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Sickness Symptoms in Kidney Transplant Recipients: A Scoping Review

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Abstract

Sickness symptoms (depressive symptoms, anxiety, and fatigue) are common among people with chronic illness, often presenting as a symptom cluster. Sickness symptoms persist in many patients with chronic kidney disease, even after kidney transplantation (KT); however, little is known about sickness symptom-induced burden in KT recipients. This scoping review synthesizes available evidence for sickness symptoms in KT recipients, including findings on symptom prevalence, predictors, outcomes, interrelationships, and clustering. Among 38 reviewed studies, none identified sickness symptoms as a cluster, but we observed interrelationships among the symptoms examined. Fatigue was the most prevalent sickness symptom, followed by anxiety and depressive symptoms. Predictors of these symptoms included demographic, clinical, and psychosocial factors, and health-related quality of life was the most researched outcome. Future research should use common data elements to phenotype sickness symptoms, include biological markers, and employ sophisticated statistical methods to identify potential clustering of sickness symptoms in KT recipients.

Keywords

kidney transplantation; depression; anxiety; fatigue; sickness behavior; scoping review

Symptom science provides a framework for addressing the debilitating consequences of symptom burden (Cashion & Grady, 2015). In recent years, multiple national and international organizations have prioritized symptom science in nephrology, recognizing the significant impact symptoms have on the physical, mental, and social function of people with chronic kidney disease (CKD) (Flythe et al., 2019; Kalantar-Zadeh et al., 2022; Tobin et al., 2022). Kidney transplantation (KT) is regarded as the gold standard renal

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Supplemental Material

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replacement therapy for patients with end-stage kidney disease. Kidney transplant recipients are considered to be a unique CKD patient group that requires special consideration of their functioning kidney graft along with their lifelong use of immunosuppressive medications (Parajuli et al., 2018).

Despite the prevailing success of KT and a general reduction in total symptom burden after KT, many KT recipients continue to experience significant symptom burden after restoration of kidney function (Carminatti et al., 2019; Fletcher et al., 2022). A common and often neglected issue, posttransplant symptom burden has a negative impact on KT recipients' ability to participate in physical and social activities of daily life (Ju et al., 2019). Multiple factors contribute to high symptom burden in KT recipients, including residual kidney dysfunction, comorbid conditions (e.g., diabetes and hypertension), and side-effects induced by immunosuppression (Sullivan et al., 2020; Wang et al., 2021). Furthermore, health care providers' limited awareness of the negative effects of symptom burden after KT poses a major challenge to developing care improvement strategies for the posttransplant period. Thus, a clear understanding of symptoms in the KT context and of precipitating factors that contribute to symptom burden is critical to identify KT recipients who may be at greater risk for adverse outcomes.

Among the multiple symptoms contributing to symptom burden after KT, depressive symptoms, anxiety, and fatigue have been the three most studied in the KT recipient population (Fletcher et al., 2022). Fatigue has been identified as among the most common and debilitating symptoms experienced after KT, and it often co-occurs with depressive symptoms and anxiety in KT recipients (Bossola et al., 2021; De Pasquale et al., 2014, 2020). However, nephrology experts have concurred that KT recipients' symptom experience is understudied and thus unclear (Fletcher et al., 2022; Kalantar-Zadeh et al., 2022; Taylor et al., 2021; Wang et al., 2021), emphasizing the need for additional symptom research.

Depressive symptoms, anxiety, and fatigue are collectively referred to herein as sickness symptoms (Corwin et al., 2021; Matura et al., 2018; Mihai et al., 2018). According to Corwin et al.'s (2021) theoretical framework of sickness symptoms, sickness symptoms are among the most prevalent and distressing symptoms in patients with multiple chronic diseases (Corwin et al., 2021; Starkweather et al., 2013). Importantly, sickness symptoms tend to co-occur as a symptom cluster, and thus it is hypothesized that they may share underlying biological mechanisms (Corwin et al., 2021). Moreover, the impact of a sickness symptom cluster is greater than that of the individual sickness symptoms because of the cluster's synergistic effect on clinical outcomes (Corwin et al., 2021; Tometich et al., 2019). Thus, understanding the interrelationships among sickness symptoms, their antecedents, and their effects on important patient outcomes represents the first step in developing patient-centered interventions to reduce symptom burden and improve quality of life.

Symptom science experts have pointed out that symptom cluster studies have been suboptimal because the use of different cluster sets impedes replication of the research (Miaskowski et al., 2017). In this light, depressive symptoms, anxiety, and fatigue were identified as sentinel symptoms constituting a priority symptom cluster in chronic disease

populations (Miaskowski et al., 2017). Application of these sickness symptoms as a prespecified cluster in the KT recipient population would facilitate identification of their characteristics and development of interventions to reduce sickness symptom-induced burden (Miaskowski et al., 2017).

Purpose

The purpose of this scoping review was to synthesize research findings on sickness symptoms— depressive symptoms, anxiety, and fatigue—in KT recipients. This review article specifically addresses prevalence of sickness symptoms, their predictors and outcomes, and interrelationships among sickness symptoms in the KT recipient population. The review was guided by Corwin et al.'s (2021) theoretical framework of sickness symptoms as adapted for this population (Figure 1).

Methods

This scoping review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist and by Arksey and O'Malley's (2005) methodological framework (Arksey & O'Malley, 2005; Tricco et al., 2018).

Search Strategy

The search strategy was designed to identify published observational studies that reported sickness symptoms (specifically: depressive symptoms, anxiety, and fatigue) in KT recipients because observational studies differ in research questions and study designs. The search strategy, including search term and database selection, was developed with the aid of an experienced research librarian (R.R.). Electronic databases (MEDLINE/PubMed, CINAHL Plus with Full Text, PsycInfo, and Embase) were searched for relevant studies and reviews. Publication limits were set in January 2009 and October 2021. We selected the lower search limit because in early 2000s, immunosuppression therapy transitioned from cyclosporine-based to modern maintenance therapy (e.g., calcineurin inhibitor), owing to their significant side-effects (Lim et al., 2017). Thus, we intentionally excluded symptoms that may have been posed by previous regimens. Furthermore, given the ongoing changes in transplant procedures, we chose to examine sickness symptoms in a relatively contemporary population of KT recipients. Search terms included fatigue OR depressive symptoms OR anxiety AND KT, and all possible combinations of these keywords were customized for each database. Specifically, sickness symptoms were operationalized as follows: depressive symptoms as depressed mood or depression; anxiety as anxious mood or anxiety-like symptoms; and fatigue as tiredness, weakness, lack of energy, or low vitality. Our PubMed search strategy is presented in Table 1.

Eligibility Criteria

Two authors (C.S. and M.B.L.) determined the study aims and key concepts. As to inclusion criteria, studies were selected for full-text screening if they (a) involved people who had undergone KT; (b) addressed two or more of the sickness symptoms (depressive symptoms,

anxiety, and fatigue) using a self-reported symptom measurement; (c) focused on adult participants aged over 18 years; (d) were original observational studies, such as cross-sectional, case-control study, or longitudinal designs; (e) were published in peer-reviewed journals; and (f) were written in English. Studies were excluded if they (a) involved participants who had undergone combined transplantation (e.g., kidney-lung, -pancreas, -heart, or -liver), as those receiving combined organ transplants may have different sickness symptom experiences than those having a single transplantation; (b) were animal studies; or (c) were literature reviews, editorials, commentaries, study protocols, case studies, or unpublished gray literature.

Data Management

All retrieved references were imported into Covidence, a web-based software platform that is used to manage the review process, including title and abstract screening, full-text review, and data extraction. A primary reviewer (C.S.) screened titles and abstracts as well as full-text articles to determine whether they met the inclusion criteria. A second reviewer (M.B.L.) conducted a confirmation screening. The reviewers discussed studies where eligibility was uncertain until a consensus was reached, and identified 38 studies eligible for the scoping review. The PRISMA diagram in Figure 2 provides the details of the search and screening processes.

The data extraction procedure was based on the methodologies developed by Joanna Briggs Institute Reviewers (Peters et al., 2015). The data extracted included study author(s), year of publication, location, sample population, aims, design, and methodology as well as key findings in the following three categories: sickness symptoms (a) prevalence, (b) predictors and outcomes, and (c) interrelationships among them. Quality appraisal for the selected studies was not conducted as it is not required for scoping review methodology (Arksey & O'Malley, 2005; Peters et al., 2015).

Results

Study and Participant Characteristics

The 38 included studies were published from 2009 to 2021 (Table 2). The studies were conducted in Europe (n = 19), Asia (n = 6), the Middle East (n = 5), the United States (n = 4), and Latin America (n = 4). Two studies employed a longitudinal design to follow up from pre-KT to the post-KT period (González-De-Jesús et al., 2011; Robiner et al., 2021). The remaining 36 studies employed cross-sectional designs. Three involved analyses of secondary data from previous primary studies that employed either a longitudinal prospective design (Klewitz et al., 2019; Koller et al., 2010) or a cross-sectional design (Müller et al., 2020).

In total, 22 of the cross-sectional studies identified factors associated with patient-reported outcomes, such as symptoms, medication adherence, frailty, and health-related quality of life. In addition, 14 studies were comparative in nature, with nine studies comparing KT recipients with patients receiving dialysis or a pre-KT population, two comparing deceased-

and living-donor KT recipients, and three comparing KT recipients with either healthy general populations (n = 2) or hematologic patients (n = 1).

A total of 6,331 KT recipients were enrolled in the 38 studies. Males comprised 56% of the participants, whose mean age ranged from 31.36 to 56.2 years. Participants varied in their posttransplantation periods, whose means ranged from 6 months to 8 years, but all KT recipients recruited were medically stable; that is, none were experiencing rejection, infection, graft loss, or were hospitalized at the time of recruitment. Details of these studies are presented in Tables 2–4. Specifically, Table 2 summarizes the characteristics of the 38 selected studies and their participants, and Table 3 summarizes symptom prevalence and the instruments used to measure each symptom. Table 4, *Predictors and Outcomes of Symptoms and Relationships among Sickness Symptoms*, is available as online supplementary material and provides a fuller description of each reviewed study.

Depressive Symptoms

Prevalence and symptom measurement.—Depressive symptoms were the most commonly measured sickness symptom (n = 23), and their prevalence varied between 4.53% and 75% (Table 3). Five studies reported a prevalence over 30%, and one study identified depressive symptoms in 75% of KT recipients (Afshar et al., 2012; Alavi et al., 2009; Anvar-Abnavi & Bazargani, 2010; Barutcu Atas et al., 2021; Zimmermann et al., 2016). In one study that examined symptom frequency and distress, depressive symptoms were found to be an infrequent but distressing symptom (Koller et al., 2010). In Vásquez et al.'s (2013) study, 13.8% of KT recipients reported depressive symptoms using self-reported instruments, and a comparable percentage of KT recipients (11.8%) were diagnosed with clinical depression based on a structured diagnostic interview. Two studies examined changes in depressive symptom score from pre- to post-KT using self-reported questionnaires and showed mixed findings (González-De-Jesús et al., 2011; Robiner et al., 2021). González-De-Jesús et al. (2011) found the decreasing trend in depressive symptom scores from pre-KT to 6 months post-KT using the Hospital Anxiety Depression Scale (HADS) and Symptom Checklist-90, but only latter scores reached statistical significance. A decrease in depressive symptoms was also observed after KT in Robiner et al.'s (2021) study. Depressive symptoms were improved at 6 months post-KT as measured by the Beck Depression Inventory-II and the Millon Clinical Multiaxial Inventory III-Major Depression Scale, but only former results reported significant changes in depressive symptom scores. Eight studies compared depressive symptoms in terms of treatment modality, finding that KT recipients had significantly lower depressive symptoms than patients receiving dialysis or waitlisted for KT (Alavi et al., 2009; Argyropoulos et al., 2018; Brito et al., 2019; González-De-Jesús et al., 2011; Gurkan et al., 2015; Kovacs et al., 2011; Ozcan et al., 2015; Rodrigue et al., 2011). Three studies reported that KT recipients experienced higher levels of depressive symptoms than general populations (Chan et al., 2016; Pascazio et al., 2010; van Sandwijk et al., 2019), only Chan et al. (2016) showed significant differences in these groups.

With regard to measurement of depressive symptoms, multiple self-reported instruments were used. The HADS was most commonly employed (in 12 studies), but the prevalence

of depressive symptoms measured using this tool varied between 5.9% and 44.3%. This wide range of prevalence is likely attributable to the different HADS thresholds used in the reviewed studies. The total HADS score ranges from 0 to 21, and the HADS developers recommended a score of ≥8 to indicate possible depression and ≥11 to indicate probable depression (Wu et al., 2021). However, HADS cutoff values used in the reviewed studies to identify depressive symptoms varied from 5 to 11.

Predictors and outcomes.—Predictors associated with depressive symptoms in KT recipients fell into three broad categories, namely demographic, clinical, and psychosocial factors. Seven studies addressed demographic factors potentially associated with depressive symptoms, including age, female sex, and less education (Argyropoulos et al., 2018; Brito et al., 2019; Lai et al., 2020; Vásquez et al., 2013; Zimmermann et al., 2016). Age showed inconsistent results in that both younger and older age were associated with greater depressive symptoms (Argyropoulos et al., 2018; Lai et al., 2020; Vásquez et al., 2013). As to clinical factors related to depressive symptoms, Anvar-Abnavi and Bazargani (2010) reported that KT recipients had high depressive symptom scores when they had longer periods of dialysis before KT, had longer time since KT, and a kidney from a deceased donor. Brito et al. (2019) examined sociodemographic and clinical characteristics of depressive symptoms and reported that poor nutritional status was a predictor of depressive symptoms. Regarding psychosocial factors, higher depressive symptoms were associated with being divorced or widowed, being retired or unemployed, and living alone (Argyropoulos et al., 2018; Brito et al., 2019; Jordakieva et al., 2020; Müller et al., 2015). Barutcu Atas et al. (2021) examined psychological distress during the COVID pandemic and identified high perceived stress as an independent predictor of depressive symptoms. Zhang et al. (2019) that examined the effect of rumination on the relationship between fatigue and depressive symptoms showed that depressive symptoms were associated with rumination in correlation analysis. Moreover, negative emotional responses to treatment and lack of social support were associated with higher depressive symptom scores in three studies (Látos et al., 2016; Vásquez et al., 2013; Zimmermann et al., 2016). Self-esteem was also negatively associated with depressive symptoms (Rocha et al., 2020).

As for outcomes associated with depressive symptoms, five studies reported the inverse relationship of depressive symptoms to KT recipients' health-related quality of life (Brito et al., 2019; Jana et al., 2014; Rocha et al., 2020; Tamura et al., 2018; van Sandwijk et al., 2019). For medication adherence, four studies reported mixed results. Two studies reported no significant associations with depressive symptoms using either the Mann–Whitney U test (Scheel et al., 2018) or multivariate logistic regression (Weng et al., 2013). Two studies supported the significant relationships between depressive symptoms and medication adherence. Reber et al. (2016) reported that a moderate level of depressive symptoms was associated with nonadherence with a medium effect size. Robiner et al. (2021) conducted a longitudinal study that examined relationships of depressive symptoms at pre- and post-KT to medication adherence in KT recipients, depressive symptoms before KT were negatively associated with post-KT medication adherence.

Anxiety

Prevalence and symptom measurement.—Anxiety was addressed in 19 studies, all of which paired anxiety with depressive symptoms as emotional distress, with instruments that include both symptoms, such as the HADS (Table 3). Of these, 11 included anxiety as a primary outcome (Alavi et al., 2009; Anvar-Abnavi & Bazargani, 2010; Argyropoulos et al., 2018; Brito et al., 2019; Czyżewski et al., 2018; González-De-Jesús et al., 2011; Müller et al., 2015; Ozcan et al., 2015; Pascazio et al., 2010; Tavallaii et al., 2009; Zimmermann et al., 2016). The prevalence of anxiety ranged from 4.03% to 63.9% with variability partly being attributable to methodological differences, such as differences in HADS cutoff scores used (Table 2). Six studies reported prevalence for anxiety as 30% or more (Afshar et al., 2012; Alavi et al., 2009; Anvar-Abnavi & Bazargani, 2010; Lai et al., 2020; Scheel et al., 2018; Zimmermann et al., 2016). Koller et al. (2010) regarded anxiety as a physical symptom, and it was the fourth most common symptom among KT recipients. Afshar et al. (2012) found anxiety to be the most distressing symptom for men and the least for women. Among 10 studies that compared KT recipients' anxiety with dialysis patients, five studies presented that KT recipients experienced significantly lower anxiety than dialysis patients (Alavi et al., 2009; Brito et al., 2019; González-De-Jesús et al., 2011; Gurkan et al., 2015; Ozcan et al., 2015). In a longitudinal assessment of anxiety, González-De-Jesús et al. (2011) found that anxiety scores significantly decreased after KT. In terms of donor type, anxiety score above cutoff scores of 8 (thresholds for clinical actions) was lower in living donor KT recipients than deceased donor KT recipients (Zimmermann et al., 2016). Among three studies that examined group differences in anxiety, Chan et al. (2016) reported that KT recipients had twice as high a median anxiety score as a healthy comparison population. The remaining two studies showed no anxiety differences between KT recipients and healthy populations (Pascazio et al., 2010; van Sandwijk et al., 2019), likely due to their use of a cross-sectional design and a small sample size.

Predictors and outcomes.—Anxiety was associated with demographic, clinical, and psychosocial factors. Demographic factors associated with greater anxiety included younger age, female sex, and less education (Argyropoulos et al., 2018; Brito et al., 2019; Lai et al., 2020; Látos et al., 2016; Zimmermann et al., 2016). Clinical factors included longer time on dialysis before KT, receiving a kidney from a deceased donor, and longer time since KT (Anvar-Abnavi & Bazargani, 2010; Zimmermann et al., 2016). In addition, high creatinine level, high number of comorbidities, and post-KT complication (e.g., graft rejection or hospitalization) were significantly associated with greater anxiety levels (Brito et al., 2019; Jana et al., 2014). As to psychosocial factors, higher anxiety was associated with being divorced or widowed and being retired or unemployed (Argyropoulos et al., 2018; Brito et al., 2019; Jordakieva et al., 2020). Low levels of recreational activities in daily living and the presence of bodily pain were predictors of greater anxiety (Brito et al., 2019). In Zimmermann et al.'s (2016) study, transplant-related emotions (greater worry about the transplant, greater responsibility to do well, and less disclosure to transplant) were associated with anxiety.

As for outcomes, four studies reported that anxiety negatively influenced health-related quality of life (Jana et al., 2014; Tamura et al., 2018; van Sandwijk et al., 2019;

Zimmermann et al., 2016). High anxiety levels were found to be a predictor of high perceived exertion (Chan et al., 2016). Four studies explored relationships between anxiety and medication adherence as an outcome. Three identified negative relationships between anxiety and medication adherence (Klewitz et al., 2019; Reber et al., 2016; Zimmermann et al., 2016). Specifically, Klewitz et al. (2019) reported that KT recipients with anxiety were less satisfied with receipt of immunosuppressive medication education. Moreover, Látos et al. (2012) measured mental representations of transplanted kidney for projective drawing test and measured serum creatinine and urea level. They reported that KT recipients with higher anxiety levels drew larger kidneys in their projective drawing tests along with significantly higher creatine and urea, supporting the relationship between anxiety and psychological rejection as an outcome. Látos et al. (2016) later confirmed such a relationship using self-reported questionnaires of anxiety and psychological rejection.

Fatigue

Prevalence and symptom measurement.—The prevalence of fatigue in KT recipients was measured in nine studies and ranged from 5.9% to 59% (Table 3). Four out of nine studies showed a prevalence of 50% or higher fatigue (Afshar et al., 2012; Chan et al., 2013; Du et al., 2021; Jordakieva et al., 2020). Fatigue was measured with either fatigue-specific or general symptom instruments. For example, when using fatigue-specific instruments, fatigue severity was measured using the Checklist Individual Strength in two studies (Goedendorp et al., 2013; van Sandwijk et al., 2019). Using these instruments, “severe” fatigue, considered to be clinically meaningful fatigue that interferes with functioning and requires treatment, was observed in 13%–59% of KT recipients from three studies (Goedendorp et al., 2013; Rodrigue et al., 2011; van Sandwijk et al., 2019). Among three studies that identified symptom clusters in KT recipients, two studies reported fatigue as the most prevalent and distressing of the symptoms present (Afshar et al., 2012; Koller et al., 2010), and one showed that fatigue ranked 4th in symptom prevalence and 5th in symptom severity among 18 symptoms.

In terms of fatigue dimensions, two studies measured five dimensions of fatigue using the Multidimensional Fatigue Inventory-20 (Chan et al., 2013, 2016); these fatigue dimensions included general fatigue, physical fatigue, reduced motivation, mental fatigue, and reduced activity. Specifically, Chan et al. (2016) focused on examining physical fatigue in KT recipients and reported a prevalence of 22%, a significantly higher level than in a healthy population. In Rodrigue et al.’s (2011) study, the Multidimensional Fatigue Symptom Inventory-Short Form was employed to measure fatigue dimensions: general, physical, mental, and emotional fatigue, as well as vigor. The researchers reported that KT recipients showed less general, physical, mental, and emotional fatigue and greater vigor than patients receiving dialysis. In van Sandwijk et al.’s study (2019), hemodialysis patients had the highest level of fatigue (50%), and 33.3% of KT recipients experienced severe fatigue, a level higher than the 12.1% observed in a healthy population.

Predictors and outcomes.—Fatigue showed patterns similar to those of other sickness symptoms, with its predictors falling into three categories. Demographic factors predicting fatigue included older age, male sex, and non-Caucasian ethnicity (Chan et al., 2013).

As to clinical factors, Chan et al. (2013) identified clinical predictors of multidimensional fatigue in KT recipients. These researchers reported that longer post-KT periods, decreased renal function (decreased estimated glomerular filtration rate), inflammation (elevated highly sensitive C-reactive protein), and reduced lean tissue index were associated with four dimensions of fatigue (but not mental fatigue). Higher body mass index was also reported to be a predictor of fatigue in KT recipients (Goedendorp et al., 2013).

Regarding psychosocial factors associated with fatigue, social factors included employment status and social support, and psychological factors included pain, sleep quality, mood, and perceived exertion. Jordakieva et al. (2020) examined differences in mental health associated with employment status and reported that unemployed KT recipients more commonly reported fatigue. Goedendorp et al. (2013) found that severely fatigued KT recipients tended to have lower social support and greater pain than KT recipients who were not severely fatigued. The researchers' results also showed that depressive symptoms and perceived poor sleep quality were predictors of severe fatigue in KT recipients (Goedendorp et al., 2013). Rodrigue et al. (2011) revealed that disturbed mood (including confusion, anger, anxiety, depressive symptoms, and vigor) was a predictor of poor sleep quality, and both sleep and mood contributed to severe fatigue. Chan et al. (2013) examined the contribution of psychosocial factors to fatigue and reported that general fatigue, reflecting a physical aspect of fatigue, was associated with poor sleep, and mental fatigue with its behavioral and cognitive aspects was associated with anxiety. In Chan et al.'s (2016) study, physical and mental fatigue were measured, and they reported that mental fatigue was a predictor of increased perceived exertion, and that perceived exertion was a predictor of physical fatigue. Moreover, Zhang et al. (2019) found positive associations of fatigue with rumination (defined as recurring negative thoughts).

With regard to outcomes associated with fatigue, five studies employed health-related quality of life as the main outcome, with greater fatigue contributing to impaired physical and mental health-related quality of life (Chan et al., 2013, 2016; Rodrigue et al., 2011; Tamura et al., 2018; van Sandwijk et al., 2019). One study reported that KT recipients with severe fatigue had more impaired social functioning than those with non-severe fatigue (Goedendorp et al., 2013). Robiner et al. (2021) revealed that pre- and post-KT medication adherence was negatively associated with energy-fatigue level after KT in correlation analysis.

Interrelationships among sickness symptoms.—Among the 38 studies, 5 identified interrelationships between depressive symptoms and anxiety using statistical methods. Two of those studies identified a symptom cluster in KT recipients using exploratory factor analysis (Afshar et al., 2012; Du et al., 2021). Their results showed that depressive symptoms and anxiety loaded to a "psychological" or "emotional" symptom cluster. Moreover, three studies confirmed this relationship using Spearman and Pearson correlation and multiple linear regression (Látos et al., 2016; Vásquez et al., 2013; Zimmermann et al., 2016). In addition, associations between depressive symptoms and fatigue were significant in seven studies using Pearson and Spearman correlation, multiple linear and logistic regression, and mediation analysis (Chan et al., 2013, 2016; Goedendorp et al., 2013; Robiner et al., 2021; Rocha et al., 2020; Rodrigue et al., 2011; Zhang et al., 2019).

Specifically, depressive symptoms were associated with four fatigue dimensions (general and physical fatigue, reduced activity and motivation) but not with mental fatigue (Chan et al., 2013). Zhang et al. (2019) investigated that fatigue had direct effect on depressive symptoms and indirect effect through rumination. Finally, the relationship between anxiety and fatigue was only supported by Chan et al. (2013), who investigated the characteristics (prevalence, predictors, and outcomes) of fatigue in KT recipients. Using multiple linear and logistic regressions, the results identified significant relationships between mental fatigue and anxiety. Although Rodrigue et al. (2011) measured depressive symptoms and anxiety as mood disturbances together with anger, vigor, and confusion, the results showed that total mood disturbances were related to higher fatigue using multiple logistic regression.

Discussion

This scoping review is the first to provide a synthesis of existing evidence for sickness symptoms in KT recipients, including symptom prevalence, predictors and outcomes, and interrelationships. As to our first research question, fatigue was found to be the most prevalent symptom, followed by anxiety and depressive symptoms. We were able to establish that sickness symptoms are moderately to highly prevalent after KT and warrant further investigation, as they may have a significant impact on health-related quality of life, medication adherence, and important clinical outcomes such as graft rejection and loss and mortality (Tang et al., 2018). Fatigue has been consistently reported as the most debilitating symptom among people with CKD and end-stage kidney disease on dialysis (Joshwa & Campbell, 2017; Lockwood et al., 2019). Both quantitative and qualitative study results showed that fatigue is a key driver of symptom clusters in patients with end-stage kidney disease (Almutary et al., 2017; Ng et al., 2020).

We identified highly heterogeneous reports of sickness symptom prevalence after KT, likely owing to differences in study designs and populations and lack of use of standardized instruments to measure symptoms. Moreover, inconsistent use of guidelines for interpretation of the clinical significance of symptom scores was problematic across studies. For example, even though a number of studies measured depressive symptoms and anxiety using the HADS and symptom measurements can serve as indicators for needed clinical action and supportive care, the use of varying cutoff points can make clinicians' decision-making about symptom management challenging. In symptom science, use of common data elements (CDE) is recommended, as standardized variables are operationalized and measured consistently across studies. Standardization of variables enables generalization of research findings by means of symptom comparison among studies (Redeker et al., 2015). Thus, the use of standardized, validated symptom instruments is critical to advancing symptom science. We encourage symptom scientists to refer to existing CDE resources, including the National Institutes of Health Common Data Elements Repository (https://cde.nlm.nih.gov/home), PROMIS measures (https://commonfund.nih.gov/promis/index), and the PhenX tool kit (https://www.phenxtoolkit.org), as examples of CDE tools to consider when designing studies interrogating symptom experience.

Regarding our second research question, a number of the reviewed studies examined the influence of demographic factors on sickness symptoms in KT recipients. Our review found

that men tended to have higher fatigue than women (Chan et al., 2013) and that women tended to have greater depressive symptoms and anxiety than men (Argyropoulos et al., 2018; Brito et al., 2019). These results are consistent with research trends in the examination of the effects of biological sex. However, the reviewed studies did not adequately highlight the potential importance of sex in their interpretations, indicating the need for greater attention to biological sex in future studies.

With regard to clinical predictors, our review revealed that KT recipients are more likely to experience sickness symptoms after a long post-KT period. This finding is supported by research on age-related factors, as increasing age has been found to lead to complications that create higher risk of sickness symptoms (Karim et al., 2014; Veroux et al., 2012). However, given that the studies focusing on transplant-related factors were cross-sectional in design (Anvar-Abnavi & Bazargani, 2010; Chan et al., 2013), such design cannot account for symptom patterns along the post-KT trajectory of treatment and outcomes (Griva et al., 2011; Kugler et al., 2009; Wang et al., 2020). Thus, additional longitudinal research focusing on the effects of immunosuppressive therapy on sickness symptoms is needed to help health care providers understand KT recipients' dynamic symptom phenotype. Moreover, biological markers—specifically renal function and inflammation—reflecting CKD progression have been associated with greater sickness symptom severity in KT recipients as a subset of CKD patients. CKD is a chronic proinflammatory state that involves the accumulation of uremic toxins and dysregulation of the hypothalamus–pituitary–adrenal axis, and these were found to result in increased risk of sickness symptom development in patients with CKD (Zalai et al., 2012). Overall, the information generated from investigating the relationships between transplant-related and biological indicators and sickness symptoms would allow nurses to assess KT recipients' risk of experiencing these symptoms and to proactively intervene.

We determined that the relative dearth of research regarding biological markers in KT recipients leaves significant gaps in our understanding of biological mechanisms that drive sickness symptom occurrence, as we found that fatigue was the only sickness symptom investigated with respect to biological markers in the reviewed studies (Goedendorp et al., 2013). It is important that nurse scientists understand the biological factors associated with symptoms because they may be modifiable and conducive to treatment (Miaskowski et al., 2017). For example, in oncology, researchers have discovered that the immune regulation response to cancer and the use of chemotherapy can interrupt the gut microbiota (microbiomics) to release microbiota-derived metabolites (metabolomics) molecules that may stimulate the brain to produce neuropeptides, contributing to sickness symptoms (Bai et al., 2020; Petra et al., 2015; Song & Bai, 2021). Based on this understanding, researchers fashioned a 12-week program of probiotics administration to reduce sickness symptoms in colorectal cancer survivors (Lee et al., 2014). With the application of this approach to KT recipients, examination of biological factors influencing sickness symptoms—such as the gut microbiota—would serve to guide nephrology researchers in designing individualized interventions to mitigate sickness symptom-induced symptom burden.

Surprisingly, only a small number of the studies reviewed evaluated the effects of different immunosuppression regimens and agents as predictors of sickness symptom experience.

Among the selected studies, only five included data on immunosuppressive regimens, and only two studies considered immunosuppressive regimens in relation to multiple symptoms observed in KT recipients (Chan et al., 2016; Du et al., 2021; Goedendorp et al., 2013; Koller et al., 2010; Reber et al., 2016). The shortage of studies on relationships between immunosuppression side-effects and sickness symptoms may be explained by symptom instruments employed in the reviewed studies. Only two studies used the Modified Transplant Symptom Occurrence and Distress Scale (MTSODS) questionnaire to measure patient-perceived symptoms associated with immunosuppressive agents (Du et al., 2021; Koller et al., 2010). As we recognize that the side-effects of different immunosuppressive regimens can impact KT recipients' symptom experience, using the MTSODS can help researchers capture not only sickness symptoms but also a full range of symptom burdens posed by immunosuppressive therapy in KT recipients (Wang et al., 2021).

As psychosocial predictors, poor sleep quality and pain have been strongly related to fatigue and depressive symptoms and have been collectively investigated with sickness symptoms in cancer populations (Starkweather et al., 2013). Sleep dysfunction and pain have been identified as important symptoms after KT and may have synergistic effects with sickness symptoms that contribute to poor posttransplant outcomes. We limited our review to the symptoms of depression, anxiety, and fatigue but endorse the inclusion of sleep dysfunction and pain in the constellation of sickness symptoms.

In addition, psychosocial factors such as being single, living alone, being unemployed, lacking support from family and friends, and having low informational support predicted sickness symptoms in KT recipients. Our results are aligned with Picariello et al.'s (2017) critical review of research involving patients with end-stage kidney disease receiving renal replacement therapy (i.e., hemodialysis, peritoneal dialysis, and KT). These researchers concluded that social and situational factors such as marital status, living situation, and social support are predictors of fatigue and could co-occur with psychological factors, including depressive symptoms and anxiety. For example, patients with CKD who live alone and lack social support may experience greater impacts of illness and may be less motivated to improve their behaviors, in turn increasing their symptom burden and its negative impact on their health outcomes. Thus, psychosocial factors should be an important consideration when evaluating sickness symptoms.

As we expected, we consistently observed that health-related quality of life was a main outcome of interest in studies of each sickness symptom in KT recipients (Brito et al., 2019; Chan et al., 2013, 2016; Jana et al., 2014; Rocha et al., 2020; Rodrigue et al., 2011; Tamura et al., 2018; van Sandwijk et al., 2019; Zimmermann et al., 2016). Our review results provide aggregated information supporting the need to measure health-related quality of life and sickness symptoms as part of usual care for KT recipients. Moreover, medication adherence is uniquely important in KT recipients. Recipients are placed on lifelong regimens of immunosuppressive medication, and nonadherence to this medication has been associated with a 60% increase in risk of graft failure (Pinsky et al., 2009). In the reviewed studies, findings regarding the contribution of sickness symptoms to medication nonadherence were mixed, with two studies reporting a significant association between them and two others

reporting no such association. Thus, we conclude that more research is needed to determine the relationships of sickness symptoms to medication adherence in KT recipients.

As to the third research question of our review, we arrived at a rationale for interrelationships among depressive symptoms, anxiety, and fatigue in KT recipients. However, we were not able to assess sickness symptoms as a cluster due to the reviewed studies' use of correlation and regression analyses to examine these interrelationships. These statistical methods may not be sufficient to verify sickness symptom clusters in KT recipients. As alternatives, cluster analysis, latent profile analysis, and latent class analysis have been recommended for the identification of a prespecified symptom cluster, as the analysis applied must be able to categorize patients based on the overall severity of the symptoms in that cluster (Miaskowski, 2016). Thus, our review results highlight the importance of employing adequate statistical methods in future research to confirm the clustering tendency of sickness symptoms in KT recipients.

This scoping review has limitations that should be noted. First, our review included only observational studies published in English in peer-reviewed journals. Intervention studies, articles published in other languages, and unpublished studies could shed additional light on the characteristics of sickness symptoms in KT recipients. Second, we only included studies of adult KT recipients. The sickness symptom experience may be different in pediatric KT recipients, a population that merits future research attention.

In conclusion, we provide an overview of the sickness symptom experience in KT recipients based on the preponderance of evidence available from the 38 reviewed studies. To support the recent movement toward recognizing unpleasant symptoms in nephrology declared by the World Kidney Day Steering Committee, our scoping review's results provide preliminary evidence for the characterization of sickness symptoms in KT recipients and reveal research gaps in this area (Kalantar-Zadeh et al., 2021, 2022). Our symptom science approach within nephrology has future implications for clinicians to understand KT recipients' voice with regard to sickness symptom-induced burden, and ultimately contribute to the development of interventions to reduce their burden. Moreover, our findings will inform health care policy makers to make decisions about allocating resources with respect to KT recipients' preferences while considering cost-effectiveness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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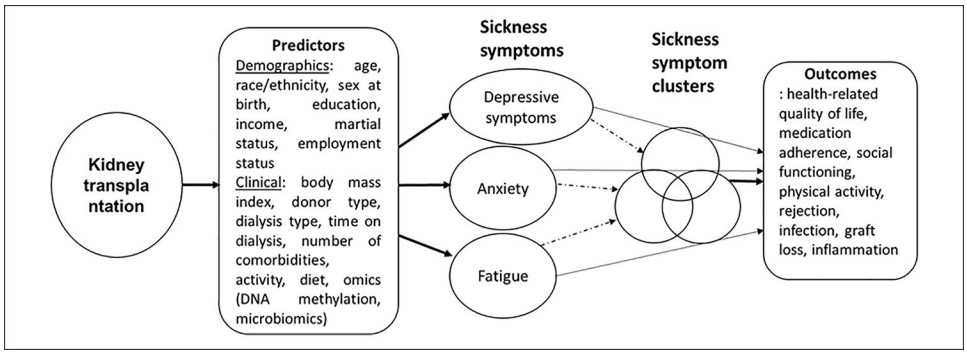

Figure 1.

Theoretical Framework of Sickness Symptoms in Kidney Transplant Recipients. Adapted from Corwin et al.'s (2021) theoretical framework.

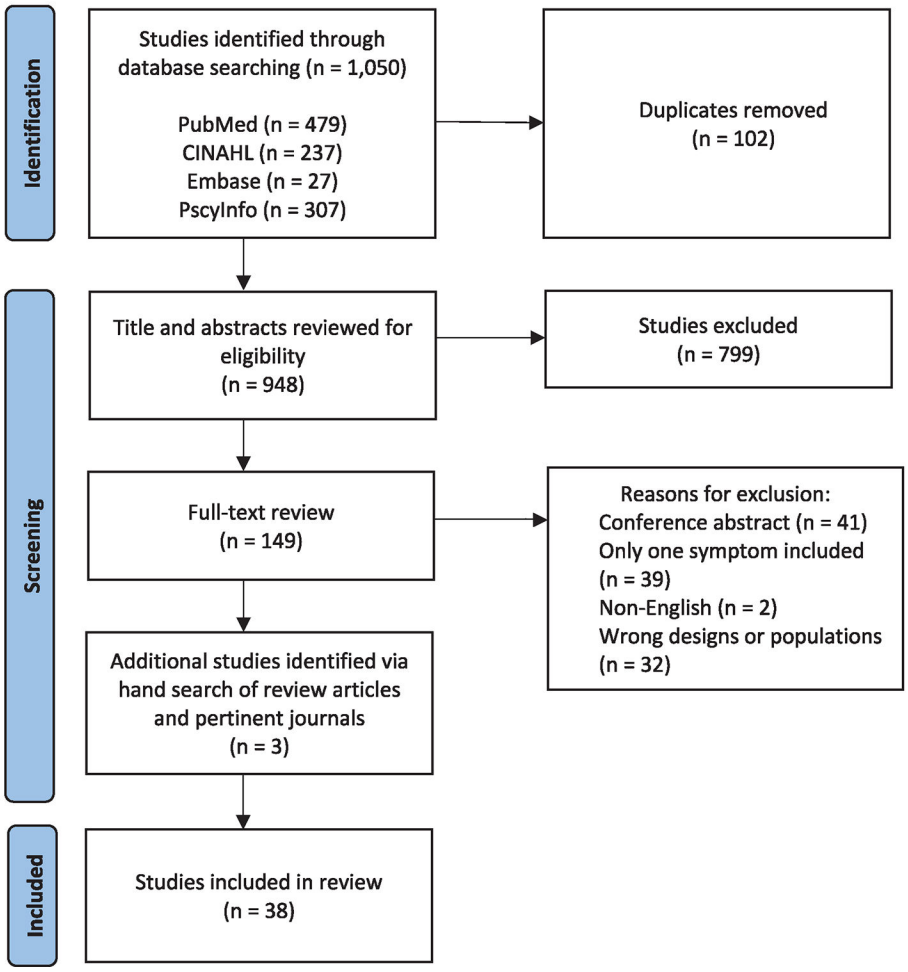

Figure 2.
Study Screening Flow Diagram.

Table 1.

Example Search Strategy in PubMed.

#1	Renal transplant* [tiab] OR Kidney transplant* [tiab] OR Kidney graft* [tiab] OR Renal graft* [tiab] OR kidney transplant* patient* [tiab] OR renal transplant* patient* [tiab] OR (Kidney Transplantation [Mesh])
#2	“Anxiety”[Mesh] OR “Anxiety Disorders”[Mesh] OR anxious* [tiab] OR anxiety [tiab]
#3	“Depression”[Mesh] OR “Depressive Disorder”[Mesh] OR Depress*
#4	“Fatigue” [Mesh] OR Fatigue* [tiab] OR Vitality [tiab] OR low energy [tiab] OR emotional fatigue* [tiab]
#5	Search #2 OR #3 OR #4 (Filter: publication date from 2009 to date of the search)
#6	Search #1 AND #5

Table 2.

Study Characteristics ($N = 38$).

Authors (Year), Country	Study Aim	Study Design	Sample	Age of KTRs (Years, $M \pm SD$)	Male KTRs (n, %)	Time Since KT ($M \pm SD$)
Afshar et al. (2012), U.K.	Assess symptom prevalence in KTRs	Cross-sectional	110 KTRs at least 1-year post-KT	47 ± 14	60 (55)	8 years
Alavi et al. (2009), Iran	Compare anxiety, depressive symptoms, HRQOL, and activities of daily living between HD patients and KTRs	Cross-sectional	63 HD patients, 100 KTRs at least 2 months post-KT	40.6 ± 14	59 (59)	64.7 ± 59.5 months
Anvar-Abnavi and Bazargani (2010), Iran	Evaluate the prevalence of depressive symptoms and anxiety in KTRs	Cross-sectional	200 KTRs	Range 17–73	109 (54.5)	N/R
Argyropoulos et al. (2018), Greece	Estimate differences in anxiety and depressive symptoms between HD patients and KTRs and investigate associations with sociodemographic variables	Cross-sectional	130 HD patients, 100 KTRs with a successful kidney graft at least 1-year post-KT	56.2	60 (60)	N/R
Barutcu Atas et al. (2021), Turkey	Investigate the association between perceived stress and sleep quality, insomnia, anxiety, depressive symptoms, and kidney function in KTRs during the Covid-19 pandemic	Cross-sectional	160 KTRs with a functioning kidney graft at least 3 months post-KT	44.2 ± 13.3	65 (61.3)	7.7 ±5.6 years
Brito et al. (2019), Brazil	Investigate the prevalence of depressive symptoms and anxiety among patients undergoing renal replacement therapy	Cross-sectional	130 dialysis patients, 75 KTRs at least 3 months post-KT	51.3	42 (56)	77.6 ± 38.0 months
Chan etal. (2013), U.K.	Investigate the nature, severity, prevalence, and clinical awareness of fatigue in medically stable KTRs and examine predictors and impacts of fatigue on QOL	Cross-sectional	106 KTRs with a functioning kidney graft at least 1-year post-KT	51 ± 14	59 (56)	Median 6.5 years
Chan etal. (2016), U.K.	Investigate the etiology of physical fatigue in KTRs through examination of muscle mass, muscular and cardiovascular function, and perceived exertion	Cross-sectional	52 healthy controls, 55 KTRs with a functioning kidney graft at least 1-year post-KT	46 ± 14	31 (57)	Median 2 years
Czyżewski et al. (2018), Poland	Assess HRQOL in KTRs	Cross-sectional	118 KTRs	45.3 ± 13.4	55 (46.6)	7.5 ± 6.6 years
Du et al. (2021), China	Explore symptom clusters in KTRs	Cross-sectional	295 KTRs	45.01 ± 12.24	183 (62.03)	<5 years: 65% >6 years: 35%
Goedendorp et al. (2013), Netherlands	Determine the prevalence of severe fatigue and investigate the relationship of severe fatigue to functional impairment and work status in KTRs	Cross-sectional	278 KTRs who received a KT in the previous 3-years	54 ± 12	119 (66)	1.6 ± 0.9 years
González-De-Jesús et al. (2011), Mexico	Assess the presence of emotional distress in ESRD patients and the effect of KT on symptoms	A two-phase longitudinal study	Phase 1: 75 ESRD patients Phase 2: 14 KTRs among the 75 ESRD patients	31.36 ± 13.02	10 (71.4)	N/R
Gurkan et al. (2015), Turkey	Determine levels of anxiety and depressive symptoms in and stress coping strategies used by HD patients and KTRs	Cross-sectional	138 HD patients, 76 KTRs	38.4 ± 11.9	47 (61.8)	7.84 ± 1.87 years

Authors (Year), Country	Study Aim	Study Design	Sample	Age of KTRs (Years, *M* ± *SD*)	Male KTRs (*n*, %)	Time Since KT (*M* ± *SD*)
Jana et al. (2014), India	Determine anxiety and depressive symptoms levels and their relationship with QOL in KTRs	Cross-sectional	105 KTRs	35.3 ± 9.75	76 (72.4)	Median 23 months
Jordakieva et al. (2020), Austria	Assess individual factors, including QOL and mental health, associated with employment after KT	Cross-sectional	139 KTRs at least 6 months post-KT	43.2 ± 9.07	80 (57.6)	N/R
Klewitz et al. (2019), Germany	Investigate satisfaction with information received about immunosuppressive medication among patients after KT	Cross-sectional using secondary data	440 KTRs	51 ± 15	236 (59.4)	53 ± 56 months
Koller et al. (2010). Switzerland	Evaluate the symptom experience related to adverse effects in adult KTRs on maintenance immunosuppressive therapy	Cross-sectional using secondary data	356 KTRs at least 1-year post-KT	52.92 ± 13.53	207 (59)	N/R
Kovacs et al. (2011), Hungary	Compare HRQOL between waitlisted patients receiving dialysis and KTRs	Cross-sectional	187 pre-KT patients, 888 KTRs	49 ± 13	515 (58)	54 ± 64 months
Lai et al. (2020), Singapore	Compare emotional outcomes between LDKT and DDKT patients and identify predictors of emotional outcomes	Cross-sectional	182 KTRs at least 6 months post-KT (106 LDKT and 76 DDKT patients)	49.3 ± 11.8	90 (49.5)	84.85 ± 72.93 months
Látos et al. (2012), Hungary	Examine the relationships between emotional factors, body and illness representations, and renal function after KT	Cross-sectional	58 KTRs	50.8	34 (58.6)	N/R
Látos et al. (2016), Hungary	Examine representations of the transplanted kidney and their relationship to emotional and mood factors, illness perceptions, and the functioning of the transplanted kidney	Cross-sectional	164 KTRs who received DDKT more than 1-year previously	51.99 ± 16.32	94 (57.32)	Nonrejection group: 5.41 ±4.17 years Rejection group: 5.61 ± 4.67 years
Müller et al. (2015), Germany	Compare mental status before and after KT and investigate relationships of patient-re ported outcomes to sociodemographic and disease-related factors	Cross-sectional	101 pre-KT patients, 151 KTRs	53.3 ± 14.1	89 (58.9)	N/R
Müller et al. (2020), Germany	Examine the impact of KT on comorbid depressive symptoms and anxiety	Cross-sectional using secondary data	25 pre-KT patients, 13 LDKT patients, 114 DDKT patients	LDKT: median 53.5 DDKT: median 52.8	N/R	N/R
Ozcan et al. (2015), Turkey	Explore cognitive, depressive symptoms, and anxiety symptoms among patients on HD, on PD, and after KT	Cross-sectional	54 HD patients, 58 PD patients, 69 KTRs	50.19 ± 16.5	N/R	N/R
Pascazio et al. (2010), Italy	Compare anxiety, depressive symptoms, and emotional aspects between KTRs and healthy subjects	Cross-sectional	42 KTRs, 42 healthy controls	45.64 ± 8.36	16 (38.1)	48 ± 28 months
Reber et al. (2016), Germany	Investigate the prevalence and modifiable determinants of medication nonadherence in adult KTRs in follow-up care	Cross-sectional	74 KTRs at least 6 months post-KT	54.1 ± 12.8	49 (66.2)	5.5 ± 5.7 years
Robiner et al. (2021), USA	Compare associations of depressive symptoms and medication adherence with QOL between KTRs and pre-KT patients	Longitudinal using secondary data	Phase 1: 139 pre-KT patients Phase 2: follow up with 81 of the 139 ESRD patients	50.91 ± 14.0	17 (60.7)	6 months

Authors (Year), Country	Study Aim	Study Design	Sample	Age of KTRs (Years, *M* ± *SD*)	Male KTRs (*n*, %)	Time Since KT (*M* ± *SD*)
			Phase 3: 28 KTRs followed up 6 months post-KT			
Rocha et al. (2020), Brazil	Assess the relationship of HRQOL to depressive symptoms and self-esteem in KTRs	Cross-sectional	47 KTRs	45.47 ± 10.9	26 (55.3)	70.2% for more than 1-year
Rodrigue et al. (2011), USA	Examine fatigue and sleep quality in patients pre- and post-KT	Cross-sectional	100 pre-KT patients, 100 KTRs	53.1 ± 11.3	46 (46)	52% for more than 3 years
Scheel et al. (2018), Germany	Investigate the association between immunosuppressive medication nonadherence and psychosocial factors in KTRs	Cross-sectional	330 KTRs at least 1-year post-KT	52.9 ± 13.8	215 (65.2)	6.8 ± 6.2
Tamura et al. (2018), Japan	Compare HRQOL between HD patients and KTRs and identify relationships between sociodemographic factors and QOL components	Cross-sectional	68 KTRs	51.7 ± 13.5	41 (60)	Median 47.0 months
Tavallaii et al. (2009), Iran	Investigate the association of socioeconomic status with HRQOL and levels of anxiety and depressive symptoms in KTRs	Cross-sectional	242 KTRs	36.0 ± 14.0	165 (68.2)	35.0 ± 13.0 months
van Sandwijk et al. (2019), Netherlands	Compare QOL, fatigue, anxiety, and depressive symptoms level in five groups: HD patients, KTRs, cancer patients receiving chemotherapy, cancer patients in remission, and healthy controls	Cross-sectional	30 HD patients, 30 KTRs at least 1-year post-KT, 20 chemotherapy patients, 30 cancer patients in remission, 58 healthy controls	56 ± 17	19 (63)	1.5 years
Vásquez et al. (2013), Panama	Examine the prevalence of depressive symptoms and its relationship with sociodemographic factors among KTRs	Cross-sectional	119 medically stable KTRs	44.19 ± 13.45	58 (48.7)	57.8 months
Weng et al. (2013), USA	Examine the prevalence of self-reported medication nonadherence and its relationships with psychosocial factors and self-reported barriers	Cross-sectional	252 KTRs at least 6 months post-KT	Median 54.7	151 (59.9)	Median 2.9 years
Zhang et al. (2019), China	Assess the prevalence of depressive symptoms and investigate whether rumination mediates the association between fatigue and depressive symptoms in KTRs	Cross-sectional	207 KTRs at least 1-year post-KT	44.50 ± 10.54	143 (69.1)	67.6% for more than 5 years
Zhang et al. (2021), China	Identify factors associated with frailty in KTRs	Cross-sectional	185 KTRs	45.17 ± 12.95	122 (65.9)	7.86 ± 7.17 years
Zimmermann et al. (2016), Germany	Investigate differences in medical, sociodemographic, and emotional factors between LDKT and DDKT patients	Cross-sectional	241 KTRs at least 1-year post-KT (68 LDKT and 173 DDKT patients)	LDKT: 47.3 ± 14.2 DDKT: 55.5 ± 12.7	LDKT:42 (61.8) DDKT: 116 (67.1)	LDKT: 70.3 ± 52.9 months DDKT: 92.5 ± 84.4 months

Note: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; DDKT, deceased donor kidney transplantation; ESRD, end-stage renal disease; HD, hemodialysis; HRQOL, health-related quality of life; KT, kidney transplantation; KTR, kidney transplant recipient; LDKT, living donor kidney transplantation; M, mean; N/R, not reported; PD, peritoneal dialysis; QOL, quality of life; SD, standard deviation.

Table 3.

Prevalence of Sickness Symptoms ($N = 38$).

Symptom	Symptom Measures (Cutoff Score)	Studies Using Symptom Measures	Symptom Prevalence
Fatigue	CIS (cutoff score of 35)	Goedendorp et al. (2013)	Severe fatigue 13%
		van Sandwijk et al. (2019)	Severe fatigue 33.3%
	MFI-20 (cutoff score varying between 12 and 15 among fatigue dimensions)	Chan et al. (2013)	59%
		Chan et al. (2016)	Physical fatigue 22%
	MTSOSD-59R	Du et al. (2021)	54.92%
	FSI (cutoff score of 3)	Rodrigue et al. (2011)	Severe fatigue 59%
	POMS (N/R)	Tamura et al. (2018)	5.9%
	POSs-renal (cutoff score of 1)	Afshar et al. (2012)	55% (30% moderate to severe)
	Fatigue presence (yes/no)	Jordakieva et al. (2020)	55.4%
Depressive symptoms	HADS (cutoff score of 5)	Vásquez et al. (2013)	13.8%
	HADS (cutoff score of 7)	Barutcu Atas et al. (2021)	44.3
		Gurkan et al. (2015)	25%
	HADS (cutoff score of 8)	Müller et al. (2015)	13.4%
		Reber et al. (2016)	16.2%
		van Sandwijk et al. (2019)	16.7%
		Weng et al. (2013)	6.8%
		Zhang et al. (2021)	5.9%
		Zimmermann et al. (2016)	37.6%
	HADS (cutoff score of 11)	Jana et al. (2014)	8.57%
		Klewitz et al. (2019)	9.6%
		Scheel et al. (2018)	16.7%
	BDI (cutoff score of 10)	Anvar-Abnavi and Bazargani (2010)	75%
	BDI (cutoff score of 11)	Brito et al. (2019)	13.3%
	BDI (N/R)	Látos et al. (2016)	8.53%
	BDI-PC (cutoff score of 4)	Goedendorp et al. (2013)	13%
	BDI-II (cutoff score: mild [>10], moderate [>15])	Robiner et al. (2021)	BDI-II: mild 29% Moderate 14%
	MCMI-MD (base rate criteria of 75 or more)	Robiner et al. (2021)	7%

Symptom	Symptom Measures (Cutoff Score)	Studies Using Symptom Measures	Symptom Prevalence
	SCL-90	Alavi et al. (2009)	39%
	POSs-renal (cutoff score of 1)	Afshar et al. (2012)	32%
	BSI-18 (N/R)	Jordakieva et al. (2020)	4.53%
	DASS-21 (cutoff score of 10)	Lai et al. (2020)	26.8%
	POMS (cutoff *t*-score of 61)	Tamura et al. (2018)	8.8%
	MINI (N/A)	Vásquez et al. (2013)	11.8%
	PHQ-9 (cutoff score of 10)	Zhang et al. (2019)	21.7%
Anxiety	HADS (cutoff score of 8)	Müller et al. (2015)	25%
		Reber et al. (2016)	24.3%
		Weng et al. (2013)	17.9%
		Zhang et al. (2021)	7.6%
		Zimmermann et al. (2016)	50.4%
	HADS (cutoff score of 10)	Barutcu Atas et al. (2021)	23.6%
		Gurkan et al. (2015)	26.3%
	HADS (cutoff score of 11)	Jana et al. (2014)	8.57%
		Klewitz et al. (2019)	12.2%
		Scheel et al. (2018)	63.9%
	BAI (cutoff score of 10)	Brito et al. (2019)	20.3%
	BAI (cutoff score of 16)	Anvar-Abnavi and Bazargani (2010)	50%
	SCL-90 (N/R)	Alavi et al. (2009)	40.6%
	POSs-renal (cutoff score of 1)	Afshar et al. (2012)	36%
	BSI-18 (N/R)	Jordakieva et al. (2020)	4.03%
	DASS-21 (cutoff score of 8)	Lai et al. (2020)	41.1%
	STAIS, STAIT (N/R)	Látos et al. (2016)	4.26%
	POMS (cutoff *t*-score of 61)	Tamura et al. (2018)	4.4%
	MINI (N/A)	Vásquez et al. (2013)	15.1%

Note: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BDI-PC, Beck Depression Inventory-Primary Care; BSI-18, Brief Symptoms Inventory-18 items; CIS, Checklist Individual Strength; DASS-21, Depression, Anxiety, and Stress Scale-21 items; FSI, Fatigue Symptom Inventory; HADS, Hospital Anxiety and Depression Scale; MFI-20, Multidimensional Fatigue Inventory-20 items; MCMI-MD, Millon Clinical Multiaxial Inventory III-Major Depression Scale; MINI, Mini-International Neuropsychiatric Interview; MTSOSD-59R, Modified Transplant Symptom Occurrence and Distress Scale-59 items Revised; N/A, not applicable; N/R, not reported; PHQ-9, Patient Health Questionnaire-9 items; POMS, Profile of Mood States; POSs-renal, Patient Outcome Scale symptom score-renal; SCL-90, Symptom Checklist-90 items; STAIS, Spielberger's State and Trait Anxiety Scale-State; STAIT, Spielberger's State and Trait Anxiety Scale-Trait.