ORIGINAL ARTICLE

Impact of COVID-19 on a cohort of hemodialysis patient: A nested case-control study in a tertiary care Hospital in Northern Pakistan

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ABSTRACT

Background: The outbreak of the highly contagious coronavirus has significantly threatened human health, particularly for individuals with underlying diseases. Despite this, the effects of the epidemic on hemodialysis (HD) patients have not been thoroughly assessed.

Material and Methods: An observational prospective nested case control study was designed that covered the epidemic period from May 2020 to June 2020 at the Hemodialysis (HD) Center in Rawalpindi. Study was devised to investigate the differences in outcomes and complications between hemodialysis patients testing positive and negative for the coronavirus. The study included a total of 294 registered hemodialysis patients, with a case group of 29 individuals testing positive for coronavirus compared to 29 COVID-negative counterparts from the same cohort. Various data, encompassing epidemiological, clinical, laboratory, and radiological characteristics, were systematically collected and analyzed.

Results: Of the 294 hemodialysis patients, 29 (9.86%) were diagnosed with COVID-19. Most COVID-19-diagnosed patients presented with mild-moderate respiratory symptoms. Only 3(10.3%) patients with a positive COVID test were admitted to the Intensive Care Unit (ICU) for severe conditions while only two deaths were recorded among COVID-19-positive HD patients, and none of them was linked to COVID-19 or its complications.

Conclusions: This study highlights the susceptibility of HD patients during the COVID-19 epidemic and underscores HD centers as high-risk areas. Patients with COVID-19 and undergoing hemodialysis typically exhibit mild clinical symptoms and are less likely to progress to severe pneumonia, attributed to compromised cellular immune function and an inability to mount cytokine storms.

Keywords: Coronavirus, Hemodialysis, Patients

BACKGROUND

Since January 2020, the epidemic of highly contagious and rapidly fatal droplet infection tilted COVID 19 has ascended to the status of pandemic and occupied center stage at global and national health care systems.[1-6]

Initially, COVID-19 was feared for its indiscriminate impact across age groups, with distressing social media videos showing both young and elderly individuals succumbing to the virus.[7,8] However, subsequent epidemiological studies reiterated that COVID-19 patients with pre-existing conditions like diabetes, hypertension, cardiovascular disease, or those who are elderly, are not only susceptible but also more likely to experience complications, contributing to the overall fatality statistics.[9]

Out of the various chronic co-morbidities noted in COVID 19 patients, the case of chronic kidney disease was considered a special case as it not only contributed to most chronic conditions but had a natural history of its own with important implications on natural immune system.[10] Considering the rising size of chronic kidney disease patients on hemodialysis, there was a need to study their susceptibility and response to COVID 19 as a special group. With around 294 registered patients receiving HD treatment in 2 centers in two medical set ups in Rawalpindi city, there is often high concentration of patients in HD centers, and the compromised immune function of uremic patients is a dreaded risk factor.[11]

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It has been postulated that patients with compromised immunity might not develop severe COVID disease owing to their impaired immune response or inability to initiate a cytokine response. But results from different studies have been contradicting where few studies have shown severe COVID in immunocompromised patients while others have done the opposite.[10-11]

The aim of the study is to follow the outbreak of Covid19 epidemic in hemodialysis centers and to provide insights into the effective management and outcome of COVID positive patients on hemodialysis.

MATERIAL AND METHODS

An observational prospective Nested Case Control study was designed. Epidemic course from the first laboratory-confirmed case of COVID-19 infections from May 5th to June 30th 2020 in the HD Center was reviewed and total 294 HD registered patients were included in this study.

The diagnosis of COVID-19 related pneumonia adheres to the New Coronavirus Pneumonia Prevention and Control Program's 5th, 6th, and 7th editions - valid from February 4 to March 4, 2020. This program is governed by a CC-BY-NC-ND 4.0 International license [15]. Within its guidelines in the fifth edition, it defines a suspected case presenting with symptoms correlating with an epidemiological history or clinical evidence such as decreased white blood cell count or lymphocyte count alongside fever and respiratory symptoms. A clinically diagnosed case is established when these indicated cases exhibit image-based features corresponding to that of pneumonia. We followed the same guidelines to identify our positive cases.

Following the pathway laid by the guidelines, a confirmed diagnosis was made if individuals designated as either suspected or clinically diagnosed patients were verified positive via pathology blood tests according to protocol procedures. It remains essential though for valid suspect cases presentation aligns precisely with criteria set forth pertaining their epidemiological histories alongside aforementioned clinical symptoms indicators. If pathogen evidence materialized - particularly through Polymerase Chain Reaction (PCR) positivity, the considered potential patient received an official confirmed diagnosis for COVID-19 infection.

All the patients were followed up and related clinical data was collected. A cohort of 29 COVID positive confirmed cases were included as incident cases among the population of 294 hemodialysis patients. A parallel cohort of 29 matched patients who tested negative for COVID among the remaining 265 hemodialysis cases were identified for comparison as control.

The research protocol received approval from the hospital's Ethics Committee, ensuring adherence to ethical standards. Given the epidemic status of infectious diseases, written informed consent was not required, likely due to the urgency and potential risks to patients.

The research team meticulously examined the medical records of all participants, compiling a wide range of data including epidemiological, clinical, laboratory, and radiological information. The collected data encompassed demographic specifics, medical backgrounds, existing health conditions, symptoms, physical indicators, blood test results, and chest CT scans, thereby offering a thorough insight into the health profiles of the participants. During the follow-up period, instances of mortality were recorded and meticulously evaluated to ascertain the presumed cause of death based on clinical manifestations, time, and location. SARS-CoV-2 detection was performed using real-time PCR (RT-PCR) on nasopharyngeal swab samples collected from participants, a widely accepted method for diagnosing COVID-19 due to its high sensitivity and specificity. Blood tests were conducted to explore the impact of SARS-CoV-2 infection on host immune responses, with comparisons made between COVID-19 HD patients and non-COVID-19 HD patients to identify potential differences in immune function.

Statistical analysis was conducted using SPSS version 22. Parametric tests were applied for normally distributed continuous data while categorical data was expressed as frequencies (%). The independent group t-test was applied for comparisons, with significance set at $p < 0.05$.

RESULTS

29 out of 294 registered patients were diagnosed with Covid19 at HD centers. Figure-I provides a schematic representation of the evolving progression of the COVID-19 epidemic, from its initial emergence to its subsequent development. The first case of COVID-19 was diagnosed on May 5th, followed by a second diagnosis on May 8th.

Between 8th to 15th May, another 4 new patients were further confirmed with COVID-19. Realizing this quick rise in infection among HD patients reporting for their

scheduled dialysis at Nephrology department, a plan was approved by hospital authorities to screen all patients with chest CT and optional blood test. On June 5, there were total 11 HD cases being diagnosed with COVID-19. To find out the infected cases post Eid ul Fitr leave, the second round of screening was initiated from June 5, 2020 to June 30, 2020 and another 18 HD patients were diagnosed with COVID 19.

Throughout the screening period, all patients found to be infected were categorized, isolated, or moved to specific hospital units according to established protocols. The data revealed that total 29 patients, constituting 9.86% of the total, were diagnosed with COVID-19, and 2 patients passed away since the onset of the epidemic. Our research team closely monitored and reviewed both fatalities. Of the infected individuals, 3 were admitted to the Intensive Care Unit (ICU) due to severe conditions. Remarkably, the two deceased patients did not experience the respiratory complications that were expected in such cases.

First fatal case of HD unit had his primary cause of death labeled as Hypertensive Encephalopathy while the second case primary cause of death was being worked up for Vasculitis. During the two rounds of screening conducted to identify infected patients in the HD center, COVID-19 diagnosis relied on the detection of positive SARS-CoV-2 nucleic acid tests from nasopharyngeal swabs. All the HD patients testing positive for COVID 19 had their CT scan COVID score of 8-30. HD patients are summarized in Table-I.

Out of the 29 confirmed COVID-19 patients, 20 were male and 9 were female, with a median age of 61 years. Hematological abnormalities such as lymphocytopenia and thrombocytopenia, which are frequently observed in COVID-19 patients according to previous reports[7, 8, 16,17], were also evident in the HD patients who contracted COVID-19 (refer to Table-II).

Among HD patients diagnosed with COVID-19, typical clinical symptoms such as fever, fatigue, dry cough, chest pain, and nausea were not frequently reported. Radiological assessment through chest CT scans revealed that 2 (6.8%) confirmed diagnosed patients exhibited bilateral involvement, while 12 (41.3%) confirmed diagnosed patients and 5 (17.24%) clinically diagnosed patients showed unilateral involvement. The average score for "ground-glass opacity" lesions in the lungs ranged between 8 to 30 in both groups. These clinical presentations suggest that the majority of COVID-19 infected HD patients experienced mild conditions, a departure from previous observations in patients with comorbidities such as diabetes, hypertension, cardiovascular disease, or older age groups.[7,8,16]

The immune system plays a critical role in defending the host against invading pathogens. Upon SARS-CoV-2 infection of the host's respiratory tract, the virus replicates in airway cells, leading to significant immune activation and the release of large amounts of proinflammatory cytokines. This excessive immune response, known as a "cytokine storm," can result in severe conditions and, in some cases, lead to death in COVID-19 patients.[16]

However, the results outlined suggest that patients with COVID-19 infection experienced mild symptoms. It is speculated that this could be attributed to compromised immunity in HD patients, as evidenced by lymphopenia observed in nearly all patients. These findings imply that HD patients may have a compromised immune system, potentially limiting their ability to mount effective antiviral responses. Nevertheless, this compromised immunity may also have a beneficial aspect, as it could help mitigate tissue damage by dampening cytokine release.

Table-I: Demographic, clinical, and radiological features of HD patients.

Variables	Total n=294	Cases n=29	Controls n=29	P
Age (Years)	**55.0±12.0**	**52.0±14.0**	**54.0±6.0**	**0.08**
Male	**265**	**20**	**9**	**0.44**
Body mass Index	**24.5±4.3**	**22.2±4.5**	**23.1±3.6**	**0.53**
Comorbidity	**n (%)**	**n(%)**	**n(%)**	
Hypertension	257(87.41)	26(89.6)	24(83)	0.01
Diabetes	185(63)	18(62)	16(55)	0.31
Coronary heart disease	130(64)	17(58)	16(55)	0.48
Dyslipidemia	280(95)	22(75)	19(65)	0.39
Chronic obstructive lung disease	107(36)	18(62)	12(41)	0.45
Symptoms	**n (%)**	**n(%)**	**n(%)**	
Fever	78(26)	26(89.6)	22(75)	0.03

Cough	102(34)	28(96)	16(55)	0.02
Fatigue	256(87)	28(96)	25(86)	0.27
Diarrhea, nausea or vomiting	124(42)	24(83)	15(52)	0.05
Admission chest X-ray	**n (%)**	**n(%)**	**n(%)**	
Bilateral peripheral opacity	40(13)	26(89)	14(48)	0.03
Unilateral opacity	86(29)	3(10)	8(27)	0.33
Normal X-ray	189(64)	NIL	7(24)	0.03
HR CT	**n (%)**	**n(%)**	**n(%)**	
Multiple peripheral basal ground glass opacities	37(12)	27(93)	10(34)	
Peripheral Consolidation	18(6)	12(41)	6(20)	

Table-II: Laboratory findings at admission and 1 week after clinical onset.

Laboratory variables	Total=294	Cases=29	Controls=29	p-value[a]
1.*Lymphocytecount10*^{9},	0.79±0.47	0.83±.41	0.67	0.42
Baseline	0.66	0.760	0.38	0.04
Day 7				
2.*Hemoglobin, g/l*	10.61	10.6	10.61	0.13
Base line	9.81	9.6	10.72	0.17
Day 7				
3.*Platelet count,10*^{9}	1.64	1.74	1.37	0.13
Baseline	1.78	1.89	1.48	0.18
Day 7				
4.*Serum LDH, U/l*	235	225	274	0.27
Baseline	329	281	490	0.01
Day 7				
5.*Serum ALT, U/l*	29.25	29.55	19.21	0.72
Baseline	32.94	33.23	17.07	0.32
Day 7				
6.*Serum Ferritn, U/l*	445.64	Nil	451.04	0.24
Baseline	845.71	Nil	452.05	0.52
Day7				
9.*SerumC-reactive protein, mg/dl*	9.67	10.38	794	0.90
Baseline	10.61	8.18	674	0.08
Day7				
10.*Serum albumin, g/d*	3.70	3.70	3.44	0.18
l Baseline	3.20	3.20	3.31	0.96
Day7				

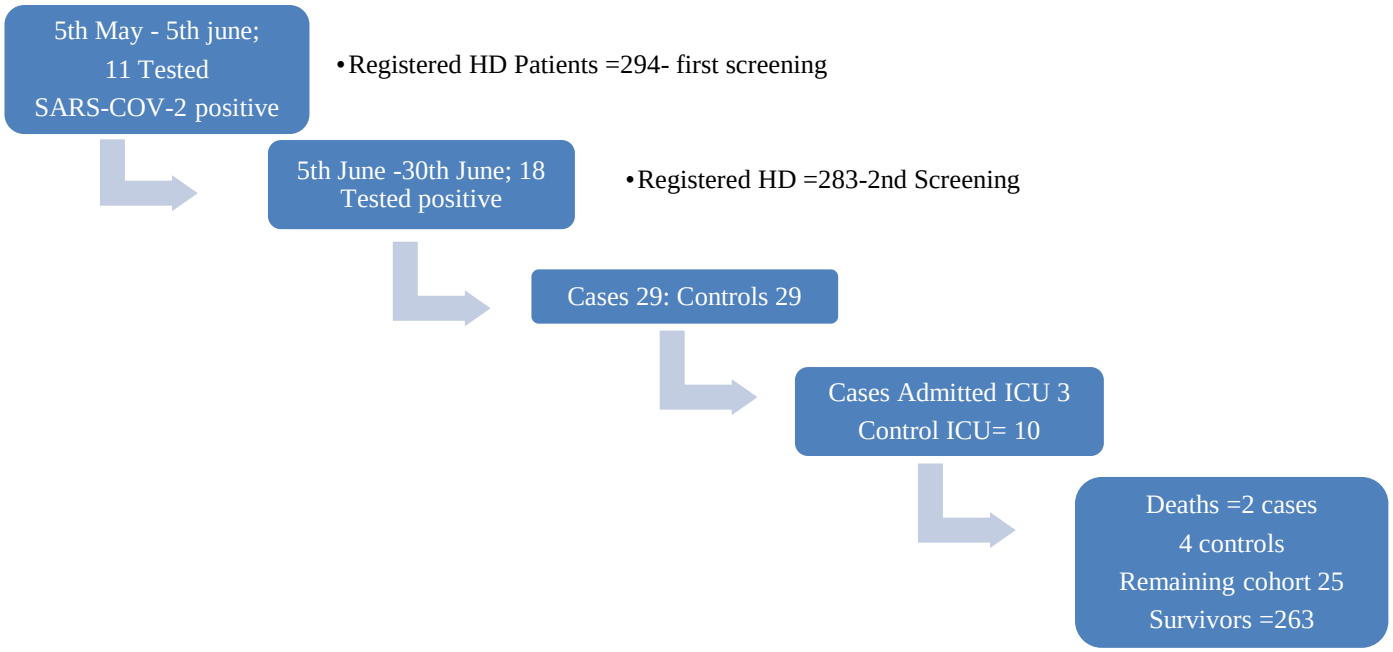

Figure-I: Follow up of outbreak of COVID among maintenance HD patients.

DISCUSSION

The COVID-19 epidemic has overwhelmed nearly all national healthcare systems worldwide and prompted the World Health Organization to declare it a pandemic, sounding a global alarm.[4] Common perception derived from epidemiological surveys indicated that the elderly or patients with comorbidities were more vulnerable to COVID-19 as well as the incidence of severe cases and the mortality risk were high.[16,18-20] However, the lack of similar reports regarding the impacts of COVID-19 epidemic on HD patients was a mystery. Patients undergoing hemodialysis (HD) constitute a unique cluster within the chronic disease population, forming a significant and specialized group that often receives concentrated dialysis treatment in spacious facilities. Additionally, their compromised immune systems raise concerns that if infected, they could potentially become "super-spreaders" of the virus.

Considering these observations, HD patients and HD centers deserve priority action for epidemic prevention and control. Wang *et al* did a systematic review on risk factors of mortality in COVID-19 patients. In their systematic review they found previous respiratory illnesses to be a greater risk factor for mortality in hemodialysis patients [21]. These findings are findings are consistent with findings of our study in which mortality was low in patients only on hemodialysis.

The COVID-19 epidemic first emerged at our center in May 2020. Despite implementing various measures such as enhancing prevention and protection, quarantine, and isolation, the most effective method we found for containing the epidemic was thorough screening to identify infected cases, primarily based on chest CT scan results. Contrary to the findings of Chen *et al*., who reported increased incidence and mortality among COVID-19 patients, our study observed no deaths directly related to COVID-19 infection. During the outbreak at our center, among 294 registered patients, two deaths were recorded, resulting in a mortality rate of 0.68%, which is higher than historical rates for the same period. However, none of the deaths were directly attributable to pneumonia; the main causes were cardiovascular and cerebrovascular complications or hyperkalemia, likely due to reduced dialysis sessions to minimize virus exposure.

While HD patients are very susceptible to COVID-19, infections in this population are less severe or fatal. Only three out of 29 infected patients required ICU admission, compared to five in the control group. Similar to the findings of Tian *et al*., cough was the most common symptom in our study, with some infected patients showing no obvious clinical symptoms.

Amid the emergence of the epidemic, implementing prevention and protection measures becomes imperative to prevent infection, while ensuring timely and sufficient dialysis remains critical for patient survival. Due to the significant biological resemblance between SARS-CoV-2 and SARS-CoV, HD patients infected with SARS-CoV-2 might require a prolonged quarantine period to contain further transmission, as they may take longer to clear the virus.

Previous studies have indicated that SARS-CoV-2 infection can reduce lymphocyte counts while significantly increasing inflammatory cytokine levels, potentially leading to cytokine storms and worsened conditions. Interestingly, the compromised immune system in HD patients may prevent the launch of an effective immune response against CoV-2 infection, thereby avoiding cytokine storms and severe organ damage which goes in parallel with our study as there was no association between individuals undergoing hemodialysis and critical Covid19 manifestation.

CONCLUSION

The findings of this investigation underscore the vulnerability of hemodialysis (HD) patients amidst the COVID-19 epidemic, emphasizing the designation of HD centers as high-risk environments. Notably, individuals undergoing hemodialysis and testing positive for COVID-19 tend to manifest mild clinical symptoms, presenting a lower likelihood of progressing to severe pneumonia. This pattern is linked to compromised cellular immune function and an inherent incapacity to incite cytokine storms.

The study illuminates the distinctive clinical trajectory of HD patients in the context of COVID-19, shedding light on factors that contribute to their relative resilience to severe respiratory complications. By elucidating the mild nature of symptoms and reduced progression to severe pneumonia, the research advocates for a nuanced understanding of the interplay between COVID-19 and the unique physiological characteristics of HD patients. These insights have implications for clinical management strategies, suggesting the necessity for tailored approaches in high-risk HD centers to enhance

patient outcomes and guide preventive measures during the ongoing pandemic.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Farhan Zaid: Literature search, study design, conceptualization

Malik Nadeem Azam Khan: Data analysis, data interpretation

Aakash Aslam: Data analysis

Ahsan Tanvir: Manuscript writing

Fahad Javed Awan, Amna Butt: Data collection

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