included patients were classified into two groups: AKI and non-AKI.

### Statistical analysis:

Statistical analysis of collected data was made using SPSS V-23 and Medcalc software. Mean and standard deviation from mean for continuous variables while frequencies for categorical variables were calculated. Univariate analysis using independent sample student's *t* test and multivariate analysis using backward logistic regression were also carried out. Relative risk (RR) and Odds ratio (OR) for categorical variables were also calculated. A *p* value of  $\leq 0.05$  was considered of statistical significance.

### Results:

A total of 176 patients out of 250 fulfilled the inclusion criteria and were included in the study. Baseline characteristics are presented in Table 1. Most 138(78.4%) patients were males and Diabetes Mellitus (DM) was the most common comorbidity observed in 70(39.8%) patients.

**Table-1:** Baseline characteristics of demographic, clinical and laboratory parameters of COVID-19 patients (n=176)

| S.No. | Variables                                     | Mean±SD       |
|-------|-----------------------------------------------|---------------|
| 1     | Age (years)                                   | 51.26 ± 15.20 |
| 2     | Length of hospital stay (days)                | 8.46 ± 4.12   |
| 3     | Respiratory Rate (breaths per minute)         | 19.77 ± 4.27  |
| 4     | SpO <sub>2</sub> (%)                          | 93.08 ± 5.03  |
| 5     | Hemoglobin (g/dL)                             | 13.43 ± 1.66  |
| 6     | Total Leukocyte Count (X 10 <sup>3</sup> /μL) | 9.16 ± 3.75   |
| 7     | Serum Creatinine at admission (mg/dL)         | 1.18 ± 0.64   |
| 8     | C-Reactive Protein (mg/L)                     | 65.62 ± 61.75 |
| 9     | D-Dimers (μg/ml)                              | 1.24 ± 1.90   |
| 10    | Ferritin (ng/ml)                              | 539.32±536.97 |
| 11    | Procalcitonin (ng/ml)                         | 0.63±0.97     |
| 12    | Chest X-ray scoring (number)                  | 8.36±5.66     |

Around half of the patients had SpO<sub>2</sub> < 94 % and CXR scoring greater than nine. Raised CRP > 10 mg/L and elevated D-dimers > 0.5 mcg/ml were noted in 133(75.6%) and 100(56.8%) patients respectively where 95(54.0%) patients showed high serum ferritin > 300 ng/ml and PCT > 0.25 ng/ml levels. AKI was found in 91(51.7%) patients. Using univariate analysis, patients who developed AKI had higher mean serum levels of inflammatory markers compared with non-AKI group, Table 2. Using student's t-test, except PCT all inflammatory markers were found to have statistically significant association with risk of AKI development having *p* values ≤ 0.05. Using multivariate analysis, CRP, D-dimers and ferritin were found to be the most statistically significant in affecting risk of AKI development with *p* values of 0.002, 0.004 and 0.046 respectively.

**Table-2:** Comparison of inflammatory markers between AKI and non-AKI groups of COVID-19 patients

| S.No. | Variables        | AKI (N=91)    | Non-AKI (N=85) | <i>p</i> value AKI vs. Non-AKI |
|-------|------------------|---------------|----------------|--------------------------------|
| 1     | CRP (mg/L)       | 84.25±59.38   | 45.66±58.21    | <b>0.000*</b>                  |
| 2     | D-Dimers (μg/ml) | 1.72±2.30     | 0.73±1.16      | <b>0.000*</b>                  |
| 3     | Ferritin (ng/ml) | 677.55±535.14 | 391.34±501.02  | <b>0.000*</b>                  |
| 4     | PCT (ng/ml)      | 0.76±0.96     | 0.48±0.95      | 0.059                          |

**BOLD\*:** *p* value of statistical significance, CRP= C -Reactive Protein, PCT= Procalcitonin

Using univariate analysis, a statistically significant correlation between each of these four raised inflammatory markers and risk of AKI development was also observed

**Table-3:** Odds Ratios for raised inflammatory markers in COVID-19 patients

| S. No. | Variables                     | Unadjusted OR <sup>1</sup> | 95% CI <sup>2</sup> | <i>p</i> value   |
|--------|-------------------------------|----------------------------|---------------------|------------------|
| 1      | Raised CRP (> 10 mg/L)        | 8.81                       | 3.64-21.31          | < <b>0.0001*</b> |
| 2      | Raised D-dimers (> 0.5 μg/ml) | 3.96                       | 2.10-7.45           | < <b>0.0001*</b> |
| 3      | High ferritin(> 300 ng/ml)    | 3.72                       | 1.99-6.96           | < <b>0.0001*</b> |
| 4      | High PCT(> 0.25 ng/ml)        | 2.50                       | 1.36-4.61           | <b>0.0030*</b>   |

<sup>1</sup> OR=odds ratio; <sup>2</sup>CI= confidence interval; **BOLD\*:** *p* value of statistical significance, CRP= C -Reactive Protein, PCT= Procalcitonin

**Discussion:** COVID-19 is a newly encountered viral illness with an established multi-systemic involvement.<sup>3</sup> Kidneys are seen commonly affected in COVID-19 with AKI being the most serious

and even life threatening complication.<sup>4</sup> The incidence of AKI in COVID-19 ranges from 0.5% to 80.3% with a reported pooled incidence of 19.4%.<sup>7-9</sup> Despite advancements in COVID-19 management, frequency of its associated AKI is still high as evident from current study where more than half of COVID-19 patients were found to have AKI. Failure to timely identify COVID-19 patients that are more susceptible to AKI is one of the possible reasons. Several risk factors influencing AKI development in COVID-19 patients have been reported including increasing age, male gender, DM, prolonged hospital stay, hypoalbuminemia, anaemia but among them severity of disease is of special importance.<sup>10</sup>

**Table-4:** Relative Risks for raised inflammatory markers in COVID-19 patients

| S. No. | Variables                          | RR <sup>1</sup> | 95% CI <sup>2</sup> | p value        |
|--------|------------------------------------|-----------------|---------------------|----------------|
| 1      | Raised CRP<br>(> 10 mg/L)          | 3.87            | 1.94-7.73           | <b>0.0001*</b> |
| 2      | Elevated D-dimers<br>(> 0.5 µg/ml) | 2.00            | 1.41-2.84           | <b>0.0001*</b> |
| 3      | High ferritin<br>(> 300 ng/ml)     | 1.91            | 1.37-2.67           | <b>0.0001*</b> |
| 4      | High PCT<br>(> 0.25 ng/ml)         | 1.57            | 1.15-2.14           | <b>0.0045*</b> |

<sup>1</sup> RR=Relative risk; <sup>2</sup>CI= confidence interval; **BOLD\***: p value of statistical significance, CRP= C -Reactive Protein, PCT= Procalcitonin

Severe COVID-19 is standardly characterized by hypoxemia (SpO<sub>2</sub> < 94%) on room air at sea level), tachypnea (respiratory rate > 30 breaths per minute), ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) <300 mm Hg or > 50% lung infiltration seen on HRCT.<sup>11</sup> Additionally, patients with severe COVID-19 have shown comparatively higher serum levels of certain inflammatory markers like CRP, D-dimers, ferritin, PCT and IL-6 than those having mild to moderate disease.<sup>5</sup> Thus these inflammatory markers can also be considered as indicators of COVID-19 severity and their presence at high levels may indicate severe disease that must be dealt accordingly.<sup>5</sup> Raised inflammatory markers in COVID-19 usually occur as a part of phenomenon termed as COVID-19 associated hyper-inflammatory syndrome (cHIS).<sup>12</sup> It is characterized by moderate to high fever and encephalopathy; low to normal hemoglobin levels, total leukocytes and platelet counts; extremely low absolute lymphocytes count and moderate to high neutrophils to lymphocytes ratio, triglycerides, aspartate aminotransferase and interleukin-6 levels.<sup>12</sup> The probable underlying mechanism involved in pathogenesis of cHIS is an uncontrolled highly exaggerated immune response to heavy viral invasion leading to production of massive amounts of pro-inflammatory cytokines (cytokine release syndrome or cytokine storm) and other inflammatory markers.<sup>12</sup> cHIS can result into multi organ failure along with end organ damage and even death may occur.

The pathogenesis of AKI in COVID-19 is multifactorial with a variety of mechanisms being involved.<sup>4</sup> It can be either pre-renal from transient reduced renal perfusion without tubular damage that resolves as renal perfusion is restored or Acute Tubular Necrosis (ATN) with tubular damage and requiring four to six weeks for resolution.<sup>4</sup> ATN can be from a direct viral insult to renal tubules

or from an indirect hypoxic (from hypoxemia secondary to respiratory failure) or ischemic insult (from hypovolemia, hypotension or thromboembolic renal vascular occlusion).<sup>4</sup> Nephrotoxic drugs used in COVID-19 patients like NSAIDs, diuretics, etc. may also precipitate ATN but an important cause of concern is sepsis and associated disseminated intravascular coagulation (DIC) in these patients particularly in severe disease.<sup>4</sup> As described earlier, cytokine storm syndrome as well as cHIS play critical role in causing AKI in patients having severe COVID-19. Thus, timely identifying this hyper-inflammatory state in COVID-19 patients from early detection of raised inflammatory markers can be helpful in predicting as well as preventing AKI.

The four major easily accessible inflammatory markers that are found to be raised in severe COVID-19 in current as well as previous studies are: CRP, D-dimers, ferritin and PCT.<sup>5</sup> CRP is a pentameric, acute phase protein secreted by liver in response to interleukin-6 produced by macrophages.<sup>13</sup> It binds to phosphocholine on surface of necrotic cells or microbes facilitating their complement mediated phagocytosis. Normal plasma concentration of CRP range from 1-3 mg/L but can be as high as 10 mg/L.<sup>13</sup> Its' levels rise physiologically with age and pathologically in acute or chronic inflammatory conditions such as infections, rheumatic disorders or malignancies. Average plasma levels of CRP in COVID-19 patients are found to be 20 to 50 mg/L and up to 86% of these patients with severe disease have shown elevated CRP levels and a marker of poor outcome.<sup>14</sup> In current study, COVID-19 patients with raised CRP levels > 5 mg/L were found to be nearly four folds more likely to develop AKI. This finding is consistent with results of a previous study.<sup>15</sup>

D-dimers is a fibrin degradation product formed as result of plasmin induced fibrinolysis.<sup>16</sup> Normally, it is not detectable in blood with plasma concentration < 0.5 mcg/ml. D-Dimer levels are physiologically elevated in pregnancy, with age, after surgery or trauma and pathologically elevated in deep venous thrombosis, pulmonary embolism or DIC.<sup>16</sup> Mean D-dimers levels in COVID-19 patients were reported to be 0.9 to 4.6 mcg/ml and 59% of those with severe disease have shown elevated D-dimers levels.<sup>17,18</sup> D-dimers are high mainly because of coagulation disorders (DIC) associated with COVID-19 and are also reported as predictors of poor outcome.<sup>17</sup> In the current study, COVID-19 patient having elevated D-dimers levels > 0.5 mcg/ml were found to be two times more likely to develop AKI.

Ferritin is mainly an intracellular cytosolic iron storing pigment, but it is also present in blood in small concentrations and may serve as acute phase reactant.<sup>19</sup> Serum levels of Ferritin range from 30-300 ng/ml (males) and 30-160 ng/ml (females) but vary with age and are abnormally lower or higher in iron deficiency or iron overload states and high in acute or chronic inflammatory conditions and infections.<sup>19</sup> Average serum ferritin levels in patients having COVID-19 are observed to be ranging from 428.5 to 1386.7 ng/ml and 86% of those with severe disease have shown high serum ferritin concentration and a predictor of mortality.<sup>20</sup> In the current study, COVID-19 patients with high serum ferritin levels > 300 ng/ml were found to be two folds more likely to develop AKI than those with normal serum ferritin concentration, similar to a previous study.<sup>15</sup>

PCT is a peptide precursor of calcitonin, a hormone secreted by parafollicular (C) cells of thyroid gland as well as neuroendocrine cells of lungs and intestine.<sup>21</sup> It also serves as an acute phase reactant

like CRP and ferritin and normally undetectable levels while elevated in inflammation, infections or sepsis. Mean PCT levels in COVID-19 patients were found to be  $0.14 \pm 0.26$  ng/ml with 52% patients with severe disease have shown elevated PCT levels.<sup>22</sup> In current study, COVID-19 patients having raised PCT levels  $> 0.25$  ng/ml are found one and a half times more likely to have AKI similar to a previous study.<sup>15</sup>

Current study is limited by its relatively small sample size, retrospective design and excluding another important inflammatory marker like IL-6 because of inadequate cost. A more comprehensive multicentric prospective study including other inflammatory markers is needed.

**Conclusions:** Raised inflammatory markers in patients having severe COVID-19 are associated with increased risk of AKI.

**Disclosure/Conflicts of interest:** The authors declared no conflict of interest.

### References:

1. World Health Organisation. Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update. Last accessed on Jan 16, 2022. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
2. Government of Pakistan. Pakistan Cases Details. Last Accessed on Jan 16, 2022. Available from: <https://covid.gov.pk/stats/pakistan>
3. Singh A, Zaheer S, Kumar N, Singla T, Ranga S. Covid19, beyond just the lungs: A review of multisystemic involvement by Covid19. *Pathol Res Pract*. 2021;224:153384. Doi: 10.1016/j.prp.2021.153384.
4. Asgharpour M, Zare E, Mubarak M, Alirezai A. COVID-19 and Kidney Disease: Update on Epidemiology, Clinical Manifestations, Pathophysiology and Management. *J Coll Physicians Surg Pak*. 2020;30(6):19-25. Doi: 10.29271/jcpsp.2020.Supp1.S19.
5. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. *Int J Infect Dis*. 2020;96:467-474. Doi: 10.1016/j.ijid.2020.05.055.
6. Tan LY, Komarasamy TV, Rmt Balasubramaniam V. Hyperinflammatory Immune Response and COVID-19: A Double Edged Sword. *Front Immunol*. 2021;12:742941. Doi: 10.3389/fimmu.2021.742941.
7. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, Paranjpe I et al. AKI in Hospitalized Patients with COVID-19. *J Am Soc Nephrol*. 2021;32:151-160. Doi: 10.1681/ASN.2020050615.
8. Qian JY, Wang B, Liu BC. Acute Kidney Injury in the 2019 Novel Coronavirus Disease. *Kidney Dis (Basel)*. 2020;323:1-6. Doi: 10.1159/000509086.
9. Raina R, Mahajan ZA, Vasistha P, Chakraborty R, Mukunda K, Tibrewal A, et al. Incidence and Outcomes of Acute Kidney Injury in COVID-19: A Systematic Review. *Blood Purif*. 2021:1-14. Doi: 10.1159/000514940.
10. See YP, Young BE, Ang LW, Ooi XY, Chan CP, Looi WL, et al. Risk Factors for Development of Acute Kidney Injury in COVID-19 Patients: A Retrospective Observational Cohort Study. *Nephron*. 2021;145(3):256-264. Doi: 10.1159/000514064.
11. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. *BMJ Open Diabetes Res Care*. 2020;8(1):e001343. Doi: 10.1136/bmjdr-2020-001343.
12. Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. *Lancet Rheumatol*. 2020;2(12):e754-e763. Doi: 10.1016/S2665-9913(20)30343-X.
13. Nehring SM, Goyal A, Bansal P, Patel BC. C Reactive Protein. 2021 Dec 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan - . PMID: 28722873.

14. Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. *J Med Virol.* 2020;92(11):2409-2411. Doi: 10.1002/jmv.26097.
15. Ortiz, A. E. T., Walker, J. B., Mohammed, A. E., Mohamed, M., Lukitsch, I., Velez, J. C. Q. Markers of inflammation and risk for AKI and need for dialysis in patients with COVID-19. *Journal of the American Society of Nephrology.* 2020;31:258-259.
16. Johnson ED, Schell JC, Rodgers GM. The D-dimer assay. *Am J Hematol.* 2019;94(7):833-839. Doi: 10.1002/ajh.25482.
17. Yu HH, Qin C, Chen M, Wang W, Tian DS. D-dimer level is associated with the severity of COVID-19. *Thromb Res.* 2020;195:219-225. Doi: 10.1016/j.thromres.2020.07.047.
18. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720. Doi: 10.1056/NEJMoa2002032.
19. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics.* 2014;6(4):748-73. Doi: 10.1039/c3mt00347g.
20. Ahmed S, Ansar Ahmed Z, Siddiqui I, Haroon Rashid N, Mansoor M, Jafri L. Evaluation of serum ferritin for prediction of severity and mortality in COVID-19- A cross sectional study. *Ann Med Surg (Lond).* 2021;63:102163. Doi: 10.1016/j.amsu.2021.02.009.
21. Davies J. Procalcitonin. *J Clin Pathol.* 2015;68(9):675-9. Doi: 10.1136/jclinpath-2014-202807.
22. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. *Int J Antimicrob Agents.* 2020;56(2):106051. Doi: 10.1016/j.ijantimicag.2020.106051.