Original research

# Depressive symptoms in lung transplant recipients: trajectory and association with mortality and allograft dysfunction

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## ABSTRACT

**Objective** Most studies observing an association between depressive symptoms following lung transplantation and mortality are limited to depressive symptom measurement at a single time point, unrelated to allograft function. We aimed to test the association of depressive symptoms over multiple assessments with allograft dysfunction and with mortality.

**Methods** We assessed depressive symptoms before and serially up to 3 years after lung transplantation in lung transplant recipients. We quantified depressive symptoms with the Geriatric Depression Scale (GDS; range 0–15; minimally important difference (MID): 2). We quantified changes in GDS using linear mixed effects models and tested the association with mortality using Cox proportional hazards models with GDS as a time-dependent predictor. To determine if worsening in GDS preceded declines in lung function, we tested the association of GDS as a time-dependent predictor with the lagged outcome of $FEV_1$ at the following study visit.

**Results** Among 266 participants, depressive symptoms improved early after transplantation. Worsening in post-transplant GDS by the MID was associated with mortality (HR 1.25, 95% CI 1.05 to 1.50), and in lagged outcome analyses with decreased per cent predicted $FEV_1$ (Δ, −1.62%, 95% CI −2.49 to −0.76). Visual analyses of temporal changes in GDS demonstrated that worsening depressive symptoms could precede chronic lung allograft dysfunction.

**Conclusions** Depressive symptoms generally improve after lung transplantation. When they worsen, however, there is an association with declines in lung function and mortality. Depression is one of the few, potentially modifiable, risk factors for chronic lung allograft dysfunction and death.

## Key messages

### What is already known on this topic

⇒ Prior studies have demonstrated an association between post-transplant depressive symptoms and mortality.
⇒ There are limited studies comprehensively assessing depressive symptoms in a longitudinal cohort of lung transplant recipients with extended follow-up, and as a result the trajectory of changes in depressive symptoms after lung transplantation is unknown.

### What this study adds

⇒ Depressive symptoms generally improve after transplantation; however, not all patients see improvements in depressive symptoms after transplantation.
⇒ Worsening in depressive symptoms post-transplant is associated with mortality, even when they occur at the range of scores that reflect low symptom burden, and some of this association may be explained by changes in allograft function.

### How this study might affect research, practice or policy

⇒ We explore the potential that depressive symptoms may represent a potentially modifiable risk factor for death and chronic lung allograft dysfunction.
⇒ We highlight the need to screen for depressive symptoms in the post-transplant period, even when they are mild.
⇒ Future studies should identify if any interventions can ameliorate the association with subsequent allograft dysfunction and mortality.

## INTRODUCTION

Lung transplantation is a therapeutic option for patients suffering from end-stage lung disease to extend survival and improve health-related quality of life (HRQL).[1] Despite advances in care, survival after lung transplantation is worse than other solid organ transplants; further, while HRQL generally improves following lung transplantation, some recipients still suffer from poor HRQL years after surgery.[2–4] Identifying upstream determinants of mortality and HRQL amenable to intervention is critically important to improve the success of lung transplantation.

Depression, common in patients with end-stage lung disease, is one of the potential upstream determinants of both HRQL and survival.[5–7] Further, trajectories of symptom change can be informative,

given that people with worsening depressive symptoms in the general population have a higher risk of death than those with stable or remitting symptoms.[8–10] While the presence of preoperative depressive symptoms is not associated with mortality after lung transplantation, depression is common post-transplant and its presence is associated with subsequent graft loss and mortality.[11–18] To date, there are limited studies comprehensively assessing depressive symptoms in a longitudinal cohort of lung transplant recipients with extended follow-up, and as a result the trajectory of changes in depressive symptoms after lung transplantation is unknown. In heart transplant recipients, who experience similar issues to lung transplant recipients, depressive symptoms generally improve after transplantation.[19 20] When present after heart transplantation, depressive symptoms are associated with an increased risk of non-compliance, incident graft vasculopathy and mortality.[21 22]

We noted that some lung transplant recipients suffer from the emergence of depressive symptoms, followed by decreased adherence to immunosuppressive therapy and subsequent allograft dysfunction, followed by death. Beyond anecdotal observations, it is unknown whether any association between post-transplant depressive symptoms and mortality reflects patients becoming more depressed due to overt or subclinical emergence of chronic lung allograft dysfunction (CLAD), whether depressive symptoms lead to non-adherence to immunosuppressant therapy and lower self-care agency, or whether other cofactors account for such an association.

Using a longitudinal single-centre cohort, where we measured depressive symptoms before and serially after lung transplantation, we sought to assess the trajectories of change in depressive symptoms over time. We tested the association between depressive symptoms and mortality in this cohort. We also used a 'lagged outcome' analysis approach to determine whether increases in depressive symptoms preceded graft loss, and we visually inspected the trajectory of depressive symptoms in participants who developed CLAD to determine if changes in depressive symptoms can precede graft loss. We have previously reported some of these data in abstract form.[23]

## METHODS

### Study design, participants and setting

We analysed participants from the University of California, San Francisco 'Breathe Again' study and 'Frailty study', two prospective cohort studies of lung transplant recipients.[3 24] The observation period began in February 2010 and ended in January 2017. All participants provided written informed consent. All surveys were collected by clinical research coordinators, outside the context of clinical care, and survey results were not available to the lung transplant team.

Participants were enrolled at the time of placement on the lung transplant waiting list and completed study visits every 3 months in the run-up to transplantation or when there were major changes in their clinical status, such as a pretransplant hospitalisation. At each study visit, participants were asked to complete a measure of depressive symptoms. After transplantation, they completed study visits at 6-month intervals until they reached 36 months after transplantation. Participants who underwent transplantation before April 2016 also had a 3-month post-transplant study visit. For participants with multiple pretransplant study visits, we used the visit most proximal to the date of transplant as the pretransplant baseline. Of note, our lung transplant programme follows the 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support.[25] As such, we work with prospective transplant candidates so that any patients with uncontrolled depression have appropriate resources to control their depressive symptoms prior to listing. Moreover, we make every effort to prevent mental health issues from being the sole contraindication for listing.

### Depressive symptoms

Depressive symptoms were quantified using the 15-item Geriatric Depression Scale (GDS), which has been validated in a variety of patient populations, including in patients with chronic illness, mild cognitive impairment, the elderly and in those who are hospitalised.[26–28] Despite its name, the GDS is also validated in younger adults and performs similarly in younger patients as it does in older persons.[29] With a sensitivity of 81% and a specificity of 75% for detecting depression, GDS outperforms shorter screening tests for depression, such as the Yale One Question Screen.[30] Because it does not query somatic symptoms which could be attributable to lung or general disease rather than depression, GDS minimises non-selective misclassification due to such factors. The range of scores on the GDS is 0–15, with higher scores denoting greater depressive symptoms. Mild depressive symptoms are considered present with a score of 5–8, moderate depressive symptoms with a score of 9–11 and severe depressive symptoms with a score of 12–15. The minimally important difference (MID) for the GDS is a change of 2 points.[31 32]

### Demographics and confounding variables

We extracted baseline demographics from the electronic medical record. These variables included age at the time of transplantation, sex, race, pretransplant body mass index, aetiology of respiratory failure which precipitated the need for transplantation as categorised by the Lung Allocation Score (LAS) grouping,[33] the participant's LAS at the time of transplantation, pretransplant 6 min walk distance (6MWD) and all clinically obtained $FEV_1$ readings conducted during the study period. We recorded date of CLAD onset, which we defined as a drop in $FEV_1$ by 20% of the post-transplant peak, sustained for greater than 30 days, as we have previously described.[34] We also recorded cause of death for participants who died during the study observation period. Given that our time-dependent predictors were collected up through 36 months after transplantation, we administratively censored our mortality outcomes at 48 months after transplantation (12 months after the last active data collection). Of note, we did not collect data on history of depression, referrals to psychiatry or use of antidepressants.

### Analytic approach

Our analytic approach is described in detail in the online supplemental methods. Briefly, we visualised the change in depressive symptoms after transplantation by plotting the mean GDS score over time. We then categorised each participant's level of pretransplant and post-transplant depressive symptoms and compared the trajectory of change in depressive categories from before transplantation to after transplantation using a Sankey diagram.

We then quantified changes in GDS using linear mixed effects models with participant-specific intercepts and a joint point set at 6 months post-transplant. We used Cox proportional hazards models with two separate predictors to test the association between depressive symptoms and mortality. To determine

if there was an association between pretransplant depressive symptoms and survival, we used the baseline GDS score as our predictor in a standard Cox model. To determine if there was an association between post-transplant depressive symptoms and survival, we used post-transplant GDS as a time-dependent predictor in a time-dependent Cox model. Additionally, we wanted to determine if the association between depressive symptoms and mortality might be mediated by changes in lung function after transplantation. As such, we fitted another model where we added post-lung transplant $FEV_1$ as a time-dependent covariate.

We were also interested in determining whether depressive symptoms preceded reductions in lung function after transplantation, or if reductions in lung function preceded worsening in depressive symptoms. As such, we used linear mixed effects models with 'lagged' outcomes to test if our predictor of interest was associated with subsequent development of an outcome, and we used a joint modelling approach to model these analyses jointly with survival data.

Additionally, we were interested to see if meeting the criteria for CLAD changed the trajectory of depressive symptoms after transplantation. As such, we plotted the trajectory of post-transplant GDS scores over time in the subset of participants who developed CLAD, using date of CLAD onset as our intercept. We also performed a chart review on the subset who developed CLAD to assess for adherence to medical care during that time period.

### Sensitivity analysis

To determine if there was any impact from including participants with a large proportion of missing data, we calculated the number of missing survey events for each participant and performed a sensitivity analysis stratified by degree of missingness. This was done by assessing the expected number of survey data points and then calculating the number missing from the expected number. Participants were stratified into those with >50% of missing data points (n=31) and those with <50% of missing data/no missing data (n=199). We then ran our models for the time-dependent Cox survival analysis and lagged outcome analyses stratified by degree of missingness.

A more thorough description of the study design, demographic variable collection, confounding and precision variables, analytic approach, justification for models, and handling of missing data is included in the online supplemental methods.

## RESULTS

There were 266 participants who completed the survey assessments during the study period and underwent transplantation (figure 1). The cohort had a mean age of 56.1±12.3 years old, 149 (56%) were male, 193 (74%) identified as non-Hispanic white, and 188 (71%) underwent transplantation for a diagnosis of interstitial lung disease (table 1). There were 36 participants who developed CLAD over 36 months and 30 participants who died during the 48-month observation period. Depressive symptoms generally improved across the entire cohort (figure 2). Improvement was not uniform (figure 3). Before transplant, the mean GDS score was 5.6±3.4, with 51 participants (21%) meeting the criteria for moderate to severe depressive symptoms. At 6 months post-transplant, the mean GDS score was 2.4±2.7, with only seven of the participants (4%) meeting the criteria for moderate to severe depressive symptoms (table 2).

Most of the improvement in depressive symptoms occurred in the early period after lung transplantation, where depressive symptoms improved by almost twofold the MID between the pretransplant baseline and 6 months after transplantation (Δ, −3.14 points, 95% CI −3.51 to −2.78). Depressive symptoms remained relatively stable after that, with a slight but statistically significant worsening in depressive symptoms between 6 months and 3 years after transplant (Δ, 0.41 points, 95% CI 0.18 to 0.64). Notably, this worsening was well below the MID.

In multivariate Cox proportional hazards models there was no association between depressive symptoms before lung transplantation and subsequent mortality (HR 0.96, 95% CI 0.80 to 1.16) (table 3). After lung transplantation, worsening in depressive symptoms by the MID (2 points) was associated with an adjusted 25% increased risk of death (adjusted HR 1.25, 95% CI 1.05 to 1.50). Since post-lung transplant allograft function is associated with mortality in our cohort (HR of 10% decline in $FEV_1$ 1.43, 95% CI 1.25 to 1.63), we tested if the association between depressive symptoms and mortality was mediated via changes in allograft function, and we found that the association between depressive symptoms and mortality was attenuated when $FEV_1$ was added to the model as a time-dependent covariate (adjusted HR 1.12, 95% CI 0.92 to 1.38). We then assessed the cause of death in participants who reported post-transplant depressive symptoms compared with participants who did not have any depressive symptoms after transplantation (table 4). Of the 11 participants who died from CLAD, majority were with at least one GDS score that met the criteria for depressive symptoms post-transplant (n=8, 73%).

In linear mixed effects models jointly modelled with survival assessing 'lagged outcomes', adjusted for age, gender, race, LAS at transplant, 6MWD at transplant and diagnostic indication for transplantation, a 10% decrease in per cent predicted $FEV_1$ was associated with a subsequent change in depressive symptoms at the following study visit, which was well below the clinically relevant threshold (Δ, 0.15 points, 95% CI 0.04 to 0.26) (table 5). We also found that each MID worsening in depressive symptoms was associated with a decreased per cent predicted $FEV_1$ at the following study visit (Δ, −1.63%, 95% CI −2.49 to −0.76). Visualisation of the trajectory of change in depressive symptoms in the 36 participants who developed CLAD demonstrated that 8 of these participants reported worsening depressive symptoms well before the onset of CLAD (figure 4). Chart review of the participants who developed CLAD demonstrated that, of the 8 participants with increase in depressive symptoms before CLAD, 6 (75%) had documentation of either multiple missed appointments, poor adherence to medical therapy and/or a relapse in smoking, a finding seen in only 6 of 28 (21%) participants without increase in depressive symptoms before CLAD.

Our sensitivity analysis assessing the association between GDS and survival in the time-dependent Cox models and the lagged outcome analyses stratified by degree of missingness demonstrated that the association between GDS and survival (time-dependent Cox) (online supplemental table 1) and the association between GDS and subsequent $FEV_1$ (lagged outcome analysis) (online supplemental table 2) were no longer present in the group of patients with >50% of missing data. However, the group of patients with more complete data had similar results to the overall cohort. Taken together, including the participants with a greater degree of missing data biased all our results to the null and the group with more complete data was similar to the overall cohort in all analyses.

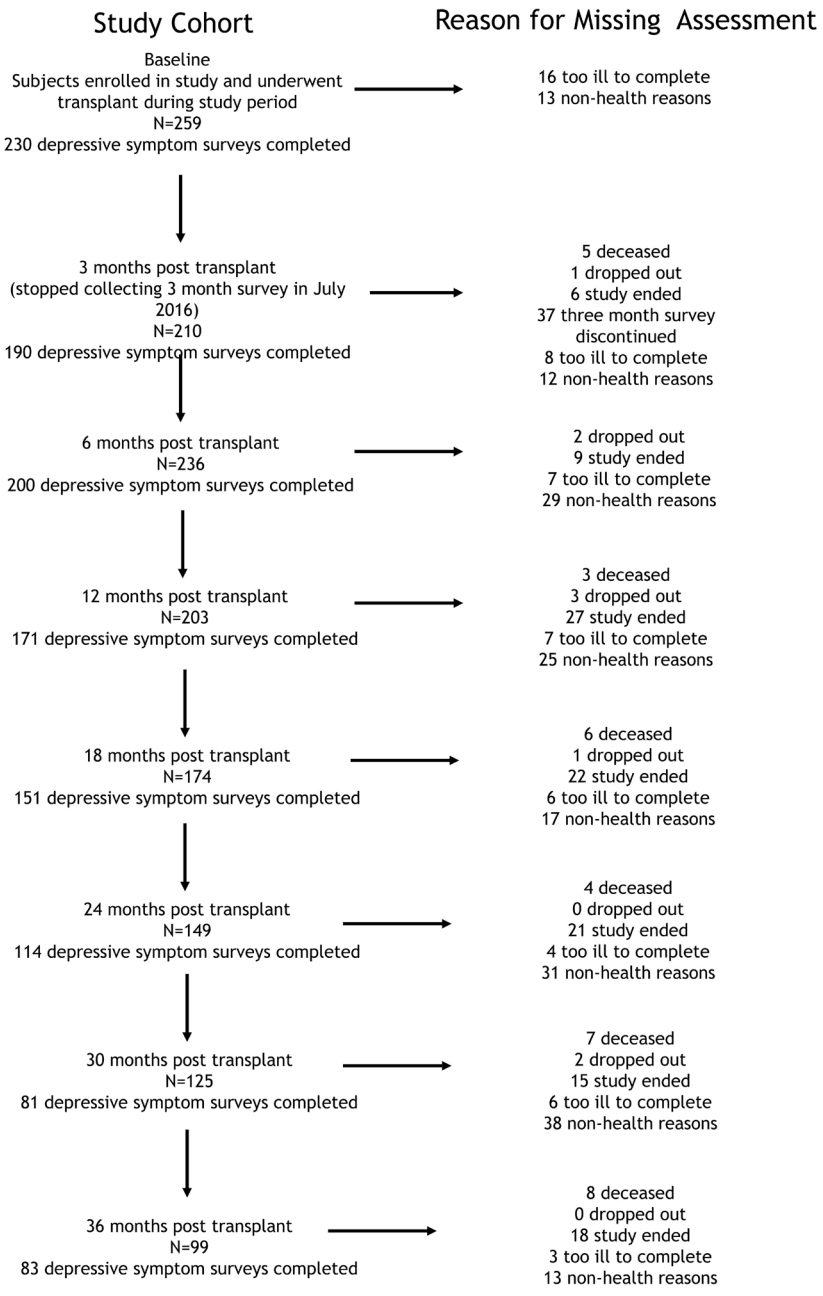


**Figure 1** CONSORT-type diagram. CONSORT, Consolidated Standards of Reporting Trials.

## DISCUSSION

In a single-centre longitudinal prospective cohort study, we found that depressive symptoms generally improve early after lung transplantation, the magnitude of which is greater than the MID. We found that these improvements were sustained well after the initial post-transplantation period. While the trajectory of the cohort demonstrated robust and sustained improvements in depressive symptoms, some participants had persistent or emergent depressive symptoms after lung transplantation. We also found that worsening in depressive symptoms is associated with subsequent mortality. While some of the associations may be explained by changes in $FEV_1$, our lagged analysis indicates that, at least for some patients, worsening in depressive symptoms precedes the onset of CLAD. Of note, 75% of the participants with worsening depressive symptoms prior to CLAD had documentation of poor adherence to medical therapy or multiple missed appointments. Further, 73% of deaths attributable to CLAD occurred in participants who reported the presence of depressive symptoms post-transplant. Our findings indicate that depressive symptoms may be an upstream determinant of both CLAD and mortality in this population, potentially via multiple mechanisms.

In this study we describe the trajectory of depressive symptoms after lung transplantation. Our findings of early improvements in depressive symptoms are consistent with prior literature on lung transplant recipients.[35 36] Among the patients either without depressive symptoms or with depressive symptoms that were acceptably controlled prior to listing, we found stability in the

**Table 1** Baseline demographics of the cohort

| Variable | Overall (N=266) |
|---|---|
| At baseline | |
| Age, mean±SD | 56.10±12.25 |
| BMI, mean±SD | 25.46±4.86 |
| Race, n (%) | |
| Non-Hispanic white | 193 (73.6) |
| Other | 72 (27.4) |
| Sex, n (%) | |
| Male | 149 (56.0) |
| Female | 117 (44.0) |
| Diagnosis, n (%) | |
| Chronic obstructive pulmonary disease | 44 (16.5) |
| Pulmonary arterial hypertension | 10 (3.8) |
| Cystic fibrosis | 24 (9.0) |
| Interstitial lung disease | 188 (70.7) |
| $FEV_1$, mean±SD | 1.41±0.71 |
| $FEV_1$ per cent, mean±SD | 45.1±21.0 |
| FVC, mean±SD | 1.99±0.82 |
| FVC per cent, mean±SD | 49.6±17.8 |
| 6 min walk distance (metres), median (IQR) | 261 (146–366) |
| At transplant | |
| LAS, median (IQR) | 52 (39–79) |

Baseline demographics of participants included in the study.
Diagnostic indication for transplantation was categorised by Group A (chronic obstructive pulmonary disease), Group B (pulmonary arterial hypertension), Group C (cystic fibrosis) and Group D (interstitial lung disease) groupings in the LAS.[33]
BMI, body mass index; LAS, Lung Allocation Score.

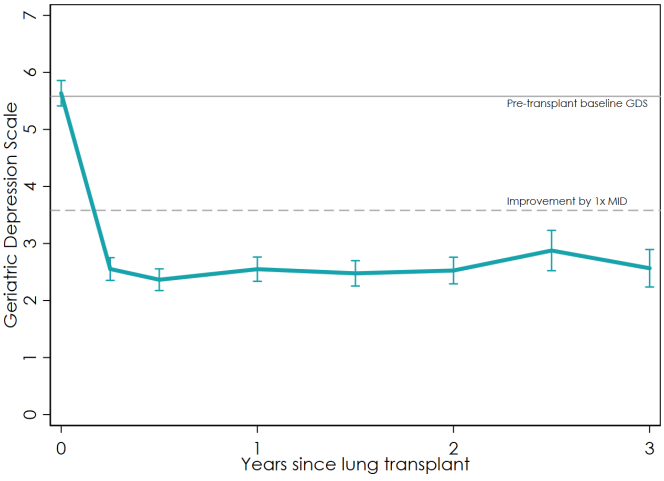


**Figure 2** Trajectory of depressive symptoms in the entire cohort over time after lung transplantation. Depressive symptoms were quantified using the Geriatric Depression Scale (GDS), with higher scores denoting greater depressive symptoms. Minimally important difference (MID) is a change of 2 points or greater. The solid blue line represents the mean GDS score in the entire cohort over time. The solid grey line represents pretransplant baseline GDS score. The dashed grey line represents 1 MID better than the baseline GDS score. Whiskers represent 1 SEM above or below the average GDS score at each time point.

improvement between 6 months and 3 years post-transplant is reassuring. We acknowledge, though, that part of this stability may be related to the clinical candidacy selection bias inherent in studies of lung transplant recipients. Additionally, our findings that depressive symptoms can persist or emerge after transplantation are important to consider in this population due to the increased healthcare utilisation, lower HRQL and increased risk of mortality seen in other non-transplant cardiothoracic surgery patients with persistent or emergent depressive symptoms after surgery.[21 37]

Moreover, our study adds to the existing literature assessing the association between depressive symptoms and mortality after lung transplantation. We confirmed the findings of prior studies that depressive symptoms after transplantation, but not before, are associated with an increased risk of mortality.[11–17] Prior studies showed that depressive symptoms present as early as 14 days or as late as 18 months post-transplant are associated with subsequent mortality.[13 17 38] Notably, our work differs from these prior studies by assessing the association between depressive symptoms and subsequent mortality across the entire range of depressive scores, and in a cohort of patients where the vast majority had a low burden of depressive symptoms. That we found any worsening in symptoms by the MID is associated with risk of mortality, even when the depressive symptom burden would be considered 'mild' by our typically applied clinical standards, raises the question on whether, clinically, by focusing on only the severe, we may be missing opportunity to improve the well-being and potentially long-term survival of lung transplant recipients. Our work is also novel by assessing depressive symptoms in a time-dependent manner, with paired assessments of lung function. Our finding that adjustment for lung function in a time-dependent manner ameliorates the association with mortality is not only novel by demonstrating that the association is mediated through lung function, but it raises important questions. Does worsening of depressive symptoms occur as a response to the development of allograft dysfunction after transplantation and therefore we find an association with death via CLAD? Alternatively, can worsening depressive symptoms drive certain behaviours that lead to allograft dysfunction and death or even death from causes other than allograft failure? Or is there a multitude of different scenarios at play? The 'lagged outcome' approach we used attempts to answer these questions and points to a multitude of scenarios; however, further studies are needed to fully understand the relationship.

In this cohort, $FEV_1$ decline was, on average, not associated with subsequent clinically relevant worsening in depressive symptoms, suggesting that clinically relevant depressive symptoms do not generally follow progressive graft dysfunction. Yet these findings do not eliminate the possibility of this happening on the individual patient level. On the contrary, we did find that worsening depressive symptoms are associated with a subsequent decline in $FEV_1$ and that the majority of deaths attributable to CLAD were found in participants with emergent or persistent depressive symptoms. Further, we demonstrated that some patients experience worsening in depressive symptoms well before the onset of CLAD. Potential mechanisms for these findings include decreased adherence to immunosuppressant therapy and disengagement with medical care, as we noted in our cohort, which may lead to inadequate immunosuppression and graft loss. We do advise caution in overinterpreting this, however, as we did not assess adherence to therapy in participants without worsening depressive symptoms, so it is not clear if similar behaviour issues are also present in participants without depressive symptoms.

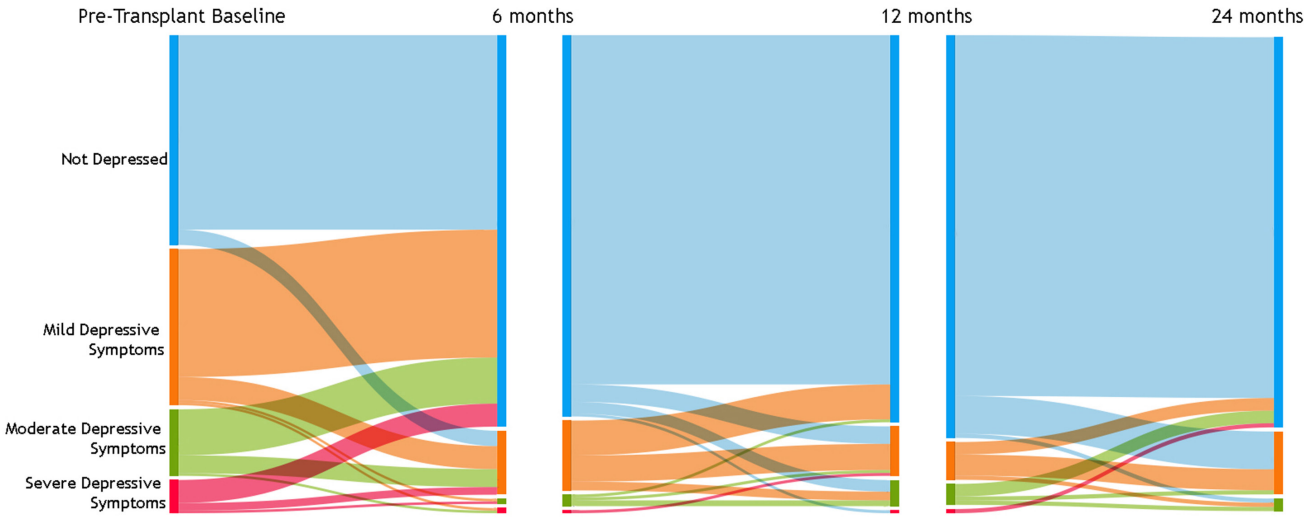


**Figure 3** Trajectory of changes in the categories of depressive symptoms in the entire cohort before and after lung transplantation. Trajectory was assessed over three distinct time periods: pretransplant baseline to 6 months post-transplant; 6 months post-transplant to 12 months post-transplant; and 12 months post-transplant to 24 months post-transplant. Each panel represents the trajectory of participants from the start of the time period to the end of the time period. The categories in the pretransplant period were derived from the study visit collected most proximal to the time of transplantation. Depressive symptoms were quantified using the Geriatric Depression Scale, with higher scores denoting greater depressive symptoms. No depression was denoted by a score of 0–4; mild depressive symptoms are present with a score of 5–8; moderate depressive symptoms are present with a score of 9–11; and severe depressive symptoms are present with a score of 12–15. Categories of depressive symptoms are represented by colours, where blue represents not depressed, orange represents mild depressive symptoms, green represents moderate depressive symptoms and red represents severe depressive symptoms.

Yet the relationships between depressive symptoms and graft loss, and depressive symptoms and mortality, are likely more than just decreased adherence to immunosuppression. A prior study which looked at immunosuppression levels demonstrated that immunosuppressant variability does not fully account for the increased risk of mortality noted in lung transplant recipients with depression.[39] Moreover, prior studies have shown that lung transplant recipients with depression also tend to have lower self-care agency and more social isolation, which supports the idea of depressive symptoms as an upstream precursor to allograft dysfunction and mortality through multiple mechanisms.[40 41] While purely speculative, one of these potential mechanistic links is through inflammation. It is well documented that increased markers of inflammation can precede the onset of CLAD.[42–44] Azithromycin, a macrolide antibiotic with anti-inflammatory properties, is effective as prophylaxis against neutrophilic reversible allograft dysfunction, a form of obstructive CLAD.[45–47] Similarly, there is increasing evidence of an association between depression and immune activation, and that response to antidepressant therapy can be predicted by changes in immune markers.[48–51]

The finding that worsening in depressive symptoms can precede graft dysfunction is also important for the clinical care of lung transplant recipients, especially because depressive symptoms are one of the few potentially modifiable predictors of graft dysfunction and mortality. Clinical care should include screening for increasing depressive symptoms post-transplant in order to identify patients with this, potentially modifiable, risk factor for CLAD and death. Once identified, these patients should be referred to a mental health professional, which is an intervention associated with decreased mortality in other patients with chronic lung disease.[52] While antidepressants might be effective

**Table 2** Mean and median depressive symptoms in the entire cohort over various study visits

| | Baseline | 3 months | 6 months | 12 months | 18 months | 24 months | 30 months | 36 months |
|---|---|---|---|---|---|---|---|---|
| | n=246 | n=190 | n=200 | n=171 | n=151 | n=114 | n=81 | n=83 |
| Mean GDS score ±SD | 5.58±3.39 | 2.55±2.75 | 2.37±2.70 | 2.55±2.79 | 2.48±2.73 | 2.53±2.49 | 2.88±3.18 | 2.57±2.99 |
| Median GDS score (IQR) | 5 (3–8) | 2 (0–4) | 1.5 (0–3) | 2 (1–3) | 1 (0–4) | 2 (1–4) | 2 (0–5) | 1 (0–4) |
| GDS 0–4, n (%) | 113 (46) | 153 (81) | 165 (83) | 142 (83) | 123 (81) | 94 (83) | 59 (73) | 66 (80) |
| GDS 5–8, n (%) | 82 (33) | 28 (15) | 28 (14) | 18 (11) | 19 (13) | 17 (5) | 17 (21) | 12 (15) |
| GDS 9–11, n (%) | 33 (13) | 8 (4) | 5 (3) | 10 (6) | 8 (5) | 3 (3) | 2 (2) | 4 (5) |
| GDS 12–15, n (%) | 18 (7) | 1 (<1) | 2 (1) | 1 (<1) | 1 (<1) | 0 (0) | 3 (4) | 1 (1) |

Depressive symptoms over time before and after transplantation as quantified by the Geriatric Depression Scale (GDS). Higher scores denote more depressive symptoms. No depression is denoted by GDS scores between 0 and 4. Mild depressive symptoms are present when the GDS score is between 5 and 8. Moderate depressive symptoms are present when the GDS score is between 9 and 11. Severe depressive symptoms are present when the GDS score is ≥12.
Data represent mean GDS score at each study visit ±SD, median GDS score and IQR, as well as the proportion of participants at each time point who fall within each category of depressive symptoms.

**Table 3** Association between depressive symptoms and mortality in lung transplant recipients

| Predictor* | Adjustment | HR (95% CI) |
|---|---|---|
| Baseline GDS | Age, sex, race, diagnosis, LAS at transplant, 6MWD at transplant | 0.96 (0.80 to 1.16), p=0.66 |
| Post-lung transplant GDS† | Age, sex, race, diagnosis, LAS at transplant, 6MWD at transplant | 1.25 (1.05 to 1.50), p=0.01 |
| Post-lung transplant GDS† | Age, sex, race, diagnosis, LAS at transplant, 6MWD at transplant, post-transplant $FEV_1$ | 1.12 (0.92 to 1.38), p=0.26 |

Data represent HR for death based on depressive symptoms, as quantified by Cox proportional hazards models, with 95% CI.
Models adjusted for age, gender, race, LAS at transplant, 6MWD at transplant and diagnostic indication for transplantation.
Depressive symptoms were quantified using the GDS. Two separate predictors used: baseline GDS represents depressive symptoms prior to transplantation, and post-lung transplant GDS represents depressive symptoms over the post-transplant time period as a time-dependent predictor. Additional model using post-lung transplant GDS included post-transplant $FEV_1$ as a time-dependent covariate.
*Models scaled to a two-unit increase in GDS score, which represents a change considered to be the minimally important difference.
†Time-dependent predictor.
GDS, Geriatric Depression Scale; LAS, Lung Allocation Score; 6MWD, 6 min walk distance.

in reducing depressive symptoms, other non-pharmacological treatments are also promising and include psychotherapy, pulmonary rehabilitation, structured physical activity, having a companion animal and improved social support.[41 52–55] Future studies should assess if any of these interventions can prevent graft loss or decrease mortality through improvements in depressive symptoms. It would also be interesting to note the impact of these interventions on inflammatory markers in lung transplant recipients. In particular, these interventions may be most effective in patients with worsening depressive symptoms who have normal allograft function. One such study is the ongoing INSPIRE-III trial, where lung transplant recipients are being randomised into either a telephone-delivered coping skills training combined with aerobic exercise arm, or a standard of care plus education arm.[56]

**Table 4** Cause of death in participants stratified by presence of post-transplant depressive symptoms

| | Persistent or emergent depressive symptoms post-transplant n (%) | Never depressed post-transplant n (%) |
|---|---|---|
| Cancer | 0 (0) | 2 (2) |
| Sudden death/unknown | 1 (1) | 2 (2) |
| Non-pulmonary organ failure | 3 (3) | 0 (0) |
| Chronic lung allograft dysfunction | 8 (9) | 3 (2) |
| Acute respiratory failure | 0 (0) | 4 (3) |
| Infection | 4 (4) | 3 (2) |
| Alive | 74 (82) | 116 (89) |

Cause of death in participants who had at least one study visit post-transplant. Participants were divided into those who had persistent or emergent depressive symptoms post-transplant and those who never had depressive symptoms post-transplant.

**Table 5** Lagged outcome analysis of depressive symptoms and lung function

| Predictor | Outcome | Effect (95% CI) |
|---|---|---|
| $FEV_1$ % predicted (10% decrease) | GDS score at subsequent study visit | 0.15 (0.04 to 0.26), p=0.01 |
| GDS (2-point increase)* | $FEV_1$ % predicted at subsequent study visit | −1.63 (−2.49 to −0.76), p<0.01 |

Generalised linear mixed effects model jointly modelled with survival using time-dependent predictors and 'lagged' outcomes.
Data represent estimate of the effect of the predictor at preceding study visit on outcome at subsequent study visit, with 95% CI.
Models were adjusted for age, gender, race, LAS at transplant, 6MWD at transplant and diagnostic indication for transplantation.
Mixed models were jointly modelled with survival. Depressive symptoms were quantified using the GDS.
*Model with the GDS as a predictor scaled to a two-unit increase in the GDS, which represents a change considered to be the minimally clinically important difference.
GDS, Geriatric Depression Scale; LAS, Lung Allocation Score; 6MWD, 6 min walk distance.

This study has limitations. It was performed in a single-centre academic transplant centre, and as such it is unclear if our findings are representative of the larger population of lung transplant recipients. We did not assess comorbid conditions or surgical risk factors so it is possible that some unmeasured variable influenced our results. Further, it is unclear if any of our centre-specific protocols on selection of candidates or clinical management influenced the findings. While we enrolled the vast majority of patients who underwent lung transplantation at our centre in this study (~90%–95% of English-speaking patients), it is possible that those who declined to participate were systematically different from those who did. Since we did not track the three to six patients per year who did not consent to participate in our research study, our results could be biased by unrecognised differences between responders and non-responders, which could limit generalisability. Finally, while we assessed depressive symptoms rather than the presence of clinically diagnosed depression, we did not collect data on whether participants had an existing psychiatric comorbidity, if they underwent psychotherapy, saw a psychiatrist or if they were on antidepressants during the study period. As such, it is possible that some of our findings may be driven by factors aside from transplant, such as referral to therapy, antidepressant use or our extensive social work evaluation prior to transplantation which helps put in place methods to mitigate depressive symptoms. Therefore, we are not certain if some of our findings could be impacted by differential use of antidepressants or other therapies for depressive symptoms.

Our study also has notable strengths. It is the only longitudinal assessment of depressive symptoms in a large cohort of lung transplant recipients with extended follow-up. We add to the literature by describing the trajectory of improvements in depressive symptoms after transplantation and by confirming the importance of post-transplant depressive symptoms in risk of subsequent mortality. Further, we identify worsening depressive symptoms as a novel risk factor for declining $FEV_1$, and that worsening in depressive symptoms can occur well before the onset of CLAD.

In addition to extending survival, lung transplantation offers respite for patients suffering from increasing depressive symptoms as a result of end-stage lung disease. The improvement is not uniform, and worsening in depressive symptoms may play

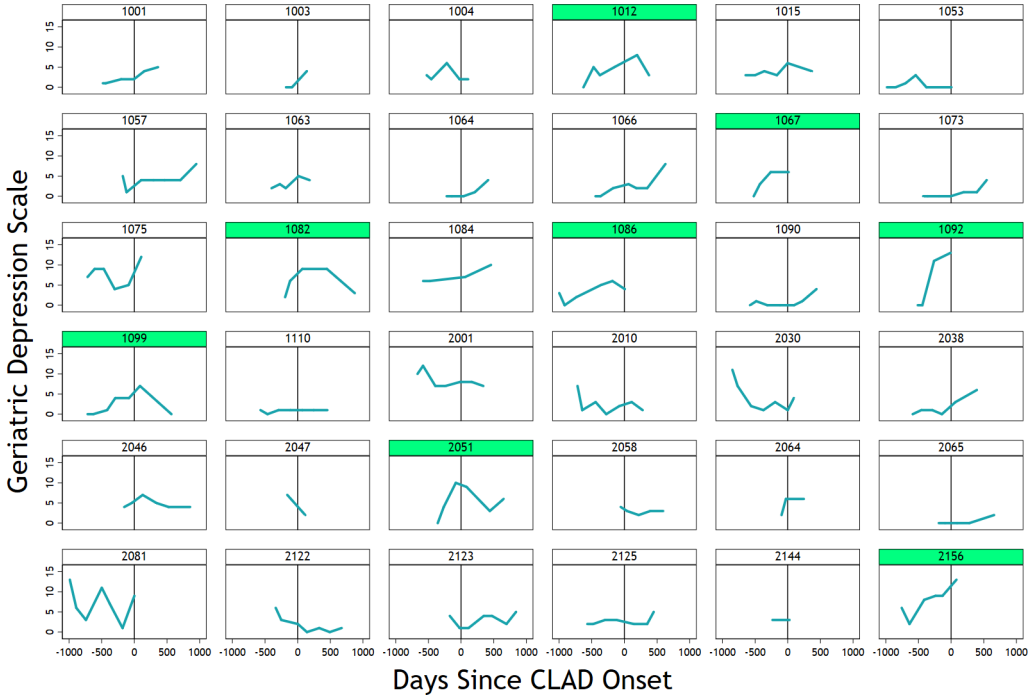


**Figure 4** Trajectory of changes in post-transplant depressive symptoms in participants who developed CLAD during the study period. The vertical line represents date of CLAD onset. Graphs are divided by study identification number and each individual plot represents GDS score in a single participant over the post-transplant study period. Identification numbers highlighted in green represent those with increasing depressive symptoms prior to onset of CLAD. Depressive symptoms were quantified using the GDS, with higher scores denoting greater depressive symptoms. CLAD, chronic lung allograft dysfunction; GDS, Geriatric Depression Scale.

an important role in the development of graft dysfunction for certain patients. The presence of depressive symptoms post-transplant is also associated with increased mortality. Screening for depressive symptoms should occur in the post-transplant period, and future studies should identify if any interventions, such as referrals to mental health professionals, medications, psychotherapy, physical exercise, companion animals or improving social support, can ameliorate the association with subsequent allograft dysfunction and mortality.

**Correction notice** This article has been corrected since it was published Online First. An additional twitter handle has been added.

**Twitter** Nicholas A Kolaitis @LungTxptMD and Aida Venado @Aida_Venado

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