

## Cognitive Impairment after Kidney Transplant: a Hidden Consequence of Depression?

To the Editor,

In their recent study, Chu *et al.*<sup>1</sup> assessed the trajectory of cognitive performance after kidney transplant for people with and without significant frailty. Cognitive function was measured serially before and after transplant using the Modified Mini-Mental State Examination (3MS). Despite its many strengths, the two major findings of the study are currently less robust than the authors suggest.

The authors firstly conclude “both frail and nonfrail recipients experience short-term cognitive improvement post-transplant,” based upon repetition of the 3MS within 3 months. However, such short-term repetition is subject to a significant practice effect—*i.e.*, implicit and explicit learning effects—such that the average person is expected to improve by 2.8 points on the 3MS when repeated at this interval.<sup>2</sup> Consequently, there is a risk that the observed improvement is an artifact of repeat cognitive testing, rather than a true change in participants’ cognitive ability.

Citing a previous study reporting a high prevalence of cognitive impairment in kidney transplant recipients,<sup>3</sup> Chu *et al.* next report greater cognitive decline over 4 years in patients with higher baseline frailty. In neither study, however, were the results adjusted for depressive symptoms. This represents a key limitation for several reasons: Firstly, significant depressive symptoms are reported by nearly a third of people who have received a kidney transplant.<sup>4</sup> Secondly, depressive symptoms commonly lead to deficits in attention, memory, and executive function, as well as poor effort on cognitive testing.<sup>5</sup> Thirdly, the prevalence of depressive symptoms in the frail subgroup, who apparently experienced cognitive decline, was three times greater than the remaining participants at baseline, yet they were not retested after transplant. As such, the apparent cognitive decline observed in frail patients may in fact be a consequence of underlying depressive symptoms. Adjustment for depressive symptoms at 4-year follow-up, or even exclusion of those depressed at baseline, would help to refute this suggestion.

The influence of depression on cognitive function has important clinical implications for people who receive a kidney transplant. The adverse effects of depression on kidney trans-

plant outcomes, including increased risk of mortality, are well established.<sup>4</sup> If accounting for depression indeed attenuates the findings of this study, this suggests that depression could lead to morbidity and mortality through deleterious effects on cognitive function. As a common and treatable comorbidity in those receiving a kidney transplant, greater scrutiny of depression as a potential cause of cognitive impairment is warranted, both in this study and beyond.

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### DISCLOSURES

None.

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## Authors' Reply

We thank Moulton *et al.*<sup>1</sup> for the valuable comments. We carefully considered practice effects when designing our study,<sup>2</sup> and improvements in cognitive function cannot be attributed to retest effects alone.

First, retest effects are attributed to the content of neuropsychological tests and the context of administration.<sup>3</sup> In this study, cognitive testing was 1 of 14 tests conducted in an hour-long assessment, making it especially difficult for patients to recall or learn content through repeated testing.

Second, the largest retest effects typically occur between the first two assessment cycles (at kidney transplantation [KT] and 1-month post-KT) and dissipate thereafter.<sup>4</sup> In a postpublication sensitivity analysis, we refined trajectories in more short-term intervals: knots at 1-month, 3-months, 6-months, and 1-year post-KT. We observed improvements between KT and 1-month in both frail (slope=0.39 points/wk) and nonfrail recipients (slope=0.30 points/wk), which may represent a combination of retest effects and KT recovery effects. However, between 3- and 6-months post-KT, we saw continued substantial improvement in cognitive function among frail (slope=0.32 points/wk) and plateaued trajectories among nonfrail recipients in spite of dissipating retest effects. This supports our original inferences that both groups improved in the short-term due in large part to recovery of kidney function.

Third, based on prior studies, retest effects may not differ by group demographics and factors,<sup>5</sup> and thus are unlikely to differ by frailty.

Furthermore, we made the critical decision not to adjust for depression for two reasons: (1) the frailty phenotype incorporates exhaustion, measured using two items from the Center for Epidemiologic Studies Depression Scale (CES-D), and (2) we believe depression to be a potential mediator on the causal pathway. As Moulton *et al.*<sup>1</sup> suggested, depression is common and related to frailty in KT. Based on the frailty phenotype model, the underlying process of multisystem dysfunction catalyzes depressive symptoms, potentially leading to clinical depression.

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Depressive symptoms were also linked to cognitive dysfunction in KT<sup>6</sup>; studies are needed to assess the temporality of this association. As such, we strongly believe depression may be one pathway linking frailty and cognitive decline in KT.

Nevertheless, we excluded recipients with severe symptoms (CES-D $\geq$ 16) at KT ( $n=74$ , 11.5%) in a postpublication sensitivity analysis. We found inferences remained robust: nonfrail (slope=+0.14 points/wk) and frail (slope=+0.18 points/wk) recipients experienced improvements by 3-months post-KT. After 1-year, frail recipients experienced significant declines in cognitive function (slope=-0.03 points/wk), while nonfrail recipients plateaued (slope=0.01 points/wk).

Given the aforementioned arguments, we believe the limitations brought forth by Moulton *et al.*<sup>1</sup> have little, if any, impact on previously published inferences.

## DISCLOSURES

None.

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