ORIGINAL ARTICLE

Evaluating symptom burden in kidney transplant recipients: validation of the revised Edmonton Symptom Assessment System for kidney transplant recipients – a single-center, cross-sectional study

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SUMMARY

We assessed the validity of the Edmonton Symptom Assessment System (ESAS-r) in kidney transplant recipients (KTR). A cross-sectional sample of 252 KTR was recruited. Individual ESAS-r symptom scores and symptom domain scores were evaluated. Internal consistency, convergent validity, and construct validity were assessed with Cronbach's α, Spearman's rank correlations, and a priori-defined risk group comparisons. Mean (SD) age was 51 (16), 58% were male, and 58% Caucasian. ESAS-r Physical, Emotional, and Global Symptom Scores demonstrated good internal consistency (α > 0.8 for all). ESAS-r Physical and Global Symptom Scores strongly correlated with PHQ-9 scores (0.72, 95% CI: 0.64–0.78 and 0.74, 95% CI: 0.67–0.80). For a priori-defined risk groups, individual ESAS-r symptom score differed between groups with lower versus higher eGFR [pain: 1 (0–3) vs. 0 (0–2), delta = 0.18; tiredness: 3 (1–5) vs. 1.5 (0–4), delta = 0.21] and lower versus higher hemoglobin [tiredness: 3 (1–6) vs. 2 (0–4), delta = 0.27]. ESAS-r Global and Physical Symptom Scores differed between groups with lower versus higher hemoglobin [13 (6–29) vs. 6.5 (0–18.5), delta = 0.3, and 9 (2–19) vs. 4 (0–13), delta = 0.24] and lower versus higher eGFR [11 (4–20) vs. 6.5 (2–13), delta = 0.21, and 7 (2–16) vs. 3 (0–9), delta = 0.26]. These data support reliability and construct validity of ESAS-r in KTR. Future studies should explore its clinical utility for symptom assessment among KTR.

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Introduction

Patients with end-stage kidney disease (ESKD) frequently experience high symptom burden that may lead to impaired health-related quality of life (HRQOL), poor clinical outcomes, and increased healthcare use [1–9]. Kidney transplantation (KT) is the optimal renal replacement therapy (RRT) option for many patients with ESKD as it improves survival and HRQOL [10–16]. Despite its overall benefits, KT is not a cure for ESKD and many kidney transplant recipients (KTR) still experience physical and emotional symptoms [17–24].

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Physical and emotional symptoms are frequently unrecognized by healthcare professionals and remain unmanaged, potentially impacting clinical outcomes [8,25,26]. Patient-reported outcome measures (PROMs) capture patients' perception of symptom burden and severity [27–30]. Their use may improve communication between patients and providers and may lead to better symptom management, patient satisfaction, HRQOL, and survival [31–37]. Nonetheless, the validity, reliability, and measurement characteristics of PROMs need to be assessed within each specific patient population prior to their research or clinical use.

The Edmonton Symptom Assessment System (ESAS) measures physical and emotional symptom burden based on 9 uniquely defined symptoms (see Methods) [38]. A revised version of the ESAS (ESAS-r) provides brief symptom descriptions in addition to listing each item [39–41]. The instrument was originally developed for use in palliative care and has since been validated in patients on dialysis, and includes symptoms that have been identified as relevant for patients with ESKD [42–47]. The ESAS-r has been incorporated into Cancer Care Ontario's "Your Symptoms Matter" survey, a set of PROMs used regularly to monitor symptom burden in patients with cancer [48]. Currently, the Evaluation of Routinely Measured Patient-reported Outcomes in Hemodialysis Care (EMPATHY) trial uses the ESAS-r for patients on maintenance dialysis for systematic symptom screening [49]. Since the ESAS-r is used among patients on dialysis in multiple jurisdictions, it may provide the opportunity for longitudinal follow-up of symptoms in patients with various stages of chronic kidney disease (CKD), improving continuity of care [50]. The use of the ESAS-r in clinical care may improve patient–physician communication, may facilitate better understanding of underlying medical or psychosocial factors potentially linked to symptom experience, and may help identify patients who benefit from additional assessment or support [51]. If validity and utility is confirmed, the ESAS-r could also be used in clinical studies to follow patients with ESKD through various stages of the CKD trajectory and allow clinicians to develop a better understanding of the evolution of their symptom burden.

Given its potential as an ultra-brief symptom assessment tool in patients with chronic conditions, the objective of our study was to assess the validity of the ESAS-r among KTR.

Patients and methods

Study design and population

This was a single-center, cross-sectional study of stable adult (≥18 years) KTR followed at the KT outpatient clinics of the Multi-organ Transplant Program, University Health Network in Toronto, Canada. A convenience sample was recruited between April 2016 and May 2018. We excluded multi-organ transplant recipients, patients who had their KT <30 days prior to enrollment, non-English speaking patients, and patients with a diagnosis of dementia and/or severe cognitive impairment or acute medical conditions. This study was approved by the University of Health Network Research Ethics Board (UHN REB #15-9645), and all patients provided written consent prior to their recruitment. The clinical and research activities that are reported in this study are consistent with the Principles and the Declaration of Istanbul regarding organ trafficking and transplant tourism.

Questionnaire administration

Patients were approached and gave written informed consent while waiting for their scheduled dialysis visits and completed the study questionnaire (sociodemographic questions, ESAS-r and legacy questionnaires) on an electronic data capture system (Data Driven Outcomes System, Techna Institute, University Health Network, Toronto) using tablet devices [52].

Sociodemographic and clinical characteristics

Self-reported sociodemographic characteristics included age, sex, educational attainment, ethnicity, marital status, and yearly income. We collected clinical information including blood hemoglobin levels, serum creatinine, comorbidity, and time since transplant from medical records. We used the Chronic Kidney Disease Epidemiology Collaboration equation [53] to calculate estimated glomerular filtration rate (eGFR). We also calculated the Charlson Comorbidity Index (CCI) to quantify comorbidity [54].

ESAS-r

The ESAS-r measures symptom severity for 9 items (pain, tiredness, nausea, shortness of breath, lack of appetite, drowsiness, depression, anxiety, and general well-being) using a 10-point Likert scale ranging from 0 (no symptom) to 10 (worst possible symptom) [38]. On this 0–10 Likert scale a score of 4–6 is considered as a moderate, and 7–10 considered as a severe symptom [55]. Individual symptom scores can be combined to generate three domain scores, including ESAS-r Global (all nine symptoms; theoretical range: 0–90), ESAS-r

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Physical (six items: fatigue, pain, nausea, shortness of breath, lack of appetite, and drowsiness; theoretical range: 0–60), and ESAS-r Emotional (two items: anxiety and depression; theoretical range: 0–20) Symptom Scores [38,45,56].

Legacy measures

The Kidney Disease Quality of Life-36 (KDQOL-36) [57–59] includes the Medical Outcomes Study 12-Item Short Form (SF-12), a 12 item generic instrument yielding a physical component score (SF12-PCS), and a mental health component score (SF12-MCS), that are weighted combinations of the 12 items. The remaining 24 items generate three kidney disease targeted scales: Burden (four items) and Effect (eight items) and Symptoms and Problems (12 items) of Kidney Disease. Each score ranges from 0 to 100, with higher scores indicating better HRQOL [60]. The reliability and validity of the KDQOL-36 have been affirmed in previous studies [58,61,62] and was selected because of its extensive use among patients on dialysis and KTR [57,63–73]. We also included the SF-PCS and SF-MCS (part of KDQOL-36) as these subscales evaluate the physical or mental aspects of generic quality of life, respectively, to assess the mental and physical ESAS-r domain scores in our study sample.

The Patient Health Questionnaire 9-item scale (PHQ-9) screens for the presence and severity of depressive symptoms [74,75], whereas the Generalized Anxiety Disorder 7-item scale (GAD-7) assesses the presence and severity of anxiety-related symptoms [76,77]. Both tools use a 4-point Likert scale measuring the frequency of experiencing either depressive or anxious behaviors, where scores of 0, 1, 2, and 3 correspond to "not at all," "several days," "more than half the days," and "nearly every day." The theoretical range for PHQ-9 and GAD-7 is 0–27 and 0–21, respectively. These tools are frequently used in patients with chronic medical conditions, including those with CKD [78,79]. The PHQ-9 and GAD-7 were chosen as they are publicly available, concise, and include questions that are easy to understand by the general public. In addition, the tools have been recommended for the screening of depression or anxiety by the American Society of Clinical Oncology [80], the Canadian Association of Psychosocial Oncology [81], and the BC Renal Agency [82]. As with the KDQOL-36, the PHQ-9 and GAD-7 were used as legacy measures for the validation of PROMIS-57 and PROMIS-29 questionnaires among KTR [83].

The 5-Level EuroQol 5D questionnaire (EQ-5D-5L) measures health status by assessing five health-related domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression [84,85]. The tool uses a 5-point Likert scale, where a score of 1 corresponds to "no perceived problem" and 5 corresponds to "extreme perceived problem". A five-digit number describing a patient's health status (ranging from 11111 to 55555) is then converted into a single utility-based index ranging from 0 to 1, and the full health state is assigned a value of 1 [86]. The EQ-5D-5L was chosen because of its ease of use and utilization in KTR [87] and patients on dialysis [85]. Furthermore, its preference-based health utility score is recommended for use in health economic analyses with an available Canadian valuation set [86,88].

Statistical analysis

Sociodemographic and clinical characteristics, as well as PROM scores, were reported as mean [standard deviation (SD)] and median [interquartile range (IQR)]. Floor and ceiling effects were reported as the proportion of patients with minimum and maximum possible scores. Moderate and severe ESAS-r symptoms were defined based on previously established ranges of 4–6 and 7–10, respectively [55]. Differences between groups in the number of moderate/severe ESAS-r symptoms were analyzed using the Kruskal–Wallis test using the STATA "nptrend" command to assess nonparametric trend across groups. Internal consistency was estimated by computing Cronbach's alpha. Alpha values >0.9 are considered to indicate excellent, 0.80–0.89 good, and 0.70–0.89 acceptable internal consistency, respectively [89]. Convergent validity was assessed by computing Spearman's rank correlations between individual ESAS-r symptom scores and ESAS-r domain scores against relevant legacy scores. A strong, moderate, and weak correlation was indicated by a Spearman's rho of >0.7, 0.5–0.7, and <0.5, respectively [90]. We considered moderate or strong correlation as an indicator of acceptable convergent validity. We hypothesized that the ESAS-r Physical Symptom Score would have a moderate to strong negative correlation with the SF12-PCS, KDQOL-36 Symptoms and Problems of Kidney Disease, and EQ-5D-5L, whereas the ESAS-r Emotional Symptom Score would have a moderate to strong negative correlation with the SF12-MCS and a moderate to strong positive correlation with the GAD-7 and PHQ-9. We also hypothesized that the ESAS-r Global Symptom Score would have a moderate to strong negative correlation with all subscales of the KDQOL-36 and the EQ-5D-5L.

The dimensional structure of ESAS-r was examined with confirmatory factor analysis (CFA) models. CFA with maximum likelihood estimation was performed to test three different models proposed by earlier studies [91–93]. Model fit was assessed using the Comparative Fit Index (CFI), standardized root mean square residual (SRMR), and root mean square error of approximation (RMSEA). CFI values ≥0.95, SRMR values ≤0.08, and RMSEA values ≤0.06 were the criteria used to indicate good model fit [94].

Construct validity was assessed using a priori-defined risk group comparisons. The Mann–Whitney *U* test was used to compare individual ESAS-r symptom scores and ESAS-r domains between groups of participants that are expected to have different symptom burden.

A priori-defined risk groups were characterized by levels of certain clinical or PROM variables that define clinically different groups. Low hemoglobin levels are associated with symptoms such as fatigue, sleep disturbance, and poor physical functioning [95]. The CCI is a widely utilized tool to assess comorbidity [96]; patients with CCI score are expected to have increased symptom burden [97]. Declining graft function, characterized by the eGFR, is associated with more symptoms and decreased HRQOL [98]. Low and high hemoglobin levels, CCI scores, and eGFR were defined as <120 and >135 g/l, <3 and >4, and <45 ml/min/1.73 m^2 and >60 ml/min/1.73 m^2, respectively, Lastly, depression is associated with higher physical and emotional symptom burden [99]. We used a PHQ-9 cutoff value of <5 and a cutoff of >10 to indicate no depression ("nondepressed") and moderate/severe depression ("moderately/severely depressed"), respectively [100,101]. Cliff's delta was used to derive effect size estimates for ESAS-r score comparisons among all a priori-defined risk groups. Weak (delta = 0.147–0.329), moderate (delta = 0.33–0.473), and strong (delta ≥ 0.474) effect sizes were defined in accordance with Romano *et al.* [102].

All statistical analyses were performed using STATA 14.0 (StataCorp, College Station, TX, USA), and a two-sided *P* value of <0.05 was considered statistically significant.

Results

Study participants

Of the 318 potentially eligible patients approached, 54 refused to provide consent and 12 did not complete all assigned questionnaires. The final study cohort included 252 participants (Fig. 1). The mean (SD) age was 51 (16) years. A total of 145 (58%) participants were male, and 146 (58%) were Caucasian. The mean (SD) estimated glomerular filtration rate (eGFR) was 57 (23) and 59 (24%) participants had diabetes mellitus. A total of 167 (69%) participants underwent kidney transplant

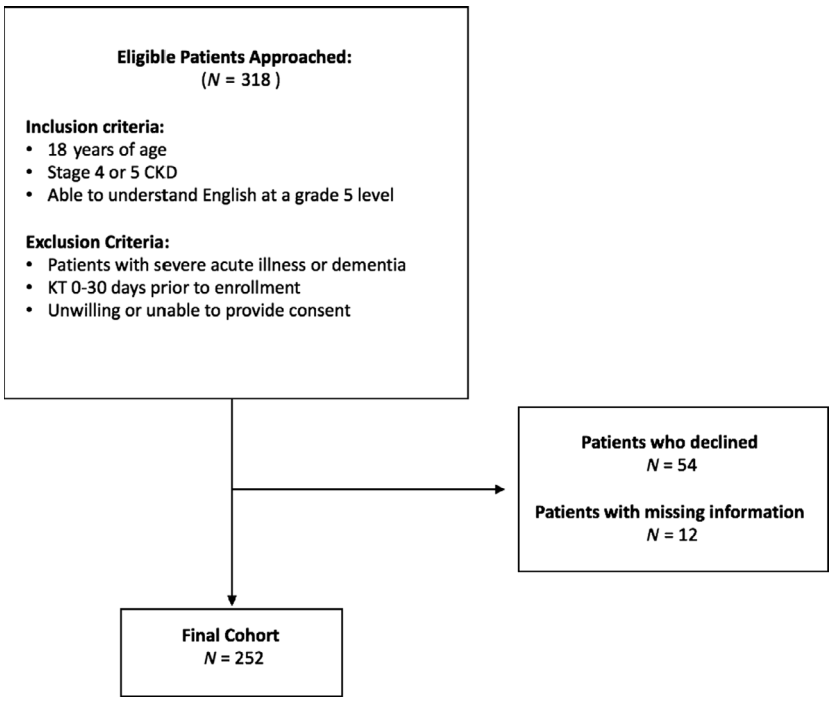

Figure 1 Patient flow diagram.

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Table 1. Study population characteristics.

Characteristics	*n* = 252
Male, *n* (%)	145 (58)
Age (years), median (IQR)	54 (41–64)
Education (less than high-school), *n* (%)	73 (29)
Diabetes mellitus (yes), *n* (%)	59 (24)
CCI Score (<3), *n* (%)	122 (49)
eGFR (ml/min/1.73 m^2), mean (SD)	57 (23)
Serum albumin (g/l), mean (SD)	42 (3)
Hemoglobin (g/l), mean (SD)	127 (17)
Ethnicity, *n* (%)	
Caucasian	146 (58)
Asian Canadian	50 (20)
African Canadian	23 (9)
Other/unknown	31 (12)
Marital status, *n* (%)	
Single or never married	63 (25)
Married or common-law	151 (62)
Divorced, widowed, or separated	30 (12)
Income (CAD/year), *n* (%)	
≤30 000	31 (17)
30 001–70 000	66 (37)
>70 000	84 (46)
Time since transplant (year), *n* (%)	
<1	49 (20)
1–3	27 (11)
>3	167 (69)
Smoking status, *N* (%)	
Yes	15 (6)
No, quit	75 (30)
No, never	156 (62)

CAD, Canadian dollars; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

more than 3 years prior to enrollment. The median CCI was 2 (IQR 2–4; Table 1).

Distribution of ESAS-r and legacy measures

The distribution of individual ESAS-r symptom scores is shown in Table 2 based on symptom severity and in Figs S1a,b and S2. Participants reported low symptom severity across most ESAS-r symptoms. The most frequently reported severe ESAS-r symptom was tiredness (11%), followed by pain (8%) and well-being (8%). Descriptive characteristics for ESAS-r domains and legacy scores are displayed in Table S1. Similar to the individual symptom scores, prominent floor effects were observed for ESAS-r domain scores.

Internal consistency

The ESAS-r Global, Physical, and Emotional Symptom Scores demonstrated good internal consistency (α = 0.87, 0.84, and 0.82, respectively, Table S1).

Table 2. Distributions of individual ESAS-r symptom scores.

	Score distributions			
	None 0	Mild 1–3	Moderate 4–6	Severe 7–10
ESAS-r symptom	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Pain	120 (49)	80 (32)	28 (11)	19 (8)
Tiredness	68 (27)	101 (40)	54 (22)	27 (11)
Drowsiness	121 (48)	82 (33)	32 (13)	16 (6)
Nausea	200 (80)	44 (17)	4 (2)	2 (1)
Lack of Appetite	185 (74)	33 (13)	20 (8)	12 (5)
Shortness of breath	156 (63)	66 (27)	16 (6)	11 (4)
Depression	158 (64)	59 (24)	23 (9)	7 (3)
Anxiety	132 (53)	87 (35)	20 (8)	9 (4)
Well-being	84 (33)	105 (42)	42 (17)	20 (8)

ESAS-r, Edmonton Symptom Assessment System Revised.

Convergent validity

The majority of individual ESAS-r physical symptoms had moderate to strong correlations with corresponding legacy items or scores (Table 3). The strongest correlations were seen for the ESAS-r pain and shortness of breath scores. Moderate correlation was seen for ESAS-r depression with PHQ-9 (r = 0.60, 95% CI: 0.50–0.68) and the ESAS-r anxiety with GAD-7 scores (r = 0.51, 95% CI: 0.40–0.60). The weakest correlation was observed for ESAS-r drowsiness item (Table 3).

The strongest correlation for the ESAS-r Physical (r = 0. 72, 95% CI: 0.64–0.78) and Global (r = 0. 74, 95% CI: 0.67–0.61) Symptom Score was observed with the PHQ-9 score. The ESAS-r Emotional Symptom Score demonstrated weak to moderate correlations with legacy measures. The strongest correlation was with the PHQ-9 (r = 0.67, 95% CI: 0.59–0.74; Table S2).

A higher number of moderate/severe symptoms was associated with worse scores on the SF12-MCS, SF12-PCS, GAD-7, and PHQ-9 questionnaires (P for trend <0.001 for all; Fig. 2a,b).

Structural validity

Goodness-of-fit indices for different proposed models of the ESAS-r are reported in Table S4 and Fig. S3a–c. The two-dimensional model (ESAS-r Physical and ESAS-r Emotional) had better fit indices compared with the 1 and 3 dimensional models with CFI, SRMR, and RMSEA values being 0.93, 0.05, and 0.11, respectively.

Table 3. Correlations (Spearman's Rho, 95% CI) between ESAS-r individual symptoms and related legacy measures.

	ESAS-r							
	Pain	Tiredness	Drowsiness	Nausea	Lack of appetite	Shortness of breath	Depression	Anxiety
KDQOL-36 symptom list items								
Pain	0.73 (0.66, 0.78)	–	–	–	–	–	–	–
Energy	–	0.64 (0.56, 0.71)	0.48 (0.37, 0.57)	–	–	–	–	–
Downhearted or blue	–	–	–	–	–	–	−0.45 (−0.55, −0.35)	–
Soreness in muscles	0.58 (0.49, 0.66)	–	–	–	–	–	–	–
Shortness of breath	–	–	–	–	–	0.68 (0.60, 0.74)	–	–
Faintness or dizziness	–	–	0.39 (0.28, 0.49)	–	–	–	–	–
Lack of appetite	–	–	–	0.29 (0.18, 0.40)	0.66 (0.58, 0.73)	–	–	–
Washed out or drained	–	0.63 (0.55, 0.70)	–	–	–	–	–	–
Nausea or upset stomach	–	–	–	0.40 (0.29, 0.50)	0.33 (0.21, 0.43)	–	–	–
Stress or worries caused by KD	–	–	–	–	–	–	0.53 (0.43, 0.61)	0.45 (0.34, 0.54)
EQ-5D-5L								
Self-care	0.29 (0.15, 0.42)	0.20 (0.06, 0.34)	0.24 (0.10, 0.37)	0.28 (0.14, 0.41)	0.16 (0.01, 0.29)	0.27 (0.13, 0.40)	0.18 (0.03, 0.31)	0.18 (0.03, .31)
Pain	0.74 (0.66, 0.80)	0.54 (0.43, 0.63)	0.43 (0.30, 0.54)	0.35 (0.22, 0.47)	0.42 (0.29, 0.53)	0.36 (0.23, 0.48)	0.43 (0.31, 0.54)	0.35 (0.22, 0.47)
Depression/anxiety	0.28 (0.15, 0.41)	0.45 (0.32, 0.55)	0.41 (0.28, 0.52)	0.36 (0.23, 0.48)	0.33 (0.19, 0.45)	0.23 (0.09, 0.36)	0.60 (0.50, 0.68)	0.43 (0.30, 0.54)
Mobility	0.49 (0.37, 0.59)	0.49 (0.37, 0.59)	0.26 (0.12, 0.39)	0.26 (0.12, 0.39)	0.32 (0.19, 0.45)	0.32 (0.19, 0.45)	0.16 (0.02, 0.30)	0.14 (−0.01, 0.28)
Usual activities	0.53 (0.42, 0.62)	0.53 (0.42, 0.62)	0.27 (0.13, 0.40)	0.27 (0.13, 0.40)	0.30 (0.17, 0.43)	0.30 (0.17, 0.43)	0.26 (0.12, 0.39)	0.25 (0.11, 0.38)
GAD-7	0.42 (0.31, 0.53)	0.53 (0.43, 0.62)	0.28 (0.15, 0.40)	0.28 (0.15, 0.40)	0.37 (0.25, 0.48)	0.21 (0.08, 0.33)	0.37 (0.24, 0.48)	0.51 (0.40, 0.60)
PHQ-9	0.45 (0.34, 0.56)	0.71 (0.64, 0.77)	0.60 (0.51, 0.68)	0.30 (0.17, 0.42)	0.49 (0.38, 0.59)	0.38 (0.26, 0.49)	0.60 (0.50, 0.68)	0.64 (0.56, 0.72)

EQ-5D-5L, EuroQol 5-level EQ-5D; ESAS-r, Edmonton Symptom Assessment System Revised; GAD-7, Generalized Anxiety Disorder 7-Item Scale; KDQOL-36, Kidney Disease Quality of Life 36-Item Short-Form Survey; PHQ-9, Patient Health Questionnaire 9-Item Scale.

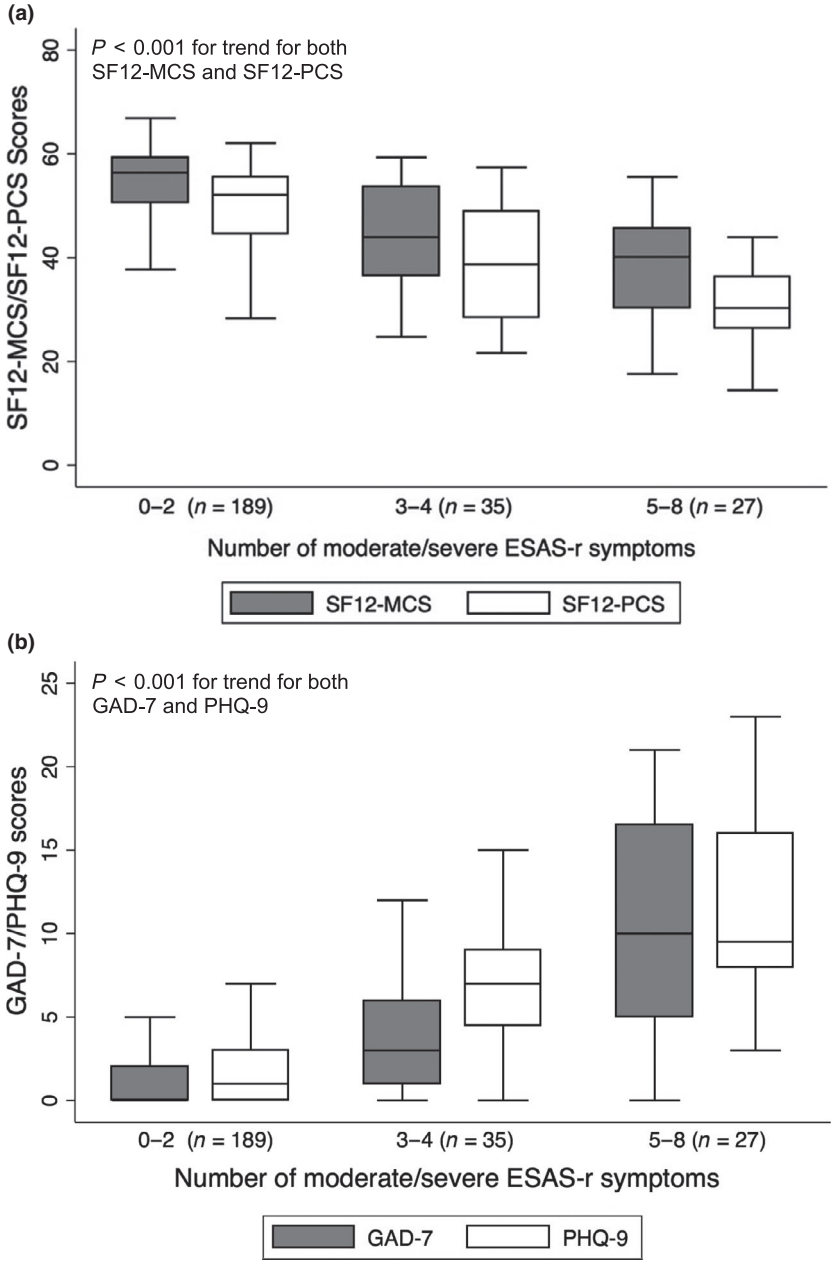

Figure 2 (a) Association between number of moderate to severe (ESAS-r symptom cutoff of> 3) symptoms and KDQOL-36 SF12-MCS and SF12-PCS scores. ESAS-r, Edmonton Symptom Assessment System Revised; SF12-PCS, Short Form-12 Physical Composite; and SF12-MCS, Short Form-12 Mental Composite. (b) Association between number of moderate to severe (ESAS-r symptom cutoff of> 3) symptoms and GAD-7 and PHQ-9 scores. ESAS-r, Edmonton Symptom Assessment System Revised; GAD-7, Generalized Anxiety Disorder 7-item scale; PHQ-9, Patient Health Questionnaire 9-item scale.

A priori-defined risk group comparisons

We compared individual ESAS-r symptom scores, ESAS-r domain scores, and legacy measures between groups of the sample formed by clinical variables or the PHQ-9 cutoff for moderate/severe depressive symptoms (Table 4a,b, and Table S3).

For individual ESAS-r physical symptoms, patients with lower eGFR displayed higher pain scores [lower eGFR: 1 (0–3), $n = 87$, vs. higher eGFR: 0 (0–2), $n = 97$, delta = 0.18] and patients with both lower eGFR and lower serum hemoglobin displayed higher tiredness scores [lower eGFR: 3 (1–5), $n = 88$, vs. higher eGFR: 1.5 (0–4), $n = 98$, delta = 0.21; lower

Table 4. (a) A priori-defined risk groups of individual ESAS-r item score. (b) A priori-defined risk groups of ESAS-r Global, Physical, and Emotional Symptom Scores.

	Serum hemoglobin (g/dl)			eGFR (ml/min/m^2)			CCI			Depression		
	<120	>135	delta	<45	>60	delta	<3	>4	delta	Non-depressed (PHQ-9 < 5)	Mod/sev. depressed (PHQ-9> 10)	delta
(A)												
ESAS-r Pain Median (IQR)	1 (0–3) *N* = 78	0 (0–2) *N* = 74	0.17	1 (0–3) *N* = 87	0 (0–2) *N* = 97	0.18	0 (0–2) *N* = 118	1 (0–4) *N* = 77	0.20	0 (0–1) *N* = 133	4 (1–6) *N* = 16	0.59
ESAS-r Tiredness Median (IQR)	3 (1–6) *N* = 79	2 (0–4) *N* = 75	0.27	3 (1–5) *N* = 88	1.5 (0–4) *N* =. 98	0.21	2 (0–4) *N* = 120	2 (0–5) *N* = 77	0.02	1 (0–2) *N* = 136	5.5 (4–8) *N* = 16	0.88
ESAS-r Drowsiness Median (IQR)	1 (0–4) *N* = 80	1 (0–2) *N* = 75	0.12	1 (0–3) *N* = 89	0 (0–2) *N* = 98	0.09	1 (0–3) *N* = 120	1 (0–3) *N* = 78	0.03	0 (0–1) *N* = 136	5 (3.5–6.5) *N* = 16	0.83
ESAS-r Nausea Median (IQR)	0 (0–1) *N* = 80	0 (0) *N* = 75	0.12	0 (0) *N* = 89	0 (0) *N* = 97	0.04	0 (0) *N* = 119	0 (0) *N* = 78	0.10	0 (0) *N* = 136	0 (0–3) *N* = 16	0.35
ESAS-r Lack of appetite Median (IQR)	0 (0–1.5) *N* = 80	0 (0) *N* = 75	0.21	0 (0–1) *N* = 89	0 (0) *N* = 97	0.09	0 (0) *N* = 119	0 (0–1) *N* = 78	0.07	0 (0) *N* = 136	1 (0–5) *N* = 15	0.07
ESAS-r Shortness of breath Median (IQR)	0 (0–2) *N* = 79	0 (0–2) *N* = 74	0.06	0 (0–2) *N* = 89	0 (0–1) *N* = 96	0.20	0 (0–1) *N* = 119	0 (0–1) *N* = 77	0.05	0 (0) *N* = 135	1.5 (0.5–5) *N* = 15	0.05
ESAS-r Depression Median (IQR)	0 (0–2) *N* = 77	0 (0–1) *N* = 74	0.16	0 (0–1) *N* = 86	0 (0–1) *N* = 97	0.03	0 (0–1) *N* = 120	0 (0–1) *N* = 76	0.07	0 (0) *N* = 136	4.5 (0.5–5.5) *N* = 16	0.07
ESAS-r Anxiety Median (IQR)	1 (0–2) *N* = 78	0 (0–2) *N* = 74	0.14	0 (0–2) *N* = 86	0 (0–2) *N* = 97	0.01	1 (0–2) *N* = 120	0 (0–2) *N* = 76	0.08	0 (0) *N* = 136	5 (3.5–6.5) *N* = 16	0.08
ESAS-r Well-being Median (IQR)	2.5 (1–5) *N* = 80	1 (0–2) *N* = 75	0.32	2 (0–4) *N* = 89	1 (0–2) *N* = 98	0.18	1 (0–3) *N* = 120	1 (0–4) *N* = 78	0.04	1 (0–2) *N* = 136	5 (3.5–6) *N* = 16	0.04
(B)												
ESAS-r Global symptom score Median (IQR)	13 (6–29) *N* = 75	6.5 (0–18.5) *N* = 72	0.30	11 (4–20) *N* = 83	6.5 (2–13) *N* = 94	0.21	6 (1–16) *N* = 115	12 (4–22) *N* = 75	0.12	4 (0–9) *N* = 132	33 (25–48) *N* = 15	0.93
ESAS-r Physical symptom score Median (IQR)	9 (2–19) *N* = 77	4 (0–13) *N* = 73	0.24	7 (2–16) *N* = 86	3 (0–9) *N* = 94	0.26	3 (0–9) *N* = 115	8 (2–15) *N* = 76	0.12	2 (0–5.5) *N* = 132	22 (10–31) *N* = 15	0.88
ESAS-r Emotional symptom score Median (IQR)	1 (0–5) *N* = 77	0 (0–3) *N* = 74	0.14	0 (0–2) *N* = 86	0 (0–3) *N* = 97	0.03	1 (0–2) *N* = 120	2 (0–4) *N* = 76	0.05	0 (0–1) *N* = 136	5.5 (9.5–12) *N* = 16	0.87

CCI, Charlson Comorbidity Index; delta, Cliff's delta; eGFR, estimated glomerular filtration rate; ESAS-r, Edmonton Symptom Assessment System Revised; IQR, interquartile Range; mod/sev, moderately/severely; PHQ-9, Patient Health Questionnaire 9-Item Scale.

serum hemoglobin: 3 (1–6), $n = 79$, vs. higher serum hemoglobin: 2 (0–4), $n = 75$, delta = 0.27]. Emotional symptoms were not different between any of the groups defined by clinical variables. However, as expected, emotional symptom scores were lower in "nondepressed" versus "moderately/severely depressed" groups [depression: 0 (0), $n = 136$, vs. 4.5 (0.5–5.5), $n = 16$, delta = 0.67; anxiety: 0 (0),

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n = 136, vs. 5 (3.5–6.5), n = 16, delta = 0.89] (Table 4a).

For ESAS-r domain scores, ESAS-r Global and Physical Symptom Scores were higher for groups with lower compared to higher hemoglobin [13 (6–29), n = 75, vs. 6.5 (0–18.5), n = 72, delta = 0.30, and 9 (2–19), n = 77, vs. 4 (0–13), n = 73, delta = 0.24, respectively]. All domain scores were higher for individuals identified as "moderately/severely depressed" compared with "nondepressed" (Table 4b).

Discussion

To the best of our knowledge, this is the first study to evaluate the ESAS-r, an ultra-brief symptom screening tool that poses minimal burden on patients [103] in KTR. Our results demonstrate that the ESAS-r Physical, Emotional, and Global Symptom domain scores display good internal consistency. Furthermore, construct validity and convergent validity were good for physical symptoms. However, the ESAS-r Emotional Symptom Score and the individual emotional symptom scores demonstrated weaker validity suggesting that the ESAS-r may have limited ability to assess emotional symptoms.

Based on our CFA-analysis, a good/acceptable fit was found for the two-dimensional model. However, summarizing the overall symptom burden of patients is also clinically relevant and based on clinical consideration we also treated ESAS-r as a unidimensional scale (ESAS-r Global Symptom Score) as suggested by others and as the scores are frequently used [104–107].

Convergent validity for most individual ESAS-r physical symptom items was good except drowsiness that was not strongly correlated with legacy items. Concerns about the ambiguity of this item has also been raised during the validation of the Spanish version [108]. This suggests that the wording of some ESAS-r items may need revision to include more comprehensive terminology for at least some of the symptoms.

The results of the a priori-defined risk group comparisons suggest good construct validity for individual ESAS-r physical symptom items and also for the Physical Symptom Score. In spite of the relatively small size of the groups, the KDQOL-36 subscales were significantly or near significantly different between most of the groups formed by clinical variables, confirming that the differences between these groups were large enough to be captured by sensitive enough tools. As expected, individual ESAS-r physical item scores and the Physical Symptom Score were different between the groups based on clinical characteristics [109].

Both individual ESAS-r emotional symptoms and the Emotional Symptom Score demonstrated only moderate correlations with corresponding legacy measures. The response to these items may also depend on culturally defined perceptions and norms of what it means to be depressed or anxious. Our results suggest that the ESAS-r emotional symptom and domain scores may not assess emotional symptoms adequately. We are conducting further detailed analysis to assess measurement characteristic of these scores in patients with CKD.

Our results suggest good construct validity for the ESAS-r Global Symptom Score. The internal consistency and discrimination of the Global Symptom Score, however, may be somewhat compromised with the inclusion of emotional items. These findings are in line with the findings by Zhang *et al.*, where the ESAS-r Physical Symptom Score was shown to be more predictive of healthcare use than the Global Symptom Score among patients on dialysis (Zhang J, El-Majzoub S, Li M, *et al.*, Unpublished conference abstract), suggesting the Physical Symptom Score may be a better measure of overall symptom burden.

It is also interesting to note that "nondepressed" versus "moderately/severely depressed" groups had significantly different scores for all ESAS-r individual symptom scores, ESAS-r domain scores, and legacy instrument scores. Depression is closely associated with self-reported symptoms and patient-reported measures as it is associated with increased symptom perception and awareness [100,110] and has been linked to lower QOL [4].

The use of the ESAS-r has been reported to improve patient-focused assessment and facilitate monitoring of symptoms and taking management actions in patients on dialysis [51]. PROMs such as the ESAS-r are central to patient-centered care as they harness the patient voice and perspectives and improve patient-clinician communication [111,112]. Moreover, these tools can identify symptoms that may not be readily discussed in the routine care of patients with CKD.

However, we also recognize potential limitations of the ESAS-r as a PROM. The prominent floor effects observed with many of the individual symptom scores may indicate that those symptoms are absent or mild among stable KTR. Comparable high floor effects were reported in studies enrolling clinically stable patients [113,114]. For ESAS-r emotional symptoms, the direct wording (anxiety and depression) may carry significant stigma and may increase the floor effect. The skewed distribution of the item scores may pose analytic difficulties when comparing ESAS-r scores between groups

and may also lead to nonresponsiveness used on a group/population level. However, having a "no symptom" category may still carry important information on a patient especially if followed throughout potential modality changes (i.e., from dialysis to transplant or vice versa). The low or absent level of a symptom, identified by "0" on an individual symptom score, may be utilized in a two-stage approach to screening when patients with this very low score will not require additional assessment for that particular symptom. For patients with a low (but not "0") score, a second assessment using a more precise PROM may be warranted, as indicated by our preliminary results assessing discrimination of several of the individual symptom scores [24,115,116].

This study has several strengths. Our sample is both ethnically and sociodemographically diverse, where 41% of our study population consisted of non-Caucasian participants and 29% were less than high-school educated. Furthermore, patients participated in the study while receiving their routine post-transplant care at our institution, demonstrating the potential feasibility and acceptability of using the ESAS-r in a real-world setting. Moreover, symptoms addressed in the ESAS-r include symptoms that have been reported to be of top priority of patients with ESKD such as pain, fatigue, and depression [46,109,117].

Nonetheless, there are important limitations to the current study that should be considered when interpreting our results. Relying on convenience sampling facilitated recruitment and we considered this a priority. However, this limits the generalizability as we excluded patients with significant acute conditions, including infections, to ensure that our sample only included clinically stable patients. These acute conditions would have likely increased the range of the observed scores. While we consider the stability of the current sample an important asset, subsequent studies that will evaluate the use of the instrument in clinical practice will need to assess the responsiveness of the ESAS-r to changes in health status. Furthermore, our decline rates were significant, but similar to other similar studies. We could not collect information for patients who refused to be a part of our study. Participants and nonparticipants may differ along sociodemographic and clinical characteristics, and this limits the generalizability of our study.

The order of questionnaires administered to each patient was identical with patients first completing the PHQ-9, followed by the GAD-7, the KDQOL-36, the EQ-5D-5L, and lastly the ESAS-r. It is possible that this may have introduced order bias, where previous questionnaires or items provide context for subsequent questionnaires or items and potentially may influence the answers. However, the legacy questionnaires used in this study are multi-item questionnaires, asking about multiple aspects of the construct assessed, whereas the ESAS-r asks one item for each symptom, using quite direct wording. Therefore, we believe that the risk of bias is likely minimal. In addition, as this was a cross-sectional validation of the ESAS-r, we did not assess test–retest reliability. Additional studies should also assess clinical utility of the ESAS-r by determining meaningful, condition-specific cutoffs to identify patients with significant symptom burden who will benefit from further assessment.

Conclusion

This study presents data to support the reliability and construct validity of the ESAS-r in KTR. Because of its brevity and ease of administration, ESAS-r may be considered in the clinical management of KTR. ESAS-r may be useful for rapid screening of specific symptoms, although condition-specific cutoff values will need to be established. Our findings indicate that the ESAS-r may be best used to assess individual physical symptoms and physical symptom burden but may not provide accurate assessment of emotional symptoms. The utility of the ESAS-r Global Symptom Score also needs further assessment in longitudinal studies, evaluating its association with subsequent clinical outcomes, such as healthcare use or mortality. Further research to confirm the psychometric properties of the ESAS-r in KTR is needed to confirm its appropriateness for clinical use.

Authorship

SD, MP, IM and MN: designed the research/study. VL, BT and HF: contributed to data acquisition. SD, MP, EV, OE and NE: analyzed the data. SD and MP: contributed to manuscript preparation. All authors contributed important intellectual content during manuscript drafting or revision and accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Conflict of interest

The authors have indicated they have no potential conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. (a) Distribution of ESAS-r Individual item scores and domain scores. (b) Distribution of legacy instrument scores.

Figure S2. Distributions of non-zero scores for individual ESAS-r symptoms.

Figure S3. (a) Confirmatory analysis for 1-dimensional model of the ESAS-r. (b) Confirmatory analysis for 2-dimensional model of the ESAS-r. (c) Confirmatory analysis for 3-dimensional model of the ESAS-r.

Table S1. Distribution and descriptive characteristics of ESAS-r domain scores and legacy instruments.

Table S2. Correlations (Spearman's Rho, 95% CI) between ESAS-r domain scores and legacy instrument scores.

Table S3. A-priori defined group comparisons of chosen legacy instruments.

Table S4. Goodness of fit indices for different proposed models of the ESAS-r.

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