



The need for a multi-disciplinary reflection about frailty and cognitive impairment in chronic kidney disease

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The paper by Robin Greinert *et al.* [1] touches upon a topic that is increasingly attracting interest from different perspectives (e.g. neurology, nephrology, ethics), but that at the same time is still in need of more focused and deeper analysis. To illustrate its relevance, the connection between chronic kidney disease (CKD) and cognitive impairment (CI) is the subject of an ongoing COST Action (CONNECT, Cognitive Decline in Nephro-Neurology, <https://connectcost.eu/>) which is devoted to clarifying the causal mechanisms of cognitive decline in CKD in order to improve its clinical treatment, in terms of both prevention and care.

The paper by Greinert and colleagues reports the result of an interview study involving 62 patients, which shows a high prevalence of CI associated with decreased mobility and muscle strength, increased frailty, and reduced Health Related Quality of Life (HRQoL). Importantly, the research by Greinert *et al.* sheds new light on the relationship between CI and frailty, which, among other things, is key in order to plan appropriate clinical and therapeutic approaches. The clinical translation of these data is still to be considered, but results like these are important to plan relevant strategies.

In order to maximize the effectiveness of these plans, it is necessary to implement a multi-disciplinary collaboration (see Fig. 1), including neuroscientific research on the molecular and cognitive dimensions of CI, neurological and neuro-psychological assessments of related physiological and behavioral factors, nephrological research on the relevant pathophysiological mechanisms, and ethico-legal reflection on the emerging ethical and regulatory issues.

A preliminary condition for this kind of multi-disciplinary approach is a specific conceptual clarification of key terms, which are relevant to all the involved disciplines but risk being interpreted differently and eventually giving rise to mutual

misunderstanding. Frailty in particular deserves specific attention.

The classical definition of frailty is as a syndrome of decreased physiologic reserve characterized by functional decline in different physiological systems and reduced capacity to resist to stressors [2, 3]. The data collected by Greinert *et al.* confirm that frailty is associated with some indicators of reduced healthy condition, like increased risk of falls, hospitalizations, CI, reduced HRQoL and even mortality [4].

Since the availability of kidneys for transplantation does not meet the need for organs actually required, some criteria for including patients in kidney transplantation list and for setting priorities among them are necessary. Frailty and CI are increasingly used for this purpose [5–7].

One possibility is referring to frailty and CI to select and prioritize patients within a utilitarian framework, for instance giving priority to less frail and younger patients with life expectancy and potential quality of life that at first glance are better. Yet things are not so straightforward. In fact, data indicate that 'Frailty is more prevalent among older hemodialysis patients, KT candidates, and KT recipients; however, there is a high prevalence of frailty among younger patients as well' [3]. Furthermore, the fact that post-transplant outcome is overall worse for frail patients is importantly counterbalanced by the fact that sometimes frailty is improved in transplanted patients. In fact, the assessment of frailty at evaluation and/or during transplantation admission combined with appropriate clinical management significantly improve the rate of positive outcome [8].

The above raises a clinical as well as an ethical concern: frailty cannot be assumed as an absolute factor in deciding about the patient's inclusion in the transplantation waitlist, because such a condition may be improved by the

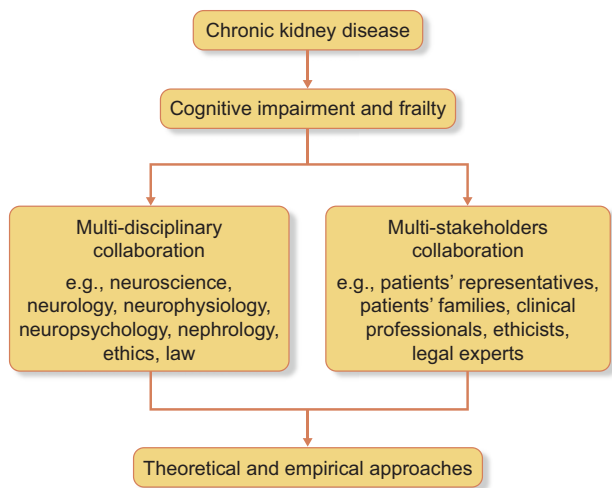


Figure 1: A model for addressing ethical and legal issues arising from CKD.

transplantation itself. Therefore, a multi-perspective (e.g. involving professionals, patients' associations and patients' families) and multi-disciplinary reflection is needed, and additional factors should be evaluated in making a final decision about the transplantation.

Like frailty, also CI is increasingly used to place patients on waitlists and to set priorities among them. However, CI also cannot be assumed as an absolute factor, since data indicate that cognitive functions improve after kidney transplantation [9]. Thus, as stressed by Shrestha *et al.*, the use of both frailty and CI in kidney allocation deserves an ethical analysis, analogous to what has already done in other medical fields [10]. Such ethical analysis should combine both theoretical (e.g. principle-based) reflection and empirical investigation (e.g. about the stakeholders' opinion). In their paper, Shrestha and colleagues investigate the patients' opinions about the ethical principles that should be considered in using frailty and CI for allocating kidneys for transplantation. Four themes emerged in particular 'in which participants: (1) valued maximizing a scarce resource (utility); (2) prioritized equal access to all patients (equity); (3) appreciated a proportional approach to the use of equity and utility (precautionary utility); and (4) sought to weigh utility- and equity-based concerns regarding social support' [3]. The tendency of the patients is to balance a utilitarian and an egalitarian approach, and they tend to call for planning strategies in order to improve frailty and cognitive function both before and after the transplantation.

These data are extremely useful in order to plan ethically informed clinical strategies for the assessment of frailty and CI in the allocation of kidneys for transplantation. However, other stakeholders should also be consulted (see Fig. 1). For this reason, a survey about 'Cognitive decline related to chronic kidney disease as an exclusion factor from kidney transplantation' is currently in progress as part of the abovementioned COST Action CONNECT. Preliminary results (154 respondents from 41 countries so far) indicate that:

- There is currently a lack of consensus on the necessity and the modality of psychological assessment of kidney

transplant candidates, with international guidelines not consistent on this point

- The majority of respondents think that all patients with CKDs should have a face-to-face psychological assessment performed by a professional in collaboration with the patient's family before being admitted to kidney transplantation
- Importantly, the majority of respondents think that cognitive decline can become a contraindication to kidney transplantation.

There are plenty of clinical, ethical and legal issues arising from the connection between frailty, CI and kidney transplantation. These issues regard not only the choice of which patients to eventually include on waitlists, but also if and how frailty and CI impact on some ability traditionally considered as key for ethical and legal requirements like autonomy and self-determination (e.g. through informed consent).

The paper by Greinert *et al.* is the kind of empirical research needed for informing this debate. It provides useful data and indicates the direction to further explore to advance in the discussion and to eventually improve the healthcare and the quality of life of affected patients.

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CONFLICT OF INTEREST STATEMENT

None declared.

APPENDIX

CONNECT Consortium Collaborators:

Members of the COST Action CA19127-Cognitive Decline in Nephro-Neurology: European Cooperative Target (CONNECT) Consortium:

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(See related article by Greinert *et al.* Subclinical cognitive impairment in chronic kidney disease is associated with frailty and reduced quality of life. *Nephrol Dial Transplant* 2023; 38: 1151–1157)

REFERENCES

1. Greinert R, Greinert D, Eger A-L *et al.* Subclinical cognitive impairment in chronic kidney disease is associated with frailty and reduced quality of life. *Nephrol Dial Transplant* 2022;gfac303. doi: 10.1093/ndt/gfac303. Online ahead of print.
2. Fried LP, Tangen CM, Walston J *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Med Sci* 2001;56:M146–57.
3. Shrestha P, Van Pilsom Rasmussen SE, Fazal M *et al.* Patient perspectives on the use of frailty, cognitive function, and age in kidney transplant evaluation. *AJOB Empir Bioeth* 2022;13:263–74.
4. McAdams-DeMarco MA, Olorundare IO, Ying H *et al.* Frailty and postkidney transplant health-related quality of life. *Transplantation* 2018;102:291–9.
5. McAdams-DeMarco MA, Van Pilsom Rasmussen SE, Chu NM *et al.* Perceptions and practices regarding frailty in kidney transplantation: results of a national survey. *Transplantation* 2020;104:349–56.
6. Gupta A, Montgomery RN, Bedros V *et al.* Subclinical cognitive impairment and listing for kidney transplantation. *Clin J Am Soc Nephrol* 2019;14:567–75.
7. Harhay MN, Rao MK, Woodside KJ *et al.* An overview of frailty in kidney transplantation: measurement, management and future considerations. *Nephrol Dial Transplant* 2020;35:1099–112.
8. Chen X, Liu Y, Thompson V *et al.* Transplant centers that assess frailty as part of clinical practice have better outcomes. *BMC Geriatr* 2022;22: 82.
9. Chu NM, Gross AL, Shaffer AA *et al.* Frailty and changes in cognitive function after kidney transplantation. *J Am Soc Nephrol* 2019;30: 336–45.
10. Wilkinson DJC. Frailty triage is rationing intensive medical treatment on the grounds of frailty ethical? *Am J Bioeth* 2021;21:48–63.

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