

# Cognitive impairment in kidney transplanted patients

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## ABSTRACT

Chronic kidney disease affects almost all of the organs. Recently, more attention has been paid to the kidney and the central nervous system connections. In patients on kidney replacement therapy, including kidney transplantation, there is an increased prevalence of cognitive impairment, and depression and other neurological complications, such as cerebrovascular disorders and movement disorders. Kidney transplant recipients need an assessment for the risk factors and the pattern of cognitive impairment (memory, attention and executive function decline). This enables an accurate diagnosis to be made at an earlier stage. Partial post-transplant cognitive impairment recovery is also important. Finally, doctors and patients alike face numerous ethical concerns and challenges regarding the transplantation of kidneys and other solid organs. In this review, we examined some key issues regarding cognitive impairment in kidney transplant patients. We focused on the mechanism of cognitive impairment in kidney transplant recipients, patterns of cognitive impairment; evaluation of patients with cognitive impairment for kidney transplantation, the potential impact of cognitive impairment on waitlisted and transplanted patients on patient care, non-pharmacological interventions and unmet medical needs, psychological and ethical issues in kidney transplantation, and unmet needs. As cognitive impairment in kidney transplant recipients is an underestimated, underrecognized but clinically relevant problem, screening for cognitive function before and after kidney transplantation would be worth considering in standard routine practice.

**Keywords:** chronic kidney disease, cognitive impairment, ethics, kidney transplantation, psychological issues

## INTRODUCTION

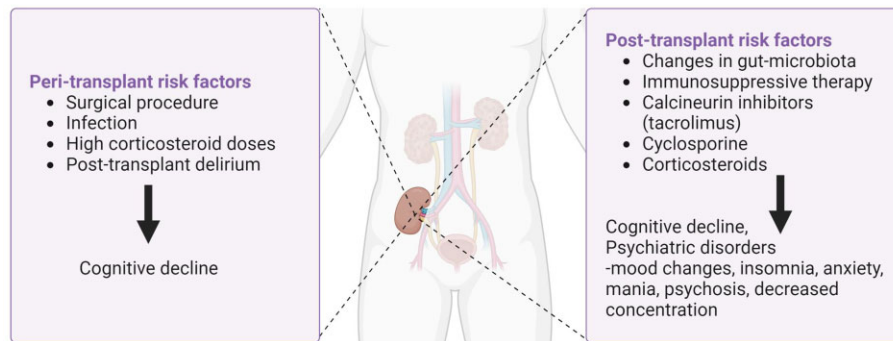
Chronic kidney disease (CKD) is considered a serious non-communicable disease becoming a global health threat [1]. Kidney transplantation (KT) is the optimal management for patients with end-stage kidney disease [2], and patients undergoing KT have a better quality of life and survival (life expectancy) compared to those treated with dialysis [2]. However, prior long-term dialysis and long-term immunosuppressive therapy can lead to a wide range of side effects, including cognitive problems [3, 4]. Patients with CKD are at greater risk of developing cognitive impairment (CI) [5]. Moreover, this risk is significantly higher in patients undergoing renal replacement therapy, including KT [6–8]. Previous studies have demonstrated that prevalence of CI in kidney transplant recipients varies between studies [8, 9]. Nevertheless, CI remains an important concern because any patient who undergoes KT can develop cognitive deficits. Although cognitive testing is not a routine practice before and after KT, it appears to be essential for identifying CI at an early stage so that appropriate management can be implemented. Patients with even mild CI may

require the support and involvement of family members in the decision-making process and assistance in adhering to medical recommendations. Furthermore, cognitive dysfunction in kidney transplant recipients may be associated with numerous complications, worse outcomes and more frequent post-transplant hospitalizations [10]. On the one hand, the number of KT is increasing every year [11]; on the other hand, it is a challenge for the physicians and everyone involved in patient care. It is the responsibility of physicians, particularly nephrologists, neurologists, and geriatricians, to address many problems related to the care of KT patients. These patients often require a multidisciplinary approach and specialized assessment. KT recipients need an assessment for the risk factors and the pattern of CI (memory, attention and executive function decline). This enables an accurate diagnosis to be made at an earlier stage. Partial post-transplant CI recovery is also important. Finally, doctors and patients alike face numerous ethical concerns and challenges regarding the transplantation of kidneys and other solid organs. In this review, we will examine some key issues regarding CI in kidney transplant patients.

Received: June 29, 2024; Editorial decision: September 16, 2024

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## Cognitive impairment in KT patients



**Figure 1:** Mechanism of cognitive impairment in kidney transplant (KT) recipients.

### MECHANISM OF COGNITIVE IMPAIRMENT IN KIDNEY TRANSPLANT RECIPIENTS (FIG. 1)

#### Vascular risk factors and brain changes in CKD

The etiology of CI in patients with CKD is multifactorial, with several causes potentially leading to cognitive decline. These include traditional risk factors for cardiovascular disease, as well as variables associated with kidney disease [4]. Both the kidney and the brain are organs with low vascular resistance, high blood flow and similar vasoregulatory systems [4]. Consequently, cerebral and glomerular small vessel disease may explain cognitive decline in CKD patients [3]. Imaging markers of cerebral small vessel disease include white matter hyperintensities, leukoaraiosis, silent brain infarction, small subcortical infarcts, lacunes, cerebral microbleeds, enlarged perivascular spaces, and brain atrophy, visible on brain magnetic resonance imaging scans [12]. Patients with CKD have more white matter lesions on brain magnetic resonance imaging than the general population [13]. Cerebral small vessel disease may result in subcortical ischemic vascular dementia, which is clinically characterized by progressive symptoms of CI, mood changes, depression, urinary tract disorders, difficulty walking (short-stepped gait), dysphagia and dysarthria [12]. Several cognitive domains may deteriorate in the course of subcortical ischemic vascular dementia, but the most prominent are impairments in executive function, complex attention, and information processing [12]. Memory problems include forgetfulness and difficulties with spontaneous recall, which are less severe than in Alzheimer's disease [12]. Conversely, the concomitant presence of Alzheimer's disease, nonvascular risk factors such as oxidative stress, chronic inflammation, hypercoagulability, and the accumulation of uremic toxins may also contribute to cognitive function decline in CKD patients [3].

#### Perioperative factors

Given the burden of peri-transplant as well as post-transplant risk factors, cognitive function can deteriorate after KT. Peri-transplant risk factors such as surgical procedure, post-transplant delirium, high corticosteroids doses, or infection may lead to further cognitive decline [4]. Post-transplant delirium is associated with a subsequent diagnosis of dementia [4]. Furthermore, alterations in the composition of the gut microbiota may also contribute to an increased susceptibility to cognitive impairment [4] (Fig. 1).

#### Immunosuppressive therapy

As previously described, post-KT immunosuppression can cause numerous and frequent neurological complications, which may contribute to CI [14]. In brief, calcineurin inhibitors (e.g. tacrolimus), cyclosporine, and corticosteroids, are the immunosuppressants most commonly associated with neurological complications [15]. Tacrolimus has been demonstrated to impair patients' performance on multidomain cognitive tasks [16]. In addition to the aforementioned negative effects on several cognitive domains such as selective attention and visual processing, corticosteroids may also lead to psychiatric disorders such as mood changes, insomnia, anxiety, mania, psychosis, or decreased concentration [17].

#### Pattern of cognitive impairment in kidney transplant recipients

CI remains highly prevalent in kidney transplant recipients, with prevalence rates ranging from 22.3% to 58% [4]. CKD is an independent risk factor for cognitive decline, with the prevalence of CI increasing with the CKD stage [18]. As previously stated, several mechanisms, such as the vascular and neurodegenerative hypotheses or disease-related factors play an important role in the development of CI in patients with kidney disease. As a result, the clinical picture of CI may vary considerably from one patient to another. Since the majority of transplant recipients are on peritoneal dialysis or hemodialysis months or years before the transplant, they are likely to have a similar CI pattern [8]. The impact of immunosuppression must also be considered [14]. It is typical for more than one cognitive domain (attention, memory, executive functions, visuospatial abilities, language, processing speed) to be impaired. However, in most hemodialysis patients, executive functions seem most affected, especially in the early stages [7, 19]. Prior research showed impaired executive function in 8.6% of hemodialysis patients with normal cognitive screening [20]. Marked deficits in executive function are characteristic of vascular dementia, while memory deficits may not become apparent in its early stages [21]. Several studies have demonstrated that patients who have undergone KT demonstrated impairment in multiple cognitive domains, when compared with healthy controls or normative data [9, 18].

## Cognitive impairment and chance of listing for kidney transplant

Although severe CI is a contraindication to KT, routine evaluation is still not a standard practice. Additionally, the presence of CI reduces the likelihood of being placed on the transplant waiting list and increases the time to transplant for those who are listed [5, 22, 23].

A large, prospective cohort study by Chu *et al.*, demonstrated that patients with end-stage kidney disease and CI were 25% less likely to be listed. Also, the median time between dialysis initiation and listing was greater among these patients than in those without CI (11.7 months vs. 4.0 months) [23]. Furthermore, in patients without diabetes, the presence of CI was associated with increased mortality on the waiting list [23]. In a study by Gupta *et al.*, patients with CI were also less likely to be on the list for kidney transplantation and had longer waiting times [22]. The median time to active listing for patients with CI was found to be longer compared with patients without CI (10.6 months vs. 6.3 months) [22].

## Improvement in cognitive domains after kidney transplantation

Several studies have shown that certain cognitive domains may recover following kidney transplantation [18, 24]. A prospective study evaluating patients pre- and at 3 months and 12 months post-kidney transplantation, showed post-transplant improvement in some cognitive domains, suggesting that impairment may be reversible [24]. In particular, episodic and verbal declarative memory showed normalization following transplantation (comparable to normative data) [24]. Subsequently, partial improvement was observed in semantic memory, verbal fluency, language, psychomotor speed, and visuospatial abilities (which remained lower than normative data) [24]. Nevertheless, attention, working memory, executive functions, and global cognition remained unaltered in comparison to the period preceding kidney transplantation [24]. In contrast to other studies in which executive function was identified as one of the most impaired cognitive domains [8], the study conducted by Gupta *et al.* [24] demonstrated that executive functions were not impaired before KT and remained unchanged after transplantation. As stated by the authors, the patients included in the study were relatively healthier than the majority of patients with end-stage renal disease and may have had less advanced cerebral small vessel disease [24]. Also, a meta-analysis of previously published studies evaluating cognitive function before and after KT showed moderate to significant improvements in global cognition, as well as domains of information and motor speed, spatial reasoning, verbal and visual memory after KT [18]. Conversely, no improvement was observed in executive function, verbal fluency and language domains in the post-kidney transplant period [18]. The observed partial improvement in various cognitive domains suggests that irreversible brain changes likely occurred in the period before and during dialysis. Moreover, the impact of immunosuppressive therapy, depression, and frailty can also have a negative effect on cognitive function [18].

## Non-pharmacological interventions

Cognitive impairment and dementia are multifactorial conditions that, according to evidence, are related to several potentially modifiable lifestyle and vascular risk factors [25]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a large trial demonstrating that multidomain lifestyle interventions can enhance the cognitive reserve

and reduce inflammation and vascular/oxidative damage in the brain in people with elevated risk of dementia [26, 27]. FINGER included a well-tolerated bundle of interventions such as nutritional guidance, physical activity, cognitive training, social activity, and monitoring vascular risk factors [26], becoming an international initiative exploring the feasibility and efficacy of different at-risk populations across diverse geographical and cultural settings (WW\_FINGER) [28]. Also, the next generation of multidomain prevention trials has started to utilize novel digital health technologies to reduce costs and achieve wider diffusion [26]. This multidomain preventive approach has already proven its effectiveness in managing age-related chronic conditions, such as diabetes mellitus and cardiovascular disease [5, 26]. However, there is a lack of data on structured, combined non-pharmacological interventions for kidney transplant recipients, even though these patients often experience medium-term post-transplant cognitive decline [29].

The Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial is to date the only study that investigated a non-pharmacological intervention aimed at preserving or enhancing cognitive function in kidney transplant recipients. The main finding was that kidney transplant recipients randomized to high doses of B-vitamin and folic acid supplements had higher processing speed and memory scores [30].

Regular physical activity (PA) after KT is known to have positive effects on cardiovascular outcomes, pulmonary function, and physical performance [31]; PA also preserves the long-term graft function [32], improves aerobic capacity, muscle performance, and quality of life [33]; lastly, exercise training reduces anxiety or depression [34], increases sleep quality and quantity [35], and facilitates better control of weight gain following a successful kidney transplant [32]; all mentioned PA targets are well-known brain health determinants [36]. Despite its benefits, less than one in three kidney transplant recipients reaches the minimum level of 150 minutes of moderate-intensity physical activity per week recommended by the World Health Organization [31]; furthermore, PA is more frequent among male and younger kidney transplant patients [32]. Kidney transplant recipients reported some general exercise barriers comparable to the general population and others specifically related to transplantation: harming the kidney, lack of guidance, self-motivation, and accessibility [31]. To date, there is no evidence of a harmful impact of exercise on kidney function, thus PA can be performed safely after transplantation [32]. A key positive strategy of exercise was social interaction [31]: exercising with someone else is a stimulating factor.

Additionally, among community-dwelling older adults, cognitive training alone, or even better when combined with PA, has been identified as another non-pharmacological intervention preventing cognitive decline [37]. One possible reason that combining cognitive and exercise training effectively impacts cognitive function is that these interventions enhance synaptic plasticity [30]. Interventions combining cognitive and physical stimulation are promising for preserving cognition in patients with end-stage kidney disease. A randomized controlled trial is currently investigating the effectiveness of intradialytic combined cognitive and exercise training in maintaining cognitive health. However, there are a lack of data and initiatives focused on cognitive preservation after transplantation.

The Mediterranean diet has been shown to have multiple positive effects on graft survival, and also on reducing the risk of post-transplantation diabetes mellitus and depression [38]. Moreover,

in transplanted individuals, depression is significantly associated with lower cognitive levels [39].

A future approach should involve combining and tailoring all described non-pharmacological interventions into a multidomain preventive program specifically designed to preserve cognition in the particularly vulnerable population of kidney transplant recipients.

### Psychological issues after kidney transplantation

The quality of life of patients with end-stage renal failure improves significantly after KT, but psychopathological disorders are still common in transplant recipients. The burden of these disorders is a common but often neglected issue that negatively affects the ability of recipients to fully participate in daily life and comply with post-transplant medical recommendations.

The most commonly observed psychopathological symptoms in transplant recipients and the most frequently studied include depression, anxiety, and fatigue. The prevalence of post-transplant depression ranges from 4.53% to 75% [8, 40]. Kidney transplant recipients have higher levels of depressive symptoms than the general population, but only in one study were these differences statistically significant [41]. The few studies evaluating the change in depressive symptoms after KT showed no clear improvement over the 6-month follow-up period [42]. However, it has been shown that kidney transplant recipients had significantly lower depressive symptoms than patients on dialysis or awaiting KT [42–44]. Risk factors for depressive symptoms in patients after KT include both younger and older age, longer periods of dialysis before KT, longer time since KT, receiving a kidney from a deceased donor, poor nutritional status, being divorced, widowed or single, being retired or unemployed, as well as negative emotional reactions to treatment and lack of social support [40].

Another common symptom in kidney transplant recipients is anxiety, the prevalence of which, according to various studies, ranges from 4.03% to 63.9% [8, 40]. Risk factors for anxiety include younger age, female gender and lower education, longer time on dialysis before KT, receiving a kidney from a deceased donor and longer time after KT, high creatinine levels, a high number of comorbidities and complications after KT (transplant rejection, hospitalization), being divorced or widowed, being retired or unemployed. Low levels of daily physical activity and the presence of pain, and emotions associated with transplantation (greater fear of transplantation, greater sense of responsibility for good results, and less knowledge about transplantation) also have a negative impact [40]. Several studies comparing the presence of anxiety in KT and dialysis patients, found that kidney transplant recipients experienced significantly lower levels of anxiety than dialysis patients [42–46]. Compared with healthy subjects, the median anxiety score in kidney transplant recipients was twice that of the healthy population [41]. The risk of anxiety depends on information related to the KT. A study evaluating the effect of information received before KT on the presence of anxiety after transplantation found that mean anxiety scores in recipients who were partially informed about the transplant process were worse than those who received no or sufficient information [47]. The presence of anxiety negatively affects health-related quality of life and reduces adherence to treatment recommendations.

Another common neuropsychological symptom in kidney transplant recipients is fatigue, the prevalence of which is estimated to be from 5.9% to 59% [40]. Patients experience less overall physical, mental, and emotional fatigue and greater vigour than dialysis patients but experience severe fatigue about three times

more often than healthy individuals. Transplant recipients experiencing severe fatigue are more likely to report lower social support, experience more pain, have poorer sleep quality, are more depressed, and are more often unemployed than kidney transplant recipients who do not experience severe fatigue [48]. Social and situational factors, such as marital status, living situation and social support, are predictors of fatigue and may co-occur with psychological factors, including symptoms of depression and anxiety.

### Ethical issues in kidney transplantation

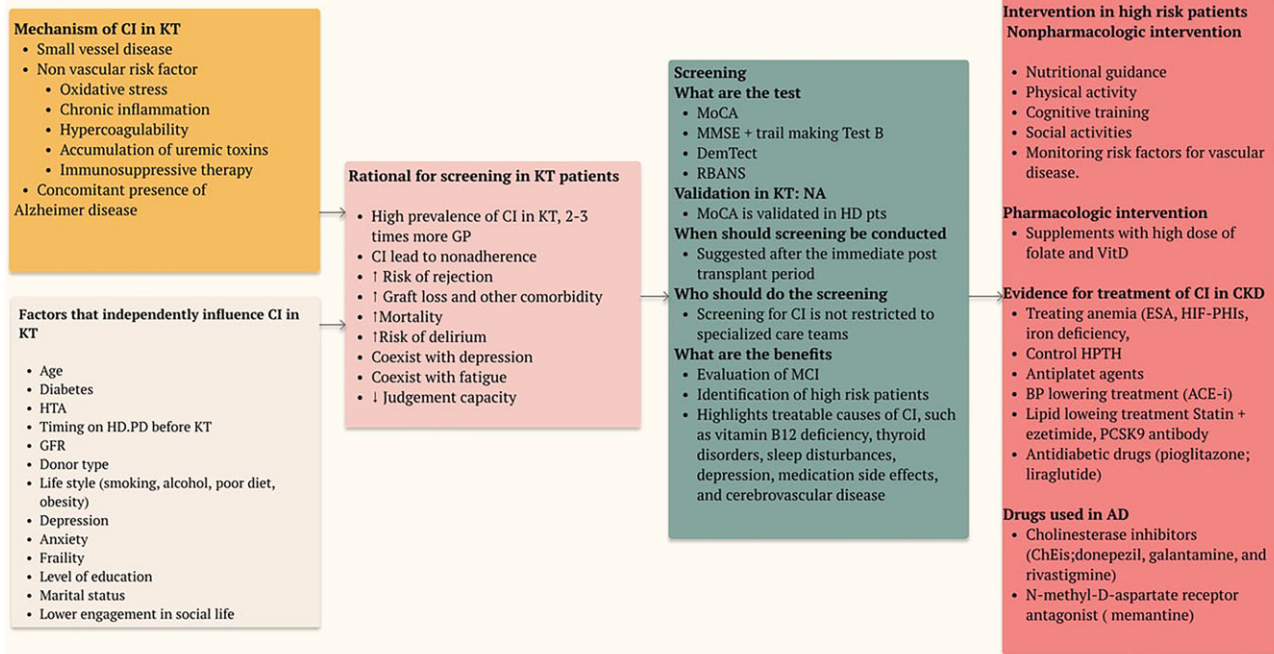
Kidney transplantation may either emphasize traditional medical ethics issues (e.g. just allocation of medical resources, informed consent, confidentiality, privacy, etc.) or raise more specific issues. For instance, the possible causal connection between CKD and CI, as revealed by recent research [49] and the uncertainty of whether CI is reversible or worsened by KT [24], raise the following ethical issues.

The risk of using a limited resource (i.e. donated organs) for a CKD patient who will possibly have limited or no benefit from it if dementia worsens challenges the principle of justice. In theory, this challenge may be assessed within different ethical frameworks. A utilitarian/consequentialist approach would give priority to those CKD patients with a better overall condition. Yet utilitarianism/consequentialism is only one possible ethical model: other frameworks are possible (e.g. virtue ethics, personalism, deontologism, etc.), with different conclusions. Also, within the same utilitarian/consequentialist approach, there is an additional factor that challenges the conclusion above. In fact, a new kidney could improve the cognitive profile of a CKD patient [24], which would eventually be an improvement of overall utility as dictated by the utilitarian/consequentialist model. To solve this ethical dilemma, two hypotheses seem reasonable: first further empirical exploration of the connection between restored kidney functionality and cognitive performance in transplanted CKD patients; second, a case-by-case assessment that takes into account additional extra-medical factors (e.g. post-transplantation treatment patient compliance, the level of psychological impairment, availability of family support, prognosis) that may eventually influence the effectiveness of KT. In the latter case, a personalized multifactorial or multidimensional decision (i.e. considering several individual medical and psycho-social factors) would be ethically recommended. In our current survey study conducted in European countries, physicians were found to have similar concerns and suggestions [50].

Kidney transplantation for CKD patients raises an ethical dilemma regarding the principles of beneficence and non-maleficence: is transplanting the right choice for serving the patient's best interest? If it is confirmed that KT improves the patient's overall cognition status, then the transplantation would comply with the ethical requirements for the patient's good and not cause them harm (where the harm may be in the negative form of not providing a benefit). Yet if no sufficient data in support of the causal connection between KT and improvement of cognition are available then performing the transplantation in CKD patients may be ethically questioned because of the risk of eventually not providing a sufficient benefit to the patients. Yet this concern is not sufficient to ethically exclude transplantation in CKD patients and should be balanced by the awareness that even if there is no direct improvement in cognition, transplantation may provide other kinds of benefits in the appropriate candidates.

Finally, KT for CKD patients raises what is probably the most challenging ethical issue concerning the principle of autonomy:

## Pathway of CI in Kidney Transplant patients



**Figure 2:** Pathway of CI in kidney transplant patients. This figure illustrates the critical aspects of cognitive impairment (CI) in kidney transplant (KT) patients. **Top left box** (Mechanism of CI in KT): This outlines the underlying mechanisms contributing to cognitive impairment in KT recipients, including small vessel disease, non-vascular risk factors (such as oxidative stress, chronic inflammation, hypercoagulability, and accumulation of uremic toxins), the impact of immunosuppressive therapy, and the presence of concomitant Alzheimer's disease. **Bottom left box** (Factors that independently influence CI in KT): This section identifies various independent factors that influence CI in KT patients. These include age, diabetes, hypertension, timing on hemodialysis/peritoneal dialysis before KT, glomerular filtration rate (GFR), donor type, lifestyle factors (e.g. smoking, alcohol, poor diet, obesity), depression, anxiety, frailty, level of education, marital status, and social engagement. **Middle box** (Rationale for screening in KT patients): This box emphasizes the rationale behind screening KT patients for CI. It highlights the high prevalence of CI in KT patients, which is 2–3 times higher than in the general population. CI in KT patients can lead to nonadherence, increased risk of rejection, graft loss, comorbidities, mortality, delirium, and coexisting conditions such as depression, fatigue, and reduced judgment capacity. **Top right box** (Screening): This section discusses the screening process for CI in KT patients, including the tests used (MoCA, MMSE with Trail Making Test B, DemTect, RBANS) and mentions that MoCA has been validated in patients on hemodialysis but not specifically in KT patients. It also advises that screening should be conducted shortly after the immediate post-transplant period and not restricted to specialized care teams. **Bottom right box** (What are the benefits): The final section outlines interventions for high-risk patients with CI in CKD and KT patients. *Non-pharmacological interventions* include nutritional guidance, physical activity, cognitive training, social activities, and monitoring vascular risk factors. *Pharmacological interventions* involve supplements with high doses of folate and vitamin D. Evidence-based treatments for CI in CKD include anemia management, controlling hyperparathyroidism (HPTH), antiplatelet agents, blood pressure-lowering treatments, lipid-lowering therapies, and antidiabetic drugs. Cholinesterase inhibitors and NMDA receptor antagonists are highlighted for Alzheimer's disease. These interventions aim to reduce CI progression, improve treatment adherence, and manage comorbidities. Hemodialysis (HD); peritoneal dialysis (PD); general practitioner; Montreal Cognitive Assessment (MoCA); Mini-Mental State Examination (MMSE); The Repeatable Battery for the Assessment of Neuropsychological Status; mild cognitive impairment (MCI); erythrocyte stimulating agents (ESA); hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs).

how to assess and facilitate the patients' capacity to express their informed consent. In fact, being cognitively impaired, the patient may be unable to fully understand the medical information provided, eventually making his informed consent invalid. Therefore, it is important to have clear and consistent standards for assessing this possible impact.

### Unmet needs

Cognitive impairment is becoming a more recognizable and growing problem in CKD. Pathways of CI in kidney transplanted patients are presented in Fig. 2 and the research agenda is provided in Table 1. However, there are still limited data on the cognitive function after kidney transplantation. The same applies to formally validated screening tests for either CKD patients or kidney transplant recipients. Almost all domains of cognitive function are affected in CKD and after kidney transplantation. It is still an open question whether kidney transplantation improves

cognition and whether the improvement is uniform across cognitive domains. In addition, there are some promising data that cognitive impairment in kidney transplant recipients is at least partially reversible; however, the level of reversibility is still unclear. The distinction between irreversible and reversible cognitive dysfunction has important implications in the everyday care of patients on kidney replacement therapy, including transplantation. It appears that cognitive dysfunction reversibility may not only be due to amelioration of the 'uremic environment' after transplantation, but also to other, so far unknown or undiscovered factors. As not all domains are improved, the possible adverse effects of immunosuppressive therapy, i.e. calcineurin inhibitors, may also play a role. We have to take into consideration that the effect of depression may also impact attention, memory, and executive functions or weaken the final result in cognitive assessment in our patients. Despite limitations in cognitive function testing, another challenge in patients on kidney replacement therapy is the very limited drug armamentarium. As our dialysed patients are getting

**Table 1:** Research agenda for addressing cognitive impairment in kidney transplant recipients.

This research aims to explore effective interventions—both social and pharmaceutical—to mitigate cognitive decline and improve the well-being of kidney transplant recipients

Key objectives include:

- Routine cognitive assessment:** Incorporate regular cognitive function assessments into the evaluation process for potential kidney transplant candidates. Post-transplant, cognitive function should be assessed at least 3 months after transplantation, followed by assessments at 12 months, and annually thereafter.
- Specialist referrals:** In cases where cognitive screening tests such as the Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE) reveal abnormalities, patients should be referred to a geriatrician or neurologist for further evaluation.
- Multidisciplinary approach:** Adopt a multidisciplinary strategy to address cognitive health, involving healthcare professionals from various specialties.
- Non-pharmacological interventions:** Encourage physical exercise and other non-pharmacological interventions post-transplant as part of the holistic care approach.
- Pharmacological interventions:** Investigate the efficacy of pharmacological treatments, including cholinesterase inhibitors (e.g. donepezil, galantamine, rivastigmine) and N-methyl-D-aspartate (NMDA) receptor antagonists (e.g. memantine) in kidney transplant recipients.
- Clinical studies:** Conduct randomized controlled trials to evaluate the effectiveness of these pharmacological agents specifically within the kidney transplant population, as current data in this area remains limited.

older, we may think of the assessment of cognitive function as a part of the evaluation of a potential kidney transplant recipient. More skills, time, and starting to work in multidisciplinary teams are required to offer the best possible care before and after kidney transplantation. We are looking forward to testing novel strategies to prevent or limit cognitive decline.

In conclusion, as cognitive impairment in kidney transplant recipients is an underestimated, underrecognized but clinically relevant problem, screening for cognitive function before and after kidney transplantation would be worth considering in standard routine practice.

## FUNDING

This article is based upon work from COST Action CA19127, supported by COST (European Cooperation in Science and Technology). [www.cost.eu](http://www.cost.eu). COST (European Cooperation in Science and Technology) is a funding agency for research and innovation networks. Our Actions help connect research initiatives across Europe and enable scientists to grow their ideas by sharing them with their peers. This boosts their research, career and innovation.

## DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

## CONFLICT OF INTEREST STATEMENT

None declared.

## APPENDIX

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Goumenos, Eugenio Gutiérrez Jiménez, Gaye Hafez, Ewout Hoorn, Pedro Henrique Imenez Silva, Raafiah Izhar, Dearbhla Kelly, Shelli Kesler, Aleksandra Klimkowicz-Mrowiec, Samuel Knauss, Justina Kurganaite, Hélène Levassort, Sophie Liabeuf, Jolanta Malyszko, Laila-Yasmin Mani, Gianvito Martino, Ziad Massy, Christopher Mayer, Armida Mucci, Alma Mutevelic-Turkovic, Rikke Nielsen, Dorothea Nitsch, Alberto Ortiz, Vasileios Panagiotopoulos, Despoina Karasavidou, Giuseppe Paolisso, Bojana Pejušković, Marion Pepin, Alessandra Perna, Andrea Perrottelli, Vesna Pešić, Pasquale Pezzella, Merita Rroji (Molla), Ivan Rychlík, Giorgos Sakkas, Mariadelina Simeoni, Maria José Soler Romeo, Goce Spasovski, Ana Starčević, Giocchino Tedeschi, Francesco Trevisani, Robert Unwin, Evgueniy Vazellov, Carsten Alexander Wagner, Franca Wagner, Christoph Wanner, Andrzej Wiecek, Hong Xu, Miriam Zacchia, Lefteris Zacharia, Irene Zecchino, Carmine Zoccali, Francesco Mattace-Raso, Karl-Hans Endlich, Norberto Perico, Giuseppe Remuzzi, Francesco Trepiccione, Mark Okusa, Vincenzo Di Marzo, Peter Blankestijn, Kai-Uwe Eckardt, Maximilian König, Ron Gansevoort, Hassan Askari, Brian Hansen, Sunna Snaedal, Elena Cuiban, Edoardo Caporusso, Vincenzina Lo Re, Jonathan Roiser, Kerry Rosenberg, Alvin Biseco, Laura Denby, Onkar Prakash Kulkarni, Kumar Sharma, Subrata Debnath, Afaf Jaafar, Anna Capasso, Michele Mulholland, Biruh Workeneh, Anna Iervolino, Simon Fraser, Isabelle Frey-Wagner, Annachiara Pastore, Romaldas Mačiulaitis, and Ana Farinha

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