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ORIGINAL ARTICLE

Heart transplant outcomes in patients with substance use disorder history: a nationwide cohort study using high-dimensional propensity score matching

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Aims History of substance use is assessed in potential heart transplantation (HT) evaluations. The evidence base for this highly consequential practice, linking substance use disorders (SUDs) with poor post-transplantation outcomes, presents methodological limitations. We conducted a retrospective cohort study to address these limitations using high dimensional propensity score matching to compare HT outcomes of patients with and without SUDs.

Methods and results Key outcomes included mortality, hospitalization, and organ rejection rates, controlling for confounders. A national dataset of electronic health records of >120 million patients in the USA (2015–23) was used to identify HT patients with SUDs ($n = 808$) and controls ($n = 7066$), matched for medical comorbidities and demographic variables. Only after adjusting for sociodemographic and comorbidities of HT recipients, the results revealed no significant differences between groups with and without SUDs at 1 year in mortality [odds ratio (OR) = 0.96 (95% confidence interval, CI): 0.54, 1.69, $P = 0.88$], hospitalization [OR = 1.02 (95% CI: 0.83, 1.25), $P = 0.840$)], organ rejection rates [OR = 0.96 (95% CI: 0.78, 1.18), $P = 0.670$)], nor at 5 years in mortality [hazard ratio (HR) = 1.15 (95% CI: 0.82, 1.61), $P = 0.410$] and organ rejection [HR = 0.98 (95% CI: 0.84, 1.14), $P = 0.810$].

Conclusion Future studies must consider confounding factors when evaluating transplant criteria and outcomes in patients with SUDs.

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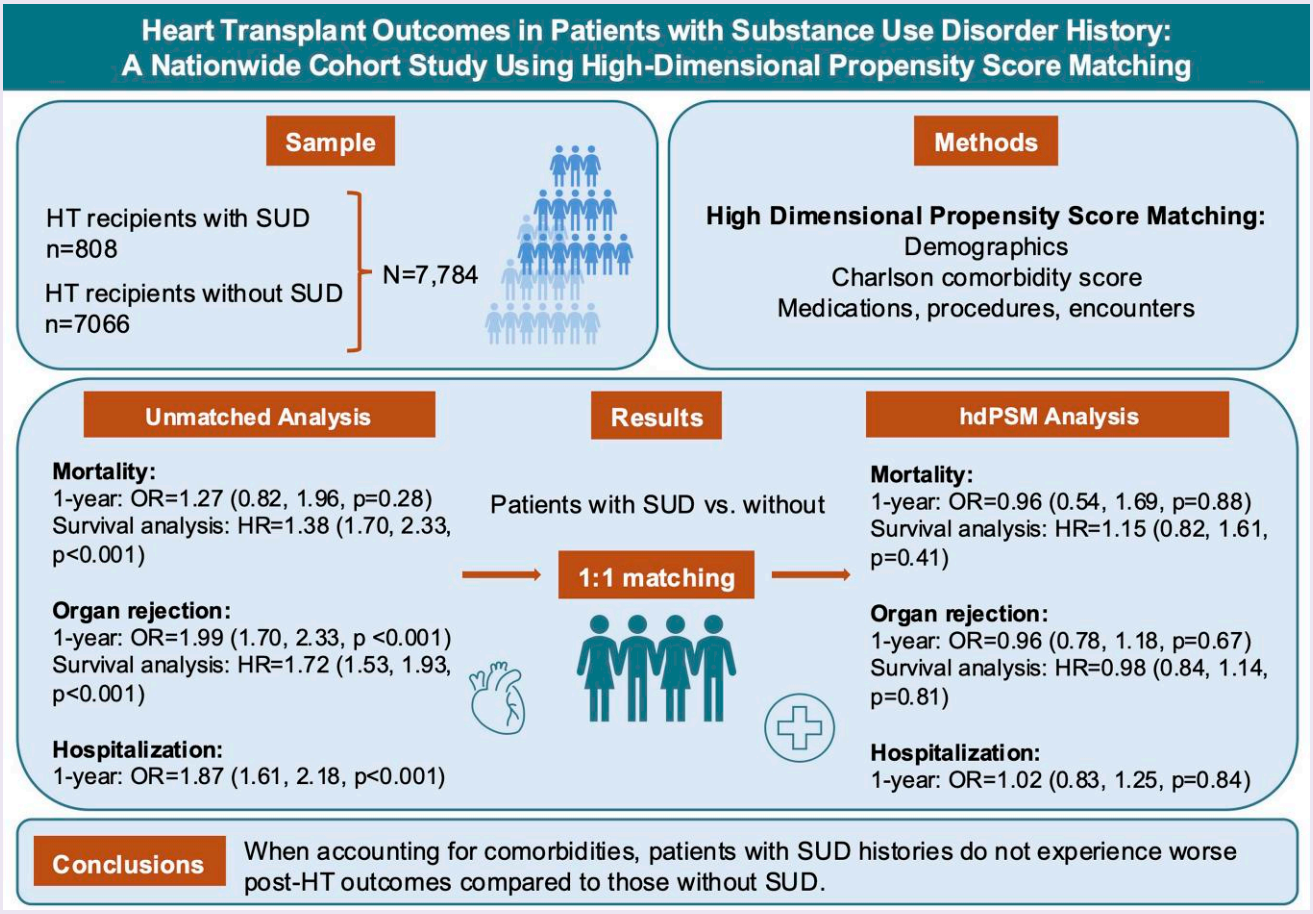
Graphical abstract



Keywords Heart transplant • Substance use disorder • Mortality • Hospitalization • Organ rejection rate

Key Learning Points

What is already known:

- Patients with a history of substance use disorders (SUDs) are often considered at higher risk for poor heart transplant (HT) outcomes.
- Existing studies linking SUD to adverse HT outcomes have shown conflicting results and often lacked proper adjustment for clinical and demographic confounders.
- SUD is frequently treated as a relative or absolute contraindication to HT, despite limited robust evidence.

What this study adds:

- In a large national cohort of 7874 HT recipients, patients with SUD had comparable short-term and long-term outcomes—including survival, hospitalization rates, and organ rejection—to those without SUD, when matched for medical comorbidities and demographic factors.
- These findings were only evident after applying high-dimensional propensity score matching, underscoring the importance of adequately accounting for medical comorbidities.
- Our findings challenge the assumption that a history of SUD alone predicts poor transplant outcomes and encourages more individualized, equitable transplant eligibility assessments.

Introduction

The success of heart transplantation (HT) hinges on numerous factors, particularly the selection of suitable candidates.[1,2] The International Society of Heart and Lung Transplantation (ISHLT) recognizes substance use as a potential risk factor for poor HT outcomes and, in its 2024 guidelines, has refined its recommendations to better address the complexities of substance use in transplant decision-making. These guidelines emphasize the importance of comprehensive evaluation of substance use behaviours and social determinants of health.[3] Yet, most transplant centres implement stringent eligibility criteria, often viewing recent active substance use as an absolute contraindication to HT.[2,4–6]

Potential recipients with substance use disorder (SUD) histories may be required to demonstrate a minimum of 6 months of abstinence before being placed on a HT recipient list, and even then, a history of SUD may reduce their likelihood for an eventual HT.[7–9] Such life-or-death clinical decisions are informed by multiple factors. Alcohol, tobacco, methamphetamine, and cocaine have established cardiac risks, with significant concerns also reported for opioids, cannabis, and prescription stimulants.[10] Additionally, individuals with SUDs may be perceived by clinicians as less reliable and having difficulties adhering to post-HT protocols.[4,7,11] Some studies support these perceptions, linking SUDs to difficulties in medical regimen adherence and inadequate self-care, as well as increased risk of post-HT morbidity and mortality.[2,12–14]

However, evidence linking SUD history with poor transplant outcomes present some shortcomings. Many studies have employed small sample sizes and have methodological limitations,[15–19] including a failure to account for key confounding factors when assessing HT outcomes in patients with SUDs.[12–14] Associations between SUDs and adverse post-HT outcomes might reflect the greater medical complexity of patients with SUDs, as opposed to substance use itself.

To address these concerns, we performed a retrospective cohort study to examine whether selected patients whose SUD did not preclude them from receiving a HT had different post-HT outcomes when compared with well-matched patients without a history of SUD. To account for the variability within different sets of guidelines across HT centres, we examined a large-scale national database encompassing diverse US healthcare systems, providing a large representative sample. Key outcomes included mortality/survival, hospitalization, and organ rejection rates using high dimensional propensity score matching (hdPSM) to control for multiple clinical and demographic variables.

Methods

Study setting

We conducted a retrospective cohort study utilizing electronic health records (EHRs) from Eos, a nationally representative dataset on the Atropos Evidence Network[20,21] (January 2015–December 2023). This database comprises de-identified, aggregated and standardized EHR data from various sources, encompassing >120 million patients across the USA. It draws from various EHR systems, including data from >2000 outpatient and ambulatory health centres, >500 hospitals, and >30 health systems, such as academic medical centres, providing an extensive overview of healthcare activities, including HT transplantation. Patient demographics reflect major geographical trends.[22] The EHR data were aligned with the Observational Medical Outcomes Partnership Common Data Model version 5.3, and used standardized vocabularies such as the Anatomical Therapeutic Chemical classification system, RxNorm, the International Classification of Diseases, tenth revision (ICD-10), and LOINC for patient and condition identification. The study was reviewed and approved by the Stanford Health Care (SHC) Institutional Review Board, which granted a waiver for informed consent for the use of EHR data (protocol #76042, January 2024). This research adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Guidelines.[23]

Sample

The study cohort comprised HT patients with and without a history of SUD who were deemed eligible for transplantation. Their eligibility was determined based on centre-specific criteria, which vary across institutions and encompass both medical and psychosocial factors. These factors included considerations such as the patients' readiness for transplantation, ability to manage their illness, available social support, psychological stability, and lifestyle. The exposed group had a positive history of SUD (i.e. alcohol, cannabis, tobacco, cocaine, hallucinogens, inhalants, opioids, other psychoactive substances, other stimulants, sedative hypnotic anxiolytics) and was identified via standardized codes from the ICD-10 (see Supplementary material online, *Table S1* for standardized code definitions). Such patients were required to have a diagnosis of SUD in the 1 year prior to transplant status. The control group had no history of SUD.

Outcomes

We evaluated three key outcomes related to HT: (i) mortality/survival, (ii) organ rejection, and (iii) hospitalization (see Supplementary material online, *Table S1* for standardized ICD-10 codes). Short-term outcomes, including mortality, organ rejection, and hospitalization, were assessed within 1-year post-transplantation. For long-term outcomes, survival and organ rejection were analysed in a Kaplan–Meier analysis.

Statistical analysis

We used odds ratios (ORs) to compare mortality, hospitalization, and organ rejection events between patients with and without SUDs at 1 year.[24] We computed cox proportional hazard ratios (HRs) to compare mortality and organ rejection occurrences between SUDs and the control group of non-SUD HT patients, accounting for missing data and lost to follow-up (LTFU). Patients were required to have at least 1 year of follow up and were followed to the end of their available data with right-censoring for the survival analysis. *P*-values, and, for statistically significant *P*-values, *E*-values were reported for each outcome to determine the robustness of the association observed against potential unmeasured confounders, indicating how strong an unmeasured confounder would need to be associated with both the exposure and outcome to fully account for the observed effect in our study.[25] A higher *E*-value suggests that the observed association is less likely to be due solely to unmeasured confounders.[25]

Pre-treatment confounders included demographics, ICD-10 diagnosis codes, current procedural terminology procedure codes, prescription medication codes (RX), the Charlson comorbidity index, and healthcare utilization measures (e.g. number of encounters in the year prior to transplant) (see *Table 1*). The Charlson comorbidity score is used to estimate a patient's 1-year mortality risk by accounting for the number and severity of comorbid conditions.[26] This scoring system incorporates 17 comorbidities, each weighted based on their potential impact on mortality, along with the patient's age, to provide a measure of mortality risk. The Charlson score has been essential in epidemiological research for evaluating patient health, particularly due to its compatibility with ICD-10 billing codes. In our study, we employed the most widely used method to calculate the Charlson score using updated weights and definitions,[27,28] which has demonstrated strong predictive power for in-hospital mortality with a *C*-statistic of 84%.[27]

To account for potential confounders, we initially employed a 1:1 matching strategy based on age and sex for the HT-SUD group and the control group. Additionally, we utilized high dimensional propensity scores (hdPS)[29] fitted to a propensity score model, which included the initial baseline confounders mentioned above. The hdPS was used to generate a composite measure of baseline confounders, ensuring that, when balanced within a calliper of 0.25, the groups were comparable. The hdPS covariate model was constructed using logistic regression with regularization, which minimizes the weights of less significant variables to zero, resulting in a streamlined model with robust predictive accuracy without overfitting in a high dimensional context. Statistical analyses were conducted using R version 4.2, with a two-sided *P*-value of 0.05 indicating statistical significance.

Table 1 Cohort characteristics of heart transplant recipients with and without a history of substance use disorder before and after high dimensional propensity score matching

	HT recipient without SUD	HT recipient with SUD[a]	HT recipient without SUD hdPS matched	HT recipient with SUD[a] hdPS matched
N	7066	808	803	803
Female, *n* (%)	2275 (32.2%)	202 (25.0%)	211 (26.3%)	200 (24.9%)
Mean age, years (SD)	54.8 (15.0)	52.4 (13.1)	52.1 (14.9)	52.5 (13.0)
18–29	709 (10.0%)	62 (7.7%)	97 (12.1%)	59 (7.3%)
30–39	530 (7.5%)	91 (11.3%)	70 (8.7%)	90 (11.2%)
40–49	918 (13.0%)	135 (16.7%)	142 (17.7%)	135 (16.8%)
50–59	1590 (22.5%)	254 (31.4%)	200 (24.9%)	254 (31.6%)
60–69	2436 (34.5%)	226 (28.0%)	232 (28.9%)	225 (28.0%)
70–79	882 (12.5%)	40 (5.0%)	62 (7.7%)	40 (5.0%)
80–89	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Race, *n* (%)				
Other	3483 (49.3%)	355 (43.9%)	402 (50.1%)	353 (44.0%)
Caucasian	2702 (38.2%)	337 (41.7%)	291 (36.2%)	334 (41.6%)
Black	627 (8.9%)	92 (11.4%)	81 (10.1%)	92 (11.5%)
Asian	254 (3.6%)	24 (3.0%)	29 (3.6%)	24 (3.0%)
Hispanic	256 (3.6%)	26 (3.2%)	32 (4.0%)	26 (3.2%)
Index year (%)				
2015–19	4517 (63.9%)	431 (53.3%)	459 (57.2%)	427 (53.2%)
2020–24	2549 (36.1%)	377 (46.7%)	344 (42.8%)	376 (46.8%)
Mean pre-index days (SD)	3547.9 (3875.8)	3645.2 (3843.0)	3472.8 (3926.0)	3634.7 (3848.8)
Mean follow up days (SD)	1248.2 (875.0)	1087.6 (795.3)	1118.4 (826.2)	1088 (796.4)
Number of encounters (SD)	4.4 (5.6)	9.5 (7.0)	8.9 (6.7)	9.4 (7.0)
Baseline SUD (%)				
Alcohol	0 (0%)	244 (30.2%)	0 (0%)	240 (29.9%)
Cannabis	0 (0%)	173 (21.4%)	0 (0%)	169 (21.1%)
Cocaine	0 (0%)	43(5.3%)	0 (0%)	43 (5.4%)
Hallucinogen	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)
Inhalants	0 (0%)	1 (0.1%)	0 (0%)	1 (0.1%)
Nicotine	0 (0%)	379 (46.9%)	0 (0%)	376 (46.8%)
Opioids	0 (0%)	101 (12.5%)	0 (0%)	99 (12.3%)
Other psychoactives	0 (0%)	118 (14.6%)	0 (0%)	115 (14.3%)
Other stimulants	0 (0%)	82 (10.2%)	0 (0%)	81 (10.1%)
Sedative hypnotic anxiolytics	0 (0%)	24 (3.0%)	0 (0%)	23 (2.9%)
Total Charlson comorbidity score (SD)	4.6 (3.2)	7.0 (4.8)	6.6 (3.5)	6.9 (4.7)
Itemized Charlson comorbidity (*n*, %)				
Malignancy	638.0 (9.0%)	112.0 (13.9%)	119.0 (14.8%)	108.0 (13.5%)
Metastatic solid tumour	134.0 (1.9%)	39.0 (4.8%)	34.0 (4.2%)	36.0 (4.5%)
Diabetes	2243.0 (31.7%)	343.0 (42.3%)	355.0 (44.2%)	338.0 (42.1%)
Diabetes complications[b]	1118.0 (15.8%)	221.0 (27.4%)	244.0 (30.4%)	218.0 (27.2%)
Congestive heart failure[b]	4208.0 (59.6%)	652.0 (80.7%)	656.0 (81.7%)	648.0 (80.7%)
Myocardial infarction[b]	1094.0 (15.5%)	297.0 (36.8%)	231.0 (28.8%)	295.0 (36.7%)
Peripheral vascular disease[b]	2709.0 (38.3%)	546.0 (67.6%)	537.0 (66.9%)	544.0 (67.8%)
Chronic pulmonary disease[c]	1387.0 (19.6%)	371.0 (45.9%)	265.0 (33.0%)	367.0 (45.7%)
Cerebrovascular disease[b]	1109.0 (15.7%)	258.0 (31.9%)	239.0 (29.8%)	255.0 (31.8%)

Continued

Table 1 *Continued*

	HT recipient without SUD	HT recipient with SUD[a]	HT recipient without SUD hdPS matched	HT recipient with SUD[a] hdPS matched
Dementia[b]	27.0 (0.4%)	23.0 (2.9%)	5.0 (0.6%)	22.0 (2.7%)
Hemi paraplegia[b]	117.0 (1.7%)	45.0 (5.6%)	39.0 (4.9%)	42.0 (5.2%)
Mild liver disease[b]	732.0 (10.4%)	221.0 (27.4%)	173.0 (21.5%)	216.0 (26.9%)
Severe liver disease[b]	158.0 (2.2%)	94.0 (11.6%)	52.0 (6.5%)	92.0 (11.5%)
Renal disease[b]	2849.0 (40.3%)	464.0 (57.4%)	481.0 (59.9%)	459.0 (57.2%)
Peptic ulcer disease[b]	165.0 (2.3%)	64.0 (7.9%)	39.0 (4.9%)	61.0 (7.6%)
Rheumatic disease	165.0 (2.3%)	34.0 (4.2%)	23.0 (2.9%)	32.0 (4.0%)
HIV[b]	13.0 (0.2%)	19.0 (2.4%)	5.0 (0.6%)	18.0 (2.2%)

hdPS, high dimensional propensity score; SD, standard deviation; SUD, substance use disorder.
[a]"Selected patients with SUD': patients with a history of SUD who were deemed eligible for transplantation. Their eligibility was determined based on centre-specific criteria, which vary across institutions and encompass both medical and psychosocial factors such as the patients' readiness for transplantation, ability to manage their illness, available social support, psychological stability, and lifestyle.
[b]Comorbidities with standardized mean difference >0.25 before hdPS,
[c]Comorbidity that stayed with standardized mean difference > 0.25 despite hdPSM.

Results

Demographic characteristics of heart transplant patients

The study analysed $n = 7874$ HT patients (SUD: $n = 808$, control: $n = 7066$); 68.5% were male, with a mean age of 54.6 years (SD = 14.9) (*Table 1*). Prior to hdPSM our analyses revealed higher rates of 13 out of 17 comorbidities in patients with a history of SUD vs. without SUD (*Table 1*). Following hdPSM analyses, the groups exhibited standardized mean differences ≤0.25 in nearly all variables (*Table 1*).

Mortality

Mortality at 1 year

One-year ORs for mortality showed no significant differences between the two groups across all analysis types: unmatched analysis [OR = 1.27 (95% confidence interval, CI: 0.82, 1.96, $P = 0.280$)], basic matched analysis [OR = 1.62 (95% CI: 0.84, 3.11, $P = 0.148$)], and hdPSM analysis [OR = 0.96 (95% CI: 0.54, 1.69, $P = 0.88$)] (*Table 2*).

Overall mortality—survival analysis

HRs for overall mortality were significantly greater in patients with SUD compared with those without SUD according to unmatched [HR = 1.38 (95% CI: 1.09, 1.76, $P = 0.009$)] and basic matched analyses [HR = 1.63 (95% CI: 1.15, 2.32, $P = 0.007$)] (*Table 3*). However, following hdPSM, mortality did not differ between SUD and controls [HR = 1.15 (95% CI: 0.82, 1.61, $P = 0.410$)] (*Figure 1*).

Organ rejection

Organ rejection within 1 year

One-year organ rejection in patients with SUD showed significantly higher rates compared with the control group across unmatched [OR = 1.99 (95% CI: 1.70, 2.33, $P < 0.001$)] and basic matched analyses [OR = 2.00 (95% CI: 1.60, 2.51, $P < 0.001$)], while hdPSM analyses revealed no differences between groups [OR = 0.96 (95% CI: 0.78, 1.18, $P = 0.670$)] (*Table 4*).

Table 2 One-year post-transplant mortality in patients with and without substance use disorders: unmatched, basic matched, and high dimensional propensity score matched odds ratios

	Negative	Positive	OR (95% CI)	*P*-value
Unmatched				
No SUD	6900	166	NA	NA
SUD[a]	784	24	1.27 (0.82, 1.96)	0.280
Basic matched				
No SUD	793	15	1.00 (1.00, 1.00)	NA
SUD[a]	784	24	1.62 (0.84, 3.11)	0.148
High dimensional propensity score matched				
No SUD	778	25	NA	NA
SUD[a]	779	24	0.96 (0.54, 1.69)	0.880

CI, confidence interval; NA, not applicable; OR, odds ratio; SUD, substance use disorder.
[a]"Selected patients with SUD': patients with a history of SUD who were deemed eligible for transplantation. Their eligibility was determined based on centre-specific criteria, which vary across institutions and encompass both medical and psychosocial factors such as the patients' readiness for transplantation, ability to manage their illness, available social support, psychological stability, and lifestyle.

Overall organ rejection—survival analysis

Overall organ rejection was significantly greater in patients with SUD compared with those without SUD across unmatched [HR = 1.72 (95% CI: 1.53, 1.93, $P < 0.001$)] and basic matched analyses [HR = 1.68 (95% CI: 1.42, 1.99, $P < 0.001$)] (*Table 5*). After controlling for confounders, hdPSM analysis revealed no significant differences between groups [HR = 0.98 (95% CI: 0.84, 1.14, $P = 0.81$)] (*Figure 2*).

Hospitalization

For hospitalization rates within 1 year, ORs were significantly higher for patients with SUDs compared with patients without in the unmatched

Table 3 Five-years survival analysis in patients with and without substance use disorders: unmatched, basic matched and high dimensional propensity score matched hazard ratios

	N	Events	HR (95% CI)	RMST (95% CI)	*P*-value	*E*-value
Unmatched						
No SUD	7066	544	NA	2718.6 (2702.8, 2734. 4)	NA	NA
SUD[a]	808	75	1.38 (1.09, 1.76)	2615.5 (2563.7, 2667.3)	0.009	1.4 (M)
Basic matched						
No SUD	808	54	NA	2747.2 (2704.3, 2790.1)	NA	NA
SUD[a]	808	75	1.63 (1.15, 2.32)	2615.5 (2563.7, 2667.3)	0.007	1.6 (M)
High dimensional propensity score matched						
No SUD	803	64	NA	2692.8 (2642.2, 2743.4)	NA	NA
SUD[a]	803	72	1.15 (0.82, 1.61)	2629.8 (2578.3, 2681.3)	0.410	NA

CI, confidence interval; HR, hazard ratio; M, medium; NA, not applicable; RMST, restricted mean survival time; SUD, substance use disorder.
[a]'Selected patients with SUD': patients with a history of SUD who were deemed eligible for transplantation. Their eligibility was determined based on centre-specific criteria, which vary across institutions and encompass both medical and psychosocial factors such as the patients' readiness for transplantation, ability to manage their illness, available social support, psychological stability, and lifestyle.

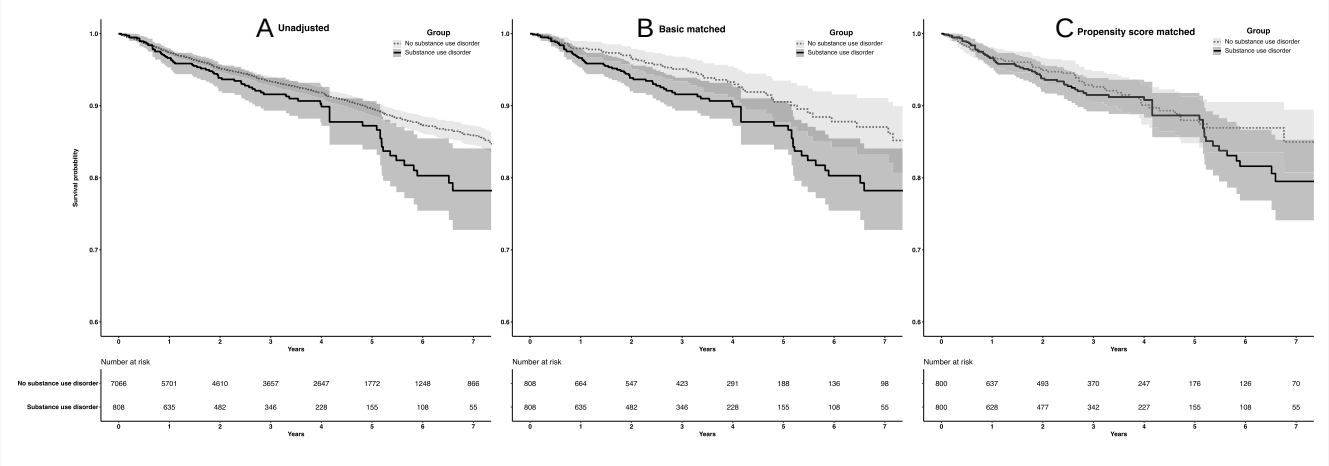


Figure 1 Survival analysis for mortality rates in selected patients with a substance use disorder and controls without a substance use disorder. Kaplan–Meier survival curves showing time to death in years. The numbers below the Kaplan–Meier curves represent the numbers of patients followed up and the numbers censored at each timepoint. (*A*) Unmatched analysis; (*B*) basic matched analysis; (*C*) high dimensional propensity score matched analysis.

[OR = 1.87 (95% CI: 1.61, 2.18, $P < 0.001$)] and basic matched analyses [OR = 1.81 (95% CI: 1.46, 2.25, $P < 0.001$)], with no significant differences observed in the hdPS-matched analysis [OR = 1.02 (95% CI: 0.83, 1.25, $P = 0.84$)] (*Table 6*).

Discussion

Our study contests the assumption that a history of SUD alone directly affects post-HT outcomes in individuals who demonstrated engagement to recovery by meeting their specific transplant site selection criteria. We observed that individuals with a history of SUDs exhibited significantly higher rates of multiple medical comorbidities, a well-documented phenomenon in this population.[30] After adjusting for sociodemographic and comorbidities of HT recipients, we observed, at 1- and 5-years post-HT, no significant differences in mortality, organ rejection, or hospitalization rates between patients with and without a history of SUD. While our study draws from a large, multi-centre US sample, the findings may not be generalizable to different healthcare systems with universal healthcare system coverage and population differences. Future research comparing outcomes across diverse international cohorts is warranted.

The literature on post-HT outcomes in patients with SUDs shows conflicting results. While some studies align with our findings, showing no significant differences in survival nor rejection rates between patients with and without SUD history,[12,13,31] others report poorer outcomes, including reduced survival, increased hospitalization, and higher rates of infection and graft failure.[15,16,32]

However, studies reporting poorer outcomes often fail to adequately adjust for confounding variables and typically limit adjustments to basic factors such as age and sex. A critical limitation in prior research is the inadequate control for medical comorbidities, particularly those

Table 4 One-year post-transplant organ rejection in patients with and without substance use disorders: unmatched, basic matched and high dimensional propensity score matched odds ratios

	Negative	Positive	OR (95% CI)	*P*-value	*E*-value
Unmatched					
No SUD	5643	1423	1.00 (1.00, 1.00)	NA	NA
SUD[a]	538	270	1.99 (1.70, 2.33)	<0.001	1.9 (M)
Basic matched					
No SUD	646	162	1.00 (1.00, 1.00)	NA	NA
SUD[a]	538	270	2.00 (1.60, 2.51)	<0.001	1.8 (M)
High dimensional propensity score matched					
No SUD	526	277	1.00 (1.00, 1.00)	NA	NA
SUD[a]	534	269	0.96 (0.78, 1.18)	0.670	NA

CI, confidence interval; M, medium; NA, not applicable; OR, odds ratio; SUD, substance use disorder.
[a]'Selected patients with SUD': patients with a history of SUD who were deemed eligible for transplantation. Their eligibility was determined based on centre-specific criteria, which vary across institutions and encompass both medical and psychosocial factors such as the patients' readiness for transplantation, ability to manage their illness, available social support, psychological stability, and lifestyle.

Table 5 Five-years post-transplant organ rejection in patients with and without substance use disorders: unmatched, basic matched and high dimensional propensity score matched hazard ratios

	N	Events	HR (95% CI)	RMST (95% CI)	*P*-value	*E*-value
Unmatched						
No SUD	7066	1993	NA	2065.9 (2037.3, 2094.5)	NA	NA
SUD[a]	808	324	1.72 (1.53, 1.93)	1693.9 (1599.4, 1788.5)	<0.001	2 (M)
Basic matched						
No SUD	808	231	NA	2056.4 (1971.7, 2140.9)	NA	NA
SUD[a]	808	324	1.68 (1.42, 1.99)	1693.9 (1599.4, 1788.5)	<0.001	1.9 (M)
High dimensional propensity score matched						
No SUD	803	331	NA	1625.9 (1532.6, 1719.1)	NA	NA
SUD[a]	803	323	0.98 (0.84, 1.14)	1690.1 (1595.3, 1785.0)	0.810	NA

CI, confidence interval; HR, hazard ratio; M, medium; NA, not applicable; RMST, restricted mean survival time; SUD, substance use disorder.
[a]'Selected patients with SUD': patients with a history of SUD who were deemed eligible for transplantation. Their eligibility was determined based on centre-specific criteria, which vary across institutions and encompass both medical and psychosocial factors such as the patients' readiness for transplantation, ability to manage their illness, available social support, psychological stability, and lifestyle.

captured by tools like the Charlson comorbidity index, which are known to significantly affect post-HT outcomes. Our study addresses this limitation by employing hdPSM and incorporating the Charlson comorbidity scoring system to account for these key factors such as diabetes, advanced age, poor hepatorenal function, and malignancy.[33–35] When controlling for these comorbidities, we found that post-HT outcomes were comparable between a pre-selected cohort of patients with SUDs who have shown adherence to their local HT eligibility protocol, (with non-harmonized criteria among centres—which tend to include active involvement in SUD treatment programs, maintained abstinence, and established support systems) and without SUDs, with similar health profiles. While our findings suggest that SUD itself is not an independent predictor of adverse post-HT outcomes, poorer HT outcomes were observed prior to hdPSM as has been reported in previous studies. These unadjusted differences may reflect the greater burden of medical comorbidities and psychosocial vulnerabilities commonly observed among individuals with SUD.[36,37] Altogether, this suggests that the poorer outcomes often attributed to substance use may reflect the broader health and social contexts of individuals with SUD, rather than the direct consequences of SUD.

Patients with SUDs are often judged on perceptions of clinicians regarding risk of relapse and compliance with medical regimen, which can make them less likely to be eligible or listed for transplantation.[7,9,17,38,39] However, studies indicate that the risk of relapse for patients with SUDs who are engaging in addiction treatment and maintaining some degree of recovery, is similar to that for other medical conditions such as diabetes, and hypertension, which can also be harmful to transplant outcomes.[40–43] Yet, despite similar relapse risks and potential for complications across these conditions, patients with SUDs face more scrutiny, stigma, and bias during the transplantation eligibility process. This disparity highlights an inconsistency in how risk factors are perceived and managed for patients with SUDs, which not only makes them less likely to be listed for HT but leads to stricter eligibility requirements that can delay their treatment and increase mortality.

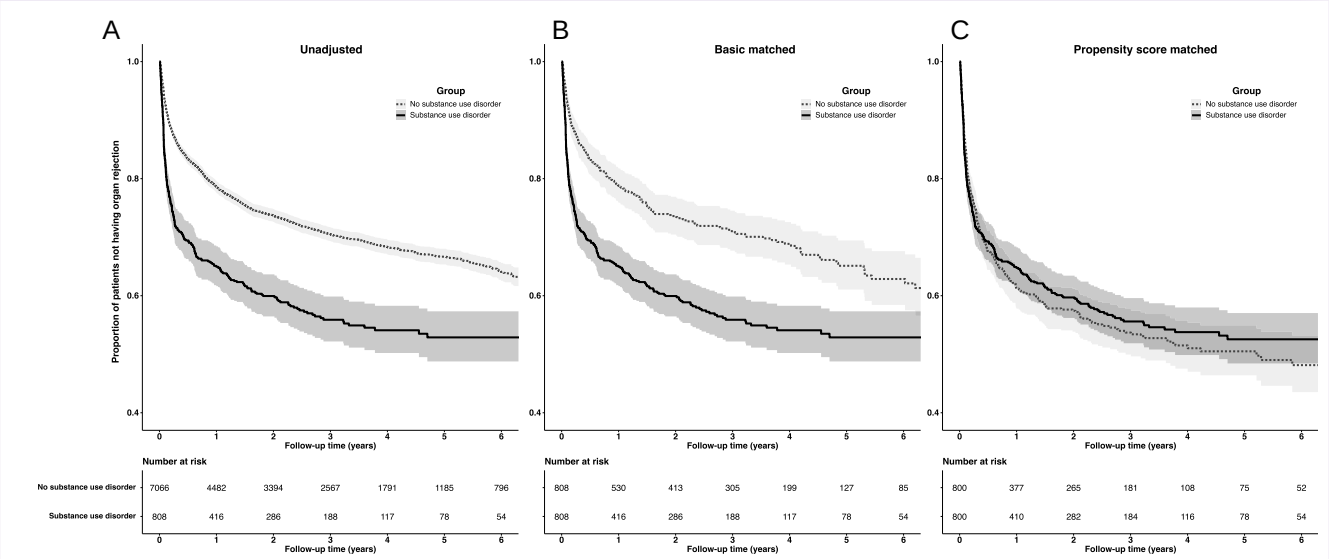


Figure 2 Survival analysis for organ rejection rates in selected patients with a substance use disorder and controls without a substance use disorder. Kaplan–Meier survival curves showing time to first organ rejection event, in years. The numbers below the Kaplan–Meier curves represent the numbers of patients followed up and the numbers censored at each timepoint. (*A*) Unmatched analysis; (*B*) basic matched analysis; (*C*) high dimensional propensity score matched analysis.

Table 6 One-year post-transplant hospitalization in patients with and without substance use disorders: unmatched, basic matched and high dimensional propensity score matched odds ratios

	Negative	Positive	OR (95% CI)	*P*-value	*E*-value
Unmatched					
No SUD	5358	1708	1.00 (1.00, 1.00)	NA	NA
SUD[a]	506	302	1.87 (1.61, 2.18)	<0.001	1.9 (M)
Basic matched					
No SUD	608	200	1.00 (1.00, 1.00)	NA	NA
SUD[a]	506	302	1.81 (1.46, 2.25)	<0.001	1.7 (M)
High dimensional propensity score matched					
No SUD	506	297	1.00 (1.00, 1.00)	NA	NA
SUD[a]	502	301	1.02 (0.83, 1.25)	0.840	NA

CI, confidence interval; M, medium; NA, not applicable; OR, odds ratio; SUD, substance use disorder.
[a]'Selected patients with SUD': patients with a history of SUD who were deemed eligible for transplantation. Their eligibility was determined based on centre-specific criteria, which vary across institutions and encompass both medical and psychosocial factors such as the patients' readiness for transplantation, ability to manage their illness, available social support, psychological stability, and lifestyle.

This is notable in the '6-month rule' requirement applied by most transplant centres before becoming eligible for transplantation.[39,44,45] While the rationale behind this rule is aimed at improving post-HT treatment adherence and outcomes, such as limiting the risk of relapse, it appears increasingly weak upon closer examination.[18,46]

The 6-month rule was initially intended to provide significant time for potential improvement in liver alcoholic transplant (to prevent premature intervention), but eventually evolved to be a surrogate marker for predictability of alcohol relapse.[47,48] A recent study investigating liver transplantation (LT) in patients with alcohol-related liver disease suggests that a longer period of abstinence is not necessarily associated with better outcomes, challenging the rationale behind this rule.[49] Moreover, one study, which did not require patients to adhere to a period of alcohol abstinence prior to LT and instead focused on structured psychosocial components, showed lower mortality on the waiting list and lower alcohol relapse rates.[50] This suggests that addressing this pre-transplantation criterion with more nuance, and focusing on post-HT support for comorbid conditions, can be beneficial for patients in need of life-saving care. As well, it suggests that patients with SUDs may face a higher risk of mortality associated with longer waiting lists due to a criterion supported by inconsistent evidence.[51] While more research is warranted on the efficacy of the 6-month abstinence rule, especially in the context of HT where the evidence is lacking, these evolving perspectives highlight the importance of reassessing traditional

eligibility criteria to ensure equitable access to life-saving interventions. Although our findings do not directly evaluate abstinence duration or relapse risk, they add to the evolving body of evidence suggesting that rigid pre-transplant criteria may oversimplify complex clinical pictures. The results support growing efforts, as reflected in guidelines such as the 2024 ISHLT update, to emphasize nuanced, individualized approaches when considering how broader health indicators of patients with SUD may impact post-HT outcomes.[3]

Some limitations are present and inherent to the study design. The study's retrospective design and the nature of EHR data limit the assessment of important potential factors, such as the mean length of sobriety before transplant and the prevalence of patients who relapsed post-HT, and more granular SUD-related risk profiles. Future research, particularly using prospective designs or linked registry data, is needed to address these important factors and compare outcomes between those who maintain abstinence and those who experience post-HT SUD relapse.

To identify SUD status, we required at least one outpatient diagnostic code within 12 months prior to transplant listing. While less stringent than definitions used in some studies, this approach was chosen to reduce selection bias in a population that is often less engaged with medical care, and thereby better reflect real-world patterns. Stricter criteria could risk excluding clinically relevant individuals though our relatively inclusive SUD criteria may have increased the variability in timing of diagnosis. Adherence to medications and treatments was also not directly measured in this study. However, our SUD cohort consisted of patients who satisfied local HT eligibility protocols (e.g. engagement in treatment, abstinence, and support systems) and thus may reflect a subset of individuals with SUD who demonstrate relatively higher adherence. The absence of direct adherence measures is a common limitation in studies using large-scale EHR data, where such behavioural and psychosocial variables are rarely captured.[52] Adherence following transplantation is a related but distinct issue that warrants consideration, and future research should explore its impact on post-HT outcomes. Although not available in our EHR dataset, transplant urgency (e.g. elective vs. emergent) is another potentially relevant variable that future studies should consider. While these limitations may affect the depth of analysis, our study provides useful information on key confounders when assessing the relationship between SUD and post-HT outcomes.

The 1-year LTFU rate (i.e. 15% in the SUD group and 16.5% in the non-SUD group) represents a potential source of bias; however, these rates are within acceptable limits for reporting ORs,[24] and the survival analysis, which accounts for attrition, yielded consistent results. That said, we were unable to investigate reasons for LTFU besides death. The study methodology was unable to distinguish between acute and chronic forms of rejection or graft failure, as the ICD-10 codes used do not capture diagnostic criteria or confirmatory procedures (e.g. confirmatory diagnostic procedures, such as tissue biopsy and laboratory findings) required to make this distinction. However, our use of short-term (≤1 year) and long-term (>1 year) follow-up periods aligns with common distinctions between acute and chronic rejection or graft failure,[53] helping to contextualize these outcomes despite coding limitations.

While we did not analyse post-transplant outcomes by specific substance categories (e.g. alcohol vs. opioids vs. nicotine), this approach aligns with current transplant society guidelines that emphasize a global assessment of substance use history.[3] Additionally, poly-substance use is highly prevalent in this population,[54] which may further limit the feasibility and generalizability of stratified analyses. Future research should nevertheless aim to disentangle the differential effects of specific substances, which may confer different post-transplant risks and thus warrant distinct clinical considerations. Finally, residual/unmeasured confounders could have also played a role.

In summary, our results indicate that HT patients with SUDs who are actively engaging in SUD treatment and early recovery do not experience worse post-HT outcomes compared with those without SUDs when accounting for their comorbidities. Given the rapid evolution of drug policies in America—such as the legalization of marijuana for medical use in 37 states—and the high prevalence of SUDs in the USA, ensuring a clearer understanding of how SUDs impact transplant outcomes is crucial, especially considering the life-saving potential of such intervention. Future research should prioritize identifying factors contributing to post-HT complications in this population and consider the length of pre-transplantation abstinence, which could provide valuable insights into the transplant selection process. Importantly, the field must address implicit and explicit biases against patients with SUDs who are frequently perceived as lacking self-control rather than being recognized as individuals coping with a medical condition to ensure they receive appropriate and equitable care.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

Author contributions

N.G., C.W.P., and A.L. had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept, design and supervision: N.G., D.J.-A., and A.L. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: K.E., P.L., K.T.G., and N.G. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: C.W.P. and G.H. Administrative, technical, or material support: N.G. and A.L.

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Data availability

The source data for this analysis can be made available upon request to the authors and with written approval from the source data vendors.

Consent

This study utilized de-identified electronic health record data. The research protocol was reviewed and approved by the Stanford Health Care (SHC) Institutional Review Board, which granted a waiver for informed consent for the use of EHR data (protocol #76042, January 2024).

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