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Atrial fibrillation in renal or liver transplant recipients: A systematic review and meta-analysis

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ABSTRACT

Background: The prevalence of atrial fibrillation (AF) in patients undergoing renal (RT) or liver transplantation (LT) has increased during the last decades. Yet, there is still uncertainty on the association between AF and patient and graft survival.
Methods: Multiple electronic databases were searched using various combinations of keywords and MeSH terms pertinent to the exposure (AF), and outcomes (graft and patient survival). Randomized or quasi-randomized controlled studies, cohort and case-control studies on adults with documented AF undergoing RT or LT were included. The quality of studies was assessed using the Newcastle-Ottawa Assessment Scale. When appropriate, data on the primary and secondary outcomes were pooled in a meta-analysis using the random-effect model. The Odds ratio was used for patients undergoing LT and the hazard ratio was used for patients who underwent renal transplantation.
Results: A total of 50,362 publications were identified. Six studies, with a total of 136,331 patients, satisfied the inclusion criteria. LT was performed on 2861 patients and RT was performed on 133,470 recipients. Overall, AF affected 6652 (4.8%) transplant recipients. Among them, 153 received a LT and 6499 underwent RT. The OR for mortality after LT was 2.375 (95% CI; 1.532–3.682) (P = 0.000) in AF(+) recipients and the HR was 1.859 (95% CI; 1.031–3.354) (P = 0.039) after RT. The OR for graft loss in AF(+) after LT r was 1.088 (95% CI; 0.311–3.804) (P = 0.894) and the HR for graft loss was 1.632 (95% CI; 1.200–2.218) (P = 0.002) after RT.
Conclusions: To the best of our knowledge, this is the first systematic review and meta-analysis to explore the association between AF and patient and graft survival after RT or LT. Our findings suggest that the presence of AF is associated with inferior patient survival. For renal transplant recipients, AF is also associated with inferior graft survival.

Contents

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1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in North America and in high-income countries with similar longevity [1]. In the United States, the prevalence of AF ranges from 1 to 2% in the general population to 9% in the group of individuals older than 80 years [2]. In addition to age, other common risk factors include arterial hypertension, valvular or ischemic heart disease, diabetes, obesity, renal failure and male gender [3]. Due to the increasing age and the incidence of other risk factors, the prevalence of AF is rising in most countries and it is expected to double among individuals older than 55 in the next four decades in many parts of the world [4]. These epidemiological estimates can be generalized to patients with end-stage organ disease who are referred for transplant surgery. Patients affected by AF have a lower quality of life [5], an increased risk of cerebrovascular embolic events [6] and higher mortality in comparison to AF(−) individuals [7]. Even if AF is a relatively common condition in patients with end-stage renal and liver disease, the correlation between the presence of AF and recipient and graft survival has not been entirely elucidated.

We hypothesized that AF(+) patients undergoing renal (RT) or liver transplantation (LT) might have an inferior graft and overall survival in comparison to AF(−) recipients. To test our hypothesis, we performed a systematic review of the literature and performed a meta-analysis with the primary aim of assessing if the presence of AF in renal and liver transplant recipients was associated with inferior patient and graft survival.

2. Material and methods

2.1. Search strategy

A systematic review of Medline (PubMed and Ovid), EMBASE, CINAHL, the Cochrane Collaboration Library, Google Scholar, (from their commencements to December 1, 2017) was performed with no language or geographical restrictions. Our search was completed with the assistance of a librarian at the Health Science Library at the University of Pittsburgh and aimed at identifying only studies on humans who underwent solid abdominal organ transplant (RT or LT). We used various combinations of keywords and MeSH terms pertinent to the exposure (AF), and outcomes of interest (graft and patient survival). MeSH terms for our search were: atrial, cardiac, heart, fibrillation, arrhythmia, transplant, transplantation, renal, kidney, liver, hepatic, graft, patient, recipient, survival. References reported in manuscripts with potential relevance and review articles were manually screened to identify any eligible studies that could have been missed by the electronic search. For duplicate publications, or for studies that reported the outcomes of cohorts at different times, only the most recent or the highest quality publications were included.

2.2. Inclusion and exclusion criteria

Studies that were appraised for this meta-analysis were selected based on their design, on the age of the study population, on what type of organs were transplanted, and on what types of outcomes were reported. The eligibility of each study was assessed independently by two investigators (MM and PS).

We included only randomized or quasi-randomized controlled studies, cohort and case-control studies on adults (age ≥ 18 years) with documented AF undergoing RT or LT. We did not differentiate if patients underwent first-time or redo transplant surgery or if they received deceased or live donor grafts.

AF had to be documented by electrocardiogram or by notes from intraoperative or postoperative medical records or cardiology consultations. For studies based on national or administrative datasets, AF had to be documented by inpatient claims or by ICD-8, ICD-9 or ICD-10 primary diagnosis codes.

To be included, studies had to report patient or graft survival using the hazard ratio (HR) with 95% confidence intervals (CI) or the

Table 1
Summary of the search strategy and the total number of potential studies retrieved and excluded during the systematic review of the literature. Medline (PubMed and Ovid), EMBASE, CINAHL, the Cochrane Collaboration Library, Google Scholar were searched with no language restrictions. Only studies on humans who underwent solid abdominal organ transplant surgery were evaluated for possible inclusion. Keywords and MeSH terms were used for our search.

	Search history	Total N. retrieved citations
1	Exp atrial fibrillation	50,362
2	Exp arrhythmias, Cardiac/	209,192
3	(Transplant or transplantation).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	606,678
4	(Renal or kidney).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	989,748
5	(Liver or hepatic).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,075,837
6	1 or 2	209,192
7	3 or 4	1,469,590
8	3 or 5	1,592,895
9	6 and 7	7040
10	6 and 8	4127
11	Limit 9 to humans	6474
12	Limit 10 to humans	3782
13	Survival Analysis/ or exp. Survival/ or exp. Survival Rate/ or exp. Graft Survival/	333,632
14	11 and 13 (renal transplant)	405
15	12 and 13 (liver transplant)	225

N. citations with abstracts that were reviewed	Number of excluded studies
Renal transplant (titles or abstracts reviewed): 405 Renal transplant (total citations entirely reviewed): 22 Liver transplant (titles or abstracts reviewed): 225 Liver transplant (total citations entirely reviewed): 15	Renal transplant: 402 Liver transplant: 221
N. citations included Renal transplant: 3 Liver transplant: 3	

Table 2
Summary of socio-demographic and clinical characteristics of the cohort of patients of included studies.

Primary author	Journal and year of publication	Total N. transplanted patients	Follow up	Socio-demographic and clinical characteristics of all patients	AF (+) patients	AF (−) patients	P value
Xia VW [24]	Am J Transpl; 2015	1387	6.5 years		Mean age = 58.8	Mean age = 54 y	P < 0.001
				Median age 56 (Range 18–80)	Body Mass Index = 29.6	Body Mass Index = 27.7	P < 0.007
					MELD Score = 35.5	MELD score = 31.7	P < 0.001
				Male gender: 64%	Previous history of AF = 28.4%	Previous history of AF = 3.7%	P < 0.001
					Combined kidney transplant = 9.2%	Combined kidney transplant = 7.7%	P = 0.606
				Mean MELD score: 32	Retransplantation = 11.5%	Retransplantation = 10.1%	P = 0.677
					Median survival = 1613 days	Median survival = 1446 days.	P = 0.003
					Acute kidney injury = 24.3%	Acute kidney injury = 11.8%	P = 0.026
				HCV infection: 41.5%	1,3,6-month recipient mortality = 10.8%, 19.6% and 23.5% respectively	1,3,6-month recipient mortality = 7.3%, 11.1% and 14.9% respectively	P < 0.001
				Alcohol cirrhosis: 23.1%	80% of postoperative AF occurred within the first week after liver transplantation. AF was present in 4.5% of patients prior to liver transplantation. Anticoagulation was used in 13% of recipients. Cardiovascular complications leading to death occurred in 3 AF (+) patients versus none in AF (−) recipients.		
Bargehr J [19]	Liver Transpl; 2015	717	5 years		Mean age = 58	Mean age = 58	P = 0.810
					Female sex = 44%	Female sex = 35%	P = 0.500
					Body Mass Index = 28.7	Body Mass Index = 29.3	P = 0.590
					MELD score = 25.3	MELD Score = 26.2	P = 0.677
					Anticoagulation = 13%	Anticoagulation = 0%	P = 0.010
					Patient survival = 1400 days (median 1613)	Patient survival = 1446 days (median 1495)	P = 0.440
					Graft survival = 1243 days (median 1516)	Graft survival = 1444 days (median 1495)	P = 0.140
					Number of patients who had died by the end of follow up period = 12 patients (38%)	Number of patients who had died by the end of follow up period = 18 patients (29%)	P = 0.440
Vannucci A [20]	Transpl Proceedings; 2014	757	1 year	AF was present in 2.5% of patients who had a mean age of 57.9 years. Males were 68.4% of AF (+) group, 26.3% were obese and average MELD score was 23.5. Alcoholic cirrhosis represented the main indication for liver transplant in 31.6% of patients, followed by hepatitis C (26.3%). All AF (+) patients had an adequate rate control.	30-day survival = 84.2% (relative risk of death at 1 month = 5.29; 95% CI 1.73–16.18; P = 0.034)	30-day survival = 97.1%	P = 0.006
					1-year survival =68.4% (relative risk of death at 1 year = 3.28; 95% CI 1.63–6.59; P = 0.008)	1-year survival = 90.4%	P = 0.011
Lenihan C [21]	Am J Transplant; 2013	62,706	5 years	AF was present in 6.4% of patients. AF (+) patients were older, had a higher burden of comorbidities. Mean follow up period was 4.9 years. During a mean follow-up period of 2.2 years, 2.8% of AF (+) patients had an ischemic stroke in comparison to 1.6% of AF (−) recipients.	Number of patients who had died by the end of follow up period = 1539 (40.6%)	Number of patients who had died by the end of follow up period = 14,642 (24.9%)	P = 0.000
					Number of graft losses by the end of follow up period = 1775 (46.8%)	Number of graft losses by the end of follow up period =	P = 0.001

(continued on next page)

Table 2 (*continued*)

Primary author	Journal and year of publication	Total N. transplanted patients	Follow up	Socio-demographic and clinical characteristics of all patients	AF (+) patients	AF (−) patients	P value
						21,466 (36.4%)	
					1- and 5-year patient survival were 85.7% (95% CI 84.5%–86.8%) and 59.3% (95% CI 57.4%–61.2%) respectively.	1- and 5-year patient survival were 94.4% (95% CI 94.2%–94.6%) and 80.2% (95% CI 79.8%–80.5%) respectively.	P = 0.001
					The hazard ratio for death = 2.40 (95% CI 2.28–2.54)		P = 0.001
					The adjusted hazard ratio for death = 1.46 (95% CI 1.38–1.54)		P = 0.001
					1- and 5-year graft survival were 79.4% (95% CI 78.1%–80.7%) and 51.7% (95% CI 49.7%–53.6%) respectively.	1- and 5-year graft survival were 89.1% (95% CI 88.9%–89.4%) and 67.6% (95% CI 67.2%–68.1%) respectively.	P = 0.001
					The adjusted hazard ratio for graft failure = 1.41 (95% CI 1.34–1.48)		P = 0.001
Lentine K [23]	Clin J Am Soc Nephrol; 2006	31,136	3 years	AF was present in 2.6% of patients at 6 months, 3.6% at 12 months and 7.3% at 36 months post-renal transplantation. The likelihood of developing AF was increased with age older than 60, male gender, white race, renal failure caused by hypertension, coronary artery disease.	The adjusted 1-year mortality after AF was 17.8% (95% CI 15.4%–20.1%) The adjusted 2-year mortality after AF was 23.7% (95% CI 20.7%–26.7%) Age-adjusted death-censored graft failure after AF at 1 year were: 10.3% (95% CI 8.2%–12.4%) Age-adjusted death-censored graft failure after AF at 2 years were: 13.8% (95% CI 11.1%–16.4%)		
					Hazard rate for death = 3.25 (95% CI; 2.92–3.63)		P < 0.05
					Hazard rate for death-censored graft loss = 1.93 (95% CI; 1.63–2.29)		P < 0.06
					Hazard rate for all causes of graft loss = 2.88 (95% CI; 2.60–3.12)		P < 0.07
Abbott KC [22]	2003	39,628	2 years	Median follow up was 1.9 years. Factors associated with an increased risk of developing AF were: age, male gender, higher body mass index, delayed graft function, renal failure caused by hypertension, rejection, graft loss. mean age: 43.4 years Male gender: 60% Body Mass Index: 25.2 Graft loss: 23.1%	Hazard ratio for patient mortality = 1.34 (95% CI; 1.06–1.69)		P = 0.013
					Adjusted hazard rate for graft loss = 1.83 (95% CI; 1.35–2.48)		P ≤0.0001

Table 3
Descriptive summary of study characteristics.

Primary author	Year of publication	Country	Transplanted organ	Study design	Case-control	Center	Time of diagnosis of AF	Study period	Total N. transplanted patients during the study period (136,331)	AF (+) total N. patients (6652)	AF (−) total N. patients (129,057)	Primary and secondary outcomes
Bargehr J [19]	2015	USA	Liver	Retrospective	Matched 1:2	Single (Mayo Clinic Florida)	Before transplantation	2005–2008	717	32	63	Patient survival Graft survival
Xia VW [24]	2015	USA	Liver	Retrospective	No matching	Single (University of California, Los Angeles)	After transplantation	2006–2013	1387	102	1285	Patient survival Graft survival
Vannucci A [20]	2014	USA	Liver	Retrospective	No matching	Single (Washington University St. Louis)	Before transplantation	2002–2011	757	19	738	Patient survival
Lenihan C [21]	2013	USA	Kidney	Retrospective	No matching	National Data (US renal Data System)	Before transplantation	1997–2009	62,706	3794	58,912	Patient survival Graft survival
Lentine K [23]	2006	USA	Kidney	Retrospective	No matching	National Data (US renal Data System + UNOS and Medicare data files)	After transplantation	1995–2001	31,136	2273	28,863	Patient survival Graft survival
Abbott KC [22]	2003	USA	Kidney	Retrospective	No matching	National Data (US renal Data System)	After transplantation	1994–1998	39,628	432	39,196	Patient survival

proportion of patients who were alive or who had died during the follow-up period. The odds ratio (OR) and their respective standard errors (SE) were calculated from the proportion of patients who were alive vs. patients who had died during the follow-up period.

2.3. Data extraction

One investigator (MM) extracted the data which were subsequently analyzed for accuracy by two other investigators (PS, AT). The data were abstracted from the published studies or their supplementary appendices or protocols when appropriate. Standardized paper forms were used to record the extracted data that were collected for this study. Variables that were recorded were: title of the published article, name of the primary author, year of publication, name of the scientific journal that published the study, number of participating centers that treated patients enrolled in the published study, sources of funding that supported the original study, recruitment period, total number of patients reported in each study, the design of the original investigation, socio-demographic and clinical characteristics of enrolled patients, estimates of patient and graft survival with their respective 95% confidence intervals (CI), if AF was diagnosed before or after surgery, country where the study was performed and what type of organ was transplanted.

2.4. Quality assessment

The systematic review of the literature did not identify any randomized controlled trial. The Newcastle-Ottawa Assessment Scale for case-control and cohort studies was used to assess the quality of the included studies. This scale contained eight multiple-choice questions that were related to the selection of patients, their comparability and their outcomes [8] and had been validated by several other investigators [9–11]. For every item of the Newcastle-Ottawa Assessment Scale that was satisfied, a symbol with the shape of stars was awarded. The maximum number of stars that each study could score was nine.

2.5. Data synthesis

The random-effect model [12], with weights calculated by the inverse variance method, was used to assess the pooled value of the estimates of the primary and secondary outcomes. The rationale for the use the random-effect model was based on the assumption that the effect sizes reported by different studies were dissimilar due to random events and that the true effect could vary from study to study [13–15].

2.6. Statistical analysis

The risk estimates for patient overall survival and graft survival (HR or OR with 95% CI) were adjusted for patients' characteristics such as age, gender and the primary cause of organ disease whenever possible. Heterogeneity among studies was assessed using the I^2 statistics [16]. I^2 values of 25%, 50%, and 75% were considered thresholds for the low, moderate, and high degree of heterogeneity [17]. Publication bias was visually evaluated by funnel plots, and quantified by Egger regression [18]. Comprehensive Meta-analysis (CMA) Version 3 (Biostat Inc) was used to conduct all statistical analyses. A 2-tailed P value of <0.05 was considered statistically significant.

3. Results

3.1. Search results

A search of Medline (PubMed and Ovid), EMBASE, CINAHL, the Cochrane Collaboration Library, and Google Scholar produced a total of 50,362 citations on AF. The number of publications on RT was

Table 4
Quality assessment based on the Newcastle-Ottawas Scale.

Primary author	Year of publication	Adequate definition of case	Representativeness of cases	Selection of control	Definition of control	Comparability of cases and controls	Exposure assessment	Same method of ascertainment for cases and controls	Nonresponsive rate	Total quality score
Bargehr J [19]	2015	★	★	★	★	★★	★	★		8
Xia VW [24]	2015	★	★	★	★	★	★	★		7
Vannucci A [20]	2014	★	★	★	★	★★	★	★		8
Lenihan C [21]	2013	★	★	★	★	★★	★	★		8
Lentine K [23]	2006	★	★	★	★	★★	★	★		8
Abbott KC [22]	2003	★	★	★	★	★	★	★		7

A study can be awarded a maximum of one star for each item except for the item for comparability that can be awarded with two stars.
A maximum of two stars can be awarded for the comparability.

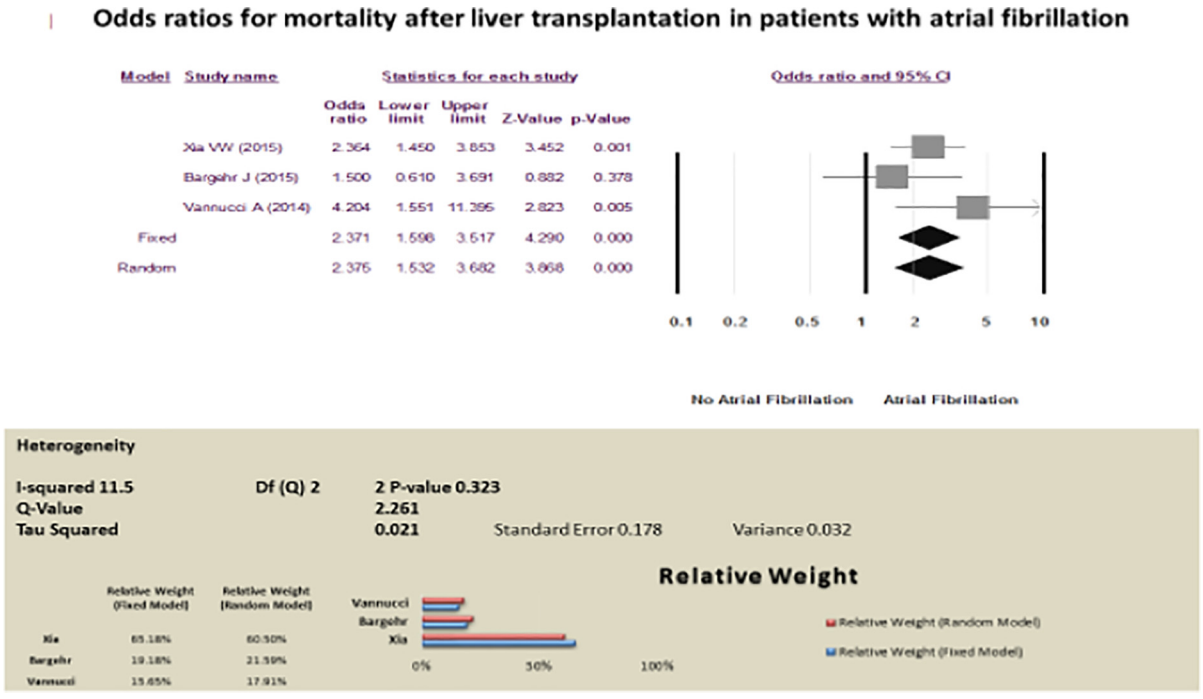
1,469,590 and on LT was 1,592,895. After Boolean logic was applied, we identified 405 citations of patients with AF and who underwent RT, and 225 citations pertinent to patients with AF and who underwent LT. Titles and abstracts of these 630 citations were reviewed and only 37 studies were suitable for the scope of our study.

After reviewing the complete content of these 37 manuscripts, we eliminated one as it was a duplicate publication, and 30 other citations because they did not meet at least one of the inclusion criteria. For the purpose of our systematic review and meta-analysis, six studies were included with a total of 135,709 patients (Table 1).

3.2. Study characteristics

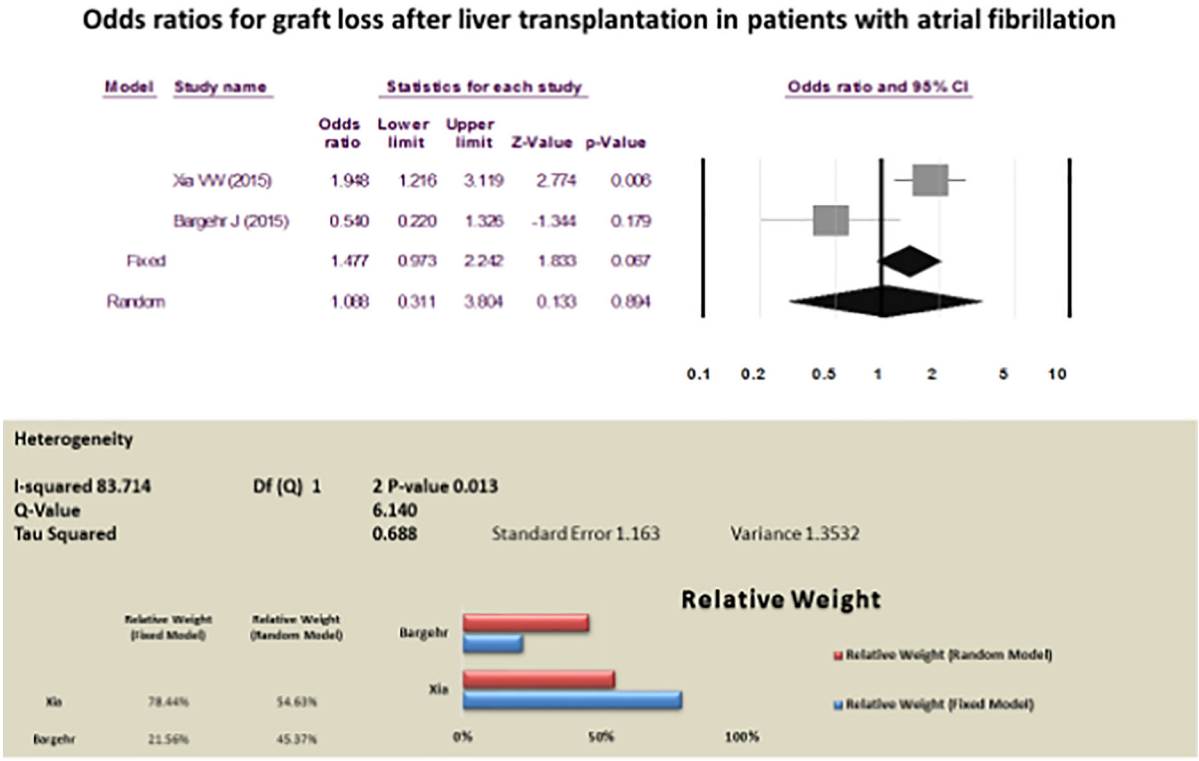
Tables 2 and 3 summarize the characteristics relative to the included studies and their patient populations, respectively. All studies were retrospective and described the outcomes of patients treated in tertiary medical centers located in the United States or reported the outcomes of patients transplanted in the United States and entered into large national datasets.

Preoperative AF was reported in three studies [19–21] and postoperative AF in the remaining citations [22–24]. Abbott et al. [22] reported



Primary Author	Year of publication	AF (+) Total N. Patients	AF (-) Total N. Patients	Transplanted Organ	AF (+) Deaths	AF (-) Deaths	AF (+) Alive	AF (-) Alive	Odds Ratio
Bargehr J [19]	2015	32	63	Liver	12	18	20	45	1.5
Xia VW [24]	2015	102	1,285	Liver	24	148	78	1137	2.364
Vannucci A [20]	2014	19	738	Liver	6	73	13	665	4.204

Fig. 1. Forest plot of patient mortality after liver transplantation in patients affected by atrial fibrillation. The size of the data maker representing each study is proportional to its weight. Outcomes of patients with preoperative atrial fibrillation were extracted from data reported by Vannucci et al. [20] and Bargehr et al. [19]. Outcomes of patients who developed atrial fibrillation after liver transplantation were extracted from the study by Xia et al. [24].



Primary Author	Year of publication	AF (+) Total N. Patients	AF (-) Total N. Patients	Transplanted Organ	AF (+) Lost Grafts	AF (-) Lost Grafts	AF (+) Viable Grafts	AF (-) Viable Grafts	Odds Ratio
Bargehr J [19]	2015	32	63	Liver	19	46	13	17	0.54
Xia VW [24]	2015	102	1,285	Liver	26	192	76	1093	1.94
Vannucci A [20]	2014	19	738	Liver	-	-	-	-	-

Fig. 2. Forest plot of Graft loss after liver transplantation in patients affected by atrial fibrillation. The size of the data maker representing each study is proportional to its weight. Xia et al. [24] reported outcomes of patients with postoperative atrial fibrillation while Bargehr et al. [19] analyzed patients with preoperative atrial fibrillation.

that 50% of patients with postoperative AF after RT were diagnosed within the first two years, and Lentine et al. [23] found that 7% of all RT recipients developed AF within three years after surgery. In contrast, AF in LT recipients occurred within the first month after surgery [24].

One study (Bargehr et al.) [19] matched AF(+) patients undergoing LT to AF(−) patients with a ratio 1:2. The rest of the studies reported the outcomes of AF(+) patients versus AF(−) recipients without matching patients by their baseline characteristics. All three studies on LT were single-center and used odds ratios (OR) to report patient survival. On the other hand, the three studies on RT recipients used national datasets (US Renal Data System, United Network of Organ Sharing (UNOS) or Medicare Data Files) and hazard ratios (HR) with respective 95% CIs were used to report patient and graft survivals.

The overall quality of the six studies was good and it is summarized in Table 4. Two studies received 7 stars and the remaining four were scored with 8 stars.

3.3. Primary and secondary outcomes for liver transplant recipients

LT was performed on 2239 recipients. Among them, 153 were affected by AF (6.8% of the cohort). During the postoperative follow-up period, 27.4% of AF(+) recipients had died in comparison to 11.4% of AF(−) patients. The OR for postoperative mortality in AF(+) recipients was significantly higher than in AF(−) patients: OR = 2.375 (95% CI; 1.532–3.682) (P = 0.000) (Fig. 1).

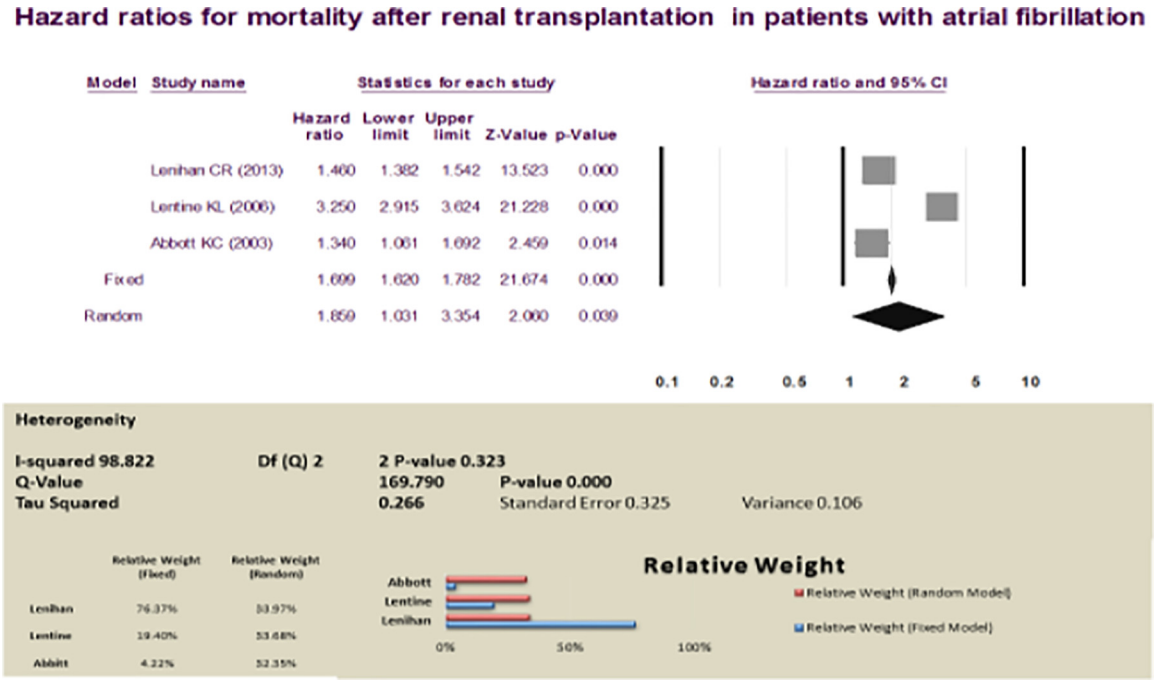
The OR for postoperative mortality in LT patients who were diagnosed with AF before undergoing LT was 2.384; 95% CI; 1.220–4.650) (P = 0.011); I^2 of 55.7%) [19,20].

Data on graft survival was available for 1482 recipients [19,24]. During the follow-up period, 33.5% of AF(+) patients experienced graft loss in comparison to 17.6% of AF(−) recipients. Due to the small number of LT patients who had AF, the OR for graft loss in AF(+) patients was not statistically significantly different to AF(−) recipients: OR = 1.088 (95% CI; 0.311–3.804) (P = 0.894) (Fig. 2).

3.4. Primary and secondary outcomes for renal transplant recipients

RT was performed on 133,470 recipients. AF affected 6499 individuals (4.8% of the cohort). The presence of AF was associated with an almost two-fold increase of the HR for postoperative mortality: HR = 1.859 (95% CI; 1.031–3.354) (P = 0.039) (Fig. 3).

When only patients diagnosed with postoperative AF were included, we found that the HR was increased but did not reach statistical



Primary Author	Year of publication	AF (+) Total N. Patients	AF (-) Total N. Patients	Transplanted Organ	Hazard Ratio	95% CI
Lenihan C [21]	2013	3,794	58,912	Kidney	1.46	1.38-1.54
Lentine K [23]	2006	2,273	28,863	Kidney	3.25	2.92-3.63
Abbott KC [22]	2003	432	39,196	Kidney	1.34	1.06-1.69

Fig. 3. Forest plot of patient mortality after renal transplantation in patients affected by atrial fibrillation. The size of the data maker representing each study is proportional to its weight. Outcomes of patients with preoperative atrial fibrillation were extracted from data reported by Lenihan et al. [21]. Outcomes of patients who developed atrial fibrillation after kidney transplantation were extracted from the study by Lentine et al. [23] and by Abbott et al. [22].

significance in comparison to AF(−) recipients: HR = 2.100 (95% CI; 0.881–5.003) (P = 0.094); I^2 of 97.8%) [22,23].

Data on graft survival was available for 93,842 recipients [21,23]. When compared to AF(−) recipients, the HR for graft loss in the presence of AF was significantly higher: HR = 1.632 (95% CI; 1.200–2.218) (P = 0.002) (Fig. 4).

3.5. Heterogeneity and publication bias

The heterogeneity among studies was high except for studies reporting patient survival after LT (I^2 = 11.5%). I^2 was 83.7% for graft loss after LT, 98.8% for patient survival after RT and 91.7% for graft loss after RT.

Funnel plots did not show significant asymmetry, suggesting that the risk of publication bias was low. Rosenthal's fail-safe N test [25] was used to calculate how many negative studies were needed to make the results of the meta-analysis not significant (i.e. the number of negative studies needed to increase the P-value above 0.05). For patient survival after LT, the number of negative studies needed was 11 and for RT, the number of negative studies was 358.

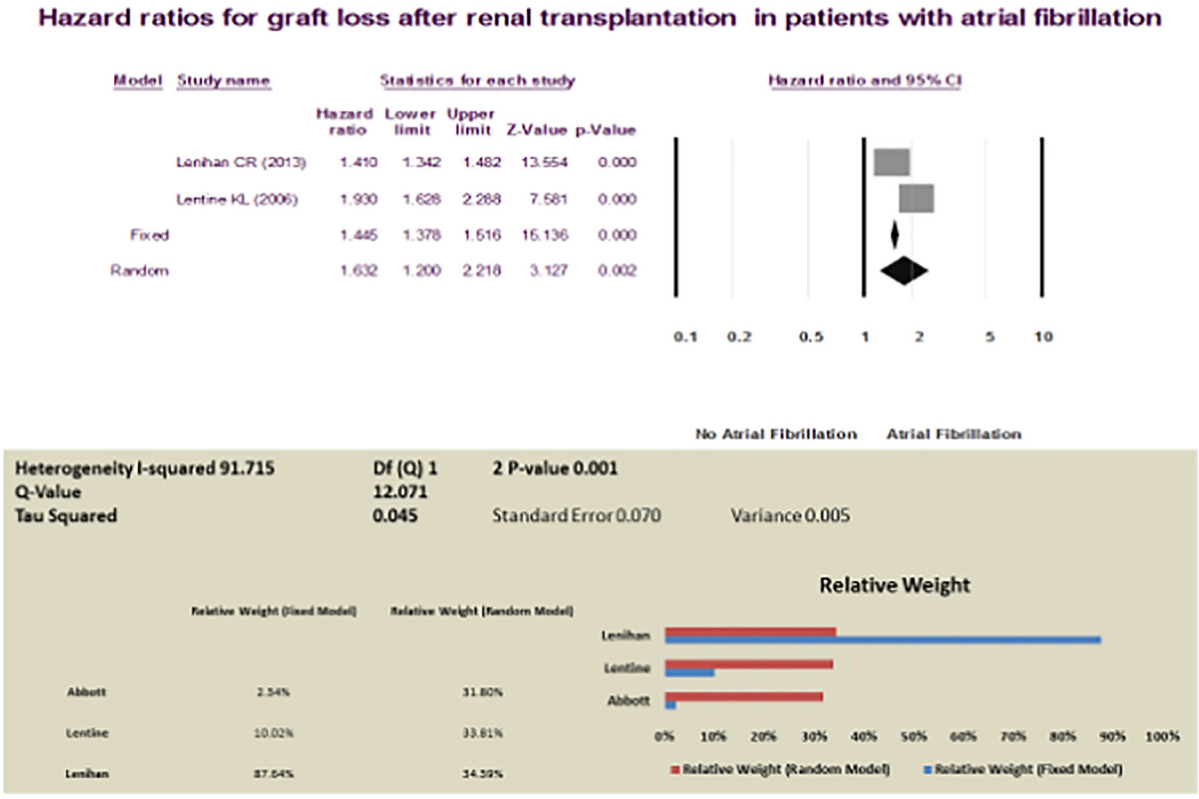
4. Discussion

The prevalence of AF increases with advanced age, the presence of obesity, diabetes and coronary ischemia that are commonly seen in the general population of high-income countries where AF affects 5 to 7% of people older than 65 [2,3].

During the last decades, the proportion of older patients undergoing abdominal transplantation has steadily increased [26]. Consequently, it is expected that the number of patients with preoperative AF or at risk of developing AF after transplant will continue to rise. Yet, the possible association of AF and patient and graft survival after RT or LT is not well understood. Recent investigations have reported conflicting results with some studies showing no significant differences while others showing that AF(+) patients have inferior overall and graft survival. Because of these inconsistencies, we performed a systematic review of the literature and, after appraising the quality of the existing studies, we aimed at assessing if they could be included in a meta-analysis. Our primary aim was to assess if AF was associated with inferior patient and graft survival.

The main findings of our study were that in the presence of AF the mortality risk was increased with an OR of 2.3 for LT recipients and a HR of 1.8 for patients undergoing RT. The risk of graft loss did not show a statistically significant difference after LT, most likely due to the small number of LT patients with AF. On the other hand, after RT, the risk of graft loss was significantly higher in AF(+) recipients with a HR of 1.6. Unfortunately, subgroup analyses to assess if there were differences between patients with paroxysmal, sustained or chronic AF were not feasible due to the limited number of publications.

AF is common in patients requiring major thoracic surgeries [27] because of the stimulation or irritation of the pericardium or the cardiac innervation during the operations [28,29]. However, this does not apply to patients undergoing abdominal transplantation. For this group of patients, the presence of AF should be viewed as a clinical manifestation of pre-existing cardiopulmonary diseases that, added to the



Primary Author	Year of publication	AF (+) Total N. Patients	AF (-) Total N. Patients	Transplanted Organ	Hazard Ratio	95% CI
Lenihan C [21]	2013	3,794	58,912	Kidney	1.41	1.34-1.48
Lentine K [23]	2006	2,273	28,863	Kidney	3.28	2.84-3.81
Abbott KC [22]	2003	432	39,196	Kidney	1.83	1.35-2.48

Fig. 4. Forest plot of graft loss after renal transplantation in patients affected by atrial fibrillation. The size of the data maker representing each study is proportional to its weight. Outcomes of patients with preoperative atrial fibrillation were extracted from data reported by Lenihan et al. [21]. Outcomes of patients who developed atrial fibrillation after kidney transplantation were extracted from the study by Lentine et al. [23].

increased risk of embolic events observed with AF, could explain why AF (+) patients had inferior outcomes in comparison to their counterparts. These findings are relevant for clinicians who are in the process of evaluating or selecting potential transplant candidates as AF(+) patients might require extra-precautions since they appear to be at an increased risk of death and graft loss.

Despite the fact that AF is a relatively common condition, our systematic review did not identify any prospective study. We also found that there was a significant heterogeneity among the included studies. However, even in the presence of heterogeneity in follow-up, immunosuppression regimens and data reporting, we came to the consensus that a meta-analysis could be performed since all the studies had comparable designs, had similar primary and secondary objectives, their patient characteristics were not excessively different, the diagnosis of AF was documented using analogous methodologies, and patient and graft survivals were reported for the majority of patients as the attrition rate was negligible.

Besides the limitations due to the small number of included studies, we think that this meta-analysis has some merits worth mentioning. First of all its novelty, and secondly the rigorous methodology used to identify and appraise the quality of the existing literature and the strict definitions for the inclusion and exclusion criteria.

In summary, to the best of our knowledge, this is the first systematic review and meta-analysis that explored the association between AF and patient and graft survival after abdominal transplant surgery. Our results suggest that the overall survival of AF(+) liver and kidney transplant recipients are inferior to their counterparts. The most probable biological reason for these findings is that AF is a manifestation of intrinsic cardiopulmonary diseases that might contribute to the increased risk of mortality. We also found a negative association between renal graft survival and AF. Due to the lack of granular data, we could not investigate what were the main causes of increased graft loss in AF(+) patients. One of the possible explanations is that patients with AF are often treated with systemic anticoagulation to prevent catastrophic embolic events. Due to the increased risk of bleeding, it is possible that AF(+) RT recipients were less likely biopsied to rule out rejection in the presence of graft dysfunction.

Because AF is a common condition, our findings indicate that further studies are needed to better understand the effects of AF on the outcomes of patients who need arenal or liver transplant.

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