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Fatigue in prevalent haemodialysis patients predicts all-cause mortality and kidney transplantation

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Abstract

Background: Fatigue affects between 49 and 92% of dialysis patients with considerable repercussions on their functioning and quality of life.

Purpose: To evaluate whether fatigue severity and its impact on functioning predict survival (all-cause mortality) and time to transplantation among in-centre haemodialysis patients.

Methods: As part of a prospective study of fatigue among in-centre haemodialysis patients, survival data was collected between April 2014 and August 2017. Fatigue severity was measured using the Chalder Fatigue Questionnaire (CFQ) and fatigue-related functional impairment using the Work and Social Adjustment Scale (WSAS). Sociodemographic, clinical, and psychological data were collected. The association between fatigue and outcomes was assessed using proportional hazard survival models, allowing for competing risks, and discrete-time survival models. All models were adjusted for relevant risk factors.

Results: The sample consisted of 174 haemodialysis patients. There were 37 deaths and 31 transplantations over 3 years. At 1095 days (36 months), cumulative survival was 70.5% and the cumulative transplantation rate was 22.2%. In unadjusted models, fatigue was significantly associated with an increased risk of death (CFQ-continuous SHR=1.06, 95% CI 1.02, 1.11; CFQ-dichotomous SHR=2.18, 95% CI 1.11, 4.31; WSAS SHR=1.03, 95% CI 1.01, 1.05) and decreased likelihood of transplantation (CFQ-continuous SHR=0.92, 95% CI 0.87, 0.98; CFQ-dichotomous SHR=0.33, 95% CI 0.15, 0.75; WSAS SHR=0.96, 95% CI 0.93, 0.99). However, these associations ceased to be significant after controlling for covariates.

Conclusions: Fatigue was predictive of an increased risk of death and decreased likelihood of transplantation among patients, possibly through distress, impaired functioning and its consequences, rather than clinical and inflammatory markers.

Keywords: fatigue, vitality, dialysis, transplantation, survival, mortality, outcome

Introduction

Chronic Kidney Disease (CKD) is a disease of the kidneys with progressive renal damage and loss in renal functioning that often progresses to kidney failure, when functioning of the kidneys drops to below 15ml/minute/1.73m² [1]. This is when renal replacement therapy is necessary to sustain life, in the form of dialysis or transplantation [1]. Haemodialysis is the most common form of renal replacement therapy, particularly at diagnosis [2], which involves an artificial extracorporeal blood circuit to remove wastes from the blood, fulfilling some essential functions of the kidneys [1]. A typical haemodialysis patient attends dialysis sessions three times a week for 3-4 hours each time [3]. In 2013, an estimated 22,570 patients were receiving in-centre haemodialysis in the UK [4]. Although, haemodialysis is life-sustaining, mortality rates still fluctuate at around 20% per year [5,6]. Kidney failure is characterised by a number of symptoms including: fatigue, pruritus, drowsiness, dyspnea, edema, pain, dry mouth, muscle cramps, restless leg syndrome, lack of appetite, poor concentration, dry skin, sleep disturbance, constipation, and sexual dysfunction [7,8]. On average, stage 5 patients, managed without dialysis, report experiencing 14 symptoms [9].

Fatigue is one of the most common and disruptive symptoms of kidney disease, affecting 42 to 89% of patients on renal replacement therapy, depending on the fatigue measurement tool used and treatment modality. [10]. Despite improvements in clinical care, fatigue remains a recurrent complaint of haemodialysis patients [11]. Fatigue is a complex and subjective symptom of distressing and persistent feeling of physical, emotional, and/or cognitive exhaustion and tiredness not proportional to exertion and not relieved by rest [12-14].

The consequences of fatigue are marked. Qualitative studies revealed that fatigue can impair dialysis patients' ability to carry out basic activities, such as preparing a meal, can

affect motivation, and act as a barrier to participation in social activities; therefore, leading to social isolation [15-18]. The effects of fatigue on functioning are further exacerbated on dialysis days [15,16]. Multiple quantitative studies have shown that fatigue negatively impacts on functioning and quality of life [19-23], and contributes to poorer sleep quality and increased bodily pain [22-26]; however, these associations are likely to be bidirectional.

Recent evidence suggests that fatigue also has implications on clinical outcomes [24,25,27]. There is evidence to suggest that fatigued haemodialysis patients have a significantly higher risk for cardiovascular events compared to their non-fatigued counterparts [27]. Furthermore, fatigue symtoms have been associated with increased mortality in dialysis patients [24,25,28]. The association between fatigue and mortality has also been previously documented in other long-term physical conditions, such as cancer and cardiovascular disease [29,30]. The underlying mechanisms and pathophysiology of the association between fatigue and mortality remain unclear, although a number of mechanisms have been proposed, including inflammation, malnutrition, and depression.

Depression is common among haemodialysis patients, with an estimated prevalence between 20 and 30% [31-34]. Extensive evidence is also available on the association between depression and mortality across long-term physical conditions [35-37], including kidney failure [32,33,38-42]. Out of the studies that have examined the prognostic role of fatigue symptoms in this patient population [24,25,27,28], only Bossola et al. [28] considered the role of depression in the association between fatigue and mortality. They found that although some variance of the association between fatigue and mortality may be explained by depression, fatigue remained a significant predictor of mortality, independently from depression. Other complex biopsychosocial relationships likely exist to help explain how fatigue can impact on clinical outcomes among haemodialysis patients. As postulated in a review [43], a number of fatigue triggers exist in this patient population, particularly

biomedical factors such as inflammation and fluid removed on dialysis. In turn, thoughts, emotions, and behaviours in response to fatigue, and the illness more broadly, may maintain and perpetuate fatigue, leading to further biological consequences over time, such as deconditioning, disruption of the sleep-wake cycle, and physiological arousal.

Additionally, to our knowledge, no studies have examined the association between fatigue and kidney transplantation. [40,42].

Rationale

Fatigue is often under-recognised and under-treated by healthcare professionals (HCPs), perceived as an inevitable consequence of the illness and treatment burden [44]. Therefore, there is a need to provide further evidence on the association between fatigue symptoms and outcomes, by replicating Bossola et al.'s [28] findings in a larger sample, whilst taking into account that in haemodialysis there are two possible competing events: death or transplantation; therefore, using traditional survival analysis is statistically inappropriate, resulting in the overestimation of risk of the event of interest [45,46]. Additionally, the contribution of fatigue-related interference to outcomes has not been previously explored. Further evidence regarding the association between fatigue and clinical outcomes may not only promote better recognition of fatigue as a serious problem in this patient population and therefore development of effective fatigue treatments, but also shed some light into the mechanisms by which fatigue may impact on clinical outcomes.

Objective

The aim of this prospective study was to evaluate whether fatigue severity and fatigue-related functional impairment are predictive of outcome (mortality or transplantation) over a

three-year period, after controlling for known risk factors, such as age, comorbidity, C-Reactive Protein (CRP), haemoglobin, albumin, and distress.

We hypothesized that baseline levels of fatigue and fatigue over time would predict outcome, survival and time to transplantation, of haemodialysis patients over the study period.

Methods

Study design

The current study utilises data from a prospective study of fatigue, in which patients completed various psychosocial questionnaires (outlined below) annually over 36 months [47]. The study ran between April 2014 and August 2017. Over the study period, mortality and transplantation events were recorded from medical records. The association between fatigue severity levels and fatigue-related functional impairment with these outcomes was evaluated here, with time-zero in the survival models being the date patients completed the baseline assessment.

The study was reviewed and received ethical approval from an NHS Research Ethics Committee (East Midlands-Leicester NRES committee, Reference number 14/EM/0037) and has received local Research and Development (R&D) approval. All participants provided written informed consent. The study adhered to the Declaration of Helsinki (1964) ethical standards.

Participants

The sample consisted of in-centre haemodialysis patients, receiving conventional three- to four-hour haemodialysis, three times a week. Patients were recruited from one specialised renal unit in the United Kingdom, and its associated satellite dialysis units. Adults (aged 18 or older) with a confirmed kidney failure diagnosis, treated with in-centre haemodialysis, for 90 days or longer, able to speak or write in English, and able and willing to provide informed

consent were considered eligible. Exclusion criteria were as follows: (i) significant visual or physical impairment preventing completion of the questionnaires, (ii) any known cognitive impairments, and (iii) serious mental health conditions as noted in the medial history (e.g. psychosis, personality disorder). Patients were not approached if they were judged to be unsuitable by the nursing staff, repeatedly unwell during the recruitment period or in the process of moving to peritoneal dialysis.

279 patients were approached for study participation, with 174 providing informed consent and completing the baseline questionnaires (62.4%). A patient recruitment flowchart is available elsewhere [47]. At 12 months 118 patients (87% of patients still alive, on dialysis, and able to complete the questionnaires) completed questionnaires, at 24 months 84 patients (98% of patients still alive, on dialysis, and able to complete the questionnaires) completed questionnaires, and at 36 months 66 patients completed questionnaires (99% of patients still alive, on dialysis, and able to complete the questionnaires). Please see the participant flow diagram for further detail on the study retention (*Figure 1*).

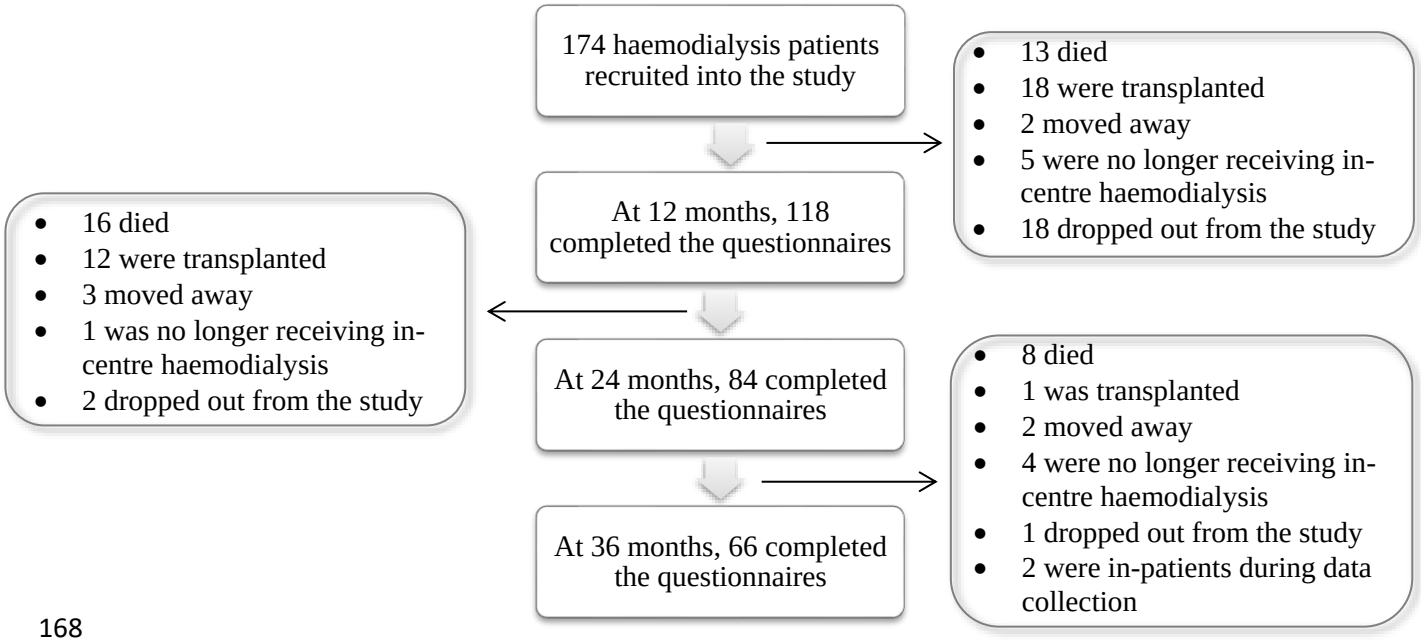


Figure 1. Flow diagram of participants through the study.

171

172 *Demographic and clinical data collection*

173 The following sociodemographic and clinical data were recorded for each patient at
174 baseline, using a self-report questionnaire: age, gender, marital status, employment status,
175 ethnicity, living arrangements, current smoking status, exercise status, primary renal
176 diagnosis, dialysis vintage (length of time on dialysis in months), access type, and perceived
177 transplant list status.

178 Comorbidity was assessed at baseline using the Charlson Comorbidity Index (CCI)
179 [48]. The CCI is a weighted index that takes into account the number and the seriousness of
180 comorbid diseases. The method of classifying comorbidity provides a simple, readily
181 applicable and valid method of estimating risk of death from comorbid disease for use in
182 longitudinal studies [48]. The CCI has been previously used in incident haemodialysis and
183 peritoneal dialysis patients [49] and was found to be the most suitable instrument to predict
184 patient survival in another study, compared to other comorbidity indices, like the Khan Index
185 score [50]. It is also simpler to score, not requiring a trained person, as compared to the Index
186 of Coexistent Disease.

187 The following clinical and laboratory data were collected at each data collection time-
188 point from medical records: haemoglobin (Hb, g/dL), albumin (g/dL), creatinine (umol/L), urea
189 (mmol/L), inter-dialytic weight loss (IDWL, Kg), C-Reactive Protein as a marker of
190 inflammation (CRP, mg/L), dialysis adequacy (Urea Reduction Ratio, %), and Body Mass
191 Index (BMI, kg/m^2). EPO dose and related treatments for anaemia (iron) and transplant list
192 status were also recorded. This clinical data is routinely collected as part of standard care.

193 *Psychological questionnaires*

All psychological questionnaires were administered at baseline, 12, 24 and 36 months follow-up.

The Chalder Fatigue Questionnaire [51]. This instrument was used to measure fatigue severity. It consists of 11 items. Scores are assigned for each response, using continuous scoring from 0 to 3. A cut-off of greater than 18 defines a fatigue case, using the continuous scoring [51,52]. A composite of the item scores represents fatigue severity. Higher scores represent greater fatigue severity. The composite score will be used here following recent psychometric evidence [53,54]. Cronbach's alpha for this scale was reported at α=0.89, representing excellent reliability [51], as well as demonstrating discriminant validity [51] and sensitivity to change [55]. In this sample, Cronbach's alpha was α=0.91. The CFQ has been used across a range of chronic illnesses to measure fatigue [56-58]. It has also been previously used and validated with renal patients [59,60].

Work and Social Adjustment Scale (WSAS)[61]. This instrument was used to measure fatigue-related functional impairment. It consists of five items that correspond to impairment in work, home management, social activities, private leisure activities and relationships as consequence of an illness or symptom, in this case fatigue. Higher scores indicate greater impairment. It has good psychometric properties, underlined by satisfactory Cronbach's α, ranging from 0.70 to 0.94 [61]. In this sample, Cronbach's alpha was α=0.94.

Hospital Anxiety and Depression Scale (HADS)[62]. This instrument is widely used for assessing depression and anxiety in patients with medical illnesses [62]. This instrument measures anxiety and depression via a 14-items scale, with 7 items pertaining to anxiety and 7 to depression. Each item is scored from 0-3, with a range from 0 to 21, 21 for severe anxiety or depression. A total score for distress can also be computed, ranging from 0 to 42, again with higher scores reflecting greater distress. A total score appears to be more

appropriate in kidney failure [63]. A review of the HADS found consistent support of its psychometric properties across samples, with an average Cronbach's alpha for HADS-A of α=0.83, and for HADS-D of α=0.82 [64]. In this sample, Cronbach's alpha for the combined subscales was α=0.90 (HADS-A α=0.85 & HADS-D α=0.80). This scale has been consistently used in kidney failure, performing well within this patient population [63,65].

Statistical analysis

Sample characteristics were summarised using descriptive statistics. To compute questionnaire scores, scores on items were added together with prorating of missing scores, with a conservative threshold of at least 50% of items on a questionnaire being completed (i.e. 6 out of 11 items on the CFQ)[66]. This method of handling item-level missing data is acceptable when a high proportion of the items (never fewer than half) are used to inform the total score, the item-total correlations are similar, and the internal consistency of the scale is high [66]. Therefore, it was deemed appropriate here.

In this patient population, there are two competing risks: death or transplantation. A transplant is a competing risk because after the transplantation, dialysis is no longer necessary; therefore, this eliminates the risk of dying while being on dialysis, while a transplant is no longer possible for someone who has died [45]. Patients were censored if they changed dialysis modality, moved away, were hospitalised during the data collection period, or dropped out. Univariate associations between sociodemographic, clinical and psychological variables with events were examined using bivariate correlations (Pearson or Spearman depending on normal distribution of the data) for continuous variables; ANOVA comparisons for normally distributed categorical variables according to survival status or the nonparametric Kruskal-Wallis H test; and the two-tailed Fisher exact test was used for dichotomous variables.

Missing data were present in the dataset, with approximately 10.9% and 18.4% of observations missing in the mortality and transplantation models, respectively. Data were missing at random, based on exploratory data analysis. Multiple imputations were conducted, according to Sterne, White, Carlin, Spratt, Royston, Kenward, Wood, Carpenter [67]; using 20 imputations and including variables in the model associated with missingness, such as total time in the study and censoring indicators. Competing risk survival models were estimated using the multiply imputed dataset.

To estimate the cumulative incidence of survival, while taking into account the presence of the competing transplantation event and vice-versa, the cumulative incidence competing risk (CICR) method was used [46]. To correctly estimate the probability of the events of interest, without over-inflation, analyses need to account for the competing risk [46].

To explore the effect of baseline fatigue severity, as a continuous score or a binary category (fatigued vs. non-fatigued using the aforementioned cut-off), and baseline fatigue-related functional impairment on events (mortality or transplantation), while accounting for the presence of competing events, the subdistribution hazards approach was used here [68].

The models with death as the event of interest were adjusted for: age at baseline, gender, ethnicity (white versus non-white), comorbidities at baseline (CCI, Charlson Comorbidity Index), dialysis vintage at baseline (months), transplant list status at baseline (fit versus unfit), intradialytic weight loss at baseline (IDWL, Kg), blood haemoglobin at baseline (g/L), serum albumin at baseline (g/L), history of cardiovascular disease (yes versus no), and distress at baseline (HADS). For time to transplantation, the following covariates were controlled for: age at baseline, gender, ethnicity (white versus non-white), employment status (working versus not working) at baseline, BMI at baseline, comorbidities at baseline

(CCI, Charlson Comorbidity Index), dialysis vintage at baseline (months), transplant list status at baseline (fit versus unfit), intradialytic weight loss at baseline (IDWL, Kg), blood haemoglobin at baseline (g/L), serum albumin at baseline (g/L), serum creatinine at baseline (umol/L), serum urea at baseline (mmol/L), history of cardiovascular disease (yes versus no), exercise status at baseline (yes versus no), and distress at baseline (HADS). Models were adjusted in steps, by sociodemographic, clinical, and self-report psychological variables, to observe their individual impact on the association between fatigue and the event of interest. These variables were selected based on previous research identifying them as known risk-factors of death and/or transplantation in this patient population, such as history of cardiovascular disease, and their univariate associations with the events in here.

Given the considerable overlap between transplant list status and transplantation events, as part of sensitivity analysis, the models looking at transplantation were rerun using subgroups of patients deemed as fit for a transplant (patients active on the transplant list or working up) and those deemed not currently fit (patients unfit temporarily, unfit permanently, and suspended).

Up to date CRP data were only available in a subsample of patients, since it is not routinely measured. Models were rerun with patients where CRP data were available at baseline, controlling for CRP, dichotomised into low (<5 mg/L) and high (>5 mg/L) based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical guidelines; in addition to the aforementioned covariates.

Owing to the repeated data collection over time, discrete-time survival analysis, where time is divided into discrete chunks, were also conducted to explore the contribution of time-varying fatigue severity, with up to three repeated measures per patient over the 3-year

289 cohort time measured at yearly intervals, to the presence of the event of interest, death or
290 transplantation, at each follow-up [69].

291 Descriptive statistics and exploratory statistics were conducted in SPSS version 23.0.
292 Survival analyses were conducted in STATA, using the *stcurve, cif* and the *stcrreg*
293 commands [70] to apply the CICR method [46]. Effects are expressed as subdistribution
294 hazard ratios (SHRs) with 95% confidence intervals (CI). Data were converted from wide to
295 long format and set as longitudinal (*xtset* [71]) before using the *cloglog* command [72] to
296 estimate discrete-time survival models. Effects of discrete-time survival models are expressed
297 as hazard ratios (HRs) with 95% confidence intervals (CI). Significance was set at $p \leq 0.05$,
298 using the standard α cut-off. To account for multiple tests resulting from treating fatigue as a
299 continuous or binary variable or looking at fatigue-related functional impairment, an adjusted
300 p-value cut-off of p=0.02 was also used, based on the Bonferroni correction (0.05/3=0.02).

301 **Results**

302 *Sample characteristics*

303 The sample consisted of 174 patients receiving in-centre haemodialysis. Demographic
304 and clinical characteristics of the sample have been previously described elsewhere [47].
305 Most of the sample was male (63.2%) with a mean age of 59.0 years old (SD=15.2). The
306 median dialysis vintage was 34.5 months (interquartile range=52). At baseline, mean fatigue
307 was 17.34 (95% CI 16.36-18.32) and 82 patients (47.1%) could be deemed as suffering from
308 clinical fatigue, scoring 18 or above on the CFQ. At baseline, the mean fatigue-related
309 functional impairment score was 18.5 (SD=13.0).

310 CRP at baseline was available in 82.2% of the sample (N=143), with 56.3% classed as
311 having high CRP (> 5 mg/L). There were no significant differences in fatigue severity scores

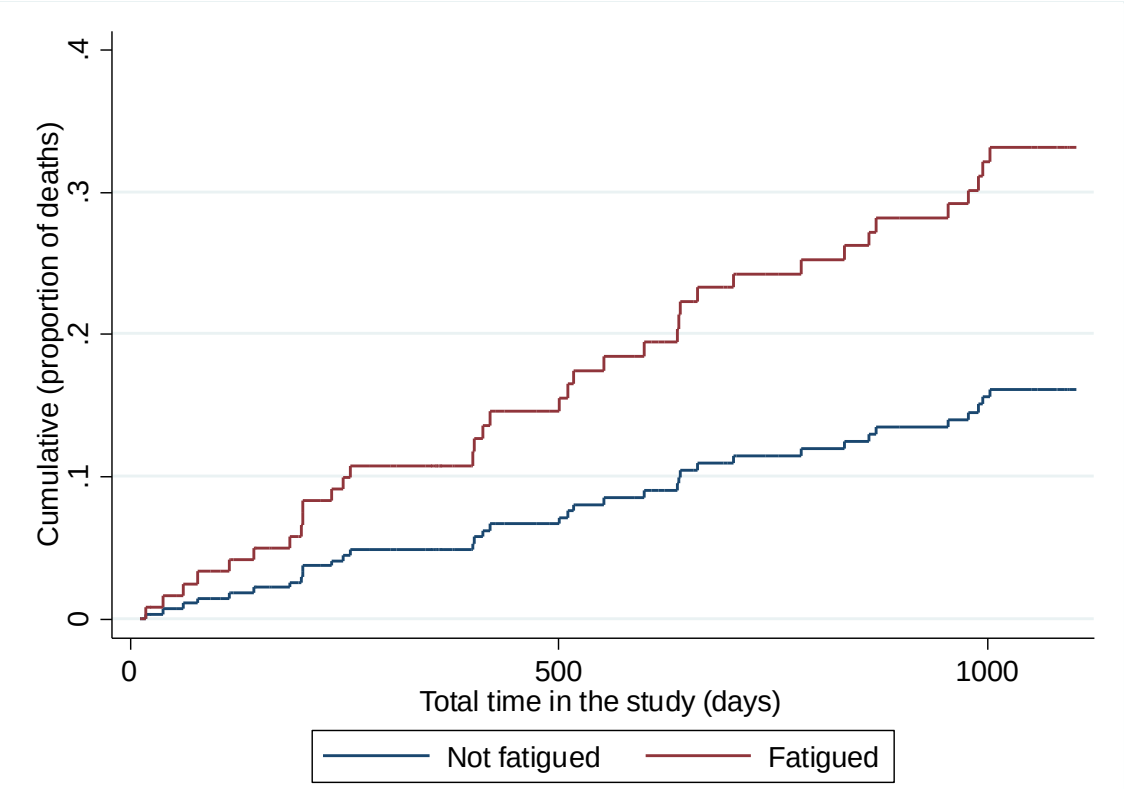
between patients with high CRP versus those with low CRP, or the proportion deemed fatigued (CFQ >18).

Outcomes characteristics

During the three-year follow-up period, there were 37 deaths and 31 transplantations. The estimated median survival time and time to transplantation could not be reported because the events were not observed for >50% cases. Cumulative survival at 1095 days (36 months) was 70.5%. The cumulative transplant event rate at 1095 days (36 months) was 22.2%. Censorship events included: drop-out (N=21), switching dialysis modality (N=10), transfer to a different hospital (N=7), and hospital admission (N=2).

Mortality and transplantation by fatigue

The mean estimated survival time for death as the event of interest was longer among patients deemed not fatigued (mean=987.93 days, standard error=30.72) compared to their fatigued counterparts (mean 896.29 days, standard error=39.06). When looking at transplantation events, the mean estimated survival time was longer among fatigued patients (mean=1012.23 days, standard error=30.99) versus not fatigued ones (mean=870.09 days, standard error=40.38). However, given the presence of competing risk, these estimates are inaccurate and cumulative incidence functions (CIFs) were estimated instead for death and transplantation events depending on fatigue status, based on the observed data (172 observations, with 1.1% missing). According to *Figure 2*, fatigued patients were more likely to die over the course of the study compared to their not fatigued counterparts (SHR=2.28, 95% CI 1.15 to 4.55, p=0.019). While, *Figure 3*, displays the CIF for transplantation events, where fatigued patients were less likely to receive a transplant over the course of the study (SHR=0.33, 95% CI 0.15 to 0.75, p=0.008).



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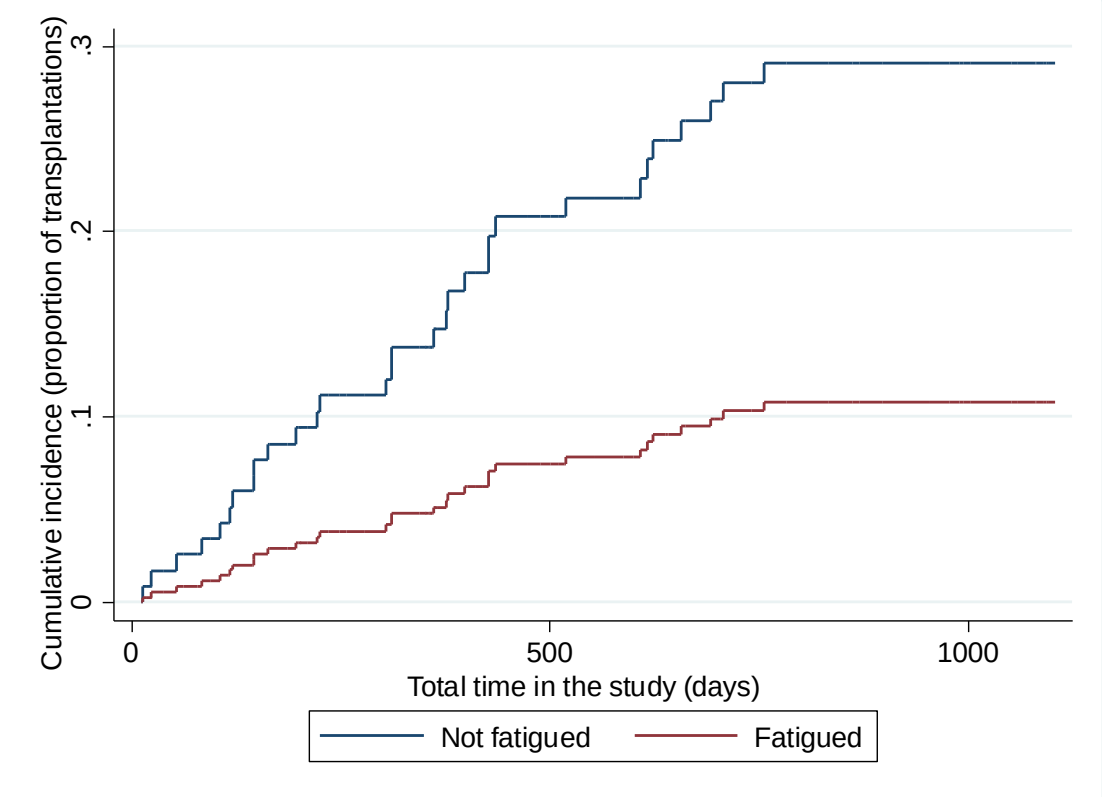
336 *Figure 2.* Cumulative incidence of death by fatigue status (not fatigued versus fatigued).



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338 *Figure 3.* Cumulative incidence of transplantation by fatigue status (not fatigued versus
339 fatigued).

Competing risk subdistribution hazard models: Association of fatigue with mortality, taking into account the competing transplantation event

In the unadjusted model, fatigue severity, treated both as a continuous or as a dichotomous variable, based on a score cut-off of ≥18; was significantly associated with an increased risk of mortality (Table 1). A one point increase in fatigue severity was associated with a 6% increase in the risk of death among patients who are alive or who have been transplanted (p=0.002, 95% CI 1.02 to 1.11). Fatigue as a clinical cut-off score was associated with a 2.18 times increase in the risk of death (p=0.02; 95% CI 1.11 to 4.31). The association between fatigue severity as a continuous variable and mortality ceased to be significant after controlling for distress (HADS)(Table 1). However, fatigue as a dichotomous variable was no longer a significant predictor of mortality, after controlling for clinical factors, which is likely due to reduced power (Table 1). A one point increase in fatigue-related functional impairment was associated with a 3% increase in the risk of death (p=0.005, 95% CI 1.01 to 1.05). This association remained significant after adjusting for sociodemographic and clinical variables, and it was marginally significant after controlling for distress (p=0.056)(Table 1).

Table 1

Association between Fatigue and Mortality: Subdistribution Competing Risks Models (N=174)

	Competing Risk Subdistribution Hazard Models (SHRs and 95% CI)			
	Model 1: unadjusted	Model 2: adjusted for sociodemographic variables[a]	Model 2: adjusted for sociodemographic and clinical variables[b]	Model 3: adjusted for sociodemographic and clinical variables, and distress[c]
CFQ (continuous)	1.06†‡ (1.02, 1.11)	1.06†‡ (1.02, 1.11)	1.06†‡ (1.01, 1.10)	1.05 (0.99, 1.12)
CFQ ≥ 18	2.18† (1.11, 4.31)	2.15† (1.10, 4.23)	1.94 (0.95, 3.96)	1.77 (0.81, 3.89)
WSAS	1.03†‡ (1.01, 1.05)	1.03†‡ (1.01, 1.06)	1.03†‡ (1.01, 1.06)	1.03 (1.00, 1.07)

[a] Model adjusted for age, gender, and ethnicity (white versus non-white).

[b] Model adjusted for age, gender, and ethnicity (white versus non-white), comorbidities using the Charlson Comorbidity Index score, dialysis vintage, intradialytic weight loss (IDWL, Kg), transplant list status (fit versus unfit), albumin (g/L), haemoglobin (g/L), and history of cardiovascular disease (yes versus no).

[c] Model adjusted for age, gender, and ethnicity (white versus non-white), comorbidities using the Charlson Comorbidity Index score, dialysis vintage, intradialytic weight loss (IDWL, Kg), transplant list status (fit versus unfit), albumin (g/L), haemoglobin (g/L), history of cardiovascular disease (yes versus no), and distress (HADS total score).

SHR=subdistribution hazard ratio, CI=confidence interval

†$p<0.05$

‡$p<0.02$; Bonferroni-corrected 5% alpha level

Competing risk subdistribution hazard models: Association of fatigue with transplantation, taking into account the competing mortality event

Similarly, fatigue severity, treated both as a continuous and as a dichotomous variable was significantly associated with a decreased likelihood of transplantation, in the unadjusted models (Table 2). A one-point increase in fatigue severity was associated with an 8% reduction in the likelihood of transplantation among patients who are alive or who have died (p=0.009, 95% CI 0.87 to 0.98). In those who did not experience the event of interest (transplantation) or a competing event (death), a change in fatigue status (not fatigued to fatigued), was associated with a 67% reduction in the odds of receiving a transplant (p=0.008, 95% CI 0.15 to 0.75). The association between fatigue severity, as a continuous variable, ceased to be significant after controlling for sociodemographic variables, including employment status, while fatigue status remained significant until clinical variables were added to the model (Table 2). Fatigue-related functional impairment was a significant predictor of a 4% reduction in the likelihood of transplantation (p=0.013, 95% CI 0.93 to 0.99), until sociodemographic factors were added to the model. The effect of fatigue on the likelihood of transplantation was further attenuated when exercise status was added to the models (Table 2).

Similar findings were obtained when looking at the association of fatigue symptoms with transplantation events in a subsample of patients who were active on the transplant list or working up and in a subsample of patients who were deemed currently unfit for a transplant (Appendix A). There was no indication for an attenuation of the effect of fatigue severity on transplantation when controlling for distress (SHR=0.93, p=0.019, 95% CI 0.87 to 0.99), while the effect of fatigue severity became non-significant after controlling for employment status (SHR=0.94, p=0.089, 95% CI 0.88 to 1.01). Adding BMI to this model attenuated the effect of fatigue severity only slightly further (SHR=0.95, p=0.164, 95% CI 0.89 to 1.02). The effect of employment status on the likelihood of transplantation ceased to

be significant after controlling for transplant list status. The same pattern was observed with fatigue-related functional impairment.

Competing risk subdistribution hazard models: CRP subgroup analysis

In the subgroup analysis, where CRP data were available, there was no evidence for an attenuation of the effect of fatigue and fatigue-related functional impairment on neither mortality nor transplantation, in the adjusted models (Table 3).

Table 2

Association between Fatigue and Transplantation: Subdistribution Competing Risks Models (N=174)

	Competing Risk Subdistribution Hazard Models (SHRs and 95% CI)				
	Model 1: unadjusted	Model 2: adjusted for sociodemographic variables[a]	Model 2: adjusted for sociodemographic and clinical variables[b]	Model 3: adjusted for sociodemographic and clinical variables, and exercise status[c]	Model 4: adjusted for sociodemographic and clinical variables, exercise status, and distress[d]
CFQ (continuous)	0.92†‡ (0.87, 0.98)	0.94 (0.88, 1.01)	0.96 (0.89, 1.04)	0.97 (0.89, 1.05)	0.94 (0.86, 1.03)
CFQ ≥ 18	0.33†‡ (0.15, 0.75)	0.36†‡ (0.15, 0.85)	0.50 (0.19, 1.37)	0.51 (0.17, 1.51)	0.28 (0.07, 1.21)
WSAS	0.96†‡ (0.93, 0.99)	0.97 (0.94, 1.00)	0.98 (0.95, 1.02)	0.99 (0.95, 1.03)	0.96 (0.90, 1.03)

[a] Model adjusted for age, gender, ethnicity (white versus non-white), and employment status (working versus not working).

[b] Model adjusted for age, gender, ethnicity (white versus non-white), employment status (working versus not working), Body Mass Index (BMI), comorbidities using the Charlson Comorbidity Index score, dialysis vintage, intradialytic weight loss (IDWL, Kg), transplant list status (fit versus unfit), albumin (g/L), creatinine (umol/L), haemoglobin (g/L), urea (mmol/L), and history of cardiovascular disease (yes versus no).

[c] Model adjusted for age, gender, ethnicity (white versus non-white), employment status (working versus not working), Body Mass Index (BMI), comorbidities using the Charlson Comorbidity Index score, dialysis vintage, intradialytic weight loss (IDWL, Kg), transplant list status (fit versus unfit), albumin (g/L), creatinine (umol/L), haemoglobin (g/L), urea (mmol/L), history of cardiovascular disease (yes versus no), and exercise status (yes versus no).

[d] Model adjusted for age, gender, ethnicity (white versus non-white), employment status (working versus not working), Body Mass Index (BMI), comorbidities using the Charlson Comorbidity Index score, dialysis vintage, intradialytic weight loss (IDWL, Kg), transplant list status (fit versus unfit), albumin (g/L), creatinine (umol/L), haemoglobin (g/L), urea (mmol/L), history of cardiovascular disease (yes versus no), exercise status (yes versus no), and distress (HADS total score).

SHR=subdistribution hazard ratio, CI=confidence interval

†$p<0.05$

‡$p<0.02$; Bonferroni-corrected 5% alpha level

Table 3

Association between Fatigue and Outcomes (Mortality or Transplantation): Subdistribution Competing Risks Models Adjusted for CRP (N=143)

	Competing Risk Subdistribution Hazard Models (SHRs and 95% CI)	
	Mortality[a]	Transplantation[b]
CRP-adjusted sub-analysis (N=143)		
CFQ (continuous)	1.05 (0.98, 1.13)	0.93 (0.80, 1.09)
CFQ ≥ 18	1.91 (0.70, 5.25)	0.11[†] (0.01, 0.92)
WSAS	1.04 (0.99, 1.09)	0.95 (0.86, 1.05)

[a] Model adjusted for age, gender, and ethnicity (white versus non-white), comorbidities using the Charlson Comorbidity Index score, dialysis vintage, intradialytic weight loss (IDWL, Kg), transplant list status (fit versus unfit), albumin (g/L), haemoglobin (g/L), CRP (low versus high), history of cardiovascular disease (yes versus no), and distress (HADS total score).

[b] Model adjusted for age, gender, ethnicity (white versus non-white), employment status (working versus not working), Body Mass Index (BMI), comorbidities using the Charlson Comorbidity Index score, dialysis vintage, intradialytic weight loss (IDWL, Kg), transplant list status (fit versus unfit), albumin (g/L), creatinine (umol/L), haemoglobin (g/L), urea (mmol/L), CRP (low versus high), history of cardiovascular disease (yes versus no), exercise status (yes versus no), and distress (HADS total score).

SHR=subdistribution hazard ratio, CI=confidence interval

[†]$p<0.05$

[‡]$p<0.02$; Bonferroni-corrected 5% alpha level

Discrete-time survival models: Association of time-varying fatigue with mortality & transplantation

According to the time-dependent models based on the observed data, fatigue severity, treated as a continuous time-varying variable, was associated with an increased risk of death at each subsequent follow-up, but this association displayed only a trend towards significance in the unadjusted model (HR=1.04, 95% CI 1.00 to 1.08, p=0.08). In contrast, fatigue-related functional impairment over time was associated with a 3% increase in the risk of death at each subsequent follow-up (95% CI 1.00 to 1.05, p=0.022), but this association was no longer significant after controlling for time-varying distress (p=0.102).

Conversely, fatigue severity over time was not a significant predictor of a 6% reduction in the likelihood of being transplanted at each subsequent follow-up, in the unadjusted time-dependent model (HR=0.94, 95% CI 0.88 to 1.00, p=0.04). Similarly, fatigue-related functional impairment over time was associated with a significant reduction in the odds of receiving a transplant at each subsequent follow-up (HR=0.96, 95% CI 0.93 to 0.99, p=0.008). However, the associations between fatigue predictors and transplantation ceased to be significant when controlling for sociodemographic factors, including age (time-varying), gender, ethnicity (white versus non-white), and employment status at baseline (working versus not working).

Detectable effect size

Based on the data here, detectable effect sizes were estimated to guide how underpowered the study may have been. The figures below relate to fatigue severity as a dichotomous variable: fatigued versus non-fatigued; which has the lowest power.

A study with the same proportion of fatigued individuals followed for 3 years, with an annual incidence rate for death of 7% in non-fatigued individuals, would be able to detect a

453 population hazard ratio of at least 2.34 with 80% power at the 5% significance level. While, a
454 study with the same proportion of fatigued individuals followed for 3 years, with an
455 annual incidence rate for transplant of 20% in non-fatigued individuals, would be able to
456 detect a population hazard ratio of at most 0.47 with 80% power at the 5% significance level.
457

458 **Discussion**

459 The aim of this paper was to assess the association between fatigue severity and
460 fatigue-related functional impairment with all-cause mortality and kidney transplantation.
461 This exploration was embedded in a longitudinal study of fatigue and its biopsychosocial
462 correlates in haemodialysis. In this study, 47.1% of patients could be deemed clinically
463 fatigued. This estimate is in line with previous estimates, suggesting that the prevalence of
464 fatigue in this patient population ranges from 42% to 92% [7,10]. Therefore, approximately
465 one in two patients suffer from clinical levels of fatigue, which only further accentuates the
466 pervasiveness of fatigue symptoms among prevalent in-centre haemodialysis patients.

467 Although, there appeared to be no direct association between fatigue and neither death
468 nor transplantation after controlling for covariates; in the unadjusted models, fatigue severity
469 and fatigue-related functional impairment were predictive of an increased risk of death and
470 decreased likelihood of transplantation. In unadjusted models, a one-point increase in fatigue
471 severity was associated with a 6% increase in the risk of death, and a change in fatigue status
472 (not fatigued to fatigued) was associated with 2.18 times increase in the risk of death. The
473 association between fatigue severity and mortality ceased to be significant after controlling
474 for distress, suggesting that fatigue severity may impact on survival indirectly through mood,
475 rather than through clinical factors. Fatigue-related functional impairment was associated
476 with a 3% increase in the risk of death and this association remained marginally significant

and was not attenuated by distress, suggesting that the impact of fatigue on daily roles may be particularly detrimental for survival.

On the other hand, in the unadjusted models, a one-point increase in fatigue severity was associated with an 8% reduction in the likelihood of receiving a transplant, and a change in fatigue status (not fatigued to fatigued) was associated with a 67% reduction in the odds of receiving a transplant. A similar effect was observed with fatigue-related functional impairment. In adjusted models, the association between fatigue severity and fatigue-related functional impairment with transplantation ceased to be significant when controlling for sociodemographic covariates, including employment status, possibly acting as a marker of functioning. On the other hand, the association between fatigue status and transplantation ceased to be significant after controlling for clinical variables, suggesting that fatigue may indirectly reduce the likelihood of getting a transplant, by increasing BMI and consequently being considered less fit for a transplant. This disparity between fatigue severity as a continuous or dichotomous predictor may be indicative of the exacerbated influence of clinical levels of fatigue on the likelihood of transplantation. In contrast to the models looking at death, there was no evidence for an attenuation of the effect between fatigue and transplantation when controlling for distress, but only after controlling for functioning-related factors.

Similarly, according to the discrete-time survival models, fatigue severity and fatigue-related functional impairment over the study period were predictive of a 6% and 4% reduction in the likelihood of being transplanted at each subsequent follow-up, respectively, but this effect became non-significant after controlling for sociodemographic covariates. However, this temporal association was not observed between time-varying fatigue severity and mortality. Only fatigue-related functional impairment over time was predictive of mortality at each subsequent follow-up, but this ceased to be significant after controlling for

distress. There was no evidence for an attenuation of the effect of fatigue on neither mortality nor transplantation when controlling for inflammation.

Previous Research

Past research has shown the prognostic value of fatigue in predicting mortality across different patient populations [29,30,73-75], including dialysis patients [24,25,28]. In a study of breast cancer patients, higher levels of fatigue were associated with a shorter recurrence-free survival time, after controlling for clinical and treatment-related covariates [29]. Furthermore, in the general population, being in the highest quartile of fatigue was associated with a 26% increase in all-cause mortality risk, after adjusting for known risk factors [76].

Similarly, there is evidence for the association between fatigue and all-cause mortality among dialysis patients [24,25,28]. For example, survival of patients who reported a decline in vitality at one year follow-up was 3.0 years versus 3.8 years in patients whose vitality was stable or improved [24]. In another study, a one-unit increase in vitality was associated with a 1.00% increase in mean survival [25]. This is in contrast to the findings here, where no significant direct association between fatigue severity and mortality was identified in adjusted models. Similarly, Koyama et al. failed to find a significant association between fatigue and all-cause mortality, yet fatigue was predictive of cardiovascular events among haemodialysis patients [27]. This disparity in findings may stem from differences in measurement of fatigue and looking at all-cause versus cause-specific mortality, suggesting that the association between fatigue and mortality is likely to be complex and multifaceted. To date, the association between fatigue and transplantation has not been investigated and it is yet to be established whether fatigue is a risk factor for mortality or graft rejection among kidney transplant recipients [77].

Underlying Mechanisms

Understanding the mechanisms at play in the association between fatigue and clinical outcomes is currently tentative at best. Potential mediators of the association between fatigue and mortality that have been proposed in the literature, include increased treatment non-adherence [78], deconditioning [28,79], malnutrition [25], and in particular increased inflammatory processes [80,81], possibly partially through depression [79,81]. For example, Jhamb et al. [25] found that a 1 g/dl increase in albumin was associated with an increase in vitality score by 7.7 points and 21% decrease in mortality risk. In kidney failure, inflammatory cytokines may contribute to pathological processes leading to cardiovascular disease (CVD) and mortality [82-85]. In fact, there is some evidence to suggest that increased inflammation may be one mechanism through which depression may exert a negative influence on survival [41,86]. Similar mechanisms may operate between fatigue and clinical outcomes, yet there was no evidence for this here. A large study in the general population found that the association between fatigue and mortality was particularly driven by CVD-related deaths and this association was attenuated after adjusting for thyroid function and inflammation [76]. Furthermore, among haemodialysis patients, both depression and interleukin-6, an inflammatory cytokine, have been found to be significantly and independently associated with fatigue [81]. In fact, the association between fatigue severity and mortality was attenuated and ceased to be significant when controlling for distress, in contrast to Bossola et al.'s findings [28]. Yet, fatigue-related functional impairment remained marginally significant, indicating that perceived limitations in daily functioning as a result of fatigue may be particularly harmful.

The mechanisms through which fatigue may contribute to a reduced likelihood of receiving a transplant remain elusive, but they are likely to be complex, including physiological and behavioural mediators. Approximately half of people with kidney failure are suitable to receive a kidney transplant [87,88], following a comprehensive evaluation

based on criteria such as age below 75, a BMI of 35 or lower, and without an ongoing infection or severe heart disease [88,89]. Elevated levels of pro-inflammatory cytokines are therefore also likely to play a mediating role in the association between fatigue and transplantation; however, according to the findings here, controlling for CRP did not attenuate the association between fatigue and transplantation in the subgroup analysis. Similarly, there was no evidence for distress playing a role in the association between fatigue and transplantation. It is important to note that many factors come into play in transplantation, including availability of organs.

The association between fatigue and transplantation appeared to be primarily driven by functioning-related factors. However, it is important to note that the relationship between fatigue and functioning is likely to be bidirectional. A consequence of the association between fatigue and reduced functioning may be increased BMI, possibly leading to transplant ineligibility. In fact, the association between fatigue and transplantation was attenuated and became non-significant when controlling for sociodemographic covariates, particularly employment status; clinical covariates, including BMI and transplant list status (fit versus unfit); and exercise status. Similarly to depression, fatigue may also lead to treatment non-adherence, which can impact on the assessment of suitability to receive a kidney transplant, but also following transplantation, it may lead to graft failure. This, in fact, has been documented when looking at depressive symptoms [90]. Lastly, some variance of the association between fatigue and transplantation may be explained by depression, as previous research has found that depression significantly reduces the odds of being on the transplant waiting-list [91], although it does not appear to be a risk factor for transplantation [41,91], as also found here.

Overall, if we consider employment status, exercise status, and fatigue-related functional impairment as tapping into functioning, there is an indication that fatigue severity

may stop patients from doing things which may then have a detrimental impact on their overall functioning, consequently leading to poorer outcomes. This serves to further illustrate the complex biopsychosocial processes at play in the relationship between fatigue and clinical outcomes.

Limitations of the Current Study and Future Directions

The strengths of the study include the use of the Chalder Fatigue Questionnaire - a fatigue-specific scale displaying excellent psychometric properties, in contrast to the vast majority of previous research that has relied on the vitality subscale of the SF-36, possibly failing to capture every aspect of the fatigue experience [43]; evaluating the contribution of fatigue-related functional impairment; controlling for functioning-related factors and distress in the models; and looking at both mortality and transplantation events in proportional hazard survival models, allowing for competing risks.

However, several limitations need to be acknowledged. Firstly, although the sample consisted of 174 patients at baseline, this may be insufficient to detect the effect of fatigue on outcomes. Additionally, only 62% of patients who were approached for participation, provided informed consent and completed the questionnaires, highlighting the risk of non-response bias, possibly where the most fatigued patients were less likely to participate. However, the fatigue scores ranged from 0 to 33, suggesting that the severe-end of fatigue was captured in the data. Additionally, cause-specific mortality was not evaluated, which may have led to the null-effect of fatigue on mortality events in the adjusted models. The evidence is currently mixed with regards to the association between fatigue with cause-specific mortality, such as cardiac events, or all-cause mortality [24,25,27]. Therefore, it would be valuable for future research to examine the predictive role of fatigue on cause-specific mortality and transplantation in a larger sample, to determine the subtle nuances between these associations.

Although important indicators of SES: ethnicity, employment status and years of education, were collected at baseline, data on income was not gathered. There is extensive evidence on the association between socio-economic status (SES) and mortality [92];

604 therefore, the lack of a commonly used measure of SES is another limitation of this study.
605 According to recent evidence, SES may act as a moderator of the effects of diabetes,
606 hypertension, and obesity on the risk of death from renal disease [93]; therefore, complex
607 non-linear relationships are likely at play. The sample was also limited to English-speaking
608 patients, limiting generalizability. Although the sample was not predominantly white (43.1%
609 white; 56.9% non-white) and a number of ethnicities were represented in the sample; a crude
610 categorization into white versus non-white was used in the analyses, due to the low frequency
611 of some ethnicities (e.g. one Chinese patient). There is evidence to suggest an interaction
612 effect of depression and ethnicity on mortality events [39,94]; similar complex relationships
613 may exist with fatigue; therefore, it would be valuable for future research to explore the
614 interaction between fatigue and ethnicity on outcomes.

615

616 **Conclusion**

617 Despite the pervasive and incapacitating nature of fatigue in haemodialysis, it is often
618 perceived as a normal consequence of the illness and treatment with little support provided
619 for fatigue to patients. This study assessed the association between fatigue and clinical
620 outcomes, specifically mortality and transplantation. Clinical levels of fatigue and elevated
621 interference afforded by fatigue on life roles were common in the sample and were
622 significantly associated with an increased risk of mortality and a reduction in the odds of
623 transplantation in the unadjusted models. Furthermore, fatigue appeared to act as an
624 antecedent predictor of an increased risk of mortality and reduced likelihood of
625 transplantation at each subsequent follow-up. After adjusting for known risk factors, these
626 associations ceased to be significant, suggesting that fatigue may impact on outcomes
627 indirectly, through distress, reduced functioning and its clinical consequences, rather than
628 clinical and inflammatory markers. The underlined mechanisms of the association between
629 fatigue and outcomes are yet to be fully defined, but they are likely to be complex, including
630 both physiological and behavioural mediators. The link between fatigue and clinical

outcomes only further accentuates the need for effective fatigue management in this patient population. In this setting, patients are likely to experience recurrent symptoms of fatigue, particularly following dialysis, and given the important role functioning-related factors appeared to play here; the focus of psychotherapy could revolve around reducing the impact of fatigue on functioning.

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