Adherence to Immunosuppression in Adult Heart Transplant Recipients: A Systematic Review

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Abstract

Background: Successful maintenance of a heart transplant (HTx) graft requires adherence to a triple-drug regimen of immunosuppression. However, achieving adequate adherence can be difficult secondary to complicated dosing regimens, side effects, and mental/emotional barriers. A detailed review of current patterns of adherence to immunosuppression in adult HTx recipients is lacking.

Objective: This systematic review aims to detail the current landscape of adherence to immunosuppression in adult heart transplant patients, including the measurement of adherence, correlates to adherence, health outcomes associated with nonadherence, as well as strategies to improve adherence in HTx patients.

Methods: We conducted searches in PubMed MEDLINE, Embase, CENTRAL register of Controlled Trials (Wiley), and Scopus, from inception to March 2020. Studies were eligible if they outlined an aspect of adherence (as noted above in the objective) to immunosuppression in adult HTx patients. The HTx cohort had to contain at least 10 patients and measurement of

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adherence had to be done with an objective or otherwise validated measure of adherence (e.g. drug levels, automated pill bottles or adherence questionnaires). Two authors independently screened the articles for inclusion, then subsequently reviewed the full texts of the included articles. Data was extracted into standardized forms and bias evaluations were done using the Newcastle-Ottawa or modified Newcastle-Ottawa tools, depending on the study type. The authors followed all guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results: The titles/abstracts of 880 articles were reviewed. Ultimately, 23 articles were included in the final review. The median number of participants was 101, with a range of 19 to 1397. Studies provided information on baseline levels of adherence (17 studies), correlates to adherence (14 studies), health outcomes related to nonadherence (3 studies) and interventions to improve adherence (3 studies). Baseline adherence estimates varied greatly depending on the adherence measure. Multiple significant correlates to nonadherence exist and appear to affect patients with certain sociodemographic backgrounds, those with psychological/psychiatric comorbidities and those with poor support structures. Nonadherence is associated with transplant coronary artery disease and acute late rejection; it may also be associated with long-term mortality. Finally, a simplified dosing regimen with once-a-day tacrolimus as well as use of a mobile phone-based intervention were associated with improved adherence. Bias scores were most deficient due to self-reported outcomes in 18 studies, and lack of controls/adjustments for confounders, in 7 studies.

Conclusions: Adherence to immunosuppression in transplant patients varies, but is associated with observable and modifiable factors which are worth addressing. Further high-quality studies regarding strategies to improve adherence are needed in the literature.

Keywords

Heart transplant; solid organ transplant; adherence; compliance; rejection; behaviors

INTRODUCTION

Heart transplant (HTx) is the definitive therapy for those with advanced heart failure. In 2018, 3440 heart transplants were performed in the USA, an increase from 3273 in 2017.[1] Recent innovations, including advanced immunosuppressive regimens, thorough preoperative psychosocial evaluations, and increased surveillance have mirrored improved survival.[2–5] Despite these advances, HTx recipients face numerous challenges to maintain a healthy graft.

One of these challenges is adherence to immunosuppression (IS). Early in the life of the transplant, HTx patients generally take 3 classes of immunosuppression. These include glucocorticoids, calcineurin inhibitors (ex. cyclosporine, tacrolimus) and antiproliferative agents (ex. azathioprine, mycophenolate mofetil).[6, 7] Patients can be maintained on a calcineurin inhibitor with or without an antiproliferative agent long term. Before the widespread use of cyclosporine, patients received only steroids and azathioprine; an early study published in 1984 with patients on this regimen noted 56 nonfatal and 6 cases of fatal rejection in a cohort of only 32 patients over a 3 year follow up.[8] A study done soon

thereafter showed that compared with dual therapy, triple therapy was associated with less renal failure, infections, lymphoma, and importantly, transplant rejection.[9]

Despite the clear value of adherence to the multidrug regimen, all three medications have certain risks and side effects to patients.[7] These difficulties are mirrored in the HTx precursor population, those with advanced heart failure. Studies note that advanced heart failure patients may have as low as 10% adherence to a medical regimen over 1 year,[10] and that <80% adherence to guideline-directed medical therapy for heart failure with reduced ejection fraction was significantly associated with combined outcomes of all-cause mortality and cardiovascular hospitalization.[11] By extension, the modern heart transplant population may also experience critical challenges in the sphere of adherence, though this has not been recently reviewed in the literature.

Objectives

The formal exploration of adherence to immunosuppression in HTx has not been performed in a recent review. This manuscript aims to systematically review the measurement of adherence, correlates to adherence, health outcomes associated with nonadherence, as well as interventions to improve adherence as they relate to immunosuppression in HTx recipients. We aim to provide a landscape of current knowledge on adherence as well as underline implemented approaches for the improvement of adherence in HTx patients.

METHODS

Study Design

The authors followed all guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search Strategy

A systematic review of studies on adherence to immunosuppression in HTx patients was conducted. A research librarian (LO) was responsible for a full literature search. We conducted searches in PubMed MEDLINE, Embase, CENTRAL register of Controlled Trials (Wiley), and Scopus, from inception to March 2020, using search strategies that were collaboratively developed by all authors. The search was employed in PubMed using a combination of MeSH terms for heart transplantation, compliance, and adherence, then applied to the other databases. No language or date limits were used (other than a publication date before March 2020, when the search was done). Search strategies can be found in Appendix 1. TH also hand-searched the bibliographies of relevant review articles and the included articles for additional references. Articles were reviewed in Rayyan by two independent reviewers with conflicts decided by discussion to reach consensus.

Eligibility Criteria

Studies were eligible if they outlined an aspect of adherence to immunosuppression in HTx patients, including but not limited to measurement of adherence, correlates to adherence, health outcomes associated with nonadherence, as well as strategies to improve adherence in HTx. Patients could be of any age, with a plan to divide studies into those primarily in adults

(as outlined here) and those in pediatric and young adult patients (published in a separate manuscript). We included studies involving multiple types of solid-organ transplants, but the cohort of HTx had to be at least 10 participants and the data pertaining only to the HTx group needed to be separately reported for inclusion here. Included studies also had to utilize an objective or otherwise validated measure of adherence (eg. drug levels, automated pill bottles or adherence questionnaires). We excluded studies that measured adherence based on unvalidated/subjective metrics including physician report or chart review unless the data was otherwise described and validated. Studies could be in a prospective, observational, cross-sectional survey, or randomized trial format.

Study Selection and Data Extraction

Two authors (TH and SB) independently screened the articles for inclusion, then subsequently reviewed the full-text of the included articles. Discordant assessments were resolved by discussion between the reviewers to reach consensus. Data extraction was standardized to include population, type of article, study design, immunosuppression used, intervention (if any), measure of adherence, duration, number of HTx participants, participant age, study attrition rate, and main outcomes.

Assessment of Risk of Bias

Bias was evaluated by two independent reviewers (TH and KN). We utilized the Newcastle-Ottawa for cohort studies[12] and a modified version of the Newcastle-Ottawa by Modesti et al.[13] for cross-sectional studies. Disagreements were resolved by discussion between reviewers to reach consensus. Cohort studies could receive up to a total of 10 points via the Newcastle-Ottawa scale and prospective cohort studies could receive up to a total of 9 via the modified Newcastle-Ottawa scale.

Data Synthesis

Data was expected to be heterogenous and primarily presented descriptively. If sufficient homogeneity were found in outcomes, we considered a meta-analysis or effect size analysis.

RESULTS

Literature Search

The titles/abstracts of 880 articles published before March 2020 were reviewed. 774 articles were eliminated in the initial screen, leaving 106 articles for full text review. Ultimately, we excluded 83 articles, leaving 23 articles for final inclusion in the review. The study flowchart and further reasoning for article inclusion/exclusion are outlined in the PRISMA flow diagram (Figure 1).

Study Characteristics

Study designs are outlined in Table 1. Studies were published between 1998 and 2020. Twelve studies were done in Europe[14–25] and 6 in the USA[26–31]; the remainder were done at multiple international sites (2 studies[32, 33]), New Zealand (1 study[34]), China (1 study[35]) and Israel (1 study[36]). The median number of participants was 101, with a range of 19

to 1397. Studies were divided into those that reviewed baseline levels of adherence (17 studies), correlates to adherence (14 studies), health outcomes related to nonadherence (3 studies) and interventions to improve adherence (3 studies). Some studies were included in two categories, as applicable. Studies included cross-sectional studies (14 studies) and prospective cohort trials (9 studies). Four studies included immunosuppressant levels or pill bottle monitoring to measure adherence; two of those also included a validated self-report of adherence. A majority of those remaining (18 studies) utilized validated adherence measures based on self-report only.

Self-reported adherence measures

Table 2 outlines the validated self-reported adherence measures utilized to measure immunosuppressant adherence in heart transplant recipients. Three of the measures (Transplant Effects Questionnaire, Assessment of Problems with the Heart Transplant Regimen and the Medication Experience Scale for Immunosuppression) were developed for use in transplant patients. Three others (Immunosuppressant Therapy Adherence Scale [ITAS], Basel Assessment of Adherence to Immunosuppressive Medications Scale, and Simplified Medication Adherence Questionnaire) were developed in other populations, but later validated in transplant cohorts.

Baseline adherence

Table 3 outlines the 17 studies that included baseline adherence measurements. Baseline adherence, both in classification as well as apparent value, varied widely. While some studies based their judgments on immunosuppression blood levels, most utilized validated self-report. These self-reports could also further classify nonadherent patients into nonadherence patterns, including taking nonadherence (missing doses), timing nonadherence (straying from the daily dosing schedule), or dose alterations.

Adherence was between 25–40% in 5 studies.[14, 18, 22, 34, 36] The lowest apparent adherence rate of 25% was seen in a study by Doesch et al. defined as self-reported nonadherence to short-acting tacrolimus on any of the 4 BAASIS items.[18] The majority of remaining articles noted an adherence rate between 50 and 80%.[14, 15, 18–21, 32, 33, 35] Several studies included an adherence rate greater than 80%.[16, 17, 19, 23, 25, 29, 32] Interestingly, the same study which observed very low (31 ± 33%) everolimus adherence by blood levels also noted much higher adherence to other IS, including 67% ± 28% for cyclosporine and 85 ± 13% for tacrolimus.[14]

One study by De Geest et al. monitored "taking" adherence rates over time, defined as missing immunosuppression doses over the past 4 weeks. It found that the nonadherence to immunosuppression steadily rose from 5.1% at 6 months posttransplant to 18.8% taking nonadherence at 36 months.[16]

Correlates to adherence

Table 4 outlines correlates to adherence and nonadherence. Correlates to adherence were stratified into 5 categories, including sociodemographic, behavioral, support, mental/ emotional wellbeing, and health/transplant-related factors.

In the sociodemographic category, factors positively associated with adherence included higher age[15, 31, 36] and female gender.[28] Interestingly, one article found higher age to be negatively associated with adherence.[28] Sociodemographic factors associated with higher risk of nonadherence included time since transplant,[16, 36] African ancestry,[26] and lower monthly income.[35]

In the behavioral category, nonadherence was significantly associated with the consumption of soft-boiled unpasteurized eggs and unpasteurized milk,[15] as well as current/recent smoking.[32] Appointment noncompliance also correlated with poorer adherence to cyclosporine.[25]

The support category primarily reviewed the difficulties patients experienced while obtaining their medicines. Denhaerynck et al. noted significantly higher adherence associated with the use of interventions to target adherence after clinician identification, and when patients had someone help them read health-related materials more frequently. The same article noted that nonadherence was significantly associated with medications that were picked up at a physician's office and when immunosuppression was more costly.[32]

The mental/emotional status category revolved around perceived barriers as well as psychological and psychiatric comorbidities that could affect adherence. Factors significantly associated with adherence included SF-12 mental health score[15], chance Locus of Control (defined as feelings of control over health outcomes),[26] self-efficacy with medication-taking[25] and life satisfaction.[30] Nonadherence-associated factors included greater perceived barriers,[32] higher self-care disability,[29] greater feelings of guilt,[36] higher depression scores and worse psychosocial functioning,[24] and high concern regarding the use of immunosuppressants.[35]

Finally, in terms of health/transplant-related factors, Grady et al. found that patients with both an ischemic as well as idiopathic etiology of their heart failure had significantly higher adherence.[28] Zhang et al. also noted that greater numbers of concomitant drugs were associated with nonadherence.[35]

Health outcomes related to nonadherence

Three studies prospectively reviewed health outcomes related to adherence and are outlined in Table 5. In the first, De Geest et al. clustered patients into different groups by several compliance-related variables. The "excellent compliers" had a 1.2% rate of late acute rejection, while the "minor subclinical noncompliers" had a rate of 14.3% and "moderate subacute noncompliers" had a rate of 22.2%, p = 0.01.[25] Dobbels et al. found that nonadherence was significantly associated with any degree of transplant coronary artery disease. Furthermore, adherence was significantly associated with longer event-free time, though it was not significantly associated with late acute rejection, retransplant, or 5-year mortality.[17] In contrast, Farmer et al. did note a significant association between both moderate and high adherence and improved mortality rates at 5–10 years.[27]

Interventions to improve adherence

Finally, two interventions were explored to potentially improve adherence, outlined in Table 6. The first strategy employed by Doesch et al. in 2010[19] and 2013[18] reviewed the effect of transitioning traditional twice-daily dosed tacrolimus and cyclosporine to once-daily dosed tacrolimus. This intervention in both the preliminary and completed study showed significantly improved nonadherence rates (from 75.0% to 40.3% in the longer 8 month study, p = 0.0001). The second intervention by Gomis-Pastor was a multifaceted mobile app to provide information to transplant patients and also collect data for the physician and research care team. Its use was associated with an improvement in adherence from 61% to 87% (p = 0.005) over 1 month of use.[21]

Studies' Methodological Quality

Table 7 outlines bias ratings for prospective cohort studies as scored by the Newcastle-Ottawa scale. Table 8 outlines bias ratings for cross-sectional studies as scored by the modified Newcastle-Ottawa scale. Overall, the 9 prospective cohort studies scored between 6 and 9 out of 9 possible points. The majority of points were "lost" due to lack of controls/adjustments for possible confounders during statistical analysis (8 points lost among 4 studies) and only self-reported outcomes (6 points lost among 6 studies). For the 14 cross-sectional studies, scores ranged from 5 to 9 out of a possible 10 points. The most points were lost for only self-reported outcomes (12 points lost among 12 studies) and lack of comparison between respondents and non-respondents (10 points lost among 10 studies). In all studies combined, self-reported outcomes were responsible for the most points lost (18 points lost among 18 studies) and lack of controls/adjustments for confounders (14 points lost among 7 studies).

Discussion

This systematic review analyzed multiple aspects of adherence to immunosuppression in adult heart transplant recipients. Adherence in this population has been measured via blood immunosuppression levels, electronic pill bottle monitoring, or most commonly, a variety of validated self-report questionnaires. Baseline adherence estimates vary greatly depending on the definition and measurement of adherence. Multiple significant correlates to nonadherence exist and appear to affect patients with certain sociodemographic backgrounds, those with psychological/psychiatric comorbidities and those with poor support structures. Nonadherence is associated with transplant coronary artery disease and acute late rejection; it may also be associated with long-term mortality. Finally, a simplified dosing regimen with once-a-day tacrolimus as well as use of a mobile phone-based intervention may improve adherence. Bias scores were most deficient due to only self-reported outcomes as noted in 18 studies and lack of controls/adjustments for confounders, as seen in 7 studies.

Our findings suggest a wide range of baseline adherence estimates, as well as several risk factors, some modifiable, that also correlate with adherence. But what rate of adherence is adequate? There is no clear value widely touted in transplant research. In solid-organ transplants, studies range from 80%[37] up to <98%[38, 39] as cutoffs for nonadherence;

the stringent higher limit was recommended in our included article by De Geest et al. in 1998 who identified the correlation between even subclinical noncompliance to cyclosporine and increased incidence of late acute rejections.[25] In the HIV literature, older manuscripts suggested 95% adherence was needed for adequate virologic suppression, though more recent studies with modern regimens note that even 80% may not be statistically suboptimal.[40]

Despite this varying set of definitions, our study suggests that populations exist where the adherence to immunosuppression still remains concerningly low or variable. Inadequate adherence to common agents such as tacrolimus may place patients at risk of acute and chronic rejection, donor-specific anti-HLA antibodies, and progressive fibrotic damage that can lead to graft failure.[41] At its extreme, poor adherence has been associated with mortality in the pediatric heart transplant literature,[42] while few studies exist regarding outcomes in the adult literature as evidenced in our study. Thus, there remains a clear need to identify and maintain a threshold of adequate adherence.

Challenges remain in the measurement and management of immunosuppressant adherence. A study by Shi et al. done in late 2020 reviewed interventions tested by RCT to improve adherence in solid-organ transplant recipients.[43] They found significantly better pooled risk ratios for overall adherence, dosing adherence, and timing adherence between the intervention groups and controls, but no significant improvement in immunosuppressant blood concentrations. This reflects a pattern seen in our review, in which the vast majority (18/23 studies) utilized self-report measures for adherence and only 4 utilized immunosuppressant levels or pill bottle monitors to more accurately observe adherence. A 2020 publication stratified measurement tools in transplant recipients and noted that rich and reliable data could be collected through more direct measures (electronic monitoring, ingestible smart sensors), though many teams continue to use more limited and biased measures including retrospective questionnaires, pharmacy refill data, and patient diaries.[44] Further studies and implemented programs may benefit in terms of limiting bias and social desirability by utilizing more objective measures of adherence.

Further studies on effective interventions in the heart transplant literature are needed. There does exist promising data that some interventions are feasible and to patients' satisfaction[45], but other strategies can suffer from high attrition as a barrier[46]. Some interventions have been associated with improved adherence in areas such as adolescent kidney transplant[47] and even solid organ transplant recipients as a whole[48]. Unfortunately, there remains a lack of data on demonstrated survival outcomes, as well as utilization of taxonomies (for example, division into *initiation, implementation*, and *discontinuation* phase-focused tools) to better understand effective interventions.[44] As underlined in a 2017 review of 21 interventions to improve adherence in solid-organ transplant recipients, no strategies were associated with improved transplant outcomes[49]. Those authors suspected a "streetlight effect" is in play – that is, adherence researchers are looking for outcomes where and how they are easy to come across, rather than focusing on the right population, interventions and outcomes. To combat this, the authors recommend further studies that 1) focus on nonadherent patients, rather than a convenience sample, 2) use direct measures of adherence and survival, and 3) utilize effective, low-effort, high-engagement methods to recruit patients

who already struggle with complex adherence tasks. The takeaways from our study are similar – that evidence regarding effective interventions and ultimately, the link between them and survival, are yet to be explored fully. To this end, mHealth, or mobile health interventions, are of potential use in this sphere as they have the advantage of being low-cost, easily disseminated, and customizable to patients at the individual level.[50]

Strengths and Limitations

The primary strength of this manuscript is its novelty and systematic approach to evaluating multiple aspects of IS adherence in adult heart transplant patients. At least 2 authors independently screened all articles and evaluated for bias, which adds credibility to our gathered conclusions. We have thoroughly examined and organized our data with the intention that a multitude of questions can be answered by perusing this manuscript and its included tables. While the data is heterogeneous and sparse in some areas, we hope that this in itself is a call to action for teams performing further research in this field.

Limitations of this paper include multiple sources of bias, especially from the focus on self-reported outcomes, as well as lack of controls/adjustment in data analysis. It remains a challenge for teams to measure medication adherence at least somewhat objectively, either through drug levels or less direct pill-bottle measurement systems. With smaller cohorts, there is also difficulty in recruiting enough participants to effectively analyze or control for multiple variables. Furthermore, some independent variables, such as race, are societal constructs and may have confounders that affect observed correlates, as seen in prior studies.[51, 52] Studies should carefully state how statistical analyses take into account controlling/adjusting for baseline factors, including age, socio-demographics, and transplant characteristics, when relevant and possible. A final challenge of ours was that we found very heterogeneous qualitative and quantitative outcomes, precluding a true meta-analysis.

Conclusions

Heart transplant is an extremely focused and resource-intensive specialty. We provide evidence that rates of IS adherence vary but that many correlates to adherence are observable and modifiable factors. Thus, we hope to provide direction for potential further intervention and action. Further high-quality studies regarding strategies to improve IS adherence are needed in the adult heart transplant literature.

Acknowledgments

Appendix 1:: Search Strategy

PubMed

(("Heart Transplantation"[MeSH Terms] OR "heart transplant*"[Title/Abstract]) OR (("Organ Transplantation"[MeSH Terms:noexp] OR "transplant*"[Title/Abstract]) AND ("heart"[MeSH Terms] OR "heart*"[Title/Abstract]))) AND (((((((("Medication Adherence"[MeSH Terms] OR "Patient Compliance"[MeSH Terms]) OR "Adherence" [Title/Abstract]) OR "Nonadherence"[Title/Abstract]) OR "non adherence"[Title/ Abstract]) OR "non adherence"[Title/Abstract]) OR "Compliance"[Title/Abstract]) OR "Noncompliance"[Title/Abstract]) OR "non compliance"[Title/Abstract]) OR "non compliance"[Title/Abstract])

Remove review[pt] and animals in title

Embase

('heart transplantation'/exp OR 'heart transplant*':ti,ab OR (('organ transplantation'/exp OR transplant*:ti,ab) AND ('heart'/exp OR heart:ti,ab))) AND ('medication compliance'/exp OR 'adherence':ti,ab OR 'nonadherence':ti,ab OR 'non adherence':ti,ab OR 'compliance':ti,ab OR 'noncompliance':ti,ab OR 'non compliance':ti,ab)

Remove review and meeting abstracts and animals in title

CENTRAL

#1 MeSH descriptor: [Heart Transplantation] explode all trees

#2 "heart transplant*":ti,ab

#3 #1 OR #2

#4 MeSH descriptor: [Organ Transplantation] explode all trees

#5 transplant*:ti,ab

#6 MeSH descriptor: [Heart] explode all trees

#7 heart:ti,ab

#8 #4 OR #5

#9 #6 OR #7

#10 #8 AND #9

#11 #3 OR #10

#12 MeSH descriptor: [Medication Adherence] explode all trees

#13 MeSH descriptor: [Patient Compliance] explode all trees

#14 ("adherence" OR "nonadherence" OR "non adherence" OR "compliance" OR "noncompliance" OR "non compliance").ti,ab

#15 #12 OR #13 OR #14

#16 #11 AND #15

Scopus

TITLE-ABS-KEY ("heart transplant*") AND TITLE-ABS-KEY (adherence OR nonadherence OR "non adherence" OR compliance OR noncompliance OR "non compliance") AND (LIMIT-TO (DOCTYPE, "ar"))

Abbreviations

HTx   heart transplant

IS   immunosuppression

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Highlights:

- Adherence to immunosuppression in heart transplant patients varies considerably

- Socio-demographics, mental health, and poor support correlate with nonadherence

- Nonadherence may lead to coronary artery disease and acute late rejection

- Simplified dosing regimen and a mobile app intervention were associated with improved adherence

Identification

Records identified through database searching
(n = 893)

↓

Records after duplicates removed
(n = 880)

Screening

↓

Records screened
(n = 880) → Records excluded
(n = 774)

Eligibility

↓

Full-text articles assessed for eligibility
(n = 106) → Full-text articles excluded, with reasons (n = 83):
- Pediatric heart transplant population (n = 14)
- No validated adherence measure (n = 39)
- Article not found or not in English language (n = 19)
- Not original research (n=5)
- Multiple organ transplant populations (n=4)
- No adherence outcomes (n=1)

Included

↓

Studies included in qualitative synthesis
(n = 23)

↓

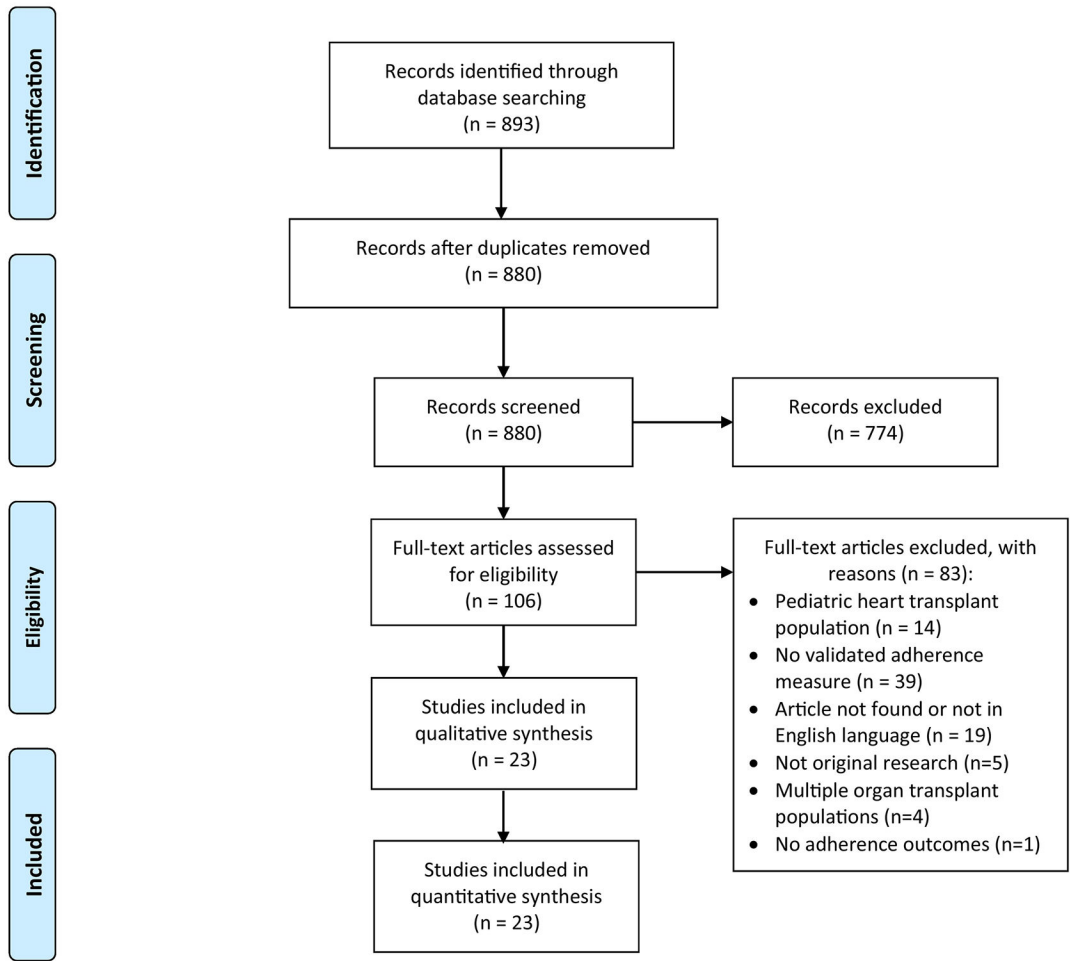Studies included in quantitative synthesis
(n = 23)

Figure 1:
PRISMA Flow Diagram

Table 1:

Design of all included studies

Author/Year	Population	Study design	Measure of adherence	Duration	Number of HTx participants	Participant Age (SD)	Attrition rate
Blanca Martinez Perez (2013)[14]	Pts who received transplant between 2001 and 2011, seen at a large hospital complex in Spain	Cross-sectional study	Morisky-Green test and immunosuppressant drug levels	N/A	99	50 (12) years old	N/A
Brocks (2017)[15]	Pts at least 18 years old, associated with a German heart transplant clinic who could speak German (survey conducted by mail)	Cross-sectional study	ITAS measure	4 months	505	Range: 18 to 90 years.	N/A
De Geest (1998)[25]	Adult patients taking cyclosporine as part of their regimen from academic centers in Leuven, Belgium.	Prospective cohort trial	Electronic pill bottle monitor	3 months	101	Median 56.0 (range 20.0–69.0)	1/101
De Geest (2014)[16]	Questionnaires completed by pts who are part of the Swiss Transplant Cohort Study; pts were evaluated and waitlisted for transplantation in Switzerland	Prospective cohort study	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	3 years	126	Age of all solid-organ transplant patients was 52.5 (13.1)	32/126
Denhaerynck (2018)[32]	Pts recruited through the Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study, which used multistaged sampling to examine 36 HTx centers in Europe, North America, South America, and Australia.	Cross-sectional study	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Not stated	1397	53.6 (13.2)	N/A
Dobbels (2004)[17]	Patients recruited at outpatient clinic visits at the Leuven Heart Transplant Program, Belgium	Prospective cohort study	Medication Event Monitoring System (MEMS)	5 years	101	55 (10)	0/101
Doesch (2013)[18]	Patients were recruited from the Department of Cardiology, Heidelberg University Hospital, Germany. Patients had to be at least 6 months post-HTx and free from acute infection or rejection for 4 months prior to study inclusion. Patients also had to be on stable doses of	Prospective cohort study	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	8 months	76	46.0 (14.4)	4/76

Author/Year	Population	Study design	Measure of adherence	Duration	Number of HTx participants	Participant Age (SD)	Attrition rate
	conventional TAC or CsA for 4 months preceding study entry (as part of a dual immunosuppressive regimen).						
Doesch (2010)[19]	Patients were recruited from the Department of Cardiology, Heidelberg University Hospital, Germany. Patients had to be at least 6 months post-HTx and free from acute infection or rejection for 4 months prior to study inclusion. Patients also had to be on stable doses of conventional TAC or CsA for 4 months preceding study entry (as part of a dual immunosuppressive regimen).	Prospective cohort study	Visual Analogue Scale (VAS) and Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	4 months	54	46.2 (14.1)	4/54
Epstein (2014)[26]	Data collected from Kaiser Permanente's Heart Transplant Service in Santa Clara, CA.	Cross-sectional study	Immunosuppressant Therapy Adherence Scale (ITAS)	N/A	52	54.46 (no SD)	N/A
Farmer (2013)[27]	4 US medical centers	Prospective cohort study	Assessment of Problems with the Transplant Regimen Scale	10 years	555	58.58 (8.93) in dead group, 59.50 (9.94)in alive group	30%
Goetzmann (2008)[20]	German-speaking patients who had received a heart at University Hospital Zurich, Switzerland	Cross-sectional study	Transplant Effects Questionnaire translated into German (TxEQ-D)	N/A	41	At follow up: mean 62.0, range (24–75)	N/A
Gomis-Pastor (2020)[21]	Adults less than 1.5 years from heart transplant recruited from cardiology outpatient clinic in Barcelona, Spain	Prospective cohort study	Simplified Medication Adherence Questionnaire (SMAQ)	mean 2.3 mos (SD 0.9)	31	54 (12)	0/31
Grady (2016)[28]	Adults transplanted 5–10 years prior at 4 US medical centers	Cross-sectional study	Assessment of Problems with the Heart Transplant Regimen	N/A	210	Age of recipient at transplant: women: 48.8 (12.0), men: 57.1 (8.5)	N/A
Grady (1998)[29]	Adults transplanted 1–2 years ago from two US academic medical centers	Prospective cohort study	Assessment of Problems with Heart Transplant Regimen	2 years	120	None given	44/120
Grady (1999)[30]	Adults transplanted 1 year ago at two US academic medical centers	Cross-sectional study	Assessment of Compliance with Transplant Regimen	N/A	232	53.9 (9.3)	N/A

Author/Year	Population	Study design	Measure of adherence	Duration	Number of HTx participants	Participant Age (SD)	Attrition rate
Helmy (2019)[33]	Pts recruited through the Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study, which used multistaged sampling to examine 36 HTx centers in Europe, North America, South America, and Australia. Pts transplanted 1–5 years ago.	Cross-sectional study	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	N/A	1397	53.7 (13.2)	N/A
Hugon (2014)[22]	French-speaking adult patients who had received a solid organ transplant at least 3 months ago. Questionnaire sent by mail.	Cross-sectional study	Scale based on Morisky-Green; IS trough levels also collected. nonadherent if the self-reported adherence score was 4 (3) and/or had a ratio of inadequate trough concentrations >0.2.	N/A	43	Age of all solid-organ transplant patients was 55.7 (13.0)	N/A
Kung (2012)[34]	English speaking patients who received transplants at least 3 months prior at one of two solid organ transplant centers in New Zealand.	Cross-sectional study	Immunosuppressant Therapy Adherence Scale (ITAS) based on scoring 12 or less, where a score of 12 indicates perfect adherence	N/A	87	54.4 (11.8)	N/A
Milaniak (2014)[23]	Adults transplanted at least 3 months ago at a transplant and surgery department in Poland	Cross-sectional study	Transplant Effects Questionnaire (TxEQ) - Subscale scores are expressed as a mean obtained by dividing the total score by the number of items ranging from 1 to 5. Tertiles were used to estimate the emotional response, so that a score of 1–2.3 represents a low emotional response, 2.4–3.6 a moderate response and 3.7–5 a high level of emotional response.	N/A	46	52.36 (13.55)	N/A
Scholz (2012)[53]	Adults transplanted with a solid organ (heart, liver, kidney, lung) at least 6 months ago at University Hospital Zurich, Switzerland	Cross-sectional study	Five-item adherence subscale of the German version of the Transplant Effects Questionnaire (TxEQ-D)	N/A	19	Age of all solid-organ transplant patients was 54.32 (13.32)	N/A
Shamaskin (2012)[31]	Pts at least 21 years old and 5 years post heart transplant recruited from one of 4 US medical centers	Cross-sectional study	Assessment of Problems with Heart Transplant Regimen	N/A	555	Age in three groups: younger: 42.2 (7.1), middle aged: 59.1 (4.2),	N/A

Author/Year	Population	Study design	Measure of adherence	Duration	Number of HTx participants	Participant Age (SD)	Attrition rate
						older: 69.4 (2.8)	
Shemesh (2017)[36]	Hebrew-speaking patients cared for at an tertiary medical center outpatient clinic in Israel.	Cross-sectional study	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) - overall nonadherence defined as that is, missing one or skipping two or more doses, not maintaining a timing of medication intake, altering the prescribed amount, or completely stopping intake of IS medications	N/A	102	56.66 (15.38)	N/A
Vitinius (2019)[24]	German-speaking patients who were inpatients or outpatients followed at the University of Cologne, Germany; recruited before transplant.	Prospective cohort study	Medication experience scale for immunosuppressants (MESI)	Pre-transplant to 6 months post transplant	20	Average age of participants of both studies included in this manuscript: 53.5 (11.75)	9/20
Zhang (2019)[35]	Adult patients at least 3 months from admission for heart transplant from a medical college and university in China.	Cross-sectional study	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	N/A	186	51.5 (interquartile range 41.0–58.0)	18/186 did not complete instrument

HTx: Heart transplant; Pt: Patient; N/A: not applicable

Table 2:

Validated adherence measures based on self-report

Author	Instrument name	Structure and development/validation references
Morisky et al.	Morisky-Green test	4-item scale with yes/no answers[54]
Chisholm et al.	Immunosuppressant Therapy Adherence Scale (ITAS)	Originally validated 5-item scale with categorical answers[55] 4-item scale also utilized[56] Later validated in solid-organ transplant recipients receiving immunosuppression[57]
University of Basel	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Most updated version contains 6 YES/NO items, with additional questioning with 5 response categories if implementation problems are detected.[58] Initially validated in patients with HIV[59] Later validated in Brazilian kidney-transplant recipients[60]
Hayes et al. (per Ahearn[61])	Visual Analogue Scale (VAS)	Single question: "In a time period, how much medicine did you take as prescribed?" with answers on an analogue scale (0–100%) Validated for HCV patients taking antivirals[62] Some data in HIV patients taking ART[63]
Ziegelmann et al.	Transplant Effects Questionnaire (TxEQ)	24-item questionnaire around 5 conceptual factors with 5-point Likert scale for answers[64] Developed for use in organ transplant patients
Knobel et al.	Simplified Medication Adherence Questionnaire (SMAQ)	6-item scale with different answer types.[65] Validated in renal transplant patients[66]
Grady et al.	Assessment of Problems with the Heart Transplant Regimen	26-item scale with 4-point Likert scale for answers[29] Developed for use in heart transplant patients
Goetzmann et al.	Medication Experience Scale for Immunosuppressants (MESI)	7-item scale with scored answers, total between 4 and 33[67] Developed for use in solid organ transplant patients

HIV: Human immunodeficiency virus; ART: Anti-retroviral therapy;

Table 3:

Studies exploring baseline adherence levels

Author (year)	Adherence measure	Definition of adherence	Outcomes
Blanca Martinez Perez (2013)[14]	Morisky-Green test and immunosuppressant drug levels	Therapeutic plasma drug levels (specific levels not noted): Tacrolimus levels Cyclosporine levels Everolimus levels Rifampin levels	Tacolimus: 85 +/− 13% were therapeutic Cyclosporine: 67 +/− 28% were therapeutic Everolimus: 31 +/− 33% were therapeutic Rifampin: 100% were therapeutic
		Morisky Green test: Said no to all: "Do you ever forget to take your medications?", "When you feel well, do you stop taking them?", and "If you feel unwell, do you stop taking the medicines?" and yes to: "Do you take medications at the right times?"	67/99 were compliant by the Morisky-Green. 30% stated that they sometimes forgot to take their medication and 14% did not take it at the time established.
Brocks (2017)[15]	Immunosuppressant Therapy Adherence Scale (ITAS)	Perfect adherence: 12/12 score on ITAS	72.4% noted perfect adherence
De Geest (1998)[25]	Electronic pill bottle monitor	Cluster analysis was done on the basis of specific variables, including medication taking compliance, dosing compliance, variability of dosing intervals, drug holidays, cyclosporine-free days, and interview rating.	The three clusters included 84% as excellent compliers, 7% as minor subclinical noncompliers and 9% as moderate subclinical noncompliers. The groups varied among the above variables p = 0.0001 via MANOVA.
De Geest (2014)[16]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Taking nonadherence: asking "How often did you miss a dose of medication (pretransplant)/ immunosuppressive medication (post-transplant) in the past 4 weeks?"	4 (5.1%) taking nonadherence at 6 months 5 (6.5%) taking nonadherence at 12 months 5 (10.6%) taking nonadherence at 24 months 6 (18.8%) taking nonadherence at 36 months
		Drug holidays: asking "Did you miss more than one consecutive dose of your (immunosuppressive) medication in the past 4 weeks?"	0 (0%) drug holidays at 6 months 1 (1.9%) drug holidays at 12 months 1 (3.1%) drug holidays at 24 months 1 (7.1%) drug holidays at 36 months
Denhaerynck (2018)[32]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Nonadherence defined as: Overall nonadherence: "any deviation in taking, timing, or dosing"	34.1% had implementation phase overall nonadherence
		Taking nonadherence (ie. Missing doses)	14.7% noted taking nonadherence
		Timing nonadherence (>2 hours deviation from dosing schedule)	26.5% of patients noted timing nonadherence
Dobbels (2004)[17]	Medication Event Monitoring System (MEMS)	Iterative partitioning methods of cluster analysis identified 1 cluster of compliers, and 2 clusters of non-compliers.	Pts were considered medication non-compliers (n = 17) or compliers (n = 84)
Doesch (2013)[18]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Overall nonadherence defined as missing one or skipping two or more doses, not maintaining a timing of medication intake, altering the prescribed amount, or completely stopping intake of IS medications	Overall nonadherence at baseline for any of the four BAASIS items was 75.0%
Doesch (2010)[19]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) and Visual Analogue Scale (VAS)	Overall nonadherence defined as missing one or skipping two or more doses, not maintaining a timing of medication intake, altering the prescribed amount, or completely stopping intake of IS medications	Overall nonadherence at baseline for any of the 4 BAASIS items was 74%
		VAS continuous score on a scale 0–100%.	The VAS score at baseline was 82.3% ± 2.6%

Author (year)	Adherence measure	Definition of adherence	Outcomes
Goetzmann (2008)[20]	Transplant Effects Questionnaire translated into German (TxEQ-D)	Continuous score; average of scores on 5-point Likert scale from "strongly disagree" = 1 to "strongly agree" = 5: (1) Sometimes, I do not take my antirejection medicines; (2) Sometimes, I forget to take my antirejection medicines; (3) When I am too busy, I may forget my antirejection medicines; (4) Sometimes, I think I do not need my antirejection medicines; (5) I find it difficult to adjust to taking my prescribed antirejection drug regime.	Heart transplant patients noted 4.27 (.79) out of 5 score on medication adherence
Gomis-Pastor (2020)[21]	Simplified Medication Adherence Questionnaire (SMAQ):	Nonadherence defined as any suboptimal answer to: - Do you always take your medications at the appropriate times? (Y/N) - When you feel bad, have you ever discontinued taking your medications? (Y/N) - Have you ever forgotten to take your medications? (Y/N) - Have you ever forgotten to take your medications during the weekend? (Y/N) - In the last week, how many times did you fail to take your prescribed dose? (Never/1–2 times/3–5 times/6–10 times/more than 10 times) - Since your last visit, how many whole days have gone by in which you did not take your medications?	According to the SMAQ, 39% (12/31) of HTxR were nonadherent to immunosuppressive treatment.
Grady (1998)[29]	Assessment of Problems with Heart Transplant Regimen	26-items on a 4-point Likert scale with different choices per question. Only presented these adherence measures: "No difficulty" taking all immunosuppressants	98% of individuals noted no difficulty taking all immunosuppressants
		Taking their IS "all of the time"	99% noted they took their IS "all of the time"
		Taking their prednisone "all of the time"	100% were adherent to prednisone
		Taking their cyclosporine "all of the time"	100% were adherent to cyclosporine
		Taking their azathioprine "all of the time"	100% were adherent to azathioprine
Helmy (2019)[33]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Overall nonadherence included any of the below (taking nonadherence, drug holiday, timing nonadherence, and/or dose alteration)	Overall nonadherence rate of 37.4%
		Taking nonadherence (missing >1 dose)	15.1%; 95% CI: (13.2, 17.0) experienced taking nonadherence
		Drug holiday (skipping >2 consecutive doses)	1.4%; (95% CI (0.8, 2.0) endorsed a drug holiday
		Timing nonadherence (taking medication >2 h before or after the prescribed time)	26.2%; 95% CI (23.9, 28.5) endorsed timing nonadherence
		Dose alteration (taking more or fewer pills than prescribed or changing dosages without a physician's order)	1.5%; 95% CI (0.8, 2.1) endorsed dose alteration
Hugon (2014)[22]	Scale based on Morisky-Green; IS trough levels also collected.	Scale was 6 questions with yes/no answers (exact questions unspecified). Considered nonadherent if the self-reported adherence score was 4 and/or had a ratio of inadequate trough concentrations >0.2.	For heart transplant, adherence rate was 34.9%, significantly lower than other organs. Mean score for self-reported adherence was 4.4 (0.9)
Kung (2012)[34]	Immunosuppressant Therapy Adherence Scale (ITAS)	Perfect adherence: 12/12 score on ITAS	37% of HTx patients had perfect adherence.
Milaniak (2014)[23]	Transplant Effects Questionnaire (TxEQ)	Subscale scores were expressed as a mean obtained by dividing the total score by the number of items ranging from 1 to 5. Tertiles were used to estimate the emotional response; a score of 1–2.3 represents a low emotional	They reported good adherence to medication (avg. 4.02 – third tertile)

Author (year)	Adherence measure	Definition of adherence	Outcomes
		response, 2.4–3.6 a moderate response and 3.7–5 a high level of emotional response.	
Shemesh (2017)[36]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Overall nonadherence defined as missing one or skipping two or more doses, not maintaining a timing of medication intake, altering the prescribed amount, or completely stopping intake of IS medications	64 patients (64%) were overall nonadherent
		Timing nonadherence (>2 hours deviation from dosing schedule)	58 participants (56.9%) noted timing nonadherence
Zhang (2019)[35]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Nonadherence defined as: "any deviation in taking, timing, or dosing"	69 (41.1%) recipients were revealed to be nonadherent in any way
		Taking nonadherence (ie. Missing doses)	14.0% of the participants endorsed "taking nonadherence"
		Timing nonadherence (>2 hours deviation from dosing schedule)	35.1% of the participants endorsed "timing nonadherence"

IS: immunosuppression

Table 4:

Studies exploring correlates to adherence

Author/Year	Measure of adherence	Variables explored	Main outcomes
Blanca Martinez Perez (2013)[14]	Morisky-Green test and immunosuppressant drug levels	Higher age (years)	Not significant: (OR 1.5; 95% CI: 0.7 – 3.3; p = 1)
		Sex (binary)	Not significant: (OR 1; 95% CI: 0.4 – 2.3; p = 0.998)
		Urgent vs elective transplant (binary)	Not significant: (OR 0.8; 95% CI: 0.4 – 1.5; p = 1)
		Dyslipidemia (binary)	Not significant: (OR 1; 95% CI: 0.99 – 1.01; p = 0.794)
		Hypertension (binary)	Not significant: (OR 0.9; 95% CI: 0.5–1.4; p =0.442)
		Diabetes mellitus (binary)	Not significant: (OR 1.6; 95% CI: 0.9–2.9; p =0.145)
		Renal failure (binary)	Not significant: (OR 1.9; 95% CI: 0.6–3; p = 0.175)
Brocks (2017)[15]	ITAS measure	Consumption of soft boiled or unpasteurized egg products, scored as (4 = daily; 3 = several times a week; 2 = occasionally; 1 = never)	Significantly associated with nonadherence: (r = −0.130; P < 0.01)
		Consumption of unpasteurized milk products, scored as (4 = daily; 3 = several times a week; 2 = occasionally; 1 = never)	Significantly associated with nonadherence: (r = −0.128; P < 0.01)
		Higher SF-12 Mental Health Score (units) ranging 0–100 where 0 represents low and 100 represents high level of health.	Significantly associated with adherence: (r = 0.016; 95% CI: 0.003–0.028; p = 0.015)
		Higher age (years)	Significantly associated with adherence: (r = 0.017; 95% CI: 0.08–0.026; p < 0.001)
		Perceptions/miscellaneous	74.8% noted being at least slightly handicapped by adverse drug effects; fewer than 15% of the group believed any of the following: "I need to take medication too often," "I need to take too many pills at 1 time," "I do not know if immunosuppression helps," "My immunosuppression sometimes runs out," "Remembering to take immunosuppression is hard," and "I neglect taking immunosuppression."
De Geest (1998)[25]	Electronic pill bottle monitor	Appointment noncompliance rates	Appointment noncompliance rates were higher in minor (28.6%) and moderate (11.1%) subclinical noncompliers compared to excellent compliers (3.6%) (p = 0.03).
		Self efficacy with medication taking as rated on questionnaire on a 5-point scale	Self efficacy was worst in the minor subclinical noncompliers (mean 4.41; Q1: 4.30, Q3: 4.81) and best in the excellent compliers (mean 4.85; Q1: 4.70, Q3: 5.00); Moderate compliers: (mean 4.81; Q1: 4.70, Q3: 4.89) (p = 0.04).
		Miscellaneous	Clusters did not differ significantly on demographic data, BMI, perceived social support, symptom frequency, symptom distress, depressive symptomatology, knowledge of the therapeutic regimen, cardiac functional status, and perceived health status.

Author/Year	Measure of adherence	Variables explored	Main outcomes
De Geest (2014)[16]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Greater time since transplant	In the adjusted model: Significantly associated with nonadherence: (aOR: 1.05; 95% CI: 1.01–1.08)
Denhaerynck (2018)[32]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Greater barriers to taking immunosuppression as prescribed, scored 1 (never) to 5 (always)	In the multiple sequential regression model, Significantly associated with nonadherence: (OR = 11.48; 95% CI: 6.66–21.05; p < 0.0001)
		Currently or recently smoking or having stopped less than a year ago	Significantly associated with nonadherence: (OR: 2.19; 95% CI: 1.35–3.56; p = 0.002)
		Medication pick-up at physician's office	Significantly associated with nonadherence: (OR: 2.31; 95% CI: 1.24–4.31; p = 0.008)
		Higher monthly immunosuppression cost, scored as 1 ($0–$20), 2 ($20.01–$60), 3 ($60.01–%110) and 4 (>$110)	Significantly associated with nonadherence: (OR: 1.16; 95% CI: 1.02–1.33; p = 0.03)
		Higher frequency of having someone to help read health-related materials, scored 1 (none of the time) to 5 (all of the time)	Significantly associated with adherence: (OR = 0.85; 95% CI: 0.76–0.95; p = 0.004)
		Clinicians reporting nonadherent patients are targeted with adherence interventions, scored 1 (never) to 4 (always)	Significantly associated with adherence: (OR = 0.66; 95% CI: 0.48–0.91; p = 0.01)
Epstein (2014)[26]	Immunosuppressant Therapy Adherence Scale (ITAS)	Chance LOC, defined as feelings of control over health outcomes, measured via the Multidimensional Health Locus of Control tool	Significantly inversely related to occassional missed doses of immunosuppressant medications: (OR 1.1527; 95% CI: 1.0394 – 1.2792); p = 0.0071)
		African American race	Significant: (p=0.0026). No other data provided.
Grady (2016)[28]	Assessment of Problems with the Heart Transplant Regimen	Female gender	Significantly associated with adherence: (0.05 point difference; 95% CI: 0.02–0.08; p = 0.005)
		Higher age	Significantly associated with nonadherence: (−0.003 point difference; 95% CI: 0.01 – 0.09; p < 0.0001)
		Idiopathic etiology of heart failure	Significantly associated with adherence: (0.05 point difference; 95% CI: 0.01–0.09; p =0.028)
		Ischemic etiology of heart failure	Significantly associated with adherence: (0.06 point difference; 95% CI: 0.02–0.11; p = 0.003)
		Miscellaneous	"No psychiatric condition", "No orthopedic illness", and "No diabetes" were not significantly associated with adherence
Grady (1998)[29]	Assessment of Problems with Heart Transplant Regimen	Higher self-care disability as noted on the Sickness Impact Profile	Significantly associated with nonadherence: (r = 0.32; p < 0.0001)
		Higher number of complications between 9 and 12 months after transplant as noted in the medical record	Significantly associated with nonadherence: (r = 0.25; p = 0.005)
Grady (1999)[30]	Assessment of Compliance with Transplant Regimen	Life satisfaction as collected from the Quality of Life Index	Significantly associated with adherence: (r = −0.42; p 0.0001)
Milaniak (2014)[23]	Transplant Effects Questionnaire (TxEQ)	Comprehensibility (the idea that confronted stimuli are are structured and predictable) collected from the Sense of Coherence instrument, Polish version	Trend toward adherence but not significant (r = 0.253; p =0.089)

Author/Year	Measure of adherence	Variables explored	Main outcomes
Shamaskin (2012)[31]	Assessment of Problems with Heart Transplant Regimen	Higher age, divided into older (>60), middle aged between 45–59 and younger (<45).	Significantly associated with adherence ($F_{(2,234.75)}$ = 9.98, p < 0.001) Values were 0.14 (SD 0.12) for younger patients, 0.12 (SD 0.10) for middle aged, and 0.08 (SD 0.07) for older patients
		Miscellaneous	Higher age was significantly associated with perceived difficulty with adherence ($F_{(2,552)}$ = 11.97; p < 0.001). Values were 0.26 (SD 0.20) for younger patients, 0.24 (SD 0.19) for middle aged and 0.16 (SD 0.17) for older patients
Shemesh (2017)[36]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Higher age (years)	Significantly associated with adherence (b=0.036, p=0.04)
		Greater guilt feelings regarding the heart donation, defined on a scale from 0 (not at all), 1 (slightly), 2 (moderately), 3 (very), and 4 (greatly)	Significantly associated with nonadherence (b=−1.497, p=0.037)
		Time since transplantation as obtained from the medical record	Significantly associated with nonadherence (b=−0.008; p = 0.027)
		Miscellaneous	There was no difference in adherence between men/women ($\chi 2(1)$=2.02; p=0.16), employment/student status ($\chi 2(1)$=3.32; p = 0.07), transplant center ($\chi 2(1)$=0.14, p=0.71) or initial support with LVAD/BiVAD/neither ($\chi 2(1)$=.25, P=0.62).
Vitinius (2019)[24]	Medication experience scale for immunosuppressants (MESI)	Anxiety and depression as measured by the HADS-D tool: Seven items form a depression subscale and the other seven items an anxiety subscale. The items are scored from 0 to 3.	Higher scores 6 months after transplant not significantly associated with adherence: (r = 0.44; P = 0.199 and r = 0.54; P = 0.106, respectively)
		Higher depression scores via the Patients Health Questionnaire (PHQ-D) score: assesses symptoms according to classifications in the DSM-IV	Significantly associated with nonadherence: (r = 0.68, p = 0.031)
		Higher Transplant Evaluation Rating Scale (TERS) score, that represents psychosocial functioning. Scores range from 26.5 to 79.5 and higher represents worse functioning.	Not significantly associated with adherence immediately after transplantation (r = −0.11, P = 0.764)
			However, was significantly associated with nonadherence 6 months after transplantation (r = 0.84; p = 0.001)
Zhang (2019)[35]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Lower monthly income (<3000 Chinese Yuan) as obtained via questionnaire.	Significantly associated with nonadherence (OR: 3.11; 95% CI: 1.58–6.12; p=0.001)
		Number of prescribed concomitant drugs gathered via medical record and patient interview	Significantly associated with nonadherence (OR: 1.23; 95% CI, 1.12–1.50; p=0.003)
		Higher concerns about immunosuppressants as gathered through the Belief Medication Questionnaire (BMQ) Each item is scored on a 5-point scale (1=strongly disagree, 5=strongly agree) and is summed resulting in a score for each subscale. High scores indicate a strong belief in the necessity and low concern for the use of immunosuppressants.	Significantly associated with nonadherence (OR: 1.09; 95% CI, 1.01–1.18; p=0.031)
		Miscellaneous	Noncompliance was significantly associated with less than a high school education, (53.6%

Author/Year	Measure of adherence	Variables explored	Main outcomes
			vs. 37.4%; p=0.037), greater likelihood of living in a rural area (36.2% vs. 20.2%; p=0.021); lower median anxiety scores (10.0 vs. 12.0, p=0.041), a poorer Physical Component Summary (PCS) score (44.6 vs. 48.0, p=0.002) and lower Mental Component Summary (MCS) score: (44.4 vs. 49.1, p=0.001) though none were statistically significant in the final logistic model.

OR: Odds ratio; aOR: Adjusted odds ratio; LVAD: Left-ventricular assist device; BiVAD: bi-ventricular assist device; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

Table 5:

Studies exploring health outcomes associated with adherence and nonadherence

Author (year)	Measure of adherence	Outcome variable	Association with preceding adherence/nonadherence
Dobbels (2004)[17]	Medication Event Monitoring System (MEMS)	Transplant coronary artery disease (CAD), defined as any degree of angiographically detectable CAD on routine annual coronary angiogram	Significantly associated with nonadherence: (OR 1.779; 95% CI: 1.20 – 2.64; p = 0.025)
		Late acute rejection defined as biopsy-proven Grade >1B rejection	Trend toward nonadherence but not significant: (OR 4.941; 95% CI: 0.75 – 32.69; p = 0.131)
		Retransplant as noted in the medical record	Trend toward nonadherence but not significant: (OR 5.4; 95% CI: 0.82 – 35.42; p = 0.114)
		5-year mortality as noted in the medical record	Not significant (OR 1.098; 95% CI: 0.26 – 4.64; p = 0.999)
		Clinical-event-free time without the above 4 events	Significantly associated with adherence: (mean 1612 days vs. 1318 days; p = 0.043)
		Adjusted relative risk of clinical event per Cox regression analysis	After controlling for other known transplant-related risk factors for poor clinical outcome, trend toward nonadherence but not significant: ARR = 2.03; p = 0.0582
Farmer (2013)[27]	Assessment of Problems with the Transplant Regimen Scale	Death at 5–10 years as observed in the medical record	High compliance significantly inversely associated with death: (HR 0.26; 95% CI: 0.08–0.81; p=0.02) Moderate compliance significantly inversely associated with death: (HR 0.34; 95% CI: 0.14–0.79; p=0.01)
De Geest (1998)[25]	Electronic pill bottle monitor	Acute late rejection during the course of the study	Significantly associated with noncompliance: rate 1.2% in excellent compliers, 14.3% in minor subclinical noncompliers and 22.2% in moderate subclinical noncompliers; p = 0.01

OR: odds ratio; CI: Confidence interval; HR: Hazard ratio

Table 6:

Studies evaluating adherence interventions

Author/ Year	Measure of adherence	Description of Intervention	Main outcomes
Doesch (2013)[18]	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Patients were switched from conventional twice-daily tacrolimus or cyclosporine A to once daily modified release tacrolimus regimen.	• Overall nonadherence at baseline for any of the four BAASIS items was 75.0% versus 40.3% after 8 months (P=0.0001). • After 8 months, adherence was improved in 41 patients (56.9%), unchanged in 27 (37.5%), and reduced in four patients (5.6%). • No significant changes were observed for hematological, renal, or liver function parameters after 8 months (all P = NS).
Doesch (2010)[19]	Visual Analogue Scale (VAS) and Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Patients were switched from conventional twice-daily tacrolimus or cyclosporine A to once daily modified release tacrolimus regimen.	• Overall nonadherence at baseline for any of the 4 BAASIS items was 74% versus 38% after 4 months (P = .0001). • Thereafter, adherence improved in 28 patients (56.0%), was unchanged in 18 (36.0%), and decreased in 4 subjects (8.0%). The VAS score improved from 82.3% +/− 2.6% to 97.5% +/− 4.8% (P = .0001). • No significant changes were observed after 4 months regarding hematologic, renal, or liver function parameters (all P = NS).
Gomis-Pastor (2020)[21]	Simplified Medication Adherence Questionnaire (SMAQ)	mHeart: mobile app bidirectionally integrated with hospital information system; had functionality to answer patients' questions about their treatment and health conditions, empower patients in terms of self-care, and facilitate professionals' interventions regarding symptoms and adverse effects.	• The theory-based multifaceted intervention improved the adherence rate from 61% to 87% (p =0.005) over 1 month.

NS = Not significant

Table 7:

Bias ratings of prospective cohort studies, via Newcastle-Ottawa scores

File name	Representativeness of the exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	that outcome of interest was not present at the start of the study	Comparability	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Bias rating	Bias reasoning
De Geest (1998)[25]	1	1	1	1	0	1	1	1	7 out of 9	No controls/ adjustment
De Geest (2014)[16]	1	1	1	1	2	0	1	0	7 out of 9	Self-reported outcomes High attrition rate
Dobbels (2004)[17]	1	1	1	1	2	1	1	1	9 out of 9	N/A
Doesch (2013)[18]	1	1	1	1	0	0	1	1	6 out of 9	No controls/ adjustment Self-reported outcomes
Doesch (2010)[19]	1	1	1	1	0	0	1	1	6 out of 9	No controls/ adjustment Self-reported outcomes
Gomis-Pastor (2020)[21]	1	1	1	1	0	0	1	1	6 out of 9	No controls/ adjustment Self-reported outcomes
Grady (1998)[29]	1	1	1	1	2	0	1	0	7 out of 9	Self-reported outcomes High attrition rate
Farmer (2013)[27]	1	1	1	1	2	1	1	1	9 out of 9	N/A
Vitinius (2019)[24]	1	1	1	1	2	0	1	1	8 out of 9	Self-reported outcomes

N/A: not applicable

Table 8:

Bias rating of cross-sectional studies, via modified Newcastle-Ottawa scores

File name	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability	Assessment of the outcome	Statistical test	Bias rating	Bias reasoning
Blanca Martinez Perez (2013)[14]	1	1	1	2	0	2	1	8 out of 10	No controls/ adjustments done
Brocks (2017)[15]	1	1	0	2	2	1	1	8 out of 10	No description of non-respondents Self-reported outcomes only
Denhaerynck (2018)[32]	1	1	1	2	2	1	1	9 out of 10	Self-reported outcomes only
Epstein (2014)[26]	1	1	0	2	2	1	1	8 out of 10	No description of non-respondents Self-reported outcomes only
Goetzmann (2008)[20]	1	1	0	2	0	1	1	6 out of 10	No description of non-respondents No controls/ adjustments done Self-reported outcomes only
Grady (2016)[28]	1	1	1	2	2	1	1	9 out of 10	Self-reported outcomes only
Grady (1999)[30]	1	1	0	2	2	1	0	7 out of 10	No description of non-respondents Self-reported outcomes only p-values given but no confidence intervals given for adherence scores
Helmy (2019)[33]	1	1	0	2	2	1	1	8 out of 10	No description of non-

File name	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability	Assessment of the outcome	Statistical test	Bias rating	Bias reasoning
									respondents Self-reported outcomes only
Hugon (2014)[22]	1	1	0	2	2	2	0	8 out of 10	No description of non-respondents No p-values or confidence intervals given specifically for heart transplant patients
Kung (2012)[34]	1	1	0	2	2	1	0	7 out of 10	No description of non-respondents Self-reported outcomes only No p-values or confidence intervals given specifically for heart transplant patients
Milaniak (2014)[23]	1	1	0	2	0	1	0	5 out of 10	No description of non-respondents No controls/adjustments done Self-reported outcomes only R given but no confidence interval
Shamaskin (2012)[31]	1	1	1	2	2	1	1	9 out of 10	Self-reported outcomes only
Shemesh (2017)[36]	1	1	0	1	2	1	1	7 out of 10	No description of non-respondents Exposure tool non-validated Self-reported outcomes only

File name	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability	Assessment of the outcome	Statistical test	Bias rating	Bias reasoning
Zhang (2019)[35]	1	1	0	2	2	1	1	8 out of 10	No description of non-respondents Self-reported outcomes only

N/A: not applicable