INVITED COMMENTARY

Clinical depression as an unfavorable prognostic factor following kidney transplantation—How can we explain it?

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In this issue, Lentine *et al.* [1] provide a well thought-out analysis of the prognostic value of antidepressant medication use (as a surrogate measure of clinical depression) on post-transplant outcome. Specifically, they show that among 72 054 SRTR patients receiving a kidney transplant during 2008–2015, antidepressant use (obtained from pharmaceutical fill records) within 1 year of transplant and during the first year post-transplant (12.6% and 18.0% of patients, respectively) correlated with a significantly higher death rate during the first and 2nd year post-transplant ($P < 0.0001$ each, aHR = 1.39 and 1.94, respectively). While antidepressant use within 1 year of transplant was not associated with death-censored graft failure (DCGF) during the first year post-transplant, its use during the first year post-transplant was correlated with a significantly higher DCGF rate during the 2nd year post-transplant ($P < 0.05$, aHR = 1.36), although lower in magnitude and significance compared with its effect on mortality. In addition to controlling for propensity to receive antidepressant therapy in these Cox models, numerous other baseline (pretransplant) variables were controlled, including employment status (not working vs. working), physical capacity status (limited vs. not limited), and development of an acute rejection (AR) episode during the first year post-transplant (used in the 2nd year modeling).

Although not explicitly stated, the HR's for antidepressant use appeared to remain essentially unchanged when transitioning from univariable to multivariable analysis; thus, the multivariable analysis offered no explanation(s) for the prognostic value of clinical depression. The authors, however, provided numerous possible explanations in their Discussion, stating that clinically depressed patients may be more likely to have (i) comorbidities, (ii) nonadherent behavior (in taking the prescribed immunosuppression and/or other medications), (iii) other higher risk behavior (e.g., less physical activity), and (iv) higher inflammatory marker levels (i.e., more direct biological consequences).

While recipient comorbidities were individually controlled in the Lentine *et al.* [1] Cox multivariable models, potential explanations (ii)-(iv) were either not controlled or poorly controlled (in our opinion). For

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instance, a distinction between being retired versus of working age but not working may have offered a clear prognostic separation among patients "not working," and within the large subgroup of patients having no physical limitations, no further subdivision according to a physical activity measure (inactive to very active) [2,3] was made.

For the most part, the Lentine *et al.* [1] findings confirm those reported in three previous kidney transplant studies showing significant associations between being clinically depressed and having higher death and DCGF rates [4–6]. Dobbels *et al.* [4] reported using USRDS and Medicare claims data that among 47 897 1st kidney transplant recipients (transplanted during 1995–2003), clinical depression (observed in 7.0% of patients) as a binary time-dependent covariate was associated with significantly higher death-with-a functioning graft (DWFG) and DCGF rates during the first 3 years post-transplant ($P < 0.001$ each, aHR = 2.24 and 1.97, respectively). However, none of the potential explanations (i)-(iv) offered by Lentine *et al.* [1] were controlled as explanatory variables in the Dobbels *et al.* [4] Cox models.

Novak *et al.* [5] analyzed 840 stable kidney transplant recipients (transplanted at a single center in Budapest, Hungary during 8/02-2/03); clinical depression at study entry was defined as a Center for Epidemiologic Studies-Depression (CES-D) score $\geq$18 (observed in 22.2% of patients). With a median follow-up of 58 months, they reported unadjusted versus adjusted HR's for the impact of baseline clinical depression being 1.90 ($P = 0.001$) vs. 1.66 ($P = 0.01$) for DWFG and 1.48 ($P = 0.10$) vs. 1.43 ($P = 0.15$) for DCGF, although use of CES-D as a continuous variable was significantly associated with DCGF (unadjusted and adjusted $P = 0.006$ and 0.01, respectively). Baseline number of comorbidities and serum C-reactive protein level were each controlled in their multivariable analysis; however, a significant aHR was still achieved (suggesting that other factors would more completely explain the effect of being clinically depressed).

Zelle *et al.* [6] analyzed 527 patients transplanted in Groningen, Holland, during 8/01-7/03 who survived at least 1 year with a functioning graft. Clinical depression at study entry was defined as a Depression Subscales of the Symptom Checklist (SCL-90) >25 (observed in 30.6% of patients). With a median follow-up of 7 years, they reported unadjusted versus adjusted HR's for the impact of baseline clinical depression being 1.96 ($P < 0.001$) vs. 1.61 ($P = 0.02$) for death and 1.77 ($P = 0.05$) vs. 1.19 ($P = 0.60$) for DCGF. While baseline renal function, physically activity, being medically unfit for work, and inflammatory markers were controlled in their multivariable analysis, number of comorbidities was not explicitly controlled, nor was patient nonadherence (not measured). Thus, in none of these reports [1,4–6] was the prognostic impact of being clinically depressed fully explained.

What if we had control over future data collection for the Lentine *et al.* [1] study? First, we would add a measured variable to summarize each of the potential explanations offered, both at pretransplant and at 1 year post-transplant: number of recipient comorbidities, degree of nonadherent behavior in taking the prescribed immunosuppression (degree of nonadherent behavior during dialysis as a pretransplant substitute), degree of physical activity, inflammatory marker levels, etc. We would then perform the Cox multivariable analysis in stages, similar to the approach used in other reports [2,3,5,6]. Specifically, at the first-stage clinical depression would be included as a single variable in the (univariable) model. At each subsequent stage, one additional explanatory variable would be added into the Cox model (thus, one additional predictor variable in the model over the previous stage). At the final stage, all of the important explanatory variables will have been included, and the aHR for the clinical depression effect would no longer be different from 1.0. Measuring reduction in aHR with inclusion of each important explanatory variable could then be used in estimating the percentage of clinical depression's prognostic value that is explained by each explanatory variable.

While Lentine *et al.* [1] included AR occurrence during the first year post-transplant as a predictor variable in their 2nd year post-transplant models, it would also be useful to directly show via a separate Cox multivariable analysis the prognostic impact of clinical depression on AR occurrence. While being clinically depressed may not directly cause AR to occur, indirect associations via having greater comorbidity or nonadherent behavior may exist.

We would also recommend that the statistical analysis be performed with longer post-transplant follow-up, as a large percentage of DWFG's and DCGF's will occur between 2 and 6 years post-transplant. Clinical depression as well as each of the potential explanatory variables could be measured on an annual basis so that prediction of outcomes during post-transplant years 3 through 6 would be based on measured clinical depression (and the other predictor variables) at years 2 through 5, respectively. Cox models could then be

developed utilizing all time intervals together in a single analysis with time-dependent covariates.

Furthermore, if possible, we would prefer to categorize severity and subtype(s) of clinical depression via an administered questionnaire, as it is likely that, for example, lethargy versus passive/aggressive behavior, while all falling under the general diagnosis of clinical depression, may, in fact, lead to different types of subsequent behaviors and clinical outcomes.

Finally, with careful measurements of the potential explanatory variables over the post-transplant period, one could analyze them instead as outcome variables. For instance, correlating clinical depression with such time-to-event outcomes as the occurrence of "major" nonadherent behavior, DCGF due to nonadherence [7], "refusal" to become more physically active, etc., would be possible. All of these approaches could greatly help in providing the most sensitive and specific explanations for the prognostic value of being clinically depressed following kidney transplantation.

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Conflicts of interest

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