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# Correlates and outcomes of alcohol use after single solid organ transplantation: A systematic review and meta-analysis

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## ARTICLE INFO

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## ABSTRACT

*Background:* Reviews on alcohol use in transplant recipients focus on liver recipients and their risk of post-transplant rejection, but do not assess alcohol use in kidney, heart, or lung transplant recipients. This systematic review and meta-analysis aims to synthesize the evidence on correlates and outcomes of any alcohol use and at-risk drinking after solid organ transplantation (Tx).

*Methods:* We searched 4 databases for quantitative studies in adult heart, liver, kidney and lung Tx recipients, investigating associations between post-Tx alcohol use and correlates and/or clinical, economic or quality of life outcomes. Paper selection, data extraction and quality assessment were performed by 2 reviewers independently. A pooled odds ratio (OR) was computed for each correlate/outcome reported ≥5 times.

*Results:* Of the 5331 studies identified, 76 were included in this systematic review (93.3% on liver Tx; mean sample size 148.9 (SD = 160.2); 71.9% male; mean age 48.9 years (SD = 6.5); mean time post-Tx 57.7 months (SD = 23.1)). On average, 23.6% of patients studied used alcohol post-transplant. Ninety-three correlates of any post-Tx alcohol use were identified, and 9 of the 19 pooled ORs were significantly associated with a higher odds for any post-Tx alcohol use: male gender, being employed post-transplant, smoking pre-transplant, smoking post-transplant, a history of illicit drug use, having first-degree relatives who have alcohol-related problems, sobriety <6 months prior to transplant, a history of psychiatric illness, and having received treatment for alcohol-related problems pre-transplant. On average 15.1% of patients had at-risk drinking. A pooled OR was calculated for 6 of the 47 correlates of post-Tx at risk drinking investigated, of which pre-transplant smoking was the only correlate being significantly associated with this behavior. None of the outcomes investigated were significantly associated with any use or at-risk drinking.

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*Conclusion:* Correlates of alcohol use remain under-investigated in solid organ transplant recipients other than liver transplantation. Further research is needed to determine whether any alcohol use or at-risk drinking is associated with poorer post-transplant outcomes. Our meta-analysis highlights avenues for future research of higher methodological quality and improved clinical care.
*Protocol registration:* PROSPERO protocol CRD42015003333



**Contents**



## 1. Introduction

Alcohol consumption is an integral part of many cultures and a common feature of social gatherings. Worldwide, 47.7% of men and 28.9% of women drink alcohol, with an average intake of pure alcohol per day of 30–57 g for men and 10–29 g for women [1]. While light to moderate intake (i.e., ≤ 2 alcohol units per day for men (28 g) and maximally 1 unit per day for women (14 g)) does not increase the risk of mortality or morbidity [2–5], the harmful impact of excessive alcohol use on a person's health cannot be ignored. In 2012, 5.9% of all global deaths were attributable to alcohol consumption [1]. Problematic alcohol use is the third most common risk factor for global disease burden, representing 5.5% of global disability-adjusted life years [6] and is a key risk factor in the onset of over 200 diseases and injuries, including cardiovascular disease, cancer, gastrointestinal disorders, diabetes and infectious diseases [7]. The annual economic cost attributable to excessive alcohol use is estimated at $125 billion Euros in Europe, and $224 billion dollars or about $1.9 dollars per alcoholic drink in the United States, corresponding to 1–3% of a country's gross domestic product globally [1,8].

Within the field of transplantation, alcohol-related research almost exclusively concentrates on alcoholic cirrhosis as an etiology of end-stage liver disease, and the prevalence and, to a lesser extent, predictors of relapse after liver transplantation [8]. Currently, about 1 out of 3 liver transplantations are performed for alcoholic liver disease [9]. Post-transplant survival and quality of life (QOL) are similar for patients undergoing transplantation for alcoholic liver cirrhosis versus for other etiologies. Some studies even suggesting a lower rejection rate and graft loss from rejection in those transplanted for alcoholic liver disease versus other indications [10]. Yet, in the case of alcohol relapse, occurring in an estimated 5.6 cases per 100 per year [11], long-term survival is poorer due to the increased risk for cardiovascular disease and cancer in those consuming alcohol post-transplant. Few studies have investigated the prevalence and clinical consequences of alcohol use in kidney, lung or heart transplant patients, with percentages between 0 and 78.2% being reported post-transplant in a recent narrative review [10]. Varying operational definitions of alcohol use, measurement and case finding methods might contribute to this large range in percentages observed. Also, risk factors for post-transplant (excessive) alcohol use have been investigated almost exclusively in liver transplant populations, and predominantly in patients with alcoholic cirrhosis as disease etiology, showing that more severe alcohol use and a shorter duration of abstinence prior to transplantation are associated with a higher risk of post-transplant relapse [12–14]. However, most studies did not use a theoretical framework underpinning the selection of variables under investigation, and without effect sizes being calculated, it is difficult to appreciate a correlate's true relationship with post-transplant drinking behavior and its subsequent association with outcome. To our knowledge, no systematic reviews have ever investigated a broad spectrum of correlates and outcomes, using a meta-analytic approach among all solid organ transplant populations, in patients abstaining from alcohol use, drinking at moderate levels, or showing at-risk drinking patterns (i.e., not only focusing on liver transplantation or a single organ type).

The aims of this systematic review and meta-analysis were to: 1) investigate the correlates of post-transplant alcohol use in adult heart, liver, kidney and lung transplant recipients, and 2) quantify the clinical, economic and health-related quality of life outcomes of post-transplant alcohol use in solid organ transplant recipients.

## 2. Materials and methods

This systematic review and meta-analysis is one of four systematic reviews conducted, investigating the relationships between correlates or outcomes and alcohol use, immunosuppressant medication nonadherence, smoking [15], or physical inactivity following transplantation through the Brocher funded grant to develop a Solid organ

transplant Endpoint model on Relationships between Influencing factors and Outcomes of transplant Self-Management behaviors Consortium.

We designed a systematic review protocol based on the methodology outlined in the Center for Reviews and Dissemination handbook [16] and followed the PRISMA guidelines for data reporting [17]. The protocol is registered in the PROSPERO database with registration number CRD42015003333 [18].

### 2.1. Electronic database searches

The electronic databases of PubMed, Embase.com, PsycINFO (Ovid), and CINAHL (Ebscohost) were searched from inception until April 30, 2016. The search string was first designed for PubMed in close collaboration with a health sciences librarian (MLK), combining controlled vocabulary (MESH terms) and free text words representing the concepts of alcohol consumption and solid organ transplantation (Table 1), and translated afterwards for the other databases (available from the researchers upon request). The bibliographic software program EndNote® was used to manage the references emerging from the comprehensive electronic database searches.

Titles and abstracts of references were screened against inclusion- and exclusion criteria by two reviewers independently. Next, the full texts of all potentially relevant references were retrieved and assessed for eligibility by two independent reviewers. Evaluations were compared and inconsistencies resolved via consensus or consultation with a third reviewer. Eligibility scores were documented using checklists programmed in a Microsoft Access database for transparency. The reference list of eligible studies was subsequently screened for additional studies meeting the pre-specified inclusion criteria. For companion or duplicate papers, only the most recent publication was considered. If similar or follow-up results were reported in different papers (i.e. companion papers), we included the paper with the largest sample size or most complete dataset only.

### 2.2. Inclusion and exclusion criteria

Studies eligible for inclusion in this systematic review had to fulfill the following criteria: 1) report on original or primary quantitative studies; 2) include adult (> 18 years of age) recipients of single heart, liver, kidney or lung transplants; 3) address alcohol use; and 4) focus either on the association between post-transplant alcohol use and clinical, economic or health-related quality of life outcomes, or on correlates of post-transplant alcohol use, or both.

**Table 1**
Search string programmed in PubMed.

(( "Heart Transplantation"[Mesh:noexp] OR heart transplant*[tiab] OR cardiac transplant*[tiab] OR heart graft*[tiab] OR heart allograft*[tiab] OR cardiac allograft*[tiab] OR cardiothoracic transplant*[tiab] OR thoracic transplant*[tiab] OR Cardiac Graft* [tiab] OR "Kidney Transplantation"[Mesh] OR kidney transplant*[tiab] OR renal transplant*[tiab] OR kidney graft*[tiab] OR kidney allograft*[tiab] OR renal allograft*[tiab] OR Renal Graft* [tiab] OR "Liver Transplantation"[Mesh] OR liver transplant*[tiab] OR hepatic transplant*[tiab] OR liver graft*[tiab] OR liver allograft*[tiab] OR hepatic allograft*[tiab] OR Hepatic Graft* [tiab] OR "Lung Transplantation"[Mesh:noexp] OR lung transplant*[tiab] OR lung graft*[tiab] OR lung allograft*[tiab] OR pulmonary transplant*[tiab] OR Pulmonary Graft* [tiab] OR "Organ Transplantation"[Mesh: noexp] OR solid organ*[tiab] OR organ transplant*[tiab])
AND
("Alcoholism"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Alcohol-Related Disorders"[Mesh:noexp] OR alcoholism[tiab] OR alcohol consumption[tiab] OR alcohol intake[tiab] OR alcoholic[tiab] OR alcohol dependen*[tiab] OR alcohol use [tiab] OR blood alcohol[tiab] OR alcohol abuse[tiab] OR alcohol drink*[tiab] OR sobriety[tiab] OR drinking[tiab] OR recidivism[tiab] OR recidivist*[tiab] OR abstinen*[tiab]))

The following papers were excluded: 1) publications that did not report results from an original quantitative research project (e.g. qualitative studies, case reports with single subjects, reviews, books, consensus reports, statements, editorials, letters to the editor, or dissertations); 2) studies on combined organ transplant populations (e.g. liver and kidney), or other forms of tissue or organ transplantation (e.g. stem cell or pancreas transplantation); 3) studies focusing on children or adolescents <18 years of age; and 4) quantitative studies focusing on a different topic or not addressing correlates or outcomes of post-transplant alcohol use. Studies were also excluded if they had insufficient information to allow effect size calculation based on the results published or full texts that could not be found.

### 2.3. Data extraction

A codebook was designed and programmed in an Access 2007 database (Microsoft, Seattle, WA, USA) to guide the data extraction, covering the following sections: a) general information on the paper (e.g., year of publication, country of origin, funding source of study, organ type); b) study methods (e.g. study design, sample size and characteristics (e.g. age, gender, time since transplant); c) theoretical framework underpinning the investigation of correlates or outcomes of alcohol use; d) clinical, economic and health-related quality of life outcomes; e) correlates; f) quality assessment criteria; and g) specific information regarding prevalence and measurement methods documenting post-transplant alcohol use.

The correlates were further divided into social/economic-related, patient-related, condition-related, treatment-related and healthcare team or system related correlates, in line with the taxonomy used by the World Health Organization to classify correlates of medication adherence [19], and to facilitate comparisons of results between the parallel systematic reviews on post-transplant smoking behavior, physical inactivity and medication nonadherence. Clinical, economic and health-related quality of life outcomes represent conditions that are not yet present at time of transplantation but occur during the post-transplant trajectory. If conditions (e.g. diabetes mellitus) were present prior to or at time of transplantation, they were classified as condition-related correlates.

We distinguished between studies reporting any alcohol use versus at-risk drinking (i.e., drinking alcohol in amounts that could cause adverse health effects; defined as drinking >2 units per day for men and > 1 unit per day for women) [2], and correlates and outcomes were extracted accordingly.

Both the codebook and taxonomy on correlates and outcomes were developed iteratively, piloted and adapted until there was 100% consensus among the consortium partners.

Data extraction was again performed by two researchers independently, and inconsistencies resolved until there was 100% agreement on the data extracted.

### 2.4. Quality of reporting

Quality assessment was performed by two reviewers independently using an adapted version of previously published quality evaluation checklists [20,21]. The quality of each study was rated in terms of definitions provided, sampling strategies, sample sizes, methodological strength, completeness of data reporting and reproducibility. Each of the 14 quality criteria are reported separately and no total score was calculated, as not all criteria were applicable to all studies.

### 2.5. Data analysis and synthesis

Study characteristics were summarized by descriptive statistics as appropriate (i.e., percentages, median, or mean depending on the measurement level and distribution of the data). An effect size, expressed as odds ratio (OR) with 95% confidence interval, was calculated for each

correlate or outcome of any alcohol use or at-risk drinking investigated by at least five independent studies. An online effect size calculator was used to facilitate the computation of effect size types per publication (i.e. standardized mean difference, correlation coefficient, odds ratio and risk ratio, depending on the input data available) [22]. All effect size types were subsequently transformed into odds ratios, after which a pooled OR was calculated under a random-effects model across all contributing studies using SAS® [23]. Effect sizes were calculated by two researchers independently and compared afterwards. For each statistically significant pooled OR, the fail-safe N was calculated to evaluate the impact of publication bias (i.e., studies with statistically significant findings were more likely to be published) [24]. The fail-safe N represents the number of non-significant studies that would need to be added so that the pooled OR would no longer be statistically significant. The Q-test documenting heterogeneity (i.e. variability in effects among pooled studies), as well as the $I^2$ statistic with 95% confidence interval to describe the percentage of variation across studies that is due to heterogeneity rather than chance were also reported, as these statistics are suitable to describe heterogeneity across small sample studies [25]. If a correlate or outcome was assessed <5 times, an overview was produced, indicating the number of publications that showed a significant association with any post-transplant alcohol use or at-risk drinking.

## 3. Results

### 3.1. Sample size

After title and abstract screening, 513 of 5331 references were eligible for full text analysis. Excluding 4 companion papers, 2 duplicate publications and 431 papers that did not fulfill the inclusion criteria, data on correlates and outcomes from 76 studies were extracted and summarized (Fig. 1) [26–101].

### 3.2. Study characteristics

Given that 2 publications enrolled the same cohort of patients, but reported different findings [89,90], study characteristics and quality appraisal was reported for 75 unique studies only.

Except for 4 studies on kidney [31,36,55,100] and 1 study on lung transplant recipients [54], all studies examined correlates and outcomes of alcohol use in liver transplant populations (93.3%). About half of the studies were conducted in Europe (48%), followed by 33 studies from North America (44%), with only 5 studies coming from Asia (6.7%) and 1 from Australia (1.3%). The sample size across the 75 studies ranged from 6 to 834 (mean = 148.9; SD = 160.2), the average patient age was 48.9 years (SD = 6.5) (reported in 62 studies only), and a mean of 71.9% male patients (SD = 15.6) (reported in 65 studies) were included. At study enrollment, patients were on average 57.7 months post-Tx (SD = 23.1; range 21 to 108 months, reported in 39 studies only). Irrespective of the operational definition of alcohol use used, the mean percentage of patients consuming alcohol post-transplant was estimated at 23.6% (SD = 11.7; range 2.6%–52.8%; mean weighted for sample size 22.4%). At-risk drinking was estimated to occur in 15.1% of the patients (SD = 7.1; range 1.4–28%; mean weighted for sample size 13.5%).

### 3.3. Quality assessment

Fig. 2 illustrates the methodological quality of included studies. Although most studies described how they assessed alcohol use and at what time, they had methodological shortcomings in terms of: unclear definitions of correlates or outcomes, insufficient reporting of the psychometric properties of the instruments used to measure them, inappropriate sample sizes for the number of factors studied, incomplete description of the statistical analysis plan, and lack of a prospective design.

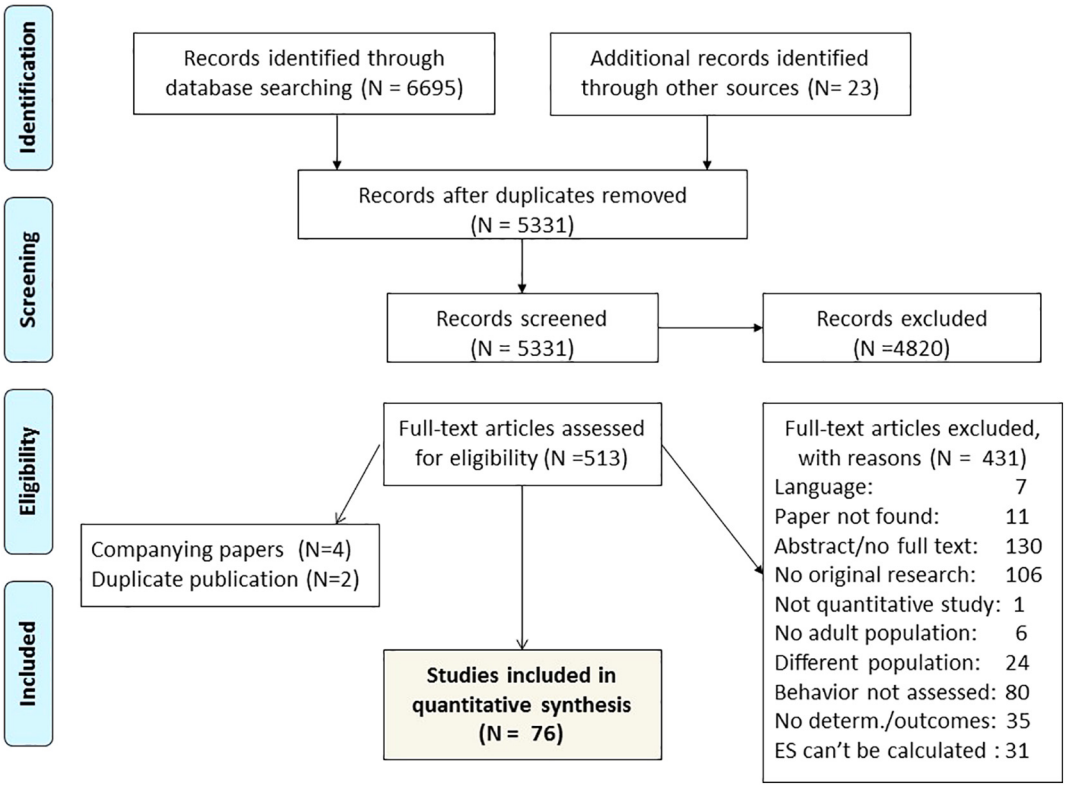


**Fig. 1.** Overview of included studies.

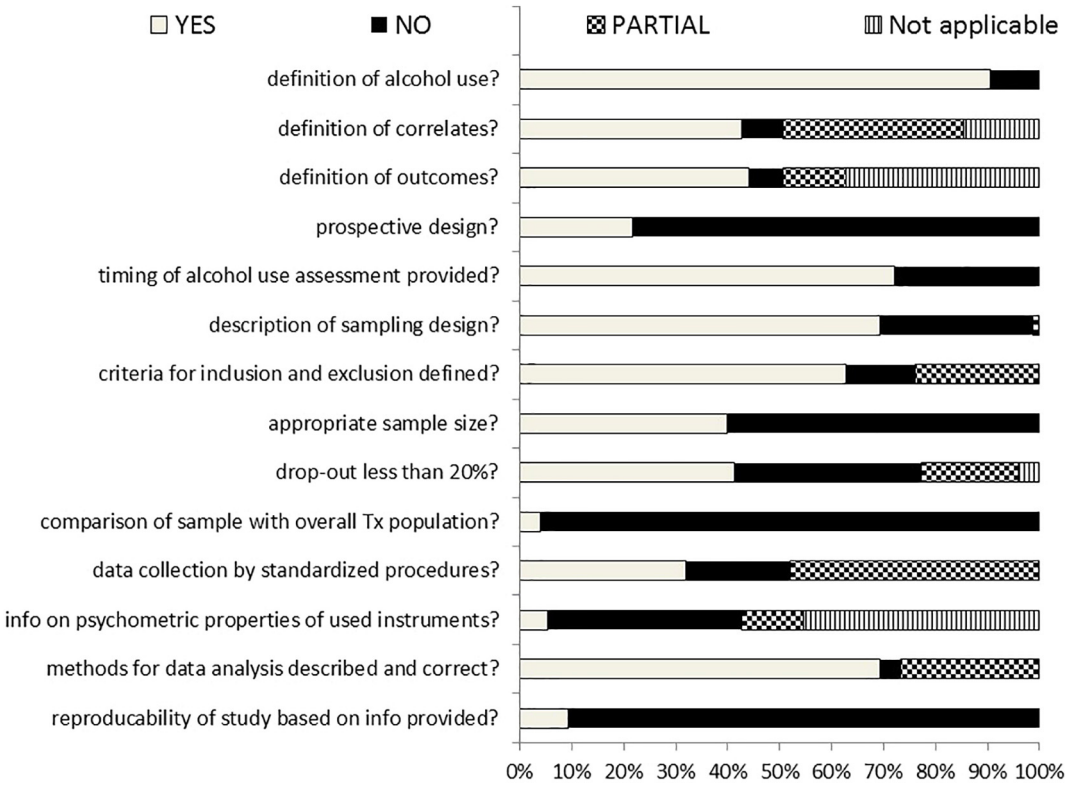


**Fig. 2.** Quality assessment.

### 3.4. Correlates of alcohol use

In total, 93 different correlates were investigated in relation to any post-transplant alcohol use, of which 36 were patient-related, 27 condition related, 17 social—/economic-related, 11 treatment-related and only 2 health-care team /system-related factors (Tables 2 and 3). Pooled effect sizes could be calculated for 19 correlates, of which 9 were significantly positively associated with any alcohol use post-transplant (Table 2), i.e. male gender, being employed post-transplant, smoking pre-transplant, smoking post-transplant, a history of illicit drug use, having first-degree relatives who have alcohol-related problems, sobriety of <6 months prior to transplant, a history of psychiatric illness, and having received treatment for alcohol-related problems pre-transplant.

Forty-seven correlates were investigated in relation to at-risk drinking, i.e. 14 condition-related, 13 patient-related, 11 social- /economic-related, 7 treatment-related correlates, and 2 factors related to the healthcare team or system (Tables 2 and 3). A pooled effect size could be calculated for 6 correlates, of which pre-transplant smoking was the only one being significantly associated with post-transplant at-risk drinking (Table 2).

Correlates of any alcohol use and at-risk drinking for which no pooled effect sizes could be calculated, are presented in Table 3.

### 3.5. Outcomes of alcohol use

Twenty-three outcomes were studied in relation to any alcohol use. None of the 3 outcomes for which a pooled effect size could be calculated was significantly associated with any post-transplant alcohol use (Table 2).

Similarly, out of 17 outcomes studied in relation to at-risk drinking, a pooled effect size could be calculated for one outcome, yet mortality was not significantly associated with post-transplant at-risk drinking. Outcomes for which no pooled effect size could be calculated are presented in Table 3.

## 5. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis that simultaneously assessed correlates and outcomes of post-transplant alcohol use in different single adult solid organ transplant populations. We had several key findings that are of importance for both research and clinical practice.

First, studies focused almost exclusively on correlates and outcomes of post-transplant alcohol use in liver transplant recipients. We could only include five studies on kidney or lung transplant patients, of which two did not had alcohol use as their prime focus [31,36]. This is not surprising, as alcoholic cirrhosis is among the leading indications for liver transplantation, and transplant teams remain concerned about the risk of alcohol use relapse. However, given that drinking alcohol is a common practice in the general population and that excessive alcohol use is the third most common risk factor for global disease burden [5], the lack of evidence on correlates of alcohol use and their impact on post-transplant outcome in other transplant populations is unexpected. A cross-sectional study revealed that about 9% of patients on the wait list for heart or lung transplantation drank above safety levels [102], a behavior that most likely will continue without follow-up. It remains to be investigated whether alcohol use, be it any use or at-risk drinking will affect graft outcomes in solid organ transplant groups other than liver transplantation. Several studies in our meta-analysis reported alcohol use and even at-risk drinking in patients undergoing liver transplantation for other indications, highlighting that regular assessment of alcohol use should be part of routine follow-up of all transplant patients both pre- and post-transplant, and irrespective of disease etiology. Self-report is still the prevailing assessment method, yet, specific attention should be given to maximize accuracy of alcohol use measures [103], in particular in populations without a known history of alcohol-related problems, as drinking patterns might be more benign and hence remain more hidden. Although this was not the purpose of the present review, our pooled prevalence of any alcohol use (23.6%) and at-risk drinking (15.1%) are consistent with prevalence rates previously documented in liver transplantation [13,14].

**Table 2**
Pooled odds ratios for correlates and outcomes of any alcohol use and at-risk drinking

| | Correlates | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Any alcohol use | | | | | | AT RISK DRINKING | | | | | |
| Social/economic | OR [95% CI] | N | Fail save N | Q ($p$-value) | $I^2$ (%) [95% CI] | References | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95% CI] | References |
| Age | 0.89 [0.69; 1.14] | 21 | – | 54.1; $P < .0001$ | 63.0 [40.8–76.9] | [60,79,90,27,29,45,46,55,56,62,64,67,70,77,80,81,83,84,88,92,100] | 0.77 [0.41; 1.46] | 10 | – | 68.5 $P < .0001$ | 86.9 [77.8–92.2] | [70,43–46,50,68,80,83,100] |
| Male gender | 1.57 [1.002; 2.45] | 24 | 0 | 165.2 P < .0001 | 86.1 [80.5–90.1] | [88–90,56,76,29,38,45–47,51,59,67,70,74,77–79,83–85,92,100] | 1.08 [0.65; 1.80] | 10 | – | 26.90 $P = .0015$ | 66.5 [34.6–82.9] | [69,42–46,50,69,70,100] |
| Lower education | 1.45 [0.99; 2.11] | 5 | – | 5.20 $P = .268$ | 23.1 [0.0–68.4] | [29,46,52,59,67] | – | – | – | – | | |
| Being married | 0.71 [0.50; 1.01] | 13 | – | 23.31 $P = .026$ | 48.5 [2.2–72.9] | [60,88,29,38,45,46,51,55,67,75,77,79,84] | 0.87 [0.38; 1.99] | 5 | – | 15.40 $P = .0036$ | 74.0 [35.3–89.6] | [44–46,68,69] |
| having social support | 0.50 [0.20; 1.22] | 6 | – | 23.7 $P = .0002$ | 78.9 [53.7–90.4] | [54,56,75,76,85,89] | – | – | – | – | | |
| Employed post-Tx | 1.46 [1.08; 1.99] | 9 | 0 | 15.03 $P = .06$ | 46.8 [0.0–75.4] | [80,29,45,46,51,52,55,96,100] | – | – | – | – | | |
| Patient-related | OR [95% CI] | N | Fail save N | Q (p-value) | $I^2$ (%) [95% CI] | References | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95% CI] | References |
| Post-Tx medication nonadherence | 2.81 [0.99; 7.98] | 7 | – | 31.42 P < .0001 | 80.9 [61.3–90.6] | [97,34,40,46,55,88,94] | – | – | – | – | – | |
| Illicit drug use pre-Tx | 1.95 [1.28; 2.98] | 10 | 2 | 12.03 $P = .212$ | 25.2 [0.0–63.9] | [76,39,41,48,56,65,67,76,79,83] | – | – | – | – | – | |
| Smoking pre-Tx | 1.67 [1.28; 2.18] | 5 | 1 | 5.22 $P = .265$ | 23.4 [0.0–68.7] | [45,51,75,89,100] | 1.74 [1.21; 2.49] | 5 | 0 | 8.04 $P = .09$ | 50.3 [0.0–81.8] | [45,63,68,69,100] |
| Smoking post-Tx | 2.11 [1.29; 3.45] | 6 | 1 | 15.53 $P = .008$ | 67.8 [23.5–86.5] | [31,51,52,55,80,100] | – | – | – | – | | |
| < 6 months sobriety pre-Tx | 1.89 [1.30; 2.75] | 28 | 15 | 88.83 P < .0001 | 68.5 [53.7–78.5] | [52,67,78,88,27,29,38,39,41,48,52,56,58,59,64,67,72,74–76,79,81,83–85,89,95,96] | 1.79 [0.99; 3.21] | 9 | – | 20.23 $P = .009$ | 60.5 [17.7–81.0] | [70,39,43,44,50,63,68,82,83] |
| Severity of alcohol use pre-Tx | 1.05 [0.66; 1.66] | 6 | – | 5.69 $P = .338$ | 12.1 [0.0–77.9] | [27,32,39,75,77,79] | – | – | – | – | | |
| Duration of alcohol use pre-Tx | 1.15 [0.73; 1.79] | 5 | – | 2.48 $P = .65$ | 0.0 [0.0–67.0] | [27,51,77,83,96] | – | – | – | – | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Family history of alcohol problems | 2.00 [1.11; 3.63] | 8 | 0 | 13.15 $P = .069$ | 46.8 [0.0–76.4] | [79,45,48,56,67,75,77,83] | – | – | – | – | | |

| Condition-related | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95%CI] | References | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95%CI] | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| History of pre-Tx psychiatric illness | 1.96 [1.12; 3.44] | 7 | – | 8.20 $p = .22$ | 26.8 [0.0–68.3] | [84,41,45,48,60,67,79] | – | – | – | – | | |
| Alcoholic cirrhosis diagnosis pre-Tx | 1.01 [0.62; 1.63] | 11 | – | 45.70 P < .0001 | 78.1 [61.2–78.7] | [91,30,32,46,70,72,75,93,94,97,99] | 2.71 [0.76; 9.68] | 7 | – | 36.69 P < .0001 | 83.6 [67.8–91.7] | [26,42,46,53,68,69,94] |
| Severity of disease at time of Tx | 0.99 [0.93; 1.05] | 5 | – | 2.31 $P = .68$ | 0.0 [0.0–64.6] | [27,29,62,74,89] | – | – | – | – | | |
| Higher pre-Tx risk scores | 1.28 [0.63; 2.61] | 6 | – | 10.38 $P = .065$ | 51.8 [0.0–80.9] | [41,51,60,74,84,101] | – | – | – | – | | |

| Treatment-related | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95%CI] | References | OR [95% CI] | N | Fail save N | Q | | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Having received pre-Tx treatment | 1.60 [1.12; 2.26] | 11 | 2 | 12.29 $P = .27$ | 18.6 [0.0–58.6] | [76,38,39,48,58,66,67,77,79,89] | – | – | – | – | | |

| Healthcare system-related | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95% CI] | References | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95% CI] | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | – | – | – | – | | | – | – | – | – | | |

| OUTCOMES | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95%CI] | References | OR [95% CI] | N | Fail save N | Q | $I^2$ (%) [95% CI] | References |
| Late acute rejection | 0.84 [0.66; 1.07] | 10 | – | 22.6 P = .001 | 60.2 [20.1–80.1] | [81,34,37,46,51,74,88,92,97,100] | – | – | – | – | – | |
| Survival time | 1.18 [0.81; 1.70] | 9 | – | 22.6 $P = .004$ | 64.6 [27.5–82.7] | [79,40,51,58,65,84,86,92,100] | – | – | – | – | – | |
| Mortality | 1.14 [0.79; 1.66] | 26 | – | 69.6 P < .0001 | 62.6 [43.4–75.3] | [41,65,79,29,35,37,38,45,56,58–60,66,71–74,76,80,84,86,88,89,92,94,100] | 1.96 [0.98; 3.91] | 10 | – | 32.75 P < .0001 | 72.5 [47.9–85.5] | [81,41–45,53,68,91,94,100] |

**Table 3**
Correlates and outcomes of any alcohol use and at-risk drinking investigated <5 times.

| Correlates investigated < 5 TIMES | | | | |
|---|---|---|---|---|
| | Social- and economic related correlates | | | |
| Times studied | Any alcohol use | Significant associations | At-risk alcohol use | Significant associations |
| 4 times | Pre-Tx employment [51,67,79,83] | 0/4 | – | |
| 3 times | – | | – | |
| 2 times | Non-white ethnicity [68,78] | 0/2 | Pre-Tx employment [68,69] | 0/2 |
| | Living arrangements [51,84] | 1/2 | | |
| 1 time | Non-Swiss nationality [55] | 0/1 | Non-white ethnicity [68] | 0/1 |
| | Having children [45] | 0/1 | Having children [45] | 0/1 |
| | Living with donor [51] | 0/1 | Pre-Tx type of profession [44] | 0/1 |
| | Pre-Tx type of profession [59] | 0/1 | Family instability [39] | 0/1 |
| | Absence of post-Tx disability [52] | 1/1 | Social instability [83] | 0/1 |
| | Family instability [39] | 0/1 | Financial status [68] | 1/1 |
| | Financial status [75] | 0/1 | Lack of stable housing [69] | 0/1 |
| | Having a life insurance [56] | 0/1 | | |
| Patient related correlates | | | | |
| 4 times | Alcohol relapse pre-Tx [52,66,77,90] | 2/4 | | |
| | Not admitting alcohol problem pre-Tx [39,63,79,90] | 3/4 | | |
| 3 times | Appointment nonadherence post-Tx [34,46,51] | 1/3 | | |
| 2 times | Having meaningful activities pre-Tx [45,56] | 1/2 | Not admitting alcohol problem pre-Tx [63,69] | 2/2 |
| | Pre-Tx nonadherence [79,90] | 1/2 | | |
| | Post-Tx nonadherence (unspecified) [38,60] | 2/2 | | |
| | Number of weaning attempts pre-Tx [77,83] | 1/2 | | |
| | History of driving under influence [56,79] | 0/2 | | |
| | Legal conviction for alcohol use [75,78] | 0/2 | | |
| | Emotional stability as a personality trait [85,98] | 2/2 | | |
| 1 time | Coping style [55] | 0/1 | Having meaningful activities pre-Tx [69] | 1/1 |
| | Pre-Tx benzodiazepine use [38] | 0/1 | Severity of smoking pre-Tx [69] | 1/1 |
| | Post-Tx benzodiazepine use [38] | 0/1 | Alcohol relapse pre-Tx [77] | 1/1 |
| | Reluctance to participate in treatment programs pre-Tx [90] | 0/1 | Age at start drinking alcohol [80] | 1/1 |
| | Age at start drinking alcohol [77] | 0/1 | Age at start heavy drinking [80] | 1/1 |
| | Time of the day of first alcoholic drink [83] | 1/1 | Number of weaning attempts pre-Tx [83] | 1/1 |
| | Continued drinking after diagnosis [90] | 1/1 | Legal conviction for alcohol use [68] | 0/1 |
| | Family admitting patient's alcohol problems [39] | 1/1 | Increased personal stressors post-Tx [68] | 1/1 |
| | Remembering having received advice to stop drinking pre-Tx [94] | 0/1 | Post-Tx depressive symptoms [68] | 0/1 |
| | Lack of behavioral consequences if drinking again [90] | 1/1 | Poor intention to adhere [69] | 1/1 |
| | Continued participation in activities with exposure to alcohol [90] | 1/1 | | |
| | Busy lifestyle post-Tx [55] | 0/1 | | |
| | Pre-Tx depressive or anxiety symptoms [79] | 0/1 | | |
| | Post-Tx depressive symptoms [55] | 1/1 | | |
| | Poor stress management skills [90] | 1/1 | | |
| | Poor self-esteem [90] | 1/1 | | |
| | Having a routine in life [55] | 0/1 | | |
| | Unable to identify substitute for drinking [90] | 1/1 | | |
| Condition related factors | | | | |
| 4 times | Hepatitis C co-infection [28,61,67,93] | 1/4 | | |
| 3 times | Type of alcoholic liver disease [39,41,45] | 0/3 | Hepatitis C co-infection [42,44,68] | 0/3 |
| | | | Post-Tx BMI [46,80,100] | 0/3 |
| | | | Diabetes pre-Tx [46,80,100] | 0/3 |
| | | | Post-Tx hypercholesterolemia [46,80,100] | 1/3 |
| 2 times | Relationship with donor [29,51] | 0/2 | Type of alcoholic liver disease [45,69] | 0/2 |
| | Post-Tx BMI [46,80] | 0/2 | History of cancer [43,68] | 0/2 |
| | Diabetes pre-Tx [46,80] | 0/2 | Post-Tx hypertension [46,100] | 0/2 |
| | Post-Tx hypercholesterolemia [46,80] | 1/2 | | |
| 1 time | Active alcoholic liver disease at Tx [76] | 0/1 | Post-Tx psychiatric disorder [68] | 0/1 |
| | Etiology of end-stage lung disease [54] | 0/1 | Hepatitis C as primary cause of liver disease [46] | 0/1 |
| | Hepatitis C as primary cause of liver disease [46] | 0/1 | History of cardiovascular disease [100] | 0/1 |
| | History of cancer [90] | 0/1 | Mallory bodies in the native liver [42] | 0/1 |
| | Liver cirrhosis complications pre-Tx [29] | 0/1 | Steatosis in the native liver [42] | 1/1 |
| | Pre-Tx waiting time [74] | 0/1 | Histologic features of alcohol use in the native liver [42] | 0/1 |
| | Post-Tx hypertension [46] | 0/1 | | |
| | Pre-Tx red and white blood cells [62] | 0/1 | | |
| | Pre-Tx bilirubin [62] | 0/1 | | |
| | Pre-Tx platelets [62] | 0/1 | | |
| | Pre-Tx creatinine [62] | 0/1 | | |
| | Post-Tx co-morbidity [55] | 0/1 | | |
| | Hemoglobin [62] | 0/1 | | |
| | Albumin [62] | 0/1 | | |
| | Mallory bodies in the native liver [74] | 0/1 | | |
| | Steatosis in the native liver [74] | 0/1 | | |
| | Histologic features of alcohol use in the native liver (0/1) [74] | 0/1 | | |

**Table 3** (*continued*)

| Times studied | Any alcohol use | Significant associations | At-risk alcohol use | Significant associations |
|---|---|---|---|---|
| **Correlates investigated < 5 TIMES** | | | | |
| | **Social- and economic related correlates** | | | |
| **Treatment-related correlates** | | | | |
| 4 times | | | | |
| 3 times | Having received post-Tx treatment for alcohol problem [38,89,90] | 2/3 | Era/year of transplant [44,50,69] | 2/3 |
| 2 times | Time since Tx [79,83] | 1/2 | Proliferation inhibitor use [46,100] | 0/2 |
| | Compliance contract signed pre-Tx [59,76] | 0/2 | Steroid use [46,100] | 0/2 |
| | | | Time since Tx [69,82] | 1/2 |
| 1 time | Tacrolimus-based regimen [46] | 0/1 | Calcineurin inhibitor use [100] | 0/1 |
| | Cyclosporine-based regimen [46] | 0/1 | Tacrolimus-based regimen [46] | 0/1 |
| | Proliferation inhibitor use [46] | 0/1 | Cyclosporine-based regimen [46] | 0/1 |
| | Steroid use [46] | 0/1 | | |
| | Received treatment for alcohol problem both pre- and post-Tx [89] | 1/1 | | |
| | Received care from mental health professional pre-Tx [51] | 1/1 | | |
| | Having received care from mental health professional post-Tx [51] | 0/1 | | |
| **Healthcare team- and system-related correlates** | | | | |
| 4 times | Tx era evaluating the impact of healthcare system change on alcohol use [29,33,34,38] | 3/4 | | |
| 3 times | | | | |
| 2 times | | | | |
| 1 time | Lack of consensus within team whether patient is suitable Tx candidate [45] | 0/1 | Late referral for Tx [69] | 1/1 |
| | | | Lack of consensus within team whether patient is suitable Tx candidate [69] | 1/1 |

| | Any alcohol use | Significant associations | At-risk alcohol use | Significant associations |
|---|---|---|---|---|
| **OUTCOMES** | | | | |
| 4 times | Retransplantation [37,70,88,92] | 0/4 | | |
| | Biopsy proven fatty changes/steatosis [74,80,94,99] | 1/4 | | |
| 3 times | Kidney function (GFR) [57,80,100] | 2/3 | Non-skin cancer [43,49,80] | 0/3 |
| 2 times | Chronic rejection [92,97] | 1/2 | Kidney function (GFR) [80,100] | 1/2 |
| | Graft loss [88,100] | 1/2 | Biopsy proven fatty changes/steatosis [43,94] | 0/2 |
| | Non-skin cancer [37,80] | 0/2 | Recurrent cirrhosis [50,80] | 1/2 |
| | Liver function [32,100] | 1/2 | Liver fibrosis [80,94] | 1/2 |
| | Liver fibrosis [80,94] | 0/2 | Portal inflammation/infiltration [91,94] | 1/2 |
| 1 time | Graft survival [88] | 0/1 | Chronic rejection [43] | 0/1 |
| | Biliary complications [88] | 1/1 | Graft survival [100] | 0/1 |
| | Metabolic syndrome [100] | 1/1 | Graft loss [100] | 0/1 |
| | Skin cancer [36] | 0/1 | Serious clinical events unspecified [43] | 0/1 |
| | Cardiovascular disease [37] | 0/1 | Metabolic syndrome [100] | 1/1 |
| | Neurological disease [37] | 0/1 | Inflammation [100] | 0/1 |
| | Inflammation [100] | 0/1 | Infection [43] | 0/1 |
| | Infection [37] | 0/1 | Liver function [100] | 0/1 |
| | Newly onset diabetes [100] | 1/1 | Newly onset diabetes [100] | 1/1 |
| | Recurrent cirrhosis [43] | 0/1 | Health-related quality of life [82] | 0/1 |
| | Portal inflammation/infiltration [94] | 0/1 | | |
| | Health-related quality of life [41] | 1/1 | | |

Second, our study is the first to disentangle any post-transplant alcohol use from at-risk drinking. A large number of correlates have been explored in relation to any alcohol use (i.e. 93 correlates), yet for only 19 (20.2%) a pooled effect size could be calculated, of which 9 factors showed a significant association with post-transplant alcohol use. Our results coincide with previous studies that focused on psychiatric risk profiles of pre-Tx alcohol use [104], showing that patients with mental health problems and patients with other addiction problems (smoking, illicit drug) require close monitoring and appropriate supportive interventions. Pre-Tx treatment might indicate more severe alcohol use. It remains unclear, however, whether patients attending pre-transplant treatment programs were successful in giving up alcohol use completely prior to transplant or whether supportive interventions were sustained post-transplant. These are two alternative hypotheses why a relationship between having received treatment pre-transplant and post-transplant alcohol use is observed. Although our findings and those of previous reviews demonstrate the relevance of the 6-months abstinence rule prior to (liver) transplant [11,12], a debate is ongoing within the literature on whether this rule should be abandoned for patients with a poor survival prognosis on the waiting list [105]. Rather than debating the pre-transplant length of sobriety, our efforts should shift towards pre-transplant screening programs and support programs, not only for people with alcoholic liver disease, but also for all transplant candidates. If starting treatment already prior to Tx is not possible (e.g. because of the medical condition of the patient or the urgency of the Tx), professionals should make every effort to provide appropriate and sustainable support after Tx. Although successful alcohol treatment programs exist [106], they unfortunately have not yet been formally tested in pre- and post-transplant populations. In addition, our finding that patients returning to work are more prone to alcohol use or relapse post-transplant is intriguing, yet, it remains unclear whether this also results in poor outcomes. Epidemiologic studies outside the field of transplantation suggest that working post-transplant might induce higher stress, which might trigger alcohol use as a stress reliever [107,108], a hypothesis that merits further investigation in transplant populations also.

Third, although most correlates investigated in relation with at-risk drinking and for any alcohol use were similar, only pre-transplant

smoking was significantly associated with at-risk drinking post-Tx. This is surprising, given that most Tx centers nowadays urge patients to give up smoking prior to listing. On the other hand, similar to excessive alcohol use, smoking is an addiction, explaining why smoking and alcohol use might often go hand in hand. Alcoholic cirrhosis as an etiology of end-stage liver disease was not a significant predictor, which is surprising, as previous reviews often leave the impression that this population is particularly at-risk for relapse and/or problematic drinking post-transplant [12–14]. Not all studies clearly define alcohol use. Future studies should pay close attention to the operational definition, alongside using a valid assessment method to detect alcohol use, and investigate risk factors for different degrees of alcohol use severity. A more comprehensive approach in assessing risk factors is also needed, as most studies a) examine single or few correlates simultaneously, b) tend to focus on factors that cannot be changed (e.g. condition-related or demographic factors), c) did not use theoretical models to guide that selection of relevant drivers of the behavior under study, and d) ignore that factors related to the healthcare provider and healthcare setting might play perhaps a bigger role than patient-level factors.

Fourth, in contrast to most reviews focusing on correlates exclusively, we also examined outcomes. The current state-of-the-art evidence does not indicate that any drinking alcohol post-transplant places transplant patients at a higher risk for poorer post-transplant outcomes. This is surprising, giving that multiple studies describe the detrimental impact of alcohol use on mortality and morbidity, yet perhaps this might only be true for harmful drinking patterns. Unfortunately, we could not calculate a pooled effect size for most of the outcomes investigated, hence this conclusion should await of future studies that clearly distinguish between mild and severe alcohol use and take time since transplantation into consideration.

Our study had some limitations. First, our review might have missed potentially relevant studies, although the chances are low, given the systematic approach we used to screen the available literature, including checking the reference lists of retrieved studies. Second, no specific taxonomy currently exists to classify alcohol-use specific correlates. However, we classified correlates using the World Health Organization taxonomy for medication adherence correlates [19], and our taxonomy allows for comparison of risk factors for other health behaviors, including medication adherence, smoking and physical activity, that are currently investigated in 3 systematic reviews conducted in parallel with ours. Moreover, by classifying risk factors, one is able to immediately see opportunities for new research, as healthcare system related factors, for instance, have not been investigated in great detail in relation to post-transplant alcohol use. Third, for most correlates and outcomes, substantial heterogeneity can be noted (for which we used a random-effects pooling technique). Fourth the fail-safe N is often small, hence our results should be interpreted with caution as it is possible that there is publication bias in that studies with significant findings are more likely to be published. Finally, although many studies suffer from methodological shortcomings, we did not stratify our findings based on study quality. Rather, we use these insights as recommendations for future studies, including the need for prospective research with sufficiently large sample sizes that clearly describe their sample, appropriately define alcohol use, and use reliable and valid measurement methods for assessing correlates and/or outcomes.

In conclusion, our systematic review is highly innovative as it is the first to assess both correlates and outcomes of post-transplant alcohol use not only in liver transplantation, but also in kidney, heart and lung transplantation. Our meta-analytic approach illuminates important avenues for further research and improvement of clinical care.

## Author contributions

Fabienne Dobbels: Participated in research design, performance of the research (design of search strategy, title and abstract screening, full text evaluation, data extraction), data analysis (effect size calculation), and wrote the paper.

Kris Denhaerynck: performance of the research (design of search strategy, title and abstract screening, full text evaluation, data extraction), data analysis (effect size calculation), and critical review of the paper

Mary Lou Klem: design of search strategy, programming of searches in different databases, feedback on methodology used to conduct the systematic review; critical revision of the paper

Susan M. Sereika: design of the Access databases for data input, advice on methodology to be used for effect size calculation, review of statistical analyses, and critical revision of the paper

Sabina De Geest: Participated in the design of the study, overall project management and quality control of methodology followed, and critical revision of the paper

Paolo De Simone: Participated in research design, performance of the research (design of search strategy, title and abstract screening, full text evaluation, data extraction), and critical revision of the paper

## Declarations of interest

None applicable to this submission

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