ORIGINAL ARTICLE

Depression, social support, and clinical outcomes following lung transplantation: a single-center cohort study

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SUMMARY

Depressive symptoms are common among lung transplant candidates and have been associated with poorer clinical outcomes in some studies. Previous studies have been plagued by methodologic problems, including small sample sizes, few clinical events, and uncontrolled confounders, particularly perioperative complications. In addition, few studies have examined social support as a potential protective factor. We therefore examined the association between pretransplant depressive symptoms, social support, and mortality in a large sample of lung transplant recipients. As a secondary aim, we also examined the associations between psychosocial factors, perioperative outcomes [indexed by hospital length of stay (LOS)], and mortality. We hypothesized that depression would be associated with longer LOS and that the association between depression, social support, and mortality would be moderated by LOS. Participants included lung transplant recipients, transplanted at Duke University Medical Center from January 2009 to December 2014. Depressive symptoms were evaluated using the Beck Depression Inventory (BDI-II) and social support using the Perceived Social Support Scale (PSSS). Medical risk factors included forced vital capacity (FVC), partial pressure of carbon dioxide (PCO_2), donor age, acute rejection, and transplant type. Functional status was assessed using six-minute walk distance (6MWD). We also controlled for demographic factors, including age, gender, and native disease. Transplant hospitalization LOS was examined as a marker of perioperative clinical outcomes. Participants included 273 lung recipients (174 restrictive, 67 obstructive, 26 cystic fibrosis, and six "other"). Pretransplant depressive symptoms were common, with 56 participants (21%) exhibiting clinically elevated levels (BDI-II $\geq$ 14). Greater depressive symptoms were associated with longer LOS [adjusted $b = 0.20$ (2 days per 7-point higher BDI-II score), $P < 0.01$]. LOS moderated the associations between depressive symptoms ($P = 0.019$), social support ($P < 0.001$), and mortality, such that greater depressive symptoms and lower social support were associated with greater mortality only among individuals with longer LOS. For individuals with LOS $\geq$ 1 month, clinically elevated depressive symptoms (BDI-II $\geq$ 14) were associated with a threefold increased risk of mortality (HR = 2.97). Greater pretransplant depressive symptoms and lower social support may be associated with greater mortality among a subset of individuals with worse perioperative outcomes.

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Introduction

Psychosocial function is increasingly recognized as an important component of pretransplant evaluation [1]. A comprehensive evaluation not only includes medical status (e.g., assessment of lung disease severity) but also typically assesses multiple areas of psychosocial functioning, one of the most common being the assessment of depressive symptoms. Elevated levels of depression are quite common among transplant candidates, with more than 20% of patients exhibiting clinically elevated levels [2]. In addition, pretransplant depressive symptoms have been associated with wait-list mortality and have been suggested to increase risk of adverse clinical outcomes following transplantation [3].

Despite a number of qualitative and quantitative research syntheses, the association between pretransplant depression and post-transplant clinical outcomes has been inconsistent [3,4]. Although several small, retrospective studies have suggested that the presence of elevated depressive symptoms is associated with greater risk of mortality, several recent, prospective cohort studies failed to find any association [5,6]. In addition, a recent meta-analytic review found no association between pretransplant depression and post-transplant mortality [7]. Nevertheless, there is some evidence that elevated levels of depressive symptoms may be associated with increased risk of adverse clinical events among some solid organ transplant recipients [5,8]. At least three prospective studies have demonstrated that elevated levels of depression assessed shortly after transplant are associated with greater risk of mortality [4,6,9,10]. In addition, pretransplant depression is a risk factor for post-transplant depression [5], suggesting that a better understanding of factors that may influence the association between depression and clinical outcomes may help inform treatment strategies among lung transplant patients exhibiting depressive symptoms.

An area of increasing interest is the association between preoperative depressive symptoms and perioperative outcomes [11]. The presence of elevated preoperative depressive symptoms has been associated with a greater incidence of perioperative complications and worse short-term outcomes among multiple patient groups [11,12]. Preliminary data suggest a similar association in solid organ transplant recipients, with greater depression predicting longer length of stay and greater mortality [13]. However, this association has never been examined in lung transplant recipients. We therefore examined the association between pretransplant depressive symptoms, perioperative outcomes, and mortality following lung transplantation. As a secondary interest, we examined the potentially moderating role of perioperative outcomes on the depression and mortality association.

Methods

Participants were approached during their comprehensive, pretransplant assessment at Duke University Medical Center. Participants in this study were enrolled between January 1, 2009, and January 1, 2015. Among included participants, the first transplant occurred on January 6, 2009, and the last occurred on December 18, 2014. The present cohort represents a convenience sample of transplant recipients. Therefore, although psychosocial and clinical outcomes data were collected and entered prospectively (i.e., regardless of participant clinical outcomes), the present sample and data collection were not based on a prospectively designed study methodology.

Depressive symptoms

Beck Depression Inventory-II

The Beck Depression Inventory-II (BDI-II), a 21-item self-report questionnaire, was used to assess symptoms of depression. Total scores range from 0 to 63, with higher scores indicating more severe depressive symptoms [14]. To examine the association between clinically elevated depressive symptoms and outcomes, we also examined individuals above a BDI-II of 14.

Perceived Social Support Scale

The 12-item Perceived Social Support Scale (PSSS) measures perceived support from family and friends [15].

Total scores range from 0 to 84, with higher scores indicating greater perceived social support.

Background and medical characteristics

All demographic and baseline medical characteristics were selected *a priori* and included age at the time of transplant, gender, ethnicity, and native disease. Specific disease severity measures and functional status at the time of the patient's transplant were assessed, including forced vital capacity (FVC), partial pressure of carbon dioxide (PCO_2), and lung allocation score (LAS). Surgical predictors included type of transplant (bilateral versus single), donor age, and primary graft dysfunction (PGD) [16,17]. To examine the influence of perioperative medical events on long-term outcomes, transplant length of stay (LOS) was used as our predictor of interest. Of note, although we considered LAS as a predictor in our final model, we chose not to use this because of its substantial overlap with other individual medical predictors. Results were unchanged if LAS was included as an additional predictor.

Functional status

Functional status was examined using six-minute walk distance (6MWD) [18]. This test of functional status and exercise tolerance measures the distance that patients are able to walk within a six-min time limit at a self-selected pace while maintaining adequate oxygen saturations of 88% or greater. Poorer 6MWD strongly predicts perioperative outcomes and mortality among lung transplant recipients [19–21].

Data analysis

All analyses were conducted using SAS 9.3 (Cary, NC, USA) and R 3.3.1 (https://cran.r-project.org/). Analyses of length of stay data were conducted using hierarchical regression modeling, with a negative binomial error structure specified. LOS was analyzed in two steps: One in which psychosocial predictors (depressive symptoms and social support) were examined and a second in which functional status was entered as an additional predictor. Because depressive symptoms and 6MWD were associated, we conducted our analyses to better characterize the interrelationships between these factors and LOS. Within all models, background and medical predictors were selected *a priori*. For our LOS analyses, we controlled for age, gender, native disease, FVC, PCO_2, donor age, and transplant type (bilateral versus unilateral). Additionally, we controlled for PGD in our LOS analyses but, because PGD was the primary determinant of longer LOS and therefore confounded, elected to control for LOS (without PGD) in our survival models, as well as controlling for 6MWD. Of note, because we were interested, the association between depression, social support, and perioperative outcomes (e.g., patients' ability to cope with a difficult hospitalization), as well as longer-term associations with survival, we paid particular attention to the manner in which perioperative events were utilized in our models. For our LOS model, participants who died during hospitalization were incorporated by imputing the longest LOS (304 days) as their outcome, which has been shown to produce valid LOS estimates [22]. In addition, we eliminated three individuals who died within 1 month of transplant from our analyses, as these participants experienced immediate postoperative complications and their clinical outcomes would therefore be highly unlikely to be impacted by psychosocial status preoperatively. In contrast, we eliminated all individuals who died during their hospitalization from our survival models ($n = 13$), so that any observed association between psychosocial function and long-term survival was not overly influenced by individuals with the poorest short-term outcomes. Survival models were examined using Cox proportional hazards models using a time-varying covariate approach, in which the time between psychosocial assessments and transplantation is incorporated into quantification of mortality risk. We also present unadjusted Kaplan–Meier curves with their associated log-rank test for illustrative purposes. Due to their collinearity and the *a priori* examination of effect modification, we modeled survival separately for depression and social support. Assumptions regarding linearity, additivity, and independence were all assessed and found to be adequate prior to analysis.

As requested by an anonymous reviewer, we conducted several additional sensitivity analyses to test the robustness of the observed associations. These analyses included (i) a re-examination of our LOS analyses in which individuals with longer LOS (i.e., ≥120 days) were eliminated, (ii) a re-examination of our LOS analyses in which LAS was included as an additional covariate, and (iii) a re-examination of our survival models in which LAS was controlled.

Results

Demographic and clinical characteristics are presented in Table 1. Between January 1, 2009, and January 1,

2015, 682 individuals underwent lung transplantation, among whom 273 (40%) consented to have their pretransplant psychosocial data included in this study. As shown in Table 1, included participants tended to be older, female, and differed slightly by native disease. The sample analyzed was comprised primarily of restrictive native lung disease patients (n = 174), followed by COPD (n = 67) and CF (n = 26). These recipient characteristics reflect our center's lung transplant demographics.

Examination of time differences between psychosocial assessments and transplant revealed that participants completed depression assessments approximately 5 months prior to transplant, on average [median = 4.8 months (IQR = 3.1, 10.2)]. Depressive symptoms tended to be elevated, corresponding to subclinical levels [mean BDI-II = 9.6 (6.3), range 0–32], with 56 individuals (21%) exhibiting clinically elevated levels (BDI-II $\geq$ 14). In terms of past psychiatric history, 37 participants (14%) reported a history of mental health treatment and 30 individuals (11%) met criteria for a past history of a depressive disorder. Self-reported levels of social support were elevated [mean PSSS = 77.8 (8.4), range 14–84], with a substantial number of participants exhibiting PSSS scores near the maximum of 84 points, suggesting a high level of perceived social support. At baseline, greater depressive symptoms were associated with lower age (r = −0.16, P = 0.007) and lower 6MWD (r = −0.20, P = 0.002).

Table 1. Background and demographic characteristics.

Variable	Completed assessments and consented (n = 273)	Did not complete and/or consent (n = 407)
Native disease (UNOS grouping)		
Obstructive (A)	67 (24%)	98 (24%)
Other (B)	6 (2%)	9 (2%)
Cystic fibrosis (C)	26 (10%)	73 (18%)
Restrictive (D)	174 (66%)	226 (56%)
Age**	59.0 (13.4)	54.5 (17.2)
Female gender*	90 (33%)	172 (42%)
Lung allocation score	48.7 (16.1)	49.5 (16.9)
Forced expiratory volume (FEV_1), % predicted	41.2 (19.6)	38.7 (21.0)
Bilateral transplant	174 (63%)	301 (74%)
Forced vital capacity (FVC)	51.3 (16.9)	50.9 (19.3)
Partial pressure of carbon dioxide (CO_2)*	46.4 (10.3)	48.3 (12.2)
Six-minute walk distance, feet	1252 (377)	1284 (424)
Perceived Social Support Scale	77.8 (8.4)	
Beck Depression Inventory	9.5 (6.3)	–

Values are mean (SD) unless otherwise indicated.

Differences between patients who did and did not complete assessments and consented to participate.

*P < 0.05 for group difference; **P < 0.01 for group difference.

Perioperative outcomes

Length of stay varied widely across the sample [median 14 days (IQR = 10, 26)], with the longest LOS lasting 303 days. There were 13 individuals who died during their hospitalization. Results from LOS models are shown in Table 2. As shown, examination of background and medical predictors demonstrated that greater donor age (b = 0.12, P = 0.009), bilateral versus unilateral transplant (b = 0.58, P = 0.001), and pretransplant depressive symptoms (b = 0.20, P = 0.018) were all predictive of longer LOS. For example, each 7-point increase in the BDI-II was associated with a 2-day longer LOS. In addition, participants exhibiting elevated depressive symptoms (BDI-II $\geq$ 14) exhibited a LOS approximately 2.5 days longer than their counterparts without elevated depressive symptoms [20.1 (15.5, 26.1) versus 17.6 (15.5, 19.9) days]. In a final model incorporating 6MWD, the association between depressive symptoms and LOS was partially attenuated (b = 0.14, P = 0.099), whereas greater 6MWD continued to be associated with shorter LOS (b = −0.39, P < 0.001) (Table 2). The observed associations between depressive symptoms and LOS were unchanged in sensitivity analyses in which individuals with the longest LOS were eliminated (b = 0.13, P = 0.023) or when LAS was included as an additional covariate (b = 0.19, P = 0.028).

Predictors of mortality

Over a median follow-up of 6.1 years (range 0–13.4), there were 113 deaths (41%). The primary causes of death tended to be associated with pulmonary etiologies or graft failure: pulmonary (n = 31, 27%), graft failure (n = 15, 13%), infection (n = 18, 16%), malignancy (n = 10, 9%), multiorgan failure (n = 9, 8%), cardio/cerebrovascular (n = 6, 5%), other (n = 1, 1%), or unknown (n = 25, 22%). Examination of pretransplant predictors revealed that 6MWD (HR = 0.62, P = 0.001)

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Table 2. Results from length of stay analyses.

Predictor (IQR)	Psychosocial + medical	Full model
Age (14 years)	0.11 (−0.11, 0.33)	0.14 (−0.08, 0.36)
Gender (male)	−0.08 (−0.37, 0.21)	0.04 (−0.26, 0.34)
IPF versus COPD	0.27 (−0.15, 0.69)	0.23 (−0.19, 0.65)
CF versus COPD	−0.05 (−0.72, 0.62)	−0.03 (−0.70, 0.64)
Other versus COPD	0.00 (−0.48, 0.48)	0.07 (−0.42, 0.56)
Partial pressure of carbon dioxide (CO_2) (11)	−0.07 (−0.24, −0.10)	−0.09 (−0.30, 0.12)
Forced vital capacity (FVC) (24)	−0.02 (−0.26, 0.22)	−0.03 (−0.27, 0.21)
Donor age (10 years)	0.12 (0.03, 0.21)**	0.11 (0.02, 0.20)*
Bilateral transplant	0.58 (0.23, 0.93)**	0.51 (0.17, 0.85)**
Primary graft dysfunction (Grades 0–1, 2, or 3)	0.35 (−0.02, 0.72)	0.35 (0.0, 0.71)*
Perceived Social Support Scale (PSSS) (9)	0.08 (−0.09, 0.25)	0.12 (−0.04, 0.28)
Beck Depression Inventory (BDI-II) (7.2)	0.20 (0.04, 0.36)*	0.14 (−0.03, 0.28)
Six-minute walk distance (6MWD) (500 ft)	–	−0.39 (−0.58, −0.20)**

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

Predictors are scaled using the interquartile range.

*$P < 0.05$; **$P < 0.01$.

and longer LOS (HR = 1.15, $P < 0.001$) were all predictive of mortality. In contrast, neither depressive symptoms nor social support was not associated with mortality in our main effects model, which did not account for potential effect modification (HR = 1.12, $P = 0.360$; HR = 1.04, $P = 0.703$). In a preplanned examination of effect modification, we found that the associations between depressive symptoms, social support, and mortality were moderated by LOS ($P = 0.025$ and $P < 0.001$), such that greater depressive symptoms and lower social support were associated with greater mortality among individuals with longer LOS. For example, model-based estimates demonstrated that individuals with elevated depressive symptoms and an LOS ≥ 1 month had substantially higher mortality compared to their counterparts with lower LOS (adjusted HR = 2.97; unadjusted HR = 3.73; Fig. 1; log-rank $P < 0.001$). Similarly, participants with lower social support and a LOS > 1 month had substantially elevated mortality (adjusted HR = 2.89; unadjusted HR = 2.87; Fig. 2; log-rank $P = 0.001$). These associations were unchanged in sensitivity analyses in which LAS was included as an additional covariate, with LOS continuing to moderate the associations between depression ($P = 0.046$ for interaction), social support ($P = 0.003$ for interaction), and mortality.

Discussion

To our knowledge, the present manuscript is the first to examine the influence of perioperative outcomes on the association between pretransplant psychosocial characteristics and post-transplant outcomes among lung transplant recipients. Although previous studies have examined the association between pretransplant psychosocial factors and long-term outcomes [1,23,24], few have attempted to account for post-transplant medical factors that may affect this association [13]. For example, longer LOS following transplantation is a well-known predictor of future clinical events due to the impact of acute infections, primary graft dysfunction, and other perioperative complications [17,25–29].

Although not frequently investigated among lung transplant recipients, numerous studies in other surgical populations have demonstrated that elevated depressive symptoms, or history of depression, may portend worse perioperative risk through several mechanisms [30], including delayed response engaging in rehabilitation [31], elevated preoperative inflammation [32], and greater incidence of postoperative delirium [33–35]. In addition, at least one study among liver transplant recipients demonstrated that the presence of pretransplant depression was associated with longer LOS and survival [13]. In their retrospective study, Rogal and colleagues found that pretransplant depression was associated with an approximately 5-day longer LOS (14 versus 19 days) and associated with more than a 50% increase in mortality risk. In addition, they found that cause of death among individuals with depression was more likely to be due to withdrawal of care, which reportedly could have included "stopping medications, stopping dialysis, or initiation of palliative care."

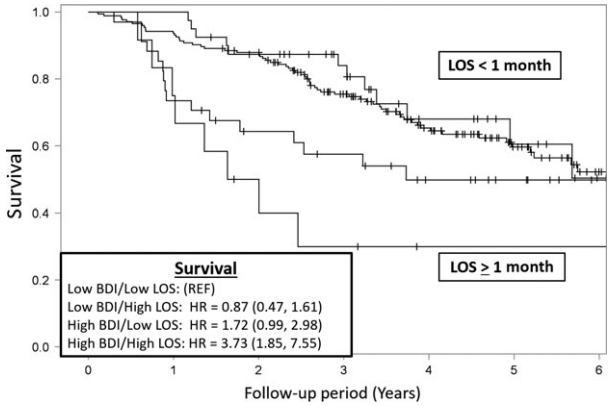

Figure 1 Unadjusted Kaplan–Meier curves for depression and mortality by length of stay (LOS) groups (Log-rank $P < 0.001$). Elevated depressive symptoms were unrelated to mortality among individuals with shorter LOS but demonstrated an increasingly stronger association with mortality as LOS increased ($P = 0.019$ for interaction). Among individuals with >1 month LOS, elevated depressive symptoms (lowest line) were associated with nearly a threefold increased risk of mortality. Cox proportional hazards model-based estimates suggested that individuals with elevated depressive symptoms and an LOS ≥ 1 month had substantially higher mortality compared to their counterparts with lower LOS [adjusted = HR = 2.97 (1.22, 7.22); unadjusted HR = 3.73 (1.85, 7.55)].

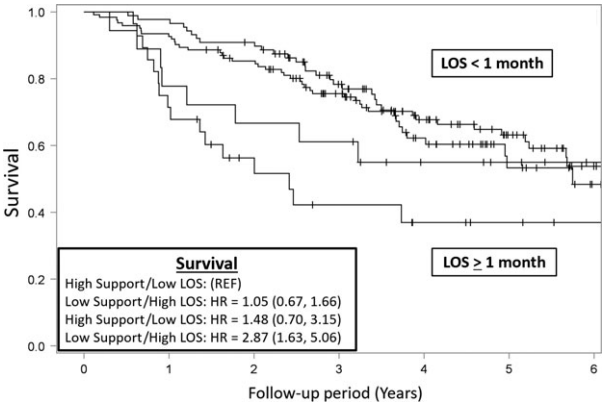

Figure 2 Unadjusted Kaplan–Meier curves for Perceived Social Support and mortality by length of stay (LOS) groups (Log-rank $P = 0.001$). Lower social support was unrelated to mortality among individuals with shorter LOS but demonstrated an increasingly stronger association with mortality as LOS increased ($P < 0.001$ for interaction). Among individuals with >1 month LOS, lower social support (lowest line, grouped based on median split for illustration) was associated with nearly a threefold increased risk of mortality. Cox proportional hazards model-based estimates suggested that individuals with lower Perceived Social Support and an LOS ≥ 1 month had substantially higher mortality compared to their counterparts with higher Perceived Social Support [adjusted HR = 2.89 (1.50, 5.60); unadjusted HR = 2.87 (1.63, 5.06)].

Previous studies have suggested that greater depressive symptoms [6,8–10] and poorer social support may be associated with greater risk of mortality among transplant recipients. Previous studies have found that elevated depressive symptoms are associated with greater risk of clinical events following transplantation [9,10], although few studies have examined social support and its association with clinical outcomes. However, numerous studies among patients with cardiovascular disease have suggested that social support plays an important role in mitigating secondary risk of cardiac events [36–38] and may be particularly important in the context of depression [39–40].

Although few studies of examined perioperative factors as a moderator of long-term clinical outcomes, the present analysis lend themselves to replication from existing cohort studies. For example, examination of our previously published paper from the inspire study demonstrated the same pattern of findings. Although pretransplant depressive symptoms were not in themselves predictive of risk (HR = 1.01), this association was moderated by length of stay ($P = 0.037$). Among individuals with longer LOS (>3 weeks), the association between depressive symptoms and mortality was comparable to that observed in the present study (HR = 3.83).

The present study must be viewed with several limitations in mind. First, although this is the largest single-center study to have examined the association between pretransplant depressive symptoms and post-transplant outcomes, only 40% of those transplanted during this time period were included in the present analyses. Second, only one assessment of depressive symptoms and social support was available for prospective analyses. Therefore, it is also possible that the present pattern of findings was influenced by declines in functionality occurring between psychosocial assessments and transplant or concomitant medical treatment. Both of these factors should be examined in future studies. Third, we chose to examine LOS as a moderator because it is frequently associated with poorer long-term survival and is well-documented within medical records, thereby increasing its precision in risk prediction. Nevertheless, we did not have access to more granular data on specific complications or other perioperative factors to help explain the observed association. Future studies may therefore benefit from a more refined examination of perioperative outcome data. For example, although we attempted to control for influential medical predictors that may have influenced the present pattern of findings, it is possible that unmeasured medical factors were both associated with depressive symptoms and also associated with worse clinical outcomes. In addition, the present analyses may have been influenced by our analytical approach for LOS, in which participants who died during their

hospitalization were retained in the analyses and given the highest LOS [41]. However, we note that results were unchanged when individuals with longer LOS (e.g., >120 days or in-hospital deaths) were removed ($b = 0.13$, $P = 0.023$), suggesting a robust pattern of results. Fourth, our outcome data were limited to mortality in future studies would benefit from the collection of additional outcome measures (e.g., chronic lung allograft dysfunction) to further elucidate the present associations.

In conclusion, the present study provides preliminary evidence that depression may provide important predictive information, but the association between pretransplant characteristics and future clinical outcomes may be influenced by perioperative medical factors. The present study suggests that screening for post-transplant depressive symptoms and verifying adequate social support are particularly important among individuals who have a more difficult and protracted hospital course.

Authorship

JAB: designed study. PJS, LDS, SMP, BMH, GLS, KKI, CKS, and JAB: collected the data. PJS: analyzed the data. PJS, LDS, SMP, BMH, GLS, KKI, CKS, and JAB: wrote and edited the paper.

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Conflict of interests

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