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SYSTEMATIC REVIEW AND META-ANALYSIS OF THE CO-OCCURRENCE OF ATRIAL FIBRILLATION AND LIVER TRANSPLANTATION: A LETHAL COMBINATION

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ABSTRACT

INTRODUCTION: This systematic review and meta-analysis is aimed to evaluate the role of new-onset atrial fibrillation (NOAF) in patients after liver transplantation (LT) and determine the effect of NOAF on the incidence of mortality and graft rejection.

MATERIAL AND METHODS: Published studies until the end of April 15, 2023, were systematically searched in PubMed, Google Scholar, Scopus, Embase, Web of Science, and the Cochrane databases. Odds ratios (ORs) with 95% confidence intervals (CI) for mortality and graft rejection were extracted.

RESULTS: Five studies with a total of 4788 unique post-LT patients were included in the meta-analysis. Pooled analysis showed that mortality in patients with and without NOAF varied and amounted to 24.1% vs 12.5%, respectively (OR = 2.51; 95% CI: 1.92 to 3.27; $p < 0.001$). Moreover, pooled analysis showed that graft rejection in the NOAF cohort was 26.3%, and was higher vs patients without NOAF (13.1%; OR = 2.98; 95% CI: 2.14 to 4.15; $p < 0.001$)

CONCLUSIONS: Post-LT NOAF is associated with increased mortality and a higher risk of graft rejection. It is likely that the development of a standard procedure for early identification of NOAF, as well as to develop recommendations for specific treatment targeted at avoiding the impacts of the illness, could provide a mortality reduction and provide an increased rate of successful LT.

KEYWORDS: ATRIAL fibrillation; risk assessment; mortality; graft rejection; liver transplant

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INTRODUCTION

For individuals with end-stage liver disease or acute liver failure, liver transplantation (LT) is a life-saving treatment. In 2021, the number of liver transplants done in the United States reached a new high of 9,234, representing a continuing trend of steady growth [1]. LT is still considered to be one of the most dangerous noncardiac surgical operations, and despite major advances in surgical procedures and postoperative treatment, problems in the immediate and long-term postoperative periods remain prevalent. In the early postoperative period following a liver transplant, infection, and rejection have been described as important causes of death [2, 3]. However, severe cardiovascular events remain a prevalent cause of long-term morbidity and mortality [4]. In patients who have a limited physiological reserve, hemodynamic instability, systemic inflammation, and electrolyte imbalances all provide a considerable risk of perioperative cardiovascular morbidity and death [5, 6]. New-onset atrial fibrillation (NOAF), is the most common cardiovascular complication occurring in LT patients. New-onset atrial fibrillation is defined as AF that develops for the first time after LT in patients without a prior history of AF. Given the presence of increased sympathetic flow, perioperative hemodynamic alterations, and the frequent need for vasopressors following surgery, patients with LT are theoretically at a greater risk of developing NOAF [7]. A recent pooled investigation reported that the frequency of atrial fibrillation following surgery was 8.5%. New-onset atrial fibrillation is particularly troublesome in the initial post-LT period as it may result in high central venous pressure with the consequence of inadequate graft venous outflow [8]. Therefore, this systematic review and meta-analysis is aimed at evaluating the role of NOAF in patients after LT and determining the effect of NOAF on the incidence of mortality and graft rejection.

MATERIAL AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. The study protocol was developed a priori, and all authors agreed to follow the protocol, which was not modified throughout the study.

Literature search strategy

An online search was conducted independently by two reviewers (F.C. and M.P.) on April 15, 2023, in PubMed, Google Scholar, Scopus, Embase, Web of Science, and the Cochrane electronic databases to detect the studies to include in the meta-analysis. Discussion with a third reviewer settled any possible differences between reviewers (L.S.). We used the keyword string "new-onset atrial fibrillation" OR "new-onset atrial fibrillation" OR "NOAF" OR "postoperative atrial fibrillation" OR "atrial fibrillation" OR "AF" OR "arrhythmia" AND "liver transplant" OR "liver transplantation" OR "hepatic transplantation" OR "hepatic transplant". Additionally, reference lists and referencing publications from the included research were examined. To eliminate queue overlapping, only the most recent or intact reports by the same author were used. When two papers related to the same group of patients were available, the one with the most participants was utilized. EndNote (version X9, Clarivate Analytic) was used to handle all references and delete duplicates.

Study selection

We restricted our search to adult human studies: 1) comparing patients after LT with and without NOAF; 2) with accessible and essential data; and 3) published in English. Excluded studies met the following criteria: (1) did not present a comparison group; (2) reviews, conference abstracts, case reports, or case series.

Data extraction

The papers were evaluated by two reviewers (F.C. and N.L.B.) who extracted data from each article using a pre-defined, standardized data form. When the first conclusions were questionable, a third reviewer (L.S.) evaluated the literature. The following information was gathered from the studies: (1) initial author, publication date, and place of origin; (2) research design; (3) kind of participant group; (4) case numbers; (5) age and sex; and (6) outcomes.

Outcomes and definitions

Based on the available outcomes of the included studies, the following end-points were assessed:

1. impact of NOAF in patients undergoing LT on mortality;
2. impact of NOAF in patients undergoing LT on graft rejection.

New-onset atrial fibrillation was defined as the first diagnosis of AF within 30 days following LT in individuals with no electrocardiogram abnormalities at the time of transplantation and no previous histo-

ry of AF in the medical record. New-onset atrial fibrillation was defined as the first diagnosis of AF within 30 days following surgery in individuals who had no ECG abnormalities at the time of LT and no previous history of AF in the medical record. Graft failure was defined as patients who required re-transplantation or died as a result of initial graft rejection.

Assessment of study quality

Two reviewers (F.C. and M.P.) independently evaluated the risk of bias in the included studies. Any differences between reviewers were settled with the help of a third reviewer (N.L.B.). The Newcastle-Ottawa Scale (NOS) [10] was used to assess the likelihood of bias in individual cohort studies. NOS assesses the quality of research using three criteria: selection, comparability, and exposure. These three aspects received maximum ratings of 4, 2, and 3 stars, respectively. Studies with NOS ratings of 7 were deemed high-quality.

Statistical analysis

The RevMan (ver. 5.4; Cochrane Collaboration, Oxford, UK) was used for all statistical analyses. The Mantel-Haenszel technique was used to calculate the pooled prevalence. The results are displayed as forest plots with 95% confidence intervals (CIs) using odds ratios (ORs). For dichotomous data, the mean difference (MD) and 95% confidence interval are used. When data were presented as medians with an interquartile range, Hozo's algorithm was used to calculate estimated means and standard deviations [11]. The I^2 test was used to examine study heterogeneity, which was classified as low, moderate, or high when I^2 was $< 50\%$, 50–75%, or $> 75\%$, respectively [12]. If I^2 was $> 50\%$, the random-effects model was used; otherwise, the fixed-effects model was utilized. If there were more than 10 trials in a single meta-analysis, Egger's test and funnel plots were employed to analyze possible bias and run funnel plot tests for asymmetry to investigate potential publication bias. All p values were calculated using a two-sided test and were defined as < 0.05.

RESULTS

Classification

Figure 1 depicts the flowchart of the literature search. Our search identified 418 articles, of which 5 remained after screening, that included a total of 4788 unique post-LT patients [13–17]. The number

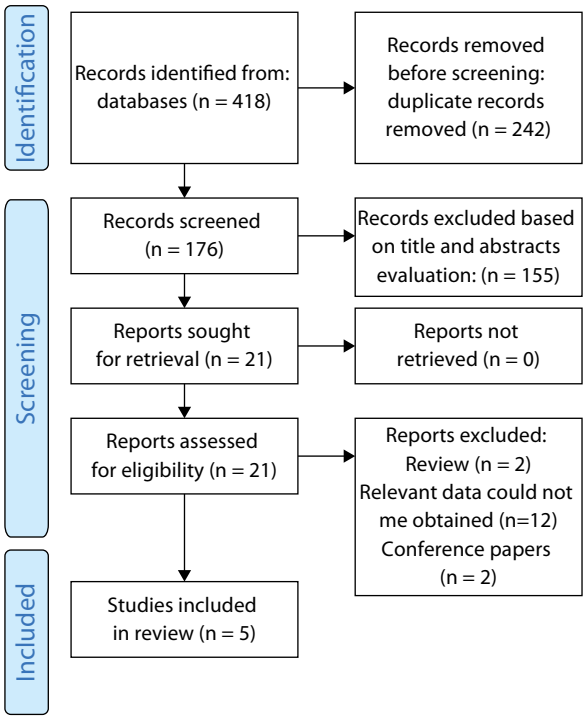

FIGURE 1. A flowchart depicting the study selection process

of patients per study ranged from 461 to 1387 (Tab. 1). All studies were performed as retrospective cohort studies. The articles analyzed in this meta-analysis were published between 2015 and 2022. Of the 5 trials, two were performed in the USA [15, 17], and one each in Australia [13], Spain [16], and the Republic of Korea [14]. The methodologic quality of the included trials was low, as summarized in Table 1.

Statistical analysis

All five included studies reported mortality among patients with and without NOAF after LT [13–17]. Pooled analysis showed that mortality in patients with and without NOAF varied and amounted to 24.1% vs 12.5%, respectively (OR = 2.51; 95% CI: 1.92 to 3.27; $p < 0.001$; Fig. 2).

A secondary outcome of this meta-analysis was the impact of NOAF on graft rejection. This parameter was reported in three studies [14, 15, 17]. Pooled analysis showed that graft rejection in the NOAF cohort was 26.3%, and was higher vs patients without NOAF (13.1%; OR = 2.98; 95% CI: 2.14 to 4.15; $p < 0.001$; Fig. 3).

DISCUSSION

In this meta-analysis, we demonstrated that NOAF after LT is a cause for concern, as our pooled analysis

Table 1. Baseline characteristics of the included trials

Study	Country	Study design	Study group	Age	Female (%)	BMI, [kg/m^2]	Hypertension	Diabetes	MELD score	NOS score
Koshy et al., 2021 [13]	Australia	Retrospective cohort study	PO-AF	63.6 ± 6	11 (23.4)	27.9 ± 5	36.20%	29.8%	21 ± 10	8
			No PO-AF	56.6 ± 12	138 (33.3)	26.7 ± 6	39%	31.5%	19 ± 9	
Moon et al., 2018 [14]	Republic of Korea	Retrospective cohort study	PO-AF	45.4 ± 8.7	8 (61.5)	NS	3 (23.1)	3 (23.1)	31.5 ± 11.2	9
			No PO-AF	50.6 ± 8.7	266 (25.4)	NS	112 (10.7)	202 (19.3)	18.8 ± 9.8	
Rachwan et al., 2020 [15]	USA	Retrospective cohort study	PO-AF	NS	27%	NS	38%	43%	NS	8
			No PO-AF	NS	34%	NS	36%	29%	NS	
Rivas et al., 2022 [16]	Spain	Retrospective cohort study	PO-AF	60 ± 8	35%	30 ± 7	45%	14%	23 ± 7	9
			No PO-AF	55 ± 10	35%	31 ± 8	57%	13%	27 ± 8	
Xia et al., 2015 [17]	USA	Retrospective cohort study	PO-AF	58.8 ± 9.1	32.4%	29.6 ± 6.3	38.0%	NS	35.5 ± 7.1	8
			No PO-AF	54.0 ± 11.4	36.3%	27.7 ± 6.0	32.7%	NS	31.7 ± 7.7	

BMI — body mass index; MELD — model for end-stage liver disease; NS — not specified; PO-AF — postoperative atrial fibrillation

discovered that it is linked with a considerably elevated mortality risk. Pooled analysis showed that mortality in post-LT patients with and without NOAF varied from 24.1% to 12.5%. Previous research has shown that individuals with NOAF are more likely to have a stroke, hemodynamic instability, a longer hospital stay, and greater healthcare costs [18]. In our study, NOAF was also linked to an increased likelihood of graft rejection, which was 26.3% in the NOAF group compared to 13.1% in those without NOAF. However, the mechanism behind this link remains unknown. The occurrence of post-LT NOAF is linked not only to acute kidney damage that occurs after the transplant but also to cerebrovascular events that occur [19]. Elevated filling pressures related to AF may result in both pulmonary and venous congestion that may contribute to inferior graft outcomes. Further, altered hemodynamics, as a result of inadequate NOAF heart rate management, may also contribute to possible pathophysiological reasons for graft failure associated with NOAF.

Our study shows that post-LT NOAF is not a benign disease and that it requires constant monitoring and management. According to the 2019 AHA as well as 2022 ERC guidelines, beta-blockers should be maintained postoperatively to minimize serious cardiovascular events [20, 21]. Furthermore, the American Association for Thoracic Surgery recommends that beta-blockers be maintained, as well as intravenous magnesium replacement to avoid hypomagnesemia, with rigorous postoperative AF monitoring [22]. However, it should be taken into account that beta-blockers may reduce the risk of AF in the postoperative period after noncardiac surgery, but this effect is achieved at the expense of an increased risk of bradycardia, and hypotension [23, 24]. Hypotension, on the other hand, may affect graft function.

The increased risk of death and graft rejection in individuals with NOAF shows that underlying causes may play a role in the development of atrial fibrillation in these patients. Identifying these characteristics might improve outcomes for post-LT NOAF patients.

There have also been several hypotheses proposed as to why LT increases the frequency of NOAF throughout the postoperative period. For example, traditional postoperative hemodynamic challenges may result in NOAF due either to hemodynamic instability or inotropic hemodynamic support [25]. NOAF after LT could be associated with autonomic dysfunction, surgical stress, increased catechola-

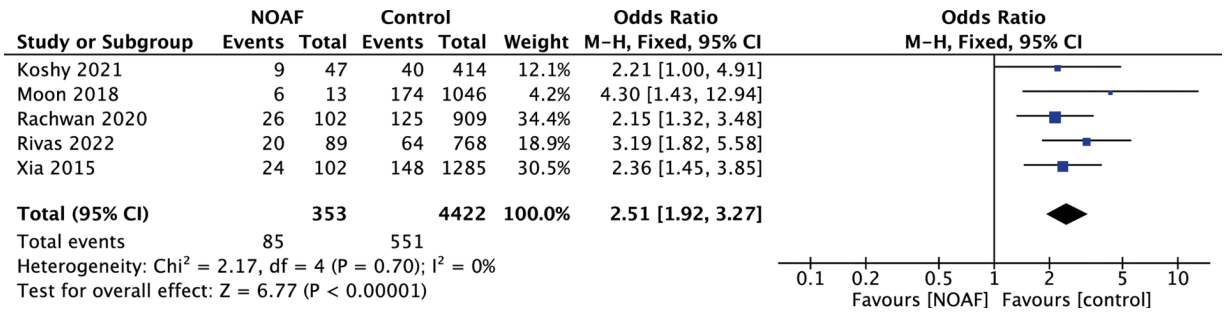

FIGURE 2. Forest plot of return of mortality among patients with and without new-onset atrial fibrillation (NOAF) after liver transplant. The center of each square represents the odds ratio (OR) for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results

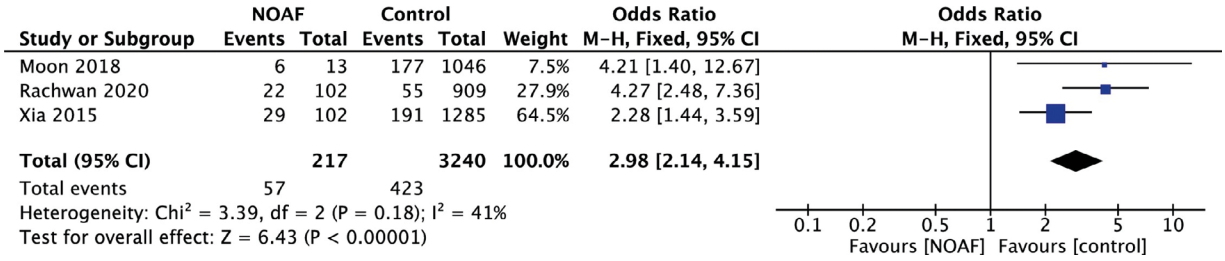

FIGURE 3. Forest plot of return of graft rejection among patients with and without new-onset atrial fibrillation (NOAF) after liver transplant. The center of each square represents the odds ratio (OR) for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results

mine levels, pre-existing pericardial inflammation, and cardiac malfunction [26]. Acidosis, hypo/hyperkalemia, hypocalcemia, hypoglycemia, hypothermia, a higher MELD score, and fulminant hepatic failure after LT may also result in NOAF [14]. Hypomagnesemia is a well-known cause of cardiac arrhythmias [27]. Further, massive bleeding, hypotension, and high-dose catecholamine use after LT can all contribute to increased NOAF risk; hence, NOAF is more likely during the anhepatic period because of the increased need for inotropic support during this phase [28]. The mentioned earlier sudden influx of blood from the inferior vena cava with a mechanical stretch of the atria and hypothermia caused by the influx of cold preservation solution should be taken into account as a stressor triggering AF during the intra-operative period [18].

Finally, the leading cause of long-term mortality in patients with LT is cardiovascular complications, which, other than AF, may include heart failure and acute myocardial infarction. These complications are predominantly driven by the development of metabolic syndrome after LT, and many studies have been conducted to determine the involvement of metabolic syndrome in the development of atrial fibrillation [29]. Further, immunosuppressive medicine increases the risk of developing insulin resistance, which also contributes to metabolic syndrome [30]. Lastly, certain cirrhosis-specific cardiac illnesses, such as the well-known condition known as congestive hepatopathy, play a crucial arrhythmogenesis function as a substrate for the etiology of NOAF prior to transplantation [31, 32].

Limitations

The fact that only observational studies involving a small number of patients were included in our investigation is the first significant limitation of our findings. However, it is important to highlight that this is a rather specialized subject that makes the preparation of randomized trials exceptionally challenging, particularly in the case of post-LT NOAF. Furthermore, we are unable to rule out the possibility that some of the patients in the studies experienced asymptomatic NOAF, which may not have been diagnosed since there was a shortage of diagnostics. In some studies, opportunistic screening was used to determine NOAF. Thus, only patients located in the critical care unit, or those on the general ward with cardiac risk factors or symptoms who were being constantly monitored on telemetry after LT surgery would be identified, as was the case

in several of the studies. Therefore, it is impossible to rule out the possibility of incomplete records for those who had minimal symptoms or were asymptomatic. This is likely to be an underestimate of the real rate. However, because our meta-analysis indicates that liver transplant patients with NOAF may have a higher risk of mortality and graft rejection, additional research, preferably population-based or national database studies, is required to assess the need for routine testing and determine its potential impact on outcomes.

CONCLUSIONS

Post-LT NOAF is associated with increased mortality and a higher risk of graft rejection. It is likely that the development of a standard procedure for early identification of NOAF, as well as recommendations for specific treatment targeted at avoiding the impacts of the illness, could provide a mortality reduction and an increased rate of successful LT. Multicenter trials on larger groups are needed to provide a broader exploration of post-LT NOAF and its consequences.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author (L.S.).

Author contributions

Conceptualization, F.C. and L.S.; methodology, F.C. and L.S.; software, L.S., N.L.B. and F.C.; validation, T.T., Z.R., F.W.P. and L.S.; formal analysis, F.C. and L.S.; investigation, F.C., N.L.B., M.P. and L.S.; resources, F.C. and L.S.; data curation, M.P., I.J. and L.S.; writing — original draft preparation, F.C., M.P., Z.R., F.W.P. and L.S.; writing — review and editing, F.C., L.S., M.P., J.R., I.J., T.T., K.J., N.L.B., Z.R. and F.W.P; visualization, L.S. and F.C.; supervision, F.W.P. and L.S.; project administration, F.C., F.W.P. and L.S.; All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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