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Psychiatric disorders as risk factors for adverse medical outcomes after solid organ transplantation

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Abstract

Purpose of review—Given that the prevalence of psychiatric disorders in transplant candidates and recipients is substantially higher than in the general population, and that linkages between psychiatric disorders and medical outcomes for nontransplant-related diseases have been established, it is important to determine whether psychiatric disorders predict posttransplant medical outcomes.

Recent findings—Most research has focused on the association between depression (both pretransplant and posttransplant) and posttransplant mortality. Some research has examined transplant-related morbidity outcomes, such as graft rejection, posttransplant malignancies, and infection. However, methodological limitations make it difficult to compare existing studies in this literature directly. Overall, the studies presented in this review indicate that psychiatric distress occurring in the early transplant aftermath bears a stronger relationship to morbidity and mortality outcomes than psychiatric distress occurring before transplant.

Summary—The literature on the impact of psychiatric conditions on the morbidity and mortality of solid organ transplant recipients remains inconclusive. More research is needed in order to investigate these associations among a broader range of psychiatric predictors, morbidity

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Conflicts of interest

There are no conflicts of interest.

outcomes, and recipient populations. Until evidence suggests otherwise, we recommend frequent monitoring of psychiatric symptoms during the first year after transplantation to aid in early identification and treatment during this critical period of adjustment.

Keywords

medical outcomes; mortality; psychiatric disorders; solid organ transplantation

INTRODUCTION

Transplant programs routinely assess the mental health of transplant candidates during the pretransplant evaluation phase. These evaluations are intended to identify psychiatric conditions that may be important to the preparation and care of the potential transplant recipient. It is clinically intuitive that identifying and treating mental heath issues before or in the early aftermath of a transplant could reduce symptoms and distress, and therefore improve overall quality of life. However, the role of psychiatric disorders in posttransplant medical outcomes has not yet been well established. This is a particularly important area of investigation given that the prevalence of these disorders in transplant candidates and recipients is substantially higher than in the general population and such linkages between psychiatric disorders and medical outcomes for other diseases have been established.

In this review, we examine the recent studies that investigate the contribution of either pretransplant or posttransplant psychiatric disorders and symptomatology to medical outcomes occurring after the transplant, including both mortality and morbidity. For reasons of parsimony, we will address the direct relationship between mental health and medical outcomes rather than the larger and more complicated literature on associations between psychiatric disorders (including personality disorders and traits) and adherence to treatment regimens, although we acknowledge that these disorders may contribute indirectly to medical outcomes via their more proximal effects on adherence. Similarly, we have also chosen to focus on Axis I disorders (e.g., depression and anxiety) rather than Axis II disorders (e.g., personality disorders) because Axis II disorders would likely contribute to medical outcomes indirectly through behaviors, coping, or adherence. Additionally, as the literature is limited, we review studies that examine the impact of both diagnosable psychiatric disorders, determined on the basis of established criteria, and psychiatric symptomatology. Despite some recent evidence suggesting that psychiatric disorders worsen medical outcomes, the inconsistencies that characterize the earlier literature still remain. We thus close by suggesting strategies to improve future study designs so that more definitive findings are obtained, as well as by offering suggestions about the use of evidence available to date in order to better prepare candidates and to monitor and treat recipients.

DEPRESSION AND ANXIETY AS PREDICTORS OF MORTALITY AND MORBIDITY

We focus on studies from the past 12–18 months, placing them in the context of older literature. The majority of studies in this recent literature have moderate sample sizes (i.e., typically greater than 100 individuals).

Mortality

Historically, survival has been the most important measure of transplant success. It continues to be one of the main outcomes reported across all types of solid organ transplants.

Liver—The largest body of recent evidence about psychiatric predictors of mortality in transplant populations comes from liver recipients, with mixed findings depending on whether pretransplant or posttransplant mental health was considered.

The studies that looked at pretransplant psychiatric symptoms and diagnoses do not find any apparent impact of depression or anxiety on survival [1▪,2,3]. However, it is important to note that two of these studies [1▪,3] used medical records to determine pretransplant depression diagnoses, which introduces the possibility that some cases of depression may have been missed because of underreporting or lack of medical record documentation.

In contrast, the studies that looked at early posttransplant depression did find an association with survival. One study reported a 17% increase in 5-year mortality risk associated with each additional depressive symptom on a scale with 13 items administered early posttransplant [4▪]. In addition, patients with elevated depression symptoms after transplant had a higher risk of mortality if the onset of their depression symptoms occurred after transplant than if their depression antedated the transplant. Interestingly, this cohort did not show any association between mortality and anxiety symptoms at any timepoint. Another study looked at the course of posttransplant depression symptomatology in liver recipients transplanted for alcoholic liver disease [5▪▪]. Those whose depressive symptoms were either consistently high or increased over the first year posttransplant had over twice the subsequent mortality risk than patients whose depressive symptoms were consistently low during this period, even after controlling for other medical comorbidities. Ten-year survival rates for patients with high and increasing depressive symptoms were 43–46%, respectively, compared with 66% among those with low-symptom levels. Both of these studies underscore the need to monitor depression during the first year posttransplant, as the transplant may provoke psychiatric symptoms that are strongly associated with poorer survival.

Heart—Heart transplant literature from the past decade suggests that diagnoses as well as symptoms of depression may increase mortality risk among candidates on the waitlist and recipients early post-transplant, respectively [6,7]. However, recent literature puts forth a role only for depressive symptoms but not for psychiatric diagnoses in predicting mortality. In one cohort, posttransplant symptoms of depression – but not diagnosable major depressive disorder (MDD) – increased mortality risk by over two-fold, suggesting that particular dimensions of a depression diagnosis, such as irritability and sense of worthlessness, may be more sensitive prognosticators than the actual diagnosis itself [8]. No association between long-term mortality and post-transplant MDD or posttraumatic stress disorder related to the transplant (PTSD-T) was found in another cohort of heart recipients [9▪▪]. The use of diagnostic criteria to assess this cohort is notable because it most closely approximates the way clinicians approach psychiatric disorders.

Previous research has suggested that other factors such as social supports and type of cardiomyopathy may influence the link between depression and mortality. Depression symptoms were found to be a risk factor for both mortality on the waitlist and delisting due to clinical deterioration only among candidates with few social contacts but not among those with a wide social network, even when controlling for disease severity [10]. Additionally, patients transplanted for ischemic but not dilated cardiomyopathy were at an elevated risk for mortality if they had experienced high levels of depressive symptoms while on the waitlist [11]. More recent studies have not further investigated the role of these and other potential moderating factors.

Lung—Among lung recipients, studies that have examined depression and anxiety symptoms have not found any links to posttransplant mortality [12▪,13–15]. To date, no studies have been conducted to examine whether actual psychiatric diagnoses are linked to increased mortality risk.

Kidney—The kidney transplant literature is inconclusive. Two studies from the past decade found that neither pretransplant depression symptoms nor diagnoses predicted mortality [16,17]. However, a recent large study of kidney recipients reported that those with posttransplant depression symptoms had a significantly higher 5-year mortality rate than those without symptoms [18▪]. In this cohort, each one-point increase on a 60-point scale of depression symptoms was associated with a 2% increase in mortality risk.

Morbidity

Several key areas of morbidity in organ transplantation include acute and chronic rejection, malignancies and infection. Given the longer survival time and older age of transplant recipients, coupled with the chronic immunosuppressant regimens recipients must follow, the risk of developing post-transplant malignancies and chronic rejection is elevated. Despite the need for research in these areas, studies in recent years have considered only a few of these morbidity outcomes.

Liver—Recent studies examining various measures of graft-related morbidity have failed to find associations with MDD or depressive symptoms. Rogal *et al.* [1▪] found no differences in rates of acute rejection, graft failure, or 1-year posttransplant rates of infection based on whether or not candidates had depression diagnoses while on the waitlist. Similarly, when looking at depression symptoms during the first year posttransplant, DiMartini *et al.* [5▪▪] did not find a difference in the likelihood of acute rejection or graft loss between patients with consistently high or increasing depressive symptoms and those without such symptoms, although patients with depressive symptoms were more likely to have consistently elevated liver enzymes. In this same cohort, the only cause of death that differed for patients who were and were not depressed was malignancy, which was significantly higher in those without depressive symptoms posttransplant. The authors hypothesized that because all-cause mortality was greater in the depressed group and because the mean survival for those with malignancies was 4 years, those with increasing and consistently high levels of depression symptoms may have died before developing cancer.

Heart—Similar to liver recipients, a recent study of heart recipients also found no role for pretransplant MDD and PTSD-T diagnoses in predicting posttransplant morbidity, namely early or late acute rejection [9▪▪]. Yet, unlike liver recipients, malignancy rates were over three-fold higher among those heart recipients with a pretransplant diagnosis of MDD, compared with those without a diagnosis. It is important to note, however, that the retrospective study design (in which individuals were assessed posttransplant for pretransplant mental health disorders) may have introduced recall bias into this study.

Lung—Although several studies have found evidence that transplant-related medical morbidities, for example, bronchiolitis obliterans syndrome, increases the risk of anxiety [13–15], no recent studies have looked at psychiatric predictors of these morbidities in lung recipients.

Kidney—Earlier studies of kidney recipients implicated both pretransplant depression diagnoses [16] and post-transplant depression symptomatology [17] in the risk of return to dialysis and graft failure, respectively. The most recent investigation of kidney recipients supports these findings, reporting that each one-point increase on a 60-point scale of depression symptoms posttransplant was associated with a 3% increased risk of graft loss over 5 years [18▪].

PSYCHOTIC DISORDERS AS PREDICTORS OF MORTALITY AND MORBIDITY

Patients with psychotic disorders (e.g., schizophrenia and bipolar disorder) represent only a small percentage of patients receiving transplants, perhaps because transplant teams often have serious reservations about listing them for transplantation. Many believe that these patients will have poorer medical outcomes due to destabilization of their psychotic disorder from the stress of transplantation or worsening psychosis from steroids, both of which could lead to nonadherence to posttransplant care.

Although no longitudinal data exist on morbidity and mortality of such patients compared with other transplant recipients, a survey of transplant programs' experiences with patients with psychotic disorders reported on some posttransplant outcomes [19]. We include this information, though it does not specifically link the psychotic disorder with medical outcomes, because it is the only relatively recent study in the literature on psychosis and transplantation. The survey identified 35 patients with a variety of psychotic disorders (schizophrenia, schizoaffective, and bipolar disorders) across 12 transplant centers. Rejection episodes occurred in 15% of patients with reduced graft function or loss and in 12% due to immunosuppressant nonadherence. These rates are consistent with those seen across multiple types of organ transplantation [20].

CONCLUSION

The impact of psychiatric conditions on the morbidity and mortality of solid transplant recipients remains undetermined. Considered as a whole, the studies presented in this review indicate that psychiatric distress occurring in the early aftermath of transplant bears a

stronger relationship to morbidity and mortality outcomes than psychiatric distress occurring before the transplant. In addition, given the universally stressful nature of being on a transplant waitlist, symptoms present during this period may reflect transient reactions to distress rather than actual psychiatric disorders, or they may represent the beginnings of actual psychiatric disorders whose duration is unknown if assessed before the transplant is completed. Overall, we recommend that studies use repeated assessments during the critical first year after a transplant in order to capture changes in symptomatology that may impact long-term outcomes. Because conducting repeated assessments is consistent with longitudinal psychiatric monitoring that occurs as part of clinical care, this study design may integrate well into care already provided by many transplant teams [21].

The choice of psychiatric assessment is also critical to consider. Studies assessing psychiatric status using structured psychiatric interviews are advantageous because they most closely approximate clinical decision-making algorithms in routine use. On the contrary, studies assessing change in psychiatric symptoms over time are better able to capture the type, timing, and change in symptom intensity that may also have an effect on outcomes. Continued research is necessary in order to make a definitive recommendation for whether diagnoses or symptom levels are most prognostic in transplant populations.

Finally, other areas of psychopathology (e.g., personality disorders and traits, behavioral issues, and coping) that are not within the scope of this review could additionally be considered to impact transplant outcomes. The literature on the role of personality disorders and traits is similarly mixed and would require scrutiny by the same methodological and clinical considerations as suggested and reviewed here.

CHALLENGES AND FUTURE DIRECTIONS

Methodological limitations make it difficult to compare existing studies in this literature directly, and thus it is challenging to reconcile disparate findings. Because most work to date has focused on depression, future studies should investigate the prognostic value of a range of other psychiatric disorders, including anxiety disorders such as PTSD-T and panic disorder. Additionally, the range of morbidity outcomes examined in relation to mental health should be expanded, as work thus far has focused on graft failure and acute rejection despite the high prevalence of infection and chronic rejection that contribute to quality of life, medical status, and, ultimately, mortality. Lastly, as most recent evidence focuses on liver recipients, more research is needed in order to study recipients of other types of solid organs.

In any case, concerns that patients with psychiatric conditions are unsuitable for transplant, although understandable, are unfounded in light of the literature reviewed here. A handful of case reports demonstrating successful outcomes in patients with psychotic disorders points to the need to assess these patients on an individual basis [22–24], a conclusion that can be applied to candidates and recipients regardless of mental health status. With expert management, good social supports and a longitudinal relationship with the transplant team, even complicated patients, such as those with severe psychiatric disorders, can have positive long-term outcomes [21,25]. Until further evidence emerges, we recommend frequent

monitoring of psychiatric symptoms during the pretransplant and especially early posttransplant phases in order to aid in early identification and treatment [21]. When developing new interventions to address mental health issues in these populations, findings suggest that posttransplant interventions might be more effective than those implemented before the transplant. More work is needed, however, to determine whether treatment of psychiatric disorders or symptoms can improve overall medical outcomes.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 208–209).

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KEY POINTS

- The impact of psychiatric conditions on the morbidity and mortality of solid transplant recipients has yet to be determined.
- Research to date has been limited by methodological inconsistencies surrounding the psychiatric disorders or condition measured, the timing and type of psychiatric assessments used, the morbidity outcomes considered, and the recipient populations studied.
- There is no consistent evidence suggesting that patients with psychiatric conditions before transplantation experience poorer long-term outcomes and are therefore unsuitable for transplant.
- Psychiatric conditions occurring after transplantation appear more prognostic for longer term outcomes; frequent monitoring of psychiatric symptoms during the first year after transplant is thus important for early identification and treatment during this critical period of adjustment.