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ABOUT COVER

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AIM AND SCOPE

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WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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META-ANALYSIS

Liver transplantation and atrial fibrillation: A meta-analysis

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Abstract

AIM

To assess prevalence of pre-existing atrial fibrillation (AF) and/or incidence of AF following liver transplantation, and the trends of patient's outcomes overtime; to evaluate impact of pre-existing AF and post-operative AF on patient outcomes following liver transplantation.

METHODS

A literature search was conducted utilizing MEDLINE, EMBASE and Cochrane Database from inception through

March 2018. We included studies that reported: (1) prevalence of pre-existing AF or incidence of AF following liver transplantation; or (2) outcomes of liver transplant recipients with AF. Effect estimates from the individual study were extracted and combined utilizing random-effect, generic inverse variance method of DerSimonian and Laird. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews, No. CRD42018093644).

RESULTS

Twelve observational studies with a total of 38586 liver transplant patients were enrolled. Overall, the pooled estimated prevalence of pre-existing AF in patients undergoing liver transplantation was 5.4% (95%CI: 4.9%-5.9%) and pooled estimated incidence of AF following liver transplantation was 8.5% (95%CI: 5.2%-13.6%). Meta-regression analyses were performed and showed no significant correlations between year of study and either prevalence of pre-existing AF (P = 0.08) or post-operative AF after liver transplantation (P = 0.54). The pooled OR of mortality among liver transplant recipients with pre-existing AF was 2.34 (2 studies; 95%CI: 1.10-5.00). In addition, pre-existing AF is associated with postoperative cardiovascular complications among liver transplant recipients (3 studies; OR: 5.15, 95%CI: 2.67-9.92, I^2 = 64%). With limited studies, two studies suggested significant association between new-onset AF and poor clinical outcomes including mortality, cerebrovascular events, post-transplant acute kidney injury, and increased risk of graft failure among liver transplant recipients (P < 0.05).

CONCLUSION

The overall estimated prevalence of pre-existing AF and incidence of AF following liver transplantation are 5.4% and 8.5%, respectively. Incidence of AF following liver transplant does not seem to decrease overtime. Pre-existing AF and new-onset AF are potentially associated with poor clinical outcomes post liver transplantation.

Key words: Atrial fibrillation; Liver; Hepatic; Transplant; Transplantation; Systematic reviews; Meta-analysis

Core tip: Atrial fibrillation (AF) occurs in a substantial number of postoperative and post-transplantation patients. In addition, postoperative AF confers both short-term and long-term morbidity and mortality in liver transplant patients. However, the incidence of postoperative AF in patients undergoing liver transplantation and its impacts remain unclear. To further investigate, we conducted a meta-analysis to assess the rates of preexisting AF and AF following liver transplantation as well as the outcomes of liver transplant patients with AF. Incidence of AF following liver transplant does not seem to decrease overtime. Pre-existing AF and new-onset AF are potentially associated with poor clinical outcomes post liver transplantation.

Chokesuwattanaskul R, Thongprayoon C, Bathini T, Ungprasert P, Sharma K, Wijarnpreecha K, Pachariyanon P, Cheungpasitporn W. Liver transplantation and atrial fibrillation: A meta-analysis. *World J Hepatol* 2018; 10(10): 761-771 Available from: URL: http://www.wjgnet.com/1948-5182/full/v10/i10/761.htm DOI: http://dx.doi.org/10.4254/wjh.v10.i10.761

INTRODUCTION

Atrial fibrillation (AF) is one of the most common heart diseases, affecting 3 to 6 million populations in the United States, almost 30 million people worldwide, which is expected to reach 50 million peoples worldwide in 2050[1-4]. Patients with AF carry a higher risk of adverse cardiovascular events and reduced survival[5,6]. Incidence of AF increases with age. At the same time, aging population is likely to develop other chronic diseases and one of them is end-stage liver disease or cirrhosis[7-9]. This treatment of cirrhosis comprises of multidisciplinary approach ranging from very simple, symptomatic treatment with diuretic or treatment of primary cause, down the road to the most advanced treatment; liver transplantation[10-13].

Liver transplantation is the treatment of choice for end-stage liver diseases[10,13]. In 2017, around 8000 patients all over the United State suffered from end-stage liver disease receiving liver transplantation and the number trends to increase 3% to 5% annually in the past 20 years along with the excellent outcomes with almost 95% survival rate at 1-year post-procedure and some patients could live even more than 30 years after liver transplantation[14-17]. Recent advances in basic and clinical sciences, including surgical technique, immunosuppressive therapy and postoperative supportive care, have led to the substantial improvement in quality of life and survival after liver transplantation[18,19]. In addition, higher risk patients tend to receive transplantation in a higher proportion than they did before. In the view of higher risk patients, they tend to carry the risk factors that accompany with older age such as cardiovascular diseases.

In transplant centers, AF and liver transplantation are entities that we commonly encounter in the practice[20-23]. However, the occurrence rates of preexisting AF and AF following liver transplantation as well as clinical outcomes of liver transplant patients with AF remain unclear[20-31]. Thus, we conduct this meta-analysis: (1) to assess prevalence of pre-existing AF and/or incidence of AF following liver transplantation, and the trends of patient's outcomes overtime; and (2) to evaluate impact of pre-existing AF and post-operative AF on patient outcomes following liver transplantation.

MATERIALS AND METHODS

Search strategy and literature review

We registered this systematic review protocol with International Prospective Register of Systematic Reviews, No. CRD42018093644 (PROSPERO). We conducted a systematic literature search of EMBASE (between January 1988 and March 2018), Ovid MEDLINE (between January 1946 and March 2018), and the Cochrane Database of Systematic Reviews (from database inception to March 2018): (1) to estimate prevalence of pre-existing AF and/or incidence of AF following liver transplantation; and (2) to evaluate impact of pre-existing AF and post-operative AF on patient outcomes following liver transplantation. Ronpichai Chokesuwattanaskul and Charat Thongprayoon, two investigators, independently performed the systematic literature review using the search strategy that consolidated the terms of "liver" OR "hepatic" AND "transplant" OR "transplantation" AND "atrial fibrillation", described in online supplementary data 1. No language restriction was implemented. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[32] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[33].

Study selection

Our inclusion criteria comprised: (1) clinical trials or observational studies such as cohort, cross-sectional, or case-control studies; (2) available data on prevalence of pre-existing AF or incidence of AF following liver transplantation or outcomes of liver transplant recipients with AF; and (3) available data on prevalence, incidence, odds ratios (OR), hazard ratios, or relative risks. Retrieved articles were individually reviewed for eligibility by the two investigators as mentioned prior. Inclusion was not restricted by the size of study. Contrarieties were discussed and solved through joint agreement. We used Newcastle-Ottawa quality assessment scale to assess the quality of study for cohort and case-control studies[34], as shown in Table 1.

Data items and data collection process

We used a structured information collecting form to collect the data from individual article including last name of the first investigator, title, year of publication, country that the research was carried out, baseline characteristics of liver transplant patients, processes utilized to diagnose AF, prevalence of pre-existing AF, incidence of post-operative AF, patient outcomes following liver transplantation.

Statistical analysis

We used Comprehensive Meta-Analysis Version 3.3.070 software (Biostat Inc., Englewood, NJ, United States) for all analyses. Estimated prevalence, incidence and estimated risks from each study were incorporated by the random-effect, generic inverse-variance approach of DerSimonian and Laird[35]. Given the possibility of between-study variance, we used a random-effect model rather than a fixed-effect model. Cochran's *Q* test and I^2 statistic were implemented to assess heterogeneity caused by between-study differences. I^2 values of 0%-25% indicate insignificant heterogeneity. I^2 values of 26%-50% indicate low heterogeneity. I^2 values of 51%-75% indicate moderate heterogeneity and I^2 value of 76%-100% indicate high heterogeneity[36]. Egger test was used to evaluate publication bias[37].

RESULTS

Study selection and characteristics

Applying our search strategy, 121 potential studies were selected. Following the elimination of 83 studies (title and abstract clearly not meeting inclusion criteria due to study design, type of study, patient population or reported outcomes), 38 studies were included for complete examination. After the complete review, twenty articles were omitted because the outcome of interest was not provided and six articles were excluded since they were descriptive studies without data of interest. Hence, we included 12 articles[20-31] into the final analysis including 9 cohort studies[20,22-24,26-30] and 3 case-control studies[21,25,31] with 38586 liver transplant recipients were enrolled, as demonstrated in Figure 1. Study characteristics and quality appraisal of studies are shown in Table 1[20-31].

Prevalence of pre-existing AF and incidence of AF following liver transplantation

Overall, the pooled estimated prevalence of pre-existing AF in patients undergoing liver transplantation was 5.4% [95% confidence intervals (CI): 4.9%-5.9%, I^2 = 66%, Figure 2]. The pooled estimated prevalence of pre-existing AF in patients undergoing liver transplantation was 5.4% (95%CI: 4.4%-6.5%, I^2 = 8%) in case-control studies and 5.4% (95%CI: 4.9%-6.0%, I^2 = 75) in cohort studies, respectively, when analysis was conducted based on type of study. The pooled estimated incidence of AF following liver transplantation was 8.5% (95%CI: 5.2%-13.6%, I^2 = 99%, Figure 3). When analysis was performed based on type of study, the pooled estimated incidence of AF following liver transplantation was 9.4% (95%CI: 5.5%-15.6%, I^2= 73%) in case-control studies and 5.3% (95%CI: 1.6%-16.3%, I^2= 99%) in cohort studies, respectively.

Meta-regression analyses were performed and showed no significant correlations between year of study and either prevalence of pre-existing AF (P = 0.08) or post-operative AF after liver transplantation (P = 0.54), as shown in Figures 4 and 5.

Outcomes of liver transplant recipients with AF

Data on the association between pre-existing AF and the risk of mortality were limited in two studies[20,21].

Table 1 Main characteristic of studies included in meta-analysis of atrial fibrillation and liver transplantation

	Fouad *et al*[24]	VanWagner *et al*[25]	Nicalau-Raducu *et al*[26]	Josefsson *et al*[27]
Country	Canada	United States	United States	Sweden
Study design	Retrospective Cohort	Case-Control	Retrospective Cohort	Retrospective Cohort
Yr	2009	2012	2014	2014
Total number	197	242	389	186
Mean age ± SD	56	55	55	52
Duration (yr)	6 mo	1 yr	3.4	4
Outcome definition	Cardiac complication after LTx	CV complication after LTx	Early (< 1 yr) and Late (> 1 yr) post LTx AF	Incident cardiac event post LTx
Outcome ascertainment	Review EKG in medical records	EKG, Echo, LHC, RHC, DSE as indicated	Review medical records	Review medical records
Incidence of pre-operative AF	NA	All 12/242 (5.0%) NASH 7/115 (6.1%) Alcohol 5/127 (3.9%)	NA	Atrial fibrillation/flutter 4/186 (2.2%)
Incidence of post-operative AF	Intraoperative 1/197 (0.5%) Early postoperative (0-30 d) 3/197 (1.5%) Late postoperative (1-6 mo) 2/197 (1.0%)	All 21/242 (8.7%) NASH 11/115 (9.6%) Alcohol 10/127 (7.9%)	All 12/389 (3.1%) Early (< 1 yr after transplant) 10/389 (2.6%) Late (> 1 yr after transplant) 2/389 (0.5%)	Arrhythmia (mainly AF or flutter) All 36/186 (19.4%) Peri-transplant 24/186 (12.9%) Late 12/186 (6.5%)
Outcomes	NA (study aim to identify predictor of cardiac complication 6 mo after LTX)	NA (study aim to compare CV event between liver disease before liver transplant)	NA (study demonstrated target DSE prior liver transplant associated with increased risk of AF)	NA (study aim to assess pretransplant EKG as a predictor of post liver transplant event)
Confounder adjustment	NA	NA	NA	NA
Newcastle-Ottawa scale	S3 C0 O3	S4 C2 O3	S3 C3 O3	S4 C2 O3
	Vannucci *et al*[20]	**Bargehr *et al*[21]**	**Xia *et al*[22]**	**Piazza *et al*[23]**
Country	United States	United States	United States	Italy
Study design	Retrospective Cohort	Case-Control study	Retrospective Cohort	Retrospective Cohort
Yr	2014	2015	2015	2016
Total number	757	717	1387	143
Mean age ± SD	57.9 ± 6.8	58	54	55
Duration (yr)	1 yr	NA	30 d	3
Outcome definition	30 d and 1-yr survival after Liver Tx.	Cardiac complication after LTX	POAF (postoperative AF in LTX)	Incident AF (also other CVE) in NASH and alcoholic s/p LTx
Outcome ascertainment	Medical records	Review Medical records	EKG, Holter and medical records	Review medical records
Incidence of pre-operative AF	19/757 (2.5%)	32/717 (4.5%)	77/1387 (5.6%)	Alcoholic cirrhosis 2/65 (3.1%) NASH cirrhosis 3/78 (3.8%)
Incidence of post-operative AF	NA	1/63 (1.6%)	New onset AF within 30 d after LT 102/1387 (7.4%)	2/143 (1.4%)
Outcomes	1-mo mortality 5.29 (1.73-16.18) 1-yr mortality 3.28 (1.63-6.59)	Intraoperative cardiac complications 7.83 (1.94-31.49) Mortality 1.50 (0.61-3.69)	Median Hospital stays 31 d (16-67) in POAF *vs* 20 d (12-37) AKI 2.5 (1.06-5.70) Mortality 2.36 (1.45-3.85) Graft failure 2.28 (1.44-3.59)	NA (study aim to compare outcome as CV event after liver transplant between patients with NASH and those with alcoholic cirrhosis who receive liver transplant)
Confounder adjustment	NA	Age, MELD, donor risk index, DM	Age, MELD, intraoperative blood transfusion	NA
Newcastle-Ottawa scale	S3 C0 O3	S4 C2 E3	S4 C2 O3	S4 C2 O3

	VanWagner *et al*[28]	VanWagner *et al*[31]	VanWagner *et al*[29]	Wange *et al*[30]
Country	United States	United States	United States	Sweden
Study design	Retrospective Cohort	Case Control	Retrospective Cohort	Retrospective Cohort
Yr	2016	2017	2018	2018
Total number	32810	1024	671	63
Mean age ± SD	55 ± 10	56	Various by renal disease classification group	45
Duration (yr)	90 d	1 yr	NA	10
Outcome definition	MACE after Liver transplantation	CVD complication *vs* No CVD complication group	1-yr CV complication	Incident AF post LTx who survive > 3 yr (LTx ATTRm amyloidosis)
Outcome ascertainment	Medical record in patient admitted by MACE	EKG, Holter and medical records	Medical record	Echo and Holter every visit
Incidence of pre-operative AF	1969/32810 (6.0%)	62/1024 (6.1%)	2145/37322 (5.7%)	1/63 (1.6%)
Incidence of post-operative AF	204/32810 (0.6%)	130/1024 (12.7%)	65/671 (9.7%)	Incident AF 20/63 (31.7%) All AF post-op 21/63 (33.3%) (Median diagnosis 2 yr)
Outcomes	Pre-transplant AF and 30-d MACE (MI, HF, AF, cardiac arrest, PE, stroke) 6.9 (5.0-9.6) Pre-transplant AF and 90-d MACE 6.1 (4.5-8.3)	Pre-transplant AF and CVD complication 8.96 (3.70-22.0)	NA (study aim to assess degree of renal disease to 1-yr CV outcome in liver transplant patient)	Cerebrovascular events (TIA, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage) 3.8 (1.1-9.5)
Confounder adjustment	Sex, age, history of stroke, type of cirrhosis, and pre-transplant creatinine	Age, sex, race, working status, education, respiratory failure on ventilator at transplant, pulmonary hypertension, HCC, hypertension, DM, heart failure	NA	Cardiomyopathy, ischemic heart disease
Newcastle-Ottawa scale	S3 C0 O3	S4 C2 E3	S4 C2 O3	S3 C0 O3

ATTRm: Amyloid-forming variant Transthyretin proteins; CVD: Cardiovascular disease; HCC: Hepatocellular carcinoma; HF: Heart failure; MACE: Major adverse cardiovascular event; MI: Myocardial infarction; AF: Atrial fibrillation; DSE: Dobutamine stress echocardiogram; EKG: Electrocardiogram; LTX: Liver transplantation; NASH: Nonalcoholic steatohepatitis; NA: Not available; RA: Right atrium; S: Selection; C: Comparability; O: Outcome; AKI: Acute kidney injury; POAF: Post-operative atrial fibrillation; MELD: Model for End Stage Liver Disease.

The pooled OR of mortality among liver transplant recipients was 2.34 (95%CI: 1.10-5.00, I^2 = 45%). In addition, pre-existing AF is associated with postoperative cardiovascular complications among liver transplant recipients (3 studies[21,28,31]; OR: 5.15, 95%CI: 2.67-9.92, I^2 = 64%). New onset AF is associated with poor outcomes after liver transplantation[22,30]. Wange *et al*[30] demonstrated a significant association between incident AF and cerebrovascular events in liver transplant patients with OR of 3.80 (95%CI: 1.10-9.50). In addition to increased mortality risk, Xia *et al*[22] demonstrated significant associations of new-onset AF with post-transplant acute kidney injury (OR: 2.50, 95%CI: 1.06-5.70), and increased risk of graft failure (OR: 2.28, 95%CI: 1.44-3.59) among liver transplant recipients.

Risk of bias across studies

Funnel plots, as demonstrated in Supplementary Figures 1 and 2, and Egger tests were conducted to assess for possibility of publication bias in analyses evaluating prevalence of pre-existing AF and incidence of postoperative AF in liver transplant patients, respectively. The graph is somewhat asymmetric and implies the possibility of publication bias towards negative studies in analysis of prevalence of pre-existing AF (P = 0.01). However, we found no significant publication bias in analysis evaluating incidence of postoperative AF in liver transplant patients, P = 0.32.

DISCUSSION

In this meta-analysis, we demonstrated that end stage liver disease patients who received liver transplantation had a prevalence of AF of 5.6%, which was higher than prevalence of AF in general patient population of 2.5%[38]. This number of higher prevalence may imply that patients who received liver transplantation appeared to carry the higher risk profiles. In addition, our study showed the pooled incidence of post-liver transplant AF of 8.5%, which is lower incidence, when compared to those patients who underwent heart transplantation (incidence of AF up to 40%)[39-44] or other open-heart surgeries (incidence of AF up to 50%)[5,45,46].

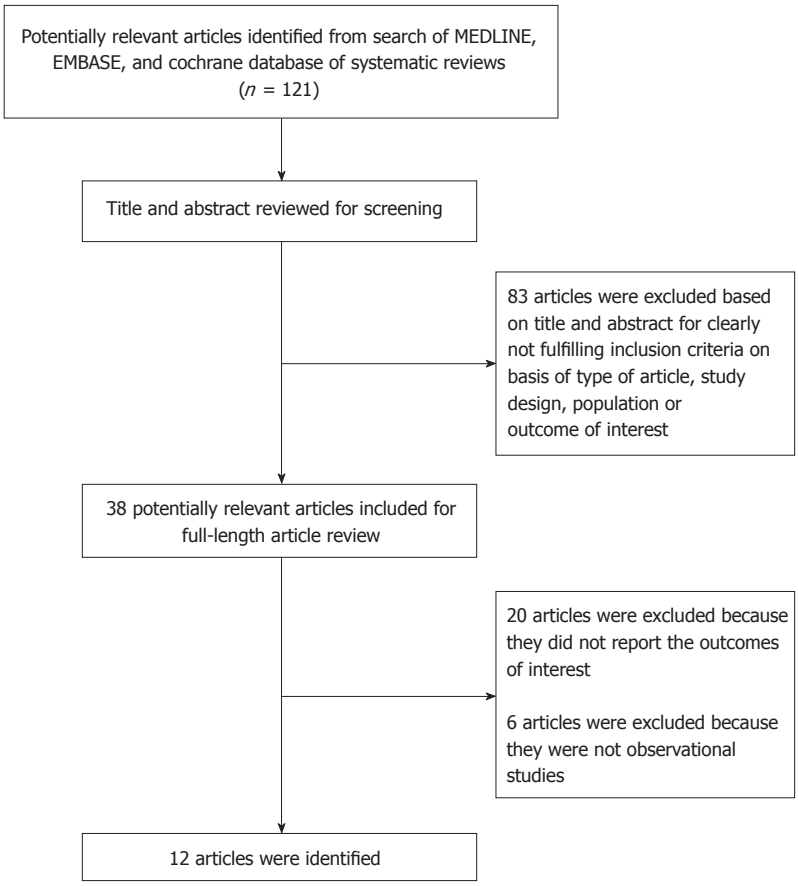

Figure 1 Outline of our search methodology.

Group by Type of study	Study name	Event rate	Lower limit	Upper limit	Z-Value	*P*-Value	Relative weight
Case-Control	Bargehr *et al*	0.045	0.032	0.062	-16.940	0.000	31.66
Case-Control	VanWagner *et al* (1)	0.050	0.028	0.085	-9.973	0.000	12.51
Case-Control	VanWagner *et al* (3)	0.061	0.047	0.077	-20.926	0.000	55.83
Case-Control		0.054	0.044	0.065	-26.917	0.000	
Cohort	Josefsson *et al*	0.022	0.008	0.056	-7.553	0.000	1.32
Cohort	Piazza	0.035	0.015	0.081	-7.288	0.000	1.61
Cohort	Vannucci	0.025	0.016	0.039	-15.750	0.000	5.55
Cohort	VanWagner *et al* (2)	0.060	0.057	0.063	-118.365	0.000	37.75
Cohort	VanWagner *et al* (4)	0.057	0.055	0.060	-125.774	0.000	37.94
Cohort	Wange *et al*	0.016	0.002	0.104	-4.094	0.000	0.34
Cohort	Xia *et al*	0.056	0.045	0.069	-24.168	0.000	15.50
Cohort		0.054	0.049	0.060	-48.512	0.000	
Overall		0.054	0.049	0.059	-55.479	0.000	

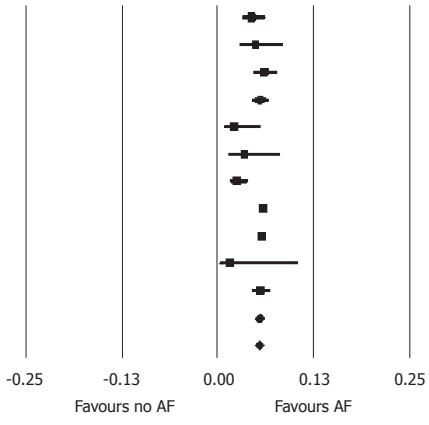

Figure 2 Forest plots of the included studies assessing prevalence of pre-existing atrial fibrillation in patients undergoing liver transplantation. AF: Atrial fibrillation.

This mitigated number of incidence of postoperative AF in liver transplantation could be explained by the use of intensive postoperative hemodynamic care and, immunosuppressive therapy, the surgical technique, and not physically direct impact to the heart[28-31].

In general population, AF can put the patients at higher mortality risk, compared to those without AF[47]. In addition to mortality risk, our study also revealed the association of pre-existing AF and incident AF with poor clinical outcomes following liver transplantation. New-onset AF following liver transplantation is also associated with post-transplant acute kidney injury, cerebrovascular events, and increased risk of graft failure among liver transplant recipients. There are several mechanisms that put the liver transplant patients with AF at higher risk of postoperative morbidity and mortality compared

Group by Type of study	Study name	Statistics for each study					Event rate and 95%CI	Relative weight
		Event rate	Lower limit	Upper limit	Z-Value	*P*-Value		
Case-Control	Bargehr *et al*	0.016	0.002	0.104	-4.094	0.000		7.32
Case-Control	VanWagner *et al* (1)	0.087	0.057	0.129	-10.307	0.000		41.00
Case-Control	VanWagner *et al* (3)	0.127	0.108	0.149	-20.542	0.000		51.69
Case-Control		0.094	0.055	0.156	-7.724	0.000		
Cohort	Fouad *et al*	0.025	0.011	0.060	-8.053	0.000		12.15
Cohort	Josefsson *et al*	0.194	0.143	0.257	-7.690	0.000		12.79
Cohort	Nicolau-raducu *et al*	0.031	0.018	0.054	-11.756	0.000		12.59
Cohort	Piazza *et al*	0.014	0.004	0.054	-5.976	0.000		11.15
Cohort	VanWagner *et al* (2)	0.006	0.005	0.007	-72.247	0.000		12.91
Cohort	VanWagner *et al* (4)	0.097	0.077	0.122	-17.105	0.000		12.86
Cohort	Wange *et al*	0.333	0.228	0.458	-2.594	0.009		12.65
Cohort	Xia *et al*	0.074	0.061	0.089	-24.629	0.000		12.89
Cohort		0.053	0.016	0.163	-4.518	0.000		
Overall		0.085	0.052	0.136	-8.903	0.000		

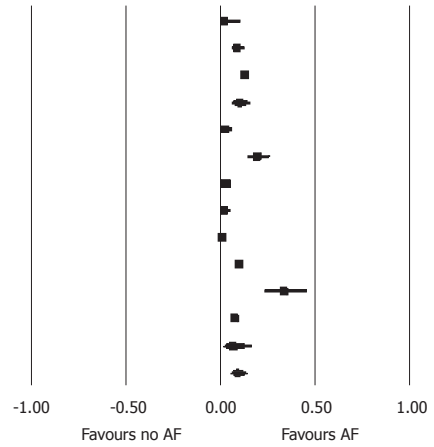

Figure 3 Forest plots of the included studies assessing incidence of atrial fibrillation following liver transplantation. AF: Atrial fibrillation.

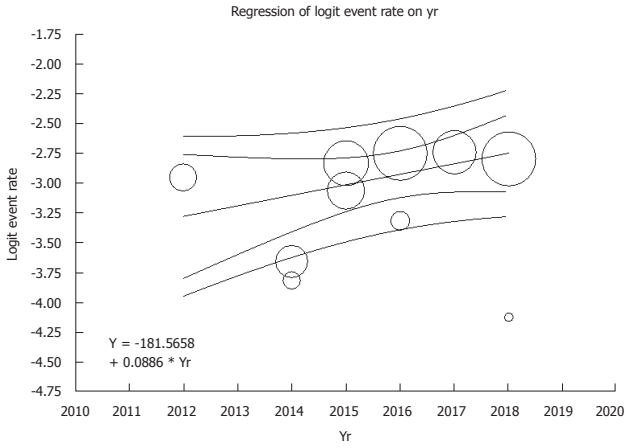

Figure 4 Meta-regression analysis showed no significant correlations between year of study and prevalence of pre-existing atrial fibrillation (*P* = 0.08).

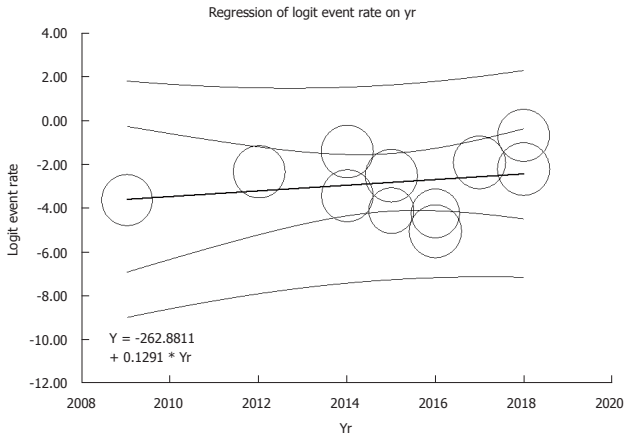

Figure 5 Meta-regression analysis showed no significant correlations between year of study and incidence of post-operative atrial fibrillation after liver transplantation (*P* = 0.54).

to those without AF[24,48]. Patients with AF reflect that they are frail and have already been at higher risk profiles accompanying with other cardiovascular risks (left ventricular hypertrophy, heart failure, stroke, *etc*.) at the time even before liver transplantation, so that they will inevitably develop higher complication rates at postoperative period[21,49,50]. Furthermore, AF itself plays a critical role as marker of underlying heart diseases that make patients vulnerable to perioperative hemodynamic challenges[51,52].

There are also several mechanisms explained why liver transplantation promotes the occurrence of AF during postoperative period (Figure 6). Firstly, conventional postoperative hemodynamic challenge could provoke AF through hemodynamic instability or inotropic administration[50]. Also, some preexisting liver diseases, such as nonalcoholic fatty liver disease (NAFLD), share a common risk factor, that is diabetes and obesity, with the AF patients[53]. In addition, NAFLD could also occur as de novo after liver transplantation and subsequently enhances the postoperative complications, contributed by systematic inflammatory mechanism[54-56]. Furthermore, immunosuppressive therapy increases the risk to develop insulin resistance which eventually leads to metabolic syndrome[57]. Various kind of cirrhosis-specific heart diseases, such as a well-known entity called congestive hepatopathy, prior to transplantation play a substantial arrhythmogenesis role as a substrate for pathogenesis of AF[50,58]. Various underlying medical problems including AF would, in the future, be used to identify high-risk patient population that needs to be optimized the treatment to achieve higher outcome after liver transplantation.

Leading cause of long term mortality in patients with liver transplantation is cardiovascular complications which, other than AF, include heart failure and myocardial infarction. These complications are predominantly driven by the development of metabolic syndrome after liver transplantation. However, this topic of interest is beyond the scope of our study and

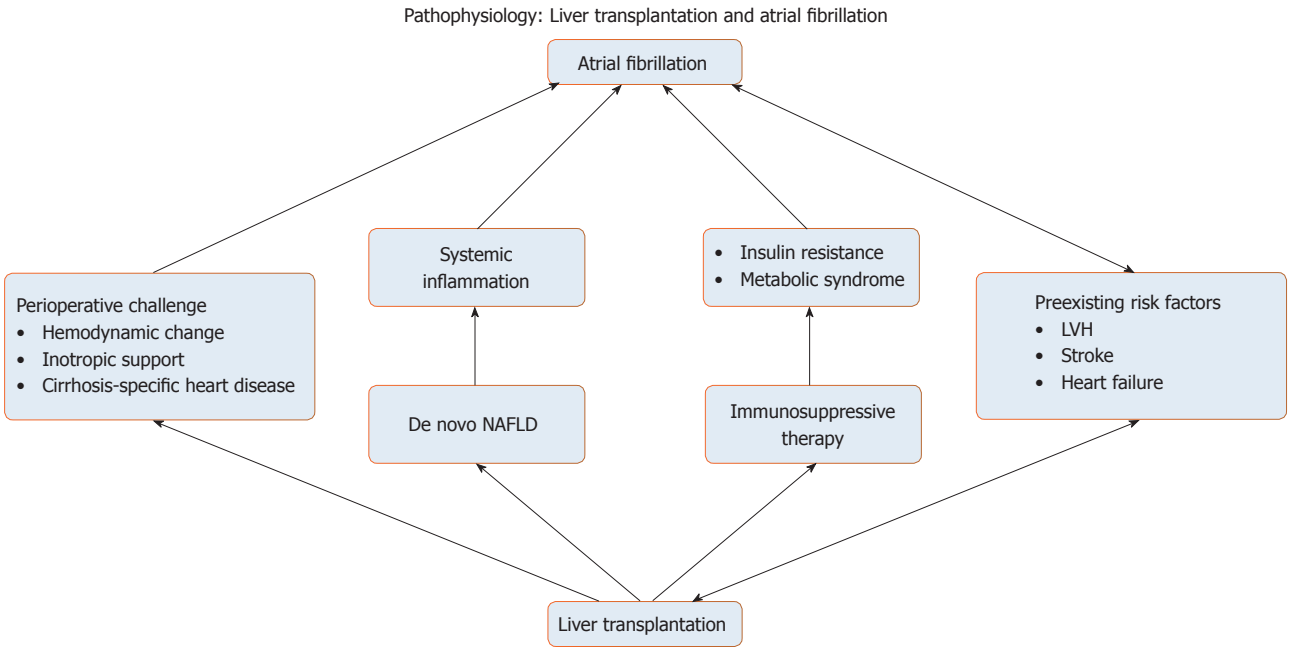

Figure 6 Potential mechanisms of atrial fibrillation in liver transplantation. NAFLD: Nonalcoholic fatty liver disease; LVH: Left ventricular hypertrophy.

could be explained elsewhere[50]. More or less, these cardiovascular complications were also considered as potential risk modification strategy that should not be overlooked. Our study has noteworthy limitations. Firstly, an inconsistent in definition, for an example how to define the timing of AF as an early or late onset, among the different studies preclude to draw the generalized conclusion. Such this limitation, data use needs tailoring to the individual patient. Secondly, duration of follow up during the postoperative period by some study prospectively monitored a cardiovascular event for just 30 d post-transplantation, which this time frame does not long enough to reveal the long-term morbidity and mortality outcome. However, with the potential of higher morbidity and mortality in liver transplant patients with AF by our meta-analysis, future studies, preferable with population-based or national database studies, are required to discover whether focused AF cares for liver transplanted patients can improve patient outcomes after liver transplantation. Finally, since our study is a meta-analysis of observational studies, it could entirely prove association, but could not demonstrate a cause-effect (causal) relationship, between liver transplantation and AF.

In conclusion, our study demonstrated the actual prevalence of preexisting AF in patient underwent liver transplantation, incidence of AF post-liver transplantation. Our study also highlighted the association of AF with higher morbidity and mortality among liver transplant recipients. Further well-designed studies are needed to explore the impact of AF in liver transplant patients, which we strongly believe that AF management, specified to liver transplant patients, would be an important strategy to augment standard of care in this particular population.

ARTICLE HIGHLIGHTS

Research background

Among liver transplant patients with atrial fibrillation (AF), there are lacks of data about incidence, prevalence and prognosis of AF in this specific group of patients. In spite of improvement of liver transplant care to the point of achieving almost 90% of 1-year survival rate, outcomes of liver transplantation related to AF remain unclear.

Research motivation

With excellent results of liver transplantation in term of survival, current indications of the transplantation have been extending into higher risk candidates due to higher amount of donors and more advanced treatment, which include preoperative preparation, surgical technique, immunosuppressive therapy and post-transplantation care. The high-risk liver transplant candidates tend to experience the adverse effects throughout perioperative period and worse outcomes, compared to those with less comorbidity. AF is one of the most common cardiac rhythm abnormalities and its prevalence increases with older age and higher comorbidities. Therefore, a number of patients with AF who received liver transplantation would definitely increase.

Research objectives

To examine outcomes of liver transplant recipients with AF, we performed this meta-analysis: (1) to assess prevalence of pre-existing AF and/or incidence of AF following liver transplantation, and the trends of patient's outcomes overtime; and (2) to evaluate impact of pre-existing AF and post-operative AF on patient outcomes following liver transplantation. Innovations and breakthroughs.

Research methods

We conducted a systematic literature search of EMBASE, Ovid MEDLINE, and the Cochrane Database (from database inception to March 2018): (1) to estimate prevalence of pre-existing AF and/or incidence of AF following liver transplantation; and (2) to evaluate impact of pre-existing AF and post-operative AF on patient outcomes following liver transplantation. Estimated prevalence, incidence and estimated risks from each study were incorporated by the random-effect, generic inverse-variance approach of DerSimonian and Laird.

Research results

There were significant associations of AF with worse clinical outcomes following liver transplantation including 2.3-fold higher risk of death and 5.1-fold higher risk of postoperative cardiovascular complications, and poor clinical outcomes such as stroke, acute kidney injury and graft failure. We also showed the incidence of postoperative AF, namely 8.5%, consistently across different type of studies without the change overtime by meta-regression.

Research conclusions

The overall estimated prevalence of pre-existing AF and incidence of AF following liver transplantation are 5.4% and 8.5%, respectively. Incidence of AF following liver transplant does not seem to decrease overtime. Pre-existing AF and new-onset AF are potentially associated with poor clinical outcomes post liver transplantation.

Research perspectives

This systematic review confirmed higher risks of death and postoperative complications in liver transplant patients with AF. Our findings indicate that AF may be an independent predictor for worse clinical outcomes following liver transplantation.

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