

# Frailty in CKD and Transplantation



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The population is aging. Although older adults have higher rates of comorbidities and adverse health events, they represent a heterogeneous group with different health trajectories. Frailty, a clinical syndrome of decreased physiological reserve and increased susceptibility to illness and death, has emerged as a potential risk stratification tool in older patients with chronic kidney disease (CKD). Frailty is commonly observed in patients with CKD and associated with numerous adverse outcomes, including falls, decreased quality of life, hospitalizations, and death. Multiple pathologic factors contribute to the development of frailty in patients with CKD, including biological mechanisms of aging and physiological dysregulation. Current interventions to reduce frailty are promising, but additional investigations are needed to determine whether optimizing frailty measures improves renal and overall health outcomes. This review of frailty in CKD examines frailty definitions, the impact of frailty on health outcomes across the CKD spectrum, mechanisms of frailty, and antifrailty interventions (e.g., exercise or senescent cell clearance) tested in CKD patients. In addition, existing knowledge gaps, limitations of current frailty definitions in CKD, and challenges surrounding effective antifrailty strategies in CKD are considered.

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By 2050, nearly 1.6 billion individuals worldwide will be older than 65 years of age.<sup>1</sup> Population aging has altered the landscape of nephrology given the interplay between renal aging and age-related comorbidities (e.g., cardiovascular disease and diabetes mellitus) that contribute to acute kidney injury and CKD in older adults. In the United States, 50% of all incident dialysis patients<sup>2–4</sup> and more than 20% of kidney transplant (KT) recipients<sup>5</sup> are older than age 65. The high death rate and perioperative morbidity and mortality in older adults with CKD underscore an unmet need to better understand and optimize their health trajectories.

Frailty, a syndrome of decreased physiological reserve and increased vulnerability to illness and death, is a robust predictor of adverse health outcomes in older adults, including falls, decreased quality of life, increased health care use, and death.<sup>6,7</sup> Correspondingly, frailty has emerged as a potential risk

stratification and prognostication tool in older adults with CKD, including KT candidates. In this article, current definitions of frailty, associations of frailty with health outcomes, mechanisms of frailty, and potential interventions for frailty in the context of CKD are reviewed. We also highlight critical knowledge gaps in these domains that need further investigation.

## How to Measure Frailty in Patients With CKD

The study of frailty is complicated by a lack of consensus regarding how best to measure it.<sup>8,9</sup> A recent systematic review highlighted the existence of over 67 different frailty measures.<sup>10</sup> Many of these measures incorporate different constructs, such as physical function, comorbidities, psychosocial factors, and patient-reported outcomes.<sup>10,11</sup> Collectively, the multitude and diversity of measures pose challenges to assessing frailty quantitatively across studies.

One of the most widely used measures of frailty in both the geriatric and nephrology literature is the Fried frailty phenotype, or physical frailty phenotype (PFP), which was initially studied by Linda Fried and colleagues in community-dwelling older adults enrolled in the Cardiovascular Health Study.<sup>9,10,12</sup> The PFP represents a syndrome of decreased physiologic reserve and

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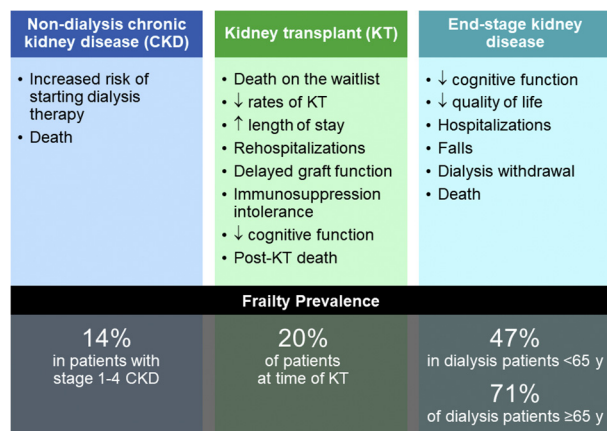
potential loss of resilience.<sup>13</sup> The PFP has been found to be overlapping but distinct from comorbidities and disabilities.<sup>12</sup> The PFP includes 5 criteria: decreased grip strength, slow walking speed, unintentional weight loss, low self-reported physical activity, and self-reported exhaustion.<sup>12</sup> Patients who meet 1 to 2 of these criteria are classified as prefrail, whereas patients who meet 3 or more of these criteria are classified as frail. The PFP has been shown to predict falls, hospitalizations, and death in community-dwelling older adults.<sup>12</sup>

Another commonly used method of measuring frailty is the cumulative deficit model. In the cumulative deficit model, frailty is directly related to the number of patient comorbidities, disabilities, and symptoms.<sup>14</sup> One of the most commonly used measures that utilizes this approach is the Frailty Index developed by Rockwood *et al.*<sup>15</sup> in community-dwelling elderly adults. Measures of physical function that have been used as measures of frailty include the Short Physical Performance Battery, a composite measure of lower extremity function (e.g., tests of balance, gait speed, and chair stand time);<sup>16</sup> the 6-minute walk test; the Timed Up and Go Test; and the sit-to-stand test. Lastly, a patient-reported measure often used to assess frailty in patients with CKD is the 36-Item Short Form Health Survey (SF-36).<sup>17</sup> The SF-36 includes a physical component subscale that assesses physical function, along with subscales assessing exhaustion, fatigue, and somatic pain. Although tests of physical function and patient-reported measures are commonly used to measure frailty, it is important to note that they are different from the multidimensional PFP.

### Frailty and Non-Dialysis-Dependent CKD

Among patients with stages 1 through 4 CKD, the prevalence of frailty as measured by the PFP is approximately 14%, more than twice as high as community-dwelling older adults.<sup>18,19</sup> Multiple studies have shown that the risk of being classified as frail increases as the glomerular filtration rate (GFR) decreases.<sup>19–21</sup> Specifically, patients with early-stage CKD have twice the risk of being classified frail, whereas patients with CKD stage 3b or higher have nearly 6 times the risk, even after adjusting for age, race, sex, and comorbidities.<sup>21</sup> In addition to decreased GFR, other risk factors for frailty in patients with non-dialysis CKD include older age, female sex, and diabetes.<sup>22</sup> The most common frailty parameters in patients with nondialysis CKD are physical inactivity and exhaustion.<sup>18</sup>

In patients with nondialysis CKD, frailty is associated with adverse outcomes (Figure 1).<sup>23</sup> In a prospective study of 336 patients with nondialysis CKD, frailty

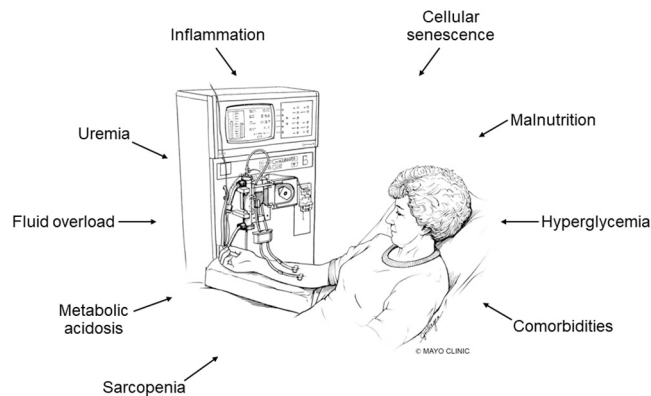


**Figure 1.** Adverse outcomes associated with frailty and chronic kidney disease.

as defined by the PFP was associated with a 2.5-fold higher risk of death or dialysis therapy.<sup>18</sup> Delgado *et al.*<sup>24</sup> found that self-reported frailty was associated with death among participants in the Modification of Diet in Renal Disease study, whereas Pugh *et al.*<sup>25</sup> found that a higher Rockwood Frailty Index was associated with worse survival in patients referred for predialysis education. Other studies have demonstrated that gait speed itself is associated with increased all-cause mortality in these patients. For every 0.1 m/s decrease in gait speed, patients with nondialysis CKD experience a 26% higher risk of death.<sup>26</sup> It should be noted that estimating GFR in frail patients with CKD is not always straightforward. Equations that estimate GFR based on serum creatinine may overestimate GFR in frail patients with sarcopenia given that serum creatinine reflects underlying muscle mass. Thus, cystatin C-based estimated GFR equations may be better markers of kidney function in this vulnerable population.<sup>27</sup>

### Frailty, End-Stage Kidney Disease, and Transplantation

Frailty prevalence is highest in patients with ESD who are dialysis dependent compared with patients with nondialysis CKD or without CKD.<sup>28</sup> Specifically, 71% of dialysis patients  $\geq 65$  years are classified as frail, whereas 47% of dialysis patients aged 65 or less are classified as frail by the PFP, a prevalence more than 5 times as high as the general population.<sup>29</sup> Studies using the Short Physical Performance Battery have shown that patients on dialysis have significantly lower scores compared with patients with other comorbidities, such as chronic obstructive lung disease and congestive heart failure.<sup>30,31</sup> In dialysis-dependent patients, frailty is associated with peripheral vascular disease, diabetes, and body composition parameters, including fat mass and extracellular water, but not with body mass index



**Figure 2.** Frailty pathogenesis in chronic kidney disease.

or dialysis modality.<sup>28,32–34</sup> Lower serum albumin, higher interleukin-6 levels, and hospitalizations are associated with worsening frailty over time in dialysis-dependent patients.<sup>35</sup>

Frailty in dialysis patients is associated with numerous adverse outcomes, including worse cognitive function,<sup>36</sup> increased falls,<sup>37</sup> deteriorating quality of life,<sup>38</sup> hospitalization,<sup>28,34,39</sup> and death (Figure 1).<sup>28,40,41</sup> Slow gait speed has also been shown to predict mortality, hospitalization, difficulty with activities of daily living, and worse quality of life in patients on dialysis.<sup>42</sup> Unfortunately, despite the self-selection of home dialysis, frail patients maintained on home dialysis are more likely to experience technique failure and death.<sup>43</sup> Finally, we found that the second most common reason for medical record–abstracted dialysis withdrawal in a maintenance hemodialysis patient cohort at our center was frailty ( $n = 1226$ ).<sup>44</sup>

A growing body of evidence describing the importance of measuring frailty in KT candidates is emerging and has previously been reviewed.<sup>45,46</sup> At the time of KT, 20% of patients are defined as frail according to the PFP.<sup>47</sup> Frailty has been associated with adverse outcomes before and after KT (Figure 1). We and others demonstrated that wait-listed candidates who are defined as frail or have decreased physical function are more likely to experience wait-list removal or death.<sup>48–52</sup> Frailty at the time of KT is associated with complications after KT, including delayed graft function, longer hospital length of stay, rehospitalizations, immunosuppression intolerance, and death.<sup>53–60</sup> Several studies have characterized changes in physical function and frailty after KT. We found that 35% of patients experienced a clinically meaningful improvement in gait speed of  $\geq 0.1$  m/s during the first 4 months after living donor KT at our center.<sup>55</sup> Applying the PFP, McAdams-DeMarco *et al.*<sup>61</sup> showed that patients initially become more frail during the first month after KT. However, by 3

months posttransplant, frailty status improves compared with pretransplant levels. In conclusion, a robust body of evidence has emerged illustrating the detrimental impact of pretransplant frailty on KT outcomes, as well as the potential reversibility of frailty after KT.

## Mechanisms of Frailty

Frailty is associated with impairment in many physiologic systems, including alterations in endocrine functions, the immune system, the autonomic nervous system, and skeletal muscle. Multiple derangements of endocrine functions have been associated with frailty including elevated cortisol,<sup>62,63</sup> decreased vitamin D,<sup>64</sup> altered glucose metabolism,<sup>65</sup> and decreased androgens.<sup>66,67</sup> In patients on dialysis, low testosterone levels have been associated with an increased prevalence and onset of frailty.<sup>66</sup> These endocrine abnormalities could contribute to the development of frailty by exacerbating muscle weakness, sarcopenia, comorbidities, and loss of appetite.<sup>63,64</sup>

Dysregulation of the immune system and maladaptive inflammation are also associated with frailty. Frail community-dwelling older adults exhibit elevated inflammatory markers, including serum interleukin-6 and C-reactive protein.<sup>68</sup> Likewise, patients with kidney failure classified as frail have higher levels of interleukin-6, C-reactive protein, and tumor necrosis factor- $\alpha$  receptor 1 compared with nonfrail patients with ESKD.<sup>69</sup> Chronic inflammation is hypothesized to contribute to frailty by inducing sarcopenia, anemia, adipose tissue dysfunction, and cardiovascular disease.<sup>68,70</sup> Because of altered cellular and humoral immunity, frail patients are less likely to mount a response to vaccinations such as influenza<sup>71</sup> or hepatitis B<sup>72,73</sup> among those who are dialysis dependent. Dysregulation of the autonomic nervous system, manifested by reduced heart rate variability, has also been described in patients classified as frail.<sup>74,75</sup> Finally, frailty effects on the musculoskeletal system are associated with lower muscle mass, loss of type II fibers, and higher fat mass.<sup>76,77</sup>

Impairment in these physiologic systems is driven by multiple mechanisms. Behavioral factors (e.g., poor nutrition<sup>78</sup> and decreased physical activity<sup>79</sup>), social factors (e.g., low income<sup>80</sup> and low educational level<sup>81</sup>), and genetics<sup>70</sup> contribute to frailty. Furthermore, metabolic factors that accompany kidney dysfunction and uremia may contribute to frailty in patients with CKD (Figure 2). CKD is a catabolic state associated with protein wasting, inflammation, fluid overload, and malnutrition.<sup>82,83</sup> Patients with CKD have increased muscle catabolism, reduced synthesis

of muscle contractile proteins, and impaired muscle regeneration leading to sarcopenia, decreased physical function, and frailty compared with similarly aged individuals without CKD.<sup>83–85</sup> In advanced CKD, chronic metabolic acidosis decreases muscle mass and strength while also diminishing bone mineral density.<sup>86–88</sup> Sarcopenia, as assessed through dual-energy X-ray absorptiometry, is more common in patients with CKD.<sup>89</sup> Anemia, hyperparathyroidism, and cognitive impairment may also contribute to frailty in patients in these individuals.<sup>82,90</sup> In KT, commonly used regimens incorporating corticosteroids and calcineurin inhibitors alter muscle metabolism and induce sarcopenia.<sup>91–94</sup>

Another aging process implicated in the pathogenesis of frailty is cellular senescence.<sup>46,95</sup> Cellular senescence is a state of essentially irreversible growth arrest that occurs in response to perturbations such as DNA damage and oxidative stress. Senescent cells can secrete a combination of cytokines, chemokines, growth factors, and other proteins. Collectively, these factors are called the senescence-associated secretory phenotype and have been shown to promote inflammation, tissue damage, and senescence in neighboring and distant cells.<sup>96</sup> Senescent cells form in tissues throughout the body, leading to tissue dysfunction, particularly in those with diabetes and CKD.<sup>97–102</sup> Elevated plasma levels of senescence-associated secretory phenotype proteins, including growth differentiation factor 15, activin A, and interleukin-15, are associated with age, frailty, and adverse health outcomes in patients with chronic disease.<sup>103,104</sup> Furthermore, sterile inflammation in surrounding adipose tissue both propagates and is influenced by cellular senescence, contributing to morbidity.<sup>97,105</sup> The accumulation of senescent cells in muscle may result in atrophy and decreased contractility.<sup>106</sup> In support of the pathogenic nature of senescence, recent studies demonstrated that transplanting senescent cells into healthy mice results in decreased physical function.<sup>106</sup> Both KT recipients and allografts have been shown to experience accelerated aging and the accumulation of senescent cells.<sup>107,108</sup> Furthermore, transplanting organs (hearts) from old mice into young mice causes spread of senescence from the old transplanted organ to the recipient's own cells, even in distant organs.<sup>109</sup> Hence, individuals with successful KT avoid chronic dialysis but carry the burden of prior CKD, are at risk of the spread of senescence from the transplanted organ, and are given immunosuppressive drugs that may further contribute to frailty.

## Interventions to Improve Frailty Parameters in CKD

Numerous studies have examined the impact of exercise on frailty in CKD. Comparing them can be challenging because they often use different outcome measures (e.g., PFP, SF-36, or 6-minute walk test).<sup>110–121</sup> Certain outcome measures may be more challenging to study than others. The PFP includes a 12-month wasting parameter that cannot be improved during short-term interventions.<sup>117</sup> Furthermore, 1 of the criteria of the PFP is low physical activity, which can be impacted by exercise interventions. Self-reported measures, such as the SF-36, can introduce bias given that interventions are often associated with overreporting of the desired behavior.<sup>122</sup> Thus, using performance-based measures like the Short Physical Performance Battery or the 6-minute walk test as benchmarks in exercise interventions or examining how change in physical activity impacts other PFP parameters may be preferable.<sup>8,9</sup>

Numerous studies have examined the impact of exercise on performance-based measures of frailty in patients with CKD. Many have demonstrated that exercise is beneficial (Table 1). However, the implementation of exercise regimens in clinical practice has been limited by a lack of consensus regarding the preferred “best option,” a lack of resources,<sup>123,124</sup> and a lack of evidence related to outcomes such as cardiovascular events and death.<sup>125</sup> In addition, the optimal location of exercise (e.g., intradialytic, home based, or center based) is unknown. Studies involving non-CKD populations suggest that supervised interventions may be more efficacious than unsupervised interventions.<sup>126–129</sup> Supervised interventions may also be safer and more feasible for extremely frail or debilitated patients. However, patients on dialysis may find it challenging to attend supervised sessions outside of dialysis. Combining exercise with dialysis sounds promising, but intradialytic interventions may be limited by low-intensity exercise and poor adherence.<sup>130</sup> How to sustain exercise and its associated antifrailty effects after study discontinuation is also unclear. Sheshadri *et al.*<sup>121</sup> found that participants returned to baseline levels of physical activity within 3 months of completing their home-based walking intervention. Lastly, although exercise interventions may improve frailty, few data on the impact of exercise on death and cardiovascular events in patients with CKD exist.<sup>118</sup> In 1 retrospective study examining patients with CKD, it was found that patients able to complete a supervised, outpatient exercise program had a lower risk of cardiovascular morbidity and mortality.<sup>113</sup>

**Table 1.** Selected studies examining the impact of exercise on performance-based measures of frailty in chronic kidney disease

	Study	Subjects	Intervention	Frailty Assessment Instrument				
				SPPB	6MWT	STS	TUG	Other
≤ 3 mo interventions	Rossi et al (2014) <sup>120</sup>	CKD stages 3-4 (N = 119)	3 months of guided exercise versus usual care	NA	+	+	NA	NA
	McAdams-DeMarco et al (2019) <sup>137</sup>	CKD stage 5 (N = 24)	2 months of supervised physical therapy sessions and home-based exercises	NA	NA	NA	NA	+ accelerometry
	Lorenz et al (2019) <sup>117</sup>	CKD stages 4-5 (N = 21)	2 months of supervised pulmonary rehabilitation sessions	+	NA	NA	NA	+ PFP <sup>7</sup> parameters
	Sheshadri et al (2020) <sup>121</sup>	Dialysis (N = 60)	3 months of pedometer-based intervention versus usual care	-	NA	NA	NA	+ weekly step counts
≥ 6 mo interventions	Koh et al (2010) <sup>116</sup>	Dialysis (N = 70)	6 months of intradialytic cycle ergometry versus home walking program versus usual care	NA	-	NA	NA	NA
	Chen et al (2010) <sup>112</sup>	Dialysis (N = 50)	6 months of intradialytic strength training versus stretching exercises	+	NA	NA	NA	NA
	Anding et al (2015) <sup>110</sup>	Dialysis (N = 46)	5 years of intradialytic cycle ergometry and resistance training	NA	-6 months +12 months	+6 months +12 months	+6 months +12 months	NA
	Bennett et al (2016) <sup>111</sup>	Dialysis (N = 171)	Up to 9 months of intradialytic resistance bands	NA	NA	+	+	NA
	Manfredini et al (2017) <sup>119</sup>	Dialysis (n=296)	6 months of a home walking program versus usual care	NA	+	+	NA	NA
	Hellberg et al (2019) <sup>115</sup>	CKD stages 3-5 (N = 151)	12 months of home endurance/balance training versus home endurance/strength training	NA	-	-	NA	+ 6MWT within groups

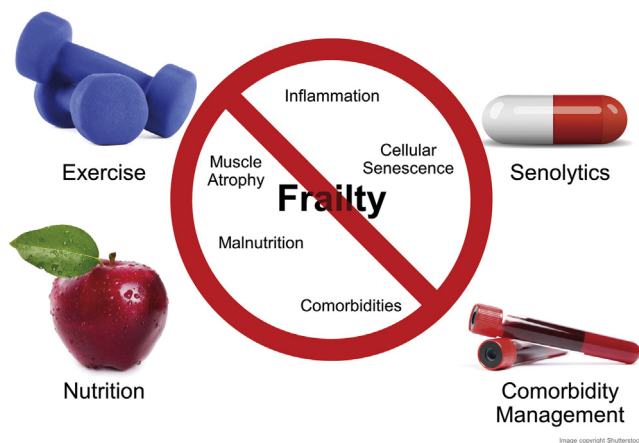
+, improved; -, no difference; 6MWT, 6-minute walk test; CKD, chronic kidney disease; PFP, physical frailty phenotype (e.g., Fried frailty phenotype); SPPB, Short Physical Performance Battery; STS, sit-to-stand test; TUG, Timed Up and Go Test.

Exercise in preparation for surgery, also known as prehabilitation, represents an exciting intervention that may be beneficial in KT candidates. The overall goal of prehabilitation is to improve patients' response to physiologic stress. Prehabilitation is associated with fewer postoperative pulmonary complications,<sup>131</sup> lower hospital cost,<sup>132</sup> improved postoperative physical function,<sup>133</sup> and decreased length of stay after non-transplant surgery.<sup>134,135</sup> Given the strong relationship between pretransplant frailty and adverse outcomes, the American Society of Transplantation developed a Frailty Consensus Statement that emphasizes the importance of developing effective frailty interventions in transplant candidates.<sup>136</sup> To our knowledge, the impact of prehabilitation in KT candidates has been examined in only 2 studies. McAdams *et al.*<sup>137</sup> studied the impact of an 8-week supervised exercise intervention in a cohort of 24 KT candidates within 3 to 6 months of transplantation. The authors found that prehabilitation was associated with a 64% improvement in physical activity based on accelerometry and decreased posttransplant length of stay compared with matched controls.<sup>137</sup> Similarly, we conducted a single-center pilot study (N = 21) examining the preliminary efficacy of an 8-week supervised exercise intervention in participants with advanced CKD, including KT candidates, and found that prehabilitation was associated with improvement in PFP parameters (e.g., physical activity, walking time, and grip strength), self-reported exhaustion, and Short Physical Performance Battery scores.<sup>117</sup>

Exercise interventions for frailty after KT have been associated with improved aerobic capacity, strength,

and quality of life,<sup>138</sup> although this has been less studied than interventions in the pretransplant and dialysis settings. In a systematic review involving 654 KT recipients, posttransplant exercise interventions were associated with improved aerobic capacity and quality of life.<sup>139</sup> The impact of walking programs after KT has been examined in several studies. The LIFT study found that an intervention using accelerometers combined with financial incentives and text messages resulted in increased step counts in a cohort of patients within 24 months of either kidney or liver transplantation.<sup>140</sup> We found that a 90-day pedometer-based physical activity intervention was associated with lower blood pressure and less impaired fasting glucose 4 months post-KT compared with a cohort of KT recipients who received usual care.<sup>141</sup> Unfortunately, clinical implementation of exercise programs after KT is limited due to a lack of evidence-based exercise guidelines, insufficient understanding of patient attitudes, and poor clinician engagement.<sup>130,142</sup>

Although exercise is 1 of the most effective anti-frailty interventions, other therapeutic targets for frailty are being actively investigated (Figure 3). Given the senescent cell burden in CKD,<sup>143,144</sup> the use of senolytics, drugs that selectively induce senescent cell removal, hold promise. Preclinical studies applying senolytics in mice both prevented and reduced physical dysfunction.<sup>106</sup> Our interim studies recently demonstrated the beneficial effect of a single 3-day regimen of the senolytic drug combination dasatanib plus quercetin to reduce senescent cell burden within adipose tissue in patients with diabetic kidney disease.<sup>97</sup> Dasatanib is a Src/tyrosine kinase inhibitor<sup>145</sup>



**Figure 3.** Components of promising antifrailty interventions in chronic kidney disease.

used to treat leukemias and other conditions, whereas quercetin is a plant flavonoid with anti-inflammatory and antioxidant properties.<sup>146</sup> In an open-label pilot trial in frail patients with idiopathic pulmonary fibrosis, a brief course of dasatanib plus quercetin was followed by an improved 6-minute walk distance, 4-m gait speed, chair stands, and Short Physical Performance Battery scores.<sup>147</sup> Larger-scale, randomized studies confirming the benefit of senolytics on frailty in patients with CKD are needed. Other promising anti-frailty interventions in CKD include the use of oral nutritional supplements, which were associated with significant improvements in the Timed Up and Go test, the 6-minute walk test, and handgrip strength in patients on dialysis,<sup>148</sup> and better management of anemia.<sup>149</sup> Although metabolic acidosis is a potential contributor to frailty in CKD, in an interventional study, sodium bicarbonate tablets had no impact on Short Physical Performance Battery scores in CKD patients with metabolic acidosis.<sup>150</sup> Others have suggested a potential role of androgens, growth hormone, and anti-inflammatory agents such as curcumin and resveratrol in improving body composition and handgrip strength in patients with CKD.<sup>151–153</sup> Finally, in KT recipients, steroid minimization may reduce frailty. It has been suggested that patients who undergo rapid steroid withdrawal after KT exhibit fewer changes in skeletal muscle structure and better self-reported physical function on the SF-36 compared with recipients maintained on prednisone.<sup>154,155</sup>

## Conclusions

Frailty, a syndrome of decreased physiological reserve, has emerged as a potential risk stratification tool in the nephrology literature. Multiple frailty measurements have been used in patients with CKD. Frailty is common among patients with nondialysis CKD, ESKD, and KT and is associated with adverse outcomes, including

decreased quality of life, increased health care use, and death. Frailty in CKD is associated with aging, physiological dysregulation, kidney function, and cellular senescence. Senescent cells contribute to inflammation and tissue dysfunction throughout the body. Exercise interventions, including short-term interventions, have been shown to improve frailty in patients regardless of CKD stage and may be an effective component of prehabilitation before KT. Promising new therapies for frailty include senolytics, which have been associated with improved frailty measures and senescent cell burden in pilot studies.

## DISCLOSURE

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## AUTHOR CONTRIBUTIONS

ECL researched data for the article. All authors contributed to the content of the manuscript and reviewed the manuscript before submission.

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