Liver transplantation and atrial fibrillation: A meta-analysis

Ronpichai Chokesuwattanaskul, Charat Thongprayoon, Tarun Bathini, Patompong Ungprasert, Konika Sharma, Karn Wijarnpreecha, Pavida Pachariyanon, Wisit Cheungpasitporn

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 revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Wisit Cheungpasitporn, MD, Assistant Professor, Division of Nephrology, Department of Medicine, University of Mississippi Medical Center, 2500 N. State St., Jackson, MS 39216, United States. wcheungpasitporn@gmail.com

Telephone: +1-601-9845670
Fax: +1-601-9845765

Received: May 2, 2018
Peer-review started: May 3, 2018
First decision: May 17, 2018
Revised: June 24, 2018
Accepted: June 28, 2018
Article in press: June 29, 2018
Published online: October 27, 2018

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, I² = 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.

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 people 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.

Chokesuwattanaskul R, Thongprayoon C, Bathini T, Ungprasert P, Sharma K, Wijampeeacha 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
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. Contrarities 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 I² statistic were implemented to assess heterogeneity caused by between-study differences. I² values of 0%-25% indicate insignificant heterogeneity. I² values of 26%-50% indicate low heterogeneity. I² values of 51%-75% indicate moderate heterogeneity and I² 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%, I² = 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%, I² = 8%) in case-control studies and 5.4% (95%CI: 4.9%-6.0%, I² = 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%, I² = 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%, I² = 73%) in case-control studies and 5.3% (95%CI: 1.6%-16.3%, I² = 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

| Country       | Study design      | Yr     | Total number | Mean age ± SD | Duration (yr) | Outcome definition | Outcome ascertainment | Incidence of pre-operative AF | Incidence of post-operative AF | Outcomes                                                                 |
|---------------|-------------------|--------|--------------|---------------|---------------|--------------------|-----------------------|-------------------------------|-----------------------------|--------------------------------------------------------------------------------|
| Foud et al[24] | United States     | 2012   | 242          | 55            | 1 yr          | Cardiac complication after LTx | Review EKG in medical records | NA                           | NA                           | 12/242 (5.0%)                                                                 |
| VanWagner et al[25] | United States     | 2014   | 389          | 55            | 3.4           | CV complication after LTx     | EKG, Echo, LHC, RHC, DSE as indicated | NA                           | NA                           | NA (study aim to compare outcome as CV event after event between liver transplant between patients with NASH and those with alcoholic cirrhosis who receive liver transplant) |
| Nicalau-Raducu et al[26] | United States     | 2014   | 55           | 55            | 4             | Early (< 1 yr) and Late (> 1 yr) post LTx AF | Review medical records | NA                           | NA                           | NA (study aim to assess posttransplant EKG as a predictor of post liver transplant event) |
| Josefsson et al[27] | Sweden            |        | 186          | 52            |               | Incident cardiac event post LTx | Review medical records | NA                           | NA                           | Alcohol cirrhosis 2/65 (3.1%) NASH cirrhosis 3/78 (3.8%) 2/143 (1.4%)                                                |
| Chokesuwattanaskul R et al[28] | United States     |        | 2015          | 54            | 3             | POAF (postoperative AF in LTx) | Review Medical records | 32/717 (4.5%)                | 1/197 (0.5%)                  | 11/115 (9.6%)                                                                 |
| Bargehr et al[29] | United States     |        | 1387         | 56            | 30 d          | Cardiac complication after LTx | EKG, Holter and medical records | 12/242 (5.0%)                | 7/115 (6.1%)                  | 7/115 (6.1%)                                                                 |
| Xia et al[30]   | United States     |        | 143          | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |
| Piazza et al[31] | Italy             |        | 2016         | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |

| Country       | Study design      | Yr     | Total number | Mean age ± SD | Duration (yr) | Outcome definition | Outcome ascertainment | Incidence of pre-operative AF | Incidence of post-operative AF | Outcomes                                                                 |
|---------------|-------------------|--------|--------------|---------------|---------------|--------------------|-----------------------|-------------------------------|-----------------------------|--------------------------------------------------------------------------------|
| Vannucci et al[32] | United States     | 2015   | 717          | 54            | 30 d          | POAF (postoperative AF in LTx) | Review Medical records | 32/717 (4.5%)                | 1/197 (0.5%)                  | 11/115 (9.6%)                                                                 |
| Bargehr et al[30] | United States     | 2016   | 1387         | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |
| Xia et al[30]   | United States     |        | 143          | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |
| Piazza et al[31] | Italy             |        | 2016         | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |

| Country       | Study design      | Yr     | Total number | Mean age ± SD | Duration (yr) | Outcome definition | Outcome ascertainment | Incidence of pre-operative AF | Incidence of post-operative AF | Outcomes                                                                 |
|---------------|-------------------|--------|--------------|---------------|---------------|--------------------|-----------------------|-------------------------------|-----------------------------|--------------------------------------------------------------------------------|
| Vannucci et al[32] | United States     | 2015   | 717          | 54            | 30 d          | POAF (postoperative AF in LTx) | Review Medical records | 32/717 (4.5%)                | 1/197 (0.5%)                  | 11/115 (9.6%)                                                                 |
| Bargehr et al[30] | United States     | 2016   | 1387         | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |
| Xia et al[30]   | United States     |        | 143          | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |
| Piazza et al[31] | Italy             |        | 2016         | 55            |               | POAF (postoperative AF in LTx) | Review medical records | 32/717 (4.5%)                | 11/115 (9.6%)                 | 11/115 (9.6%)                                                                 |
The pooled OR of mortality among liver transplant recipients was 2.34 (95%CI: 1.10-5.00, I² = 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, I² = 64%). New onset AF is associated with poor outcomes after liver transplantation[22,30]. Wang 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%)[39-46] or other open-heart surgeries (incidence of AF up to 50%)[35,47].
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
Chokesuwattanaskul R et al. Liver transplantation and atrial fibrillation

| Group by Type of study | Statistics for each study | Event rate and 95%CI | Relative weight |
|------------------------|---------------------------|----------------------|----------------|
| Case-Control           |                           |                      |                |
| Banghø et al            | 0.016                     | 0.002 0.104          | -4.094 0.000   | 7.32            |
| Case-Control            | 0.087                     | 0.057 0.129          | -10.307 0.000  | 41.00           |
| Case-Control            | 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                  | 0.194                     | 0.143 0.257          | -7.690 0.000   | 12.79           |
| Cohort                  | 0.031                     | 0.018 0.054          | -11.756 0.000  | 12.59           |
| Cohort                  | 0.014                     | 0.004 0.054          | -5.976 0.000   | 11.15           |
| Cohort                  | 0.006                     | 0.005 0.007          | -7.247 0.000   | 12.91           |
| Cohort                  | 0.097                     | 0.077 0.122          | -17.105 0.000  | 12.86           |
| Cohort                  | 0.333                     | 0.228 0.458          | -2.594 0.009   | 12.65           |
| Cohort                  | 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
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.

REFERENCES

1 Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest 2012; 142: 1489-1498 [PMID: 22459778 DOI: 10.1378/ chest.11-2888]

2 Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet 2015; 386: 154-162 [PMID: 25960110 DOI: 10.1016/ S0140-6736(14)61774-8]

3 Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol 2014; 6: 213-220 [PMID: 24966695 DOI: 10.2147/CLEP.S47385]

4 Andrade J, Khairi P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among common clinical features, epidemiology, and mechanisms. Circ Res 2011; 114: 1453-1468 [PMID: 24763464 DOI: 10.1161/ CIRCRESAHA.111.302211]

5 January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64: e1-76 [PMID: 24685669 DOI: 10.1016/ j.jacc.2013.03.022]

6 Oudutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal death, and systemic: systematic review and meta-analysis. BMJ 2016; 354: i4482 [PMID: 27599725 DOI: 10.1136/bmj.i4482]

7 Lee H, Choi KE, Rhee TM, Lee SR, Lim WH, Kang SH, Han KD, Cha MJ, Oh S. Cirrhosis is a risk factor for atrial fibrillation: A nationwide, population-based study. Liver Int 2017; 37: 1660-1667 [PMID: 28432810 DOI: 10.1111/liv.13459]

8 Mwaibita JP, Mainmone S, Filomia R, Aliibrandi A, Saicta C, Caccamo G, Cacciola I, Spinella R, Oliva G, Lembo T, Vadala D, Gambino G, Raimondo G, Squadrito G. Atrial fibrillation in patients with cirrhosis. Liver Int 2016; 36: 395-400 [PMID: 26325428 DOI: 10.1111/liv.12928]

9 Biviano AB, Nazif T, Dizon J, Garan H, Abrams M, Fleitman J, Hassan D, Kapadia S, Babalarios V, Xu K, Rodes-Cabau J, Szeto WY, Fearon WF, Dvir D, Dewey T, Williams M, Kindsvater S, Mack MJ, Webb JG, Craig Miller D, Smith CR, Leon MB, Kodali S. Atrial Fibrillation is Associated with Increased Pacemaker Implantation Rates in the Placement of Aortic Transcatheter Valve (PARTNER) Trial. J Atr Fibrillation 2017; 10: 1494 [PMID: 29250217 DOI: 10.4022/jafibl.1494]

10 Foundation AL. Liver Transplantation. 2018. Available from: URL: https://www.liverfoundation.org/or-patients/about-the-liver/ the-progression-of-liver-disease/liver-transplant/information-for-the- newly-diagnosed

11 Martin P, D’Mmartin A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014; 59: 1144-1165 [PMID: 24716201 DOI: 10.1002/hep.26972]

12 Kling CE, Perkins JD, Carifihrs RL, Donovan DM, Sibulesky L. Recent trends in liver transplantation for alcoholic liver disease in the United States. World J Hepatol 2017; 9: 1315-1321 [PMID: 29359014 DOI: 10.4240/wjg.v9.i13.1315]

13 Dutkowski P, Linecker M, DeOliveira ML, Mulllhaubt B, Clavien PA. Challenges to liver transplantation and strategies to improve outcomes. Gastroenterology 2015; 148: 307-323 [PMID: 25224524 DOI: 10.1053/j.gastro.2014.08.045]

14 Organ Procurement and Transplantation Network. National data on liver transplantation. 2018. Available from: URL: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data

15 Reddy KR, Ellerbe C, Schilsky M, Stravitz RT, Fontana RJ, Durkalski V, Lee WM; Acute Liver Failure Study Group. Determinants of outcome among patients with acute liver failure listed for liver transplantation in the United States. Liver Transpl 2016; 22: 505-515 [PMID: 26421889 DOI: 10.1002/lt.24347]

16 Young K, Liu B, Bhuket T, Younossi Z, Saab S, Ahmed A, Wong RJ. Long-term trends in chronic hepatitis B virus infection associated liver transplantation outcomes in the United States. J Viral Hepat 2017; 24: 789-796 [PMID: 28273387 DOI: 10.1111/ jvh.12703]

17 Urrunaga NH, Rachakonda VP, Magder LS, Minkikoglu AL. Outcomes of living versus deceased donor liver transplantation for acute liver failure in the United States. Transplant Proc 2014; 46: 219-224 [PMID: 24507055 DOI: 10.1016/j.transproceed.2013.08.011]

18 Wan P, Yu X, Xia Q. Operative outcomes of adult living donor liver transplantation and deceased donor liver transplantation: a systematic review and meta-analysis. Liver Transpl 2014; 20: 425-436 [PMID: 24478109 DOI: 10.1002/lt.23836]

19 Mathur AK, Talwalkar J. Quality measurement and improvement in liver transplantation. J Hepatobiliary Pancreat Sci 2018; 25: 1300-1310 [PMID: 29555934 DOI: 10.1002/jhbs.20036]

20 Vannucci A, Rathor R, Vachharajani N, Chapman W, Kangra I. Atrial fibrillation in patients undergoing liver transplantation-a single-center experience. Transplant Proc 2014; 46: 1432-1437 [PMID: 24935310 DOI: 10.1016/j.transproceed.2014.02.020]

21 Bargehr J, Trejo-Gutierrez JF, Patel T, Rosser B, Aranda-Michel J, Yataco ML, Tamer CB. Preexisting atrial fibrillation and cardiac complications after liver transplantation. Liver Transpl 2015; 21: 314-320 [PMID: 25486693 DOI: 10.1002/20460]

22 Xia VW, Worapot A, Huang S, Dhillon A, Gudzenko V, Backon A, Agopian VG, Aksoy O, Vorobiof G, Busuttil RW, Steadman RH. Postoperative atrial fibrillation in liver transplantation. Am J Transplant 2015; 15: 687-694 [PMID: 25657037 DOI: 10.1111/ajt.13034]

23 Piazza NA, Singal AK. Frequency of Cardiovascular Events and Effect on Survival in the Placement of Aortic Transcatheter Valve (PARTNER) Trial. J Atr Fibrillation 2016; 14: 79-85 [PMID: 26581602 DOI: 10.4022/jafibl.2015.0089]

24 Fouad TR, Abdel-Razek WM, Burak KW, Bain VG, Lee SS. Prediction of cardiac complications after liver transplantation. Transplantation 2009; 87: 763-770 [PMID: 19295324 DOI: 10.1097/ TP0b013e318198d734]

25 Vanwagner LB, Blvue M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at
increased risk for postoperative cardiovascular events. *Hepatology* 2012; 56: 1741-1750 [PMID: 22611040 DOI: 10.1002/hep.25855]

26 Nicolau-Raducu R, Gittman M, Ganier D, Loss GE, Cohen AJ, Patel H, Girghrahi N, Sekar K, Nossmann B. Adverse cardiovascular events after orthotopic liver transplantation - a cross-sectional study in 389 consecutive patients. *Liver Transpl* 2015; 21: 13-21 [PMID: 25213120 DOI: 10.1002/lt.23997]

27 Josefsson A, Fu M, Björnsson E, Kalaitzakis E. Prevalence of pre-transplant electrocardiographic abnormalities and post-transplant cardiac events in patients with liver cirrhosis. *BMC Gastroenterol* 2014; 14: 65 [PMID: 24780856 DOI: 10.1186/1471-230X-14-65]

Van Wagner LB, Serper M, Kang R, Levitsky J, Hohmann S, Abeccasis M, Skaro A, Lloyd-Jones DM. Factors Associated With Major Adverse Cardiovascular Events After Liver Transplantation Among a National Sample. *Am J Transplant* 2016; 16: 2684-2694 [PMID: 26946333 DOI: 10.1111/ajt.13779]

29 Van Wagner LB, Montag S, Zhao L, Allen NB, Lloyd-Jones DM, Das A, Skaro AI, Hohmann S, Friedewald JJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AM, Anan I, Ericzon BG, Pilebro B, Suhr OB, Waxner J. Atrial Fibrillation and Central Nervous Complications in Liver Transplanted Hereditary Transthyretin Amyloidosis Patients. *Transplantation* 2018; 102: e59-e66 [PMID: 29019809 DOI: 10.1097/TP.0000000000001975]

30 Wange N, Anan I, Ericzon BG, Pilebro J, Suhr OB, Waxner J. Heart Transplantation and the Influence of Bicaval Anastomoses on Late Atrial Arrhythmia after Heart Transplantation. *J Thorac Cardiovasc Surg* 1981; 81: 287-295 [PMID: 7202705 DOI: 10.1016/S0022-5223(81)80674-1]

31 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4: e296 [PMID: 17941714 DOI: 10.1371/journal.pmed.0040296]

32 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med* 2009; 6: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

33 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

34 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]

35 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

36 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; 337: 867-872 [PMID: 1672966 DOI: 10.1016/0140-6736(91)90201-Y]

37 Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Ezekowitz MD, Field ME, Levy D, Vaziri SM, D’Agostino RB, Belanger AM, von Elm E, Howard VJ, Muntner P. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the FHREasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol* 2011; 108: 227-232 [PMID: 21530935 DOI: 10.1016/j.amjcard.2011.03.026]

38 Pollock VR, Collins GS, Mancini DM, D’Agostino RB, Belanger AM, von Elm E, Howard VJ, Muntner P. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the FHREasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol* 2011; 108: 227-232 [PMID: 21530935 DOI: 10.1016/j.amjcard.2011.03.026]

39 Callegaro M, Pasquini A, Krishnan B, Heroux AL. Incidence, risk factors, and clinical outcomes of atrial fibrillation and atrial flutter after heart transplantation. *Am J Cardiol* 2010; 106: 737-741 [PMID: 20723655 DOI: 10.1016/j.amjcard.2010.04.035]

40 Rivinius R, Helmschrott M, Rupharwar A, Erbel C, Gleissner CA, Darge FF, Thomas D, Bruckner T, Katus HA, Doesch AO. The influence of surgical technique on early posttransplant atrial fibrillation - comparison of bilateral, bicaval, and total orthotopic heart transplantation. *Ther Clin Risk Manag* 2017; 13: 287-297 [PMID: 28831331 DOI: 10.2147/TCRM.S128699]

41 Sattiraju S, Vats S, Krishnan B, Kim YH, McAnulty JH Jr, Eber B. Risk factors of postoperative atrial fibrillation after cardiac surgery. *J Card Surg* 2005; 20: 425-431 [PMID: 16153272 DOI: 10.1111/j.1540-8191.2005.2004123.x]

42 Auer J, Weber T, Berent R, Ng CK, Lamm G, Eber B. Risk factors of postoperative atrial fibrillation after cardiac surgery. *J Card Surg* 1997; 12: 49-54 [PMID: 8942741 DOI: 10.1016/S0887-3074(96)00064-1]

43 Gallegos-Orozco JF, Charlton MR. Predictors of Cardiotoxic Events After Liver Transplantation. *Clin Liver Dis* 2017; 21: 241-255 [PMID: 11232187 DOI: 10.1016/S1098-3261(05)70106-9]

44 Bargehr J, Trejo-Gutierrez JF, Rosser BG, Patel T, Yatco ML, Pungapong S, Taner CB, Aranda-Michel J. Liver transplantation in patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 2014; 130: 2071-2104 [PMID: 24682348 DOI: 10.1161/CIR.0000000000000404]

45 Keefe EB. Liver transplantation at the millennium. Past, present, and future. *Clin Liver Dis* 2000; 4: 241-255 [PMID: 11232187 DOI: 10.1016/S1098-3261(05)70106-9]

46 Benjamin EJ, Levy D, Vaziri SM, D’Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994; 271: 840-844 [PMID: 8114238 DOI: 10.1001/jama.271.11.840]

47 Stewart S, Hart CL., Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002; 113: 359-364 [PMID: 12401529 DOI: 10.1016/S0002-9343(02)01236-6]

48 Tanner RM, Baber U, Carson AP, Voeks J, Brown TM, Soliman EZ, Howard VJ, Muntner P. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the REasons for Geographic and Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol* 2011; 108: 227-232 [PMID: 21530935 DOI: 10.1016/j.amjcard.2011.03.026]

49 Patil A, Dasarathy S, Eghtesad B, McCullough AJ. Post-transplant metabolic syndrome: an epidemic waiting to happen. *Liver Transpl* 2009; 15: 1662-1670 [PMID: 19938136 DOI: 10.1002/lt.21952]

50 Laryea M, Watt KD, Molinari M, Walsh MJ, McAlister VC, Marotta PJ, Nashan B, Peltkeman KM. Metabolic syndrome in...
liver transplant recipients: prevalence and association with major vascular events. *Liver Transpl* 2007; 13: 1109-1114 [PMID: 17663411 DOI: 10.1002/lt.21126]

56 Moon JI, Barbeito R, Faradj RN, Gaynor JJ, Tzakis AG. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: Long-term follow up. *Transplantation* 2006; 82: 1625-1628 [PMID: 17198248 DOI: 10.1097/01.tp.0000250361.60415.96]

57 Pisano G, Fracanzani AL, Caccamo L, Donato MF, Fargion S. Cardiovascular risk after orthotopic liver transplantation, a review of the literature and preliminary results of a prospective study. *World J Gastroenterol* 2016; 22: 8869-8882 [PMID: 27833378 DOI: 10.3748/wjg.v22.i40.8869]

58 Möller S, Bernardi M. Interactions of the heart and the liver. *Eur Heart J* 2013; 34: 2804-2811 [PMID: 23853073 DOI: 10.1093/eurheartj/eht246]
