

## CKJ REVIEW

# Frailty in kidney transplantation: a review on its evaluation, variation and long-term impact

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## ABSTRACT

The problem of frailty in kidney transplantation is an increasingly discussed topic in the transplant field, partially also generated by the multiple comorbidities by which these patients are affected. The criteria currently used to establish the presence and degree of frailty can be rapidly assessed in clinical practice, even in patients with chronic kidney disease (CKD). The main objectives of this work are: (i) to describe the method of evaluation and the impact that frailty has in patients affected by CKD, (ii) to explore how frailty should be studied in the pre-transplant evaluation, (iii) how frailty changes after a transplant and (iv) the impact frailty has over the long term on the survival of renal transplant patients.

**Keywords:** chronic kidney disease, frailty, graft survival, renal transplantation

## INTRODUCTION

Frailty in kidney transplantation is an increasingly discussed topic in the transplant field. In clinical practice, nephrologists frequently care for frail patients affected by multiple comorbidities [1–3]. It is important to remember that 'frailty', is not always associated with ageing and even relatively young patients may be affected to some extent [4]. The state of frailty in patients with chronic kidney disease (CKD) is more prevalent today than in the past [5], reflecting the better ability of the nephrologist to improve patient survival. As recently reported, the mortality of the CKD population over the age of 65 years has progressively declined [6]. In addition, diseases with a high impact of frailty are increasingly frequent and increasingly involve ageing subjects [7, 8].

This work aims to describe the impact of frailty in CKD patients. The pre-transplant evaluation of frailty, its course following a renal transplant (RTx), and its impact on the long-term survival of patients will also be discussed.

## FRAILTY: WHAT IS IT REALLY ABOUT?

Over the years, many efforts have been made to obtain a more precise definition of frailty in the general population [9–11]. Unfortunately, a consensus on the exact operational definition of frailty is still lacking. For this reason, a comprehensive geriatric assessment is still considered the gold standard to define frailty. In research settings, frailty is mostly operationalized by the Fried phenotype or the Frailty Index (FI) [12, 13].

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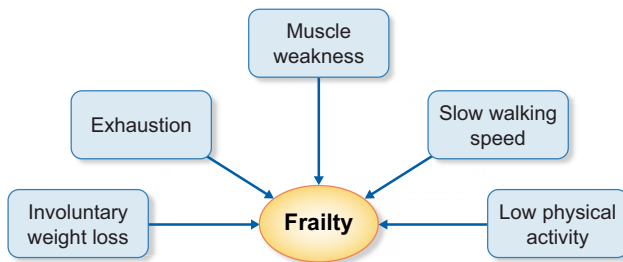


FIGURE 1: The components of frailty, according to the criteria proposed by Fried et al.

This aspect has been minimally explored in CKD patients, and even less so in RTx patients. Harhay et al. [14] have summarized most of the available frailty instruments that have been applied to populations with CKD, dialysis dependence and RTx. The different tools are variably composed of objective and/or subjective measurements of general health status and morbidity, functional performance and disabilities, with some scales including also social support, medication use, nutrition and cognition. In particular, the presence of frailty as measured with Clinical Frailty Scale, physical frailty phenotype (PFP), Groningen Frailty Indicator (GFI), FI, FRAIL scale and SF-12 PCS, was significantly related to complications and/or mortality in dialysis or RTx patients [15–19].

Currently, in the nephrology field, in the absence of clear guidelines, the operational definition of frailty is usually that proposed by Fried et al. [12] in 2001, the so-called frailty phenotype, one of the most commonly adopted in the literature. In this model, frailty is assessed through the evaluation of five criteria (Fig. 1): involuntary weight loss, exhaustion, muscle weakness, slow walking speed and low physical activity. Frailty is thus phenotypically described as a multicomponent syndrome, which considers objective and subjective factors, and is characterized by an increased vulnerability to stressors.

Every component has a score of 0 if negative and 1 if present. The sum of the points obtained from each factor composes a final score from 0 to 5:

- non-frail: score equal to 0;
- pre-frail: score of 1 or 2;
- frail: score between 3 and 5.

The major strength of this evaluation is that it can be easily obtained in clinical practice in no more than 10 min since it is based on a phenotypic evaluation and simple measurements [20].

Of note, many definitions of frailty are present in the literature. The FI, differently from the Fried score, is composed of 30–70 deficits. They are measured by clinical symptoms, functional impairments, laboratory findings, disabilities and comorbidities. The ratio of the number of deficits present to the total number of items assessed gives the index score. So, it gives a less subjective measure of the severity of frailty [13].

Sarcopenia, defined as low muscle mass and function, has also been used as an objective indicator of frailty. It can be assessed through dual-energy X-ray absorptiometry or estimated by computed tomography, magnetic resonance imaging or bioimpedance [21].

The Short Physical Performance Battery concentrates on measuring the lower extremity function, which is associated with physiologic reserve muscle mass and therefore has also been used to assess frailty. However, at the moment, no application of the Short Physical Performance Battery in CKD is validated [22].

The Clegg score is based on 36 variables from primary care data, including symptoms, signs, diseases, disabilities and abnormal laboratory values, referred to as deficits. The score is the number of deficits present, expressed as an equally weighted proportion of the total [23].

The Minnesota Leisure Time Activity Scale is a questionnaire used in the general population. Its use is not reliable in the advanced organ failure population because it is concentrated principally on moderate to strong activities [24].

## FRAILITY IN PATIENTS WITH CKD

For many years, attempts have been made to identify the prevalence and impact of frailty in patients with CKD [25, 26].

Table 1 summarizes the most relevant and numerous studies concerning the evaluation of frailty in CKD patients, differentiating them on the basis of the subpopulation under study (patients with CKD stage 1 through 5, on dialysis or kidney transplant recipients) and the utilized frailty assessment tool.

Table 1. Most relevant and numerous studies concerning the evaluation of frailty in CKD patients, differentiating them on the basis of the subpopulation under study and the utilized frailty assessment tool

| Type of CKD population | Type of study and date of publication             | Numerosity      | Frailty assessment tool                     | Geographic area | Main findings                                                                                                                                                                                                                                   |
|------------------------|---------------------------------------------------|-----------------|---------------------------------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CKD                    | Wilhelm-Leen et al. 2009 [27] retrospective study | 10 256 patients | PFP                                         | USA             | Frailty was significantly associated with CKD, particularly with stages 3b–5 CKD (OR 5.5; $P = .05$ )<br>Frailty and CKD were independently associated with mortality                                                                           |
| ESRD                   | Bao et al. 2012 [28] retrospective study          | 1576 patients   | Modification of PFP by Johansen et al.      | USA             | Frailty was associated with mortality (HR 1.57; $P < .001$ ) and time to first hospitalization (HR 1.26; $P < .001$ )                                                                                                                           |
| Dialysis patients      | Chao et al. 2015 [18] prospective study           | 46 patients     | SQ, EFS, SFS, GFI, G8 questionnaire and TFI | Asia            | Each questionnaire showed significant association with each other, except the G8 questionnaire<br>Only simple FRAIL scale correlated significantly with age, lower serum albumin and creatinine levels and higher ferritin levels ( $P = .05$ ) |

Table 1. Continued.

| Type of CKD population            | Type of study and date of publication                                | Numerosity                                                                                                  | Frailty assessment tool                                                                                                                                      | Geographic area | Main findings                                                                                                                                                                                                                                                               |
|-----------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| KT waiting list candidates        | McAdams-DeMarco et al. 2019 [29] observational and prospective study | 24 patients                                                                                                 | PFP<br>Short physical performance battery                                                                                                                    | USA             | 5 prehabilitation participants had shorter length of hospital stay at KT than age-, sex- and race-matched control (5 versus 10 days; RR = 0.69; P = .02)                                                                                                                    |
| Solid organ transplant candidates | Varughese et al. 2021 [30] retrospective study                       | 794 patients                                                                                                | 40 variables FI                                                                                                                                              | Canada          | Higher FI was associated with an increased risk of death or delisting (HR 1.03/0.01 FI score; P = .01)                                                                                                                                                                      |
| KT waiting list candidates        | Pérez-Sáez et al. 2021 [31] prospective study                        | 455 patients                                                                                                | PFP                                                                                                                                                          | Spain           | Frailty was more prevalent in CKD women (OR 1.91; P = .047)<br>Frailty criteria distribution and phenotype seem to differ among sexes, with possible influence on type of interventions to adopt before transplantation                                                     |
| KT recipients                     | McAdams-DeMarco et al. 2013 [32] prospective study                   | 383 patients                                                                                                | PFP                                                                                                                                                          | USA             | Frailty was an independent predictor for EHR following KT in recipients (45.8% versus 28.0%; P = .005)                                                                                                                                                                      |
| KT recipients                     | McAdams-DeMarco et al. 2015 [33] prospective study                   | 663 patients                                                                                                | PFP                                                                                                                                                          | USA             | Frailty was associated with a higher risk of death (HR 2.17; P = .047)                                                                                                                                                                                                      |
| KT recipients                     | McAdams-DeMarco et al. 2015 [34] prospective study                   | 525 patients                                                                                                | PFP                                                                                                                                                          | USA             | Frail recipients had more MDR (HR 1.29; P = .04), which was associated with an increased risk of graft loss (aHR 5.24; P = .001)                                                                                                                                            |
| KT recipients                     | McAdams-DeMarco et al. 2017 [35] observational Study                 | 663 patients                                                                                                | PFP<br>they also measured activities of daily living, instrumental activities of daily living (IADL), Centres for Epidemiologic Studies Depression and HRQOL | USA             | Older recipients were more likely to be frail (PR = 2.22; P = .05)<br>IADL disability (PR = 3.22), depressive symptoms (PR = 11.31), less than a high school education (PR = 3.10) and low HRQOL (fair/poor PR = 3.71) were independently associated with frailty (P = .05) |
| KT recipients                     | McAdams-DeMarco et al. 2018 [36] prospective study                   | 443 patients                                                                                                | PFP<br>they measured QOL with kidney disease QOL instrument short form                                                                                       | USA             | Frail recipients experience more improvement than non-frail recipients in post-KT physical (1.35 points/month versus 0.34 points/month, P = .02) and kidney disease specific HRQOL (frail: 3.75 points/month versus 2.41 points/month, P = .01)                             |
| KT recipients                     | Chu et al. 2019 [37] prospective study                               | 665 patients                                                                                                | PFP<br>they measured cognitive function with 3MS                                                                                                             | USA             | Recipients experienced short-term cognitive improvement post-KT<br>Frailty was associated with medium-term cognitive decline post-transplant (slope = -0.04 points of 3MS/week; P = .05)                                                                                    |
| KT recipients                     | Harhay et al. 2020 [14] systematic review                            | 641 unique articles. EMBASE, community index to nursing and allied health literature and Cochrane databases | Clinical frailty scale, PFP, GFI, TFI, FI, EFS, FRAIL scale, SQ, SF-12 PCS, SPPB, timed up and go, gait speed                                                | Worldwide       | The PFP is the most commonly used frailty metric in ESKD research, and KT recipients who are frail at KT (~20% of recipients) are twice as likely to die as non-frail recipients                                                                                            |
| KT recipients                     | Quint et al. 2021 [38] systematic review and meta-analysis           | 18 studies                                                                                                  | 15 studies used the PFP; the Kihon checklist, the frailty risk score and the GFI were used in 1 study each                                                   | Worldwide       | Frailty was associated with lower rates of preemptive transplantation (relative risk 0.60; P = .05), older recipient age (mean difference 3.6; P = .05), higher rates of DGF (relative risk 1.80; P = .05) and longer length of stay (OR 1.64; P = .05)                     |

3MS, modified mini-mental state examination; CI, confidence interval; EHR, early hospital readmission; ESRD, end-stage renal disease; HRQOL, health-related quality of life; KT, kidney transplant; MDR, mycophenolate mofetil dose reduction; OR, odds ratio; PR, adjusted prevalence ratio.

In 2009, Wilhelm-Leen et al. [27] estimated a prevalence of frailty in CKD patients of ~2.8%. However, it is essential to note that among people with moderate to severe CKD (GFR < 45 mL/min), it increased up to 20.9%. A sub-analysis, which observed the different prevalence of the physical frailty criteria through the different states of CKD, identified sedentary behaviour and muscle weakness as the most represented. The presence of frailty also independently and significantly increased the risk of short-term mortality in CKD patients.

Some attempt was also made to evaluate the impact of frailty in the haemodialysis population [39, 40]. In particular, Bao et al. [28] demonstrated how the presence of frailty is associated with a significant increase in the risk of hospitalization and long-term mortality in a cohort of 1576 haemodialysis patients. A study from Chao et al. [18] compared six types of self-report questionnaires for assessing frailty in chronic dialysis patients [Strawbridge questionnaire (SQ), Edmonton Frail Scale (EFS), simple FRAIL scale (SFS), GFI, G8 questionnaire and Tilburg Frail Indicator (TFI)]. The results showed that the simple FRAIL scale might had a closer relationship with dialysis complications, having a consistent correlation with age ( $P = .02$ ), lower serum albumin ( $P = .03$ ), creatinine levels ( $P < .01$ ) and higher ferritin levels ( $P = .02$ ). It is nowadays common knowledge that muscle mass, muscle strength and inflammation are all important predictors of outcomes in the CKD population, with low serum albumin and low serum creatinine having a direct correlation with mortality [41, 42].

## RENAL TRANSPLANTATION AND FRAILTY

Although RTx frequently grants an almost complete resolution of uremia, it is often unable to completely resolve some metabolic complications, typical of advanced CKD [43, 44]. Furthermore, from the very beginning of his/her transplant history, the transplant recipient presents immunological, metabolic and psychological conditions, which must be considered at the time of acceptance on the RTx waiting list [45, 46]. These factors also need to be regularly reassessed and eventually treated (when possible) throughout the transplant life. To further complicate the issue, there are still no guidelines to help clinicians decide whether to admit a frail older patient to the transplant waiting list. This means that the decision on whether or not to consider a frail patient suitable for RTx is mainly related to subjective opinions or policies varying across centres.

### Frailty in the pre-transplant time

The problem of assessing frailty in the dialyzed population and how this can affect any RTx is still much debated [30]. In 2019, an international meeting was organized to report the available evidence on frailty in patients waiting for solid organ transplantation. The ambition of the meeting was also to develop and validate a standard definition and characterization for frail patients, to apply in this specific clinical practice. At the end of this meeting, however, it was decided that the knowledge on such an important issue was still relatively small and limited. It was confirmed that frailty represents a common condition in patients with end-stage organ disease waiting for transplantation and is associated with poor prognosis in those remaining on the active transplant list. However, it was particularly emphasized that the optimal method to measure frailty in these patients is still far from being determined, leaving a certain degree of freedom in the choice of the instruments to adopt [47].

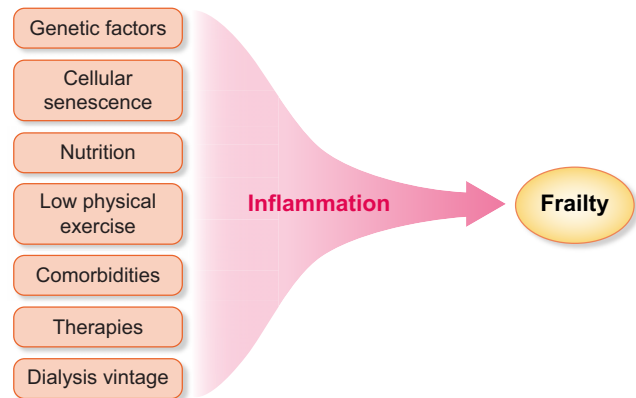


FIGURE 2: Main factors related to underlying inflammation and frailty in patients with CKD.

In a paper published by McAdams-DeMarco et al. [33], 537 patients on the RTx waiting list were evaluated and classified according to the PFP. A state of overt frailty was present in ~20% of patients. Pre-frailty was found in 33% of this population, meaning that >50% of patients on the active RTx list presented an increased vulnerability to endogenous and/or exogenous stressors. We will evaluate below how this frailty can influence the success of the transplant and the patient's short- and long-term survival.

## BUT WHAT ARE THE POTENTIAL FACTORS DETERMINING THE DEVELOPMENT OF FRAILTY IN RTx PATIENTS?

Some are universal factors, such as cellular senescence and mitochondrial decline, typical of old age, that can favour the establishment of a condition of frailty. However, CKD patients have some peculiarities (Fig. 2); for example, frailty is significantly linked to time on dialysis before transplantation [48]. Polypharmacy, malnutrition and low physical exercise are factors that in the long run can certainly favour, maintain and increase frailty. Furthermore, it should not be forgotten that these patients often have comorbidities such as peripheral vascular diseases, diabetes mellitus and depression. The result of all this is a major increase in the degree of underlying inflammation and therefore a further stimulus to the development of frailty. On the other hand, it is sometimes difficult to understand what comes before or after. For example, many diseases have a pathogenic substrate based on inflammation. Chronic inflammation is also the basis of 'inflamm-aging' and could also be a strong determinant of the conditions causing frailty.

The impact of inflammation on frailty was recently demonstrated in 2300 patients with CKD, noting the relationship between frailty, cognitive functions and urinary biomarkers of tubular damage. Frail patients had higher levels of inflammatory cytokines compared with controls, supporting the association between inflammation and frailty [49]. A recent work from Pérez-Sáez et al. [31] also showed a higher prevalence of frailty in female CKD patients (47.2% of frail females versus 22.5% of frail men;  $P < .001$ ), as described in the general population. This is possibly because of females having lower lean mass and a higher level of sarcopenia and the impact of social factors (for example, lower income); comorbidities were instead more present in frail men. This phenomenon needs to be further evaluated, especially because the higher frailty prevalence in female

patients is in contrast to their lower mortality in advanced CKD stages.

As proof that the concept of frailty is not just related to ageing, frailty may also be present in chronologically young and adult individuals. A work published in 2017 based on 663 RTx patients showed signs of frailty in 45% and 40% of people aged 46–65 years and 18–45 years, respectively. The main factors involved in defining frail patient status were sedentariness and muscle weakness. Moreover, frail transplant patients were at greater risk of early re-hospitalization after transplantation, regardless of age [35]. The state of frailty also seems to improve the discriminating power of previously published statistical registry models in estimating the risk of early re-hospitalization after transplantation. In fact, the area under the curve of receiver operating characteristic models increased from 0.63 to 0.70 after adding frailty to the 11 traditional factors. These data further show that frailty might be considered an age-independent predictor of potential complications in post-transplantation, even in the short term. Therefore, a pre-transplant assessment of frailty could allow clinicians to identify those patients who are at the highest risk of developing post-transplant complications [32].

However, two important questions remain still open: Is it possible in some way to decrease the state of frailty in the pre-transplant period? And, if possible, can this have an impact on the patient's post-operative outcome?

In 2019, a study was published regarding the role of 'pre-habilitation' before RTx in patients on the active waiting list. Pre-habilitation was defined as the process of increasing functional operational capacity to improve tolerance to stressful events. The aims of the study were to evaluate the feasibility of a centre-based weekly pre-habilitation programme and its effects on post-transplant hospital stay. Patients showed a significant improvement in their physical and motor capacity after only 2 months of the programme. Furthermore, patients also reported a significant amelioration of their overall health status. Of the 18 patients studied, 5 received RTx in the follow-up period. These patients, compared with patients matched for age, sex and race, had shorter post-transplant hospital stay (5 versus 10 days) [29]. This study demonstrates the importance of targeted physical therapy and maintenance of physical activity for patients on the transplant list, aiming to positively impact short-term outcomes. These results agree with what has been observed in the general population [50].

### Does the renal transplant modify the frailty status?

As previously mentioned, frailty at the time of transplantation is a relatively frequent occurrence in patients with CKD. It is important to evaluate whether it can change in the post-transplant period. A work published in 2015 has shown that ~50% (out of 349 transplanted patients) were affected by some degree of frailty (20% overtly frail) at the RTx time. A re-assessment of frailty was conducted after 1, 2 and 3 months. Although the first evaluation showed an increased prevalence of frailty (from 20% to 33%), frailty declined in the months following RTx (frail patients, 17%). This work unequivocally demonstrates that frailty may worsen soon after transplantation, but positive effects from the intervention are visible over the longer term. Moreover, the study confirms the reversible nature of the frailty condition [51].

The evaluation of the effects of RTx on self-reported quality of life (QOL) is similarly important. In a recent work, QOL (perceived in both physical and mental domains) was evaluated in 443 frail RTx patients; the assessment especially considered the burden of CKD. In this case, the assessments were

conducted after 1 and 3 months from the transplantation. The results showed a significant improvement in the perceived QOL, especially after the third month. It should also be noted that significant improvements (especially in the mental domain) were present after 1 month. These results have special implications for candidates for RTx in a condition of frailty and insufficient dialysis tolerance [36].

If the results derived from the state of frailty in general and from the QOL are absolutely encouraging, the same cannot be said for long-term cognitive function. In a recent work published by Chu et al. [37] 665 renal transplant patients were evaluated for cognitive function at 3 months, 6 months, 1 year and then up to 4 years post-transplant (median follow-up of 1.5 years post-transplant); 15% of them had a state of frailty after transplantation. An improvement in general cognitive functions in both the frail group and the non-frail group was observed. Unfortunately, between 1 year and 4 years post-transplant, frail patients had a major decline in cognitive function, an event absent in the non-frail cohort.

### Does frailty affect survival?

Another debated topic is the effect of pre-transplant frailty on long-term RTx survival. Three main areas of frailty have particularly been explored and need to be considered: immunosuppressive therapy; RTx functional recovery and long-term survival of frail patients.

In 2015, McAdams DeMarco et al. [34] explored the relationship between mycophenolate mofetil (MMF) therapy, frailty and kidney loss in 525 transplant patients (prevalence of frailty: 19.5%). During the first year of RTx, a reduction or discontinuation of MMF became necessary in half of the patients. These patients were older and had a higher prevalence of deceased donor RTx. In the 4 years following RTx, MMF was more frequently decreased in frail patients versus non-frail patients. Indeed, frailty represented a significant and independent risk factor for the reduction or discontinuation of the drug [hazard ratio (HR) 1.29]. Furthermore, patients who decreased or discontinued the immunosuppressant presented a higher risk of graft rejection during the first year of follow-up. The mechanism linking immunosuppressive therapy and frailty remains unclear. Likely, poor tolerance to immunosuppression and decreased physiological reserves in patients with frailty are involved.

It has been reported that frail patients have an 80% increased risk of having a delayed recovery of renal function after transplantation, requiring dialysis during the first week, the so-called 'delayed graft function' (DGF). It is noteworthy, however, that

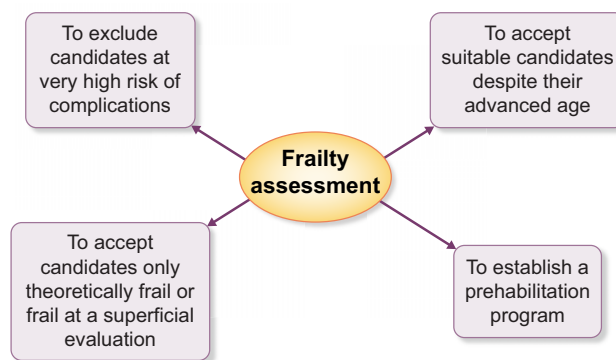


FIGURE 3: The main conclusions of the literature review: usefulness of frailty assessment in pre-transplant assessment.

only four papers have, to date, explored this relationship, thus leaving the matter open to the need for further studies [38]. The cellular damage and cell death caused by ischemic and reperfusion damage, typical of the immediate post-transplantation period, may lead to the release of inflammatory mediators. The pro-inflammatory scenario may then activate immune cells and further inflammation determining renal tubular epithelial cell damage. In this context, the inflammatory background characteristic of frailty can actively contribute. At the same time, inflammation is associated with a decreased effective immune response to immunogenic stimulation and an inability to effectively dispose of cellular debris [52–54]. These aspects might explain the association between frailty and the risk of DGF.

The role played by frailty in mortality in RTx patients is particularly relevant. Data published in 2015 showed 5-year survivals of 91.5%, 86.0% and 77.5% for non-frail, mildly frail and frail recipients of RTx, respectively. Furthermore, being frail was independently associated with a >2-fold increased risk of death [48].

More recent data coming from almost 20 000 RTx candidates have shown a longer stay on the transplant waiting list for frail patients; this finding might be associated with the possible deterioration of the clinical status and worsening of frailty. There was, however, a significant reduction in mortality in frail patients who received a RTx, noticeable as early as the sixth month post-transplant, compared with patients remaining on dialysis [55]. This fact supports the usefulness and importance of performing an RTx in all possible cases.

## CONCLUSIONS

In conclusion, RTx should always be considered in the spectrum of therapeutic options for frail patients (Fig. 3).

The assessment of frailty in clinical practice should be routinely incorporated in the evaluation of potential RTx candidates. It provides complementary information for better estimating the individual's reserves and better identifying those who might benefit more from the transplantation. The assessment of frailty in the dialysis population would allow transplantation programmes and clinicians to recognize more easily patients who might be unfit to receive a RTx because of their conditions or because of a high risk of complications. Furthermore, identifying frailty might introduce the patient to multidisciplinary programmes aimed at offering adapted protocols/solutions. These may include pre-habilitation strategies or management of comorbidities that negatively affect the individual's risk profile. In this way, every patient will be offered the most suitable solution for his condition, regardless of his/her chronological age.

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## AUTHORS' CONTRIBUTIONS

Conceptualization: C.A. S.M., M.C. and G.C.; methodology: C.A.; writing—original draft preparation: C.A., S.M., M.C., S.V., M.B., E.C., R.M., L.C., A.P., A.C. and G.C.; all authors have read and agreed to the published version of the manuscript.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest

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