Abstract: To assess the social, demographic, clinical and health factors impacting the referral time to a nephrologist in chronic kidney disease patients. A prospective study was carried out at Nephrology Department of Nishtar Medical Hospital, Multan from October 2021-October 2022. A total of 150 chronic kidney disease patients who were undergoing dialysis were selected for the study. Early and late referral time was evaluated by the time period between referral and dialysis initiation. All the patients were interviewed for evaluation of factors affecting the referral time. The analysis showed that 92 patients (61.3%) were in early referral and 58 patients (38.6%) were in late referral among which 21 patients were referred to a nephrologist almost 90 days prior to the dialysis initiation. Patients in the late referral mostly had diabetes, congestive heart failure or hypertension, whereas patients in early referral were non-smokers, women and patients with glomerulonephritis. The multivariate analysis revealed the following independent risk factors for late referral: kidney disease (diabetes mellitus, hypertension, male sex, congestive heart failure, profession (labourer, mechanic, farmer) and assisted walks. Diabetes and hypertension patients have a later referral time than patients with glomerulonephritis. In addition, men with congestive heart failure practicing physically active professions and assisted ambulation were referred late.

Keywords: Dialysis, chronic kidney disease, nephrology

Introduction

The two factors that play an important role in the improvement of chronic kidney disease patients are appropriate care and timely consultation with the nephrologist. According to research, the patients who were referred to the nephrologist at an initial stage mostly did not require immediate dialysis or catheters and urgent renal replacement therapy and were recommended peritoneal dialysis or kidney transplant as initial treatment (Shlipak et al., 2021). The management of the disease is also better in early referral patients in spite of comorbidities like cardiovascular disorders (de Boer et al., 2020). In addition, timely referral results in an increased chance of survival, better lifestyle and nutritional status (Marie Patrice et al., 2019; Shah et al., 2018). The treatment costs and hospital stays are also reduced in such patients. Studies have reported that dialysis patients who were referred at an early stage had a low risk of cardiovascular mortality, lower medical costs and better lifestyle (Clyne, 2021; Pyart et al., 2020).

Although the importance of early referral has been highlighted repeatedly, the majority of chronic kidney disease patients are referred to nephrologists late before the initiation of dialysis. The recurrence of late referrals varies significantly across the globe. On average, 20-35% of CKD patients are referred late to the nephrologist (Ghimire et al., 2022). In Pakistan, the ratio of late referrals is comparatively low than developing countries such as the UK (30%), Denmark (38%), Mexico (50%) and the USA (34.7%) (Anees et al., 2018). To analyze the causes of late referral, the clinical and socio-economic factors influencing it must be evaluated. Very limited data regarding this subject is available in Pakistan. We conducted this study to assess the social, demographic, clinical and health factors impacting the referral time to a nephrologist in chronic kidney disease patients.

Methodology

A prospective study was conducted in the Nephrology Department of Nishtar Medical Hospital, Multan from October 2021-October 2022. A total of 150 chronic kidney disease patients older than 18 years undergoing dialysis were selected for the study. The patients with incomplete data on
nephrologists' visits and start dates of dialysis were excluded. All the patients signed informed consent to become a part of the study. The Ethical board of the hospital approved the study design of the study. Early and late referral time was evaluated by the time period between referral and dialysis initiation. An early referral was defined as a referral to the nephrologist more than 1 year before the start of dialysis and a late referral was defined as a referral within less than 1 year before the start of dialysis. The patients in the ultra-late referral group were referred to the nephrologist 3 months before the start of dialysis. All the patients were interviewed about their demographics, marital status, employment status, education, history of smoking, medical history, laboratory tests, dialysis modality, medications and comorbidities. The e-GFR was calculated for each patient and the Charlson comorbidity index was used at the time of dialysis. All the data were analyzed by SPSS version 21. Mean and standard deviation and the percentage were used to express continuous and categorical variables respectively. T-tests were performed for the comparison of data between groups. The logistic regression method was used to evaluate factors affecting late and ultra-late referrals. A p-value less than 0.05 was regarded as statistically significant.

Results

A total of 150 patients were included in the study among which 93 patients were referred early, 22 patients were referred late and 35 patients were referred ultra-late. In the early referral group, age, blood pressure, BUN, serum creatinine, and phosphorus levels were less at the time of referral than in late referral patients. Early referral patients mostly had glomerulonephritis and late referral patients had diabetes or hypertension. At the start of dialysis, age, haemoglobin and calcium levels in the early referral group were higher. The late referral patients mostly had congestive heart failure and the ultra late referral had hypertension. The patients' characteristics are shown in Tables I and II. With respect to factors affecting late referral time, the following were the independent risk factors: kidney disease (diabetes mellitus, hypertension, male sex, congestive heart failure, profession (labourer, mechanic, farmer) and assisted walks. These factors are shown in Table III.

Table I: Patients’ Characteristics According to Referral Time

| Findings at the time of referral | Total (n=150) | Early referral (n=93) | Late referral (including ultra late referrals) (n=57) | P-value |
|----------------------------------|--------------|----------------------|--------------------------------------------------|---------|
| **Time from referral to dialysis, month** | 40.4 ± 53.6 | 63.8 ± 57.1 | 2.0 ± 2.4 | <0.001 |
| **At the time of dialysis** | | | | |
| Age, years | 54.3 ± 12.6 | 55.2 ± 12.1 | 53.3 ± 13.1 | 0.001 |
| Modified Charlson comorbidity index | 4.6 ± 1.7 | 4.7 ± 1.7 | 4.0 ± 1.8 | 0.010 |
| Systolic BP, mm Hg | 140.3 ± 21.4 | 139.6 ± 21.3 | 141.8 ± 22.0 | 0.169 |
| Diastolic BP, mm Hg | 77.0 ± 13.1 | 76.4 ± 12.7 | 78.4 ± 13.2 | 0.004 |
| BMI, kg/m2 | 22 ± 2.6 | 22 ± 2.6 | 22 ± 2.4 | 0.900 |
| Haemoglobin, g/dL | 8 ± 1.2 | 8 ± 1.2 | 7.9 ± 1.2 | 0.012 |
| Calcium, mg/dL | 7.1 ± 1.0 | 7.2 ± 1.0 | 7.2 ± 1.0 | 0.010 |
### Table II: Patients’ characteristics of Late and Ultra-late referral

|                          | Late referral (including ultra-late referrals) (n=57) | Ultra-late referral (n=35) | P-value |
|--------------------------|------------------------------------------------------|----------------------------|---------|
| **Findings at the time of referral** |                                                       |                            |         |
| Age, years               | 53.2 ± 13.0                                          | 54.2 ± 13.4                | 0.480   |
| Gender, male             | 36 (63.1%)                                           | 23 (65.7%)                 | 0.419   |
| Underlying kidney disease|                                                       |                            |         |
| Diabetes mellitus        | 34 (59.6%)                                           | 19 (54.3%)                 | 0.004   |
| Hypertension             | 10 (17.5%)                                           | 8 (22.8%)                  |         |
| Glomerulonephritis       | 8 (14.0%)                                            | 4 (11.4%)                  |         |
| Others                   | 5 (8.7%)                                             | 4 (11.4%)                  |         |

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At the time of dialysis

| Parameters                        | Mean ± SD  | P-value |
|-----------------------------------|------------|---------|
| Age, years                        | 53.3 ± 13.1| 0.479   |
| Modified Charlson comorbidity index | 4.0 ± 1.8  | 0.002   |
| Diastolic BP, mm Hg               | 78.4 ± 13.2| 0.045   |
| Haemoglobin, g/dL                 | 7.9 ± 1.2  | 0.118   |
| Calcium, mg/dL                    | 7.2 ± 1.0  | 0.482   |
| Phosphate, mg/dL                  | 4.5 ± 1.8  | 0.092   |
| PTH, Intact                       | 255.1 ± 215.4| 0.018 |
| h2-Microglobulin                  | 20.0 ± 8.3 | 0.031   |
| HbA1c, %                          | 5.9 ± 1.1  | 0.009   |
| LDL cholesterol, mg/dL            | 92.0 ± 36.5| 0.049   |

| Profession                        | Count (%)  | P-value |
|-----------------------------------|------------|---------|
| Professional specialist           | 2 (3.5%)   | 0.372   |
| Office worker                     | 2 (3.5%)   |         |
| Housewife and student             | 12 (21.0%) |         |
| Mechanic                          | 3 (5.2%)   |         |
| Labourer                          | 3 (5.2%)   |         |
| Farmer                            | 3 (5.2%)   |         |
| Unemployed                        | 32 (56.1%) |         |

| Comorbidities                     | Count (%)  | P-value |
|-----------------------------------|------------|---------|
| Peripheral vascular disease       | 3 (5.2%)   | 0.023   |
| Congestive heart failure          | 8 (14.0%)  | 0.763   |
| Connective tissue disease         | 4 (7.0%)   | 0.639   |
| Mild liver disease                | 2 (3.5%)   | 0.548   |

| Ambulation status                 | Count (%)  | P-value |
|-----------------------------------|------------|---------|
| Normal                            | 47 (82.4%) | 0.771   |
| Walks with assistance             | 6 (10.5%)  |         |
| Wheelchair                        | 3 (5.2%)   |         |
| Bedridden                         | 1 (1.7%)   |         |

| Medications                       | Count (%)  | P-value |
|-----------------------------------|------------|---------|
| ACE inhibitor                     | 5 (8.7%)   | 0.321   |
| Diuretics                         | 20 (50.8%) | 0.001   |
| Calcium channel blocker           | 34 (59.6%) | 0.045   |

Table III: Factors Affecting Referral Time

| Gender                                | Time From Referral to Dialysis, Month | P-value |
|---------------------------------------|---------------------------------------|---------|
| Male                                  | 45.0 ± 58.3                           | 0.009   |
| Female                                | 37.7 ± 50.5                           |         |

| Underlying kidney disease             | Time From Referral to Dialysis, Month | P-value |
|---------------------------------------|---------------------------------------|---------|
| Diabetes mellitus                     | 30.2 ± 39.2                           | <0.001  |
| Hypertension                          | 40.2 ± 54.0                           |         |
| Glomerulonephritis                    | 62.1 ± 70.9                           |         |
| Others                                | 63.4 ± 73.6                           |         |

| Profession                            | Time From Referral to Dialysis, Month | P-value |
|---------------------------------------|---------------------------------------|---------|
| Professional specialist               | 47.1 ± 53.9                           | 0.025   |
| Office worker                         | 51.8 ± 66.4                           |         |
| Housewife and student                 | 44.5 ± 58.0                           |         |
| Mechanic                              | 32.1 ± 51.1                           |         |
| Labourer                              | 37.3 ± 46.5                           |         |
| Farmer                                | 34.9 ± 60.3                           |         |
| Unemployed                            | 40.0 ± 52.4                           |         |

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Discussion

This study was conducted to assess the social, demographic, clinical and health factors impacting the referral time to a nephrologist in chronic kidney disease patients. It was found that diabetes, profession, assisted ambulation and congestive heart failure were independent risk factors of late referral. On the other hand, patients who were smokers and had congestive heart failure were associated with early referral.

The cause of kidney disease also determines the referral time as glomerulonephritis is always referred to early worldwide as this disease is associated with the nephrology department (Caro Martínez et al., 2019; Dhanorkar et al., 2022; Greer et al., 2019). Similarly, CKD patients with diabetes mellitus are also referred early to increase the chances of survival and disease treatment (Smart et al., 2014; Wu et al., 2020). Other studies have also reported the early referral of diabetes mellitus patients before the start of dialysis (Chen et al., 2019; Mutatiri et al., 2022). Kessler et al (Kessler et al., 2003) and Kinchen et al (Kinchen et al., 2002) noted an average time of 4 to 12 months for referral of diabetes mellitus patients. However, our study showed contrary results as diabetes patients were referred to later than glomerulonephritis patients. This discrepancy may be due to differences in definitions of referral time.
With regards to comorbidities, the late referral group mostly had congestive heart failure as advanced kidney failure is a risk factor for heart failure (Kottgen et al., 2007). Heart failure in CKD patients may increase the mortality risk by accelerating the disease progression (McClellan et al., 2004; Xiong et al., 2019). Congestive heart failure was less common in early referral patients due to proper medication, diet and awareness which resulted in low diastolic blood pressure.

Early referral results in the delayed need for renal transplant, better lifestyle, less hospital stay and costs and increased survival (Chou et al., 2022). Jones et al (Jones et al., 2006) reported that nephrologist referral had a positive impact on the glomerular filtration rate due to appropriate care. Early referral patients had a high haemoglobin level, low phosphorus levels, and low LDL cholesterol levels.

Our study had some limitations including a small sample size and a short study period.

Conclusion

Diabetes and hypertension patients have a later referral time than patients with glomerulonephritis. In addition, men with congestive heart failure practicing physically active professions and assisted ambulation were referred late.

Conflict of interest

The authors declared absence of conflict of interest.

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