Original Article

The Risk Factors of Poor Outcomes in Chronic Kidney Disease Patients with Coronavirus Disease -19

Omer Sabir[1], Aijaz Zeeshan Khan Chachar[2], Adnan Hussain Shahid[2], Syeda Arzinda Fatima[2] and Muhammad Kamran Rauf[2]

ABSTRACT

Objective: To analyze the epidemiological and clinical characteristics of COVID-19 in patients with chronic kidney disease (CKD) and identify risk factors predictive of mortality in this population.

Study Design: A retrospective study.

Place and Duration of Study: This study was conducted at the Department of Nephrology, Fatima Memorial Hospital, Lahore from September, 2020 to September, 2021.

Methods: This was a retrospective Study analysis of data collected during the first and second waves of COVID in Lahore, Pakistan. We split the dataset into CKD and Non-CKD Groups after excluding all patients with AKI (including AKI on CKD). Then an extensive descriptive and inferential data analysis was carried out on statistical software R both in-between groups and within-group (CKD).

Results: The study cohort consisted of 454 non-CKD and 121 CKD patients with COVID-19. The mean age was comparable between groups (54.02 ± 15.88 years for non-CKD vs. 51.97 ± 15.32 years for CKD, p=0.29). Males were significantly less likely to present with CKD (OR 0.324, p<0.001). While diabetes mellitus, hypertension, cardiovascular disease, and other comorbidities showed no significant differences, CKD patients exhibited higher total leukocyte counts (TLC) and oxygen requirements at presentation compared to non-CKD patients. Additionally, CKD patients had a significantly higher mortality rate (13.2% vs. 5.7%, p=0.009).

Conclusion: The epidemiology of COVID 19 in patients with CKD in Pakistan is not well defined. A few risk factors of death are described however further efforts are required to elucidate other risk factors.

Key Words: COVID-19, Coronavirus Disease 2019, Chronic Kidney Disease, CKD, Neutrophil-to-Lymphocyte Ratio, NLR.

Citation of article: Sabir O, Chachar AZK, Shahid AH, Fatima SA, Rauf MK. The Risk Factors of Poor Outcomes in Chronic Kidney Disease Patients with Coronavirus Disease -19. Med Forum 2024;35(11): 113-117 .doi:10.60110/medforum.351124.

INTRODUCTION

The coronavirus disease has proved to be a pandemic of a lifetime. It has taken its toll on the health care systems all around the world. A lot of research has been spurred by this disease. Most of the studies identified preexisting organ damage (chronic kidney disease, chronic liver disease, cardiovascular disease etc.)[1] as significant risk factors of mortality relatively early in the course of this pandemic.

Chronic Kidney Disease (CKD) affects almost 700 million people in the world and is the 12th leading cause of death.[2]

[1.] Department of Nephrology / Medicine[2], Fatima Memorial Hospital, Lahore.

Correspondence: Omer Sabir, Department of Nephrology, Fatima Memorial Hospital, Lahore.
Contact No: 03214177790
Email: omersabir77@gmail.com

Received: February, 2024
Reviewed: March-April, 2024
Accepted: September, 2024

The healthcare burden of CKD with requirement for dialysis is huge especially for a country like Pakistan where the prevalence of CKD has been variously given as 12.1 – 30%.[3]

Pakistan has had its share of COVID burden. Till date a total of 1.5 million infections and more than 30000 deaths have been reported. The non-communicable chronic disease burden is also significant (cardiovascular diseases: 18%, Asthma: 5- 10% COPD: 2.1%, Diabetes: 26 – 30%, chronic kidney disease: 21.2%)[3]. It is but understandable that many of the patients with chronic diseases contracted COVID, thus the outcome of these patients may not be the same as those without premorbid illnesses.

The patients with chronic kidney disease (CKD) are at the added disadvantage of having inadequate healthcare resources. The lack of nephrologists, delayed referral by the primary care, difficult to obtain or expensive medications and, in later stages, refusal to accept renal replacement therapy are a few reasons why these patients are neglected and often present with complications. As the kidney disease advances, the immune system dysregulation becomes more prominent[4], hence making these patients more prone to

acquiring infections including, but not limited to, COVID 19.

The patients with chronic kidney disease and COVID represent even lower presentation in the current research scenario in Pakistan. For instance, a search on the leading Pakistani medical database using keywords "chronic kidney disease" and "COVID" retrieved a total of 6 articles. Out of these six articles, none focused primarily on the CKD patients. This is in spite of the fact that the prevalence of CKD is quite high and many of these patients must have presented with CKD (possibly advanced) and COVID as in our data collection.

We understood this deficiency in the current Pakistani literature and decided to undertake the effort to understand the demographics and outcomes of patients with CKD and COVID.

METHODS

This was a retrospective Study analysis of data collected Department of Nephrology, Fatima Memorial Hospital, Lahore, the second largest city of Pakistan. The data was collected from September, 2020 to September, 2021 during the first and second waves of COVID-19. The dataset contained 635 patients and was collected on a specially designed proforma. For the purpose of the current retrospective analysis this data was Studyed by both the lead authors of this study (Sabir O., Chaacher A.). During the data transformation, we added eGFR based on gender, age and serum creatinine of the patients utilizing CKD-EPI equation. The stages of CKD were designated on the base of the eGFR.

1. Patients coded as AKI, or patients with elevated serum creatinine who were not coded as having CKD were excluded.
2. Patients were included in the analysis if they were not coded as AKI and had an eGFR of more than 60 ml/min. (the Non-CKD Group)
3. Patients were included in the analysis if they were coded as CKD or had elevated serum creatinine and were not coded as having AKI (CKD Group). For CKD designation, we used an eGFR of < 60 ml/min.

Data Analysis Procedure: A total of 575 patients (Non-CKD Group: 454, CKD Group: 121) were included in the final analysis. We excluded 60 patients having AKI as defined above. We planned to employ statistical software R and SPSS for analysis. Categorical variables (nominal and ordinal) were presented as frequencies and percentages, numerical variables as means and SDs. We decided to employ significance tests based on the normality distribution of the data which was checked with Shapiro Wilk test. Logistic regression analysis was carried out to bring out the effect of numerical variables on outcome variable. Survival analysis was also planned. Wherever applicable a conventional p value of <0.05 was considered significant.

RESULTS

CKD patients showed distinct differences compared to non-CKD patients regarding oxygen requirements and TLC at presentation, both of which were significantly elevated (p=0.000 and p=0.03, respectively). Furthermore, the mortality rate was more than double in CKD patients, highlighting their vulnerability to severe outcomes. Gender was also a significant determinant, with males less likely to have CKD on presentation (p<0.001). CKD patients required higher oxygen supplementation upon hospital admission (mean: 13.20 ± 5.47 L/min) compared to non-CKD patients (11.09 ± 8.21 L/min). Despite differences in inflammatory markers like CRP, ferritin, and D-dimer, these did not reach statistical significance between groups. Overall, CKD patients presented with worse clinical profiles and outcomes, necessitating tailored management strategies. The demographics of the cohort are given in Table 1.

Table No. 1: Comparison of CKD and Non-CKD COVID 19 patients

Variable	Non-CKD patients	CKD patients	p-value
n	454	121	
Age (mean (SD))	54.02 (15.88)	51.97 (15.32)	0.29
Gender = Male (%)	330 (72.7)	56 (46.3)	0.000
Diabetes Mellitus (%)	186 (41.0)	53 (43.8)	0.60
Hypertension (%)	216 (47.6)	55 (45.4)	0.68
Cardiovascular Disease (%)	71 (15.6)	20 (16.5)	0.78
Obesity (%)	55 (12.1)	14 (11.6)	1
Smoker (%)	83 (18.3)	21 (17.4)	0.89
Lung disease (%)	57 (12.6)	17 (14.0)	0.64
Malignancy (%)	9 (2.0)	3 (2.5)	0.72
COVID PCR (%)			
Negative	19 (4.2)	3 (2.5)	-
Positive	433 (95.4)	118 (97.5)	0.74
ICU admission (%)	138 (30.4)	44 (36.4)	
IPPV (%)	54 (11.9)	8 (6.6)	0.10

Receiving kidney replacement therapy (%)	N/A	0 (0)	-
Septic shock (%)	41 (9.0)	11 (9.1)	1
Xray findings (%)			
<50% infiltrates	136 (30.0)	44 (36.4)	0.18
>50% infiltrates	116 (25.6)	23 (19.0)	0.15
Bilateral consolidations	31 (6.8)	10 (8.3)	0.55
Bilateral patchy ground glass opacities	170 (37.4)	43 (35.5)	0.75
Normal	1 (0.2)	1 (0.8)	
Presentation O2 sats (mean (SD))	88.73 (5.68)	88.47 (4.91)	0.19
Presentation O2 requirement (mean (SD))	11.09 (8.21)	13.20 (5.47)	0.000
Presentation TLC (mean (SD))	9.74 (8.57)	10.83 (8.44)	0.03
Presentation D dimer (mean (SD))	865.48 (1331.51)	967.40 (2286.69)	0.89
Presentation CRP (mean (SD))	128.56 (296.06)	99.97 (128.75)	0.98
Presentation Ferritin (mean (SD))	720.10 (707.44)	623.03 (484.14)	0.05
Presentation LDH (mean (SD))	416.92 (369.90)	437.51 (398.88)	0.95
Presentation Creatinine (mean (SD))	0.80 (0.29)	1.55 (0.72)	-
Presentation eGFR (mean (SD))	99.08 (26.21)	46.14 (10.06)	-
Presentation NLR (mean (SD))	9.93 (7.07)	9.68 (8.84)	0.69
Presentation PLR (mean (SD))	98.36 (55.13)	90.16 (43.16)	0.29
Time till outcome (means (SD))	8.28 (3.32)	9.25 (4.37)	0.09
Outcome (Death)	26 (5.7)	16(13.2)	0.009

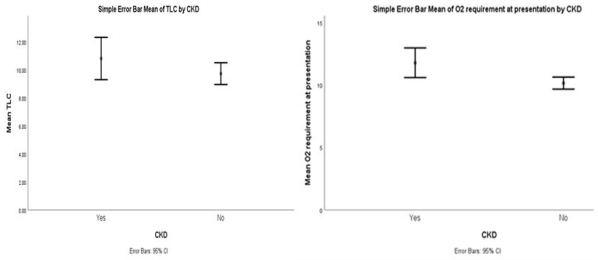

Figure No. 1: Boxplots depicting the differences Total Leucocyte Counts and Presentation O2 Requirement across CKD and Non-CKD Groups.

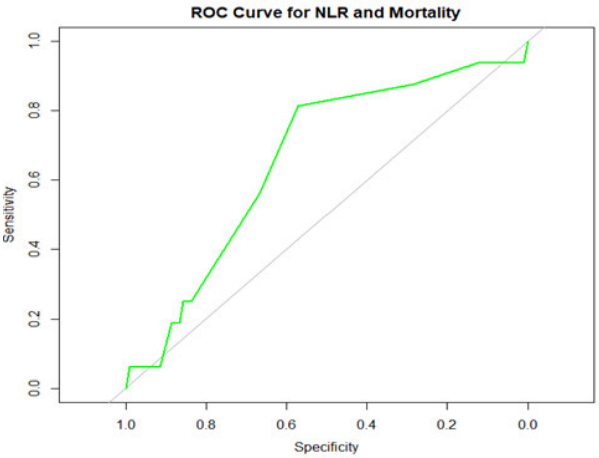

Figure No. 2: AUROC for Neutrophil-to-Lymphocyte Ratio predicting Death.

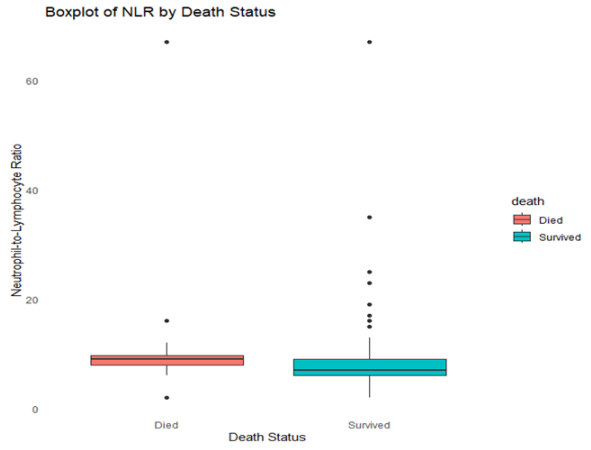

Figure No. 3: Boxplot for NLR and outcome.

Kaplan-Meier survival curves are given in Fig 4.

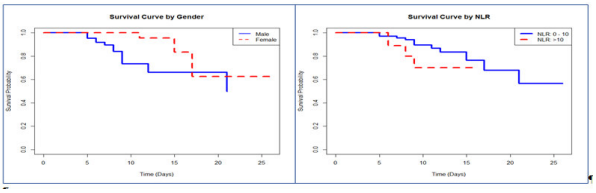

Figure No. 4: Kaplan Meier survival curves for significant variables' interaction with outcome (CKD Group)

DISCUSSION

The results of our study suggest a notable inter-group and intragroup gender-based disparity in COVID-19 outcomes. Our findings revealed that male gender was associated with worst outcomes compared to their

female counterparts. This finding confirms the conventional understanding, as existing literature has consistently associated male gender with poorer COVID-19 outcomes[5]. However, it is essential to highlight that the risk factors associated with higher male mortality, commonly identified in previous research, may not align with our dataset. For instance, indicators such as hypoxemia, oxygen requirement, smoking status, and obesity did not exhibit significant differences between males and females in our study. These male gender-specific risk factors, which have been strongly linked to mortality in Western countries and China, did not manifest in our population. Furthermore, it is crucial to acknowledge the potential influence of our country's social structure on the observed gender-based mortality trends. In our setting, males being the bread winners of the family may tend to present later for emergency care and treatment. However, we also feel that there may be, as yet, some other hidden explanations of this observation.

In our study, Total Leucocyte Count (TLC) which emerged as a significant differentiator between the CKD and non-CKD groups, further serving as a predictor of mortality within the CKD cohort. This observation aligns with prior research, specifically a study by Xiao et al[6] which highlighted the clinical significance of TLC in assessing the severity of COVID-19. The elevated TLC levels observed in our CKD patients may also signal the presence of superimposed bacterial infections, further complicating the clinical trajectory of these individuals.

Additionally, our investigation identified the requirement for supplemental oxygen to maintain saturation levels above 93% as a significant risk factor for mortality within the CKD population. This finding resonates with established knowledge, as oxygen requirement serves as a surrogate marker for disease severity. The strong association between oxygen requirement and mortality is well-documented in the general population affected by COVID-19, given that the primary manifestations of the disease predominantly involve the respiratory system. The three-pronged pathophysiology of increased oxygen requirement with COVID infection including the effect of virus itself by causing consolidations, the superimposed bacterial invasion of the lung tissues and the development of pulmonary edema secondary to COVID infection[7] all explain this observation.

Neutrophil to Lymphocyte Ratio (NLR) was proposed as a marker of poor outcomes in COVID patients as early as April 2020[8]. Further research showed that it was a reliable marker of mortality and morbidity in patients with COVID 19. The pattern commonly reported for severe disease or non-surviving patients is the gradual downward trend in lymphocytes accompanied by a gradual upward trend of neutrophils through the course of illness thus increasing NLR[9-11]. NLR has been sparsely studied in patients with CKD and has been found to be a predictor of inflammation[12] and poor outcomes across some patient populations[13]. It is also a marker of poor outcome in diseases other than CKD and COVID 19 as well[14]. NLR in our patients came out to be a predictor of mortality as well (see results). Our AUROC value are similar to previously reported. We suggest that NLR be checked and reported in COVID cases regularly.

CONCLUSION

The study highlights that COVID-19 patients with chronic kidney disease (CKD) present with higher oxygen requirements, total leukocyte counts, and mortality rates compared to non-CKD patients. These findings emphasize the need for targeted management strategies for CKD patients during COVID-19.

Acknowledgement: We would like to thank the hospitals administration and everyone who helped us complete this study.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Omer Sabir, Aijaz Zeeshan Khan Chachar, Adnan Hussain Shahid
Drafting or Revising Critically:	Syeda Arzinda Fatima, Muhammad Kamran Rauf
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No. FMH/07/2020-IRB/765/M dated 12.08.2020

REFERENCES

1. Fekadu G, Bekele F, Tolossa T, Fetensa G, Turi E, Getachew M, et al. Impact of COVID-19 pandemic on chronic diseases care follow-up and current perspectives in low resource settings: a narrative Study. Int J Physiol Pathophysiol Pharmacol 2021; 13(3):86-93.
2. Cockwell P, Fisher L-A. The global burden of chronic kidney disease. Lancet 2020;395 (10225): 662-664.
3. Hasan, M., Sutradhar, I., Gupta, R.D. et al. Prevalence of chronic kidney disease in South Asia: a systematic Study. BMC Nephrol 2018;19: 291. https://doi.org/10.1186/s12882-018-1072-5.
4. Espi M, Koppe L, Fouque D, Thaunat O. Chronic Kidney Disease-Associated Immune Dysfunctions: Impact of Protein-Bound Uremic Retention Solutes

on Immune Cells. Toxins 2020;12(5):300. https://doi.org/10.3390/toxins12050300.
5. Kharroubi SA, Diab-El-Harake M. Sex-differences in COVID-19 diagnosis, risk factors and disease comorbidities: A large US-based cohort study. Front Public Health 2022;10:1029190.
6. Xiao LN, Ran X, Zhong YX, et al. Clinical value of blood markers to assess the severity of coronavirus disease 2019. BMC Infect Dis 2021;21:921.
7. Cui X, Chen W, Zhou H, Gong Y, Zhu B, Lv X. Pulmonary Edema in COVID-19 Patients: Mechanisms and Treatment Potential. Front Pharmacol 2021;12:664349.
8. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020;84:106504.
9. Toori KU, Qureshi MA, Chaudhry A, Safdar MF. Neutrophil to lymphocyte ratio (NLR) in COVID-19: A cheap prognostic marker in a resource constraint setting. Pak J Med Sci 2021;37(5):1435-1439.
10. Li, X., Liu, C., Mao, Z. et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic Study and meta-analysis. Crit Care 2020;24:647.
11. Prozan L, Shusterman E, Ablin J, Mitelpunkt A, Weiss-Meilik A, Adler A, et al. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 compared with Influenza and respiratory syncytial virus infection. Sci Rep 2021;11(1):21519.
12. Uduagbamen P, Oyelese A, AdebolaYusuf A, Thompson M, Alalade B, Ehioghae O. Neutrophil Lymphocyte Ratio as an Inflammatory Marker in Chronic Kidney Disease: Determinants and Correlates. Open J Nephrol 2022;12:23-35.
13. Yoshitomi R, Nakayama M, Sakoh T, Fukui A, Katafuchi E, Seki M, et al. High neutrophil/ lymphocyte ratio is associated with poor renal outcomes in Japanese patients with chronic kidney disease. Ren Fail 2019;41(1):238-243.
14. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. Int J Mol Sci 2022; 23(7):3636.