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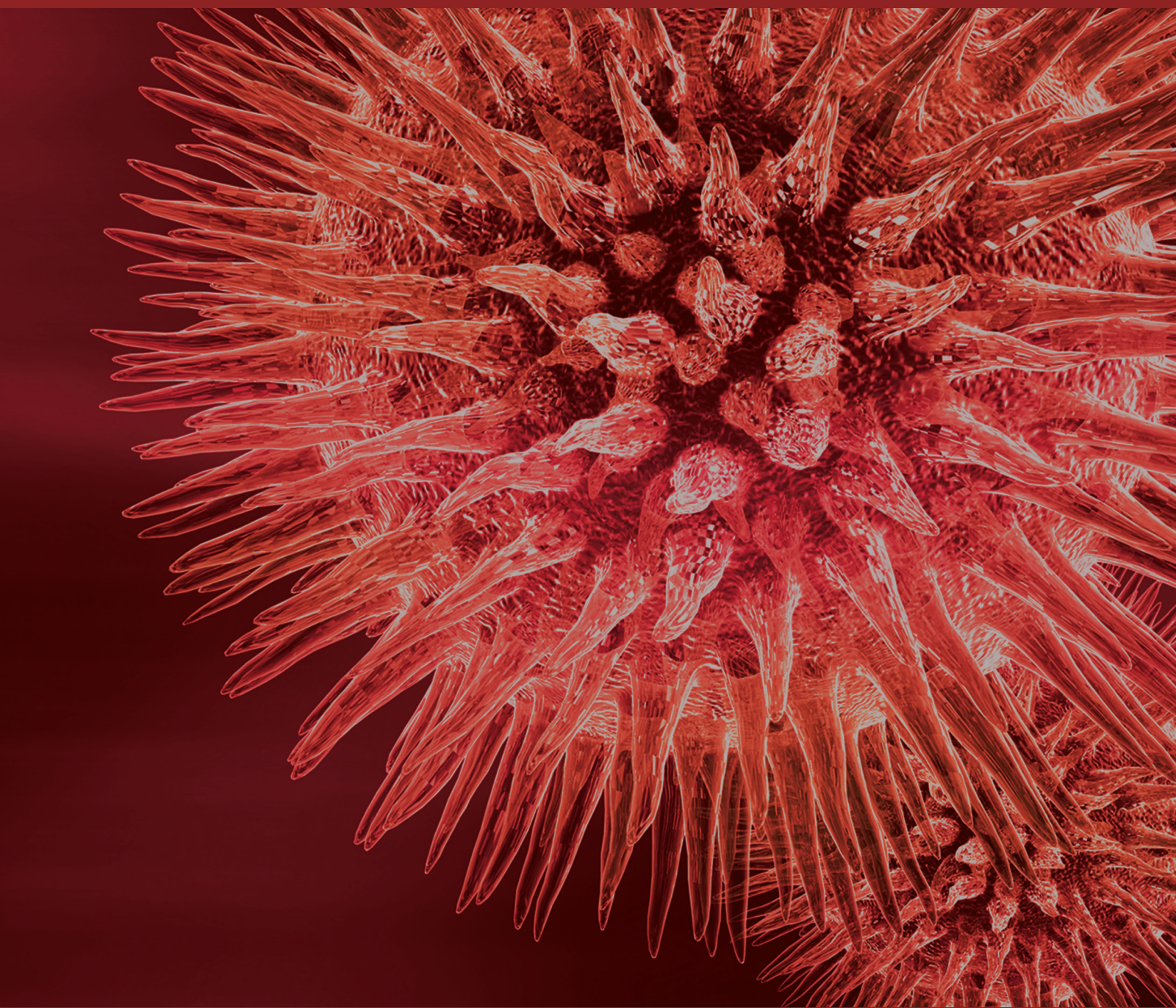
Insights into Living with Kidney Disease

Guest Editors: Veronica Swallow, Houry Puzantian, Leah Krischock, and Ulf Gunnar Bronas



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Editorial

Insights into Living with Kidney Disease

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There are many implications for those across the life-course who are living with kidney disease and their relatives/carers [1, 2]. Chronic kidney disease (CKD) is an important cause of reduced quality of life, morbidity, and death, so early identification is needed to help reduce these dire consequences. Public health approaches to enabling early identification are, therefore, receiving increasing attention. As part of these approaches, self-care is an integral part of daily life for persons across the life-course who are living with kidney disease and often means that patients and/or their carers take responsibility for day-to-day management of complex clinical interventions and treatment regimens, with support (that is often provided remotely) from the health professionals involved in their care [3]. People living with kidney disease can benefit enormously if they receive appropriate support for self-care. However, to understand the best ways to support them we need detailed insights into the challenges of living with kidney disease. The papers presented in this special issue report and discuss current evidence and new innovations; these insights will help professionals who are managing patients living with kidney disease.

In the management of patients receiving hemodialysis therapy, it is notable (as reported by B. El Ghoul et al.) that the etiology of end-stage renal disease is independently associated with arterial stiffness. This is higher among patients who developed renal sequelae of either diabetes mellitus or hypertension as compared with those with a history of either diabetes mellitus or hypertension alone. The clinical implication of this finding can translate into earlier interventions to reduce end-organ complications. Moreover, M. Majernikova et al. note that clinical evaluation and treatment of even mild anemia might reduce the higher risk of mortality in patients with posttransplant anemia in early stages of CKD after kidney transplantation. Furthermore, understanding the cerebro-vascular-renal axis pathophysiological link and its interconnection with the possible protective role of exercise is important for clinicians supporting patients with CKD in order to minimize the risk of loss of independence and improve quality of life (as reported by U. G. Bronas et al.)

Two papers in this issue focus on the psychosocial impact of CKD, in relation to dialysis for adult patients (N. Thomas et al.), and posttransplantation for children and young people (J. Bamford and L. Wirz). Posttransplant psychology annual reviews introduced into one Pediatric Renal Service enabled measurement of psychological distress and quality of life and helped identify those families most likely to benefit from psychological intervention. In N. Thomas et al.'s study, most patients were satisfied with the amount of information they received, although it was recommended that the quality of the information they received could have been improved, in particular concerning the effect of dialysis on individuals' day-to-day life.

Finally, the importance of lobbying policy makers and local water departments to ensure the availability of robust infrastructures support to sustain dialysis, the life-saving therapy for many people living with end-stage renal disease, including at times of natural disasters such as earthquakes, is highlighted by N. Ikegaya et al.

Overall, the new knowledge contained in this special issue makes an important contribution to the literature and can help shape the services and support offered to patients and families living with kidney disease.

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Review Article

Cognitive Impairment in Chronic Kidney Disease: Vascular Milieu and the Potential Therapeutic Role of Exercise

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Chronic kidney disease (CKD) is considered a model of accelerated aging. More specifically, CKD leads to reduced physical functioning and increased frailty, increased vascular dysfunction, vascular calcification and arterial stiffness, high levels of systemic inflammation, and oxidative stress, as well as increased cognitive impairment. Increasing evidence suggests that the cognitive impairment associated with CKD may be related to cerebral small vessel disease and overall impairment in white matter integrity. The triad of poor physical function, vascular dysfunction, and cognitive impairment places patients living with CKD at an increased risk for loss of independence, poor health-related quality of life, morbidity, and mortality. The purpose of this review is to discuss the available evidence of cerebrovascular-renal axis and its interconnection with early and accelerated cognitive impairment in patients with CKD and the plausible role of exercise as a therapeutic modality. Understanding the cerebrovascular-renal axis pathophysiological link and its interconnection with physical function is important for clinicians in order to minimize the risk of loss of independence and improve quality of life in patients with CKD.

1. Introduction

Chronic kidney disease (CKD) affects 45% of adults older than 70 years of age in the US [1]. The incidence of CKD will increase significantly over the next decade due to the increasing incidence of diabetes and hypertension in the rapidly aging US population. The economic cost of CKD is staggering with Medicare spending for patients with CKD aged 65 and older exceeding $50 billion in 2013, representing 20% of all Medicare spending in this age group [2]. Contributing to the high cost of CKD is the remarkably high prevalence of cognitive impairment or overt dementia that ranges 20–50% in older patients with moderate CKD [3–8] and may reach as high as 70% in severe CKD/dialysis [9]. Cognitive impairment impacts patients negatively by contributing to functional dependence and behavioral symptoms that result in poor outcomes and decreased medication and medical care compliance. These negative consequences result in a downward spiral of functional decline and an accelerated loss of independence, which leads to premature institutionalization [10–16]. The negative impact of cognitive impairment on quality of life and emotional wellbeing is significant, and it even affects employment rates negatively [17–20]. Moreover, cognitive function for incident dialysis patients has been found to be correlated with frailty and measures of depression [21]. Additionally, it more than doubles mortality risk and increases days spent in the hospital [15, 22], contributing to the tremendous individual, societal, and economical burden of CKD. We will review the vascular milieu as it is associated with cognitive decline in patients with kidney disease and the potential therapeutic role of exercise.

2. Measurement of Cognitive Impairment

Cognitive impairment is commonly referred to as a reduction in global cognition that is new and affects at least 2 areas of cognitive function that can be measured using a standard cognitive function test (e.g., Mini Mental State Exam (MMSE) or the Montreal Cognitive Assessment (MOCA)) [23, 24]. Impairment can be evident in various cognitive domains: executive function (judgement and planning), language, attention, memory, and visual-spatial learning. Mild cognitive impairment (MCI) is commonly defined as a deficit

in global cognition that is not consistent with aging and has not progressed to overt dementia. Although there is a lack of a consensus for a standard definition of MCI, it is known to be present with a performance of 1.5–1.99 standard deviations below the standard norm on a given cognitive test. MCI is mostly manifested in short-term memory loss but can also be manifested as impaired language and executive functions [25, 26]. Importantly, progression from MCI to overt dementia is approximately 15% per year in older patients [26]. Dementia on the other hand is used as the umbrella term for moderate/severe progressive cognitive impairment often defined as scoring 2 standard deviations below population norms in at least 2 cognitive domains [27]. Importantly, overt dementia leads to a loss of independent daily function whereas MCI does not appear to significantly affect independent daily function.

3. Cognitive Impairment and Dementia in CKD

It is well established that patients with kidney disease commonly have some degree of cognitive impairment and that kidney dysfunction is associated with a more rapid decline in mental function than in age matched comparisons [28, 29]. As many as 20–50% of patients with moderate CKD have established cognitive impairment or overt dementia [3–8, 30]. It should be noted that the actual population prevalence and incidence of cognitive impairment are likely underreported because published studies are primarily clinic-based and not true population studies. The United States Renal Data System Annual Data Report found a lower prevalence of cognitive impairment in CKD patients (7.6–16.8%) [22]. However, the true population prevalence is likely substantially higher. This is evidenced by Kurella et al. [6] who reported a 23–28% prevalence of cognitive impairment in stages 3-4 CKD patients ($n = 80$) seen in clinical practice and Murray et al. [9] who reported a prevalence of MCI or dementia in 87% of older dialysis patients. Most published studies have reported a prevalence of cognitive impairment of 20–50% in CKD patients and up to 70% in older patients on dialysis [3–9]. Unfortunately, less than 5% of all renal disease patients with cognitive impairment have been screened or received a medical diagnosis [9, 31]. This suggests that cognitive impairment in this group of patients is severely underdetected and not adequately addressed.

The degree of renal dysfunction appears to be correlated with the degree of cognitive impairment. Cognitive impartment has been shown in multiple studies to be associated with deteriorating renal function well before requiring dialysis, although this association is particularly strong in patients requiring dialysis [31]. Increased serum cystatin C and albuminuria are also associated with accelerated cognitive decline [32–34]. Studies have shown a 15-25% increased risk of cognitive impairment for every 10 ml/min per 1.73 m^2 reduction in the estimated glomerular filtration rate (eGFR). Further, there is an increased odds ratio of 2.43 (95% CI 1.38 to 4.29) for cognitive impairment in patients with an eGFR of <45 ml/min/per 1.73 m^2 even after adjustment for confounders [7, 35]. Thus, patients with CKD appear to have at least a twofold increased risk of cognitive impairment than those without CKD [7, 8, 30]. This risk increases to fourfold with further reductions in eGFR to <30 ml/min per 1.73 m^2 independent of potential confounders [8, 35]. These findings translate to patients with CKD having an increased and accelerated risk of cognitive aging equivalent to 3.6–7 years compared to the general population [32, 36]. However, current physical examination and medical history for patients with CKD or end-stage renal disease (ESRD) do not include cognitive function measures.

In terms of the clinical implications of cognitive impairment in CKD, improving support and access to psychology and social professionals, support groups, and patient education are likely to improve outcomes, although this has yet to be determined. Support of patients with CKD should also include counseling with pharmacists and providers regarding the risk of polypharmacy and potential interactions with patient-initiated supplements. The prevalence of cognitive impairment and dementia in the growing CKD population is likely to cause strain on the healthcare system, individuals, and family members. It is imperative that clinicians recognize the risk of cognitive impairment in the CKD population and include screening for cognitive impairment and initiate prompt treatment and coping strategies.

4. Brain Structure in Renal Disease

Magnetic resonance imaging (MRI) techniques have been used to assess brain structure and function in patients with CKD. Older MRI techniques have shown general cerebral atrophy of the hippocampus, cortical atrophy, and prominent lesions of the frontal lobes [37–39]. More recent MRI studies have been able to show deterioration of functional structures including reduced deep white matter volume, white matter hyperintensities representing small vessel disease, white matter lesions, and overt white matter disease [40–44]. Moreover, white matter lesions (degeneration of cells in the white matter) are frequent (up to 70% in dialysis patients) in CKD patients, even before requiring dialysis, suggesting that structural alterations begin early in the CKD disease process [40–44]. White matter lesions likely reflect vascular damage and cerebral ischemic areas. Advanced MRI techniques including diffusion tensor imaging (DTI) have shown subtle alterations in brain structural connectivity of the white matter via mean diffusivity (MD) and fractional anisotropy (FA). The white matter is important for coordinating interactions between different regions of the brain and is essential for normal functioning of the brain [45–49]. Impaired white matter integrity appears to be a primary contributor to cognitive decline in CKD and is strongly affected by the internal vascular milieu [45, 46]. Several studies have reported a correlation between MD and FA values and neuropsychiatric testing for patients with CKD, on hemodialysis, and after transplant [50–52]. The use of advanced MRI measures such as DTI may provide a method to diagnose early risk of cognitive decline before symptom presentation [53]. Moreover, several newer MRI techniques

are emerging such as multicomponent relaxometry techniques that may provide a tool to understand the etiology and the impact of risk factor contribution to cognitive decline in patients with renal disease [47, 50–55]. Notably, structural and functional brain changes appear to occur in conjunction with reduced cerebral blood flow, likely related to systemic and cerebral endothelial dysfunction and arterial calcification [45, 56, 57]. Interestingly, Zhang et al. (2016) attempted to evaluate potential changes in white matter integrity in a small nonrandomized single arm study by assessing patients' brain functional connectivity before and after kidney transplantation [55]. They reported that structural connectivity values were abnormal before transplantation but returned close to normal values one-month after transplantation. Radić et al. (2011) observed improvement in cognitive function following transplantation, which was maintained at 2-year follow-up [58]. The reasons for these findings are not clear and need to be confirmed in appropriately powered randomized, controlled trials. However, these studies are encouraging and suggest that the adverse brain structural changes may be susceptible to reversal although it is clear that much additional research is needed before any conclusions can be made.

5. Etiology of Cognitive Decline in Kidney Disease

The most common type of dementia in the general population is neurodegenerative dementia (as seen in Alzheimer's disease) often manifested as atrophy of the hippocampus. Patients with renal disease are more likely to have large and small blood vessel disease, which causes white matter disease and reduced white matter integrity related cognitive impairment that often is superimposed on neurodegenerative disease. This vascular disease results in a high rate and susceptibility of cerebrovascular disease including subclinical microvascular cerebral disease and overt stroke [59–62]. Cerebral microbleeds occur in up to 60% of all patients with CKD and appear to be more frequent in patients with black ethnicity [63, 64]. Moreover, CKD patients have a fivefold increased risk of developing clinical and subclinical cerebrovascular disease, and the annual incidence of stroke is approximately 10%, compared to 2.5% in an age and sex matched population without CKD [22, 65]. This rate is even higher in the dialysis population and may reach as high as a tenfold increased incidence of stroke compared to the general population [66, 67]. There is therefore a strong likelihood that patients with CKD are at an increased risk for cognitive impairment due to vascular disease-related causes, manifested as cerebral microinfarcts and white matter disease, and not overt Alzheimer's disease per se [68]. The cerebral vascular disease appears to act in conjunction with a neurodegenerative disease process mediated in part by uremic toxins, creatinine levels, and even cystatin C levels [62]. It should be noted that the pathophysiology and etiology of cognitive decline in CKD are complex and multifaceted, and far from completely understood.

6. Risk Factors Associated with Cognitive Decline in CKD

Risk factors for cognitive decline in patients with CKD are listed as follows:

Demographic Factors

- African American
- Hispanic
- Female sex
- Older age
- Low education

Clinical Factors

- Hypertension
- Diabetes
- Dyslipidemias
- Polypharmacy
- Sleep quality
- Depression

Vascular Milieu

- Oxidative stress
- Inflammation
- Hyperhomocysteinemia
- Uremia
- Albuminuria

Dialysis Procedure Specific Risk Factors for Cognitive Impairment in End-Stage Renal Disease

- Volume and electrolyte fluctuation
- Cerebral edema
- Cerebral hypoperfusion
- Hypotension during dialysis
- Excessive cytokine release
- Microembolism
- Delirium

The traditional risk factors for cerebrovascular disease include African American and Hispanic ethnicity, dyslipidemia, hypertension, diabetes mellitus, female sex, education status, and older age [7, 31, 35, 69–75]. Vascular risk factors will be discussed in detail below. Various clinical factors that are unique to the CKD population contribute to cognitive impairment. These include a high rate of undiagnosed depression and polypharmacy-related side effects or interactions [19, 20]. Patients with renal disease often have significant fatigue and daytime sleepiness related to poor sleep quality, which could contribute to further cognitive decline [76]. It should be noted that patients undergoing hemodialysis have many additional risk factors predisposing them to

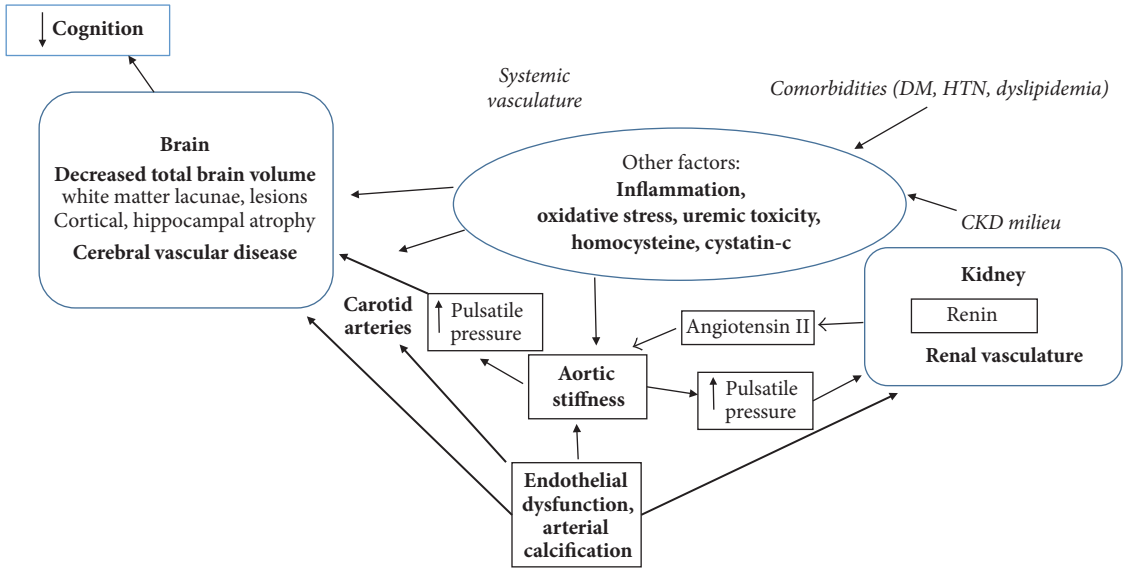

Figure 1: Systemic and cerebral vasculature and cognition in CKD.

cognitive impairment, including the dialysis procedure itself. The dialysis procedure predisposes patients to potential risk factors for cognitive impairment and cerebrovascular disease including volume and electrolyte fluctuations, cerebral edema and hypoperfusion, and excessive cytokine release [60]. Interestingly, the frequency of hypotensive episodes during dialysis has been associated with cerebral atrophy and lacunae frequency, while microembolisms may contribute to the burden of both large and small vessel cerebrovascular disease although much research is needed in this area [77, 78]. Moreover, secondary and recurrent delirium (often related to hypoperfusion) and encephalopathy (i.e., untreated renal failure related neurotoxicity) appear to be associated with the development of cognitive impairment [79]. Finally, we recognize that anemia and derangements in serum vitamin D levels also contribute to the CKD milieu and potentially cognitive decline. In cross-sectional studies, anemia has been found to be associated with cognition in ESRD; however, in a longitudinal study, anemia was not an independent predictor of cognitive decline in elderly patients with CKD [80]. In terms of vitamin D, a review by Cheng et al. (2016) notes that reduced levels of 25(OH)-vitamin D may be contributing to cognitive impairment in CKD [81]. Clinical trials are needed to investigate the effect of vitamin D supplementation on cognitive outcomes.

7. The Cerebrovascular-Renal Axis (Figure 1)

The accelerated cognitive decline in older CKD patients appears to be due, in part, to the CKD disease process itself, which creates a toxic vascular and metabolic milieu that consists of chronic inflammation, oxidative stress, uremia, and systemic vascular endothelial dysfunction [82–88]. This toxic internal vascular and metabolic milieu is postulated to cause vascular dysfunction related impairment of the white matter that is superimposed on neurodegenerative damage caused by homocysteine, uremic toxins, creatinine, and cystatin C [62, 89]. Homocysteine appears to be an especially strong risk factor for stroke in CKD patients via a direct neurotoxic effect, initiation of systemic inflammation, and endothelial dysfunction [90–94]. The increase in homocysteine is probably due to reduced renal clearance. Unfortunately, interventions with folate to reduce homocysteine levels have thus far been conflicting and disappointing [95–97]. Patients with CKD have increased levels of oxidative stress, caused by uremia, production of reactive oxygen species via physiological pathways (e.g., impaired/damaged/malfunctioning mitochondria), and an inability to produce adequate antioxidative enzymes [98, 99]. These changes all contribute to a vascular milieu that consists of systemic inflammation, high levels of oxidative stress, and endothelial dysfunction that is unique to the CKD patient and creates a vascular pathway to cognitive decline.

8. Vascular Mechanisms Related to Cognitive Decline in CKD

Patients with CKD are at an increased risk for vascular disease-related cognitive impairment rather than Alzheimer's disease per se as described above. Vascular calcification in advanced stages of CKD, possibly including intracranial calcification, could be influencing cognition. Interestingly, there appears to be a significant influence of chronic hypertension on the progression of cognitive decline. This may be related to the high volume of blood flow and pressure that the brain and the kidney are exposed to.

The association between systemic arterial stiffness and cognitive performance has been established in cross-sectional studies [100]. More recently, Pase et al. (2016) studied the Framingham Offspring cohort and found that aortic stiffness predicts incident mild cognitive impairment and incident dementia in nondiabetic patients over 10 years [101]. Apart

from aortic (central arterial) stiffness, stiffness in arteries in close proximity to the brain may need to be considered. One study reports that, in swines, carotid artery stiffness seems to be associated with impaired memory [102]. Additionally, although intracranial artery stiffness is even more challenging to measure, it may also be associated with cognitive decline [103].

Hypertension is associated with changes in brain tissue and cerebral vasculature. For example, mean arterial pressure was associated with white matter hyperintensity volume in the Framingham Offspring cohort, even in the absence of associations between changes in brain tissue and tonometry measures (such as arterial stiffness or central pulse pressure) [104]. Importantly, increased duration of hypertension is an important contributor to cognitive outcomes. Midlife hypertension has a significant impact on long-term cognitive impairment, as reviewed by Iadecola et al. (2016) [105]. Although some studies have shown a relationship between elevated blood pressure and cognitive impairment in the absence of a stroke, whether intensive hypertension control results in prevention or reversal of cognitive outcomes is unclear [106]. Upcoming results from the SPRINT-MIND trial (Systolic Blood Pressure Intervention Trial, Memory and Cognition in Decreased Hypertension) may address some of these unanswered questions.

The Strain Vessel Hypothesis states that "strain vessels" found in vital organs play a protective role [107]. Strain vessels help maintain a pressure gradient between the larger arteries and capillaries. High-pressure flow from large arteries, in addition to low resistance to flow in small vessels in vital organs, causes subsequent damage to vessels exposed to high pulsatility [108]. In the brain, small perforating arteries are exposed to high pressure; cerebral hemorrhage and infarction occur frequently in these small arteries [107, 109]. As decreasing kidney function is associated with arterial stiffness [110] and high blood pressure, patients with CKD are likely to have their blood vessels exposed to high pulsatility flow. Therefore, CKD patients are at high risk of developing injury to cerebral vasculature. The latter, in turn, would impact cognitive function.

It is challenging for drugs to influence the aorta and large arteries; and thus interventions may target other conduit arteries to reduce wave reflection. Although drugs such as angiotensin-converting enzyme inhibitors and calcium channel blockers seem to be beneficial in hypertensive elderly individuals, blood pressure levels that are optimal for cognitive function are yet to be identified [106]. Apart from medications, regular exercise may be employed to target this phenomenon.

9. Exercise as a Potential Therapeutic Approach

Higher levels of physical activity and cardiorespiratory fitness levels are associated with increased levels of cognitive function in healthy individuals. Exercise appears to prevent cerebral atrophy or even increase hippocampal volume in the general population [111, 112]. It is conjectured that these observations are related to an increase in brain-derived neurotrophic factor and an exercise-induced increase in angiogenesis, neurogenesis, and synaptogenesis. It is conceivable that physical activity and fitness levels are related to cognitive function in patients with kidney disease, but there have been a minimal number of studies in this area and the results are inconsistent. Patients on hemodialysis with the highest self-reported activity levels had the highest cognitive scores in one study [113]. Conversely, one smaller study found no association between maximal oxygen consumption and scores on the MMSE in patients on hemodialysis [114]. Several exercise intervention studies have shown promise in improving cognition in healthy elderly participants with and without MCI [111, 115–126], whereas others have reported no improvement [127–130]. Regular exercise and higher fitness levels in non-CKD patients with and without cognitive impairment have been associated with improved cognitive function, white matter integrity, and hippocampal volume suggesting a possible neuroprotective effect of exercise [111, 113, 115–125]. This is conjectured to be due to an improvement in vascular function-related increases in cerebral blood flow [116]. It is therefore plausible that exercise training may improve the vascular milieu and thereby contribute to improved cognitive function in patients with CKD. However, the impact of exercise on cognitive function in the CKD population is currently unknown. Only one study has reported on cognitive function following exercise training in the dialysis population. Martins et al., 2011, reported an improvement in cognitive function measured via the MMSE following exercise training [131]. Unfortunately, this study was not randomized and the MMSE is not a sensitive measure for change in global cognition, which limits any conclusions. Studies investigating the impact of exercise on cognition in CKD patients are needed. Exercise training appears to improve the vascular milieu in patients with CKD by reducing systemic inflammation and oxidative stress, arterial stiffness, and improving vascular function [132]. However, not all studies have shown improvements in these vascular risk factors, likely due to differences in sample characteristics, exercise program, and outcome measures. Moreover, exercise training may reduce traditional risk factors for cerebrovascular disease such as blood pressure and lipid profile although it should be noted that randomized controlled trials are scarce in patients with CKD and most data are based on secondary analyses from smaller trials. Exercise training is also known to improve glucose control in diabetic patients and may reduce homocysteine levels. Importantly, the pleiotropic effect of exercise provides additional benefits that are important to patients with CKD including improved quality of life, improved physical function, and reduced risk of frailty. Moreover, higher levels of physical activity have been associated with reduced risk of initiation of renal replacement therapy and higher survival rate in patients with CKD stages 3–5 [133]. Finally, emerging studies suggest that there is an independent association between prolonged sedentary time and kidney function decline, whereas higher levels of physical activity are associated with reduced levels of creatinine and lower risk of kidney impairment [134, 135]. Thus, it is plausible that exercise may affect renal function itself and thereby provide a protective effect. Despite lack of

data on the impact of exercise on cognitive function, it is prudent for clinicians to recommend that patients with CKD consider initiating an exercise program and increase their daily physical activity levels to gain the mental and physical health benefits of exercise.

10. Summary and Conclusions

Cognitive impairment is common in patients with CKD and negatively affects health-related quality of life and other health-related outcomes. It is imperative that clinicians recognize the value of early screening for cognitive impairment and initiate preventive and treatment measures. Importantly, the decline in cognitive function appears to be multifaceted with a major involvement of vascular dysfunction in a unique CKD metabolic milieu that predisposes patients to an accelerated cognitive decline. Multidisciplinary healthcare teams are needed to provide psychosocial support and patient education on essential topics such as control of blood pressure, risks of polypharmacy, and other individualized self-care practices. Current research investigating exercise-induced improvement in cognition in non-CKD population is promising, but there are conflicting reports in the literature. As exercise training may be a plausible adjunctive therapeutic approach to improve cognitive outcomes and quality of life in patients with CKD, further research should focus on exercise as a promising approach that may retard the progression of cognitive impairment in CKD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Posttransplant Anemia as a Prognostic Factor of Mortality in Kidney-Transplant Recipients

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Background. Findings on the association between posttransplant anemia (PTA) and mortality in posttransplant patients are scarce. This study explored whether PTA shortly after kidney transplantation (KT) predicts mortality at up to 10 years' follow-up, stratified for chronic kidney disease (CKD) stages. *Methods.* PTA was divided into 3 categories according to the hemoglobin (Hb) value: severe (Hb < 10 g/dl), mild (10.0 g/dl ≤ Hb < 11.9 g/dl), or no PTA (Hb ≥ 12 g/dl). CKD stages were estimated using the CKD-EPI formula and divided into 2 groups: CKD1-2 and CKD3–5. Cox regression, stratified according to CKD, was performed to identify whether different categories of PTA predicted mortality in KT recipients. *Results.* Age, being female, and both mild and severe PTA contributed significantly to the Cox regression model on mortality in CKD1-2. In the Cox regression model for mortality in CKD3–5, age and severe PTA contributed significantly to this model. *Conclusion.* PTA shortly after KT increased the risk of mortality at up to 10 years' follow-up. Even mild PTA is associated with a 6-fold higher risk of mortality and severe PTA with a 10-fold higher risk of mortality in CKD1-2. Clinical evaluation and treatment of anemia might reduce the higher risk of mortality in patients with PTA in early stages of CKD after KT.

1. Introduction

The definition and grades of anemia were established decades ago by the World Health Organization (WHO) as being among the important factors influencing health outcomes: decreased hemoglobin concentration predicts morbidity and mortality in the general population [1], and this definition was consequently adopted by nephrologists. According to "The National Kidney Foundation Disease Outcomes Quality Initiative" (NKF/KDOQI), "Kidney Disease Improving Global Outcomes" (KDIGO), and "European Best Practice Guidelines" (EBPG), anemia is defined as a target hemoglobin (Hb) <13.5 g/dl in adult males/postmenopausal females, <12.0 g/dl in premenopausal females, and <5th percentile for children [2–4]; alternatively, the target Hb should generally be <11.0 g/dl [5, 6].

However, in most individuals there is a considerable amount of variation in the Hb-value over time, and the consequences of this variability in Hb-levels have been thoroughly studied in dialysis patients, though not in transplant recipients [7]. Renal anemia after transplantation, or posttransplant anemia (PTA), has a multifactorial etiology including the progress of transplant kidney failure, comorbidity, infections, inflammation, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB), and immunosuppressive treatment [2–6, 8–10]. Thus far, some evidence has

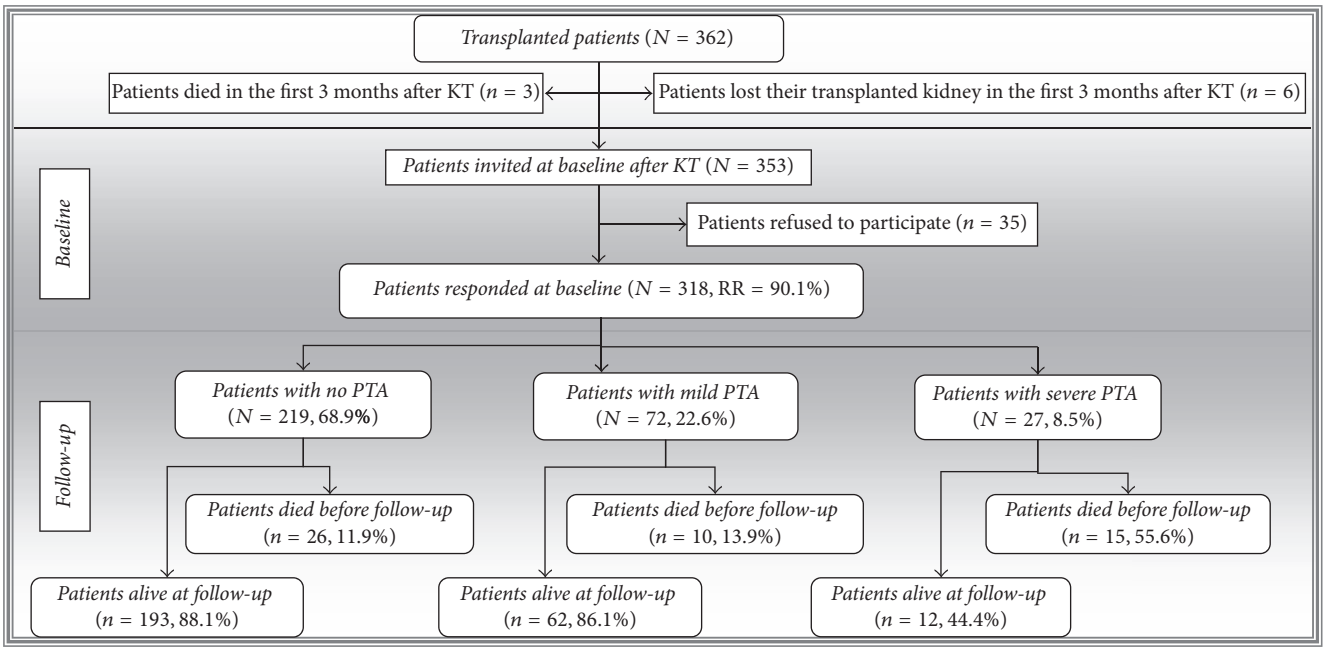

Figure 1: Flow-chart diagram of the participants. *N*/*n*: number; RR: response rate; KT: kidney transplantation; PTA: posttransplant anemia.

been found suggesting that kidney-transplant recipients may have Hb-level lower than what can be expected based on the level of their kidney function [2].

Guidelines from NKF/KDOQI, KDIGO, and EBPG recommend treating anemia of renal origin in order to reduce both morbidity and mortality [2–5]. KDIGO guidelines for kidney-transplant recipients state that treatment should be directed at the underlying cause. In contrast, regular testing for anemia is not recommended by the above-mentioned guidelines, and treatment of posttransplant anemia should be managed according to the guidelines for chronic kidney disease (CKD) in the predialysis period, with no specific recommendation for treatment of this specific population [2].

Additionally, the impact of the variability of hemoglobin over time in transplant recipients as compared with dialyzed patients has been considered in only a few studies. Some relationships between rejection episodes, immunosuppressant use, and increased anemia prevalence [9, 10], as well as between anemia of renal origin and mortality [11–13], have been shown.

Renal anemia after transplantation and its association with transplant outcomes have not been sufficiently explored; moreover, longitudinal studies on the association between anemia and mortality are rather rare, and PTA is still an underestimated problem [7, 13–15]. Therefore, the aim of this study was to explore whether anemia shortly after kidney transplantation predicts mortality at up to 10 years' follow-up.

2. Materials and Methods

2.1. Sample and Procedure. A total of 362 consecutive patients who underwent KT between January 2001 and January 2011 at the Transplant Centre of Kosice in the eastern region of Slovakia were enrolled in the study. The presented findings are part of a bigger study focused on quality of life measured using several questionnaires; the collection of medical data for this study took place during the collection of the questionnaires. The baseline examination of the participants took place between the 3rd and 12th month after successful KT during regular outpatient clinical visits in our centre. The inclusion criterion was graft survival at 3 months after KT, because the first 3 months after KT are usually considered as the most problematic period associated with dramatic changes and increased morbidity and even mortality [16]. All recipients were previously included on the waiting list for a kidney transplant. Therefore, they were tested for all serious comorbidities, such as cancer, which is always an exclusion criterion for transplantation; thus, no transplanted recipients had a cancer diagnosis at baseline. Additionally, the degree of renal anemia during a period shorter than 3 months after successful transplantation depends on the pre- and peritransplantation period [2]. In the case of any severe medical problem (infection, rejection, surgery, etc.) data collection was postponed by one month after overall clinical stabilization.

Nine patients dropped out prior to reaching 3 months after transplantation: 3 (0.8%) died and 6 (1.7%) lost their transplanted kidney. In total 353 kidney-transplant recipients after successful transplant surgery were invited to participate. Out of these, 35 (9.9%) refused to participate, resulting in a total of 318 patients (an effective response rate of 90.1%) at the start of the study. Figure 1 presents more detailed information about the sample (Figure 1). Only patients who signed an informed consent form prior to the study were included. The Institutional Ethics Committee of the University Hospital in Kosice approved the study. All data and information used from the documentation, including demographic and clinical

ones, were used in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

2.2. Measures

2.2.1. Sociodemographic Data. Sociodemographic data included age and gender. Age was treated as a continuous variable. Male gender was the reference category.

2.2.2. Clinical Data. Clinical data were retrieved from medical files. These included serum hemoglobin, creatinine (laboratory methods by Scheffe), primary kidney diagnosis, previous duration of dialysis (in years), source of transplanted kidney, comorbidities, current and antirejection immunosuppressive treatment, acute rejection episodes, chronic renal allograft dysfunction, uroinfection (which included pyelonephritis and diagnosis of graft loss), and mortality. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula in milliliters per minute and 1.73 m^2 [17]. CKD stages were determined as recommended by the "Kidney Disease Initiative for Global Outcomes" (KDIGO) guideline. This proposes a classification of chronic kidney disease [2, 6]; the classification reflects the impact of CKD (stages) for risk evaluation, diagnosis, patient management, and treatment options. In order to explore the effect of the CKD stages on anemia, we stratified the sample into two groups, as groups consisting of the separate CKD stages were too small for stratification: CKD stages 1-2 versus CKD stages 3–5, according to the known impact of deceased kidney function on increasing anemia of renal origin from CKD stage 3 [2, 6]. Acute rejection episodes and chronic renal allograft dysfunction were diagnosed from a biopsy according to the Banff 2009 update of diagnostic categories for renal allograft biopsies [18]. Depending on the hemoglobin value, PTA was divided into 3 categories: (1) severe PTA (Hb < 10 g/l), (2) mild PTA (10 ≤ Hb < 12 g/l), and (3) no PTA (Hb ≥ 12 g/dl) according to the "European Renal Best Practice" (ERBP) Guidelines [3, 4]. Severe cardiac failure was classified by the New York Heart Association (NYHA) Functional Classification as Classes III and IV [19].

2.2.3. Mortality Data. Mortality data were obtained from our database of medical reports and completed with data from the "Health Care Surveillance Authority of the Slovak Republic" up to 10 years after KT.

2.3. Statistical Analyses. Frequencies, means, and standard deviations were calculated for the sample description. The Mann–Whitney U test and χ^2 test were used to identify the association between mortality and the following baseline variables: age, gender, duration on dialysis before KT (in years), eGFR and CKD stages, PTA (severe, mild, and no anemia, which was the reference category), uroinfection (pyelonephritis included), number of acute rejection episodes, chronic renal allograft dysfunction, source of transplanted kidney, cardiovascular disease (coronary artery disease, cardiac failure, myocardial infarction), hypertension, and categories of diabetes mellitus (no diabetes mellitus, already existing diabetes mellitus, and new-onset diabetes mellitus after transplantation). Stratification by CKD was performed with regard to the known impact of decreased kidney function on anemia of renal origin [6] in order to study the potentially different associations between PTA and other incorporated variables independently of kidney function. These variables were included in the analysis due to the past research evidence outlined in the Introduction [2, 5]. Kaplan–Meier plots and log-rank test were used to display the differences between mortality risks by PTA categories separately for CKD stages 1-2 compared to CKD stages 3–5. Cox regression was performed in order to identify the predictors of mortality (censored for graft loss). The independent variables in both stratified Cox regression models were all variables with a level of significance set at $p < 0.1$ in the Mann–Whitney U test and the χ^2 test, as appropriate. The Statistical Package for the Social Science (IBM SPSS Inc., Chicago, IL, USA) version 24 was used for statistical analyses.

3. Results

No significant differences were found at baseline between participants and nonparticipants regarding age, gender, graft loss, and mortality. The observation period of follow-up was from 1 to 10 years (mean 5.6 ± 2.7); the mean period for severe PTA was 4.3 ± 2.6 years, for mild PTA 5.3 ± 2.6 years, and for the category without PTA 5.9 ± 2.7 years. The prevalence of renal anemia therapy was 14% with Erythropoiesis-Stimulating Agents (ESA), 48% iron supplementation, 33% folic acid, 14% ascorbic acid, 10% pyridoxine, and 6% cobalamin. Table 1 displays detailed information about the characteristics of the sample ($N = 318$) (Table 1).

The Mann–Whitney U test found that those who died were older ($p < 0.001$) and had a lower eGFR ($p < 0.001$) in the first year after KT. χ^2 test indicated that they were also more likely to be of female gender ($p < 0.1$), to have a higher degree of PTA ($p < 0.001$), to have a more advanced stage of CKD ($p < 0.001$), and to show the presence of severe cardiac failure ($p < 0.1$) in the first year after KT (Table 1). The risk of death in patients with mild and severe PTA in CKD stages 1-2 compared with no PTA starts to rise at 3 years after KT; the hazard ratio for mild and severe PTA compared with no PTA increased after this period independently of kidney function. However, the risk of death in patients with severe PTA in CKD stages 3–5 starts to rise already at 2 years after KT. Figures 2 and 3 display the differences in mortality between those with severe PTA, those with mild PTA, and those with no PTA. (Figures 2 and 3).

3.1. Model 1: Cox Regression Model for Mortality in CKD Stages 1-2. Age (HR 1.1, $p \leq 0.001$), female gender (HR 0.1, $p \leq 0.05$), mild PTA (HR 6.2, $p \leq 0.05$), and severe PTA (HR 9.8, $p \leq 0.001$) contributed significantly to Cox regression model 1 for mortality in CKD stages 1-2. The risk of death increased by 10% for each year of age, while, on the other hand, the risk of death decreased by 90% among females. In addition, the

Table 1: Characteristics of the sample ($N = 318$).

Characteristics of the sample at baseline	Died after transplant ($n = 51$) n (%) or mean ± SD	Survived after transplant ($n = 267$) n (%) or mean ± SD	p value
Age	48.4 ± 6.8	46.9 ± 7.4	0.001
Gender			
Male	24 (47.1%)	159 (59.6%)	0.05
Female	27 (52.9%)	108 (40.4%)	
Duration on dialysis before KT (in years)	3.7 ± 2.1	3.5 ± 2.9	n.s.
Primary diagnosis of kidney failure			
Glomerulonephritis	19 (37.3%)	96 (36.0%)	
Tubulointerstitial nephritis	12 (23.5%)	66 (24.7%)	
Vascular disease	3 (5.9%)	28 (10.5%)	n.s.
Polycystic kidneys adult type	2 (3.9%)	19 (7.1%)	
Diabetic nephropathy	8 (15.7%)	13 (4.9%)	
Others or unknown	7 (13.7%)	45 (16.8%)	
Source of transplanted kidney			
Deceased donor	47 (92.2%)	256 (95.9%)	n.s.
Living donor	4 (7.8%)	11 (4.1%)	
Function immediately after KT			
Immediate function	27 (52.9%)	150 (56.2%)	n.s.
Delayed function	24 (47.1%)	117 (43.8%)	
Estimated glomerular filtration rate (ml/min/1.73 m^2)	61.2 ± 19.8	63.8 ± 20.1	0.001
CKD stage			
1	5 (9.8%)	18 (6.7%)	
2	20 (39.2%)	115 (43.2%)	
3a + 3b	21(41.2%)	101 (37.8%)	0.07
4	3 (5.9%)	11 (4.1%)	
5	2 (3.9%)	22 (8.2%)	
Hemoglobin value (g/dl)	11.9 ± 1.9	12.7 ± 2.1	0.001
Posttransplant anemia			
Severe (Hb < 10.0 g/dl)	8 (15.8%)	19 (7.1%)	
Mild (10.0 ≤ Hb < 12.0 g/dl)	17 (33.3%)	55 (20.6%)	0.001
No anemia (Hb 12.0 g/dl)	26 (50.9%)	193 (72.3%)	
Therapy for anemia			
ESA	3 (5.9%)	11 (4.1%)	
Iron	8 (15.7%)	39 (14.6%)	
Folic acid	14 (27.4%)	19 (7.1%)	n.s.
Cobalamin	2 (3.9%)	4 (1.5%)	
Pyridoxine	1(2.0%)	9 (3.4%)	
Ascorbic acid	3 (5.9%)	11 (4.1%)	
Acute rejection episodes	17 (33.3%)	78 (29.2%)	n.s.
Type of rejection treatment			
Steroids	9 (17.6%)	63 (23.6%)	
Antithymocyte globulin	2 (3.9%)	8 (3.0%)	n.s.
Plasmapheresis	1(2.0%)	5 (1.9%)	
Plasmapheresis + i.v. immunoglobuline	1(2.0%)	6 (2.2%)	
Chronic renal allograft dysfunction	8 (15.7%)	34 (12.7%)	n.s.
Uroinfection (including pyelonephritis of graft)	14 (27.4%)	71 (26.6%)	n.s.
Immunosuppression treatment			
CsA + P	7 (13.7%)	29 (10.9%)	
CsA + AZA/CsA + AZA + P	8 (15.7%)	16 (6.0%)	
CsA + MMF/CsA + MMF + P	23 (45.1%)	131 (49.0%)	n.s.
Tac + MMF/Tac + MMF + P	11 (21.6%)	86 (32.2%)	
SIR + MMF + P/EVER + CsA + MMF	2 (3.9%)	5 (1.9%)	

Table 1: Continued.

Characteristics of the sample at baseline	Died after transplant (n = 51) n (%) or mean ± SD	Survived after transplant (n = 267) n (%) or mean ± SD	p value
Comorbidities			
Coronary artery disease	11 (21.6%)	67 (25.1%)	n.s.
Severe cardiac failure	15 (29.4%)	57 (21.3%)	0.09
Myocardial infarction	3 (5.9%)	14 (5.2%)	n.s.
Hypertension	37 (72.5%)	189 (70.8%)	n.s.
Diabetes mellitus identified before KT	8 (15.7%)	22 (8.2%)	n.s.
NODAT	3 (5.9%)	14 (5.2%)	n.s.
CKD-MBD	23 (45.1%)	140 (52.4%)	n.s.
Other comorbidities: ≥2	1(2.0%)	8 (3.0%)	n.s.

Level of significance $p < 0.1$; N/n: number, SD: standard deviation, AZA: azathioprine, CKD: chronic kidney disease, MBD: mineral bone disorder, NODAT: new-onset diabetes mellitus after transplantation, CsA: cyclosporine A, ESA: erythropoiesis-stimulating agents, EVER: everolimus, Hb: hemoglobin, KT: kidney transplantation, n.s.: not significant, MMF: mycophenolate mofetil/mycophenolate sodium, P: prednisone, SIR: sirolimus, and Tac: tacrolimus.

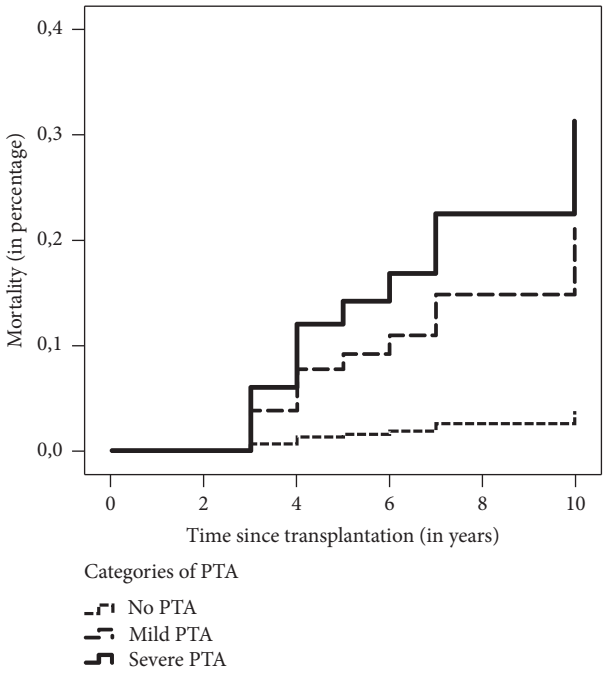

Figure 2: Differences in mortality between severe PTA, mild PTA, and no PTA over 10 years in CKD stages 1-2. Kaplan–Meier plots showing higher mortality during 10 years after transplantation in patients with CKD stages 1-2 with mild or severe anemia compared with patients without PTA. Log-rank test: $\chi^2 = 39.62$ and p value of the model < 0.001.

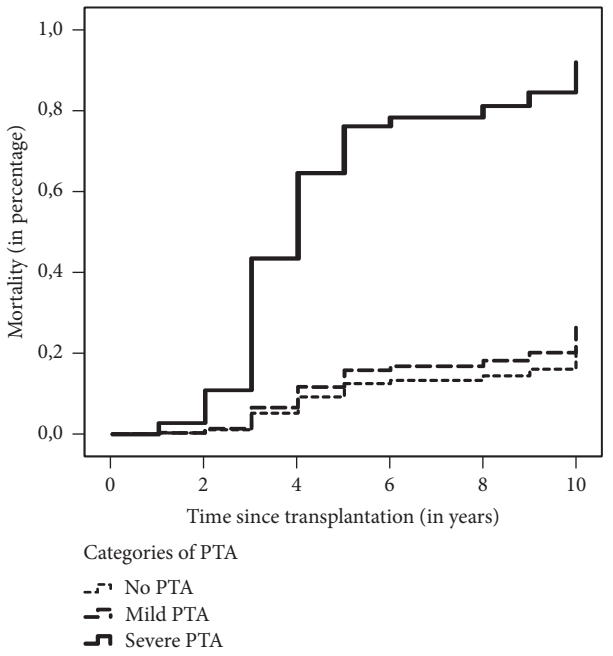

Figure 3: Differences in mortality between severe PTA, mild PTA, and no PTA over 10 years in CKD stages 3–5. Kaplan–Meier plots showing higher mortality during 10 years after transplantation in patients with CKD stages 3–5 with severe PTA compared with patients without PTA. Log-rank test: $\chi^2 = 32.09$ and p value of the model < 0.001.

presence of mild PTA increased the risk 6-fold and severe PTA 10-fold (Table 2).

3.2. Model 2: Cox Regression Model for Mortality in CKD Stages 3–5. Age (HR 1.1, $p \leq 0.01$) and severe PTA (HR 10.8, $p \leq 0.001$) contributed significantly to Cox regression model 2 for mortality in CKD stages 3–5. The risk of death increased by 10% for each year of age, and the presence of severe PTA increased the risk 10-fold (Table 2).

4. Discussion

We explored the independent effect of anemia on mortality in the early period after kidney transplantation. Mild and severe PTA in the first year after transplantation increased the higher risk of mortality independently of kidney function at up to 10 years' follow-up. Mild PTA predicted a 6-fold higher risk of mortality and severe PTA a 10-fold higher risk of mortality compared with no PTA in CKD stages 1-2. However, patients with more advanced stages of CKD showed no association of mild PTA with mortality, probably as this only reflects their

Table 2: Final models of Cox regression [stratified due to 2 CKD groups (CKD stages 1-2 and 3–5)] containing predictors of mortality.

Models for mortality (N = 318)	HR	95% CI for HR	p value
Model 1 in CKD stages 1-2 (n = 158)			
Age	1.12	1.05; 1.20	0.000
Gender			
Male	Reference		
Female	0.09	0.09; 0.82	0.033
Severe cardiac failure			
No	Reference		
Yes	1.82	0.60; 4.23	0.316
PTA			
No	Reference		
Mild	6.16	1.12; 34.33	0.038
Severe	9.79	2.57; 37.26	0.001
Model 2 in CKD stages 3–5 (n = 160)			
Age	1.06	1.02; 1.09	0.003
Gender			
Male	Reference		
Female	0.59	0.29; 1.20	0.593
Severe cardiac failure			
No	Reference		
Yes	1.92	0.82; 5.56	0.835
PTA			
No	Reference		
Mild	1.29	0.56; 2.98	0.554
Severe	10.78	4.15; 28.08	0.000

PTA: posttransplant anemia, CI: Confidence Interval, HR: hazard ratio.

worse kidney function; however, severe PTA predicted a 10-fold higher risk of mortality. The other factor associated with increased risk of mortality was advanced age and that with decreased mortality was female gender, which is in line with the other studies [20, 21].

NKF/KDOQI and KDIGO guidelines for diagnosis and treatment of renal anemia recommend a global assessment of the patient, which should consist of an inventory of complications of the dialyzed, perioperative, and posttransplantation period, including inflammatory diseases, rejections, comorbidities, ACEi/ARB, and immunosuppressant treatment [2, 3, 6]. In our study uroinfection (including pyelonephritis), rejection episodes, chronic renal allograft dysfunction, cardiovascular disease, already existing diabetes mellitus, new-onset diabetes mellitus after transplantation, and the total number of other comorbidities were not associated with mortality in patients after KT.

In line with our results, Amaral et al. showed that patients with mild and severe anemia of renal origin independently of CKD had an increased risk for mortality [22]. A few other studies have also shown that a low level of Hb is strongly associated with mortality [7, 12, 13]. In our sample, 31.1% of respondents had various grades of anemia, fitting in the range from 20 to 57%, as was found earlier for Central Europe [23].

The study of Lawler et al. (2010), with CKD in the predialyzed period, showed that anemia in this group was underestimated, with an absence of relevant blood tests and a lack of treatment [24]. Iseki and Kohagura showed that renal anemia is a marker of kidney failure and is associated with a higher incidence of stroke and heart failure and relevant lower quality of life and survival [25]. Regarding the above-mentioned outcomes, Amaral et al. suggested that the hazard ratio of mortality is increased proportionally according to the severity of the anemia. They discovered that a serum hemoglobin concentration of 11.0 g/dl and higher showed a 60–70% reduction in the risk of mortality [22].

The prevalence of renal anemia treatment after KT is, according to the NKF/KDOQI guidelines, relevant to CKD in the predialyzed period [5]. Surprisingly, Molnar et al. found in ten renal transplant units across Europe that the prevalence and management practices related to renal anemia after transplantation were quite variable and overall have remained largely unchanged over the last 5 years [11]. In our sample, more than two-thirds of the patients were treated by a combination of two drugs. Similar to our results, Spiegel and Chertow (2009) showed the benefit of renal anemia treatment by ESA and iron therapy [8].

The most recent studies regarding renal anemia therapy have shown that there is a narrow boundary between safe treatment and therapy causing increased morbidity and mortality risk [26]. Reports on the relative adequate serum concentration of hemoglobin and iron and other essential components have shown a higher risk of stroke, thrombosis, and progression of cancer [26, 27]. These conclusions bring up new questions about dosing algorithms aimed at achieving and maintaining optimal target hemoglobin levels without endangering the patient.

4.1. Strengths and Limitations. The main strength of this study is the prospective follow-up for 10 years, which enabled us to explore anemia and other factors as predictors of mortality in kidney-transplant recipients. Moreover, all consecutive patients originating from one major transplant centre in Slovakia over a number of years were asked to participate in the study to prevent selection bias. Additional strengths of this study are the exclusion of problems in the first 3 months, the long follow-up, and the exclusion of preexisting cardiovascular disease and rejection episodes. Moreover, this study compares the PTA impact on mortality separately for well-functioning graft versus advanced stages of CKD and addresses the underreporting and undertreating of renal anemia in patients with a well-functioning graft (CKD1-2). The findings demonstrated the ability of using PTA in patients with a well-functioning graft for predicting mortality.

In contrast, stratification of the sample into only two groups according to CKD stages is the main limitation of this study. We were unable to compare each CKD stage regarding the mortality prediction by anemia separately due to the

low number of participants in CKD stages four and five. Additionally, the level of PTA was based on the Hb-value at baseline. The next limitation of the study might be the lack of certain other biomarkers (serum concentration of ESA, iron, ferritin, transferrin, vitamins, etc.) and additional information (inflammatory markers, catabolism). These factors, therapy, and inflammatory markers are associated with a decrease in the hemoglobin value; in addition, they play an important role in exploring the causes of PTA and in its incidence. Therefore, these factors have to be considered in future research. The variable observation period between minimum and maximum (1 and 10 years) is also a limitation. Testing for anemia in this study was not conducted immediately after transplantation to prevent false findings due to perioperative complications. Therefore, patients who died or lost their transplanted kidney within the first 3 months after KT were not included in the study. It could be of interest to control for a potential effect of pretransplantation anemia and potential progression of PTA, as they may predict mortality and graft loss, as well.

4.2. Recommendations. Our findings imply that mild and severe anemia in CKD stages 1-2 may be an independent element of the pathway to survival in kidney-transplant recipients. In line with our results, we suggest treating mild and severe anemia in patients after the third month following successful transplantation to increase their probability for survival. Further studies should also be carried out to shed more light on this important pathway. It would be worthwhile to plan a similar study based on the individual CKD stages in the future. According to these results, a randomized controlled trial in ESA treatment of posttransplant anemia with a target Hb-value above 10.0 g/dl would be appropriate. We could then verify whether treatment of anemia after KT decreases mortality in kidney-transplant recipients and thus fills a gap in the guidelines for ESA in posttransplant anemia regarding the Hb-value. Furthermore, the pathways between other medical determinants associated with anemia and mortality should be studied as well.

5. Conclusion

Posttransplant anemia in an early period after transplantation increased the risk of mortality independently of kidney function at up to 10 years' follow-up in CKD stages 1-2. Mild PTA is associated with a 6-fold higher risk of mortality and severe PTA with a 10-fold higher risk of mortality compared with no PTA in CKD stages 1-2. Thus, patients with a well-functioning transplanted kidney but with posttransplant anemia might benefit from clinical evaluation as well as treatment (e.g., Erythropoiesis-Stimulating Agents, iron therapy) to reduce their higher risk of mortality. However, patients with more advanced stages of CKD showed no association of mild PTA with mortality, probably as this may only reflect their worse kidney function; however, severe PTA predicted a 10-fold higher risk of mortality.

Disclosure

(1) Maria Majernikova, Jaroslav Rosenberger, and Robert Roland are employees of Dialysis Services, Fresenius Medical Care, Slovakia; (2) none of the authors have had any relationship with any company or funding source that might have an interest in the submitted work during the previous 3 years; and (3) their spouses, partners, or children do not have any financial relationships that may be relevant to the submitted work.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

Etiology of End-Stage Renal Disease and Arterial Stiffness among Hemodialysis Patients

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Background. Prior studies have demonstrated that conventional and emerging CV risk factors are associated with worsening arterial stiffness among end-stage renal disease (ESRD) patients on hemodialysis. The present cross-sectional study evaluates the association between the etiology of ESRD and arterial stiffness among a cohort of hemodialysis patients. *Methods*. Etiology of ESRD was identified from patients' medical records and classified as either vascular renal disease, diabetic nephropathy, nondiabetic glomerulopathy, tubular interstitial nephropathy, hereditary nephropathy, or ESRD of unconfirmed etiology. *Results*. A total of 82 subjects were enrolled. cfPWV was independently associated with the composite of either diabetic nephropathy or vascular renal disease ($p = 0.022$), pulse pressure ($p = 0.001$), and a history of CV events ($p = 0.025$), but not history of hypertension or diabetes mellitus alone. The median cfPWVs in diabetic nephropathy and vascular renal disease were comparable and significantly higher than median cfPWVs in other etiologies of ESRD. *Conclusion*. The study suggests that the etiology of ESRD is independently associated with arterial stiffness among hemodialysis patients. Furthermore, arterial stiffness was higher among patients who developed renal sequelae of either diabetes mellitus or hypertension as compared with those who have a history of either diabetes mellitus or hypertension alone.

1. Introduction

Cardiovascular (CV) disease is the most common cause of morbidity and mortality among patients with end-stage renal disease (ESRD) on hemodialysis (HD) [1]. Compared with the general population, the incidence of CV events among these patients is significantly higher, but it does not seem to be fully explained by the increased incidence of conventional risk factors alone. It has been hypothesized that HD patients are exposed to unique renal- and HD-related risk factors that predispose them to an increased rate of CV events [2, 3].

Arterial stiffness, a functional marker of arterial disease, may be measured by carotid-femoral pulse wave velocity (cfPWV), a noninvasive and reproducible technique to evaluate large artery stiffness [4]. The independent association between cfPWV and CV risk has been previously demonstrated in several patient populations, including those on HD [2, 5]. Compared with age-matched controls, HD patients are at an increased risk of developing arterial stiffness and vascular calcifications, both of which may contribute to the development of CV disease and subsequent CV events [3, 4, 6]. While the physiological interaction between the

kidney and the vascular system has been well established, the etiology of ESRD among HD patients has been poorly investigated in the context of arterial stiffness and CV risk. The present cross-sectional study evaluates the association between the etiology of ESRD and cfPWV in a cohort of HD patients.

2. Materials and Methods

2.1. Study Participants. A total of 93 subjects with ESRD undergoing HD at the North Hospital Center in Zgharta, Lebanon, and who had been stable for at least 3 months were invited to participate in this cross-sectional study. Of those, 82 subjects consented and were enrolled. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments. All subjects provided written informed consent, and the study was approved by the North Hospital Center institutional review board.

2.2. Measurements. Relevant medical and biological patient information was obtained from patients' electronic medical records and confirmed by means of a personal interview, which included demographic information as well as confirmation of personal and family medical and social history and adherence with home medications. Etiology of ESRD was classified as either vascular renal disease, diabetic nephropathy, nondiabetic glomerulopathy, tubulointerstitial nephropathy, hereditary nephropathy, or ESRD of unconfirmed etiology. Vascular disease was defined as either nephroangiosclerosis (defined as either biopsy-proven or presumed based on either the presence of long-standing hypertension of nonrenal origin for >10 years, development of hypertensive target organ damage, or normal baseline glomerular filtration rate with progressive worsening of renal function) or ESRD due to renal artery stenosis. Diabetic nephropathy was defined as either severely increased albuminuria that is macroalbuminuria (urinary albumin excretion rate > 300 mg/24 hr) among subjects with prior history of diabetes mellitus or moderately increased albuminuria that is microalbuminuria (urinary albumin excretion rate between 30 and 300 mg/24 hr) among subjects with diabetic retinopathy or type I diabetes mellitus for more than 10 years [7]. ESRD secondary to diabetic nephropathy was defined as ESRD with a history of diabetic nephropathy and no evidence of other renal or systemic diseases. Nondiabetic glomerulopathy was biopsy-proven and was defined as glomerulopathy with no evidence of diabetes mellitus or features of diabetic nephropathy on biopsy. Tubulointerstitial nephropathy was defined as ESRD secondary to either pyelonephritis, analgesic nephropathy, congenital obstructive or nonobstructive malformations, such as reflux nephropathy, renal dysplasia, or acquired obstructive uropathy. Hereditary nephropathy was defined as either ESRD secondary to polycystic kidney disease, ESRD secondary to confirmed genetic etiology, or early-onset (<40 years) ESRD of undetermined etiology among patients with first-degree family history of early-onset ESRD.

Hypertension was defined as either intake of antihypertensive therapy or an average systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥90 mmHg over 6 consecutive measurements. Diabetes mellitus was defined as either HbA1c > 6.4% or intake of antidiabetic drugs. History of CV events was defined as either prior acute coronary syndrome or stroke.

Aortic stiffness was estimated by the measurement of cfPWV using an automated device (Complior, France) as previously described and validated in the hemodialysis population [8]. All measurements were obtained one hour following a hemodialysis session by the same trained operators. Simultaneously recorded pulse waveforms were obtained transcutaneously over the common carotid and femoral arteries. cfPWV was then calculated automatically by the device using the distance between the carotid and femoral artery recording sites divided by the time interval of the pressure waves (averaged over 10 cardiac cycles).

2.3. Statistical Analysis. All statistical analyses were performed using Stata® 13 (StataCorp LP, Texas, USA). Baseline characteristics of the study population were evaluated using descriptive statistics. Data were expressed as frequencies and percentages for categorical variables, means ± SD for parametric continuous variables, and median (IQR) for nonparametric continuous variables. The associations between cfPWV and patients' clinical and biological variables were tested using Spearman test for means comparison between 2 groups and Kruskal-Wallis test for associations with categorical variables. To evaluate differences in cfPWV between various etiologies of ESRD, one-way ANOVA with post hoc Bonferroni method of pairwise comparison was performed. Variables with a p value ≤ 0.10 in the univariate analysis were held for inclusion in the multivariate regression model, in addition to parameters of interest, and those with historical association with cfPWV. Testing for multicollinearity was performed, and it was predetermined that when variables were strongly correlated with each other, only the variable with the stronger correlation with cfPWV would be retained in the multivariate regression model. All tests were double-sided. A two-sided p value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics. Patient characteristics are summarized in Table 1. Mean patient age was 52.8 ± 18.5 years, 56% of patients were males, 70% had hypertension, and 23% had diabetes mellitus. The etiology of ESRD was identified among 78% ($n = 64$) of patients and was distributed as follows: vascular renal disease (18.3%, $n = 15$), diabetic nephropathy (18.3%, $n = 15$), nondiabetic glomerulopathy (11%; $n = 9$), tubulointerstitial disease (11%; $n = 9$), and hereditary nephropathy (19.4%; $n = 16$). Among those with vascular renal disease, nephroangiosclerosis was the main etiology of ESRD among 13/15 patients (87%), whereas only 2/15 (13%) were diagnosed with renal artery stenosis. The etiology could not be confirmed among 18 patients due to the lack of identifying clinical features and/or renal biopsy.

Table 1: Baseline characteristics of the study population.

Characteristic	Value ($N = 82$)
Age (years), mean ± SD	52.8 ± 18.5
Male gender, % (n)	55% (45)
Age at dialysis initiation (years), mean ± SD	47.8 ± 19.2
Length of time on dialysis (months), median (IQR)	49.4 (23.7, 87.5)
Consanguinity, % (n)	34% (28)
Etiology of ESRD	
Vascular renal disease, % (n)	18.3% (15)
Diabetic nephropathy, % (n)	18.3% (15)
Nondiabetic glomerulopathy, % (n)	11.0% (9)
Tubulointerstitial disease, % (n)	11.0% (9)
Hereditary nephropathy, % (n)	19.4 (16)
Unconfirmed etiology of ESRD, % (n)	22.0% (18)
History of HTN, % (n)	71.0 (58)
Pulse pressure (mmHg), mean ± SD	52.4 ± 14.5
Mean blood pressure (mmHg), mean ± SD	83.7 ± 12.4
History of diabetes mellitus, % (n)	23.2% (19)
History of CV events, % (n)	34.2% (28)
History of coronary artery disease, % (n)	34.2% (28)
History of stroke, % (n)	2.4% (2)
History of significant PAD, % (n)	6.1% (5)
Hypercholesterolemia, % (n)	52.4% (43)
Active smoking, % (n)	34.2% (28)
Calcium (mg/dL), mean ± SD	8.52 ± 0.92
Phosphorus (mg/dL), mean ± SD	5.20 ± 1.86
iPTH (ng/L), mean ± SD	494.7 ± 378.3

CV: cardiovascular; ESRD: end-stage renal disease; HTN: hypertension; iPTH: intact parathyroid hormone level; IQR: interquartile range; PAD: peripheral artery disease; SD: standard deviation.

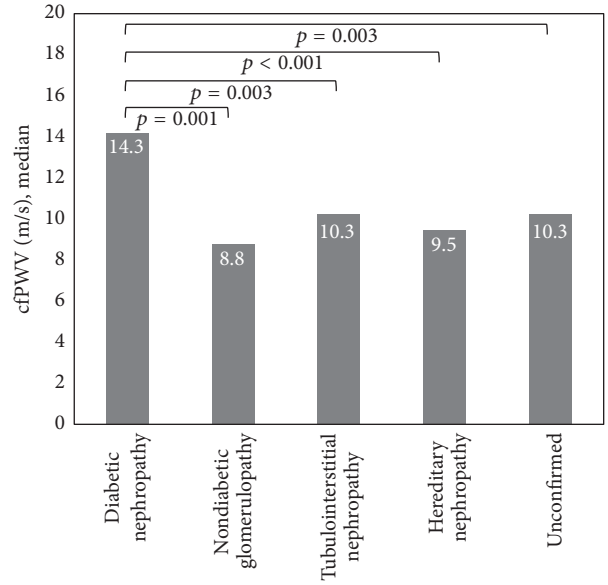

Figure 1: Median cfPWV among patients with diabetic nephropathy as compared with median cfPWV among patients with nondiabetic, nonvascular renal disease.

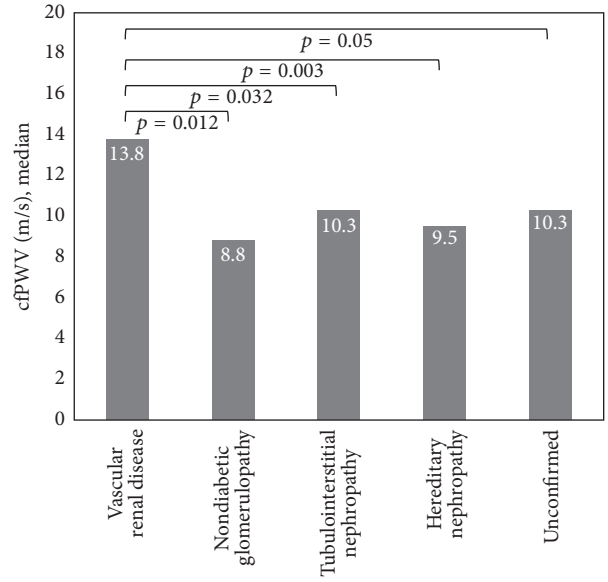

Figure 2: Median cfPWV among patients with vascular renal disease as compared with median cfPWV among patients with nondiabetic, nonvascular renal disease.

3.2. Association between cfPWV and Etiology of ESRD. Univariate analysis demonstrated a significant association between cfPWV and patient age, etiology of ESRD, age at dialysis initiation, length of time on dialysis, weekly dialysis hours, history of hypertension, history of diabetes mellitus, history of hypercholesterolemia, history of CV events, systolic blood pressure, pulse pressure, and iPTH concentration. Multivariate regression adjusted for patient age, length of time on dialysis, weekly dialysis hours, history of hypercholesterolemia, and serum iPTH concentration demonstrated a significant association between cfPWV and vascular renal disease ($p = 0.036$), pulse pressure ($p = 0.001$), and history of CV events ($p = 0.025$), but not diabetic nephropathy ($p = 0.084$), history of hypertension ($p = 0.58$), or history of diabetes mellitus ($p = 0.74$). One-way ANOVA with post hoc Bonferroni method of pairwise comparison demonstrated that median cfPWVs were comparable between patients with diabetic nephropathy (14.3 m/s) and vascular renal disease (13.8 m/s) (Figures 1 and 2), both of which were significantly higher than the median cfPWVs observed among other etiologies of ESRD (9.9 m/s) ($p < 0.001$) (Figure 3). Accordingly, the etiologies of ESRD were then dichotomized into diabetic nephropathy and vascular renal disease versus all other etiologies. Multivariate regression demonstrated a significant, positive association between cfPWV and the composite of either diabetic or vascular nephropathy ($p = 0.02$), when adjusted for all other parameters previously described. Similarly, neither history of hypertension, history or diabetes mellitus, nor the composite

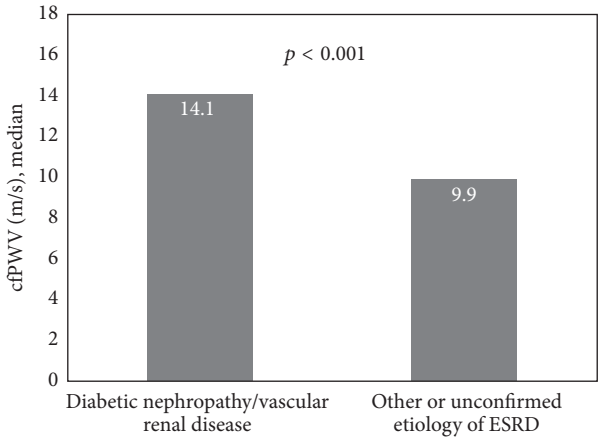

Figure 3: Median cfPWV among patients with either diabetic nephropathy or vascular renal disease as compared with median cfPWV among patients with nondiabetic, nonvascular renal disease.

Table 2: Association between cfPWV and the composite of either diabetic nephropathy or vascular renal disease.

Variable	cfPWV (m/s) $R^2 = 0.55$, $p \leq 0.001$		
	Coefficient	95% CI	p value
Composite of either diabetic nephropathy or vascular renal disease	2.4	0.4, 4.4	0.022
Pulse pressure	0.1	0.03, 0.1	0.001
History of CV events	1.7	0.2, 3.2	0.025
History of hypertension	0.3	−0.9, 1.6	0.59
History of diabetes mellitus	−0.3	−3.1, 2.6	0.84

Multivariate model adjusted for age, length of time on dialysis, weekly dialysis hours, history of hypercholesterolemia, and serum iPTH concentration.
CI: confidence interval; CV: cardiovascular; cfPWV: carotid femoral pulse wave velocity.

of both was significantly associated with cfPWV (Tables 2 and 3).

4. Discussion

The impact of increased arterial stiffness on all-cause and CV-related mortality among HD patients has been previously described, and it suggests that the strongest correlates of CV mortality among these patients relate to large artery structure and function [2, 9–12]. The present study provides primary data on the association between the etiology of ESRD and cfPWV among HD patients, where vascular renal disease and diabetic nephropathy were independently associated with higher cfPWV as compared with other etiologies of ESRD. Prior studies have demonstrated that a history of either hypertension or diabetes mellitus is associated with increased arterial stiffness among HD patients [13, 14], but investigations that address the association between the renal sequelae of both diseases and arterial stiffness in this population are scarce [15, 16]. The current results suggest that development of renal disease due to either chronic hypertension (vascular

Table 3: Association between cfPWV and either diabetic nephropathy alone or vascular renal disease alone.

Variable	cfPWV (m/s) $R^2 = 0.55$, $p \leq 0.001$		
	Coefficient	95% CI	p value
Vascular renal disease	2.3	0.2, 4.5	0.036
Diabetic nephropathy	2.5	−0.4, 5.4	0.084
Pulse pressure	0.08	0.03, 0.1	0.001
History of CV events	1.7	0.2, 3.2	0.025
History of hypertension	0.4	−0.9, 1.6	0.58
History of diabetes mellitus	−0.4	−2.9, 2.1	0.74

Multivariate model adjusted for age, duration of dialysis, hours of dialysis per week, history of hypercholesterolemia, and serum iPTH concentration.
CI: confidence interval; CV: cardiovascular; cfPWV: carotid femoral pulse wave velocity.

renal disease) or diabetes (diabetic nephropathy) is more strongly associated with arterial stiffness than either disease alone, demonstrating the direct role of the kidneys on arterial stiffness that extends beyond the risks attributed to hypertension and diabetes alone.

Accordingly, these findings reflect the impact of the kidneys on the structure and function of large arteries and the bidirectional relationship between the renal and the vascular systems. More importantly, results from this analysis may help confirm the association between arterial stiffness and CV risk factors and additionally be hypothesis-generating to suggest that more in the clinical context, a more aggressive management may be indicated among ESRD patients due to diabetic or vascular nephropathy as compared with either ESRD patients due to nondiabetic, nonhypertensive etiology or patients with diabetes and hypertension alone.

The role of managing modifiable CV risk factors after HD is not as well understood as it is among patients with CKD without ESRD. Unfortunately, it has been speculated that once patients are on HD, further control of diabetes and blood pressure becomes less pressing, and patient compliance to further control diabetes and blood pressure decreases following the onset of HD. However, this study provides early hypothesis-generating insight to both healthcare professionals and ESRD patients that continuing aggressive control of modifiable CV risk factors is independently associated with improved arterial stiffness and possibly reduced risk of CV events after the onset of HD. Interestingly, the study demonstrated that arterial stiffness among patients who develop ESRD due to modifiable etiologies, such as diabetes and hypertension, is significantly higher than among those with hereditary, nonmodifiable causes. The study suggests that further research is needed to evaluate the role of healthcare professionals in closely monitoring and supporting patients on HD following the onset of HD, and stratification of patients with regard to risk of CV outcomes remains possible after the development of ESRD.

Consistent with prior studies, both pulse pressure and a history of CV events were also associated with cfPWV [8, 17, 18]. Pulse pressure is a result of the intermittent

ventricular ejection of blood, which is minimized by the inherent elasticity of large conduit arteries, such as the aorta. This physiological mechanism supports the positive correlation between pulse pressure and arterial stiffness, where stiffer large arteries have a diminished capacity to reduce vascular pulsatility resulting in an increase in pulse pressure [18]. With stiffer arteries, the risk of future CV events increases significantly, and population-based studies have previously demonstrated that an elevated cfPWV is independently associated with an increased CV risk. While a history of CV events is a well-established predictor of future CV events, the current findings confirm the association between a prior history of CV events and arterial stiffness, another surrogate of future CV risk.

In this study, 18 HD patients had ESRD with unconfirmed etiology. Among these patients, there were no clinical indices of either a diagnosis of diabetes mellitus or a history of long-standing hypertension to suggest a diabetic or vascular etiology of ESRD. In addition, the mean age of patients with unconfirmed ESRD etiology was also significantly lower than those with either vascular renal disease or diabetic nephropathy (67.5 years versus 47 years, $p < 0.001$) but was similar to those with ESRD due to either nondiabetic nephropathy, tubulointerstitial nephropathy, or hereditary nephropathy. Accordingly, given their clinical profiles, the etiologies of ESRD in this group of patients were most likely nondiabetic and nonvascular in origin. Compared with cfPWV of patients with vascular renal disease and diabetic nephropathy, cfPWV among patients with unconfirmed renal disease was significantly lower when these patients were analyzed alone and when they were combined with other nondiabetic, nonvascular ESRD etiologies.

The cross-sectional nature of the data should not be considered sufficient to support any recommendation on CKD management based on ESRD etiology or to shed light on the effect of aggressive CV risk factors management on arterial stiffness in HD patients. Results from the current investigation may be considered hypothesis-generating for future research. Although the study is limited by its cross-sectional design, small sample size, monocentric model, and its missing data, the limitations are not thought to significantly affect the validity of the study results. Given the findings from the additional analysis among the 18 patients without a confirmed etiology of ESRD, the interpretation of the missing data does not seem to necessarily alter the interpretation of the study results.

In conclusion, the study suggests that the etiology of ESRD is independently associated with arterial stiffness among hemodialysis patients, and patients with either diabetic nephropathy or vascular renal disease have significantly higher cfPWV than those with other etiologies of ESRD. Furthermore, arterial stiffness was higher among patients who developed renal sequelae of either diabetes mellitus or hypertension as compared with those who have a history of diabetes mellitus or hypertension alone.

Competing Interests

The authors declare they have no conflict of interests.

Authors' Contributions

Balsam El Ghoul and Yazan Daaboul contributed equally to this paper.

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Review Article

How Should Disaster Base Hospitals Prepare for Dialysis Therapy after Earthquakes? Introduction of Double Water Piping Circuits Provided by Well Water System

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After earthquakes, continuing dialysis for patients with ESRD and patients suffering from crush syndrome is the serious problem. In this paper, we analyzed the failure of the provision of dialysis services observed in recent disasters and discussed how to prepare for disasters to continue dialysis therapy. Japan has frequently experienced devastating earthquakes. A lot of dialysis centers could not continue dialysis treatment owing to damage caused by these earthquakes. The survey by Japanese Society for Dialysis Treatment (JSDT) after the Great East Japan Earthquake in 2011 showed that failure of lifelines such as electric power and water supply was the leading cause of the malfunction of dialysis treatment. Our hospital is located in Shizuoka Prefecture, where one of the biggest earthquakes is predicted to occur in the near future. In addition to reconstructing earthquake-resistant buildings and facilities, we therefore have adopted double electric and water lifelines by introducing emergency generators and well water supply systems. It is very important to inform politicians, bureaucrats, and local water departments that dialysis treatment, a life sustaining therapy for patients with end stage renal diseases, requires a large amount of water. We cannot prevent an earthquake but can curb the extent of a disaster by preparing for earthquakes.

1. Introduction

Mass natural disasters cause widespread and severe damage on the delivery of dialysis services. Disasters such as earthquakes may result in two nephrologic patient populations to manage those with crush syndrome and AKI and those already undergoing chronic dialysis. On August 29, 2005, Hurricane Katrina resulted in the worst urban disaster in modern American history. Katrina forced the closure of 94 dialysis facilities in New Orleans and the Gulf region, largely due to loss of electrical power or flooding [1]. Nearly 6,000 dialysis patients were affected, and most missed dialysis care and had to find another dialysis clinics [2, 3]. The event highlighted the vulnerability of the poor, the elderly, and patients with chronic diseases, and especially of patients with end stage renal disease (ESRD).

In addition, major earthquakes are followed by a considerable numbers of patients with crush syndrome. The incidence of crush syndrome has been assessed at 2 to 5% at least. Approximately 50% of the patients with crush syndrome develop AKI, and approximately 50% of those with AKI will need dialysis. In the 1999 Marmara earthquake, 477 patients with crush syndrome needed dialysis therapy [4]. In the 1995 Hanshin-Awaji earthquake in Japan, 123 patients with crush syndrome were dialyzed [5, 6].

On the other hand, disasters result in the damage of infrastructure such as medical facilities, lifelines, and transportation routes. The ability to provide hemodialysis to chronic dialysis patients and patients with AKI is impacted [7–10].

In April 2016, this year, a series of earthquakes struck Kumamoto Prefecture in Japan's Kyusyu Region and dozens

of people died. Twenty-two out of 94 dialysis facilities in Kumamoto Prefecture could not continue dialysis therapy because of damage in medical infrastructures [11]. From now on, the precise data about the damage caused by these earthquakes will be announced. Japan, located in an area with frequent earthquakes, has experienced devastating earthquakes in the past. The aim of this article is to review the damage in dialysis facilities caused by the recent earthquakes in Japan, where hemodialysis (HD) is much more popular than peritoneal dialysis [12]. In addition, we wish to emphasize the importance of preparedness for earthquakes by introducing well water supply system.

2. Previous Earthquakes in Japan and Dialysis: *The Great Hanshin Earthquake and Dialysis*

In January 1995, the Hanshin-Awaji Earthquake, with a magnitude of 7.2 on the Richter scale, struck the Hanshin area around the city of Kobe, where the social and economic functions are concentrated, and killed more than 6,000 people. About 50 out of 104 dialysis facilities were affected [17]. Of all the dialysis centers in the affected areas, two were completely destroyed, and 28 lightly damaged. Only two centers escaped destruction. Public facilities, such as water pipes, communication lines, and gas pipes, were damaged. Electric power failures occurred all over the city, but 80% of the affected areas recovered within 24 h and within 5 days the problem was solved. Every HD center or hospital was provided with a water tank, which has a capacity to meet about half the normal daily consumptions. During the earthquake, more than 20% of centers lost the major part of stored water. Restoring water supply and drainage required 12.8 days on average, the maximum being 37 days. Forty-three hospitals received water wagon services. It was not sufficient so that 15 hospitals had to keep water by their own efforts. At that time, the local government and the local water authority did not fully recognize the necessity of such a large quantity of water for dialysis treatment, a life sustaining therapy for patients with end stage renal diseases. Since then, many nephrologists who have experienced this disaster at dialysis centers thought it very important that the local government and water department recognize and share the idea that dialysis treatment is a life sustaining therapy requiring about 120 L of pure water for a single standard dialysis. After The Great Hanshin-Awaji earthquake, the Ministry of Health, Labour and Welfare (MHLW) instituted the disaster base hospital in 1996. The disaster base hospital is expected to play a key role in the most acute phase of a large-scale disaster. The requirement criteria as a disaster hospital by MHLW are described as follows [18].

Disaster Base Hospital Designation Requirements [18]

(1) Accepting all seriously injured or ill patients from the stricken area around the clock

(2) Conducting the aeromedical shuttling by helicopter for patients and medical supplies between the disaster base hospital in the stricken area and disaster base hospital outside the stricken area

(3) Holding disaster dispatch medical care team (DMAT (disaster medical assistance team))

(4) Having surge capacity (two times for inpatients and five times for outpatients)

(5) Earthquake-resistant structure

(6) In-hospital generator, capable of operation 60% of the hospital's electrical needs, and with fuel for three days

(7) Tray water tank of appropriate capacity and possession of the well

(8) Helicopter landing pad at the hospital site

(9) Having the following practice equipment:

(i) Satellite phone
(ii) Satellite line Internet
(iii) Multiple means of communication
(iv) Emergency Medical Information System (EMIS)
(v) Lifesaving medical care kits for the seriously ill emergency patients
(vi) Carrying-type lifesaving medical care equipment, medical supplies, tent, generator, drinking water, food, life supply, and triage tag
(vii) Emergency vehicle or ambulance

By April 2016, 712 hospitals including ours had been designated as disaster base hospitals [19].

3. Previous Earthquakes in Japan and Dialysis: *The Great East Japan Earthquake and Dialysis*

On March 11, 2011, the Great East Japan Earthquake triggered a massive tsunami along the Pacific Coast of northeastern Japan and killed nearly 20,000 people. The survey performed by Japanese Society for Dialysis Therapy (JSDT) showed that 315 out of 3886 dialysis facilities in the Eastern Japan were nonfunctional by damage caused by the earthquake [20]. They identified eight causes for HD center failure at that time: (1) structural damage to buildings by earthquake, (2) damage to dialysis equipment by earthquake, (3) failure of the electrical power supply, (4) damage by tsunami, (5) damage by nuclear power plant accident, (6) interruption of the water supply, (7) shortage of dialysis materials, and (8) lack of dialysis workforce. They showed that the leading two causes for long-term (more than 3 days) malfunction were interruption of water supply and damage to buildings. The survey concluded that serious effects on HD centers were classified into three types of failures: (1) failure of lifelines such as electric power and water supply (80%), (2) damage to buildings (15%), and (3) damage by special causes such as tsunami, nuclear power plant accident, and shortage of supply such as dialysis material and fuel forth (5%). Hence HD centers must prepare for disasters in terms of these three factors.

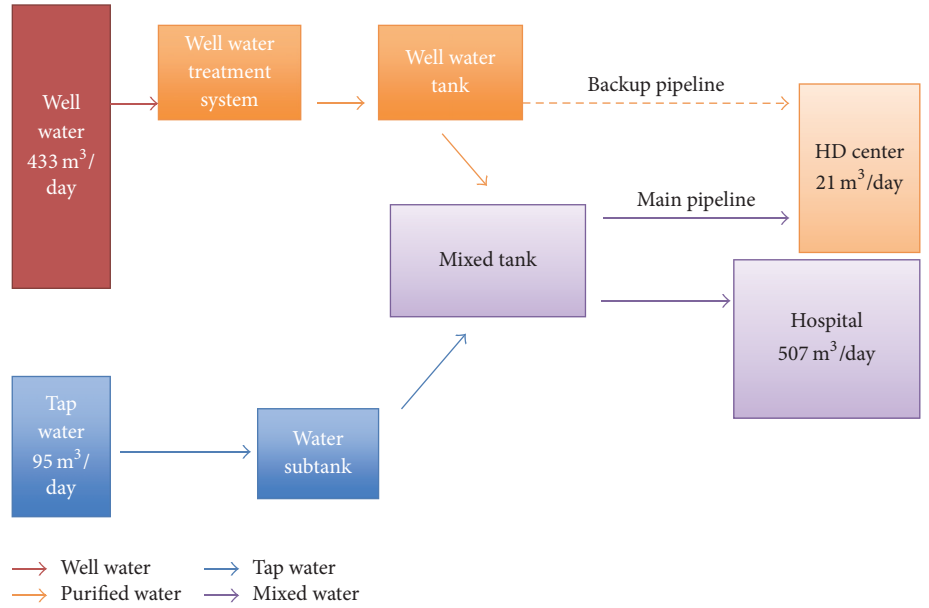

Figure 1: Water treatment system in Yaizu City Hospital. Double water pipelines for the HD center have been installed in our hospital.

4. Damage in Water Supply System in the Great East Japan Earthquake

Matsumura et al. reported the damage to water supply facilities and state of water resource operation at disaster base hospitals in Miyagi Prefecture (Japan) in the wake of the Great East Japan Earthquake [21]. Nine out the 14 hospitals experienced cuts to their water supplies, with a median value of three days (ranging from one to 20 days). Three out of 4 hospitals, which had well water supply facilities, were able to obtain water from their wells even after the disaster. The volume of water from these wells was quite comparable to that supplied under normal operating conditions. The survey proved that well facilities that can produce pure water are very effective in the event of an emergency. They concluded that it is possible to minimize the disruption or reduction of hospital functions in the event of a disaster through the proper maintenance of water facilities by securing alternative sources of water, such as well water. At the same time, it is desirable to conclude water supply agreements and to formulate water allocation plans. However, frequent personnel shifts in Japanese local governments sometimes make it difficult to continue such agreements or plans. For this reason, several dialysis centers in Fukushima Prefecture, after experiencing the difficulty in getting water for dialysis therapy at the Great East Japan Earthquake, proposed a bill to the municipal council to secure sufficient water for dialysis treatment from the local government with priority at a disaster [22].

5. Future Earthquakes

Shizuoka Prefecture, where our hospital is situated, is considered to have one of the biggest earthquakes in the near future. In 1976, Mr. Katsuhiko Ishibashi, an assistant at the Faculty of Science, University of Tokyo, theorized: "It would not be surprising if a large-scale earthquake occurred in the Tokai area centering around Shizuoka Prefecture tomorrow [23]." After a serious social problem brought about by the publication of this earthquake theory, it has become the most urgent task for the prefecture, cities, and families to prepare for a Tokai Earthquake. Over forty years have passed without a major earthquake in this area since this theory was published, but seismologists are in agreement with each other that "the occurrence of a Tokai Earthquake is more likely day by day." The recent data suggest that a megathrust earthquake is predicted to occur in not only Tokai but also Nankai area almost at the same time [15]. The local government reconstructed earthquake-resistant hospitals, schools, and social welfare facilities. Japanese Ministry of Health, Labour and Welfare reported in 2015 that the rate of earthquake-resistant buildings in disaster base hospitals is 95.5% in Shizuoka Prefecture, highest in Japan, while it is 85.2% in Japan, on average.

6. How Should We Prepare for Earthquakes?

Above results have suggested a means by which HD center of disaster base hospitals can prepare for earthquakes. In addition to earthquake-resistant buildings and facilities, it is essential to secure water supply systems. Since our hospital is a disaster base hospital and maintained by the city, the director of our hospital regularly meets the mayor and governmental officials and informs them of the necessity of a large amount of water for hospital functions. Now our city bureaucrats well recognize the requirement of water supply for maintaining hospital roles. In addition to securing water allocation plans by the city, a well water facility and double water piping circuits have been installed in our hospital (Figure 1) [13]. Our hospital, having 471 inpatient beds and 35 HD beds, usually consumes about 500 m^3 of water daily.

Table 1: Online resources for dialysis units and patients.

Organization	Contact	Target audience	Resources
Centers for Disease Control and Prevention	http://www.cdc.gov/disasters/dialysis.html	Dialysis providers	Dialysis Care After a Disaster [13]
National Kidney Foundation	https://www.kidney.org	Patients	Planning for Emergencies [14]
Kidney Community Emergency Response (KCER) Program	http://www.kcercoalition.com	Dialysis providers	Disaster Preparedness: A Guide for Chronic Dialysis Facilities [15]
The ISN Renal Disaster Relief Task Force (RDRTF)	http://www.theisn.org	Dialysis providers	Renal Disaster Relief [16]

This well water system equipped with a reverse-osmosis purification devise can supply ultrapure water in a volume corresponding to 85% of daily water consumption in our hospital. Moreover, emergency electric power supply systems have been employed, making our lifelines even more stable.

7. Discussion

In this paper, we presented damage of dialysis facilities observed in recent earthquakes. Earthquakes resulted in the damage of infrastructure such as buildings, lifelines, and transportation routes. The leading two causes for the long-term malfunction of dialysis facilities were interruption of water supply and damage to buildings. Hence we reconstructed earthquake-resistant buildings and facilities, and we have adopted double water lifelines by introducing well water supply systems in our hospital. In addition, the director of our hospital regularly meets the officials of the water department in the city and stresses that a large amount of pure water is vital in the dialysis treatment.

In 2005, Hurricane Katrina disclosed serious problems in preparedness for dialysis patients, facilities, and ESRD networks. In 2006, The Kidney Community Emergency Response (KCER) Coalition was organized in 2006 [14]. The mission of KCER is to collaboratively develop, disseminate, implement, and maintain a coordinated preparedness and response framework for the kidney community. KCER provides resources specifically for dialysis facilities to help them prepare, respond, and recover from disasters. One of the resources for dialysis facilities is "Disaster Preparedness: A Guide for Chronic Dialysis Facilities" in their HP. The guide describes that dialysis units with access to on-site water via a well were able to function during the Hurricane Katrina and it is necessary to establish a good working relationship with the municipal water supplier, educate them about the importance of water to your patients, and teach them about your water treatment system and its limitations. There are several resources to guide planning preparation for a disaster [14, 16, 24–26] and a list of online resources are shown in Table 1.

Irrespective of the event of Hurricane Katrina, most dialysis patients in North Carolina were unprepared for a disaster. Dialysis providers should educate dialysis patients and rehearse a disaster plan with patients regularly [26].

8. Implications for Practice

Dialysis providers should be aware that a disaster results in the failure of the provision of hemodialysis services. In addition, patients with crush syndrome and AKI may appear after major earthquakes. The leading two causes for the long-term malfunction of dialysis facilities were interruption of water supply and damage to buildings. It is necessary for dialysis providers to prepare in advance for a disaster using online resources such as KCER.

9. Conclusions

An earthquake is a geological event that is beyond human control. But we can at least curb the extent of a disaster. Now is the time to draw lessons from malfunction in HD treatment we have experienced during the previous large earthquakes.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

The Experience of Older People in the Shared Decision-Making Process in Advanced Kidney Care

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Introduction. This qualitative descriptive study was designed to understand the experiences of older people (>70 years) when making a decision about renal replacement therapy. This was a coproduced study, whereby patients and carers were involved in all aspects of the research process. *Methods*. A Patient and Carer Group undertook volunteer and research training. The group developed the interview questions and interviewed 29 people who had commenced dialysis or made a decision not to have dialysis. Interview data were transcribed and analysed, and common themes were identified. *Results*. 22 men and 7 women (mean age 77.4 yrs) from two hospitals were interviewed. 18 had chosen haemodialysis, 6 peritoneal dialysis, and 5 supportive care. The majority of patients were involved in the dialysis decision. Most were satisfied with the amount of information that they received, although some identified that the quality of the information could be improved, especially how daily living can be affected by dialysis. *Conclusion*. Our findings show that overall older patients were involved in the dialysis decision along with their families. Our approach is innovative because it is the first time that patients and carers have been involved in a coproduced study about shared decision-making.

1. Introduction

Shared decision-making (SDM) is the conversation that happens between a patient and their health professional to reach a healthcare choice together. This conversation needs patients and professionals to understand what is important to the other person when choosing a treatment [1]. The purpose of this study is to find out about the experiences of older people who have recently made a choice about having dialysis or not, in order to contribute to the evidence base for advanced kidney care practice.

It is possible that some people who have advanced kidney disease (AKD) may not wish to participate in decision-making; some may wish to share their decisions solely with their family; others may prefer to use a structured decision aid. In a systematic review of the factors that influence decision-making in adults living with kidney disease, Murray et al. [2] suggested in their conclusion that although patient decision aids and implementation of shared decision-making have been evaluated in patients with other medical conditions, little is known about interventions to support patients with AKD when making quality decisions.

It is hoped that the findings will inform the practice of members of local AKD teams, to provide a range of different decision-making models which are individualised according to patient preference.

2. Literature Review

Shared decision-making is a process by which "clinicians and patients work together to select tests, treatments, management, or support packages, based on clinical evidence and the patient's informed preferences" [3]. Shared decision-making (SDM) is important for patients because of potential benefits such as improved physiological parameters through self-management programmes [4] and increased patient satisfaction [5].

People with AKD have to make difficult and complex decisions about their future care including which type of dialysis may suit them best or whether to have dialysis at all. A recent systematic review into the needs of older people with advanced kidney disease [6] made recommendations for further study into this area, as their review revealed a lack of research regarding the education requirements of the older person with AKD who has been asked to make a decision regarding dialysis or supportive care.

Two systematic reviews in kidney care found that patients' participation in the decision-making process was influenced by relationships with others; possible disruption to current lifestyle; desired degree of control (such as whether to self-care or not); and personal views on the benefits and risks of the treatment [2, 7].

A National US Study of Public Preferences [8] found that older people tended to prefer a physician-directed style of care, independent of health status. A survey of patients in Sweden [9] also found that older patients were more likely to defer to physicians for decisions about treatment independent of the presence of chronic illness. Whilst a number of other studies have suggested this pattern, limitations in study design have confounded age-related decline in health with preferences for a physician-directed style [8].

There is anecdotal evidence that people of different ages and also those from different cultures and ethnic groups have differing approaches to SDM. However, there is little evidence to back up this assertion. In the systematic review of the factors that influence decision-making in adults living with kidney disease, Murray et al. [10] suggested in their conclusion that more research is required to enhance our understanding of how these factors vary across the course of the disease by culture. Some studies undertaken in other conditions and contexts which suggest that patient preferences in SDM may be based on cultural-ethnic beliefs. Various studies have identified a family-centred model of decision-making, in contrast with an informative or shared model of decision-making [11]. Tariman et al. [12] found a diverse group of factors that informed clinical decision in older people with cancer, including personal beliefs and values, ethnicity, and previous health-related experience.

This research is important as it is the first study to our knowledge that aims to understanding of the experience of older people who have recently had to make difficult choices about their long term renal therapy.

3. Aims/Objectives

The overall aim of this study was to explore, during face-to-face interviews, the experiences of older people (>70 years) in the shared decision-making process in advanced kidney care. The objectives were

(i) to convene a specific Patient and Carer Group (PCG) to colead the project;

(ii) to train the PCG members on the research process and in addition to facilitate volunteer training for the group members as per each hospital's requirements;

(iii) for members of the PCG to develop interview questions and to then undertake semistructured interviews with older people who have had to make a decision about dialysis care in the past six months;

(iv) to transcribe and analyse the data using thematic data analysis;

(v) to evaluate the role of the PCG in the project.

Findings will indicate if adaptations of existing decision-making models or decision aids and/or available material are required for the older person. Learning from this project (e.g., key messages about patient and carer training needs) will inform future projects that will involve service users as coresearchers.

4. Methods

This was a qualitative descriptive study, carried out in two hospitals in the UK: a large inner-city teaching hospital with a diverse population and a smaller hospital with a mostly white population. Ethical approval was obtained from the national Integrated Research Application System (IRAS) in the UK and, in addition, the local ethics committee in each hospital. Data on age, gender, ethnicity, and type of therapy (haemodialysis, peritoneal dialysis, or supportive care) were recorded but anonymised. Transcripts of interviews were identified by code (not name).

4.1. Patient and Carer Group Involvement. Coproduction is a term that refers to a way of working whereby decision-makers and service providers and users work together to create a decision or a service which works for them all [13]. The consultant nurses in each hospital approached members of their existing patient participation groups (such as those already involved in patient education) and invited them to take part in the PCG for this study. The PCG members were an integral part of the research team and participated in the research design, ethical approval process, design of the interview questions, undertaking of the interviews, data analysis, and dissemination of findings.

Members of the PCG had a role description and were reimbursed for their involvement, according to University and INVOLVE [14] guidance. Members of the PCG also underwent training for volunteers in each hospital and held a volunteer's contract which included a confidentiality agreement. They were supported by a renal counsellor and members of the research team throughout.

The training programme of three half-day sessions was delivered separately at each site over a four-week period. An outline of the training programme is shown in Table 1 and was delivered by both the university and hospital-based researchers.

4.2. Recruitment of Participants. In early 2015, participants were recruited by invitation letter. The inclusion criteria were those who were 70 years of age or older and who had commenced dialysis or made a decision not to dialyse within the previous six months. Those who were acutely ill and

Table 1: Patient and Carer Group training sessions.

Learning Outcomes	Content
(i) To understand the role of the Advisory Group members in undertaking interviews	Aims of project and rationale for method (group work)
(ii) To be aware of the knowledge, skills, and attitudes required to be a competent interviewer	What makes a good interviewer (brainstorm)
(iii) To be confident in undertaking an interview alone	Peer review of interviewing skills (role play)
(iv) To identify the practical issues involved in interviewing	Practicalities of interviewing (group discussion)
(v) To be competent and feel confident to carry out one-to-one interviews with support	Preparation for interviews: individualised learning needs (one-to-one support)

those who did not have the capacity to make a decision were excluded.

4.3. Interviews. One-to-one semistructured interviews with participants were undertaken. Semistructured interviews were chosen as the most appropriate method, as the alternative, which is structured interviews, can force respondents to choose from answers already provided and there is little opportunity for free expression [15]. In addition, semistructured interviews can allow the interviewer to focus on issues that are of particular importance to the research question, to probe and clarify comments made by the informant and to use prior knowledge to help him or her in this process [16].

Semistructured interview questions were originally devised from the literature review and based on a shared decision-making model as suggested by Stacey et al. [17]. Later, during the training sessions, the questions and prompts were more fully developed by the PCG (see Table 2), to enable the interviewers to encourage the participants to tell their story, as if in informal conversation.

Interviews were undertaken in the local hospital, usually in a private clinic room, and were scheduled according to patient preference (e.g., on dialysis days). There was provision made for interviewees who preferred to converse in their native language (e.g., Bengali), to have their interviews conducted by a bilingual member of the PCG and then translated into English. A renal counsellor was available for pastoral support of interviewees if required.

Participant identifiable data were only accessed by those in the direct health care team. Once participants were recruited, they were allocated a participant number (P1, P2, etc.).

Data on age, gender, ethnicity, and type of therapy (haemodialysis, peritoneal dialysis, or supportive care) were recorded but anonymised.

4.4. Analysis. Interviews were recorded using a digital recorder and transcribed by an external transcriber. Interview data were analysed by clinical members of the research team and the PCG together, using thematic data analysis. This is a conventional practice in qualitative research which involves searching through data to identify any recurrent patterns [18, p. 205]. Themes are a cluster of linked categories that convey similar meanings and usually emerge through an inductive analytic process, undertaken by the person(s) who has conducted the interview. Themes were identified using the technique of thematic analysis [19]. See "*Thematic Analysis (adapted from [19])*" below. The researchers and PCG members were provided with anonymised transcripts of the interviews. These transcripts were read by each researcher/PCG member separately (Stage 1) and codes were generated (Stage 2). A PCG meeting then facilitated Stages 3 and 4. Stage 5 was carried out by electronic communication.

Table 2: Interview questions.

Theory of SDM (adapted from [17])	Interview questions
Recognition of the decision	Can you remember when you were told about having dialysis or not? Can you remember how you felt?
Knowledge transfer and exchange	Were you given any information? How far did you understand all the information you were given?
Expression of values and preferences	How much input did the doctors and/or nurses have in making the decision? How far do you think the decision was shared between you and your family?
Deliberation	Were you given an opportunity to think about the information? Was anyone with you to help explain the information? Did you try and find out anything more yourself?
Implementation of the decision	Did you feel supported in making your choice? Did you feel your own views were taken into account? Do you feel you made the right decision? Do you have any suggestions for improving the process?

Thematic Analysis (adapted from [19])

Stage 1. Becoming familiar with the data.

Stage 2. Generating initial codes.

Stage 3. Searching for themes.

Stage 4. Reviewing themes.

Stage 5. Defining and naming themes.

4.5. Evaluation of Service User Involvement in the Project. Additionally, there needed to be a greater understanding on exactly what differences a PCG can make to the overall research process, especially implementation. A recent review has provided evidence of a range of benefits to researchers

and participants of public and patient involvement (PPI) in health research [20]. We undertook an informal evaluation of the impact of the PCG on the research process (adapted from [20]) but explored how far PCG members felt valued as equal members of the research team and how far there was a measurable impact on the research design and delivery. A renal counsellor facilitated the evaluation of the focus group using some key questions to provoke discussion.

5. Results

5.1. Sample. In total 22 men and 7 women were interviewed, with a mean age of 77.4 years. One participant had an unplanned start to dialysis whilst the remainder had been referred in a timely way to nephrology services. 18 had chosen haemodialysis (HD), 6 had chosen peritoneal dialysis (PD), and 5 had chosen supportive care.

There were challenges in recruiting people who were representative of the diverse patient population in one hospital. Although more than 50% of adult incident population for RRT in one hospital is non-white [21], only 4/14 (28.5%) participants were non-white.

5.2. Themes. Overall the majority of participants felt that the medical and nursing staff were professional and caring and provided a range of comprehensive information sources (such as education sessions, written material, and DVDs) to aid in the decision-making process. There was much positive feedback from attendance at the regular seminars/patient days to enable questions to be asked face-to-face. The majority had the view that the dialysis decision was shared and that there was no undue influence from the medical or nursing staff.

Three main themes were identified following data analysis. These were *Delaying the Decision*, *The Decision-Making Continuum,* and *The Reality of Dialysis*.

5.3. Delaying the Decision to Start Dialysis. Many participants did not want too much information about dialysis too early in the decision-making process. In addition, if a decision to start dialysis did not need to be made within the forthcoming couple of months, then a number of participants said they would prefer to delay the decision until nearer the time.

One participant said

> *He wanted to put me on dialysis for about nine months before I eventually went on because I kept putting him off, because we're great holiday people and we like to go on holiday and everything and I was trying to put him off all the time. (P1)*

Other participants realised that they were putting the decision off because they were anxious about dialysis and in denial of their symptoms.

> *Yes, again I had the opportunity to go into the dialysis room and I thought, no, I'm putting that off tonight. It's like the execution day isn't it? (P5)*

Many participants spoke of feeling very scared about dialysis, especially following education input, and this may be one reason for putting off the decision to start replacement therapy.

> *When I saw what happens on this big machine, wow, I had the fright of my life." and "I saw this big thing on his hand (the fistula), and got the fright of my life. (P26)*

5.4. The Decision-Making Continuum. The continuum of shared decision-making was demonstrated by the majority saying they had been involved in the decision, yet one or two saying that they trusted the doctor to make the decision for them. Many people explained how the dialysis decision was truly shared, often between the individual and the health care professional (HCP). Participants felt that they had the opportunity to ask questions which were answered clearly and were also able to include members of their family/carers in the discussions.

When interviewees were asked whether their questions were answered, one participant said the following:

> *They tell you to ask questions, they say is there anything you want to know, but you don't know the right questions to ask because you have no idea what the hell you're getting into. (P16).*

A number of participants explained the importance of having a family member with them, when dialysis options were being explained.

> *They (family members) come with me. When I come here, they bring me. . .and they are educated people - they understand better than I do. (P29)*

We asked the participants if they felt their family influenced their decision; the response varied with one person saying

> *Well I've only got one daughter and she's a nurse anyway, you know, she gave me advice on it with regards to was it worth it or such, and her verdict on it was that, yes, go for it. (P1)*

Another participant explained that family members did not influence their decision.

> *I've got two daughters and a son and I spoke to them. His wife said to me, (because she's a little bit on the bossy side), you've got to have dialysis and I said why and she said you've got to go down that road and I said no. I said if I was younger I wouldn't think twice about it. (P2)*

However, some felt that although there were discussions they did not always understand what the doctor said and just trusted them to guide the decision. A smaller number described a process whereby the HCP had influenced the decision, with age being a particular theme in the context of the decision about whether to have dialysis or not. One said

> *I did ask questions, and I said to him 'The thing is, you tell me my age is against me', he said 'Yes, it is against you', but he said it's entirely up to me, so I decided not to have it (dialysis). (P2)*

Some participants found the information provided about dialysis was too complex and was not easily understood. Several felt that although the information was good it was difficult to take it all in.

> *I suspect that I had all the information at the time. What I didn't have was understanding. (P23)*

Others said there was too much information, especially the information gleaned from casual discussions in the waiting areas. One participant commented

> *. . .so it's a waste of time listening to them or talking to them about it, because a lot of things I thought it's not as bad as it was. They all come here. . .and I thought I wish you hadn't said that because I've got to sit here listening to this, am I going to be alright, so the more information you've got is not really helping you at all. (P7)*

However, another found this type of casual information useful.

> *When I was waiting to see the specialist, the ones that had come for dialysis, I listened to their conversations, and you can learn a lot that way. (P11)*

Others commented that peer support would not be useful.

> *The only thing mentioned in that line is that there was a Patient's Association or some such name like that, that you could join and talk to other people in the same situation as you basically. Well I'm afraid I'm not one to join these sorts of clubs because I don't want to be bored with their hard luck stories and even more than that, I don't want to bore them with my hard luck stories. They are my problems, nobody else's problems and vice versa. (P6)*

5.5. The Reality of Dialysis. Although the availability of information was generally thought to be comprehensive, sometimes it appeared difficult to get answers about activities of daily living. One comment was that the one-to-one consultations and the group education sessions did not cover the bad points of dialysis. Particular reference was made to the need to hold large amounts of stock at home when undertaking peritoneal dialysis.

> *Unfortunately I didn't realise there were other boxes as well with the tubes,. . .and of course it mean there were more boxes than I anticipated and as I say, it more or less took over the house. (P16)*

This participant also mentioned travel arrangements.

> *Anyway I think the hardest part, the most aggravating part for me is the getting here, the parking, because I live in the middle of nowhere and I have to drive. (P16)*

The impact of dialysis was mentioned by a few participants to be understated.

> *Both of them gave the impression that it was very easy, but nobody actually used the words life changing, and it is life changing. (P22)*

> *Although they did glamorise it (the dialysis) a bit, they give the impression that you could sit and crochet for the four hours. (P22)*

A few participants asked for a single point of contact whilst on their kidney journey.

> *I think if there was a bit more continuity, and I don't mean a personal relationship, but a best personal treatment where you could get the same nurse or staff nurse or sister on a more regular basis, because each time you go in you never know who you're going to get and they all seem to perform the function slightly differently from each other. (P17)*

And

> *I think the only thing is you end up seeing so many different people, so there isn't anyone that actually controls your own situation, apart from yourself I suppose. So it might be helpful to have some sort of a managing agent effect, if you like, who's dealing with your treatment. . .. (P18)*

In summary, the participants in this study generally felt that the decision was shared and valued their family's involvement in the decision. However, at times, the information that was required to make the decision was sometimes provided too early and on occasion did not reflect the reality of dialysis.

5.6. Focus Group with PCG Members. The aim of the focus group was to evaluate, in a qualitative way, the impact that the PCG had on the research process [22]. Questions were developed by the research team following a review by Staley [22], and questions focused specifically on the impact of PCG involvement on the research delivery and the impact on the participants. The focus group was facilitated by a renal counsellor, who was part of the research team but not directly involved in the study. The focus group lasted for one hour and all members of the PCG ($n = 6$) were present. The focus group was recorded and thematic analysis was undertaken. Three main themes that arose from the focus group were *Experience of Interviewing*; *Personal Gain;* and *Feeling Valued.*

5.7. Experience of Interviewing. For the majority of the PCG members, this was the first type of research project they had been involved in, although two had acquired interviewing skills from previous jobs.

> *I'd interviewed all my career, but this is a completely different type of interview. . . .As the interviews progressed I felt I was able to get more information out of people because I became more comfortable with the whole process.*

And

> *What was different in this whole experience was asking people about their emotional experience . . . for me, finding the right questions and actually listening to myself making those questions was quite important because you don't want to come across at interrogatory, you want to come across as caring.*

Another member of the PCG spoke of how it was challenging to make the interviewees feel comfortable and trying not to pry into their personal lives. Another found it difficult to deal with emotional responses and said

> *There was one person who started crying and it's a tough deal and you have to realise that people have had a life changing experience and listening to people saying I've just had enough of all this it's really quite tough. I came away feeling quite sad from a couple of the interviews.*

Overall the PCG feedback on the interview process was very positive and all members felt they had been as well prepared as they could have been. They learned a lot about themselves in the process and it helped them understand about listening and how to ask questions to this particular client group.

5.8. Personal Gain. Another theme that arose from the focus group was the variety of positive outcomes that arose serendipitously during the study. One member of the PCG said

> *I was quite inspired by some people because you think when you're going through something yourself you suddenly realise that personally all I've got is kidney failure, I haven't got diabetes, I haven't got cancer or other organ failure. I found them just so positive and quite inspiring just to think my God, these people are making this decision not to have treatment at all and they seemed to be incredible people.*

Another said

> *I thoroughly enjoyed it and glad I've been involved and hopefully the patients will have got something out of it, I certainly have and if nothing else met other people.*

5.9. Feeling Valued. The feedback from the focus group highlighted how much the members had benefited from being able to participate in a study which they could contribute to, rather than just being a participant. They felt they were listened to by the healthcare professionals, and their opinion mattered. They had an equal voice and one member of the PCG said

> *We felt part of the whole project from the very beginning, although at times we found it hard to understand some of the processes such as ethical approval and the volunteer training.*

The PCG members talked about the advantages and disadvantages of involving patients in research, including an immediate camaraderie between interviewer and interviewee.

> *It helped because they felt that you understood what they were telling you, there's almost that immediate bond.*

There were some issues with illness amongst PCG members. This did not delay the study, although it meant that one interviewer only undertook one interview.

6. Discussion

In general terms the findings suggested that participants were happy with the dialysis decision they had made and had been involved in the decision with their family and HCPs. This contrasts with previous studies that suggest that older patients feel insufficiently involved in the treatment choice [23].

6.1. Comparison with Other Study Findings. There are few previously published papers with a similar research question with which to compare findings. Harwood & Clark [24] suggested that dialysis modality decision-making processes for the older adult are very similar to how younger adults with CKD make modality decisions. A survey study in the USA [23] found that a significantly higher percentage of older patients felt the dialysis decision was made by the doctor rather than on their own or with their family or collaboratively with the doctor. In Harwood and Clark's [25] study, gender differences were noted between men and women. Compared with the women, the men in that study were less likely to seek out information regarding dialysis and more likely to delay making modality decisions.

Our study findings suggest that decision-making processes in our older population appear no different from a generic population, with few participants wanting a physician- or nurse-directed decision. Gender differences were not apparent, although only seven women were interviewed.

6.2. Impact on Research Design and Delivery. This is the first time a study on shared decision-making has been completely designed with patients and patients/carers being directly involved in interviewing patients who are from similar backgrounds. The PCG were able to empathise with the participants. There were occasions when information was provided by the interviewees about their dialysis experiences which (it was felt) may not otherwise have been forthcoming if a HCP had been interviewing them, in particular, with regard to the interviewees' personal and sometimes difficult decisions they made. The PGC felt that their relationship with the interviewees significantly reduced barriers that might otherwise have not been overcome. We also felt that it helped to put the interviewees at their ease when recalling what must have been a very difficult time in their lives.

Some PCG members did not undertake as many interviews as originally planned, with one interviewer undertaking just one interview because of illness. This did not impact our study as we had other interviewers who could step in; however this could potentially impact the trustworthiness of the data [26] if there is only one other interviewer available. It is important for coproduced projects to have processes in place for when coinvestigators are unwell. However, solutions to this potential issue do not appear to be well-reported, as no identified studies on user involvement in research appeared to discuss this in detail.

There were some issues with recruitment of participants from different ethnic groups, and, on reflection, these issues might have been ameliorated if the PCG members had been able to recruit participants directly. However, as Brett et al. [27] identified from a systematic review of 66 studies involving patients and the public, much of the evidence base concerning impact of patients and carers on research remains weak and needs significant work over the next ten years.

6.3. Limitations of Study. Rigour was maintained in the design and conduct of this study as far as possible using verification methods to ensure reliability and validity [28]. As with any novice interviewer, members of the PCG were supported by the research team and feedback given on the early interviews concerning interview technique and depth of probing.

An additional limitation was the recruitment difficulty in the inner-city trust with ethnic representation. This issue has been reported before [29] with individuals from minority ethnic backgrounds remaining frequently underrepresented in clinical studies. As these authors suggest, the forming of trusting relationships is pivotal to the successful recruitment of minority ethnic groups into research, and if a similar study is funded in future, members of the PCG would be involved in recruitment of participants.

6.4. Recommendations for Practice. The themes from the interviews suggest that healthcare professionals should consider tailoring information and patient education sessions to meet the needs of older people to support them in the decision-making process regarding renal replacement therapy. As Williams [30] suggests, there are many specific questions for older people who are making a dialysis decision: predictions about survival, quality of life, burden of the therapy, and the amount of recovery expected that must be answered by HCPs. At the same time, it must not be assumed that simply sharing this information equates to shared decision-making.

One specific way in which the findings of this study could inform clinical practice is involving peer supporters in disseminating the findings. Peer supporters are more widely being used in UK renal units to support those who are starting on their dialysis journey. One way in which peer supporters could help patients in their dialysis-decision is to provide real-life stories of others who have been through the decision, especially those who have delayed starting dialysis. For example, this quote "*when I walk out of here (the dialysis unit), I feel like a youngster again*" could be used to illustrate how much better people feel once they start renal replacement.

6.5. Recommendations for Future Research. It is recommended to repeat the study with younger patients and compare the findings with those from different age groups. In addition, it is important to measure the impact that patients and carers have on the research process. As Brett et al. [27] suggested that few studies have attempted any quantitative measurement of impact of patient involvement, reflecting the lack of robust tools available.

7. Conclusion

This coproduced study has highlighted the benefits of involving patients and carers in the design and process of qualitative research. It has enriched the findings of the study and enabled us to have a greater insight into the information needs of older people approaching dialysis. The involvement of patients as coresearchers has been a significant factor in its success. There has been a strong sense of ownership and responsibility to make it work and this is reflected in the comments from the PCG.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Piloting Psychology Annual Reviews as a Method of Measuring Psychological Distress and Quality of Life in Paediatric Renal Transplant Patients

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Psychosocial distress and poorer quality of life after renal transplantation are common in children and young people. This has implications for medication adherence and survival. Posttransplant psychology annual reviews were introduced in one Paediatric Renal Service in the UK as a means of measuring psychological distress and quality of life, as well as facilitating identification of patients and parents/carers who would benefit from psychological intervention. The process of completing posttransplant psychology annual reviews is discussed within this paper. The posttransplant psychology annual review appointments identified patients experiencing depression and/or anxiety and problems in quality of life. These assessments have led to appropriate referrals to, and engagement with, the renal psychology service as well as with community tier 3 child and adolescent mental health services. The posttransplant psychology annual review will continue to be completed at this UK site and discussions will be undertaken with other paediatric renal transplant services to consider whether these could be introduced at a national level to facilitate collection of longitudinal data regarding long-term psychosocial impact of paediatric renal transplantation and its effect on quality of life.

1. Introduction

There has been a growing body of research into the psychosocial impact of renal transplantation and its impact on quality of life. Children and young people after renal transplantation report higher mental health difficulties and lower quality of life compared with their healthy peers [1]. Examples of the difficulties experienced by children and young people include depression [2, 3], generalised, social and health anxiety [3, 4], cognitive difficulties [3, 5], body image concerns [4, 6, 7], difficulties adjusting to a "healthy" status [4], sleep disturbances [4], and pain [3]. All of these difficulties can make it harder for young people to attend school and spend time with peers [8] thus further impacting on quality of life.

Greater levels of psychological distress have been found to be correlated with poorer medication adherence after transplantation [9]. This suggests that psychological well-being can have a direct impact on the longer-term outcome of a transplant. Therefore maintaining and promoting positive psychological well-being also has positive implications for medical outcomes.

Risk factors associated with psychological distress after renal transplantation include shorter time since transplant; younger age at time of transplantation; congenital disease; existing psychological diagnosis; neurological disease; low sociodemographic status; family conflict; parental factors, for example, parental anxiety, psychosocial distress, difficulties in parents' physical functioning, or lower parental quality of life; and individual/transplant factors, for example, adherence, frequency of rescheduled appointments, and presence of a transplant rejection episode [8, 10].

In order to provide holistic care to paediatric renal transplant patients, it is important to identify those who are experiencing psychological distress. Within the Paediatric Renal Service at this UK site, pretransplant assessments of psychosocial well-being are carried out routinely for all renal

transplant patients. Pretransplant assessment is an opportunity to identify the areas of strengths and needs for a patient and their family and offer timely intervention for those experiencing psychological distress. Having an increased awareness of the risk factors for psychological distress assists but does not ensure reliable prediction of patients who will experience psychological difficulties after transplant [9]. An assessment of psychosocial well-being after transplant is, therefore, recommended to identify signs of psychological distress [4, 9].

The Paediatric Renal Service at this UK site introduced psychology annual review appointments for all posttransplant patients as a method of screening for psychosocial issues. The aim of the psychology annual review appointment is to facilitate a more holistic model of care by identifying areas of difficulties for patients and families to enable psychologists to provide timely and targeted intervention to improve quality of life and reduce symptoms of psychological distress.

This paper outlines and evaluates the process of introducing psychology annual reviews for paediatric renal transplant patients at one UK site. It aims to investigate whether psychology annual reviews have facilitated identification of patients and families experiencing psychosocial difficulties. Reported psycho-social difficulties were compared with accessing of psychological services (e.g. renal psychology service, Child and Adolescent Mental Health Services) to assess whether the psychology annual reviews were predictive of need for psychological input.

2. Materials and Methods

2.1. Procedure. A psychology annual review appointment was offered to all patients with a kidney transplant engaged in the Paediatric Renal Service at one UK site and this formed part of the medical transplant annual review. Medical transplant annual reviews are completed one year after kidney transplant and then each consecutive year until the patient transitions to adult renal services, usually aged 17-18 years. 31 patients were eligible to complete the psychology annual review between January and December 2014.

The psychology annual review was conducted by a supervised assistant psychologist and consisted of a combination of clinical interview and psychometric measures. Firstly, the assistant psychologist discussed the psychology annual review process with the parent and/or patient and requested completion of a consent form. The assistant psychologist gave instructions on how to complete all psychometric measures. Most psychometric measures were completed in a clinic room supervised by the assistant psychologist. The assistant psychologist reviewed the psychometric measures with the parents and/or patient and conducted a clinical interview. Several patients and parents/carers did not have time to complete the consent form and measures during the appointment and took them home. All measures taken home were accompanied by a pre-paid stamped addressed envelope to return them in the post once completed. Following completion of the clinical interview and psychometric measures, a letter was written to patients/families to provide an outline of the discussion and any key issues identified. With parental consent, this letter was copied to the medical and nursing team for the purpose of information sharing. Previous involvement with psychological services and/or involvement with Child and Adolescent Mental Health Services (CAMHS) was recorded for all consented patients.

2.2. Psychometric Measures. Psychology annual review appointments utilised a battery of six psychometric measures to screen for psychosocial concerns. These measures were selected because they have been developed and validated for measuring patient and carer psychological well-being and quality of life in the context of physical health problems [11–15].

The measures completed by patients and/or parents/carers are detailed below (see Table 1 to identify questionnaires administered dependent on age of patient).

2.2.1. Paediatric Quality of Life Generic Core Scales: Parent Version (Peds-QL Version 4.0) [12, 16]. The Peds-QL measures parents'/carers' feelings about their child's quality of life. There are specific questionnaires for 0–12 months and 13–24 months. It provides information about physical functioning, physical symptoms, emotional functioning, social functioning and cognitive functioning.

A 5-point response scale is utilised (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem).

2.2.2. Paediatric Quality of Life Transplant Module: Parent Version (Peds-QL Version 4.0) [12, 16]. The Peds-QL measures parents'/carers' feelings about their child's health related quality of life following a transplant. There are specific questionnaires for parents/carers of children aged 5–7 years, 8–12 years, and 13–18 years. It provides information about barriers to medical regimen adherence, medication side effects, social relationships and transplant, physical discomfort, worries related to health status, treatment anxiety, impact of transplant on appearance and communication with medical staff and others regarding transplant issues.

A 5-point response scale is utilised (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem).

2.2.3. Paediatric Quality of Life Transplant Module: Patient Version (Peds-QL Version 4.0) [12, 16]. The Peds-QL measures patients' feelings about their health related quality of life following a transplant. There are specific questionnaires for patients aged 5–7 years, 8–12 years, and 13–18 years. It provides information about barriers to medical regimen adherence, medication side effects, social relationships and transplant, physical discomfort, worries related to health status, treatment anxiety, impact of transplant on appearance, and communication with medical staff and others regarding transplant issues.

For the questionnaires for 5–7 years a 3-point response scale is utilised (0 = not at all a problem; 2 = sometimes a problem; 4 = almost always a problem). For the questionnaires for 8–12 years and 13–18 years, a 5-point response scale is utilised (0 = never a problem; 1 = almost never a problem;

2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem).

2.2.4. Paediatric Inventory for Parents (PIP) [13]. The PIP is a parent report questionnaire, measuring the frequency and difficulty of different events which parents/carers of children who have a serious illness sometimes face. The questionnaire looks at four domains: communication, medical care, emotional distress, and role function.

Parents are asked to rate how frequent and how difficult each event is using a 5-point response scale (frequency: 1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = very often; difficulty: 1 = not at all, 2 = a little, 3 = somewhat, 4 = very much, and 5 = extremely).

2.2.5. Paediatric Index of Emotional Distress (PI-ED) [17]. The PI-ED is a questionnaire completed by patients (8–15 years) to assess if they are experiencing symptoms of emotional distress. The questionnaire is designed to be used with children with physical health problems that is, in paediatric clinics and hospitals, but can also be used with the general population. Patients are asked to rate the frequency of positive and negative feelings and emotions.

A 4-point response scale is utilised (always, a lot of the time, sometimes, and not at all).

2.2.6. Hospital Anxiety and Depression Scale (HADS) [18]. The HADS is completed by patients (16–18 years) to assess if they are experiencing symptoms of anxiety and depression. The questionnaire is designed to be used with adults with physical health problems that is, in clinics and hospitals but can also be used with the general population. The measure also provides an indication of symptom severity.

A 4-point response scale is utilised (e.g., most of the time; a lot of times; from time to time; not at all).

2.3. Clinical Interview. Following completion of psychometric measures, the assistant psychologist reviewed the responses with the parents and/or patients; this formed part of the clinical interview. The assistant psychologist raised with the parent and/or patient any responses suggesting clinical concern. Clinical concern and further exploration was deemed to be required in the following circumstances.

2.3.1. Peds-QL Transplant Parent and Patient Version. Any individual questions in the Peds-QL which received a score of 2 (sometimes a problem), 3 (often a problem) or 4 (almost always a problem) were further explored with the responder (parent or patient) to assess for psychological distress or negative impact on quality of life.

2.3.2. PIP. Any individual questions in the PIP which received a score of 3 (sometimes), 4 (often) or 5 (very often) for frequency of events and/or which received a score of 3 (somewhat), 4 (very much) or 5 (extremely) for difficulty of events were further explored with the parent. This provided a forum for parents to discuss the challenges presented to themselves as carers for a child or young person with a physical illness.

2.3.3. PI-ED. Total scores above the level of clinical significance (10 for boys, 11 for girls) were explored further with the patient and discussed with the parents providing the opportunity to assess the mood of the child/young person.

2.3.4. HADS. Total scores above the level of clinical significance (8) for anxiety and/or depression were explored further with the patient and discussed with the parents providing the opportunity to assess the mood of the young person.

Supplementary information was gathered from the parent and/or patient during the clinical interview. Topics explored included challenging behaviour and conduct difficulties; sleep difficulties; toileting; obsessive and compulsive behaviours; eating and feeding; peer relationships and social skills; confidence and self-esteem; and impact on parents, siblings, and other family members.

The combination of psychometric measures and supplementary information allowed the assistant psychologist, under the supervision of a consultant clinical psychologist, to determine whether or not a patient and/or family required ongoing psychological support. This has been termed the "psychology outcome." There were 5 possible psychology outcomes following the completion of the psychology annual reviews:

(1) Patient already seeing renal psychologist: patients with this outcome are actively seeing an assistant psychologist or clinical psychologist within the Paediatric Renal Service.

(2) Patient referred to renal psychology: patients with this outcome are newly referred to the psychology service within the Paediatric Renal Service as a result of their psychology annual review appointment and have opted in to an appointment with an assistant psychologist or clinical psychologist.

(3) Patient referred to renal psychology but did not engage: patients with this outcome are newly referred to the psychology service within the Paediatric Renal Service as a result of their psychology annual review appointment but have opted out of an appointment with an assistant psychologist or clinical psychologist.

(4) Patient referred to CAMHS: patients with this outcome are newly referred to CAMHS following an identified complex mental health need that is not related to their kidney disease and/or kidney transplant, for example, assessments for Autism Spectrum Disorder or Obsessive Compulsive Disorder. Alternatively, due to the nature of the service providing regional care, some parents/patients may request a referral to CAMHS, rather than the renal psychology service, if the distance of travel between home and the regional hospital base is felt to be too burdensome.

(5) No further action/referral needed: patients with this outcome were identified to not require any ongoing psychological support or assessment at the current time. They may have received support from the psychology service within the Paediatric Renal Service

Table 1: Overview of psychometric measures administered to patients and/or parents/carers depending upon patient age.

Age of patient	Parent/carer to complete			Patient to complete		
	Peds-QL Generic Core Scales	Peds-QL Transplant Module	PIP	Peds-QL Transplant Module	PI-ED	HADS
0–2 years	√		√			
2–4 years		√	√			
5–7 years		√	√	√		
8–12 years		√	√	√	√	
13–15 years		√	√	√	√	
16–18 years		√	√	√		√

Table 2: Number of completed questionnaires and percentage completed from those eligible within the sample that completed a psychology annual review.

Questionnaires	Number of questionnaires completed by parents/patients (percentage of parents/patients completed from eligible age range)
Peds-QL Generic Core Scales, parent-rated	0 (100%)
Peds-QL Transplant Module, parent-rated	16 (80%)
Paediatric Inventory for Parents	12 (60%)
Peds-QL Transplant Module, patient-rated	17 (100%)
Paediatric Index of Emotional Distress	11 (100% + 2 patients aged 16 years)
Hospital Anxiety and Depression Scale	6 (75% remaining, 25% completed PI-ED)

or from CAMHS previously but are not actively receiving support at present.

3. Results

3.1. Demographics. In 2014, there were 31 transplant patients in the Paediatric Renal Service at this UK site. Psychology annual reviews were conducted with 20 (64.5%; 9 male, 11 female) patients and/or parents/carers. 11 patients and parents/carers did not complete the psychology annual review because questionnaires were taken home by families and not returned (4); patient did not attend their scheduled annual review appointment in 2014 (2); no psychologist was able to be present in clinic during the patient's annual review appointment (2); and patients transitioned to adult renal services before their annual review appointment in 2014 (3). The age of patients who completed, or whose family completed, questionnaires ranged from 3 to 17 years (mean = 13.4 years) and number of years post-transplant ranged from 1 to 13 years (mean = 6.1 years).

As summarised in Table 1, the psychometric measures administered depended upon patient age. Table 2 outlines how many questionnaires of each type were completed by patients and by parents/carers. Table 3 outlines patients' psychological involvement prior to the psychology annual review appointment in 2014.

Table 3: Psychological involvement before patients' 2014 psychology annual review appointment.

Psychology involvement before psychology annual review	Number of patients (out of 20*)
Patient already sees renal psychologist	4
Patient already sees CAMHS	0
Patient has previously seen renal psychologist but is now discharged	12
Patient has previously seen CAMHS but is now discharged	3
No previous psychological intervention needed	4

*Note: 2 patients have previously seen renal psychologist and CAMHS but are now discharged from both services. 1 patient was seeing renal psychologist at time of review and has previously seen CAMHS but is now discharged from CAMHS.

Table 4: Psychological involvement following completion of patients' 2014 psychology annual review appointment.

Psychology outcome as a result of psychology annual review	Number of patients (out of 20)
Patient already sees renal psychologist	4
Patient referred to renal psychology	3
Patient referred to renal psychology but did not engage	2
Patient referred to CAMHS	2
No further action/referral needed	9

3.2. Psychology Outcome. Table 4 demonstrates that as a result of the psychology annual review appointment, three patients have been newly referred to renal psychology and two patients have been newly referred to CAMHS. A further two patients were identified to have ongoing psychological need but the patient and their family chose to not engage with renal psychology services.

Presenting psychological needs which led to referral to renal psychology services included: patient adjustment to their health condition, child behaviour issues, procedural

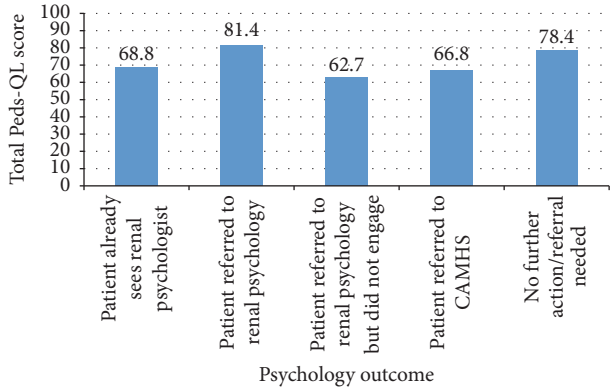

Figure 1: Mean total scaled score, as rated by parents/carers, for each psychological outcome.

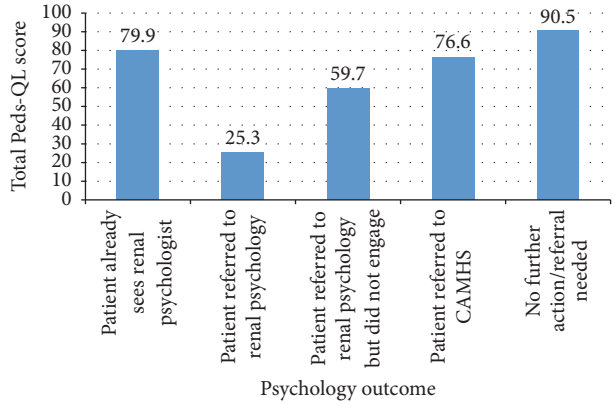

Figure 2: Mean total scaled score, as rated by patients, for each psychological outcome.

anxiety and self-harm. Patients were referred to CAMHS if they presented with complex mental health needs not specifically related to their physical health condition and/or at parental request when the families geographical location did not enable them to routinely access the regional hospital base.

3.3. Measures

3.3.1. Parent Questionnaire: Paediatric Quality of Life Generic Core Scales (Peds-QL). No patient included in this study was aged 2 years or below and therefore the Peds-QL Generic Core Scales was not administered and shall not be discussed further in the results or discussion. However, it is helpful moving forward to highlight the methodology for assessing younger children using the psychology annual review process.

3.3.2. Parent Questionnaire: Paediatric Quality of Life Transplant Module (Peds-QL). Scores on individual items on the Peds-QL are converted into a total scaled score ranging from 0 to 100. Higher scores indicate fewer problems with quality of life. Total scaled scores as rated by parents, ranged from 40.2 to 96.2 (mean = 73.9). Figure 1 displays the mean total scaled score for each psychological outcome.

Figure 1 suggests that lower scores on the parent report Peds-QL is not predictive of need for psychological intervention.

3.3.3. Patient Questionnaire: Paediatric Quality of Life Transplant Module (Peds-QL). Scores on individual items are converted into a total scaled score ranging from 0 to 100. Higher scores indicate fewer problems. Total scaled scores as rated by patients, ranged from 25.3 to 96.6 (mean = 79.6). Figure 2 displays the mean total scaled score for each psychological outcome.

Figure 2 suggests that patients that did not require further psychological intervention have the highest quality of life, in the sample of 17 patients that completed the questionnaire. Patients who were already accessing renal psychology services had higher quality of life relative to those who were newly referred to renal psychology services. Patients referred to CAMHS reported higher quality of life on the Peds-QL relative to patients referred to renal psychology service, suggesting that patients referred to CAMHS were experiencing mental health difficulties not directly related to their physical health condition. The patient rated Peds-QL therefore appears to be more predictive of need for psychological intervention and can distinguish between patients with psycho-social difficulties specific to their health condition and patients with generic mental health difficulties.

Figure 3 demonstrates that the greatest areas of concern for children and young people in relation to their transplant are their perceived physical appearance as a result of transplantation; physical discomfort, pain and hurt; communication with medical staff and others regarding transplant issues; and how their transplant affects their social relationships with others. Figure 3 suggests that the areas of least concern for children and young people were adherence to medication; side effects of medication; worry about future ill-health; and treatment anxiety.

3.3.4. Paediatric Index of Emotional Distress (PI-ED). Each response on the PI-ED has a corresponding score between 0 and 3. All scores are summed together to get a total distress score. Higher scores indicate greater levels of emotional distress. Elevated emotional distress (clinical caseness) is 11 and over for girls and 10 and over for boys. 11 patients completed the PI-ED.

Nine patients (82%) who completed the PI-ED scored within the clinically significant range for symptoms of anxiety and/or depression. Figure 4 summarises the psychology outcome for these nine patients who scored within the clinically significant range. Figure 4 shows that 66.6% of patients who reported that they were experiencing clinically significant levels of emotional distress were already receiving support from the renal psychologists or were newly referred to psychology services in the renal team or in CAMHS. Two patients (22.2%) were referred to psychology services but did not engage. Only 1 patient (11.1%) scoring clinically significant for symptoms of emotional distress did not require any psychological follow-up or intervention as determined by their clinical interview. In this case, patient's responses on the

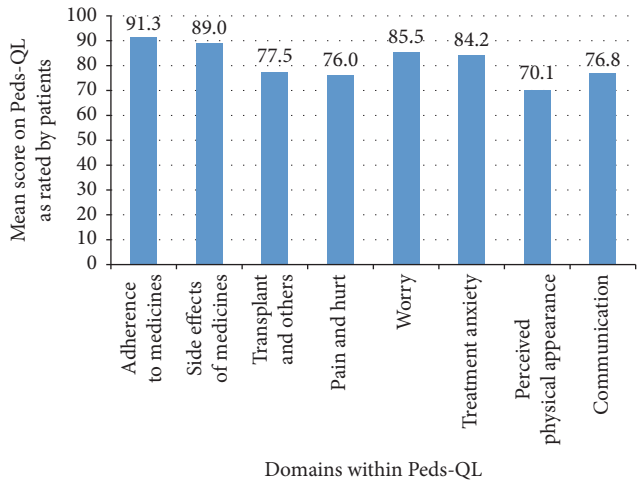

Figure 3: Mean score on Peds-QL as rated by patients for each of the 8 domain scores.

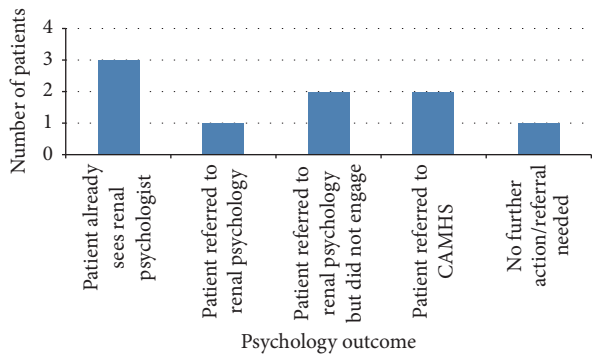

Figure 4: Psychology outcomes for patients in the clinically significant range for symptoms of emotional distress as reported on the PI-ED.

PI-ED may have been elevated as a result of other factors such as sleep difficulties or physical symptoms.

3.3.5. Hospital Anxiety and Depression Scale (HADS). Responses to each question in the HADS has a corresponding a score between 0 and 3. Scores are summed together to get an overall anxiety symptom score and an overall depression symptom score. Total symptom scores indicate the severity of anxiety and depression (0–7 = normal; 8–11 = mild; 12–14 = moderate; 15–21 = severe).

Six patients completed the HADS. All six patients (100%) scored within the normal range for symptoms of depression and four patients (67%) within the normal range for anxiety symptoms. Two patients (33%) reported experiencing mild symptoms of anxiety, but neither required any psychology follow-up or intervention following further exploration during the clinical interview. Scores between 8 and 10 are in the borderline range and thus not decisively indicative of mood disorder [19]. Therefore, our findings that mild anxiety did not require psychological intervention are consistent with other studies.

3.3.6. Paediatric Inventory for Parents (PIP). Scores for each event are totaled together to give a total frequency and total difficulty score. Higher scores indicate greater frequency and greater perceived difficulty of events. Scores can range from 42 to 210. Total frequency scores ranged from 45 to 138 (mean = 78.5). Total difficulty scores ranged from 44 to 112 (mean = 69.4). This highlights that all parents were experiencing some events (i.e. reported events occur at least "rarely") related to their child's medical condition and that all of them found this to be at least a little difficult (i.e. rated events to be above "not at all difficult"). The difficulty of events relating to their child's medical condition was further explored during the clinical interview. Parents were signposted to relevant agencies as required to support them with their personal well-being, for example, signposting to GP, Paediatric Renal Service social worker or adult mental health practitioner.

4. Discussion

Posttransplant psychology annual review appointments have been successfully introduced within the Paediatric Renal Transplant Service as a routine element of the posttransplant annual review process. Studies have previously demonstrated that there is stigma attached with acknowledging psychological difficulties [20–22]. Familiarity with the psychologists and the role of psychologists through routine psychology appointments at annual review may help to reduce this stigma within the patient/parent group, enabling psychosocial concerns to be raised more openly and targeted psychological intervention to be provided. However, the time that is required to complete the psychology element of the annual review could be perceived as an additional demand by some families. It would be beneficial, in the future, to gather feedback from patients and parents/carers about the acceptability of the psychology annual review process including the appropriateness of questionnaires.

The questionnaires, in combination with clinical interviews, used in the psychology annual review appointment have helped to identify patients experiencing psychological distress and problems in quality of life. This has increased opportunities to offer advice and psychological support, including engaging new patients with the renal psychology service, and new referrals to CAMHS. These patients have previously not presented overtly with concerns when seen by the medical and nursing team and therefore identifying psycho-social issues that have been overlooked on other occasions is a positive outcome. For those patients who were already engaged with the renal psychology service, the psychology annual review has acted as an opportunity to evaluate patient progress. Some patients were identified as having psychological need during their annual review but did not wish to engage in psychology support at this time. Identifying this group of patients allowed all members of the multidisciplinary renal team to be mindful of potential psychological risk and to rediscuss issues at subsequent clinic appointments, where appropriate. Of those patients who did not require further intervention following the psychology annual review appointment, two thirds have previously seen a psychologist for psycho-social issues related to their

transplant and thus having a mechanism for yearly follow-ups with this patient group is beneficial.

Incorporating the psychology annual review into the medical posttransplant annual review has increased recognition within the team of the psychosocial impact of kidney transplantation. Copying letters to the medical and nursing staff to outline key issues presented by patients has been valuable information sharing to support patients. On the Peds-QL, patients frequently reported difficulties communicating with doctors and nurses. Therefore, young people may not always feel able to raise issues relating to their transplant or psychological well-being with a medical or nursing member of the team. For this reason, it could be helpful to have the psychology annual review appointment as an alternative forum for these discussions. Delivering more psychoeducation and training to the medical/nursing team about the psychosocial impact of renal transplantation may also be helpful in further promoting appropriate discussion and engagement with young people.

There was some consistency between the main issues reported by patients on the Peds-QL and the literature [4, 6, 7], for example, physical discomfort and physical appearance. Having the mechanism to identify these issues has facilitated appropriate and timely psychological intervention. The areas on the Peds-QL in which patients reported fewest concerns (adherence to medication, side effects of medication, worry about future ill-health, and treatment anxiety) are most frequently monitored by the medical team due to the immediate impact on a young person's physical health. It is therefore not surprising that there were fewest concerns reported in these areas. A young person with treatment anxiety, for example, would have an immediate impact on their receipt of medical intervention and therefore it is likely that a referral would have already have been made to the renal psychologists for support regarding these issues. Previous studies have identified that patients over-estimate treatment adherence [23] and therefore, on the Peds-QL, patients may have chosen to not acknowledge that there is a problem with adherence. In the adult transplant population, disclosures regarding medication adherence were found to be more accurate when this was disclosed to an independent researcher, rather than to clinical staff [24]. This suggests that there may be a benefit of having a non-medical member of the team to also ask about medication adherence.

The literature highlighted that paediatric kidney transplant patients are at an increased risk of experiencing symptoms of depression and anxiety [2–4]. During the psychology annual review appointment, 11 (64%) patients who completed either the PI-ED or the HADS scored within the clinical range for symptoms of depression and/or anxiety. Of these 11 patients, only three (28%) did not require ongoing psychological support when this was further explored during the clinical interview. This suggests that the PI-ED and the HADS, accompanied by the clinical interview, were effective in identifying low mood and anxiety in this patient population. It also underlines the significance of psychological services within Paediatric Renal Services nationally, and the pertinence of enquiring actively about more internalising psychological difficulties such as anxiety and low mood. Often these difficulties are less readily highlighted by children and young people, and are usually less obvious to others including parents/carers, schools and medical teams, compared to more externalising difficulties such as aggressive or oppositional behaviour.

The questionnaires used within the psychology annual reviews did not measure all of the problem areas reported when clinical interviews were conducted with young people and their families. For example, a common difficulty reported by parents during the clinical interview was behavioural issues. None of the questionnaires administered account for behaviour and thus it could be helpful to consider incorporating an additional questionnaire such as the Strengths and Difficulties Questionnaire (SDQ) [25], which assesses emotional-behavioural difficulties more generally. Incorporating this questionnaire would increase the demands placed on parents and may affect the acceptability and engagement with the annual review process and therefore should be considered carefully. Patterns of referrals to the paediatric renal psychology service suggest that parents/carers and the medical team are more able to recognise where input is needed around externalising issues such as challenging behaviour.

Parental well-being in the context of having a child with health issues was assessed using the PIP. All parents reported that they experienced events which they found difficult in relation to their child's physical health condition. Parents have been signposted, as appropriate, to GP, adult mental health services, benefits advisers and to the Paediatric Renal Service social worker as a result of responses on psychometric measures and information collected during clinical interview. Details of signposting and engagement with services have not been recorded as part of this study and so cannot be reported at the present time. Moving forward, it would be useful to record advice and signposting given to parents during the psychology annual review appointment with the research data to monitor informal psychological support provided. It is also important to continue to collect information regarding parental well-being as this has been identified as a risk factor for psychological distress post-kidney transplantation [8, 10].

The administration of questionnaires and conducting clinical interviews requires the use of psychology staff resource which is limited within paediatric renal psychology services nationally. The psychometric measures provide an indication of patients who are experiencing emotional distress and lower quality of life. However, administration of the measures alone does not reliably identify patients who do and do not require ongoing psychological support or which service would be best placed to provide that support. The PI-ED and the HADS are designed to be suggestive of mood and anxiety disorders and therefore require further exploration by an experienced clinician. Currently, there are no established cut-off points for clinical significance on the Peds-QL Transplant and the PIP. Further collection of Peds-QL and PIP data in the paediatric renal transplant population may facilitate the development of normative data for this population which would provide an indication for when scores are elevated and therefore when patients/parents are experiencing greater levels of distress. This may help in identifying patients requiring psychological input; however,

the incorporation of the clinical interview to gain additional qualitative information from families is invaluable.

5. Conclusion

The introduction of psychology annual reviews has enhanced the quality of care provided to patients and families accessing the Paediatric Renal Service at this UK site. The posttransplant psychology annual review appointments have enabled patients and families who are experiencing psychosocial difficulties to be identified and supported. Referrals to the renal psychology service and to CAMHS have been made as a direct result of the questionnaires and clinical interview administered at psychology annual review appointments.

The conclusions which can be drawn from this study at the present time are somewhat limited due to the small sample size (sample size = 20) and collection of data from 2014 only. Continuing to collect this data over an extended time-frame would provide longitudinal information about the difficulties young people face post-kidney transplant and provide an indication of whether psychological interventions have improved psychological well-being and quality of life. The authors have begun discussions with psychologists working within paediatric renal transplant services across the UK to consider whether post-transplant annual reviews could be introduced at a national level. This would facilitate collection of longitudinal data from a larger sample regarding long-term psychosocial impact of paediatric renal transplantation and its effect on quality of life.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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