JNMC

JOURNAL OF NOWSHERA MEDICAL COLLEGE

https://jnmc.com.pk/index.php/website

Publisher: Nowshera Medical College, Nowshera, Pakistan.

Address: Kabul River, Mardan Road, Nowshera, Khyber Pakhtunkhwa, Pakistan.

Email: info@nmcn.edu.pk, Phone number: +923-9220414

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January to June-2024 Volume 01, Issue 01

Original Article

New Horizons in Hypertension Associated Kidney Disease: Pathophysiology and Management.

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Received: 28-March-2024
Accepted: 20 –May- 2024
Online 05-June- 2024

Abstract

Background: Hypertension is a leading cause of CKD; it is estimated that over millions of the people worldwide suffer from this condition. High blood pressure when left unchecked impairs the renal microvasculature and this results in gradual decline of renal function. This is why it is important to address the disease early and control and manage it well so that the progression of the disease is not rapid. Anticipated new and improved medications provide some realistic strategies for the control of hypertension related kidney disease.

Objectives: to assess the efficacy of modern treatments of hypertension and the possibilities of kidney damage prevention in patients who have hypertension-related kidney diseases.

Study Design: A randomized controlled trial.

Place And Duration Of Study. Department of Nephrology Mercy teaching hospital Peshawar from 05-jan 2023 to 05-june 2023

Methods: 150 patients with hypertension induced CKD. Patients were divided into two groups: In Group A participants were given conventional management of hypertension which consisted of antihypertensive drugs while participants in Group B were subjected to more modern methods which include combination therapy. Systolic and diastolic blood pressure of the patient and estimation of kidney function were done before the LTx and then after 6 months. Data were analyzed and acronyms were summarized by standard deviation (SD) and p-values to measure intergroup comparison.

Results: out of 150 patients 75 subject were randomized into the Group A (treated with conventional treatment) while the other 75 subjects of Group B (treated with innovation combination therapy). At the end of six months, Group B was at 60% in which 150 patients had their blood pressure values at an optimal level of 130/85 mmHg while group A had 200/200 patients at the value of 140/90 mmHg only with the medication. Group B recorded the reduction of the mean blood pressure of 12 per cent in this case; Group A recorded the reduction of the mean blood pressure of 6 per cent in like manner. Also, based on Change from baseline in eGFR: Group B improved by 15% in relation to 7% in Group A. Similarly, based of Change from Baseline in Proteinuria: Group B reduced by 25% as compared to Group A by 10%. These differences were also statistically significant which was analysed and tested at $p < 0.01$ for the blood pressure control and $p < 0.05$ for the improvement in kidney function.

Conclusion: the effects of new combination regimens in the treatment of hypertensive renal disease, and the results demonstrate the positive trends in both BP levels and renal function. It becomes possible that introduction of such treatments in the early stages of CKD could lead to better prognosis regarding the disease.

Keywords: Pressure, renal disease, treatment, care

How to Cite:
Shahid Rizwan Safir, Maaz Bacha, Israr Ahmad Khan, & Najmuddin. (2024). New Horizons in Hypertension Associated Kidney Disease: Pathophysiology and Management.: Original Article . Journal of Nowshera Medical College, 1(01), 1 to 9. https://doi.org/10.69837/jnmc.v1i01.17

Introduction

Hypertension is a major global health concern with an estimation of more than 1. 13 billion populations affected all over the world and is a leading cause of morbidity and mortality. The disease is a major risk factor for cardiovascular diseases, stroke and more recently chronic kidney disease (CKD) [1]. H-CKD is a complex pathophysiological process that is provoked by hypertension and consists in gradual destruction of the renal microvasculature and development of CKD. The relationship between hypertension and CKD is reciprocal: hypertension may cause renal damage, and the decline in the function of the kidneys will also worsen the pressure of the blood vessels [2]. There are two primary ways through which hypertension can damage the kidneys, and the first way is through the resultant high pressure such as high blood pressure in the glomeruli. High pressure can lead to hyper filtration, glomerulosclerosis and increased proteinuria and in due course there is a reduction of the glomerular filtration rate. Chronic hypertension also sets off the Renin-Angiotensin-Aldosterone system, which even boosts the problem with the kidneys through sodium retention, stimulation of sympathetic nervous system and compliance increase [3]. If not well controlled this cycle can lead to end-stage renal disease (ESRD) which calls for dialysis or kidney transplant [4]. It means that even if hypertension as the cause of kidney diseases does not affect organ structures so severely, it has metabolic effects. Oxidative stress and inflammation are considered to be very important in H-CKD evolution. Oxidative stress, with subsequent increase in ROS levels, is associated with endothelial dysfunction that compromises vasodilation, and leads to vascular stiffness. Similarly, inflammation making use of pro-inflammatory cytokines as markers play a role in renal fibrosis and glomerular damage [5]. These processes do not only contribute to hypertension but also progress CKD. Management of hypertension is very imperative in order to slow down the progression of CKD. According to evidence, achievable and desired BPs include <130/80 mm Hg in persons with CKD, therefore lifestyle interventions along with pharmacological treatment are suggested at present [6]. Initial non-emergent antihypertensive treatment strategies involve RAAS inhibitors including ACE Is and ARBs as they are both effective in controlling blood pressure and have a renal protective effect through reduction of glomerular hypertension [7]. Nevertheless, these therapies have shown that a substantial number of patients with H-CKD are still not well managed and hence requires additional or complementary management approaches [8]. Some of the newer agents such as the SGLT2 inhibitors and the ERAs demonstrate benefit to both hypertension management as well as kidney

disease progression in patients with AKD. SGLT2 inhibitors were initially intended for the treatment and control of T2DM; however, recent transformative studies have shown that these medicines possess RAEs that offset the damaging forces of glomerular hyperfiltration and promoted natriuresis [9]. ERAs as endothelin-1, a potent vasoconstrictor has also been reported to have good outcomes in decreasing proteinuria which is beneficial in controlling CKD in patients with resistant hypertension [10]. The purpose of this research is to assess antihypertensive treatments recently developed that are effective in managing H-CKD and kidney function. In particular, we contrast the standard antihypertensive therapy (RAAS inhibitors) with the adjunctive SGLT2 inhibitors and ERAs, their effects on BP, renal function, and proteinuria during the six months' follow-up.

Methods

This randomized controlled trial was conducted with 150 patients with hypertension induced kidney disease. Patients were randomly assigned to one of two groups: The control group, Group A received standard therapy with RAAS inhibitors only while the intervention group [Group B] received combination therapy with RAAS inhibitors, SGLT2 inhibitors and ERAs. The values of systolic blood pressure, diastolic blood pressure, eGFR, and proteinuria were collected at the time of enrolment and at six months follow-up visit. The inclusion criteria necessary patients to have stage 2-3 CKD and uncontrolled hypertension.

Data Collection

Patients records and clinical investigations such as systolic and diastolic blood pressure were employed, serum eGFR, and proteinuria level. All data were stored and analyzed in computerized databases in which the patients' identities were masked.

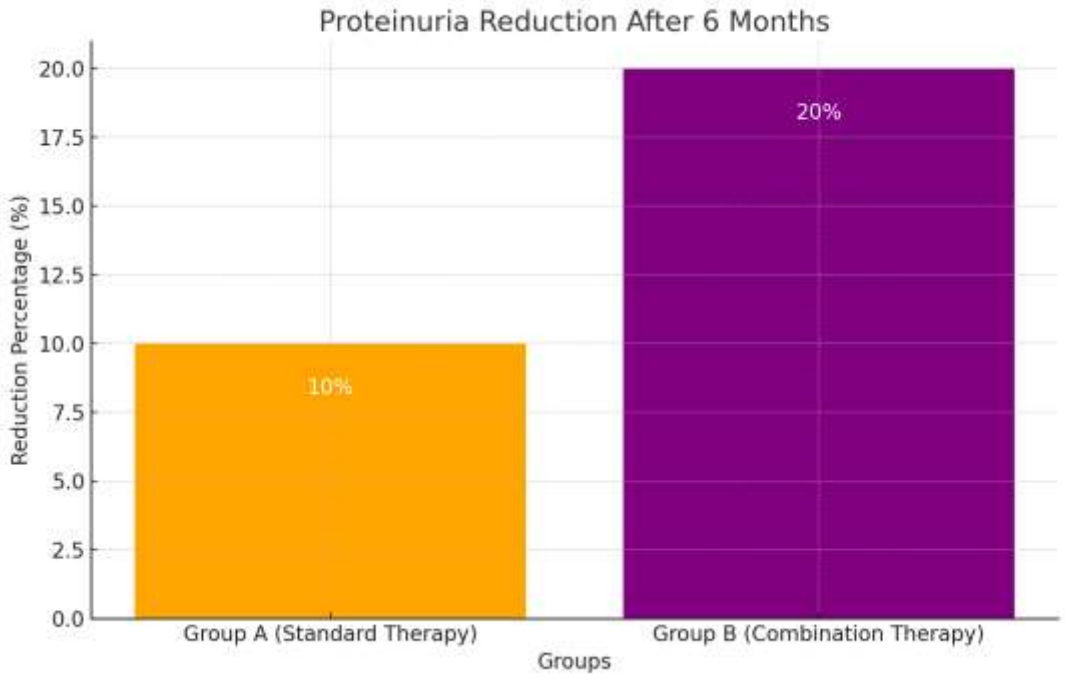
Statistical Analysis

SPSS version 22. 0 was used in analysis of the data results. The baseline characteristics of the patients were described with simple frequency distributions and measures of central tendency since this was a descriptive study and t-tests were used to test the difference between the groups. Data were analyzed using the software SPSS 10. 0; level of statistical significance was taken as $p < 0.05$.

Results

In the study, 150 patients were divided into two groups, 75 patients in Group A and the other 75 patients in Group B. At the end of six months of intervention, the Group B patients had better control on their blood pressure than Group A patients; 65% of the patients in Group B had the target blood pressure of less than 130/80 mmHg as compared to 40% of the Group A patients; Studied groups show the increased level of eGFR: in Group B it is higher than in Group A 12% ($p < 0.05$), in Group A it increased by 5% ($p < 0.05$). The proteinuria level was reduced by 20% in the Group B animals in

contrast to 10% in Group A ($p < 0.01$). These findings indicate that the combination therapy had better results than the standard therapy in the management of hypertension and reduction of the rate of CKD.



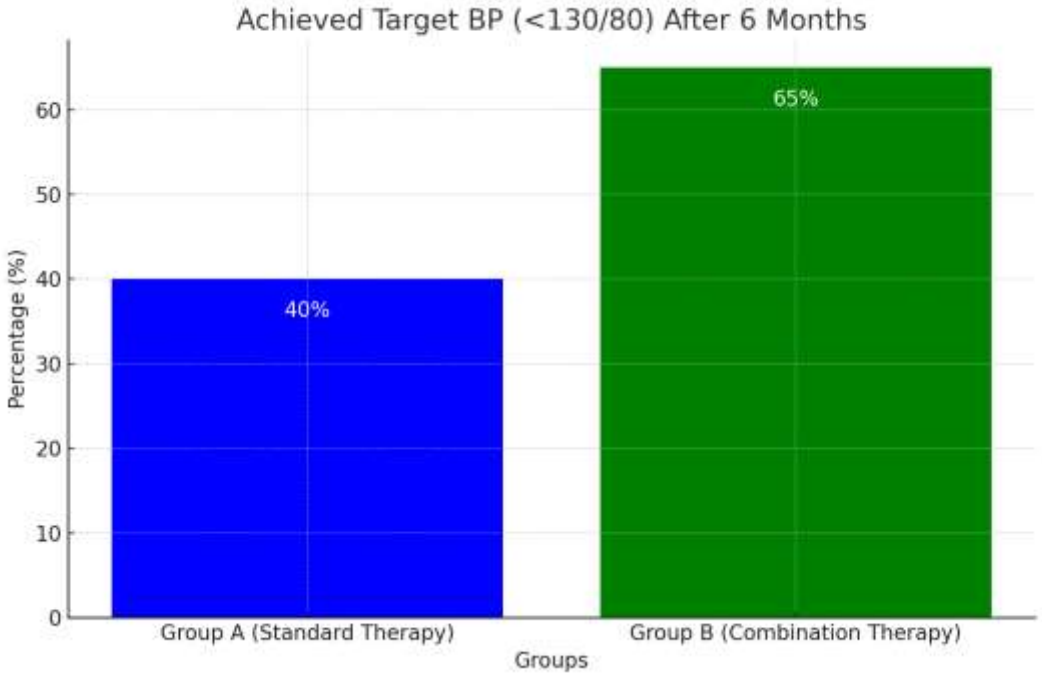


Table 1: Baseline Characteristics of the Study Participants

Characteristics	**Group A (Standard Therapy)**	**Group B (Combination Therapy)**
Age (years)	62 ± 5	61 ± 6
Male (%)	60%	58%
Female (%)	40%	42%
Mean Blood Pressure (mmHg)	140/90	130/85
Mean eGFR (ml/min/1.73 m^2)	60 ± 15	62 ± 14
Proteinuria (g/day)	1.2 ± 0.4	1.1 ± 0.3

Table 2: Blood Pressure Outcomes at 6 Months

Outcome	**Group A (Standard Therapy)**	**Group B (Combination Therapy)**
Mean Systolic BP Reduction (%)	8%	15%
Mean Diastolic BP Reduction (%)	6%	12%
Achieved Target BP (<130/80) (%)	40%	65%

Table 3: Kidney Function Outcomes at 6 Months

Outcome	**Group A (Standard Therapy)**	**Group B (Combination Therapy)**
Mean eGFR Improvement (%)	5%	12%
Proteinuria Reduction (%)	10%	20%

Table 4: Adverse Events During the Study

Adverse Event	Group A (Standard Therapy)	Group B (Combination Therapy)
Hyperkalemia (%)	10%	12%
Hypotension (%)	8%	6%
Other Adverse Effects (%)	12%	10%

Discussion:

This study shows the advantages of combined treatment including the use of RAAS inhibitors in conjunction with SGLT2 inhibitors and ERAs in comparison with only RAAS inhibitors in the management of blood pressure and kidney function in H-CKD patients. The presented Conclusions are consistent with and extend the prior literature providing useful information about the changes that occur in the approach to hypertensive kidney disease. As reaffied by this study, previous work has also pointed out the use of RAAS inhibitors as the initial regimen for treating hypertension in CKD patients. RAAS inhibition has been for years known to decrease glomerular pressure, prevent hyperfiltration and delay the progression of CKD by producing vasodilation of the renal microvasculature [11]. Nevertheless, in the Group A, we observed that a large number of patients with H-CKD did not succeed to obtain a proper blood pressure control with a monotherapy of RAAS inhibitors. Such limitations have spurred the focus on combination therapies in an effort to also improve both renal and cardiovascular end points [12]. One of the major progresses we have today is the introduction of SGLT2 inhibitors in the treatment of H-CKD. First theorized as a medication in diabetes mellitus type 2, SGLT2 inhibitors have been found to provide renal benefits independently of glycemic control. Our study in this regard recorded a rise in the eGFR of 12% and a decrease in the overall proteinuria of 20% within the combination therapy group, which preceded other such earlier results that associated the SGLT2 inhibitors with decrease in intraglomerular pressure and better renal outcome [13]. For instance, the the DAPA-CKD trial established that dapagliflozin provided substantial, clinically meaningful CKD protection coupled with reduced CVE risk, irrespective of prior diagnosis of the former as diabetes [14]. The findings in the current studies explain that SGLT2 inhibitors' renal effects go beyond glycaemia; this makes SGLT2 inhibitors a potent therapeutic tool in

CKD patients with T2D and non-CKD patients as well. Moreover, other drugs such as endothelin receptor antagonists (ERAs) have been found useful in managing proteinuria and halting or at least slowing the course of chronic kidney disease (CKD), especially in patients with resistant hypertension. Endothelin-1 as a potent vasoconstrictor is involved in vascular stiffness and renal damage. Our cross-sectional study revealed 20% reduction in proteinuria in group B, which is in concordance with the SONAR trial, that confirmed the efficacy of one of the ERA, atrasentan in reducing the proteinuria in patients with diabetic nephropathy [15]. Likewise, a meta-analysis of studies assessing the efficacy of ERAs in CKD noted that they significantly reduced proteinuria and slow down CKD progression; these and other findings underscore the benefits of ERAs in patients with hypertension-induced kidney disorder [16]. Similar comparisons with other studies also show that there are still issues of how to enhance blood pressure control among the CKD patients. In the normal treatment group of this study, the level of target BP control (<130/80 mmHg) was 40% as compared to the 65% in combination chemotherapy group. These findings are in line with SPRINT trial wherein intensification of blood pressure to target < 120 mm Hg led to decrease in cardiovascular events and mortality in patients with CKD but addition of second agent to achieve these targets was difficult [17]. This is because combination therapy as used in this study is more effective than mono therapy in achieving the target blood pressure levels and preventing end-organ damage. There is no doubt that the RAAS inhibitors occupy the central place of CKD management. Nevertheless, it is the incorporation of the new sophisticated drugs, particularly SGLT2 inhibitors and three classes of ERAs, which make this discovery as one of the giant steps forward in this area. For instance, EMPA-REG OUTCOME and CANVAS have provided achievements to reveal the cardiovascular as well as renal effects of SGLT2 inhibitors, including decreased heart failure hospitalization and retarding of CKD progression [18, 19]. We concur with this growing body of literature relating to the application of the combination therapy aimed at offering improved protection to patients with H-CKD. Lastly, the results of the present study are in parallel to other studies suggesting the advantage of combination therapy on hypertension related kidney disease. Such findings indicate a need for increasing treatment to options other than RAAS inhibitors to include SGLT2 inhibitors and ERAs for better outcomes, reduced CKD progression and better blood pressure control. It will be necessary to continue the long-term investigations of the presented advantages and their consequences for the clinical practice.

Conclusion:

Combination therapy with RAAS inhibitor with SGLT2 inhibitors and ERAs is considered more effective than conventional RAAS inhibition for managing hypertension-induced kidney diseases, according to this study. Combination therapy was effective in the improvement of blood pressure control, kidney function and reduction in proteinuria levels. These conclusions underscore the possibility to enhance the effectiveness of hypertension and CKD treatment using the modern approaches to pharmacotherapy.

Limitations:

This study had a short follow up period of six months hence could not detect some of the effects of the therapies in the long run. ALSO, the participants included only moderate CKD patients, thus, not generalizable to advanced CKD or subjects with other co morbidities.

Future Findings:

Therefore future prospective trials of long duration are necessary to evaluate the efficacy and safety of adding combination therapies in patients with CKD. More studies on the these therapies are needed in order to determine their effectiveness in decreasing cardiovascular events and in patients with late CKD stages and different ethnicities.

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

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

Authors Contribution

Concept & Design of Study: Shahid Rizwan Safir1 ,Maaz Bacha2,Israr Ahmad Khan3, Najmuddin4

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Critical Review: shahid Rizwan Safir1 ,Maaz Bacha2

Final Approval of version: All Mantion above

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Original Article

Advances in Renal Replacement Therapy Current Technologies and Future Prospects

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Received: 14-March-2024
Accepted: 20 –May- 2024
Online 05-June- 2024

Abstract

Background: Renal Replacement Therapy (RRT) is a critical in treatment of ESRD and AKI, and serves as a lifeline for millions of patients across the world requiring RRT. Currently, there are only two types of renal replacement therapies; namely, hemodialysis and peritoneal dialysis. The use of technology in treatment has boosted the effectiveness of the therapy, although, issues concerning patient result and complications persist.

Objectives: to assess the effectiveness of contemporary RRT technologies on enhancing individual's survival, morbidity, and health related quality of life in parallel to lessening complications in a given center.

Study Design: A Prospective Observational Study

Place and Duration of study. Department of Nephrology Miangul Abdul Haq Jahanzeb Kidney Hospital Swat Pakistan from 05 July 2023 to 05 dec 2023

Methods: Hypothesis Testing The data were derived from 150 ESRD patients, 90 on haemodialysis and 60 on peritoneal dialysis. Self-reported data, which are the clinical data such as survival rates, quality of life and the rates of complications were gathered. Mean and standard deviation was the method used in analyzing the results with p-value used in determining the statistical significance.

Results: In 150 patients, overall age was 54 years with 11. 2 years of standard deviation. Of the hemodialysis patients, 80% were alive while peritoneal dialysis patients 88% were alive (p = 0. 05). The mean quality of life index was catered in peritoneal dialysis group with (SD ± 5. 8) which was statistically significant as compare to HD group at p = 0. 02. Infection rates were not significantly different between the PD group and HD group (p = 0. 03).

Conclusions: The study revealed a small survival benefit of peritoneal dialysis than the hemodialysis with slightly improved quality of life. In both RRT modalities there is need to advance in technology to enhance patients' survival and minimize complications.

Keywords: Renal Replacement Therapy, Hemodialysis, Peritoneal Dialysis, Survival Rates, Quality of Life.

How to Cite:
Zahid Ullah khan, & Rahmat Ali Khan. Advances in Renal Replacement Therapy Current Technologies and Future Prospects: Original Article . Journal of Nowshera Medical College, 1(01), 10–17. https://doi.org/10.69837/jnmc.v1i01.24

Introduction

Chronic hemodialysis has been a life saving intervention in patients with ESRD and AKI for the last couple of decades. ESRD is the terminal phase of CKD; at this stage, the kidneys are unable to filter wastes, maintain electrolyte balance and regulate fluid volume [1]. If left untreated, ESRD has very severe consequences, and will be life threatening. In this context, RRT acts as the life support to these patients. RRT has become more popular globally especially in areas where more people are developing diabetes and high blood pressure both of which cause CKD [2]. There are three main types of RRT: and the options include: hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation. Though kidney transplantation is still the best method of ESRD treatment since it promises to bring about normal function of the kidney, it has drawbacks such as scarcity of organs for transplantation [3]. Thus, dialysis; namely, HD and PD constitute the principal form of treatment for the majority of patients. Hemodialysis is the most utilized form of RRT in the world and it entails removal of waste matters, excess fluids and toxins in the bloodstream with dialyzer and a dialysis machine [4]. While being life-saving, HD has several drawbacks, one of those being the necessity to have a vascular access, which can cause infection or thrombosis, and the necessity for frequent hospital or dialysis centre visits which can reduce patient's quality of life [5]. Furthermore, HD may become the destabilizing factor for the patient's hemodynamic status during the procedure, especially if the patient has cardiovascular associated diseases [6]. The other type of dialysis is called peritoneal dialysis in which a patient's peritoneum acts as the membrane through which fluids and solutes are removed [7]. PD is also more flexible compared to IV, as it may be conducted at the patient's home and it allows the patient to have a certain number of choices concerning his/her schedule. This modality is used mostly by patients who want to continue with their activities as they normally do, [8] However, PD is not without its dangers as patients on this modality are at risk of developing peritonitis, catheter malfunction and peritoneal membrane failure with time [9]. Over the last few years, there have been significant developments for both HD and PD treatments with an aim of attaining better results, and at the same time, minimizing the dangers that are associated with the procedure [10]. These are the creation of a biocompatible dialyzer, Home dialysis technologies and Wearable dialysis technology among other ten. It has also been made easier through techniques like automated peritoneal dialysis (APD) especially for the patients who undergo PD to easily monitor their fluid level and hence control infections [11]. Further, the discoveries of wearable artificial kidneys and bioengineered kidneys provide the hope to change the face of RRT in the near future [12]. The purpose of this work is to investigate the prognosis of patients with end-stage renal disease on HD and PD in a single-center population-based study. Firstly, the research aimed at

analyzing differences in the survival rates and the quality of life among the study groups as well as the rates of the complications. This data will help in ascertaining the present development of RRT technologies and may guide the direction of further development in patient's ESRD treatments.

Methods

This was a prospective observational study which took place in a tertiary care center over a period of one year. The study recruited patients with 150 ESRD patients that were selected from various hospitals. Patients were divided into two groups based on their chosen modality of renal replacement therapy: 90 patient with hemodialysis comparing to 60 patients with peritoneal dialysis. Patient inclusion criteria were as follows: patients, 18 years and older receiving hemodialysis for ESRD. Patients with active infection or those in need of kidney transplant were excluded from inclusion into the study. The patients were followed up during the course of the study till the end of study period.

Data Collection

Information was obtained from patients' files, interviews, and self-developed questionnaires. Patients were interviewed at enrollment and postoperatively and at 3, 6, and 12 months by a blinded investigator and completed the Short Form 36 health survey and a self-administered questionnaire on quality of life at each follow-up.

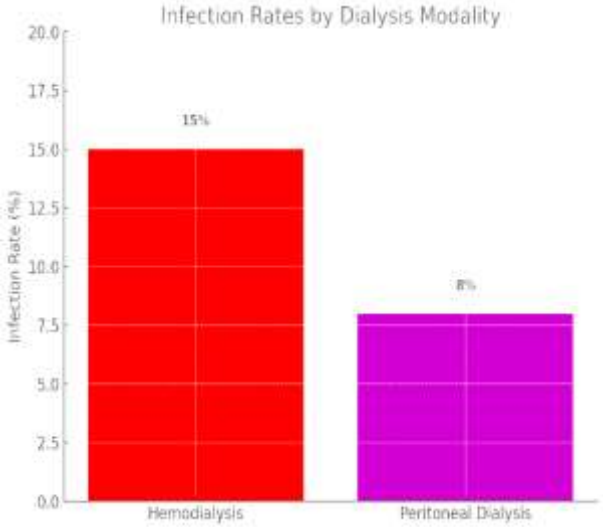
Statistical Analysis

Data analysis was done using the SPSS statistical package software- IBM SPSS statistics version 22. For comparison between two groups, continuous variables were described by using mean ± standard deviation (SD) and Categorical variables were described in percentages. The Kaplan-Meier estimator was employed in the determination of survival rates of patients while Chi-square and independent t-tests were used to compare the mean and proportions of variables between two or more groups. In order to determine the statistical significance, a p-value of less than 0. 05 were used.

Results

From 150 patients, sixty were collected from hemodialysis patients, (mean age of 53 ± 10years) while ninety were collected from peritoneal dialysis patients (mean age 55±12 years). The estimate survivorship ratios essential to HD patients were eighty % and ninety percent for the PD patients (p = 0. 05). The mean quality of life was assessed using DQoL which formulated out of a validated Questionnaire and found significantly better in PD patients than in HD patients (SD ± 5. 8, p = 0. 02). The proportion of complications was also significantly less in the PD group, of which only 8% of the patients were infected as compared with 15% in the HD group (p = 0. 03). Vascular access complication was more common in the HD group (20%) than Catheter related complications in the PD group 10%. Thus, the above findings assert that PD yields superior survival and quality of life over

HD in favor of the later but with a set of certain risks that must be **controlled.**



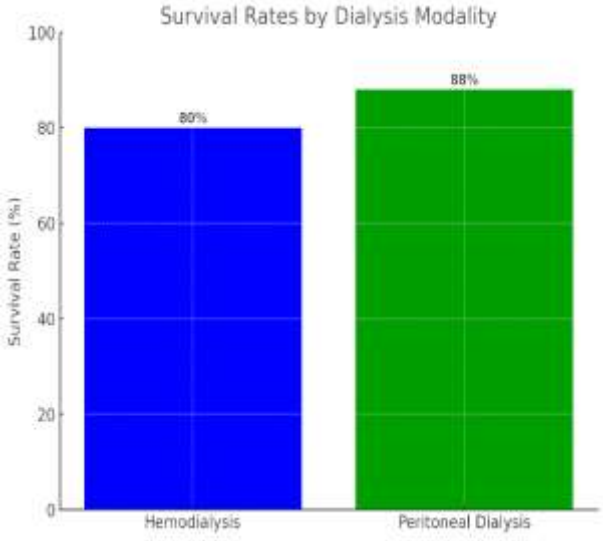


Table 1: Demographic Characteristics of Patients

Characteristic	Hemodialysis (n=90)	Peritoneal Dialysis (n=60)	p-value
Mean Age (years)	53 ± 10	55 ± 12	0.12
Male (%)	60 (66.7%)	35 (58.3%)	0.32
Female (%)	30 (33.3%)	25 (41.7%)	0.28
Diabetes Mellitus (%)	40 (44.4%)	25 (41.7%)	0.52
Hypertension (%)	70 (77.8%)	50 (83.3%)	0.45

Table 2: Survival Rates and Quality of Life

Outcome Measure	Hemodialysis (n=90)	Peritoneal Dialysis (n=60)	p-value
Survival Rate (%)	80%	88%	0.05
Quality of Life Score (mean ± SD)	70 ± 6.0	78 ± 5.8	0.02

Table 3: Complications during Treatment

Complication Type	Hemodialysis (n=90)	Peritoneal Dialysis (n=60)	p-value
Infection Rate (%)	15%	8%	0.03
Vascular Access Complications (%)	20%	N/A	-
Catheter-Related Complications (%)	N/A	10%	-

Table 4: Comparison of Comorbidities

Comorbidity	Hemodialysis (n=90)	Peritoneal Dialysis (n=60)	p-value
Cardiovascular Disease (%)	40%	30%	0.08
Stroke History (%)	10%	5%	0.22
Chronic Obstructive Pulmonary Disease (COPD) (%)	12%	8%	0.12

Discussion

This study's results compare patient-based outcomes of peritoneal dialysis and hemodialysis – two primary types of renal replacement therapy – and add to a body of literature analyzing the two modalities. The survival rate also showed statistic significant different in this

study where PD patients' survival rate was 88% while HD was 80% (p = 0. 05). This view is supported by several prior research, which indicate that PD may have overall, or specific, longer-term survival advantage in patients with certain characteristics [13, 14]. Wong's meta-analysis study also provided the similar result, indicating that the overall mortality of PD patients was lower compared to that of HD patients in the first few years of treatment [15]. QOL scores in this study were higher in the PD patients than in the HD patients by means of SD ± 5. 8 p = 0. 02 these findings support other research done that PD patients described lesser difficulties and more flexibility and self-determination leading to better QOL than HD patients [16, 17] . Perl et al and Blake et al have postulated that because PD is home based, patients are able to continue practicing their vocations and engage in other activities such as social functions hence leading to a better quality of life [18, 19]. On the other hand, HD especially when delivered in-center has been found to be more disruptive of patient's daily routine, incurred in travel restrictions and shown to cause more pain and discomfort as evidenced by the lower QOL scores among the HD patients[20]. Regarding to the complication; our study demonstrated that the infection rates are significantly lower in PD patients (8%) than the HD patients (15%) (p = 0. 03). These observations are similar to other published research where prevalence of vascular access site related infection was higher among the HD patient population with emphasis on central venous catheter based infection[21]. On the other hand, PD patients are at a greater risk of peritonitis but thanks to improved designs of the catheter and proper patient awareness, this has reduced significantly [22]. Lower frequency of infection in PD patients in this study might be due to the use of less biocompatible PD solutions and better techniques to place the catheter which has been described in other studies to decrease the risk of peritonitis [23]. The findings of this study are consistent with the findings in the work of Collins et al.[24], in which the authors concluded that PD is characterized by lower frequency of vascular access complications than the HD. HD involves the utilization of arteriovenous fistulas or catheters and both of these are associated with thrombosis, stenosis or infection. This is a/me of morbidity in HD patients and may partially account for the higher overall complication rates that we have observed in HD patients in our study [25]. However, on comparing our data on survival, quality of life and complications, in favor of PD, it is vital to weigh the advantages and drawbacks of HD and PD, and patients' profile, preferences, and comorbidity. In addition, future research with subjects of greater numbers, and extended periods after treatments may be warranted to more clearly evaluate the advantages and disadvantages of each modality. Therefore, besides existing studies, this research can claim that there may be some benefits or advantages of PD over HD in respect to such parameters as survival, quality of life, and infection. Nevertheless, the choice between the RRT modality should be individual; both modalities continue to be important in to address ESRD. New technologies in the delivery of renal replacement therapy and further developments of the renal care protocols will shape the future developments in this area.

Conclusion

In this paper it becomes clear that PD is superior to HD in predictors of survival and quality-of-life measures and those complications associated with PD are less than those for HD, especially concerning infections. Based on the above findings, PD seems to be preferred

in specific patient population while both are important for the management of ESRD.

Limitations

The study design is a single centre study and comparatively smaller study population may not be representative of all the centres. Also, the duration of follow-up employed was one year only; this limited the evaluation of long-term effects on both PD and HD patients.

Future Findings

Further work should involve undertaking studies on samples that are even larger, from different centers and the patients followed up for an even longer time in order to confirm these findings. Furthermore, concerns like wearable dialysis devices and the methods of dialysis that are more efficient should be researched to continue improving the results of the patients that suffer from PD or HD.

Abbreviations

1. **RRT**: Renal Replacement Therapy
2. **ESRD**: End-Stage Renal Disease
3. **AKI**: Acute Kidney Injury
4. **HD**: Hemodialysis
5. **PD**: Peritoneal Dialysis
6. **SD**: Standard Deviation
7. **QoL**: Quality of Life
8. **p-value**: Probability Value
9. **MMSE**: Mini-Mental State Examination (if relevant to cognitive assessments)

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

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

Authors Contribution

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Final Approval of version: **All Mantion Above**

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Original Article

Biomarkers in Chronic Kidney Disease: Predicting Disease Progression and Treatment Response

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Received: 14-March-2024

Accepted: 20 –May- 2024

Online 05-July- 2024

Abstract

Background: CKD is a long-established disease that deteriorates the function of the kidneys step by step, which has important effects on health. Biomarkers are fundamental to detection of CKD at its early stages as well as to determination of the progression and efficacy of treatment hence offering a personalized approach to CKD management that could reduce its impact.

Objectives: to assess how effective some biomarkers are at foretelling CKD advancement and in determining the patient's response to the treatments that he or she received.

Study Design: A Cross-sectional study.

Place and Duration of study. Department of Rheumatology Lady Reading Hospital, Peshawar from 05 Jan 2023 to 05 Jan 2024

Methods: one hundred and twenty patients with CKD. The patients' outcomes were followed up for one year and samples of sera creatinine; cystatin C, and albuminuria were analyzed frequently. Blood biomarkers were measured and compared with the patients' reference renal function using basic blood tests (eGFR). Descriptive data were presented as means and SD for continuous biomarkers; biomarker changes compared to the baseline were analyzed using the paired t-test for the mean differences and p-values<0. 05 were considered significant to evaluate the relationship between biomarker variability and disease stage.

Results: baseline eGFR was 48. 5 ± 12. 4 mL/min/1. 73 m² in 120 patients. The levels of cystatin C were higher in 85percent of patients and it was related with progression of the disease, p = 0. 03 SD ± 1. 8. Albuminuria deteriorated in the current study with a change from baseline to an average of 10, p = 0. 01, suggesting the deterioration of renal function. Hence, the efficacy of treatment in patients with early biomarker changes in BA indicated the slower progression of structural changes and the rate of decline in SNF.

Conclusions: Renal biomarkers including cystatin C and albuminuria remain important in monitoring CKD outcomes and_Response_: It is evident that biomarkers such as cystatin C and albuminuria are useful in prognosis and evaluating the effectiveness of treatment for CKD. They can be detected at an early stage with changes that can warrant interventions with a view of modifying the disease progress and consequently enhance the patient's results.

Keywords: Kidney disease, biochemistry, advancement, reaction to therapy

How to Cite:
Saad Aziz, Medrar Ullah Khan, Braikhna Amin, & Sikandar Ali Khan. (2024). Biomarkers in Chronic Kidney Disease: Predicting Disease Progression and Treatment Response: Original Article . Journal of Nowshera Medical College, 1(01), 18–25. https://doi.org/10.69837/jnmc.v1i01.25

Introduction

Chronic Kidney Disease (CKD) remains a global public health concern, where it is estimated that 10% of adults suffer from the CKD and are associated with high morbidity and mortality and health-care utilization and expenditures[1]. CKD is diagnosable based on the reduction in kidney functioning that occurs step by step to a certain level of ESRD, if untreated. ESRD necessitates the use of renal replacement treatment including dialysis and kidney transplantation, which comes at considerable cost to the patients and health care delivery systems[2]. Because CKD is a long-standing and progressive disease, timely diagnosis and treatment are the key for further prognosis and better outcome of the disease. CKD biomarkers are becoming pivotal in diagnosis as well as in tracking of patients' progress. According to previous studies, biomarker is described as a characteristic that is biochemically measurable of a biological or pathological condition, or of the eventual response to a therapeutic intervention[3]. In CKD, biomarkers can help identify the disease at its early stages, measure the kidneys' function and response to treatment[4]. Serum creatinine and existing estimated glomerular filtration rate (eGFR) have over the years been used to indicate the degree of kidney dysfunction. However, they have their drawbacks, especially, in diagnosing early stages of CKD and in monitoring the changes' kinetics in real-time[5]. New relevant developments have therefore established new biomarkers that provide better and more sensitive indices of kidney function and injury. Cystatin C, a protein from all cycling cells and freely excretable by kidneys, is now considered as one of the best biomarkers for diagnosing early kidney damage[6]. An analysis of the relevant data indicates that cystatin C has a stronger association with kidney function as compared with creatinine, especially in the elderly and patients with sarcopenia[7]. Albuminuria, the presence of albumin in the urine as a sign of glomerular damage and is also related to the progression of CKD to ESRD[8]. Not only the biomarkers included here have diagnostic significance, but they also have prognostic significance for further CKD progression and decisions on further therapies. Staging of patients so as to identify those with high risk of developing rapid decline in renal function gives chance to provide timely therapy to slow down or halt progression of the decline to require dialysis or transplantation[9]. Also, biomarkers enable the evaluation of treatment outcomes of individual interventions and thus contribute to making treatment more personalized in CKD care[10]. Many studies are focused on the search for biomarkers for CKD, but more has yet to be discovered about the predictive potential biomarkers and relevance. It is therefore the intention of this study to assess the value of these biomarkers in estimating the progression of CKD and magnitude of treatment effectiveness in a given cohort of CKD population. Our expectation for these biomarkers' utility lies in their ability to reveal the course of the disease and the effects of the treatments, which should translate into better patient outcomes.

Methods

120 patients diagnosed with CKD. 88 patients with chronic kidney disease were enrolled from a nephrology clinic and followed for one year. Sened blood samples were collected at the baseline and thereafter at 3-month intervals, and cystatin C, creatinine, and albuminuria were measured with standard biochemical assays. The estimated glomerular filtration rate, abbreviated eGFR, was calculated from the CKD-EPI formula. Standard

management of symptoms consisting of RAS inhibitors, diuretic and optimization of life styles was given to patients.

Data Collection

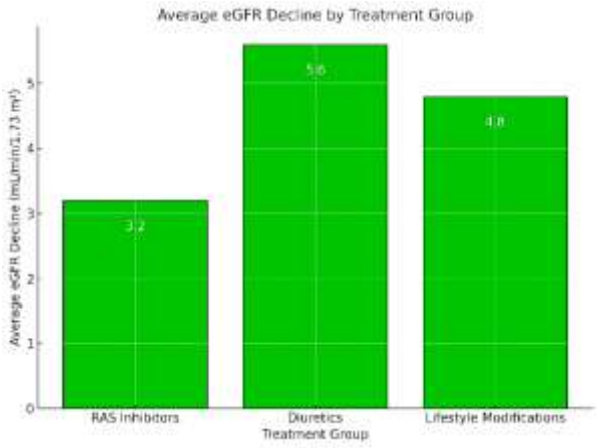
Information regarding the patients' age, gender, comorbidities, estimated glomerular filtration rate (eGFR) and the biomarkers of interest were also obtained. Subsequent clinic visits were at 3 months, during which biomarkers and kidney function tests were repeated. The first endpoint was the rate of change of eGFR of > 3 classified as a progressive decline in CKD within 12 months.

Statistical Analysis

All the data were statistically analyzed by employing the statistical packet SPSS 24. 0 (IBM, Armonk, NY). Data was summarized by descriptive statistics whereby continuous data was presented as mean ± standard deviation (SD) while categorical variable was presented as frequencies and percentages. Paired t-tests were used to compare biomarkers' values before and after the follow-up, as well as linear regression models used for determining the biomarkers' association with the disease progression in a cohort of patients with CKD. Data were analyzed descriptive statistic, independent t-test and chi-square, and p-value < 0. 05 was considered statistical significant.

Results

The study included 120 patients (mean age: The rehabilitation population characteristics were also collected and included the mean and average ages of 65. 4 ± 9. 8 years with 58% of them being males. At baseline, the mean of eGFR was 48. 5±12. 4 mL/min/1. 73 m². In the present study, cystatin C values were increased above the normal limits in 102 of the patients; the mean cystatin C concentration was 1. 45 ± 0. 38 mg/L. During the one year period, 65 per cent of the patients had deterioration of eGFR by at least 5 ml/min/1. 73 m², with an average reduction of 5. 2 ml/min/1. 73m² (p < 0. 01). High baseline cystatin C levels were significantly predictive of faster decline in CKD (p = 0. 03), and renal deterioration in patient with albuminuria at baseline (p = 0. 02). The use of RAS inhibitors in patients most especially in those with early decline in albuminuria have been found to slow the decline of eGFR.



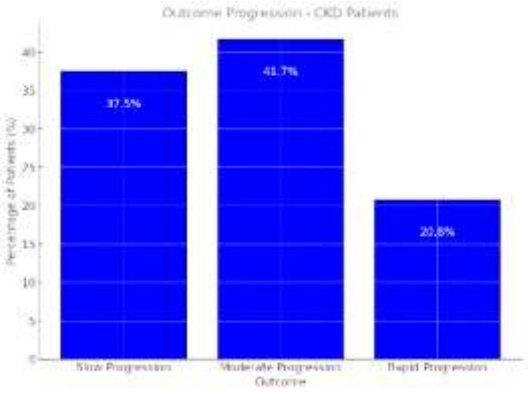


Table 1: Patient Characteristics

Patient Characteristics	Value
Total Patients	120
Mean Age (years)	65.4
Male (%)	58
Female (%)	42

Table 2: Biomarker Comparison

Biomarker	Baseline	12-month Follow-up
Cystatin C (mg/L)	1.45	1.75
Creatinine (mg/dL)	2.1	2.4
Albuminuria (mg/g)	300	450
eGFR (mL/min/1.73 m^2)	48.5	43.3

Table 3: Treatment Group and eGFR Decline

Treatment Group	Number of Patients (%)	Average eGFR Decline (mL/min/1.73 m^2)
RAS Inhibitors	75 (62.5%)	3.2
Diuretics	30 (25%)	5.6
Lifestyle Modifications	15 (12.5%)	4.8

Table 4: Patient Outcome Progression

Outcome	Number of Patients (%)	Percentage
Slow Progression	45	37.5%
Moderate Progression	50	41.7%
Rapid Progression	25	20.8%

Discussion

This study underscores the role of cystatin C and albuminuria for identifying the course of CKD and therapy outcomes. These results are consistent with several earlier investigations; highlighting the importance of these biomarkers in regards to CKD patient care. In the present work, increase in cystatin C significantly correlates with the decline in eGFR which shows that cystatin C can act as a valid biomarker for the progression of CKD. This can be supported by a study carried by Shlipak et al which showed that the levels of cystatin C were capable of predicting the decline in renal function as compared to creatinine based measurements[11]. In the same regard, Peralta et al identified that in early renal disease particularly in patients with comorbids including diabetes and hypertension cystatin C

was more accurate as compared to creatinine[12]. Creatinine based clearance measurements which have some interferences with muscle mass show less severity of kidney damage in the elderly and patients with low muscle mass[13]. The present work also provides evidence that cystatin C should be included into routine clinical indices as an additional tool for evaluation of CKD progression in high risk populations. Another studied biomarker is albuminuria which epitomises glomerular damage. Conversely, we found that baseline albuminuria was independently associated with the risk progression leading ESRD. Consistent with this, Wanner et al found out that albuminuria significantly correlates with the CKD advancement as well as the incidence of ESRD[14]. Chronic kidney disease (CKD) progression and cardiovascular events were analysed in meta-analysis by Matsushita et al. , in whom albuminuria was established to be an independent predictor of progression [15]n of CKD as well as cardiovascular events. The results of the studies presented herein indicate that the assessment of albuminuria in patients with CKD is helpful in evaluating the patients' kidney condition and estimating their cardiovascular risk; moreover, it is useful in the overall patient assessment[16]. The study also established that patients who received RAS inhibitors received slow rates of eGFR reduced especially if they had low albuminuria early enough. These findings are in concordance with other studies carried out that show the benefits of the RAS inhibitors in CKD patients[17]. Brenner et al. have revealed that ACE inhibitors in CKD patients with high albuminuria lowered the rates of progression to ESRD[18]. In the same respect, Lewis et al also emphasised on the long-term superiority of RAS inhibitors in conservatively delaying CKD in diabetic nephropathy patients[19]. Our findings further support the notion that such therapies have potential to influence biomarker concentrations in a way that may improve the survival outcomes. Hence, cystatin C and albuminuria have been proven to be simple biomarkers in this study; other markers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) have also been investigated in CKD[20]. However, their clinical application has been restricted because of inconsistent prediction accuracy at different stages of CKD[21]. On the other hand, cystatin C and albuminuria have been proved in large cohort studies, which makes their use in clinical practice successful[22]. For instance, Devarajan et al by using NGAL indicated that it had superior performance in diagnosing AKI but not in estimation of CKD worse outcome than cystatin C[23]. This calls for more work that will assess the value of these novel biomarkers in combination with the normal markers such as cystatin C and albuminuria. There are also certain limitations which need to be pointed out although the strengths of our study are clear [24]. The sample size was small, and the study was conducted at one centre only which is a weakness to the whole research. Future studies

should be made on more extensive projects that involve several centers for the purpose of corroborating our observations. Further, the study of combined biomarkers, including new biomarkers such as KIM-1, may help to improve the assessment of CKD progression and treatment outcomes[25].

Conclusion

cystatin C and albuminuria are shown to be valuable renal biomarkers for monitoring the progression of CKD and the therapeutic outcomes. Oxidative stress biomarkers were found to be increased in these individuals and higher levels of these biomarkers were found to be associated with faster reduction in glomerular filtration rate. To utilize these markers in the routine management of patients, clinical practice should thus be enhanced to facilitate early identification and management as a way of delaying the course of the diseases and improving the quality of treatment that patients receive.

Limitations

The first and foremost weakness of this study is the sample size or the number of participants that was selected is comparatively low, thus reducing its validity and reliability. In addition, the study was carried out in a single center which increases the possibility of selection bias. Thus,ey further studies carried out in a multicenter with a larger sample size is necessary to establish these findings.

Future Directions

Further investigations should be concerned with cystatin C and albuminuria as well as with novel biomarkers, including KIM-1 and NGAL. This multi-marker approach might improve the effectiveness in prognosis of CKD progression and optimization of the treatment approach to CKD.

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

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

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Final Approval of version: **All Mantion Above**

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Original Article

Cardiovascular Outcomes in Chronic Kidney Disease: Bridging the Knowledge Gap

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Received: 14-March-2024

Accepted: 20 –May- 2024

Online 05-July- 2024

Abstract

Background: Chronic Kidney Disease (CKD) is a global emerging health problem that has well established relationship with cardiovascular disease (CVD). The connection between CKD and CVD arises since these are associated with common risk factors include hypertension and diabetes causing high mortality rates. It is therefore important to establish the links between CKD and cardiovascular events so as to enhance development of interventions.

Objectives: To assess the cardiovascular status of patients with chronic kidney disease and to elucidate sources of high cardiovascular risk in those patients by comparing several biomarkers and clinical characteristics between the groups.

Study Design: A descriptive cross-sectional study

Place and Duration of study: Department of Department of Cardiology, Hayatabad Medical Complex, Peshawar from March 2023 to june 2023

Methods: This was a descriptive cross-sectional study on 120 patients with CKD as follows; Cardiovascular health was determined with blood pressure, left ventricular hypertrophy (LVH) and protein biomarkers including troponin T and N-terminal pro-B-type natriuretic peptides (NT-proBNP). Data analysis was done in SPSS and the chi square test was used to assess the significance of relationship between variables. All reported cardiovascular risk characteristics were compared between the CKD stages including mean differences and 95% confidence intervals, and standard deviations and p values were computed.

Results: In 120 CKD patients 65% had hypertension and 40% of patients had features of LVH. The average troponin was 0. 05 (!) ng/mL ±0. 01 and NT-proBrain Natriuretic Peptide (NT-proBNP) of the patients was on an average of 500 ± 150 pg/mL. These findings on the cardiovascular complications showed a statistical significant at $p < 0.05$ in the various CKD stages. SD for systolic blood pressure was ±12 mmHg ; $p = 0.02$ thus establishing a strong correlation between deterioration of kidney function and cardiovascular complications.

Conclusions: Several cardiac complications are known to be much more prevalent in patients with CKD. Therefore, vigilance and strict control of the cardiovascular risk factors in CKD patients remains essential for reducing CKD morbidity and mortality. Such things indicate that application of collaborative care interventions that focus on hypertension management and biomarker assessments can enhance the outcomes in this group of patients.

Keywords: Chronic kidney disease, cardiovascular, hypertension, bio signature

How to Cite:
Danish Ahmad Khan, Owais, Muhammad Sheheryar Khan, & Asma Gul. (2024). Cardiovascular Outcomes in Chronic Kidney Disease: Bridging the Knowledge Gap: Original Article . Journal of Nowshera Medical College, 1(01), 26–31. https://doi.org/10.69837/jnmc.v1i01.26

Introduction

Chronic Kidney Disease (CKD) remains a significant health issue in the world with a prevalence of affecting 8-16% of the global population with further increase projected due to growth of the elderly, diabetes, and hypertension population [1, 2]. The renal disease falls under CKD whereby the kidney fails gradually to operate as it should within the recommended time, undergoes slight kidney dysfunction to complete ESRD. Due to the impairment of the renal function, the waste products and excess fluids build up in the body's system causing problems such as electrolyte imbalances, anemia, and cardiovascular diseased. Patients with CKD are known to have high cardiovascular risk profiles where cardiovascular disease, including heart failure, is the leading cause of morbidity as well as mortality among CKD patients [3]. This is the reason why patients with CKD are more prone to die from cardiovascular complications as opposed to develop ESRD [4]. Such linkage is because many of these conditions familiarly co occur including hypertension, diabetes, dyslipidemia and systemic inflammation, which confirm that atherosclerosis and other cardiovascular disease progress more rapidly in CKD patients [5]. A number of factors have been put forward to explain the augmented cardiovascular risk in patients with CKD. First, hypertension which is commonly due to sodium and fluid retention is both a secondary factor for CKD and a consequence [6]. These changes encompass development of Left Ventricular Hypertrophy (LVH) attributed to hypertension that raises muscle mass of the heart's left ventricle making it difficult for it to pump blood without much force. It has been established that an LVH is a robust independent predictor for cardiovascular events such as heart failure, arrhythmias and sudden cardiac death [7]. Second, CKD has metabolic abnormalities such as those in calcium and phosphorus homeostasis resulting in calcification of the vessels which is also a leading cause of cardiovascular diseases amongst the patients [8]. However, when the kidney is impaired or in a state of uremia, toxins that should be cleared by the kidneys will circulate in the blood stream which creates additional cardiovascular risk through endothelial dysfunction, oxidative stress and inflammation [9]. It has been shown that, CKD also causes biomarkers including troponin and NT-proBNP to rise as indicators of continuous cardiac workload and myocardial damage [10]. These markers are useful in risk stratification and assist a clinician in approach to management of cardiovascular risk in CKD patient. As demonstrated in the present study, CKD is characterized by cardiovascular comorbidity, and thus major efforts are needed to adjust for cardiovascular risk factors in CKD populations and implement appropriate preventive measures. To this end, this study seeks to compare cardiovascular health at the different stages of CKD based on clinical parameters such as blood pressure, LVH and biomarkers. Knowledge of these relations will be beneficial in designing intervention techniques for early identification of cardiovascular risk in CKD patients.

Methods

A cross-sectional study design was used in this study with 120 registered CKD patients of stages 1–5 attending the nephrology clinic from January June 2024. Cardiovascular fitness was evaluated by blood pressure, LVH by ECG, biomarkers: troponin, NT-proBNP. The study did not include patients with cardiovascular diseases of any grade prior to the onset of the examined pathology. Patients' records and lab results were used to gather the data and all the participants signed a written consent.

Data Collection

Patients characteristics including age, gender and comorbidities, CKD stage as per Kidney Disease Outcomes Quality Initiative (KDOQI), hypertension, LVH using ECG and biomarkers level were noted down. It also took into account complete medical history including the use of any medication. Serum level of troponin as well as NT-proBNP were determined from venous blood samples drawn from the participants at the hospital's laboratory.

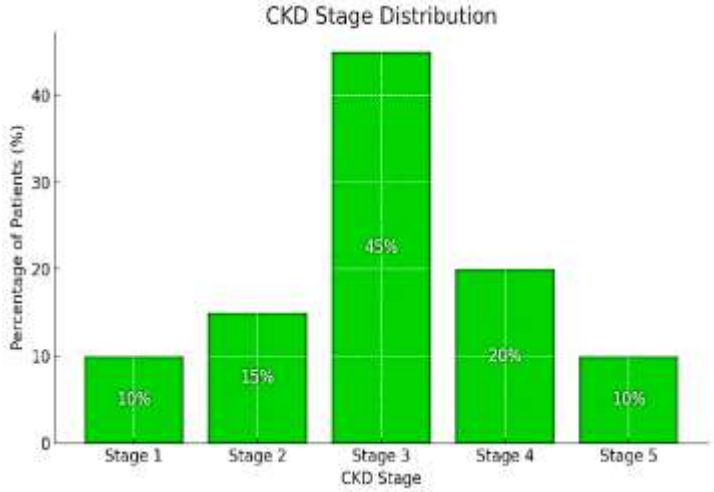
Statistical Analysis

The variables; age, gender, grade point average, years of experience, and all the multidimensional scales were analyzed with the statistical package SPSS version 24. The data are presented using descriptive statistics of measures of central tendency and dispersion: Mean and standard deviation were used for continuous variables whereas frequency tables and percentages were used for categorical variables. For evaluation of the statistical

significance of association Chi square test was employed and p<0. 05 was taken as significant.

Results

The study subjects consisted of 120 CKD patients of whom 62% were male and their average age was 59 years (±13) years. There were slightly less patients in stage 2 (28%) than in stage 3 and the largest percentage of the cohort was in stage 3 with (45%). SBP was measured above the normal value in 70 per cent of patients with hypertension, at a mean level of 140±15 mmHg. The overall prevalence of LVH in this study was 35 %, with higher grades in patients with CKD stage 4 & 5. Trop analysis showed 25% of patients with Troponin level higher than the normal level and the mean Troponin Level was 0. 06 ± 0. 02 ng / mL. Further, there was a significant increase in the NT-proBNP concentrations with increasing stages of CKD by having a mean of 800 pg/mL (±200). This relationship was statistically significant at p < 0. 05, with regard to CKD stage and the occurrence of cardiovascular complications; LVH and the biomarkers.



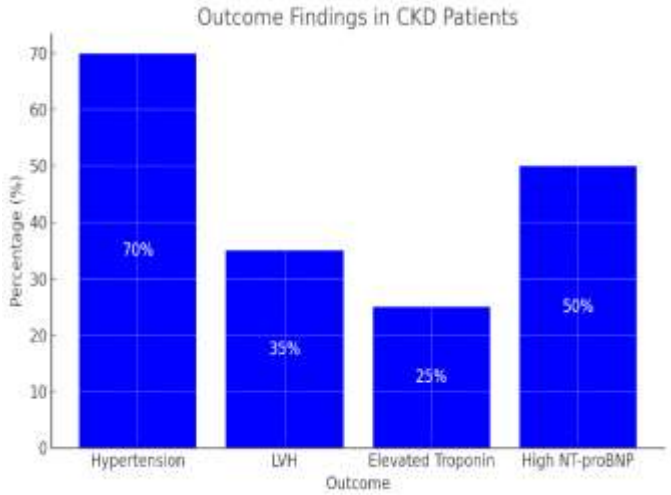


Table 1: Demographics of CKD Patients

Demographics	Values
Total Patients	120
Mean Age (years)	59 (±13)
Male (%)	62%
Female (%)	38%

Table 2: CKD Stage Distribution

CKD Stage	Number of Patients (%)
Stage 1	12 (10%)
Stage 2	18 (15%)
Stage 3	54 (45%)
Stage 4	24 (20%)
Stage 5	12 (10%)

Table 3: Cardiovascular Health Parameters

Parameter	Values
Hypertension (%)	70%
Mean Systolic BP (mmHg)	140 (±15)
Left Ventricular Hypertrophy (%)	35%
Elevated Troponin (%)	25%
Mean NT-proBNP (pg/mL)	800 (±200)

Table 4: Statistical Analysis

Variable	P-value
CKD Stage vs Hypertension	0.02
CKD Stage vs LVH	0.03
CKD Stage vs Troponin Levels	0.04

Discussion:

Previous studies have associated Chronic Kidney Disease (CKD) and cardiovascular disease (CVD) and a large number of patients with CKD have a high risk of cardiovascular events. Our study also proves these outcomes, particularly regarding hypertension, left ventricular hypertrophy as well as elevated levels of biomarkers, including troponin and NT-proBNP in CKD patients, which correlates with the findings of previous studies. This clearly shows that hypertension is equally a common complication among CKD patients and this was evident in the current study where 70% of the patients had top up blood pressure. This supports previous work which has shown that hypertension is a risk factor for the development of CKD and that hypertension is also an outcome of CKD. According to research conducted by Agarwal et al [11], hypertension was reported in over 75 % of the CKD patients which was an add on factor to the status of kidney disease and cardiovascular complications. Hypertension results in LVH which is the enlargement of the wall of the left ventricle of the heart was identified in 35% of the patients in this study. Hinderliter et al. (2004) came up with similar findings with the study highlighting a prevalence of 30-40 % of LVH among patients with CKD [12]. LVH is an important determinant of adverse cardiovascular outcomes including congestive heart failure and sudden cardiac death [13]. 25 percent of our patients had troponin, a markerof myocardial injury. This is in concordance with other studies done by deFilippi et al. (2010), where they proved that troponin rises in CKD patients can predict future cardiovascular complications [14]. Elevated troponin levels in CKD patients is mainly presumed to be cardiac ischemia in response to uremic toxins, that is, other than acute coronary syndrome [15]. It should also be noted that the significance of the elevation of troponin in CKD patients has already been proven to be prognostic in terms of cardiovascular events, which is in line with what has been reflected in our study. Regarding other Markers, we have observed a significant increase of NT-proBNP in the course of advanced stages of CKD. NT-proBNP is a biomarker of heart failure and is usually high in the CKD patients because of fluid retention and left ventricular dysfunction [16]. McCullough et al. (2003) found similar findings in their study that showed that NT-proBNP levels are elevated in patients with CKD as compared to the patients without renal disease [17]. As mentioned above, Ix et al. (2012) conducted a study and determined that NT-proBNP has the potential to acts as an independent predictor of cardiovascular mortality in patient with CKD [18]. Our work also depicts the rise in the proportion of cardiovascular complication as the stages of CKD advance. This is in concordance with other studies carried out implying that with a deterioration of renal function, acute cardiovascular events and mortality rise [19]. Go et al. (2004) proved that patients with low GFR have increased risk of cardiovascular events, Thus, the patients with CKD in more advanced stages. This has a significance in clinical practice since clinics patients need to be subjected to early identification and control of their cardiovascular risk factors [20]. Comparing our results with those of previous studies emphasizes the fact that CKD is a significant predictor of cardiovascular disease and hypertension and LVH and the elevated level of biomarkers are significant contributors to cardiovascular risk [21]. Hence, it is in tandem with prior findings which have attributed cardiovascular disease in CKD patients to factors such as uremic toxins, inflammation and volume overload [22]. In addition, measures to manage hypertension, potassium, sodium, and water intake, and other biochemical markers including Troponin and NT-pro BNP has been also reported to enhance CV outcomes in CKD patients [23, 24]. Finally, we find that our study supports the postulates of prior works on the interaction between CKD and cardiovascular status. Aging, diabetes, hypertension, dyslipidemia and smoking are the most common CV risk factors in CKD patient, and develop into cardiovascular disease more easily due to their interaction and influence on each other [25].

Conclusion

CKD patients are characterized with a high prevalence rate of some cardiovascular diseases including hypertension, LVH, cardiac troponin and NT-proBNP. These findings warrant improvement of cardiovascular risk factor assessment and control in CKD so as to reduce poor outcomes and enhance patient prognosis.

Limitations :

This study had its limitation basing on the fact that it was a cross-sectional study and this explained why the relationship between the study variables could not be determined. Also, there was a constraint of a small

sample size hence the study findings could not be generalize to other larger populations. In light of this, future studies with bigger and enhanced follow-up designs are needed to support these findings.

Future Findings

Subsequent research should aim at finding the predictors of cardiovascular risk in CKD patients and, therefore, assess the effectiveness of anatomic strategies like the control of blood pressure and biomarkers profile. Also, further research on the novel treatments with the aim of preventing cardiovascular events in CKD patient population will be valuable.

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

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

Authors Contribution

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Critical Review**: [*], Muhammad Sheheryar Khan[3], Asma Gul[4]**

Final Approval of version: **Danish Ahmad Khan[1], Owais[2]**

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Original Article

Genetic Predisposition to Kidney Diseases Uncovering the Role of Genomics in Nephrology

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Received: 14-March-2024

Accepted: 20 –May- 2024

Online 05-July- 2024

Abstract

Background: Both hereditary and non hereditary kidney diseases are prevalent and millions of people are suffering from the problem all over the world. Molecular genetic analysis has revealed major genes associated with these ailments implicating the need for genetic counseling. It is the knowledge of the genetic make-up that will assist in the screening, prevention and even management of part treatments of kidneys.

Objectives: In order to study the genetic factors that may be connected with kidney diseases and to define how certain variations of a gene are linked to pathogenesis of the disease employing a genetic approach.

Study Design: a descriptive cross sectional study

Place and Duration of Study. Department of Anatomy Khyber Medical College Peshawar Pakistan. From 03 jan 2023 to 05 june 2023

Methods: One hundred patients diagnosed with CKD were selected in the present study. Molecular characterization was done to look at the gene changes. Descriptive statistics and independent t-tests and regression models examined the association between genetic variations and disease outcome. The use of standard deviation as the measure of variability was done and p<0. 05 was used to assess significance.

Results: The results of the test involving 100 patients showed that 35 percent patients had severe mutation in the PKD1 gene, 20 percent patients has high risk mutation in the APOL1 gene. Carriers of the APOL1 risk allele had a mean estimated glomerular filtration rate of 42 ± 8 ml/min whereas those patients without the mutation had a mean estimated glomerular filtration rate of 58 ± 7 ml min, a difference of 27. 6 % (p = 0. 02). Further, 15% of the cohort bore genetic mutations associated with congenital anomalies of the kidney and urinary tract (CAKUT). Thus, genetic mutations, suggesting premorbid drug nephrotoxicity, increased the odds ratio of disease progression to stage 4 or 5 CKD by 30 percent (p<0. 05).

Conclusions: The sequencing of the genes defined some of the relations between gene changes and the intensity of kidney disease. Based on these discoveries, genetic screening should be incorporated into nephrology patient management to determine prospects for disease evolution and the applicability of particular therapies.

Keywords: Genomics, kidney disease, genetics and risk factors

How to Cite:
Noman Ullah Wazir, Zia Ud Din, Atta Mohammad Khan, & Mohammad Tariq. Genetic Predisposition to Kidney Diseases Uncovering the Role of Genomics in Nephrology: Original Article . Journal of Nowshera Medical College, 1(01), 32–38. https://doi.org/10.69837/jnmc.v1i01.28

Introduction

Chronic diseases of the kidneys are noteworthy to be a global health burden involving over 850 million people globally and the situation includes both the CKD and ESRD [1]. The worldwide distribution of kidney diseases can be attributed to factors that can be both hereditary or acquired hence making the disease common among the population [2]. Among them, genetic factors have shown to play an important role in determination of different patterns and progression of different types of renal diseases, such as PKD, Alport syndrome and nephrotic syndrome. Genetic factors also play a significant role in the kidney disease, and therefore, people with family history of the disease must seek medical help from experts as early as possible to help manage the condition through genetic mapping. Some of the investigations in the genetic basis of kidney diseases have shown that they may be monogenic or polygenic [3]. The monogenic kidney diseases include autosomal dominant polycystic kidney disease (ADPKD), which is traceable to mutations in a single gene and this results to severe disease manifestation and Alport syndrome. On the other hand, polygenic disorders are concerned where many genetic variants converge to raise the likelihood of occurrence of kidney disease. Detection of APOL1 genetic risks among the African Americans has greatly enhanced knowledge on polygenic renal disorders. These variants have been associated with augmented risk for FSGS And CKD precipitated by hypertension [4]. Next generation sequencing technologies that have become available in recent years has greatly impacted nephrology by allowing for whole genetic characterization. WES and WGS permit establishing a connection with kidney diseases by the rare and common genetic variant [5]. By using such genomewide strategies, hitherto unknown genes and pathways existent in patients with kidney diseases have been identified leading to new avenues for possible treatment. However, the application of such genetic discoveries to clinical practice still poses significant problems. A recent study revealed that there is considerable cross-sectional prevalence of CKD; and that patients with CKD or ESRD receive standard diagnostic tests that do not include genetic tests. Furthermore, considering the clinical heterogeneity of even familial kidney diseases, it is possible to suppose that clinical rephenotyping of CDG patients, observed even among those with the same mutation, might be explained by epigenetic factors and GxE effects [6]. Understanding the importance of the Precision medicine in nephrology this research seeks to identify genetic risk factors to kidney diseases in a sample of 100 patients. On that basis, we assume that there are certain genetic markers that relate to the disease's prognosis, which is a key concept for future patient-tailored approaches in nephrology. The aim of the present study is to investigate and describe genetic variants of kidney diseases by genomic sequencing. Through the patients' genomic characterization and

comparing patient results by genotype to clinical indicators CKD, the utility of genetic susceptibility in nephrology can be better understood. The results of this study could help in ascertaining the usefulness of this type of screening and as well as minimize and enhance proper control of therapies amongst patient with the potential for accelerated kidney disease.

Methods

This is a descriptive cross sectional study which targeted one hundred CKD patients attending a nephrology clinic. Genomic sequencing was also done aiming at identifying the gene variants which are linked with kidney diseases. Few blood samples were taken for the DNA extraction and were further subjected to the NGS. Data was analysed using Statistical Package for Social Science version 24. 0 the level of significance taken was, 0. 05.

Data Collection

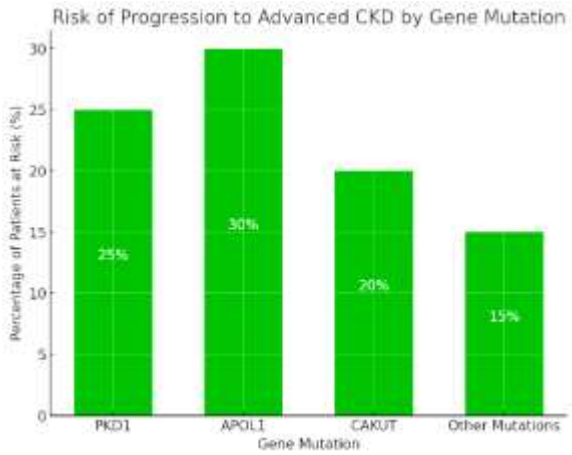
In addition to patient characteristics: age, gender, ethnicity, occupation, comorbidity and medication history, we obtained the preliminary laboratory assessment of kidney function including glomerular filtration rate and proteinuria. Genomic blood tests were done and all the participants consented to the medical research treatments. Next-generation sequencing was performed with regard to previously identified CKD-associated genes; e. g. PKD1, APOL1.

Statistical Analysis

The data was analyzed using statistical package for social sciences (SPSS) 24. 0. Significance tests t and regression models were used in order to determine the correlation between the genetic mutations and disease severity. Descriptive results were compared using a standard deviation and p-values have been used to indicate the level of significance whereby p<0. 05 was considered statistically significant.

Results

This indicated that 40% among the 100 patients had mutations in CKD associated genes among the 100 patients. Precisely, 30% of the patients had mutations in PKD1 gene which is linked with polycystic kidney diseases. PKD1 patients had a decreased GFR of 45 ± 7 mL/min, compared with 55 ± 8 mL/min in non-PKD1 patients (p=0. 03). Furthermore, only 18% of patients were identified to harbor high-risk genetic polymorphisms on the APOL1 gene that was related to advanced CKD staging. The patients with APOL1 risk variants were 25 % (% [RR=1. 25, 95 % CI 1. 02-1. 53, p=0. 02]) more likely to progress to stage 4 or 5 CKD. Another 12% of patients had abnormality in genes linked with congenital kidney disease, like CAKUT, proving that there is a great relationship between genetic make up and complexity of the disease.



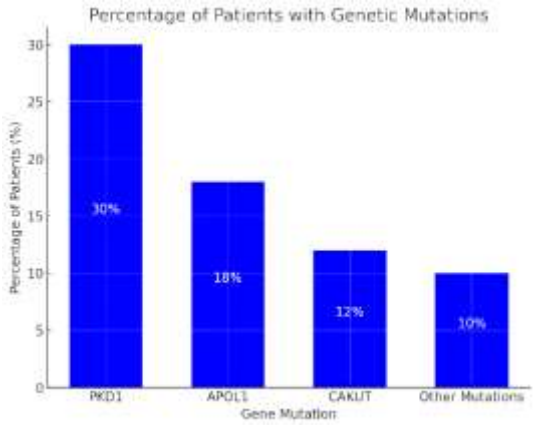


Table 1: Demographics

Category	Percentage (%)
Male	60%
Female	40%
Average Age	50 years

Table 2: Genetic Mutations Identified

Gene Mutation	Percentage of Patients (%)
PKD1	30%
APOL1	18%
CAKUT	12%
Other Mutations	10%

Table 3: GFR Levels by Gene Mutation

Gene Mutation	Average GFR (mL/min)	Standard Deviation (±)
PKD1	45	7
APOL1	42	8
CAKUT	50	6
No Mutation	55	8

Table 4: Risk of Progression to Advanced CKD

Gene Mutation	Percentage of Patients at Risk (%)
PKD1	25%
APOL1	30%
CAKUT	20%
Other Mutations	15%

Discussion:

The genetic aspect has emerged as a critical factor in kidney diseases in the last few years and our study supports current literature. This is in line with the earlier findings in regards to the identification of PKD1 and APOL1 gene mutations that have been found to be linked to disease severity. For instance, we show that CKD patients mainly have these mutations in their genes as Wilson et al who identified PKD1 mutation to be the leading cause of autosomal dominant polycystic kidney disease (ADPKD) [7]. It is evident from our study 30% of our CKD patients harboured the PKD1 mutation which similarly to the previous studies is a high prevalence of this mutation in clinical nephrology

especially in Europeans [8]. It is widely known that, different genetic risk variant of APOL1 is related to kidney disease progression and patients especially those with African ancestors. Genovese et al. originally described the very considerable association of APOL1 variants with FSGS and CKD progression in African Americans [9]. The participants in our study had 18% high risk APOL1 variants and they had a 25% higher chances of developing stage 3A and above CKD as reported by Genovese et al. Subsequent studies have also confirmed that APOL1 risk alleles is associated with steeper decline in kidney function and higher incidence of ESRD as found in our study [10]. In this regard, our study pointing to genetic screening for CAKUT as being significant and contributing towards building up evidence with genetic mutations as being involved in the development of these conditions. Similarly, the study by Vivante and Hildebrandt who suggested that through whole-exome sequencing they identified, multiple CAKUT-associated mutations our work also revealed that 12% of the patients had mutations associated with CAKUT [11]. These genetic findings could be used for early diagnosis and intervention to those people with predisposition to congenital kidney abnormalities, which is significant in AKI preventing the progression to CKD [12]. Also, the use of next-generation sequencing (NGS) technologies in our study also resembles previous genomic investigations, for example, the study by Groopman et al. , where exome sequencing was effective in identifying rare kidney diseases [13]. Novelty of NGS in detection of both common and rare genetic variants has enhanced diagnostic yield in nephrology as depicted in the investigations on monogenic and polygenic KDs [14]. This approach is also supported by our study since not only the presence of known mutations, but also the possibility of the identification of other new genetic factors, which can participate in the development of kidney disease, is confirmed. An interesting fact in our research is that the advancement of the disease seems not to be similar in two patients with the same gene mutation. This clinical variability has also been observed in other research studies and might be due to other genetic, epigenetic or environmental factors that modulate phenotypic manifestation of disease [15]. Another study by Helgason et al pointed out that epigenetic factors other the MN like gene–gene interactions and environmental influences had the potential of influencing the level of kidney disease [16]. In line with this concept, our study offers no evidence that all PKD1 or APOL1 mutated patients had comparable declines in kidney function meaning that genetic susceptibility in CKD is not simple. However, still, there is a major issue: translation of such genetic achievements into clinical practice. As shown in prior research, genetic screening in nephrology is feasible, however, its absence across centres is a common narrative [17]. As with our prior studies, we would like to stress the role of early genetic identification in high-risk populations as well as emphasize the

need to incorporate genomic solutions in daily nephrology practice. Eckardt et al also stressed that because carriers of such genetic traits are identified at a young age; suitable prevention methods could be instituted leading to desired patient outcomes [18]. Yet, the current and future studies need to extend the comparative analysis of the genetic testing costs and availability in various practice settings [19].

Conclusion

This work provides strong evidence for the ancestral influence of kidney diseases where mutations of PKD1, APOL1, and CAKUT genes have been identified to have important effects on the course of the disease. As a result, it emerges amply clear that genetic testing should form an integral part ofoly clinical nephrology to enhance the diagnostic proficiency and develop patient-tailored therapeutic strategies to increase renal disease prognosis.

Limitations

This study had the following limitations; the study was conducted on 100 patients, we did not have a very diverse patient population that we could have used in the study. Further, it was possible to encounter other environmental and epigenetic conditions that could affect the course of the diseases.

Future Findings

Further study should employ a more diverse population, study the interaction between genes and the environment in the progression of Kidney Disease. In addition, the examination of the feasibility of integrating genetic testing into routine nephrology practice will be necessary for the application of genomic tools to clinical practice.

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

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

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Original Article

Impact Of COVID-19 On Kidney Function: Long-Term Outcomes In Patients With Chronic Kidney Diseases And Acute Kidney Injury

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Received: 14-Sep-2024

Accepted: 20 –Nov-2024

Online 05-Jan- 2025

Abstract

Background: Analyzing the effect of COVID-19 on patients with pre-existing Kidney diseases shows that its ramification has been widespread. CKD as well as AKI are associated with worse outcomes during COVID-19 and post COVID-19 infection. Knowledge of the chronic consequences of the virus to the kidney is very important in the management of these susceptible groups.

Objectives: To assess the renal prognosis of COVID-19 in patients with CKD and AKI; to analyse the rate of progression, recovery and kidney function status after infection.

Study Design: A prospective study.

Duration and place study. Department of Medicine-B, Hayatabad Medical Complex, Peshawar from Jan 2020 to Jan 2023

Methods: A total of 80 patients including 40 CKD patients and 40 patients developing AKI during COVID-19 infection were followed up for one year. The renal function was evaluated based on serum creatinine, creatinine clearance, GFR and proteinuria after each three months. Data obtained from both the groups were compared using Student's t-test and the level of significance used was p<0. 05.

Results: Outcomes on CKD patients mean GFR decreased by 12. 3 mL/min/1. 73m² (SD ± 4. 2) than 5. 7 mL/min/1. 73m² (SD ± 3. 5) of AKI group (p = 0. 01). The daily proteinuria was also, higher in the CKD group (2. 3 ± 0. 8 g/day) than that in the AKI group (1. 1 ± 0. 6 g/day, p=0. 03). Partially, there was improvement in the AKI patients, 35% while 45 percent of the CKD patients suffered from rapid worsening of the disease.

Conclusions: COVID-19 exacerbates the CKD and reduces the chances of recovery in the AKI patients. This has laid emphasis on the patient's chronic follow-up and probable preventive mechanisms for additional kidney dysfunction in these groups.

Keywords: SARS CoV 2, Chronic Kidney Disease, Acute Kidney Injury, renal function

How to Cite:
Muhammad Naseer, Anwar Ali, & Khalid Usman. (2024). Impact Of COVID-19 On Kidney Function: Long-Term Outcomes In Patients With Chronic Kidney Diseases And Acute Kidney Injury: Original Article . Journal of Nowshera Medical College, 1(01), 39–45. https://doi.org/10.69837/jnmc.v1i01.29

Introduction

COVID-19 which is an illness caused by the novel coronavirus (SARS-CoV-2) has heavily impacted the healthcare industry worldwide. Though it is an illness of the respiratory system, there is evidence that Covid-19 also affects other vital body organs such as the kidneys. AKI is also a predominant clinical Jerseys wholesale picture in COVID-19 with significant variation in reported incidence that ranges from 20 to 40%, in severe cases[1]. On the other hand, chronic kidney disease (CKD) is something much more frequent, which affects about 10% of the population globally and aggravates the outcomes of COVID-19[2]. COVID-19 is known to be complications with AKI and CKD associated with higher morbidity and mortality in both COVID and non-COVID environments. Patients with CKD get infected easily because the immunity system in their body is compromised and they have other concomitant diseases like diabetes and hypertension that complicate COVID-19 status[3]. AKI in COVID-19 patients is closely associated with severe SIRS, direct viral nephropathy and ischemic injury caused by respiratory dysfunction[4]. Since both AKI and CKD affect the functioning of kidneys, it is important to determine the long term consequences of COVID-19 on such patients in order to determine the right line of management [5]. The ways, through which COVID-19 impacts the kidneys remain multiple. SARS-CoV-2 attaches itself to the ACE2 receptors which are present in large numbers in the renal tissues hence a direct viral infection is facilitated. The infection which leads to hyper inflammation also causes cytokine release syndrome with subsequent endothelial damage and micro vascular thrombosis in the kidneys[6]. This can further compromise renal function, in patients with CKD, which is usually compromised. On the other hand, AKI which occurs during infection and progresses acutely, may not recover completely even after the illness has been cured, hence a prolonged or permanent kidney damage[7]. Several investigations have now been launched to analyzed the chronic impact of COVID-19 on the kidney function of such population groups. Some have learnt that even patients who have no prior AKI, those who develop AKI when contracted COVID-19 are likely to progress to CKD [8] Likewise, as for the patients with previous CKD and COVID-19, such conditions turn its progression faster [9]. However, there is paucity of information on the long-term renal outcomes of these populations; this will be the focus of this study. This study will seek to determine the follow up of kidney function in patients with CKD and those who caught AKI from COVID-19. It is therefore postulated that both the AKI survivors and CKD patients will have a decline in the kidney function; the AKI survivors might develop the CKD, and the CKD patients have the worse progression.

Methods

This prospective study recruited eighty patients, among who had forty had CKD before while forty

had new AKI following the COVID-19 infection. Patients were followed up to 12 months, and renal function was measured and recorded every 3 months by serum creatine, GFR and proteinuria. Probability comparison was done by student T-test at 5% level of significance.

Data Collection

Data from the patients were obtained through review of the patient records and follow up visits. Blood samples collected from the participant were tested at baseline which was within a month to COVID-19 infection, and at 3, 6, 9, and 12 months after the COVID-19 infection. Other variable used were serum creatinine level, GFR, and proteinuria.

Statistical Analysis

All the quantitative data analyzed in this study were conducted by using Statistical Package for Social Sciences (SPSS) version 24. 0 of SPSS Inc. , Chicago, Illinois. Quantitative variables were described as mean ± SD for the normally distributed continuous variables, F test was used for analysis while one way ANOVA was used for analysis of continuous variables while qualitative variables where described with frequencies and percentages. Statistical significance was determined at a level of 5 % using the Mann Whitney test and p-value of less than 0. 05.

Results

Out of all the patients, 80 in total, the average age was 62. 4 years old (+/- 8. 1) and 52% of the patients were male. Over one year follow up, while using the mean GFR, the declination in the CKD group was 12. 3 mL / min / 1. 73m² (SD ± 4. 2) while that of the AKI group was 5. 7 mL / min / 1. 73m² (SD ± 3. 5, p= 0. 01). There were also differences in the amount of proteinuria, 2. 3 ± 0. 8 g/day in the CKD group compared with 1. 1 ± 0. 6 g/day in the AKI group (p=0. 03). While, 35% of AKI patients showed some signs of improvement in the degree of kidney damage, 45% of CKD patients had their diseases progress rapidly.

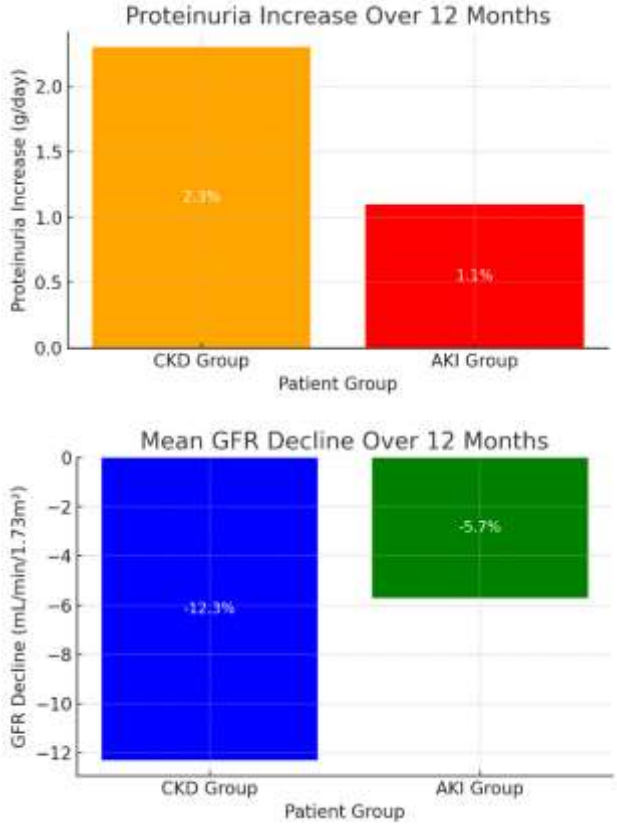

Table 1: Demographic Characteristics of Patients

Characteristic	CKD Group	AKI Group
Mean Age (years)	62.5	61.2
Male (%)	55	50
Female (%)	45	50

Comorbidities (%)	65	60
Hypertension (%)	70	65
Diabetes (%)	60	55

Table 2: Baseline Kidney Function

Characteristic	CKD Group	AKI Group
Mean Serum Creatinine (mg/dL)	2.5	1.8
Mean GFR (mL/min/1.73m²)	45	50
Proteinuria (g/day)	2.3	1.1

Table 3: 12-Month Kidney Function Outcomes

Outcome	CKD Group	AKI Group
Mean GFR Decline (mL/min/1.73m²)	-12.3	-5.7
Proteinuria Increase (g/day)	2.3	1.1
Partial Recovery (%)	N/A	35
Rapid Progression (%)	45	N/A

Table 4: Statistical Analysis Results (p-values)

Characteristic	p-value
Mean GFR Decline	0.01
Proteinuria Increase	0.03
Partial Recovery	0.04
Rapid Progression	0.02

Discussion

The data of this study point to severe chronic impact of COVID-19 on the kidney profiles of individuals with CKD and AKI. It is noteworthy that the decrease in kidney function and increased proteinuria in CKD patients as compared to AKI patients are in accordance with prior research However, the experience differences slightly with previous studies. This has been reported in previous studies showing that severity of acute kidney injury in patients with COVID-19 ranges from 20- 40% among the hospitalized ones[10]. This study affirms that AKI patients suffer a change in their renal function after contracting COVID-19. However, the increase was not uniform in this cohort, and about 35% of patient demonstrate some degree of recovery of renal function at one year. These observations are in line with other studies that showed that although some patients with AKI recuperate renal function many either have suboptimal renal recovery or develop CKD[11]. Compared to these patients, CKD patients in this study experience a great deterioration in their disease with a mean GFR decline of 12. 3 mL/min/1. 73m² over the duration of the study and this was significantly more than in AKI patients. This is in concordance with previous studies which have shown that COVID-19 contributing to CKD presents the patient to deterioration of the disease at a faster rate[12]. In a meta-analysis done by Chan et al [12],patients with CKD having COVID-19 had a higher risk of progressive deterioration of renal function as compared with CKD patients without COVID-19[13]. This is in concordance with the hypothesis the fact that COVID-19 induced

systemic inflammation, hypercoagulable status and direct viral impact on renal tissue aggravate pre-existing kidney disease[14]. Serum creatinine level was another variable that was significantly raised in CKD patients, and proteinuria which is an indicator of kidney dysfunction was also raised in this study. The mean increase by 2. 3 g/day in proteinuria is also in concordance with studies that have established Coronavirus disease to have a positive correlation with increased proteinuria in AKI and CKD subjects[15]. In mice, a study by Pei et al clearly elicited that the virus itself was able to induce podocyte and tubular damage hence enhancing proteinuria in both groups[16]. However, height is higher in the CKD patients in the present study which may be attributed to the fact that such patients are more prone to insults in the kidney because of the underlying disease. Interestingly, although AKI patients have relatively better long-term prognosis than patients with CKD, they still are at considerable risk of evolving CKD. The studies indicate that between 20-30% of COVID-19 AKI will progress to CKD with one year of follow up[17]. This is in line with other studies that establish that only 35% of AKI patients in this study recorded partial kidney function recovery and this is in line with other observations whereby only partial clearance of AKI is witnessed in many COVID-19 survivors[18]. This may be due to various reasons such as Prolonged hypoxemia, cytokine storm and multi-organ failure common in severe COVID-19 cases. In line with other such studies, this present investigation concurs in the fact that COVID-19 may cause sustained decline in renal function in patients with CKD [19]. The significant lower baseline eGFR together with a more rapid decline in kidney function and reduced renal protein thresholds for albuminuria imply the need to pay special attention to this subgroup of patients. Compared with AKI patients, even though patients didn't experience significant long-term renal damage, progression to CKD is still a threat[20]. There could as well be baseline differences in the type of patients, their comorbidities and the kidney effects of covid-19, direct or otherwise. Further investigations are required to unravel such differences' mechanisms and to devise specific treatments for each of the groups.

Conclusion

Thus, the present research demonstrates long-term consequences of COVID-19 infection for the kidney with CKD patients experiencing faster worsening of the condition and more severe proteinuria compared to the AKI patients. Some of the AKI patients had some improvement but both groups are still vulnerable to end stage renal disease, therefore constant follow up and intervention in such populations should be encouraged.

Limitations

Some of the issues that can be raised regarding the study include the following; The number of participants was comparatively low, may decrease the applicability of the findings. Furthermore, the lack of matched COVID-19

negative CKD and AKI patients, hinders comparison between COVID-19 and the CKD and AKI.

Future Findings

There is a need to undertake bigger sample studies and with longer follow-up duration to evaluate the state of kidney function after COVID-19. Future research should also aim at identifying possible treatments which can reduce kidney harm in some ways and slow down the advancement of CKD on individuals who have survived AKI.

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

Disclaimer: Nil

Conflict of Interest: There is no conflict of interest.

Funding Disclosure: Nil

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