Transplantation Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

# Is social support associated with post-transplant medication adherence and outcomes? A systematic review and meta-analysis

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A B S T R A C T

Although social support is used to determine transplant eligibility, the relationship between social support, medication adherence, and survival among transplant recipients remains unclear. We estimated the relationship between social support and post-transplant medication adherence and outcomes using 10 electronic databases from inception to January 2016. Study quality was assessed and all review stages were conducted independently by 2 reviewers. Systematic review and meta-analysis were conducted. Thirty-two studies (9102 participants) met inclusion criteria: 21 assessed medication adherence (5197 participants), and 13 assessed clinical outcomes (3905 participants). Among high quality studies, neither social support nor marital status was predictive of medication adherence or post-transplant outcomes. Social support was not associated with medication adherence. It was associated with superior post-transplant outcomes, but the relationship was not significant among high quality studies. Compared to unmarried recipients, married recipients were more likely to adhere to medication post-transplant, but this relationship was not significant among high quality studies. Marital status was not significantly associated with transplant success. Social support is weakly and inconsistently associated with post-transplant adherence and outcomes. Larger prospective studies using consistent and validated measures are needed to justify the use of inadequate social support as a contraindication to transplantation.



## 1. Introduction

Transplantation is the optimal treatment for people with organ failure, and for many, represents the only life-saving therapy. In the United States, approximately 120,000 people await transplantation and waiting times for some organs can exceed 7 years [1]. In 2015 alone, 6287 people died on the waiting list [1]. Therefore, transplant clinicians increasingly must balance concerns for equity and efficiency (medical utility) when selecting candidates [2]. Clinical guidelines issued by the Centers for Medicare and Medicaid Services (CMS) and professional societies provide explicit recommendations for use of medical, demographic, psychological, and lifestyle factors to assist transplant centers in determining eligibility and balancing equity and efficiency [3–8]. However, vague CMS guidelines have raised concerns about potential ambiguity and lack of evidence for some waitlist criteria, including social support [9–12]. Lack of specificity regarding social support definitions and acceptable support thresholds has resulted in significant variation in transplant centers' approaches to using social support to determine eligibility. No guideline explicitly defines social support, however, it often is considered to be services, care, or encouragement provided by social network members, often spouses or partners, family, and friends [13,14]. Consequently, patients may experience disparate access to the transplant waiting list [15–18].

Currently, inadequate social support is a contraindication to transplantation (Appendix 1) [3–7]. Consequently, patients who cannot demonstrate sufficient social support may be excluded or delayed from receiving life-saving treatment [13,19,20]. Persons of low socioeconomic status, racial and ethnic minorities, and those living in rural areas continue to face disproportionate difficulty in successfully completing transplant evaluations, the first step in the transplant process [9,16–18,21–26]. This may be partly due to greater difficulty meeting eligibility requirements, including social support [23,27]. Using social support to determine eligibility could disproportionately impact vulnerable populations, who may face greater difficulty demonstrating adequate social support because of strained support systems, greater difficulty identifying caregivers who can take time away from work, and inability to self-finance home-based assistance [28,29]. Given its potential for increasing inequality and federal regulations that mandate equity in access to the transplant waitlist [30,31], it is important to understand how predictive social support is of post-transplant adherence and outcomes.

Lack of an established evidence base for using social support as an eligibility criterion distinguishes it from other evidence-based eligibility

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http://dx.doi.org/10.1016/j.trre.2017.04.001
0955-470X/

criteria, leaves it susceptible to personal bias, and illustrates the importance of synthesizing available data. While some studies have found that less social support is associated with worse transplant outcomes [32–37], others have concluded that this relationship is spurious [26,38–40]. Although clinicians often cite the importance of social support for ensuring medication adherence post-transplant, the degree to which social support is predictive of adherence remains unclear [41]. Compared to other evidence-based criteria used to determine transplant eligibility, social support is controversial not only because of the variability and subjectivity of its assessment and the inconsistency in its measurement and use between centers [12], but because its relationship to post-transplant outcomes remains uncertain [42,43]. Furthermore, social support is the only evaluation criterion that uses information about other people to determine an individual's transplant eligibility.

We attempt to resolve these discordant findings, and expand upon this meta-analysis to include more recent data, and specifically assess the importance of marital status which is often used in clinical assessments and clinical outcomes post-transplantation (graft survival, morbidity, and mortality). This study aims to estimate the impact of social support and marital status on (1) medication adherence and (2) clinical outcomes following solid organ transplantation.

## 2. Methods

We defined social support as services, care, or encouragement provided by social network members, including spouses or partners, family, and friends. We included measures of perceived support (patient's subjective perception of available support) and received support (objective assessment of informational, instrumental, tangible, emotional, and appraisal support received) [13,14,44–46]. Marital status was analyzed separately because it is frequently used in clinical practice as a primary measure of social support, and is considered among the more comparable social support measures [47]. To avoid confounding, we distinguished social support from psychiatric history, financial status, and socioeconomic status (although these are often all included in psychosocial evaluations for transplant eligibility), and restricted our analysis to include studies that have assessed the independent effect of social support on post-transplant outcomes.

Our outcomes were medication adherence and post-transplant clinical outcomes, including graft loss, mortality, and morbidity. In the case of multiple outcomes, we selected the most significant outcome for our primary analysis and performed sensitivity analyses using the other measures. In studies using overlapping samples, we selected the largest or the one with longest follow-up.

We searched Pubmed, Ovid Medline, PsychINFO, Cochrane Library, and Google Scholar for English-language studies published before December 1, 2015. Search terms included *social support*, *organ transplantation*, *and non-adherence* (Appendix 2). We supplemented our search with reference mining of included articles.

Studies eligible for inclusion were those which involved adults (≥18 years) who underwent solid organ transplant and reported quantitative outcomes relating to at least one specific aim (i.e., medical adherence, post-transplant clinical outcomes). Due to the paucity of studies examining pre-transplant social support, we included studies that assessed social support preoperatively and postoperatively.

We required that studies report social support explicitly using validated instruments measuring social support, marital status, or measures of perceived and received support. As there is no standard measure for evaluating social support, all measures were considered (e.g., self-report, questionnaire, interviewer rating, and formal evaluation), with the exception of global psychosocial measures that conflate social support with psychological, psychiatric, financial, and other factors.

Two independent reviewers with expertise in social support assessments (KL, AD), transplantation (KL), and meta-analysis (MO, RB) assessed each study for inclusion (KL, AD) and extracted data (MO, RB) including country, follow-up time, method of recruitment, sample demographics, type of transplant, type of social support assessed (perceived vs. received; marital status, etc.), methods of assessment for social support, outcome assessed (medication adherence, clinical outcomes), and methods of outcome assessment. Discrepancies were reconciled through discussion leading to consensus.

Two reviewers (KL, AD) independently assessed the quality of included studies using a validated tool that has been used to assess the quality of observational studies and particularly in studies relating to transplantation [48,49]. Reviewers evaluated risk of selection, non-response, and information biases, as well as potential confounding, on a 3-point scale, with designated a priori values, based on six study parameters: number of subjects, study design, statistical soundness, medical factors controlled, demographic factors controlled, and psychosocial measures (psychometric properties) (Table 3). Scores ≥15 were considered high quality, and scores below 14 were considered low quality. Discrepancies in quality assessments were resolved by discussion.

We first conducted a narrative systematic review, qualitatively categorizing the main factors by which studies differed. These included: type of support (perceived vs. received); support status (married/spouse vs. other support); study design (prospective, retrospective/cross-sectional); method of adherence assessment (electronic, multiple methods, self-report); organ type (kidney, liver, thoracic); and timing of social support assessment (pre vs. post-transplant). We then qualitatively assessed the impact of marital status and social support on adherence and outcomes, using these groupings.

In a second step, we estimated the association between social support (marital status or measured social support) and adherence or clinical outcomes using a random-effects meta-analysis. We performed formal tests of heterogeneity by calculating the $I^2$ statistic [50]. Using the categories identified in the systematic review, we further explored potential heterogeneity by stratifying our analyses on variables potentially related to risk of bias (e.g. study design, study quality), and related to different types of support and outcomes, including transplanted organ (kidney, liver, pancreas, heart, lung), type of social support (perceived vs. received), and method of assessment (self-report, scale, clinical interview). All analyses were conducted using Comprehensive Meta-Analysis software (Biostat, Englewood, NJ).

If studies used multiple methods to evaluate social support, we selected the measure which was validated and most robust, and we included others in sensitivity analyses. If studies used multiple methods to evaluate adherence or clinical outcomes, we consulted experts in the appropriate transplant field (e.g. liver transplantation) to select the most relevant measure.

## 3. Results

The literature search identified 550 potential articles from electronic databases, and 45 additional studies were procured through bibliographic review. After removal of three duplicate publications, 547 remaining studies were screened during title and abstract review, 116 of which addressed the specific aims. After full-text screening, 32 studies met inclusion criteria: 21 studies assessed medication adherence and 13 studies assessed clinical outcomes (Fig. 1).

Included studies were published between 1992 and 2015 and were conducted in seven countries. Studies included a number of different organ transplant types (with some including multiple organ types): 9 heart, 11 liver, 16 kidney, 8 lung, and 1 pancreas. Five studies included multiple organ types. There was wide variation in social support measures, follow-up time, and population characteristics. Included covariates and potential confounders were not consistent across studies. Studies used either marital status or a validated instrument to assess social support. In the absence of such measurements, social support was reported using modified instruments, semi-structured interview, or chart review with investigator rating (Table 1).

Eighteen (56%) of the included studies were of high quality (Table 3). Twelve (38%) of them were prospective studies. Twelve

Please cite this article as: Ladin K, et al, Is social support associated with post-transplant medication adherence and outcomes? A systematic review and meta-analysis, Transplant Rev (2017), http://dx.doi.org/10.1016/j.trre.2017.04.001