

# The Surprise Question and Self-Rated Health Are Useful Screens for Frailty and Disability in Older Adults with Chronic Kidney Disease

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## Abstract

**Background:** Self-rated health (SRH) and the surprise question (SQ) capture perceptions of health and are independent risk factors for poor outcomes. Little is known about their association with physiologic and functional decline.

**Objective:** Determine the association of SRH and SQ with frailty and functional status in older adults with chronic kidney disease (CKD) and their utility as screening tools.

**Design:** Prospective cohort study.

**Setting/Subjects:** Two hundred seventy-two adults, age  $\geq 60$  years, with advanced CKD seen in nephrology clinic.

**Measurements:** Patients completed SRH and were evaluated for frailty (Fried criteria and Clinical Frailty Scale [CFS]) and functional status (Katz and Lawton indices of activities of daily living [ADLs] and instrumental ADLs [iADLs]). Providers completed the SQ. Correlations were evaluated using Spearman's rho.

**Results:** Fifteen percent of patients were frail, 8% had  $\geq 1$  ADL deficit, and 29% had  $\geq 1$  iADL deficit. SRH and SQ were moderately correlated with frailty and iADLs. A SRH of excellent, very good, or good was predictive of nonfrail status (Fried negative predictive value [NPV]: 0.92; CFS NPV: 0.92) and preserved ADL function (NPV for  $\geq 1$  deficit: 0.96). A SQ response of 5, 4, or 3 (i.e., surprised) was predictive of nonfrail status and preserved ADL function (CFS NPV: 0.90; ADL  $\geq 1$  deficit NPV: 0.95). A SQ response of 1 or 2 had a positive predictive value of 0.64 for  $\geq 1$  iADL deficit.

**Conclusions:** Subjective health measures may be useful screening tools for frailty and functional status.

**Keywords:** activities of daily living; chronic; diagnostic self-evaluation; disability evaluation; frailty; prospective studies; renal insufficiency

## Introduction

CHRONIC KIDNEY DISEASE (CKD) is common in older adults,<sup>1</sup> is associated with frailty and functional limitations,<sup>2,3</sup> and has a heterogeneous natural history.<sup>4,5</sup> Patients and providers struggle with uncertainty regarding CKD course and quality of life when anticipating health trajectory and preparing for future disability, long-term placement, or treatments like dialysis.<sup>6–9</sup> As countries worldwide face ag-

ing populations with increasing chronic disease burdens, simple tools to identify patients who would benefit from careful geriatric assessments, rehabilitation, and advance care planning discussions are necessary.

Subjective health assessments are simple efficient measures that capture patients' and providers' perceptions of health<sup>10–16</sup> and are independent risk factors for poor outcomes in the general population and in patients with CKD.<sup>10–12,14,17–20</sup> However, the relationship between

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subjective health assessments and common geriatric conditions, including frailty and disability in activities of daily living (ADLs) or instrumental ADLs (iADLs), has not been well studied.

One tool for assessing a patient's subjective health is self-rated health (SRH), a single item question: "In general, would you say your health is: excellent, very good, good, fair, or poor." One provider-based subjective health measure is the surprise question (SQ): "Would you be surprised if this patient died in the next 12 months?" Both measures have been found to be valid and reliable in the CKD population through association with key outcomes such as mortality and kidney disease progression.<sup>15-18</sup>

## Objective

To investigate the association between subjective health assessments and Fried frailty phenotype, clinical frailty, and measures of functional status (i.e., ADLs, iADLs) in older adults with advanced CKD and to assess their performance as screening tools for frailty and functional status.

## Methods

### Study design, setting, and participants

As part of a larger prospective cohort study,<sup>21</sup> we enrolled adults aged 60 years or older with nondialysis dependent CKD stages 4 to 5 being followed by a provider at an academic nephrology clinic and conducted subjective health assessments, Fried frailty measures, clinical frailty assessments, and ADL/iADL assessments. Exclusion criteria were dialysis dependence, history of kidney transplantation, initial visit with the provider, or recent acute kidney injury. Because the study included a provider-based subjective health measure, we excluded visits where providers evaluated a patient for the first time to allow greater familiarity. Providers included 12 attending physicians and 1 nurse practitioner.

From November 2016 through January 2018, 293 patients were approached and 277 consented (with 16 [5%] declining to participate). Six patients were missing a subjective health assessment, leaving 271 patients in the current analysis. The study was approved by the Vanderbilt University Medical Center Institutional Review Board (No. 161523) and adhered to the principles of the Declaration of Helsinki.

### Subjective health measures

Patients completed the SRH assessment ("In general, would you say your health is: excellent, very good, good, fair, or poor") item during their enrollment visit. SRH has been shown to have excellent reliability and validity in the general population<sup>10-12,14,16,19,20</sup> and predicts adverse outcomes in CKD.<sup>17</sup>

Providers' answered the SQ ("Would you be surprised if this patient died within the next 12 months?") immediately following their clinic visit. Responses included a binary (i.e., "yes" or "no") and five-point Likert scale (i.e., very surprised to not at all surprised). The SQ has been shown to predict mortality in CKD and end-stage renal disease<sup>22-24</sup> and has shown adequate reliability in advanced CKD.<sup>18</sup> For this study, we *a priori* chose to use providers' Likert scale responses for the SQ since these responses take advantage of providers' demonstrated ability to rank order patients ac-

ording to prognosis (even when their estimated survival times are generally inaccurate),<sup>25</sup> provided enhanced specificity to the SQ in our prior evaluation,<sup>18</sup> and allowed additional granularity when evaluating rank order correlations than a binary tool.

### Frailty phenotype

We used the Fried frailty phenotype<sup>26</sup>: grip strength, walk speed, physical exhaustion, involuntary weight loss, and low physical activity. A patient with  $\geq 3$  criteria was considered frail and 1-2 criteria was considered prefrail (see Supplementary Data for further details). In determining the correlation with other measures, we scored Fried frailty using a 5-point ordinal scale (i.e., 1 point for each criterion). The Fried frailty phenotype has been associated with death, hospitalizations, and disability.<sup>27</sup>

### Clinical frailty

We used the Clinical Frailty Scale (CFS), a validated measure of clinical frailty, that consists of a single-item ordinal scale ranging from 1 to 9 with scores  $\geq 5$  indicating the presence of frailty.<sup>28,29</sup> Trained research personnel interviewed the patient and reviewed the electronic health record (EHR) to assess clinical frailty. In determining the correlation with other measures, the full range of scores was used.

### Functional status

We measured ADLs and iADLs using the Katz and Lawton indices, respectively.<sup>30,31</sup> Scores on the Katz excluded continence with an index range from 0 to 5, while Lawton index scores range from 0 to 8. Higher scores indicate greater independence for both scales.

### Covariates

As part of their initial assessment, patients completed a medical history questionnaire. Members of the research team also performed manual review of the EHR using standardized chart abstraction forms to supplement this information. We used these data to define comorbidities and to calculate the Charlson comorbidity index.<sup>32</sup>

### Data analysis

Relationships between trinary SRH and trinary SQ with frailty and functional status categories were assessed using Pearson's chi-squared test. Rank correlations between SRH, SQ (Likert scale), Fried Frailty, CFS, ADLs, and iADLs were determined using Spearman's Rank correlation. Because the variables of interest were ordinal and the estimates of their rank correlations could be affected by the frequency of ties, correlations were also examined by Goodman and Kruskal's Gamma.<sup>33-35</sup> When determining correlation coefficients, the SQ and Katz and Lawton indices were reverse coded so that higher scores represented poorer health or function in all variables of interest. Separate proportional odds models were also used to test for interactions between the variables of interest and age, gender, presence of diabetes or cardiovascular disease, and Charlson comorbidity index score. Age was included in the models as a nonlinear term with three knots.

To assess test characteristics of the subjective health assessments, we set an SRH threshold of excellent, very good, or good and a SQ threshold of 5, 4, or 3 (i.e., surprised to ambivalent) to calculate the sensitivity, specificity, and negative and positive predictive values (given the sample prevalence) for Fried frailty, clinical frailty,  $\geq 1$  ADL deficiency, and  $\geq 1$  iADL deficiency. The binomial exact method was used to calculate the 95% confidence intervals. *p*-Values less than 0.05 were considered statistically significant, and all analyses were performed using R (version 3.4.4).<sup>36</sup>

## Results

Participants had a median age of 71 years (25th, 75th percentile: 66, 77), 81% were white, 46% were female, 49% had diabetes, and 43% had cardiovascular disease. Participants had a median Charlson comorbidity score of 5 (25th, 75th percentile: 3, 7) (Table 1 and Supplementary Table S1). Patients reported their health as poor, fair, good, very good, and excellent in 23 (8%), 105 (39%), 100 (37%), 40 (15%), and 3 (1%) instances, respectively. Providers responded 1 (not at all surprised), 2, 3, 4, and 5 (very surprised) for 10 (4%), 40 (15%), 50 (18%), 85

TABLE 1. BASELINE CHARACTERISTICS BY TRINARY SELF-RATED HEALTH RESPONSE

	Total cohort (N=271)	SRH		
		Excellent or very good (N=43)	Good (N=100)	Fair or poor (N=128)
Age	71.0 [66.0, 77.0]	72.0 [68.0, 77.5]	71.0 [66.0, 76.0]	70.5 [65.0, 78.0]
Female	126 (46%)	11 (26%)	43 (43%)	72 (56%)
Race				
White/other	223 (82%)	35 (86%)	79 (81%)	105 (82%)
Black	48 (18%)	6 (14%)	19 (19%)	23 (18%)
Marital status				
Divorced	33 (12%)	3 (7%)	14 (14%)	16 (12%)
Married	173 (64%)	30 (70%)	57 (57%)	86 (67%)
Single/other	18 (7%)	2 (5%)	10 (10%)	6 (5%)
Widow/widower	47 (17%)	8 (19%)	19 (19%)	20 (16%)
Education				
Less than 12th grade	29 (11%)	3 (7%)	7 (7%)	19 (15%)
12th grade	68 (25%)	7 (16%)	24 (24%)	37 (29%)
Some college	60 (22%)	5 (12%)	23 (23%)	32 (25%)
College degree or higher	114 (42%)	28 (65%)	46 (46%)	40 (31%)
Income <sup>a</sup>				
Less than \$20,000	42 (15%)	3 (7%)	9 (9%)	30 (23%)
\$20,000 to \$39,999	69 (25%)	8 (19%)	28 (28%)	33 (26%)
\$40,000 to \$59,999	51 (19%)	9 (21%)	24 (24%)	18 (14%)
\$60,000 to \$79,999	43 (16%)	11 (26%)	12 (12%)	20 (16%)
\$80,000 to \$99,999	16 (6%)	3 (7%)	8 (8%)	5 (4%)
\$100,000 or above	46 (17%)	8 (19%)	17 (17%)	21 (16%)
Insurance				
Private	77 (28%)	14 (33%)	30 (30%)	33 (26%)
Medicaid	12 (4%)	0 (0%)	3 (3%)	9 (7%)
Medicare	182 (67%)	29 (67%)	67 (67%)	86 (67%)
Hypertension	265 (98%)	42 (98%)	97 (97%)	126 (98%)
Diabetes	133 (49%)	13 (30%)	47 (47%)	73 (57%)
Cardiovascular disease	117 (43%)	12 (28%)	45 (45%)	60 (47%)
Heart failure	65 (24%)	4 (9%)	28 (28%)	33 (26%)
Chronic lung disease	36 (13%)	5 (12%)	9 (9%)	22 (17%)
Malignancy	68 (25%)	12 (28%)	26 (26%)	30 (23%)
CCI	5 [3, 6]	4 [2, 5]	5 [3, 6]	5 [4, 6]
CCI				
[2–4]	126 (46%)	29 (67%)	48 (48%)	49 (38%)
[5–12]	145 (54%)	14 (33%)	52 (52%)	79 (62%)
BMI <sup>b</sup>	30 [26, 35]	29 [25, 33]	30 [26, 35]	31 [26, 37]
eGFR <sup>c</sup>	23 [17, 28]	25 [17, 30]	22 [18, 28]	22 [16, 28]

Continuous variables expressed as median (25% percentile, 75% percentile); categorical variables expressed as *n* (%). Patient characteristics grouped into trinary responses for parsimony and due to limited responses at the extremes.

<sup>a</sup>Four patients declined to answer.

<sup>b</sup>One patient with no BMI measurement.

<sup>c</sup>Calculated using the Modification of Diet in Renal Disease equation.

ADL, activities of daily living; BMI, body mass index; CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate; iADL, instrumental ADL.

(31%), and 86 (32%) patients, respectively (Supplementary Table S2). Patients who rated their health as “poor” or “fair” tended to be more likely to identify as female, have diabetes, and have a modestly higher Charlson comorbidity score, and they were less likely to have graduated college.

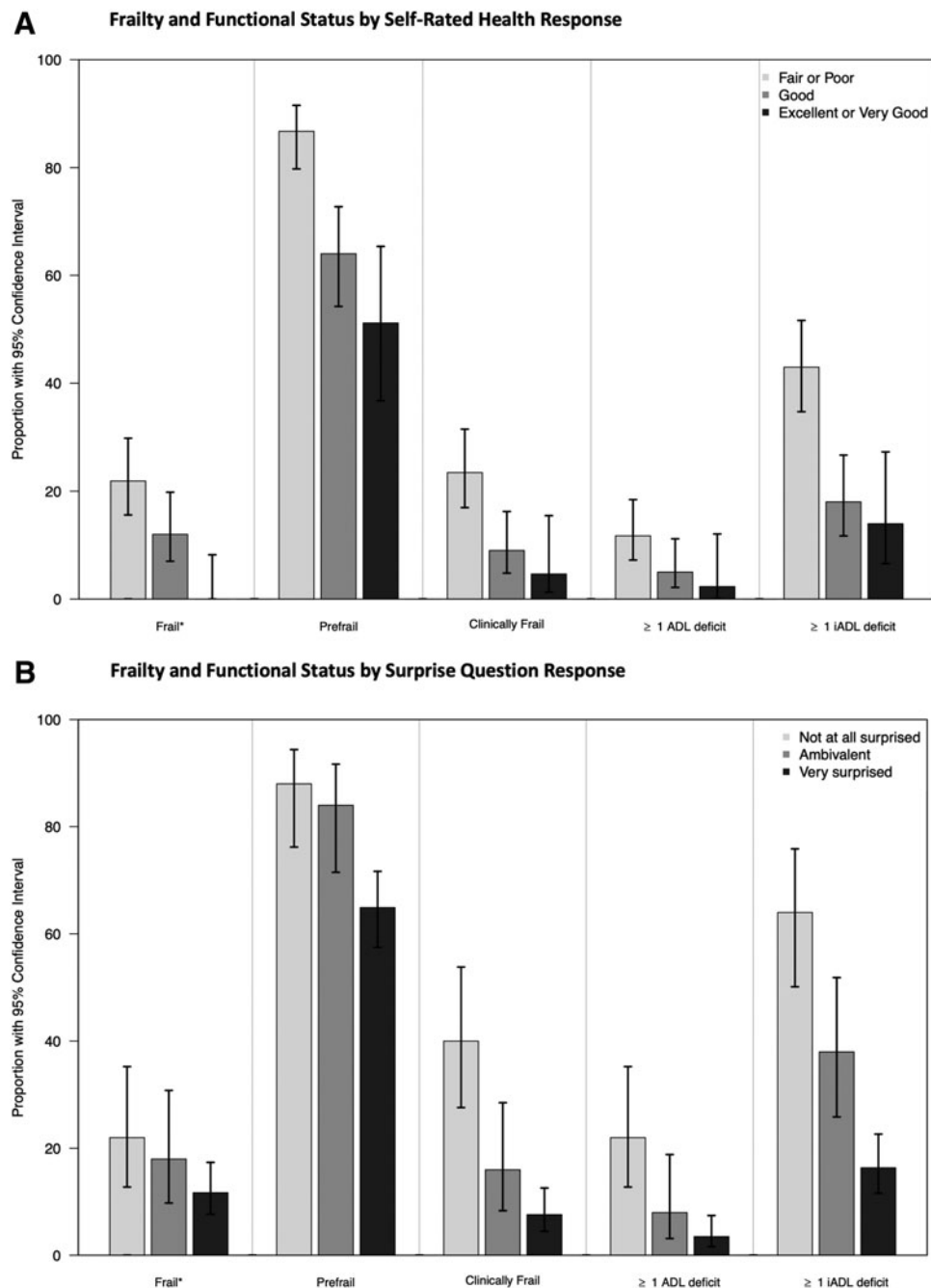
### Associations of SRH and SQ with frailty and functional status

About 15% ( $n=40$ ) and 15% ( $n=41$ ) of patients were frail by the Fried criteria and CFS score, respectively. Nearly three

quarters (73%,  $n=197$ ) of patients were prefrail or frail by the Fried criteria. About 8% ( $n=21$ ) and 29% ( $n=79$ ) of patients had at least 1 ADL or iADL deficit, respectively.

We observed significant associations between SRH and frailty (by Fried criteria), prefrail status (by Fried criteria), clinical frailty (by CFS), ADL scores, and iADL scores (Fig. 1a). Similarly, we observed significant associations between SQ and prefrail status, clinical frailty, ADL scores, and iADL scores (Fig. 1b).

Spearman correlations between SRH and Fried frailty score, CFS score, and iADL score were fair to moderate



**FIG. 1.** (A) Self-rated health response is associated with frailty and functional status, (B) Surprise question response is associated with prefrailty, clinical frailty, and functional status. \*Frail or prefrail determined using Fried criteria scores  $\geq 3$  or  $\geq 1$ , respectively. Clinical frailty determined using Clinical Frailty Scale score  $\geq 5$ . ADL, activity of daily living; iADL, instrumental ADL.

TABLE 2. CORRELATION BETWEEN SUBJECTIVE HEALTH MEASURES, FRAILITY, AND FUNCTIONAL STATUS

	<i>Fried frailty</i>	<i>Clinical Frailty Scale</i>	<i>ADL</i>	<i>iADL</i>	<i>SRH</i>
SRH	0.43 (0.32–0.52)	0.45 (0.35–0.54)	0.16 (0.04–0.26)	0.33 (0.23–0.44)	—
SQ	0.31 (0.20–0.42)	0.45 (0.40–0.58)	0.23 (0.11–0.36)	0.40 (0.29–0.50)	0.29 (0.18–0.40)

Correlations are presented as Spearman's rho with 95% confidence intervals.  
SQ, surprise question; SRH, self-rated health.

(ranging from 0.33 to 0.45) (Table 2). Similarly, Spearman correlations between the SQ Likert scale and Fried frailty score, CFS score, and iADL score were fair to moderate (ranging from 0.31 to 0.45) (Table 2). ADLs were weakly correlated with both SRH and the SQ with Spearman Rho values of 0.16 (95% CI 0.04–0.26) and 0.23 (95% CI 0.11–0.36), respectively (Table 2). Correlations assessed using Goodman and Kruskal's Gamma to account for ties in ordinal ranking showed similar or stronger correlations (Supplementary Table S3). When testing for interactions, we found that only the relationship between the SQ and CFS had significant interaction terms (see Results section in Supplementary Data and Supplementary Fig. S1).

#### **Correlation of patient and provider-based subjective health assessments**

SRH and the SQ were correlated with each other (rho 0.29; 95% CI 0.18–0.40), and we did not find evidence of significant interaction terms for this association (see also Results section in Supplementary Data).

#### **Test characteristics**

When using a SRH response of "Poor" or "Fair" as a positive test, we found negative predictive values ranging from 0.83 to 0.96 for frailty and impairments in ADLs and iADLs (Table 3). Similarly, a SQ Likert response of not surprised (using the 5-point Likert scale) had negative predictive values ranging from 0.87 to 0.95 for frailty or impairments in ADLs (Table 3). In general, SRH appeared more sensitive (ranging from 0.56 to 0.73) in screening for frailty and functional impairments, while the SQ was more specific

(ranging from 0.83 to 0.91). Notably, a SQ score of 1 or 2 had a positive predictive value for  $\geq 1$  iADL deficit of 0.64 (95% CI 0.49–0.77) in a sample with a prevalence rate for iADL deficits of 29%.

## **Discussion**

### **Findings**

We found that in older adults with advanced CKD, both patient and provider subjective health assessments were moderately correlated with Fried frailty score, CFS score, and measures of functional status. We also found that SRH and the SQ demonstrated a fair correlation with each other. These findings were generally consistent regardless of age, the presence of diabetes or cardiovascular disease, or overall comorbidity burden. In addition, we found that SRH was generally more sensitive, while the SQ was more specific when testing for Fried frailty, clinical frailty, and ADL/iADL disabilities. Our study provides further evidence for the criterion validity of SRH and the SQ as measures of overall health status in patients with advanced CKD. It also suggests that patient and provider subjective health assessments should be further evaluated as a clinical strategy to identify patients with advanced CKD who could benefit from advance care planning.

### **Potential for clinical integration**

Older patients with advanced CKD are the fastest growing dialysis subgroup,<sup>37</sup> and for some, the burdens of dialysis outweigh the benefits.<sup>38–41</sup> Many older patients who initiate dialysis experience high rates of disability, mortality, and

TABLE 3. TEST CHARACTERISTICS FOR SELF-RATED HEALTH VALUE OF "POOR" OR "FAIR" AND SURPRISE QUESTION VALUE OF "NOT SURPRISED"\*

<i>SRH: poor or fair</i>	<i>Fried frailty</i>	<i>Fried prefrailty</i>	<i>Clinical Frailty Score</i>	<i>ADL impairment</i>	<i>iADL impairment</i>
Sensitivity	0.70 (0.53–0.83)	0.56 (0.49–0.63)	0.73 (0.57–0.86)	0.71 (0.48–0.89)	0.70 (0.58–0.79)
Specificity	0.57 (0.50–0.63)	0.77 (0.66–0.86)	0.57 (0.51–0.64)	0.55 (0.48–0.61)	0.62 (0.55–0.69)
PPV	0.22 (0.15–0.30)	0.87 (0.80–0.92)	0.23 (0.16–0.32)	0.12 (0.07–0.19)	0.43 (0.34–0.52)
NPV	0.92 (0.86–0.96)	0.40 (0.32–0.48)	0.92 (0.87–0.96)	0.96 (0.91–0.98)	0.83 (0.76–0.89)
<i>SQ: not surprised</i>	<i>Fried frailty</i>	<i>Fried prefrailty</i>	<i>Clinical Frailty Score</i>	<i>ADL impairment</i>	<i>iADL impairment</i>
Sensitivity	0.28 (0.15–0.44)	0.22 (0.17–0.29)	0.49 (0.33–0.65)	0.52 (0.30–0.74)	0.41 (0.30–0.52)
Specificity	0.83 (0.78–0.88)	0.92 (0.83–0.97)	0.87 (0.82–0.91)	0.84 (0.79–0.89)	0.91 (0.86–0.94)
PPV	0.22 (0.12–0.36)	0.88 (0.76–0.95)	0.40 (0.26–0.55)	0.22 (0.12–0.36)	0.64 (0.49–0.77)
NPV	0.87 (0.82–0.91)	0.31 (0.25–0.37)	0.90 (0.86–0.94)	0.95 (0.92–0.98)	0.79 (0.73–0.84)

Patients were determined to be frail or prefrail by Fried criteria with scores  $\geq 3$  or  $\geq 1$ , respectively, and clinically frail by Clinical Frailty Scale scores  $\geq 5$ . Prevalence rates: Fried frailty: 15%, Fried prefrailty or frailty: 73%, clinical frailty: 15%,  $\geq 1$  ADL impairment: 8%,  $\geq 1$  iADL impairment: 29%

\*Table values represent proportions.

NPV, negative predictive value; PPV, positive predictive value.

declines in life satisfaction.<sup>40–42</sup> Similarly, many advanced CKD patients who are hospitalized undergo aggressive and invasive procedures that are not consistent with their stated health care preferences.<sup>43,44</sup> Furthermore, the care delivered to older CKD patients near the end of life frequently conflicts with their stated preferences.<sup>44,45</sup> These findings emphasize the need for providers to engage older patients with advanced CKD in longitudinal shared decision making and advance care planning conversations.<sup>46–48</sup> Indeed, many older, advanced CKD patients expect their practitioners to engage in advance care planning.<sup>47,49</sup> Our findings suggest that patient- and provider-based subjective health assessments can be used to identify patients who are at higher risk for poor outcomes. Providers should target these patients for thoughtful discussions of the trade-offs of maximal conservative management and dialytic therapies. Similarly, these patients are likely to benefit from longitudinal advance care planning conversations, where treatment preferences and goals of care are carefully considered, and a health care proxy is identified.

### ***Anticipating health trajectory***

Clinicians and researchers could benefit from pragmatic measures that help capture the risk of disability and death in patients with chronic illnesses. For older patients with CKD, all-cause mortality is 10- to 13-fold more likely end point than end-stage renal disease.<sup>8,50</sup> For patients  $\geq 80$  years, the relative likelihood of long-term placement compared to developing dialysis dependence reaches 30-fold.<sup>8</sup> However, identifying patients at increased risk for disability and nursing home residence has garnered less research attention than understanding risk factors for kidney disease progression.<sup>51,52</sup> Pragmatic and efficient methods to identify patients at increased risk for future disability and long-term institutionalization may facilitate efforts to uncover modifiable and nonmodifiable risk factors that contribute to these outcomes. Our study provides evidence that subjective health measures are associated with geriatric syndromes and could serve a useful role in risk stratifying older populations for adverse outcomes beyond mortality. Longitudinal research will need to assess how strongly SRH and the SQ associate with outcomes like disability and institutionalization and how well they track with health trajectories of functional status.

### ***Implications for frailty assessment***

Frailty rates are high in the CKD population, and multiple studies have shown frailty to be an independent risk factor for death and other poor outcomes.<sup>27,53–55</sup> While frailty measures have been used to monitor health status in CKD,<sup>56</sup> widespread implementation of frailty assessments in this setting and other chronic disease settings is limited, likely related to feasibility concerns.<sup>57–59</sup> Our findings that patients who reported SRH as excellent, very good, or good were unlikely to be frail or have functional deficits suggest that this can be a simple screening tool for frailty in patients with advanced CKD. This approach may be useful in clinical settings where more thorough evaluations (e.g., comprehensive geriatric assessments) can be targeted, thereby reducing the associated resource burden. Similarly, we found that the SQ (Likert-scale response “not surprised”) had a positive predictive value for  $\geq 1$  iADL deficit of 64%. This suggests

that the SQ Likert response may be helpful in identifying patients with higher order disabilities. Future studies should examine pairing the SQ with geriatric assessments, exploration of support services available in the patient’s current home environment, and advance care planning.

### ***Implications for subjective health measures***

While one prior study showed fair correlation between self and provider rated health in the general population,<sup>60</sup> we are not aware of studies that have examined the relationship between patient SRH and provider SQ assessments. The fair correlation of these measures is not surprising as they arguably assess related although distinct concepts, general health, and the perceived risk of near-term death.<sup>18,45</sup> Notably, in patients whose providers responded “No” to the SQ, the correlation between SRH and the SQ was not changed. Unfortunately, the previously documented low rates of advance care planning conversations in our study setting precluded a meaningful assessment of the impact of advance care planning conversations on the correlation of patient and provider subjective health measures.<sup>45</sup> Future research should examine whether patients who have had advance care planning discussions with their providers have a higher correlation between patient and provider subjective health assessments.

### ***Strengths and weaknesses***

Our study had several strengths. First, our study measures have previously demonstrated predictive validity in the CKD population. Second, our study focused on older adults with advanced CKD. Patients within this population have substantial variability in health trajectory, and new tools need to be explored to best stratify this population. Third, 95% of the patients we approached to enroll in this study consented, reducing selection bias. Finally, the consistent association of subjective health assessments across multiple measures related to aging and physical function supports our findings.

We also acknowledge several weaknesses. First, while patient age, diabetes, and comorbidity did not modify most of the associations we observed, we were underpowered to detect these effects. Similarly, the correlation of the SQ and SRH may demonstrate significant heterogeneity in other populations and settings with disparate educational attainment and racial backgrounds. Second, our population was recruited from a nephrology clinic at an Academic Medical Center. Our findings may not be generalizable to settings where the educational attainment is lower and the patient case mix or provider characteristics are different. Finally, our study was cross-sectional and did not assess whether subjective health measures were associated with dialysis initiation or institutionalization. However, we previously showed that the SQ associates with mortality in the same environment.<sup>18,45</sup>

### ***Conclusion***

In conclusion, SRH and the SQ are associated with frailty and disability and may be helpful in screening patients for these conditions. Further studies should explore their usefulness as screening tools in clinical research and routine practice, as well as understanding how these measures associate with patients’ clinical course.

### Author Disclosure Statement

No competing financial interests exist.

### Supplementary Material

Supplementary Data  
 Supplementary Table S1  
 Supplementary Table S2  
 Supplementary Table S3

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