Post-Transplant Cognitive Impairment

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Introduction

Cognitive impairment (CI) is common in solid organ transplant recipients. In fact, given that organ transplantation is performed as a treatment of end-organ disease, sometimes it is difficult to differentiate how much of the witnessed cognitive disorder is due to residual symptoms of the organ failure, the trauma of the surgery (e.g., post-transplant delirium), the side effects of immunosuppressant agents, or a combination thereof. Another possibility of newly diagnosed or appreciated CI is that patient might not actually have a new decline in cognition after transplantation, but rather they did not experience the improvement in cognitive functioning after transplantation.

In patients with end-stage liver disease (ESLD), hepatic encephalopathy (HE) is an expected complication of progressive liver failure, which is often associated with CI. The available evidence suggests that the prognosis of patients with HE is not uniform [1]. Advanced HE is a marker of the severity of liver dysfunction and of the presence of intracranial hypertension. Severe HE (grade 3–4) upon admission and during hospitalization is a significant determinant of poor outcome [2]. A study of patients with cirrhosis ($n = 226$) demonstrated that there are residual effects on cognitive function, especially executive functions that result in learning impairment and working memory problems in patients with overt HE, even after adequate therapy and the attainment of clinical "normal mental status" [3]. Furthermore, the psychometric performance deterioration continues and expands to the more basic cognitive domains of psychomotor speed, set shifting, and divided attention with increasing numbers of episodes and hospitalizations for overt HE [3]. Despite previous thoughts that HE is a neuropsychiatric syndrome fully reversible by liver transplantation, an increasing body of data demonstrated, which is not uniformly the case [4–7]. Some studies have found that patients with a history of HE are at higher risk of developing neurological complications following liver transplantation [8], while others have found evidence for a "dementia like" parameter of minimal HE that is irreversible following liver transplantation [7]. Some have found that global cognitive function after liver transplantation was poorer in patients with a lower educational level, alcohol etiology, diabetes mellitus, or a history of HE prior to liver transplantation, and that recipients with prior HE had persistent impaired cognitive and motor function after LT [3, 9].

Similarly, cognitive impairment is very common in chronic kidney disease (CKD). For example, the prevalence of cognitive impairment ranges from 10 to 30%, rising to 30 to 55% in patients older than 75 years [10]. In fact, compared to age-matched controls, the prevalence of cognitive impairment is increased threefold in end-stage kidney disease (ESKD) [11]. It is believed that contributors to cognitive impairment among ESKD patients include (a) the negative effects of various uremic toxins (e.g., uric acid, indoxyl sulfate (IS), p-cresyl sulfate (PCS), homocysteine, interleukin-1β, interleukin-6 and TNF-α) [12], (b) hyperparathyroidism, (c) chronic inflammation associated with ESKD, and (d) the direct negative effects of dialysis (e.g., osmotic shifts, hypotension) [13]. Among kidney transplant recipients, available data reveal that the prevalence of CI was 58.0% [14]. Multivariable linear regression demonstrated that older age, male gender, and absence of diabetes were associated with lower Montreal Cognitive Assessment (MoCA) scores ($p < 0.01$ for all) [14]. After renal transplantation, there are many factors that might further contribute to CI, including (a) ischemia-reperfusion injury causing upregulation of pro-inflammatory neurotoxic molecules (e.g., IL-1β, IL-6, and TNF-α); (b) the direct effect of immunosuppressive medications; and (c) secondary

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complications, such as infections and post-operative delirium [13].

Among heart transplant candidates, studies have found that cognitive impairment occurs in up to 40% of patients [15, 16]. The post-surgical data suggest that although there might be improvement in some transplant recipients, not all subjects return to a normal level of cognitive functioning [17]. It is also important to consider the fact that in recent years, there has been an increased use of left ventricular-assist device (LVAD) as a bridge to transplantation. The use of this device has been associated with an increased risk for CI, thus, potentially increasing the risk of poorer cognitive outcome after successful heart transplantation [18, 19]. As in other solid organ transplant recipients, a number of factors might contribute to cognitive dysfunction among this patient population, including recipients' age, immunosuppressant side effects, altered cerebral blood flow and cerebrovascular pathology, post-surgical complications (e.g., delirium, seizures), and residual effects of pre-transplant decline [16].

Whatever the cause, the presence of CI after organ transplantation is distressing to patients and their loved ones, impairs their quality of life, makes taking care of oneself and adherence to complex post-transplant regimen more challenging, and can worsen post-transplant outcomes [20, 21]. Yet, it is not discussed enough among transplant recipients and transplant care teams. Thus, frequently, providers are not sure when and how to evaluate it and what interventions they can offer to their patients.

Case History

Our patient is a 65-year-old man who underwent lung transplantation for interstitial lung disease (ILD) 2 years ago. His transplant course was complicated by delirium, which resolved prior to discharge from the hospital with the assistance of short-term use of risperidone. He was followed by a transplant psychiatrist for depression after transplantation and was treated with sertraline 100 mg daily. Now he presents 2 years after transplantation with a complaint of memory problems. The patient expressed concerns that he might be developing "early dementia". He notes that he is forgetful about names of new people he meets, it is harder for him to concentrate when he is reading books, and that overall, he just feels "duller." The patient described that after transplantation, it has just been "harder for him to make cognitive connections and be quick in his thinking, the way it felt before."

Of note, the patient lives with his wife of 35 years. She manages their finances, as she has done since he became ill before transplantation. The patient takes medications on his own, but wife helps him to arrange them into his weekly pill box every Sunday. He is taking care of all his activities of daily living (ADLs) on his own. Family history is significant for a mother who was diagnosed with Alzheimer's type dementia at the age of 72. The patient has a college degree.

During the initial psychiatric evaluation, the patient was awake, alert, and overall attentive. He was oriented fully. Montreal Cognitive Assessment (MoCA) was performed, revealing a score of 25 out of 30 with patient losing 2 points within the visuospatial/executive domain, 2 points on language, and 1 point on his recall. He was evaluated for depression and anxiety using the Patient Health Questionnaire (PHQ)-9 and Generalized Anxiety Disorder Scale (GAD)-7, obtaining a score of 5 (points for poor sleep and increased fatigue) and 5, respectively. His medication list was reviewed for psychoactive meds. He was asked about alcohol, tobacco, pain medication, and recreational drug use, which he denied, except for a glass of wine twice per week.

Recent laboratory values were reviewed, and they were significant for renal impairment, with creatinine clearance of 54. Tacrolimus levels were reviewed, and while he had several elevated levels throughout the years, they were within therapeutic range in the last half a year. Additional laboratory work-up for reversible causes of dementia, including thyroid studies, vitamin levels, and screening for HIV and syphilis were done.

He was then referred for a neuropsychiatric evaluation, which revealed that the patient performed "at or near expectation in almost all domains during the current evaluation, however, demonstrated mild weaknesses in working memory and processing speed that are possibly related to reported sleep problems/fatigue and medication side effects."

The patient was, thus, further referred to sleep clinic where he was diagnosed with obstructive sleep apnea (OSA), and the use of continuous positive pressure airway (CPAP) was recommended. The patient was also started on melatonin and suvorexant for sleep. He was reassured about his overall functioning. The transplant team and patient/family were encouraged to use written documentation to convey clinic recommendations. The patient was also educated about the effects of sleep deprivation and cognition and instructed to increase his exercise to help with sleep, energy, and perceived cognition. A scheduled follow-up with neuropsychological evaluation was scheduled in a year to evaluate for any progression of the symptoms.

Clinical Questions

1. What is the frequency and what are the possible etiologies of cognitive impairment in transplant recipients?
2. What should an evaluation of cognitive impairment entail in transplant recipients?
3. What are potential treatment options for cognitive impairment in transplant recipients?

Discussion

Epidemiology and Etiologies of Post-Transplant Cognitive Impairment

Post-transplant cognitive impairment is common in all solid transplant recipients. Based on several studies, it is prevalent in lung transplant recipients. For example, a study of 42 patients up to 64 months after lung transplantation demonstrated that mild cognitive impairment with a MOCA score of 18–25 was observed in 67% of post-transplant patients, while moderate cognitive impairment (score 10–17) was seen in 5% of patients [22]. Similarly, in a study of 124 lung transplant recipients, transplanted between 1 and 264 months (mean 60.1 ± 44.1 months) prior to detailed neuropsychological assessment, 70% of patients demonstrated cognitive impairment in at least one domain [23]. Out of 4 tested domains (executive functioning, verbal memory, visual memory, and concentration/attention), the most frequent impairment was noted in executive function (78% of recipients) followed by verbal memory impairment (72%) [23]. Of note, the cognitive deficits in this study were not correlated with age, gender, education, particular immunosuppressive medications, or time since transplantation.

In another study of 49 lung transplant recipients, at least 20% of individuals exhibited at least one impairment on the test battery at their 6-month neurocognitive assessment [20]. Of significance, during a 13-year follow-up, better neurocognition was associated with longer survival (hazard ratio [HR] = 0.49 [0.25–0.96], $p = 0.039$), with strongest association for tests assessing processing speed and executive function [20].

Cognitive impairment has also been evaluated in heart transplant recipients. In a study of 37 patients, comparing 20 patients on everolimus and 17 patients on calcineurin inhibitors (CNIs) (i.e., tacrolimus and cyclosporine), 40% of subjects had cognitive impairment in at least one domain, defined as performance at least 1.5 standard deviations below normative mean [24]. Of note, there was no statistically significant differences between immunosuppressant groups across cognitive domains, but some postulated predictors of cognitive impairment in this group included estimated premorbid IQ, age of donor, cold ischemic time, creatinine at time of cognitive assessment, and lifetime cerebral bleeding/infarction [24].

Similarly, cognitive impairment has been identified in up to 50% of liver transplant recipients [25] and in more than 50% of kidney transplant recipients [14]. In general, overall cognitive function may be impaired after liver transplantation in the absence of major neurological complications related to the surgical procedure or the postoperative management, due to evidence of central nervous system damage [9, 26]. There are also data to indicate that patients suffering from HE at the time of liver transplantation may be more vulnerable to the metabolic stresses of surgery and the neurotoxicity of the drugs used, and were at highest risk for such complications [27]. In fact, in a study of perioperative neurological complications after liver transplantation, 90% of HE recipients experienced neurological complications, compared with 6.5% of recipients without HE prior to liver transplant [27]. In this study, logistic regression identified active preoperative HE as the strongest predictor of postoperative morbidity (OR 10.7, 95% CI 3.8–29.9) [27]. Others have found that patients with a history of overt hepatic encephalopathy (OHE) before liver transplantation had worse cognitive performances ($p < 0.001$) and EEG performances in comparison with their counterparts with a negative history [28]. The same study showed significant cognitive improvement after liver transplantation ($p < 0.01$); however, their global cognitive performance remained slightly impaired ($p < 0.01$), even though electroencephalograms (EEGs) normalized for 98% of the patients ($p < 0.01$).

The etiology for post-transplant cognitive impairment is likely multifactorial, including various pre-operative, peri-operative, and post-operative factors. The pre-operative factors comprise pre-transplant cognitive impairment and frailty. Pre-transplant cognitive impairment is common in patients with end-stage disease as discussed above and can be due to brain hypoxia in patients with end-stage lung or heart disease, uremia in patients with end-stage kidney disease, and hepatic encephalopathy in liver patients. Pre-transplant frailty has been shown to predict eventual worsening of cognition in kidney transplant recipients [29].

Peri-operative factors contributing to post-transplant cognitive impairment include allograft ischemic time, primary graft dysfunction, time spent on mechanical ventilation, intraoperative hypoxia, micro-emboli, and length of intensive care unit stay [20, 22, 30, 31].

Finally, postoperative factors include development of delirium, physical functioning after transplantation, presence of acute rejection, and immunosuppressive medications. Delirium is common after organ transplantation with up to 40% of lung transplant recipients [32, 33], up to 25% of heart transplant recipients [34], and up to 47% of liver transplant recipients affected by this neuropsychiatric complication [35]. Post-operative delirium has been associated with worsened cognition in transplant recipients and other critically ill patients [20, 36].

In addition, drug neurotoxicity can influence cognition in transplant recipients. The most likely medications to contribute to neurotoxicity in this patient population include corticosteroids and CNIs. Prolonged exposure to endogenous cortisol levels is associated with decreased hippocampal volume on magnetic resonance imaging (MRI) and results in memory impairment [13]. In fact, it has been demonstrated that kidney transplant recipients treated for rejection with

high doses of prednisolone experience memory impairment. Mild calcineurin neurotoxicity (e.g., tremor, neuropathies) occurs in about 40% of kidney transplant patients, while severe toxicity (e.g., psychosis, seizures, posterior reversible encephalopathy) affects up to 5% of patients [13]. While CNIs do not readily cross the blood–brain barrier (BBB), in the presence of underlying comorbidity (such as neurodegenerative disease, systemic infections or hypertension), the BBB can be disrupted. Once CNIs have entered the brain, they might lead to altered neurotransmission via calcineurin inhibition, further leading to changes of calcium homeostasis and gene expression [13]. This can in turn affect memory and other aspects of cognition.

Evaluation

The evaluation of post-transplant cognitive impairment follows the general guidelines (Please see Table 16.1 for full suggested work-up). It is important to carefully review the patient's history to understand potential risk factors, potential etiologies, and contributors of CI, and to identify any reversible factors. The patient's medication list should be carefully evaluated for the presence of any psychoactive medications, both prescribed and over the counter which could further impair the patient's cognition (e.g., anticholinergic medications, antihistaminic agents, benzodiazepines). We should also evaluate for the presence of any mental health contributors, such as depression and anxiety. The patient should be questioned about the use of any psychoactive substances that might affect cognition (e.g., alcohol, cannabis). The laboratory work-up should include a complete metabolic and blood count panel, as well as evaluation of thyroid tests, vitamin levels (thiamine, B12, D), RPR, and HIV. Imaging, such as head CT scan and/or brain MRI might be important to evaluate for volume loss, ischemic events, or trauma sequalae. Neuropsychiatric testing might be helpful to further identify and specify cognitive deficits, query the etiology, and help develop strategies for better patient functioning and communication between the team and the patient. There is no specific neuropsychiatric battery for transplant recipients. Most commonly in clinical practice, neuropsychologists choose tests that allow a detailed assessment of various cognitive domains: visuospatial function, memory, attention, executive function, language, and praxis. Neuropsychiatric testing also allows for more detailed behavioral observations which are not always overt during the psychiatric encounter (e.g., dependent traits, poor effort, sensorial deficits).

Table 16.1 Work-up and differential of cognitive impairment in transplant recipients

Neuropsychological testing • Bedside cognitive tests (e.g., MOCA and MMSE) • Detailed neuropsychological testing • Screening tests for depression and anxiety (e.g., PHQ-9, GAD-7, HADS, GDS)
Laboratory work-up • Complete metabolic panel, complete blood count, thyroid tests, vitamin levels (thiamine, B12, D), RPR, HIV
Imaging • Head CT scan • Brain MRI
Review of medications • Review of any medications for potential sedating and anticholinergic effects
Discussion of psychoactive substance use • Alcohol • Benzodiazepine agents • Antihistaminic agents • Pain medications • Nicotine • Recreational drugs (including THC) • Caffeine
Consideration of sleep/energy/exercise patterns
Consideration/evaluation of underlying organic factors • Obstructive sleep apnea

Treatment

The appropriate treatment of course will depend on the identified etiology of the CI, understanding that some deficits might be irreversible. In addition to addressing the underlying contributors (e.g., sleep disorders, anxiety, depression, medication side effect), the treatment of cognitive impairment in transplant recipients can consist of both pharmacological (if available) and non-pharmacological interventions, including improvements in the psychosocial support of both the patient and his/her caregivers. If identified, the underlying etiology should be addressed.

Pharmacological

There are no studies evaluating the use of cognitive enhancers (e.g., rivastigmine), NMDA antagonists (e.g., memantine), or psychostimulants (e.g., methylphenidate, modafinil, dextroamphetamine) in the management of transplant-related cognitive impairment. However, in our clinical experience, these agents can be useful in carefully selected cases.

Contributors

Depression is a significant comorbidity after transplantation and can affect cognition, quality of life, and outcomes. Thus, depression should be evaluated for and treated in all organ transplant recipients, especially when patients present with cognitive complains [37]. If depression is identified as a contributor, psychotherapy and/or medications can be helpful. If medications are

considered, the clinician can select among SSRIs with the lowest degree of sedation and minimal drug–drug interactions. Thus, sertraline, citalopram, and escitalopram are the preferred agents, when depression is associated with significant symptoms of anxiety. On the other hand, bupropion, a dopamine-norepinephrine reuptake inhibitor, might be the preferred agent when major symptoms are associated with symptoms of impaired attention, concentration, low energy, and/or amotivation.

Substance Use

In the case prescribed or over the counter medications with adverse effects on cognition are identified, these should be tapered off and adequate treatment substitution should be provided. When opiates or benzodiazepines are identified as potential culprits, these should be cautiously tapered off to minimize the possibility of substance withdrawal or symptom rebound, and when indicated, these agents should be substituted, as appropriate, with appropriate alternative agents with no effect in alertness and cognition. In the case, a substance use disorder is identified, and patients should be provided necessary resources, referrals, and treatment—this might include medication-assisted treatment or psychotherapeutic interventions for addictive disorders such as cognitive behavioral therapies or 12-step programs.

Non-pharmacological

Exercise and Diet

Available research data suggest that exercise can improve cognition in patients with end-stage organ disease and transplant recipients. In particular, the literature in kidney recipients suggests that exercise and cognitive exercises can improve cognition and decrease the risk of developing dementia [38]. Among lung transplant recipients, post-transplant exercise and improved physical functioning have been associated with better neurocognition [22].

Social Support

It is important for the team to provide the patient and his caregivers with the necessary psychoeducation regarding the changes patients might experience. Some patients might need more assistance with working on adherence to their complicated medication regimen. Family members can help patients with filling out the medication boxes and setting the reminders to take medications at the right time on alarms or smart phones. A variety of apps are available to help patients with adherence to medications. While the evidence for the overall effectiveness of these apps varies, some patients, such as those with CI, might benefit from such interventions. Moreover, the team should be sensitive to modes of communication that work best for the patients.

Take Home Points

1. Cognitive impairment is common in transplant recipients and can affect patients' quality of life, ability to adhere to their complex post-transplant care, and mortality. Pre-transplant, pre-surgical, and post-transplant factors can contribute to such impairment.
2. It is important to further evaluate and to investigate treatable and reversible causes of CI in transplant recipients, including medical contributors, medications that can impair cognition, substance use, and psychiatric disorders.
3. Treatment of CI in transplant recipients can include treatment of medical contributors (e.g., OSA); tapering off medications that can worsen cognition (e.g., benzodiazepines); treatment of contributing substance use or psychiatric disorders; use of cognitive enhancers; and psychoeducation and team support.

References

1. Garcia-Martinez R, Simon-Talero M, Cordoba J. Prognostic assessment in patients with hepatic encephalopathy. Dis Markers. 2011;31(3):171–9.
2. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. Liver Transpl. 2008;14(Suppl 2):S67–79.
3. Bajaj JS, Schubert CM, Heuman DM, Wade JB, Gibson DP, Topaz A, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. Gastroenterology. 2010;138(7):2332–40.
4. Sotil EU, Gottstein J, Ayala E, Randolph C, Blei AT. Impact of preoperative overt hepatic encephalopathy on neurocognitive function after liver transplantation. Liver Transpl. 2009;15(2):184–92.
5. Mechtcheriakov S, Graziadei IW, Mattedi M, Bodner T, Kugener A, Hinterhuber HH, et al. Incomplete improvement of visuo-motor deficits in patients with minimal hepatic encephalopathy after liver transplantation. Liver Transpl. 2004;10(1):77–83.
6. Tarter RE, Switala JA, Arria A, Plail J, Van Thiel DH. Subclinical hepatic encephalopathy. Comparison before and after orthotopic liver transplantation. Transplantation. 1990;50(4):632–7.
7. Lewis MB, Howdle PD. Cognitive dysfunction and health-related quality of life in long-term liver transplant survivors. Liver Transpl. 2003;9(11):1145–8.
8. Pujol A, Graus F, Rimola A, Beltran J, Garcia-Valdecasas JC, Navasa M, et al. Predictive factors of in-hospital CNS complications following liver transplantation. Neurology. 1994;44(7):1226–30.
9. Garcia-Martinez R, Rovira A, Alonso J, Jacas C, Simon-Talero M, Chavarria L, et al. Hepatic encephalopathy is associated with posttransplant cognitive function and brain volume. Liver Transpl. 2011;17(1):38–46.
10. Kurella Tamura M, Larive B, Unruh ML, Stokes JB, Nissenson A, Mehta RL, et al. Prevalence and correlates of cognitive impairment in hemodialysis patients: the frequent Hemodialysis network trials. Clin J Am Soc Nephrol. 2010;5(8):1429–38.

11. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, et al. Cognitive impairment in hemodialysis patients is common. Neurology. [Randomized Controlled TrialResearch Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2006;67(2):216–23.
12. Watanabe K, Watanabe T, Nakayama M. Cerebro-renal interactions: impact of uremic toxins on cognitive function. Neurotoxicology. 2014;44:184–93.
13. Van Sandwijk MS, Ten Berge IJ, Majoie CB, Caan MW, De Sonneville LM, Van Gool WA, et al. Cognitive changes in chronic kidney disease and after transplantation. Transplantation. 2016;100(4):734–42.
14. Gupta A, Mahnken JD, Johnson DK, Thomas TS, Subramaniam D, Polshak T, et al. Prevalence and correlates of cognitive impairment in kidney transplant recipients. BMC Nephrol. 2017;18(1):158.
15. Roman DD, Holker EG, Missov E, Colvin MM, Menk J. Neuropsychological functioning in heart transplant candidates. Clin Neuropsychol. 2017;31(1):118–37.
16. Cupples SA, Stilley CS. Cognitive function in adult cardiothoracic transplant candidates and recipients. J Cardiovasc Nurs. 2005;20(5 suppl):S74–87.
17. Roman DD, Kubo SH, Ormaza S, Francis GS, Bank AJ, Shumway SJ. Memory improvement following cardiac transplantation. J Clin Exp Neuropsychol. 1997;19(5):692–7.
18. Fendler TJ, Spertus JA, Gosch KL, Jones PG, Bruce JM, Nassif ME, et al. Incidence and predictors of cognitive decline in patients with left ventricular assist devices. Circ Cardiovasc Qual Outcomes. 2015;8(3):285–91.
19. Dew MA, Kormos RL, Winowich S, Harris RC, Stanford EA, Carozza L, et al. Quality of life outcomes after heart transplantation in individuals bridged to transplant with ventricular assist devices. J Heart Lung Transplant. 2001;20(11):1199–212.
20. Smith PJ, Blumenthal JA, Hoffman BM, Davis RD, Palmer SM. Postoperative cognitive dysfunction and mortality following lung transplantation. Am J Transplant. 2018;18(3):696–703.
21. Jurgensen A, Qannus AA, Gupta A. Cognitive function in kidney transplantation. Current transplantation reports. 2020;7:145–53.
22. Cohen DG, Christie JD, Anderson BJ, Diamond JM, Judy RP, Shah RJ, et al. Cognitive function, mental health, and health-related quality of life after lung transplantation. Ann Am Thorac Soc. [Research Support, NIH, Extramural Research Support, Non-US Gov't. 2014;11(4):522–30.
23. Sommerwerck U, Jokisch D, Weinreich G, Neurath M, Heinze C, Bessa V, et al. Cognitive function after lung transplantation. Adv Exp Med Biol. 2021;1324:91–101.
24. Burker BS, Gullestad L, Gude E, Relbo Authen A, Grov I, Hol PK, et al. Cognitive function after heart transplantation: comparing everolimus-based and calcineurin inhibitor-based regimens. Clin transplant [Comparative Study Multicenter Study Randomized Controlled TrialResearch Support, Non-US Gov't. 2017;31(4)
25. Ko D, Bratzke LC. Cognitive function in liver transplant recipients who survived more than 6 months. Prog Transplant. 2020;30(4):335–41.
26. Rose C, Jalan R. Is minimal hepatic encephalopathy completely reversible following liver transplantation? Liver Transpl. 2004;10(1):84–7.
27. Dhar R, Young GB, Marotta P. Perioperative neurological complications after liver transplantation are best predicted by pre-transplant hepatic encephalopathy. Neurocrit Care. 2008;8(2):253–8.
28. Campagna F, Montagnese S, Schiff S, Biancardi A, Mapelli D, Angeli P, et al. Cognitive impairment and electroencephalographic alterations before and after liver transplantation: what is reversible? Liver Transpl. 2014;20(8):977–86.
29. Chu NM, Gross AL, Shaffer AA, Haugen CE, Norman SP, Xue QL, et al. Frailty and changes in cognitive function after kidney transplantation. J Am Soc Nephrol [Multicenter Study Research Support, NIH, Extramural. 2019;30(2):336–45.
30. Smith PJ, Blumenthal JA, Carney RM, Freedland KE, O'Hayer CV, Trulock EP, et al. Neurobehavioral functioning and survival following lung transplantation. Chest. [Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S. 2014;145(3):604–11.
31. Smith PJ, Blumenthal JA, Hoffman BM, Rivelli SK, Palmer SM, Davis RD, et al. Reduced cerebral perfusion pressure during lung transplant surgery is associated with risk, duration, and severity of postoperative delirium. Ann Am Thorac Soc. 2016;13(2):180–7.
32. Sher Y, Mooney J, Dhillon G, Lee R, Maldonado JR. Delirium after lung transplantation: association with recipient characteristics, hospital resource utilization, and mortality. Clin Transpl. 2017;31(5)
33. Smith PJ, Rivelli SK, Waters AM, Hoyle A, Durheim MT, Reynolds JM, et al. Delirium affects length of hospital stay after lung transplantation. J Crit Care. 2015;30(1):126–9.
34. van de Beek D, Kremers W, Daly RC, Edwards BS, Clavell AL, McGregor CG, et al. Effect of neurologic complications on outcome after heart transplant. Arch neurol. [Research Support, Non-US Gov't. 2008;65(2):226–31.
35. Wang SH, Wang JY, Lin PY, Lin KH, Ko CJ, Hsieh CE, et al. Predisposing risk factors for delirium in living donor liver transplantation patients in intensive care units. PLoS One. 2014;9(5):e96676.
36. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38(7):1513–20.
37. Moulton CD, Tharmaraja T, Dumbrill JL, CWP H. Cognitive impairment after kidney transplant: a hidden consequence of depression? J Am Soc Nephrol. [LetterResearch Support, Non--U.S. Gov't Comment. 2019;30(8):1547.
38. Chu NM, Segev D, McAdams-DeMarco MA. Interventions to preserve cognitive functioning among older kidney transplant recipients. Curr transplant Rep. 2020;7(4):346–54.