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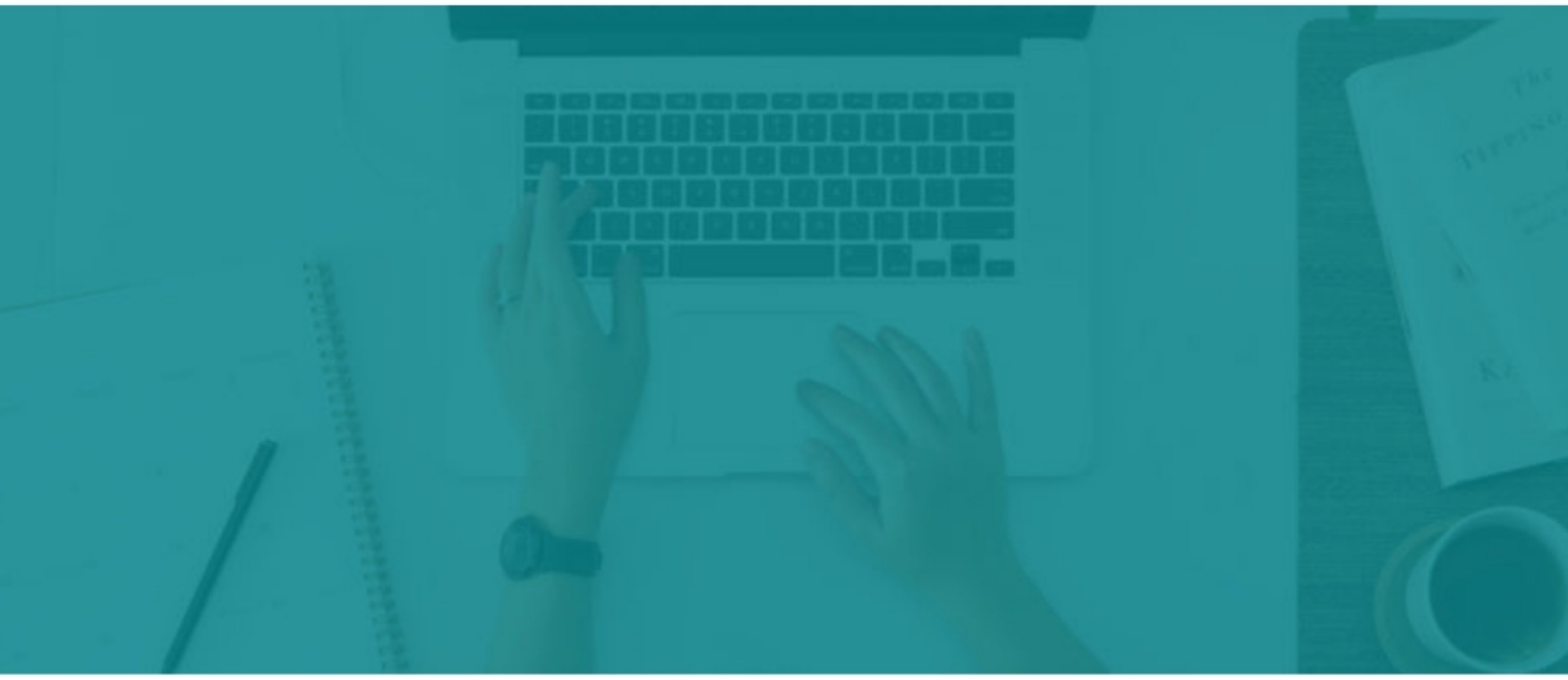

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LETTER TO THE EDITORS

Postoperative delirium in kidney transplant patients

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Dear Editor,

Delirium, also known as acute brain failure, is a medical condition characterised by recent onset of confusion, fluctuating awareness, disorganised thought, with memory and attention impairment. Postoperative delirium (POD) generally arises 1 to 3 days after surgery, in 25–37% of the hospitalised patients and in >65% of those admitted to intensive care unit [1].

Data regarding POD in the kidney transplant (KT) population are scarce. Herein, we present the result of a systematic review (SR), showing an incidence of 5.48% among patients undergoing single organ KT and 7% in recipients of multiple organ transplant, in accordance with other reports for transplanted patients[2].

Among the preoperative risk factors, electrolyte disorders including hyponatremia, hypernatremia and hypercalcaemia significantly increase POD risk; thus, medical conditions as end-stage renal disease predispose to the development of delirium early postoperatively. Furthermore, in the KT scenario, delayed graft function requiring dialysis is a specific risk factor, explaining POD major incidence in recipients of deceased donor grafts compared with living donor kidneys: 9.07% versus 6.85%, respectively. These data are of interest and highlight the role of high-quality organs for frail older patients, to improve their short- and long-term outcomes[3].

Table 1 summarises the results of the four studies analysed [4–7] in our SR: clinical trials, prospective and retrospective reports with >10 patients, from 01 January 1955 to 13 December 2020 with "kidney transplant" AND "postoperative delirium" or "renal transplant" AND "postoperative delirium" as keywords. In the 128.258 adult KT patients identified in total, mean age was 50.9 years. Specific risk factors comprised: frailty, 31% frail versus 15% non-frail patients, older age, 5.1% versus 1.36% if ≥65 years, and underlying comorbidities, according to the Charlson Comorbidity Index (CCI), with POD incidence of 3.71% if CCI ≥ 2, versus 1.01%.

Other recognised contributing factors included poor hydration and nutritional status, very common in dialysis patients, sensory loss, pre-existing cognitive impairment, alcohol or substance use and polypharmacy, especially benzodiazepine use, either during premedication/anaesthetic time or in-hospital stay. Interestingly, cytokine storm and/or immune dysregulation are documented triggers for neuroinflammation and hypercoagulability determining acute brain failure[1]. Thus, we could speculate a parallelism that frail immunosuppressed patients with dysregulation of their immune system, as for example secondary to graft rejection, are at higher risk of POD.

In the registry analysis from Haugen *et al.* [4], POD occurred in 42 patients (4.7%): 8 (19%) characterised by the hypoactive subtype, 7 (16.7%) by the hyperactive one and 27 (64.3%) with both aspects. The cumulative incidence ranged from 2% (18–48 years old patients) to 13.8% (≥75 years). Of note, POD was rarely registered in medical records, but when captured, it was associated with dementia diagnosis. KT recipients who developed POD had 5.4-fold odds of 2-week length of stay (LOS), 22.4-fold increased risk of institutional discharge to nursing facility or rehabilitation centre, 2.7-fold increased risk of death-censored graft loss and 3.1-fold increased risk of mortality.

Konel *et al.* [5] reported a cohort of KT recipients from the John Hopkins and the University of Michigan Hospitals (2009–2017). The authors measured the Fried frailty phenotype and the modified 18-question Centre for Epidemiologic Studies-Depression Scale (CES-D): 10% of KT recipients had depressive symptoms and

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Table 1. Systematic review results.

Authors	Year of publication	Number of patients	Mean age (years)	Cognitive test	Comorbidities – POD	Frailty – POD	Graft loss – POD	Mortality – POD	Outcome
Haugen *et al.* [4]	2018	125 304	52.2	Kaplan–Meier approach	2.6%	30%	2.73%	3.12%	Delirium incidence increased with age, 20% of frail recipients aged ≥75 experienced delirium
Konel *et al.* [5]	2018	773	54	CES-D test	1%	3.6%	25%	2.62%	Co-occurrence of depressive symptoms and frailty was associated with a synergistically longer LOS as well as an increased risk of DCGF and mortality
McAdams DeMarco *et al.* [6]	2018	730	≥18	Modified Mini-Mental Status Exam	1.37%	2.2%	3.02%	3.6%	There were 33 delirium cases (4.5%). Delirium was more common in recipients who were frail (9.2% vs. 3.6%; $p = 0.01$), who had cognitive impairment (10.6% vs. 3.9%; $p = 0.02$), and who were older (8.8% vs. 3.3%; $p = 0.01$) at admission for KT
Park *et al.* [7]	2020	257	47.4	NDR	NDR	NDR	NDR	NDR	Delirium occurred in a total of 19 (7.4%) patients and was more frequent in the endotracheal tube group (3.0% vs 10.3%, p 0.029), but all postoperative pulmonary and nonpulmonary complications were comparable after matching

A search through PubMed, EMBASE, Cochrane and SCOPUS was carried out for English written publications. Inclusion criteria: all clinical trials and randomised clinical trials, prospective and retrospective studies with > 10 patients, from 01 January 1955 to 13 December 2020. Keywords used: kidney transplant AND postoperative delirium and renal transplant AND postoperative delirium.

DCGF, death-censored with a functioning graft; DGF, delayed graft function; LOS, length of stay; POD, postoperative delirium.

16.3% were frail. Interestingly, the presence of depression was associated with a 3.97-fold higher likelihood of being frail. The co-occurrence of depressive symptoms and frailty was observed in 3.6% of KT recipients and again associated with a longer LOS.

Another study from the John Hopkins University, by McAdams DeMarco *et al.* [6], looked at KT recipients between 2009 and 2011, recording 33 POD cases (4.5%). POD was more common in recipients who were frail (9.2% vs 3.6%), ≥65 years old (8.8% vs. 3.3%) and with underlying comorbidities. Frailty was measured by the Fried frailty phenotype and global cognitive function using the Modified Mini-Mental Status Exam. Authors' conclusion was that POD is a strong risk factor for subsequent mortality and graft loss.

Finally, Park *et al.* [7] retrospectively studied patients undergoing KT at the Samsung Medical Centre, Seoul, Korea (2010–2017). The authors compared the incidences of postoperative pulmonary and non-pulmonary complications including hoarseness, vocal cord palsy, nausea, vomiting, arrhythmia and POD among endotracheal tube. Findings showed that delirium occurred in a total of 19 patients (7.4%) and was more frequent in the latter group (3% versus 10.3%, p 0.029).

From a public health point of view, delirium represents a clear target to improve transplant outcomes. It might also be considered a biomarker for an already compromised cerebral function that is revealed by surgery or anaesthesia. There is good evidence, in fact, that the extension of the surgical trauma and the total operative time directly affect POD onset. In this view, those who develop delirium postoperatively would have declined more steeply even if delirium was not present [8], but POD predicts long-term cognitive decline and mortality.

Depressive symptoms and frailty assessment at KT admission may have the potential to identify KT recipients at higher risk of adverse outcomes and may also provide further insights into the mechanisms leading to these adverse outcomes. Exploring interventions aimed to reducing the burden of both depressive symptoms and frailty, such as prehabilitation programs, may be warranted to improve post-KT outcomes [9,10]. Transplant centres should be aware of the risks associated with post-KT delirium and implement interventions to reduce this risk. Multicomponent interventions, the use of antipsychotics, BIS-guided anaesthesia and administration of dexmedetomidine during anaesthesia can successfully reduce the incidence of POD. Ideally, also the avoidance of corticosteroids and anti-CMV therapy (valganciclovir) could decrease the risk of POD, so a careful balance of the risk of rejection versus infection and/or POD are recommended in the elderly and frail, with the ongoing debate what is the ideal immunosuppressive regimen in this KT population.

In conclusion, prevention of delirium in the elderly surgical patient is essential, although no evidence-based guidelines regarding specific pharmacological agents exist. POD incidence in the KT population could be underestimated; thus, more awareness for a correct diagnosis is essential.

REFERENCES

1. Inouye SK. The importance of delirium and delirium prevention in older adults during lockdowns. *JAMA* 2021. https://doi.org/10.1001/jama.2021.2211
2. Patrono D, Rigo F, Bormida S, *et al.* Graft factors as determinants of postoperative delirium after liver transplantation. *Updates Surg* 2020; **72**: 1053.
3. Bellini MI, Courtney AE, McCaughan JA. Living donor kidney transplantation improves graft and recipient survival in patients with multiple kidney transplants. *J Clin Med* 2020; **9**: 2118.
4. Haugen AJ, Langberg NE, Dahle DO, *et al.* Long-term risk for kidney donors with hypertension at donation – a retrospective cohort study. *Transpl Int* 2019; **32**: 960.
5. Konel JM, Warsame F, Ying H, *et al.* Depressive symptoms, frailty, and adverse outcomes among kidney transplant recipients. *Clin Transplant* 2018; **32**: e13391.
6. McAdams DeMarco M, Mountford A, Warsame F, *et al.* Risk factors and sequelae of post-KT delirium. *Am J Transplant* 2018; **18** (Suppl 4): 928.
7. Park S, Kim GS, Choi DH, *et al.* Comparison of pulmonary gas exchange during kidney transplantation: second-generation laryngeal mask airway vs endotracheal tube. *Transpl Proc* 2020; **52**: 1695.
8. Sato T, Hatakeyama S, Okamoto T, *et al.* Slow gait speed and rapid renal function decline are risk factors for postoperative delirium after urological surgery. *PLoS One* 2016; **11**: e0153961.
9. Aldecoa C, Bettelli G, Bilotta F, *et al.* European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol* 2017; **34**: 192.
10. Bilotta F, Lauretta MP, Borozdina A, Mizikov VM, Rosa G. Postoperative delirium: risk factors, diagnosis and perioperative care. *Minerva Anestesiol* 2013; **79**: 1066.