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Impact of hemodialysis on interleukin-6 in COVID-19-positive patients with chronic kidney disease

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Original Article

Abstract

BACKGROUND: In patients with coronavirus disease 2019 (COVID-19) with multiple organ involvement, interleukin-6 (IL-6) is an important biomarker of the hyperinflammatory immune response, cytokine storm, and fatal outcomes. Our research aims to comprehend the value of polysulfone membrane-based hemodialysis (HD), not only in terms of lowering renal load but also in terms of enhancing outcomes by addressing the IL-6 levels in patients with chronic kidney disease (CKD) on maintenance HD (MHD).

METHODS: This prospective observational analysis was conducted from July 2020 to January 2022 at a tertiary care hospital in Prayagraj, Uttar Pradesh, India. 181 patients, with a history of CKD on MHD, hospitalized in COVID-19 wards were chosen for this study. The usual baseline blood values of the patients were assessed. HD was done on the Fresenius polysulfone membrane (FX-8) with an effective surface area of 1.4 m^2 and an ultrafiltration coefficient of 12 (ml/h × mmHg). Patients' IL-6 levels were initially checked before dialysis, and in patients who survived, they were repeated on the day of discharge. Data were analyzed using SPSS software.

RESULTS: Out of a total of 181 patients, 95 were survivors and 86 were non-survivors. Most non-survivors were elderly ($P < 0.001$). The mean neutrophil-lymphocyte ratio (NLR) and D-dimer levels were substantially greater in non-survivors than in survivors ($P < 0.001$). Non-survivors had considerably higher mean serum levels of IL-6, creatinine, and urea ($P < 0.001$). The average number of HD treatments received by survivors was higher ($P < 0.001$). The relationship between delta IL-6 and delta serum creatinine for survivors had a strong positive correlation of $r = 0.775$ ($P < 0.001$).

CONCLUSION: This study demonstrates that IL-6 is a subpar predictor of prognosis in convalescent CKD patients with COVID-19. It also emphasizes the use of HD as a life-saving therapeutic strategy that is also cost-effective. Lowering IL-6 levels can both enhance renal outcomes and calm the cytokine storm.

KEYWORDS: COVID-19; Hemodialysis; Chronic Kidney Disease; Cytokine Storm; Interleukin-6

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Introduction

In Wuhan, China, many occurrences of a respiratory ailment with an unclear etiology that resembled atypical pneumonia were reported to the World Health Organisation (WHO) in December 2019. The pathogenic virus was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the third novel coronavirus to be discovered in 17 years and one that is phylogenetically related to coronaviruses that are similar to severe acute respiratory syndrome (SARS) and are generated from bats. SARS-CoV-2, unlike

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any of its predecessors, infamously grew into a full-blown worldwide pandemic, as declared by WHO on March 21, 2020, putting the entire world on hold.[1]

Fever, a dry cough, tiredness, diarrhea, nausea, vomiting, headaches, and breathing difficulties are some of the signs and symptoms of coronavirus disease 2019 (COVID-19). A small percentage of patients experienced complications that led to higher mortality rates, including acute respiratory distress syndrome (ARDS), secondary infections, septic shock, acute renal injury, hypoxemia, and acute cardiac injury.[2]

Acute phase responses and immunological responses are influenced by interleukin-6 (IL-6), which, in turn, is generated in response to infections or inflammation. It increases $CD4^+$ T cells, T helper type 17 (Th17) differentiation, and T helper type 2 (Th2) response as well as the synthesis of inflammatory indicators like C-reactive protein (CRP) and mediates the generation of antibodies.[3] These characteristics make IL-6 the flag bearer of the inflammatory response. The COVID-19 clinical profile might range from asymptotic infection to ARDS. IL-6 is the major mediator for the latter, which is typically compounded by the cytokine release syndrome.[4] Several experimental strategies, such as steroids, IL-6 receptor blockers, or extracorporeal procedures to remove cytokines, have been used to treat COVID-19-associated inflammatory responses.[5,6] Hemodialysis (HD) patients with COVID-19 have a significant mortality rate, which may be related to immunological dysfunction in this population.[7] Pro-inflammatory cytokines may become more prevalent as a result of HD.[8] On the other hand, it has already been demonstrated that using medium cut-off (MCO) membranes as dialyzers reduces inflammatory mediators.[9]

Our study targeted patients with diagnosed chronic kidney disease (CKD) on polysulfone-based membranes maintenance HD (MHD) to evaluate the role of IL-6 as a biomarker of COVID-19 cytokine storm and if there were any changes in its levels post HD amongst survivors.

Methods

This was a prospective observational study. The participants included were patients admitted to COVID-19 wards, in Swaroop Rani Nehru Hospital, Prayagraj, India, from July 2020 to January 2022. The primary objective was to study the differences in levels of IL-6 pre- and post-dialysis among survivors of COVID-19 undergoing HD for CKD.

The inclusion criteria included All patients aged > 18 years, men and women, were taken. The CKD group included patients who had a history of CKD and were on MHD.

The exclusion criteria included patients aged < 18 years, patients treated with nephrotoxic drugs such as remdesivir and amphotericin B, and patients undergoing HD for acute kidney injury (AKI) were excluded from the study.

181 patients who were admitted to COVID-19 wards with a history of CKD and underwent MHD were included. Patients were tested for COVID-19 using reverse transcription polymerase chain reaction (RT-PCR) or Truenat, and were categorized into survivors and non-survivors based on their outcomes. Patients' history, co-morbidities [hypertension (HTN), diabetes mellitus (DM), cardiovascular, pulmonary, or malignancy], and baseline investigation parameters like complete blood count (CBC), liver function test (LFT), kidney function test (KFT), and glycated hemoglobin (HbA1C), were done on the day of admission. Patients were monitored for urine output, blood pressure, respiratory rate, pulse rate, oxygen saturation, KFT, and other parameters daily. Based on the changes in kidney function and urine output, patients underwent HD using Fresenius polysulfone membrane (FX-8) with an effective surface area of 1.4 m^2 and ultrafiltration coefficient of

12 (ml/h × mmHg). IL-6 levels were done in Tejas Micro Diagnostic Center, Prayagraj, using Maglumi in vitro chemiluminescence immunoassay. The estimated molecular weight of IL-6 was 22-27 kilodalton (kDa). IL-6 was measured in both groups of survivors and non-survivors on the day of admission and again only in the survivor group on the day of discharge from the COVID-19 ward.

Statistical analysis: The presentation of the categorical variables was done in the form of numbers and percentages. On the other hand, the quantitative data were presented as the mean ± standard deviation (SD) and as the median with 25th and 75th percentiles [interquartile range (IQR)]. Comparison of quantitative variables were performed using paired t-test. The data entry was done in a Microsoft Excel spreadsheet and the final analysis was done with the use of SPSS software (version 21, IBM Corporation, Armonk, NY, USA). For statistical significance, a P-value of less than 0.05 was considered statistically significant.

Institutional Ethics Committee for Human Research approved the study. The study procedures followed the ethical standards of the responsible committee on human experimentation and the 1975 Declaration of Helsinki, as revised in 2000. The protocol was approved by the Ethics Committee (Registration No.: ECR/922/Inst./UP2017 issued under rule 122DD of the Drugs and Cosmetics Rule 1945) of Moti Lal Nehru Medical College, Prayagraj.

Results

The 181 patients with CKD who tested positive for COVID-19 were chosen in total. Depending on the outcome, they were split into survivors (n = 95) and non-survivors (n = 86). When baseline characteristics were compared, non-survivors had a mean age of 53.41 years whereas survivors had a mean age of 42.19 years (P < 0.001).

Men made up an identical number of non-survivors (51/86, 59.30%) and survivors (52/95, 54.74%) (P = 0.55) as demonstrated in table 1. The distribution of smokers and drinkers among survivors and non-survivors was not statistically significant.

When compared to non-survivors, survivors' mean hemoglobin (Hb) levels were higher, at 8.95 mg/dl (P = 0.64). For survivors and non-survivors, the mean platelet count was 1.91 lac/mm^3 and 1.03 lac/mm^3, respectively (P < 0.001). In survivors and non-survivors, respectively, the mean neutrophil-lymphocyte ratio (NLR) was 7.59 ± 3.91 and 13.66 ± 5.09, and the mean D-dimer level was 1.02 mg/l and 5.41 mg/l, respectively (P < 0.001).C

Table 1. Comparison of baseline characteristics of survivors and non-survivors in coronavirus disease 2019 (COVID-19)-positive patients with chronic kidney disease (CKD)

	Survivors (n = 95)	Non-survivors (n = 86)	P
Demographics			
Age (year)	42.19 ± 19.31	53.41 ± 12.11	< 0.001
Gender (men)	52 (54.74)	51 (59.30)	0.551
BMI (kg/m^2)	21.28 ± 2.62	24.38 ± 3.71	< 0.001
Smokers	39 (41.05)	23 (26.74)	0.059
Alcohol	29 (30.53)	22 (25.58)	0.510
Haematological parameters			
Hb (g/dl)	8.95 ± 2.09	8.31 ± 2.93	0.640
NLR	7.59 ± 3.91	13.66 ± 5.09	< 0.001
Platelet count (lac/mm^3)	1.91 ± 0.41	1.03 ± 0.71	< 0.001
D-dimer (mg/l)	1.02 ± 0.81	5.41 ± 3.71	< 0.001

Data are presented as mean ± standard deviation (SD) or number and percent
BMI: Body mass index; Hb: Hemoglobin; NLR: Neutrophil-lymphocyte ratio

A renal function test revealed that the mean blood urea level in survivors was lower (155.22 ± 38.97 mg/dl) than that in non-survivors (225.38 ± 72.81 mg/dl), with a P-value of 0.001. In contrast to survivors' levels of 7.01 ± 1.98 mg/dl, non-survivors mean serum creatinine levels were substantially higher at 11.61 ± 5.09 mg/dl (P < 0.001) as shown in table 2. As indicated in figure 1, the mean IL-6 level in non-survivors was substantially higher (336.75 ± 69.92 pg/ml), whereas the mean level in survivors was 149.91 ± 49.2 pg/ml (P < 0.001).

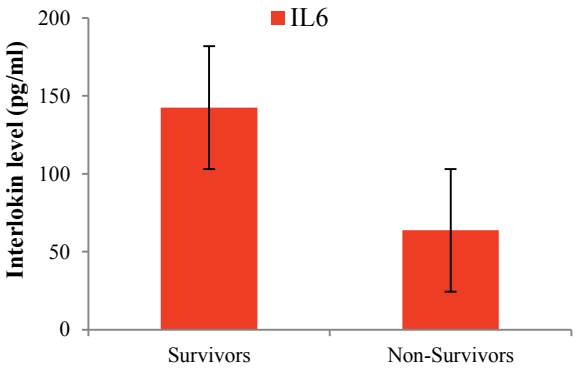

Figure 1. The difference between interleukin 6 (IL6) serum level among non-survivors and survivors

The mean number of HD sessions received by survivors was 2.92 ± 0.99 in comparison to 1.56 ± 0.91 in non-survivors with a significant P-value of < 0.001 as seen in table 2.

The curve between delta IL-6 (difference between pre-dialysis and on-discharge IL-6 level) and delta serum creatinine (difference between pre-dialysis and on-discharge serum creatinine) for survivors showed a significant positive association (r = 0.775) (P < 0.001) as shown in figure 2.

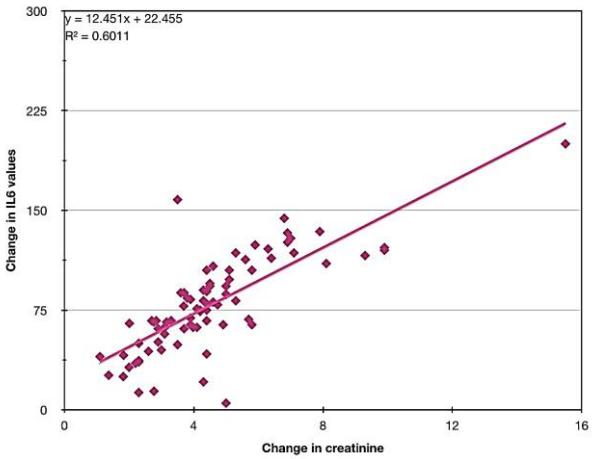

Figure 2. The difference between pre-analysis and on-discharge serum creatinine level

Discussion

Our research sheds light on how timely HD based on polysulfone membranes can be employed to calm cytokine storm associated with COVID-19. It investigated the variation in IL-6 levels between pre- and post-HD among COVID-19 survivors undergoing treatment for CKD and showed an association between delta IL-6 and delta serum creatinine levels in survivors.

At its core, the SARS-CoV-2 hyper-inflammatory process known as hypercytokinaemia or cytokine storm determines which infected individuals will survive and which ones will not.

IL-6 is one of the most significant mediators of the immunologic response to COVID-19 and plays a role in the progression of viral infections.[10]

Table 2. Comparison of baseline kidney function tests (KFTs) of coronavirus disease 2019 (COVID-19)-positive chronic kidney disease (CKD) survivors and non-survivors

	Survivors	Non-survivors	P
Blood urea (mg/dl)	155.22 ± 38.97	225.38 ± 72.81	< 0.001
Serum creatinine (mg/dl)	7.01 ± 1.98	11.61 ± 5.09	< 0.001
IL-6 (pg/ml)	149.91 ± 49.21	336.75 ± 69.92	< 0.001
No HD done	2.92 ± 0.99	1.56 ± 0.91	< 0.001

Data are presented as mean ± standard deviation (SD)
IL-6: Interleukin-6; HD: Hemodialysis

While pro-inflammatory mediators are released in the uremic milieu and are removed more slowly, chronic HD patients are already more susceptible to inflammation.[11] Each HD session may also trigger an inflammatory reaction.[12] It has been demonstrated in the past that IL-6 is linked to HD patients' short-term mortality.[13] In an acute inflammatory condition like COVID-19, as demonstrated in our investigation, dialysis-related variations in IL-6 levels may also be a predictor of short-term death.

We observe a substantial difference in the mean levels between survivors and non-survivors when looking at IL-6 as the precursor of COVID-19 ($P < 0.001$). Similar findings were found in other investigations, which demonstrated that patients with severe illness had elevated blood IL-6 levels of 100 to 1000 pg/ml.[14,15]

In comparison to survivors, non-survivors' mean age was significantly greater at 53.41 years ($P < 0.001$). The inflammatory response is complicated by COVID-19, which is more severe in older patients and causes higher mortality.[16] The findings of our investigation were consistent with Biswas et al.'s observation that older patients had higher fatality rates.[17]

A relatively equal percentage distribution of smokers and alcohol consumers among the groups can be used to rule out their confounding effects as potential risk factors.

In contrast to other cytokine storm illnesses, COVID stress scales (CSS) is characterized by characteristically lower lymphocyte numbers, which may be brought on by enhanced T-lymphocyte destruction or tissue infiltration.[18] The increased NLR among non-survivors in our study is consistent with prior findings and has a significant outcome ($P < 0.001$). These results can be corroborated by the analysis of Erdogan et al., which showed that higher NLR was associated with severe clinical symptoms and also predicted the prognosis of patients.[19]

The considerably higher D-dimer levels ($P < 0.001$) in non-survivor groups in comparison to survivors plausibly explain the increased frequency of thromboembolic events related to endothelialitis in COVID-CSS as compared to other CSS.[20] Similarly, increased D-dimer levels were independent risk factors for death in patients with COVID-19 on HD [odds ratio (OR): 4.974, 95% confidence interval (CI): 3.315-6.263, $P = 0.007$] observed by Zou et al.[21]

The interaction of elevated cytokine production and impaired kidney function in patients with COVID-19 demonstrates the co-association of both factors, which ultimately results in patients needing HD. The findings of this investigation showed that non-survivors had considerably higher mean serum urea and creatinine levels than survivors ($P < 0.001$). Additionally, patients in the survivors' group underwent a significantly higher number of HD sessions than non-survivors ($P < 0.001$), which could be explained by several variables including the severity of COVID-19, the timing of the patient's presentation (early or late depending on how many hospitals the patient was referred through), the length of the hospital stay, etc.

Studies have been conducted in the past to reduce cytokines in COVID-19 patients with CKD utilizing specialized high and MCO HD membranes.[22] Yet in patients with CKD, using polysulfone membrane-based HD, our study indicates a distinct positive correlation ($r = 0.775$) with a declining trend of IL-6 levels and serum creatinine before dialysis and on the day of discharge from the COVID unit.

The limitations may be being a single-center study and having a small sample size. It is suggested that HD not only aids in lowering the renal burden but also lowers cytokine load and inflammatory insult without raising the financial burden.

Conclusion

Cytokine storm syndrome is at the heart of the

chaos unleashed by COVID over the past three years. Our work reinforces IL-6 as the novel biomarker of COVID-19 CSS and as a powerful predictor of short-term death in patients with CKD requiring MHD. Our study only uses polysulfone membrane-based HD, establishing it to be beneficial in lowering the cytokine load about the renal insult without increasing the financial burden. More than half of the patients timely intervened with HD survived despite grave prognosis, proving it to be a boon in the face of the COVID cytokine storm.

Conflict of Interests

Authors have no conflict of interests.

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