Health-Related Quality of Life, Depressive Symptoms, and Kidney Transplant Access in Advanced CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study

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Rationale & Objective: Among individuals with chronic kidney disease (CKD), poor self-reported health is associated with adverse outcomes including hospitalization and death. We sought to examine the association between health-related quality-of-life (HRQoL) and depressive symptoms in advanced CKD and subsequent access to the kidney transplant waiting list.

Study Design: Prospective cohort study.

Setting & Population: 1,676 Chronic Renal Insufficiency Cohort (CRIC) study participants with estimated glomerular filtration rates ≤ 30 mL/min/1.73 m² at study entry or during follow-up.

Exposures: HRQoL ascertained by 5 scales of the Kidney Disease Quality of Life-36 Survey (Physical Component Summary (PCS), Mental Component Summary, Symptoms, Burdens, and Effects), with higher scores indicating better HRQoL, and depressive symptoms ascertained using the Beck Depression Inventory.

Outcomes: Time to kidney transplant wait-listing and time to pre-emptive wait-listing.

Analytic Approach: Time-to-event analysis using Cox proportional hazards regression.

Results: During a median follow-up of 5.1 years, 652 (39%) participants were wait-listed, of whom 304 were preemptively wait-listed. Adjusted for demographics, comorbid conditions, estimated glomerular filtration rate slope, and cognitive function, participants with the highest scores on the Burden and Effects scales, respectively, had lower rates of wait-listing than those with the lowest scores on the Burden (wait-listing adjusted hazard ratio [aHR], 0.70; 95% CI, 0.57-0.85; P < 0.001) and Effects scales (wait-listing aHR, 0.74; 95% CI, 0.59-0.92; P = 0.007). Participants with fewer depressive symptoms (ie, Beck Depression Inventory score < 14) had lower wait-listing rates than those with more depressive symptoms (aHR, 0.81; 95% CI, 0.66-0.99; P = 0.04). Participants with lower Burden and Effects scale scores and those with higher Symptoms and PCS scores had higher pre-emptive wait-listing rates (aHR in highest tertile of PCS relative to lowest tertile, 1.58; 95% CI, 1.12-2.23; P = 0.01).

Limitations: Unmeasured confounders.

Conclusions: Self-reported health in late-stage CKD may influence the timing of kidney transplantation.

A central priority of the recent Advancing American Kidney Health Initiative is to increase the rate of kidney transplantation as the first modality of kidney replacement therapy for people with end-stage kidney disease (ESKD) in the United States. 1 Currently, <10% of people with ESKD in the United States are either placed on a waiting list or undergo transplantation before starting dialysis2 despite national policy that permits appropriate kidney transplantation candidates to begin accruing time on the waiting list when their estimated glomerular filtration rate (eGFR) reaches ≥ 20 mL/min/1.73 m².3 Therefore, improving knowledge on which factors might promote or hinder early access to the kidney transplant waiting list is a public health priority.

Advanced chronic kidney disease (CKD) is associated with profoundly negative effects on health-related quality of life (HRQoL).4–7 As CKD progresses, people may be burdened by more dietary and travel restrictions, decrements in physical and cognitive function,8,9 and increasing dependence on caregivers. Prior studies have shown that poor HRQoL is associated with higher risk for cardiovascular events and death among individuals with CKD,5 and that individuals with depression before starting dialysis are more likely to be hospitalized10 and die after starting dialysis.11 Therefore, although the desire to improve HRQoL may motivate many people with CKD to pursue kidney transplantation, existing evidence suggests that poor HRQoL could also be a barrier to achieving kidney transplantation. However, no studies to date have examined the association between self-reported health in advanced CKD and access to the kidney transplant waiting list.

The goal of this study was to evaluate whether, independent of traditional markers of disease burden, differences in HRQoL and depressive symptoms in advanced
CKD influence the timing of subsequent kidney transplant wait-listing. Among participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study with stages 4-5 CKD, we assessed the independent association of HRQoL and depressive symptoms with time to wait-listing.

**METHODS**

**Study Population**

The CRIC Study is an ongoing multicenter prospective study of risk factors for CKD progression and cardiovascular disease. The design and methods of the study and inclusion criteria for study participants have been described previously. Briefly, the CRIC Study recruited 3,939 participants aged 21 to 74 years with eGFRs between 20 and 70 mL/min/1.73 m² from 2003 to 2008. Study participants completed extensive clinical evaluations at enrollment, including physical and laboratory assessments and questionnaires about medical history. During yearly re-evaluation visits, participants provided updated medical histories and underwent repeat laboratory and physical assessments. All participants provided informed consent. The study protocol was approved by the University of Pennsylvania Institutional Review Board (IRB Protocol 807882) and is in accordance with the Declaration of Helsinki.

The current analyses were restricted to participants with eGFR ≤ 30 mL/min/1.73 m² at enrollment or during the course of CRIC Study follow-up. This cutoff was chosen to include individuals with stage 4 CKD, when guidelines suggest that patients should begin to be educated on options for kidney replacement therapy and referred for kidney transplantation evaluation. We estimated participants’ eGFR using the validated CRIC equation that includes serum creatinine level, serum cystatin C level, age, sex, and race.

Participants contributed time to the current analysis from the calculated date of eGFR eligibility (ie, eGFR ≤ 30 mL/min/1.73 m²), defined as the index date, until they were wait-listed, died, or the end of the follow-up period in January 2018. We estimated index dates by assuming a linear decline in kidney function between annual CRIC visits. Individuals who were wait-listed or underwent transplantation before having a CRIC eGFR ≤ 30 mL/min/1.73 m² and those who reported a new diagnosis of cancer were excluded from the cohort (Fig 1).

**Primary Exposures: HRQoL Domains and Depressive Symptoms**

The Kidney Disease Quality of Life-36 (KDQOL-36) is a measure of HRQoL that includes 2 generic scales from the 12-item Short Form Survey (SF-12) version 1 (Physical Component Summary [PCS] and Mental Component Summary [MCS]; 12 items total) and 3 kidney-specific scales (4-item Burden of Kidney Disease [Burden], 12-item Symptoms and Problems of Kidney Disease [Symptoms], and 8-item Effects of Kidney Disease [Effects]).

The first item of the SF-12 asks participants to rate their overall health: “In general, would you say your health is: Excellent, Very Good, Good, Fair, or Poor.” The PCS is a measure of functional status that includes items about physical well-being, including activity limits and the ability to accomplish physical tasks. The MCS includes items that rate respondents’ emotional well-being, including levels of depression, anxiety, energy, and

**Figure 1.** Participant inclusion diagram. Abbreviations: CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate; USRDS, US Renal Data System.
and somatic symptoms of depression.\textsuperscript{18} The BDI has 21 items that measure respondents’ depressive symptoms in the prior week. Each question has 4 possible responses to indicate different levels of intensity. To score the test, each answer is assigned a value ranging from 0 to 3, with a minimum score of 0 and a maximum score of 63. CRIC participants completed the BDI at study entry and every 2 years thereafter. We included each participant’s BDI score that was less than 24 months before the index date and closest in time to the index date. We examined BDI cutoff scores of ≥11 and ≥14 because both thresholds have been described in the literature to screen for depression and related health outcomes in CKD and ESKD populations, respectively.\textsuperscript{19–21}

**Outcomes**

Wait-listing, dialysis, and kidney transplantation dates were ascertained from CRIC medical event questionnaires, administered yearly to participants, and verified by linkage of CRIC data to the US Renal Data System (USRDS) data set. All-cause death was confirmed by report from next of kin, a review of hospital records if death occurred in the hospital, or through the Social Security Death Index.

Our primary outcome was time from the index date to wait-listing for a kidney transplant. Our secondary outcome was time from the index date to pre-emptive wait-listing for a kidney transplant. The USRDS data set provided exact dates of wait-listing, dialysis onset, and kidney transplantation through February 26, 2015. In cases for which wait-listing occurred after February 2015 (n = 379), we used the date of the first study visit at which the participant reported kidney transplant wait-listing as the event date. The follow-up period for the present study ended on January 7, 2018.

**Analytic Strategy**

Descriptive statistics were summarized as mean with standard deviation (SD) or median with interquartile range for continuous variables and as frequency and proportion for categorical variables. Continuous and categorical variables were compared using Kruskal-Wallis tests or χ\(^2\) test, as appropriate. All hypothesis tests were 2 sided, with a significance level of 0.05. We estimated wait-listing rates by KDQOL-36 scales, in tertiles, and by BDI threshold scores (ie, ≥11 and ≥14) using the Kaplan-Meier method and log-rank test to compare unadjusted survival curves. We then fit Cox proportional hazards models to evaluate the associations between HRQoL, depressive symptoms, and wait-listing for a kidney transplant.

We compared unadjusted models, models adjusted for sociodemographic characteristics (model 1), and models that were fully adjusted for clinically important covariates that may influence the likelihood of kidney transplant candidacy (model 2).\textsuperscript{5,8,22} Because we focused on estimating the effects of HRQoL and depressive symptoms on wait-listing (as opposed to the cumulative incidence of wait-listing),\textsuperscript{23} participants were censored at death, study withdrawal, or end of study follow-up. Participants were additionally censored at the time of dialysis for the secondary outcome of pre-emptive wait-listing. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc).

**Covariates**

Models 1 and 2 included participant age, sex, race/ ethnicity, income level, educational attainment, and insurance status immediately before the index date. Model 2 also included CRIC clinical site and the following variables,
ascertained as close to the index date as possible: history of diabetes, hypertension, ischemic heart disease, peripheral arterial disease, chronic obstructive pulmonary disease, cognitive impairment (defined as Modified Mini-Mental State Examination score < 80), nephrology care, systolic and diastolic blood pressure, body mass index, tobacco use, alcohol use, recreational drug use, living alone, eGFR at index visit (mL/min/1.73 m²), eGFR slope from baseline to index visit (mL/min/1.73 m² per year), 24-hour urinary protein excretion, serum albumin level, and glycated hemoglobin level.

Missing Data
Data were missing in <9% of participants for all variables with the exception of 24-hour urinary protein excretion (missing in 13% of participants). The following numbers of participants were missing values for the main exposure variables: KDQOL overall (n = 12), Burden (n = 8), Effects (n = 7), Symptoms/Problems (n = 6), SF-12 MCS (n = 29), SF-12 PCS (n = 29), and BDI (n = 76). Missing data were imputed using the fully conditional specification method of multiple imputation with 10 iterations. The final estimates were combined using Rubin’s formula.

Sensitivity Analyses
There were 45 CRIC participants who reported dates for kidney transplantation but were missing dates of wait-listing in the CRIC data set. In the primary analyses, we used the date of kidney transplantation as the date of wait-listing for these participants because most (64%) were living donor recipients and kidney transplantation programs were not required to wait-list living donor candidates before kidney transplantation until September 2014. In sensitivity analysis, we censored these participants at the last CRIC visit date before the kidney transplantation date. Further, changes in the US kidney allocation system that occurred during our study period may have influenced wait-listing trends. Therefore, we examined whether post–kidney transplantation events (defined as post-2014) modified associations between HRQoL, depressive symptoms, and time to wait-listing. We tested era effects by including interaction terms in separate models that were adjusted for all other covariates. We tested interaction terms using Wald tests. Finally, we examined whether associations between HRQoL, depressive symptoms, and wait-listing were consistent in a subgroup that was younger (aged ≤ 65 years) at the index date.

RESULTS
Baseline Characteristics
Among 3,939 participants enrolled in CRIC, 1,838 reached eGFR ≤ 30 mL/min/1.73 m², and 1,676 met inclusion criteria for the study. Mean age of included participants was 59 years, 48% were women, and 46% were non-Hispanic Black. Average time from KDQOL-36 to the index date was 189 (SD, 223) days, and time from BDI to index date was 127 (SD, 145) days. Table 1 displays participant characteristics closest to the index date, stratified by responses to the overall health status question on the KDQOL-36 (cohort characteristics at CRIC study entry are displayed in Table S7). Figure 2 displays the cohort distributions of KDQOL-36 subscale scores. With respect to depressive symptoms, 505 (32%) participants had BDI scores ≥ 11 and 338 participants (21%) had scores ≥ 14.

Association Between HRQoL Domains and Kidney Transplant Wait-Listing
During a median follow-up of 5.1 (interquartile range, 3.0–8.3) years, 652 (39%) participants were wait-listed for a kidney transplant and 547 (33%) died without wait-listing. Participants who scored in the highest tertile of the PCS, indicating those with the best physical health, had a higher unadjusted hazard of wait-listing than those in the lower 2 tertiles (log-rank P < 0.001; Fig S1). In the unadjusted Cox model, compared with participants in the lowest PCS score tertile, those in the highest tertile had a higher rate of wait-listing (hazard ratio [HR], 1.59; 95% confidence interval [CI], 1.30–1.93; P < 0.001). The association between higher PCS score and wait-listing was attenuated after adjustment for participant demographics and other covariates (Fig 3; Table S1).

Participants who scored in the lower 2 tertiles of the Burden and Effects scales, indicating worse quality of life from the burdens and effects from CKD, respectively, had a higher unadjusted hazard of wait-listing than participants who scored in the highest tertiles of the Burden and Effects scales (Fig S1). In the fully adjusted model, compared with participants who scored in the lowest tertile of the Effects scale (ie, those most bothered by the effects of CKD), those in the highest tertile had a lower rate of wait-listing (model 2 adjusted HR [aHR], 0.74; 95% CI, 0.59–0.92; P = 0.007; Fig 3; Table S1). Compared with those who scored in the lowest tertile of the Burden scale (ie, those most burdened by CKD), participants in the highest tertile had a lower rate of wait-listing (model 2 aHR, 0.70; 95% CI, 0.57–0.85; P < 0.001). Other scales of the KDQOL-36 were not independently associated with differences in wait-listing.

Association Between Depressive Symptoms and Kidney Transplant Wait-Listing
Participants with fewer depressive symptoms, using either BDI score < 11 or BDI score < 14 as threshold scores, had similar unadjusted rates of wait-listing as those with more depressive symptoms (Fig 3; Table S1). After adjustment for demographics (model 1) and in the fully adjusted model, participants with BDI scores < 14 (ie, fewer depressive symptoms) had a lower rate of wait-listing than those with BDI scores ≥ 14 (model 2 aHR, 0.81; 95% CI, 0.66–0.99; P = 0.04). The BDI score threshold of <11 was not associated with differences in wait-listing in the fully adjusted model.
### Table 1. Demographic and Clinical Characteristics of CRIC Participants with Stage 4 Chronic Kidney Disease, Stratified by Responses to the Overall Health Status Question on the KDQOL-36 Survey

| Characteristics at Index Visit | Overall (N = 1,664) | Excellent/Very Good (N = 214) | Good (N = 620) | Fair (N = 631) | Poor (N = 199) |
|-------------------------------|---------------------|-------------------------------|----------------|----------------|----------------|
| **Race-ethnicity category**   |                     |                               |                |                |                |
| Hispanic                      | 300 (18.0%)         | 14 (6.5%)                     | 107 (17.3%)    | 119 (18.9%)    | 60 (30.2%)     |
| Non-Hispanic Black            | 759 (45.6%)         | 74 (34.6%)                    | 266 (42.9%)    | 337 (53.4%)    | 82 (41.2%)     |
| Non-Hispanic White            | 537 (32.3%)         | 111 (51.9%)                   | 223 (36%)      | 153 (24.2%)    | 50 (25.1%)     |
| Other                         | 68 (4.1%)           | 15 (7%)                       | 24 (3.9%)      | 22 (3.5%)      | 7 (3.5%)       |
| **Annual Income**             |                     |                               |                |                |                |
| $≤$20,000                     | 661 (39.7%)         | 39 (18.2%)                    | 212 (34.2%)    | 295 (46.8%)    | 115 (57.8%)    |
| >$20,000                      | 752 (45.2%)         | 136 (63.6%)                   | 316 (51%)      | 249 (39.5%)    | 51 (25.6%)     |
| **Do not wish to answer**     | 251 (15.1%)         | 39 (18.2%)                    | 92 (14.8%)     | 87 (13.8%)     | 33 (16.6%)     |
| **High school graduate**      | 1,205 (72.4%)       | 195 (91.1%)                   | 476 (76.8%)    | 419 (66.4%)    | 115 (57.8%)    |
| **Insured**                   |                     |                               |                |                |                |
| No                            | 164 (10.7%)         | 15 (7.2%)                     | 67 (11.5%)     | 61 (10.7%)     | 21 (11.9%)     |
| Unknown/incomplete            | 279 (18.2%)         | 59 (28.4%)                    | 122 (20.9%)    | 81 (14.2%)     | 17 (9.6%)      |
| Yes                           | 1,094 (71.2%)       | 134 (64.4%)                   | 394 (67.6%)    | 427 (75%)      | 139 (78.5%)    |
| **Diabetes**                  | 1,000 (60.1%)       | 87 (40.7%)                    | 336 (54.2%)    | 418 (66.2%)    | 159 (79.9%)    |
| **Hypertension**              | 1,560 (93.8%)       | 187 (87.4%)                   | 583 (94%)      | 597 (94.6%)    | 193 (97%)      |
| **Ischemic heart disease**    | 449 (27.0%)         | 33 (15.4%)                    | 162 (26.1%)    | 195 (30.9%)    | 59 (29.6%)     |
| **History of COPD**           | 75 (4.6%)           | 4 (1.9%)                      | 18 (2.9%)      | 39 (6.3%)      | 14 (7.1%)      |
| **Vascular disease**          | 175 (10.5%)         | 5 (2.3%)                      | 58 (9.4%)      | 78 (12.4%)     | 34 (17.1%)     |
| **eGFR closest to index date**| 31.43 (7.46)        | 32.36 (6.70)                  | 31.73 (7.64)   | 31.23 (7.40)   | 30.13 (7.66)   |
| **Yearly change in eGFR before index date** | -0.17 (1.01) | -0.29 (0.91) | -0.20 (1.00) | -0.16 (1.02) | -0.03 (1.06) |
| **Body mass index, kg/m²**    | 32.54 (8.11)        | 29.94 (6.43)                  | 31.92 (7.56)   | 33.51 (8.41)   | 34.24 (9.46)   |
| **Systolic blood pressure, mm Hg** | 133.78 (23.10) | 126.83 (19.22) | 131.80 (22.70) | 136.68 (24.46) | 138.27 (21.40) |
| **Diastolic blood pressure, mm Hg** | 70.94 (13.05) | 70.45 (12.80) | 70.87 (12.95) | 71.19 (13.58) | 70.91 (11.93) |
| **3MS score ≥ 80**            | 1,377 (86.1%)       | 186 (92.1%)                   | 519 (86.6%)    | 519 (86.1%)    | 153 (78.5%)    |
| **Live with others**          | 1,307 (78.7%)       | 166 (77.6%)                   | 498 (80.3%)    | 491 (78.1%)    | 152 (78.8%)    |
| **Tobacco use**               |                     |                               |                |                |                |
| Current smoker                | 238 (14.3%)         | 19 (8.9%)                     | 98 (15.8%)     | 88 (13.9%)     | 33 (16.6%)     |
| Nonsmoker                     | 735 (44.2%)         | 108 (50.5%)                   | 266 (42.9%)    | 278 (44.1%)    | 83 (41.7%)     |
| Previous smoker               | 691 (41.5%)         | 87 (40.7%)                    | 256 (41.3%)    | 265 (42%)      | 83 (41.7%)     |
| **Consumes alcohol**          | 891 (53.5%)         | 152 (71%)                     | 354 (57.1%)    | 303 (48%)      | 82 (41.2%)     |
| Any illicit drug use           | 541 (32.5%)         | 66 (30.8%)                    | 186 (30%)      | 223 (35.3%)    | 66 (33.2%)     |
| **Recent visit to nephrologist** | 1,440 (86.5%) | 187 (87.4%) | 541 (87.3%) | 545 (86.4%) | 167 (83.9%) |
| **24-h urinary protein, g/24 h** | 2.05 (3.11) | 1.26 (1.99) | 1.90 (2.94) | 2.20 (3.21) | 2.89 (3.96) |
| **Serum albumin, g/dL**       | 3.78 (0.49)         | 3.92 (0.42)                   | 3.80 (0.49)    | 3.75 (0.49)    | 3.65 (0.52)    |
| **Glycated hemoglobin, %**    | 6.91 (1.67)         | 6.53 (1.59)                   | 6.76 (1.60)    | 6.98 (1.66)    | 7.55 (1.78)    |

*Note: Data for categorical variables expressed as number (percent); data for continuous variables expressed as median (interquartile range). Overall health question: In general, would you say your health is: Excellent, Very Good, Good, Fair, or Poor? Abbreviations: 3MS, Modified Mini-Mental State Examination; COPD, chronic obstructive pulmonary disease; CRIC, Chronic Renal Insufficiency Cohort; eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); KDQOL-36, Kidney Disease Quality of Life-36.

*Missing in 12 participants.

### Association Between HRQoL, Depressive Symptoms, and Pre-emptive Wait-listing

Among 652 participants who were wait-listed, 304 (47%) were wait-listed pre-emptively. In fully adjusted Cox models in which death and dialysis initiation were treated as censoring events, findings were similar with respect to Burden and Effects scale scores (Fig 3; Table S2). In addition, compared with participants in the lowest tertile of PCS scores (ie, lowest physical health), those in higher tertiles were more likely to be wait-listed pre-emptively (model 2 aHR for highest PCS tertile, 1.58; 95% CI, 1.12-2.23; P = 0.01). Further, compared with those who scored in the lowest tertile on the Symptoms scale (ie, those with the most symptoms and problems from CKD), participants in the middle tertile (ie, fewer symptoms) were more likely to be pre-emptively wait-listed (model 2 aHR, 1.40; 95% CI, 1.02-1.92; P = 0.04). Differences in other KDQOL scale scores and depressive symptoms were not associated with differences in pre-emptive wait-listing.

### Results of Sensitivity Analyses

Results were similar in analyses of wait-listing and pre-emptive wait-listing in which participants with missing...
Panel A. Associations between HRQOL, Depressive Symptoms, and Wait-Listing

| Scale/Subscale                      | HR (95% CI)   |
|-------------------------------------|---------------|
| **KDQOL Overall (Ref=Poor)**        |               |
| Fair                                | 0.89 (0.69, 1.16) |
| Good                                | 0.88 (0.67, 1.15) |
| Very Good/Excellent                 | 0.85 (0.61, 1.18) |
| **MCS (Ref=Worse)**                 |               |
| Middle                              | 0.96 (0.79, 1.17) |
| Best                                | 0.91 (0.74, 1.12) |
| **PCS (Ref=Worse)**                 |               |
| Middle                              | 1.20 (0.96, 1.49) |
| Best                                | 1.23 (0.98, 1.55) |
| **Symptoms (Ref=Most Symptoms)**   |               |
| Middle                              | 0.99 (0.81, 1.21) |
| Least Symptoms                      | 0.90 (0.74, 1.10) |
| **Burdens (Ref=Most Burdens)**     |               |
| Middle                              | 0.75 (0.62, 0.92) |
| Least Burdens                       | 0.70 (0.57, 0.85) |
| **Effects (Ref=Most Effects)**     |               |
| Middle                              | 0.86 (0.71, 1.04) |
| Least Effects                       | 0.74 (0.59, 0.92) |
| **BDI (Ref=<=11)**                 |               |
| <11                                 | 0.93 (0.78, 1.12) |
| **BDI (Ref=<=14)**                 |               |
| <14                                 | 0.81 (0.66, 0.99) |

Panel B. Associations between HRQOL, Depressive Symptoms, and Pre-emptive Wait-Listing

| Scale/Subscale                      | HR (95% CI)   |
|-------------------------------------|---------------|
| **KDQOL Overall (Ref=Poor)**        |               |
| Fair                                | 1.01 (0.66, 1.55) |
| Good                                | 0.95 (0.61, 1.47) |
| Very Good/Excellent                 | 0.94 (0.57, 1.55) |
| **MCS (Ref=Worse)**                 |               |
| Middle                              | 0.91 (0.68, 1.20) |
| Best                                | 0.81 (0.60, 1.10) |
| **PCS (Ref=Worse)**                 |               |
| Middle                              | 1.44 (1.02, 2.05) |
| Best                                | 1.56 (1.12, 2.10) |
| **Symptoms (Ref=Most Symptoms)**   |               |
| Middle                              | 1.40 (1.02, 1.92) |
| Least Symptoms                      | 1.21 (0.86, 1.65) |
| **Burden (Ref=Most Burdens)**      |               |
| Middle                              | 0.82 (0.61, 1.09) |
| Least Burdens                       | 0.62 (0.46, 0.84) |
| **Effects (Ref=Most Effects)**     |               |
| Middle                              | 0.96 (0.72, 1.28) |
| Least Effects                       | 0.67 (0.46, 0.93) |
| **BDI (Ref=<=11)**                 |               |
| <11                                 | 0.79 (0.60, 1.03) |
| **BDI (Ref=<=14)**                 |               |
| <14                                 | 0.76 (0.56, 1.03) |

**Figure 3.** Adjusted associations between self-reported health assessments and (A) wait-listing and (B) pre-emptive wait-listing. Abbreviations: BDI, Beck Depression Inventory; CI, confidence interval; HR, hazard ratio; HRQOL, health-related quality of life; KDQOL, Kidney Disease Quality of Life; MCS, Mental Component Summary; PCS, Physical Component Summary; Ref, reference.
Inability to work or travel, dependence on physicians and lifestyle, including limits on fluid and dietary intake, transplantation the most to avoid dialysis and its punishing effects of advanced CKD may also be those who prioritize kidney transplantation relative to dialysis.29

In contrast to our findings on the burdens and effects of CKD, we also observed that individuals with better physical health and fewer symptoms in late-stage CKD had higher rates of pre-emptive wait-listing than those with poor physical health and more symptoms, respectively. These findings may indicate that physical health and symptoms are useful proxies of disease severity in late-stage CKD. Prior work has also suggested that individuals with poor physical health or more symptoms from CKD may have difficulty completing the kidney transplantation evaluation process or may be deemed too frail by transplantation providers.36,37 Our findings that higher predialysis physical health and fewer symptoms were associated with pre-emptive wait-listing but not overall wait-listing may be related to the changes in HRQoL that many people experience after initiating dialysis.38 Among those who report good physical health after starting dialysis, studies have shown higher rates of wait-listing, kidney transplantation, and posttransplantation survival.39–41 Interestingly, evidence suggests that among dialysis patients, self-reported overall health correlates poorly with self-reported physical health.42 Therefore, knowledge of several different domains of HRQoL may help providers better understand potential motivators for and barriers to pre-emptive kidney transplantation.

Numerous studies have highlighted the high prevalence and clinical implications of depression, poor physical function, frailty, and functional dependencies among patients receiving dialysis.43–48 and KDQOL normative data have recently been published for US dialysis patients.49 Our findings are consistent with prior work establishing that, similar to dialysis patients, many individuals with advanced CKD report very poor psychosocial health. For example, we found that 1 in 5 individuals with late-stage CKD had a BDI score ≥14, indicating a substantial burden of depressive symptoms.19,20 Importantly, although our findings do not point to poor self-reported health as a universal barrier to kidney transplant wait-listing, prior studies suggest that worse HRQoL and depression increase the risk for adverse outcomes, such as hospitalization and death, among individuals with CKD.5,10,11 Studies are needed to learn whether targeted interventions, such as counseling and prehabilitation,50 can improve the transition to ESKD and access to kidney transplantation among individuals with poor self-reported health.

Our study has several strengths. To our knowledge, ours is the first study to assess the influence of psychosocial factors in advanced CKD on access to kidney transplantation. Our study design enabled us to adjust for several known confounders, including cognitive function, that are not typically available in registry data. Given the long follow-up
period of the CRIC Study and linkage to the USRDS database, we were also able to confirm important outcomes.

However, our study was subject to certain limitations. For example, generalizability is a potential limitation because most CRIC sites are academic centers that are affiliated with kidney transplantation programs and may explain the overall high rate of wait-listing in this population. Nonetheless, our cohort characteristics mirror those of national dialysis cohorts such as the Dialysis Outcomes and Practice Patterns Study.40 There is also the possibility for type I error due to our examination of multiple health scales. Finally, although we adjusted for several known confounders including income and social support, there are likely to be other unmeasured confounders that influence wait-list eligibility (eg, severity of illness, timing of referral for kidney transplantation, availability of other laboratory results to qualify for wait-listing, and type of insurance coverage22) and are important in understanding differences in early access to kidney transplantation.

In summary, we found that in a large diverse cohort of individuals with late-stage CKD, those with the most effects, burdens, and depressive symptoms had the highest rates of subsequent wait-listing, whereas having better physical health and fewer symptoms was associated with more rapid pre-emptive wait-listing. Incorporating metrics of patient-reported health into predialysis CKD care may be useful to guide conversations about the potential benefits of kidney transplantation relative to dialysis and promote timely interventions to improve HRQoL regardless of kidney replacement therapy modality.

**SUPPLEMENTARY MATERIAL**

**Supplementary File (PDF)**

**Figure S1:** (A) Probability of Wait-listing for KT by tertile of Physical Health, (B) Effects of Kidney Disease, and (C) Burdens of Kidney Disease.

**Table S1:** Associations Between Self-reported Health Assessments and Time to Wait-listing.

**Table S2:** Associations Between Self-reported Health Assessments and Pre-emptive Wait-listing.

**Table S3:** Results of Sensitivity Analysis for Time to Wait-listing in Which Individuals With Nonmissing Transplant Dates But Missing Wait-listing Dates (N = 45) Are Censored at Their Last CRIC Visit Before Their Transplant Date.

**Table S4:** Results of Sensitivity Analysis for Time to Pre-emptive Wait-listing in Which Individuals With Nonmissing Transplant Dates But Missing Wait-listing Dates (N = 45) Are Censored at Their Last CRIC Visit Before Their Transplant Date.

**Table S5:** Results of Sensitivity Analysis for Time to Wait-listing in the Subgroup of CRIC Participants Who Were Younger Than 65 Years at the Index Date.

**Table S6:** Results of Sensitivity Analysis for Time to Pre-emptive Wait-listing in the Subgroup of CRIC Participants Who Were Younger Than 65 Years at the Index Date.

**Table S7:** Demographic and Clinical Characteristics of Study Participants at CRIC Study Entry, Stratified by Responses to the Overall Health Status Question* on the KDQOL-36 Survey.

**ARTICLE INFORMATION**

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**Table S7:** Demographic and Clinical Characteristics of Study Participants at CRIC Study Entry, Stratified by Responses to the Overall Health Status Question* on the KDQOL-36 Survey.

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How do depression and health related quality of life influence kidney transplant listing?

**EXPOSURE**
Participants from Chronic Renal Insufficiency Cohort (CRIC)
eGFR < 30 ml/min/1.73m²

**PRIMARY OUTCOME**
Time to KT wait listing

**SECONDARY OUTCOME**
Time to preemptive KT wait listing

| HRQOL & KT wait listing                                                                 | RESULTS                                    |
|----------------------------------------------------------------------------------------|--------------------------------------------|
| High PCS score associated with faster rate of pre-emptive wait listing                  | HR: 1.59                                   |
| Highest tertile scores of Effects scale (i.e., best QOL) associated with slower rate of wait listing | aHR: 0.74                                  |
| Highest tertile scores of Burden scale (i.e., best QOL) associated with slower rate of wait listing | aHR: 0.70                                  |

| Depression & KT wait listing                                                                 | RESULTS                                    |
|---------------------------------------------------------------------------------------------|--------------------------------------------|
| BDI score <14 associated with lower rate of wait listing                                    | aHR: 0.81                                  |

| HRQOL, Depression and pre-emptive KT wait listing                                           | RESULTS                                    |
|---------------------------------------------------------------------------------------------|--------------------------------------------|
| Lower Burden & Effects score, higher Symptoms and higher PCS scores had faster wait listing | aHR: 1.58 for PCS                          |

**Conclusion:** Self reported health in late stage CKD may influence timing of kidney transplant listing.

**Visual Abstract by Krishnam Raju Penmatsa MD, DM, DNB**

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