

# Incidence, Predictors, and Outcomes of Early Atrial Arrhythmias After Lung Transplant

## A Systematic Review and Meta-Analysis

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### ABSTRACT

**OBJECTIVES** This study sought to determine the incidence, predictors, and prognostic implications of early post-lung transplant atrial arrhythmias (AAs).

**BACKGROUND** Although frequently encountered, the prognostic implications of early AAs after lung transplant remain uncertain.

**METHODS** A systematic review of MEDLINE and the Cochrane Library was conducted for all studies that reported early post-lung transplant AAs. Random-effects DerSimonian-Laird risk ratios (RRs) were calculated for categorical variables and standardized mean difference (SMD) for continuous variables.

**RESULTS** A total of 12 studies with 3,203 patients (mean age  $57 \pm 3$  years; 52% males) were included. The incidence of early post-lung transplant AAs during hospitalization was 26.6% at mean follow-up duration of 6.7 days. Predictors of post-lung transplant AAs included advanced age (SMD: 0.50; 95% confidence interval [CI]: 0.35 to 0.64), male gender (RR: 1.37; 95% CI: 1.28 to 1.47), history of smoking (RR: 1.23; 95% CI: 1.05 to 1.46), hypertension (RR: 1.35; 95% CI: 1.13 to 1.59), hyperlipidemia (RR: 1.39; 95% CI: 1.18 to 1.63), coronary artery disease (RR: 1.40; 95% CI: 1.12 to 1.7), left atrial diameter (SMD: 0.25; 95% CI: 0.07 to 0.44), and restrictive lung disease (RR: 1.34; 95% CI: 1.13 to 1.59). Post-lung transplant AAs were associated with increased all-cause mortality (adjusted RR: 1.63; 95% CI: 1.22 to 2.19) at mean follow-up of 27.8 months and length of hospital stay ( $36.5 \pm 16.5$  days vs.  $26.1 \pm 14.3$  days;  $p < 0.001$ ).

**CONCLUSIONS** Early AAs post-lung transplant are associated with increased mortality and length of hospital stay. Advanced age, male sex, smoking, hypertension, hyperlipidemia, coronary artery disease, increased left atrial diameter, and restrictive lung disease are independent predictors of early AAs in post-lung transplant patients. (J Am Coll Cardiol EP 2017;■:■-■) © 2017 by the American College of Cardiology Foundation.

In the United States, the rate of lung transplantation has dramatically increased in the past 2 decades, with 1,946 surgeries reported in 2013 (1,2). Unfortunately, 5-year survival for lung

transplant patients has plateaued at 54%, which is significantly lower than the 5-year survival for other solid organ recipients (2-5). In addition, implementation of the Lung Allocation Score in 2005 (6) resulted

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## ABBREVIATIONS AND ACRONYMS

**AA** = atrial arrhythmia

**CABG** = coronary artery bypass grafting

**CI** = confidence interval

**LAD** = left atrial diameter

**OR** = odds ratio

**RR** = risk ratio

**SMD** = standardized mean difference

in sicker patients becoming candidates for this surgery, thus adding to the challenges of post-operative care in these patients (2). Atrial arrhythmias (AAs) commonly occur after lung transplantation, complicating 20% to 45% of cases (7-10). This is comparable to the incidence of AAs after major cardiac surgeries, including heart transplantation and coronary artery bypass grafting (CABG) (11,12). Although early AAs are associated with increased morbidity and mortality after cardiac surgery (13), there are limited data on its prognostic implications after lung transplant (7-10,14-17). The aim of this study was to determine the incidence and predictors of early AAs after lung transplantation and to establish their prognostic implications by assessing all-cause mortality and length of hospital stay in these patients.

## METHODS

This meta-analysis was conducted according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (18). A systematic review of MEDLINE and the Cochrane Library was conducted from inception until July 2016, without language restriction, using the keywords “lung,” “transplant,” “atrial,” and “arrhythmia.” The references of the yielded articles were reviewed for additional studies not retrieved from the original search. Figure 1 shows the study selection method used for this analysis. This meta-analysis was registered with the International Prospective Register for Systematic Reviews or PROSPERO (CDR42016033229).

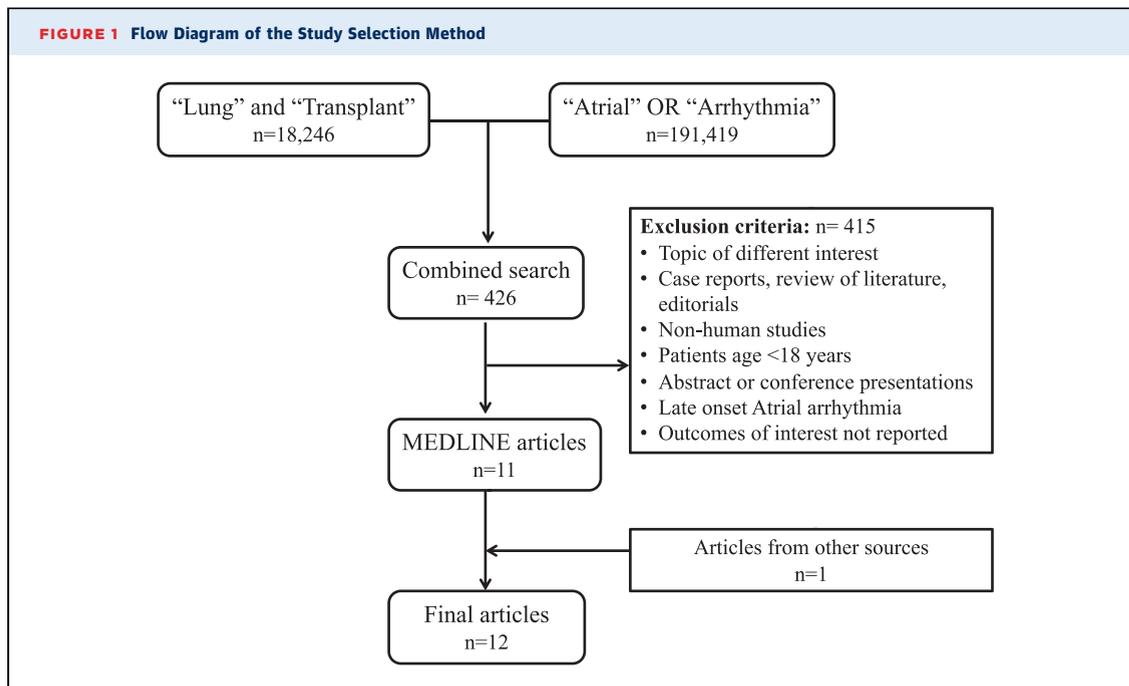
**SELECTION CRITERIA AND DATA EXTRACTION.** Studies that reported the incidence and/or predictors of early post-lung transplant AAs were included. In order to fulfill the definition of early AAs, we included only studies with a mean AA incidence of a maximum 2 weeks from lung transplant operation. Each study had to include a group of patients experiencing AAs and a control group that did not experience AAs post-transplant for comparison. In order to calculate the risk ratio (RR), only articles that reported quantitative raw data for predictors and outcomes were considered. For the purpose of this study, we defined AAs as atrial fibrillation and/or atrial flutter. Data extracted were independently reviewed by 2 authors (M.S. and A.N.M.), and discrepancies were resolved by consensus. Data retrieved included study design, patient characteristics, underlying lung disease, type of transplant (i.e., single lung, double lung, or heart-lung transplant),

procedure characteristics (i.e., cardiopulmonary bypass, ischemic time, and use of vasopressors), various cardiovascular parameters (i.e., left atrial diameter [LAD], left ventricular ejection fraction, and history of preoperative AAs), all-cause mortality outcome, and in-hospital length of stay. All-cause mortality events and mean in-hospital length of stay were tabulated. The quality of included studies was assessed using the Newcastle-Ottawa Scale for cohort studies (19). The overall quality of evidence of all-cause mortality outcome was assessed by the Grading of Recommendations Assessment, Development and Evaluation score (GRADE) tool as recommended by Guyatt et al. (20).

**OUTCOMES AND DEFINITIONS.** The outcomes of this meta-analysis included 1) total incidence of early AAs after lung transplant; 2) predictors of early post-lung transplant AAs; and 3) impact of early AAs after lung transplant on all-cause mortality and hospital length of stay. The outcome of stroke could not be evaluated because it was reported by only 1 study (16). Other outcomes such as mechanical ventilator days and immediate post-operative length of stay also could not be obtained.

Predictors included in the analysis were agreed on by consensus after reviewing the previous literature on risk factors and incidence of AAs after heart transplant (9,15,21). Such predictors included, but were not limited to, baseline characteristics (i.e., age, gender, race and comorbidities such as hypertension, hyperlipidemia, and diabetes mellitus), peritransplant parameters (i.e., etiology of lung disease, type of lung transplant, and procedure characteristics), and cardiovascular parameters as stated previously.

**STATISTICAL ANALYSIS.** Descriptive analyses were conducted using frequency for categorical variables and mean  $\pm$  SD for continuous variables. Hazard ratio, odds ratio (OR), and 95% confidence interval (CI) for various predictors of AA and mortality were gathered if reported by the study. DerSimonian and Laird's random-effects model (22) was used to calculate summary RR for all categorical outcomes/predictors of interest and standardized mean difference (SMD) for all continuous outcomes/predictors. Summary unadjusted RRs were calculated for all predictors of AA using the reported events in each arm. In case of absence of reported events for any predictor, the adjusted effect size was used for calculation of summary adjusted RRs. The incidence of post-lung transplant AA was plotted over time to evaluate whether a correlation between the incidence of AA and year of patients' enrollment (i.e., time era) exists.



For the outcome of all-cause mortality, we calculated both unadjusted and adjusted summary RRs (using the adjusted hazard ratio reported in each study). If adjusted OR was reported by the individual study, we converted OR to RR using a previously published formula (23). CIs were calculated at the 95% level for the overall estimates effect, and 2-tailed  $p < 0.05$  was considered significant. Statistical heterogeneity was evaluated by  $I^2$  statistic value, with values  $<25\%$  considered of low heterogeneity and values  $>50\%$  considered of high heterogeneity (24). Publication bias was calculated using the Egger method (25). All analyses were performed using STATA software version 14 (StataCorp, College Station, Texas).

## RESULTS

A total of 12 observational studies with 3,203 patients (mean age  $56.8 \pm 3.1$  years; 51.8% males) were included for analysis (7-10,14-17,21,26-28). Of these studies, 3 explicitly excluded patients with preoperative AAs; 4.7% of the population in the other 9 studies had a history of preoperative AAs. AAs were defined in 7 studies (7,8,10,15,16,21,26) as either atrial fibrillation or flutter and in 5 studies (9,14,17,27,28) as atrial fibrillation only. Lung transplant was performed for obstructive lung disease (chronic obstructive lung disease, alpha<sub>1</sub>-antitrypsin deficiency and cystic fibrosis) in 39.3%, restrictive lung disease (interstitial lung disease, idiopathic pulmonary fibrosis, and

sarcoidosis) in 41.5%, and other etiologies including pulmonary vascular disease in 19.2% of the cohort. Data on the type of lung transplant were reported in 9 studies; double lung transplant, single lung transplant, and combined heart-lung transplant were performed in 68%, 31.4% and 0.6%, respectively. Data about cardiopulmonary bypass were reported in 2 studies (14,15). Baseline characteristics of both the early AAs and control groups are summarized in Table 1. Of the 12 included studies, 10 were considered high quality according to the Newcastle-Ottawa Scale for cohort studies (Table 2).

**INCIDENCE AND PREDICTORS OF EARLY POST-LUNG TRANSPLANT AA.** The overall incidence of early post-lung transplant AAs was 26.6% (95% CI: 21.8% to 31.5%) at a weighted mean duration of  $6.7 \pm 2.5$  days after surgery (Online Figure 1). Predictors of early post-lung transplant AAs included advanced age ( $55.22 \pm 5.6$  years in AAs group vs.  $49.23 \pm 6.6$  years in control group; SMD: 0.49; 95% CI: 0.35 to 0.64;  $p < 0.001$ ), male gender (RR: 1.37; 95% CI: 1.28 to 1.47;  $p < 0.001$ ), previous smoking history (RR: 1.23; 95% CI: 1.05 to 1.46;  $p = 0.01$ ), hypertension (RR: 1.35; 95% CI: 1.13 to 1.59;  $p = 0.001$ ), hyperlipidemia (RR: 1.39; 95% CI: 1.18 to 1.63;  $p < 0.001$ ), coronary artery disease (RR: 1.40; 95% CI: 1.12 to 1.7,  $p = 0.004$ ), LAD (SMD: 0.25; 95% CI: 0.07 to 0.44;  $p = 0.008$ ), and restrictive lung disease (RR: 1.34; 95% CI: 1.13 to 1.59;  $p = 0.001$ ) (Figure 2). Diabetes mellitus (RR: 0.84; 95% CI: 0.55 to 1.27;  $p = 0.40$ ), double lung transplant (RR: 1.01; 95% CI: 0.91 to 1.12;  $p = 0.83$ ), chronic

**TABLE 1** Baseline Patient Characteristics in the Included Studies

Study Authors (Ref. #)	Study Year	Patients, n	Type of LT	Age, yrs	Male, %	HTN, %	CAD, %	Double LT, %	Obstructive LD, %	Restrictive LD, %	Mean Follow-Up, months
D'Angelo et al. (21)	2016	198/454	Single and double	N/A*	66/55	47/33	30/22	83/86	36/35	55/44	60
Chaikriangkrai et al. (16)	2015	73/220	Single and double	60/56	74/52	58/53	45/40	73/69	23/27	70/63	28
Raghavan et al. (14)	2015	46/85	Single and double	60/55	65/54	NR	NR	91/85	30/26	57/53	17.4
Orrego et al. (9)	2014	65/273	Single and double	NR	79/53	39/30	23/10	71/65	32/29	51/36	12
Malik et al. (27)	2013	27/147	Single, double and heart	56/49	74/54	30/24	7/7	NR	41/19	56/58	NR
Henri et al. (15)	2012	65/159	Single and double	54/44	66/43	23/15	11/3	57/56	NR	40/10	0.6†
Azadani et al. (17)	2011	35/234	Single and double	60/52	74/53	NR	NR	69/85	14/25	71/45	NR
Isiadinso et al. (10)	2011	62/75	Single, double and heart	59/57	65/47	NR	23/24	42/37	48/57	34/33	6.6
Lee et al. (26)	2010	94/233	Single and double	NR	NR	NR	NR	NR	NR	NR	NR
See et al. (28)	2009	78/120	Double	42/36	36/42	NR	NR	NR	NR	NR	NR
Mason et al. (8)	2007	68/265	Single and double	54/47	65/48	22/10	35/22	29/45	54/51	34/25	NR
Nielsen et al. (7)	2004	78/120	Single and double	53/48	NR	NR	NR	NR	53/49	24/13	NR

\*Reported as categorical values. †Median follow-up duration reported.

AA = atrial arrhythmia; CAD = coronary artery disease; HTN = hypertension; LD = lung disease; LT = lung transplant; N/A = not applicable; NR = not reported.

obstructive pulmonary disease (RR: 1.04; 95% CI: 0.91 to 1.20;  $p = 0.55$ ), reduced left ventricular ejection fraction (SMD:  $-0.008$ ; 95% CI:  $-0.18$  to  $-0.17$ ;  $p = 0.93$ ), and ischemic time (SMD:  $0.01$ ; 95% CI:  $-0.22$  to  $-0.25$ ;  $p = 0.91$ ) were not significant predictors for early AAs after lung transplant. In addition, pre-operative AAs were not a predictor of early post-transplant AAs (adjusted RR: 1.66; 95% CI: 0.22 to 12.24;  $p = 0.62$ ). Furthermore, the incidence of post-lung transplant AA did not change by the time of enrollment (Online Figure 2). Online Table 1 summarizes the variables used in each study for determination of the predictors of AA.

**ALL-CAUSE MORTALITY AND IN-HOSPITAL LENGTH OF STAY.** All-cause mortality was reported by 7 studies (8-10,14-16,21). All of these were considered high-quality studies according to the Newcastle-Ottawa Scale. The overall quality of evidence for all-cause mortality outcome was moderate by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment tool (Online Table 2). The incidence of all-cause mortality was higher in subjects who developed early AAs compared with those who did not (37.1% vs. 21.9%; unadjusted RR: 1.69; 95% CI: 1.34 to 2.13,  $p < 0.001$ ;  $I^2 = 40\%$ ) at a weighted mean follow-up of  $27.8 \pm 22.7$  months (Figure 3). Four studies reported adjusted RRs for all-cause mortality (10,15,16,21). Summary random-effects analysis of the adjusted RRs showed an increased risk of all-cause mortality with early post-lung transplant AAs compared with the control group (RR: 1.63; 95% CI: 1.22 to 2.19;  $p = 0.001$ ) (Figure 4). There was no evidence of publication bias ( $p = 0.52$ ). Online Table 3 summarizes the independent variables used in each study for calculating adjusted effect size of all-cause mortality with AA. Subjects who developed early AAs after lung transplant had a longer hospital stay compared with those with no AAs ( $36.5 \pm 16.5$  days vs.  $26.1 \pm 14.3$  days; SMD: 0.40; 95% CI: 0.19 to 0.62;  $p < 0.001$ ;  $I^2 = 66$ ).

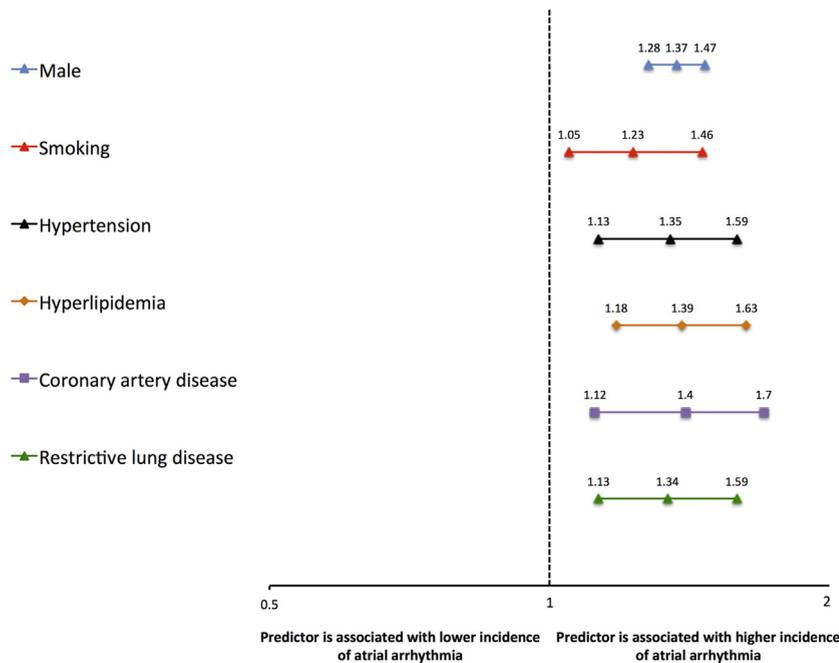
## DISCUSSION

The current meta-analysis of 12 studies with 3,203 patients who underwent single or double lung transplant demonstrated a high incidence of early post-operative AAs, similar to previously reported

**TABLE 2** Quality of Included Studies According to Newcastle-Ottawa Scale for Cohort Studies

Study Authors (Ref. #)	Study Year	Selection	Comparability	Outcome
D'Angelo et al. (21)	2016	***	*	***
Chaikriangkrai et al. (16)	2015	***	*	****
Raghavan et al. (14)	2015	**	*	***
Orrego et al. (9)	2014	***	*	*****
Malik et al. (27)	2013	**	n/a	**
Henri et al. (15)	2012	***	*	****
Azadani et al. (17)	2011	***	*	***
Isiadinso et al. (10)	2011	***	*	***
Lee et al. (26)	2010	****	**	***
See et al. (28)	2009	***	*	****
Mason et al. (8)	2007	***	**	*****
Nielsen et al. (7)	2004	**	*	****

A study with 7 or more \* is considered of high quality.

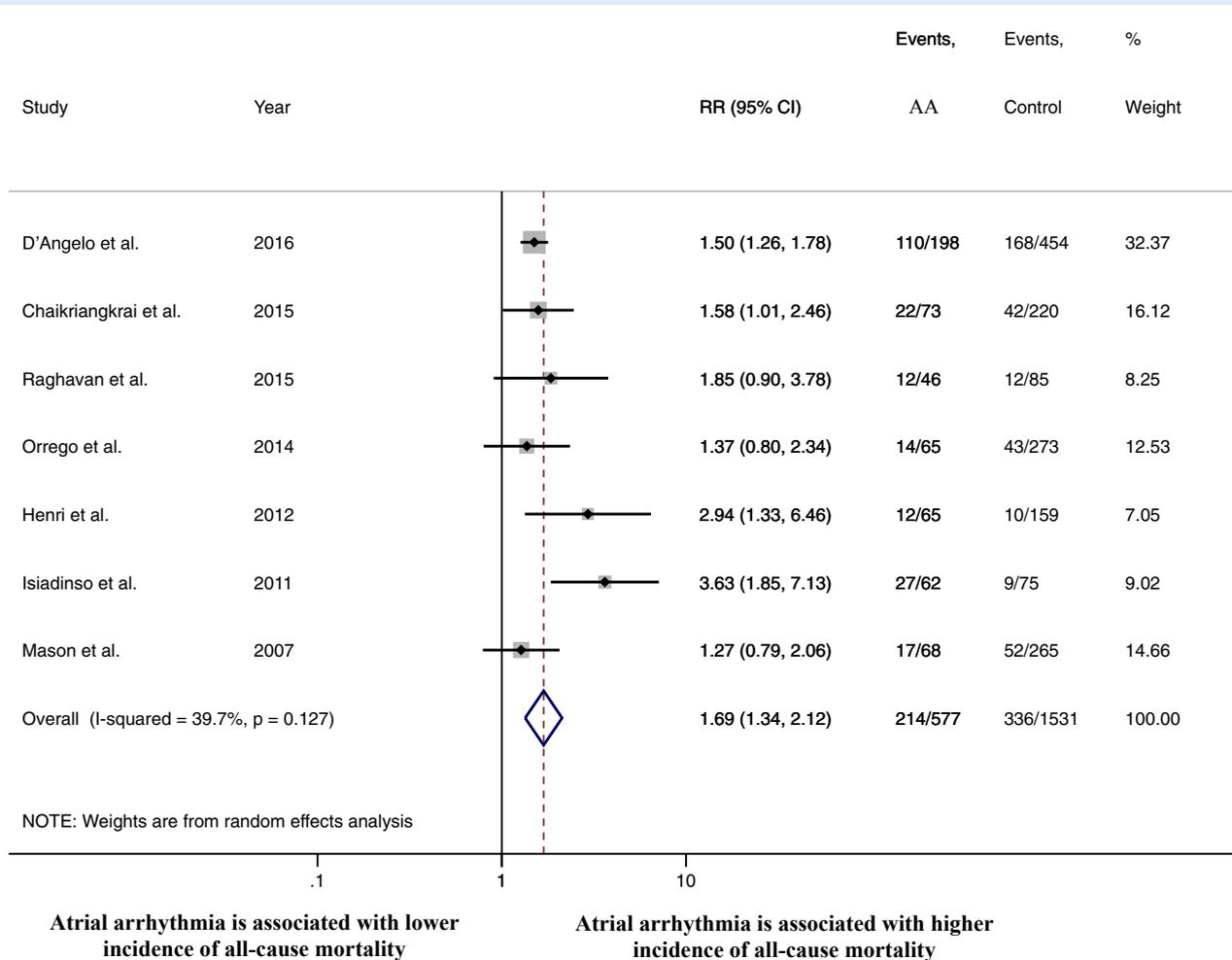
**FIGURE 2** Summary Unadjusted Risk Ratios of Statistically Significant Predictors of Atrial Arrhythmia by DerSimonian and Liard Random-Effects Model

incidences after major cardiothoracic surgeries such as CABG and heart transplant (29-31). Major predictors for early post-lung transplant AAs included increased age, male gender, history of smoking, hypertension, hyperlipidemia, coronary artery disease, LAD, and underlying restrictive lung disease. We also demonstrated that the development of early AAs after lung transplant may have important prognostic implications. Early AAs after lung transplantation were associated with an increased risk of all-cause mortality. This association was observed even after adjustment for several comorbidities, including age, hypertension, and coronary artery disease, arguing for an independent association between early post-transplant AA and all-cause mortality. However, it is possible that early post-transplant AAs represent a marker of an underlying sicker population of patients who have higher chances of both short- and long-term mortality.

It is hypothesized that the increased incidence of early AAs after lung transplantation is a result of high circulating levels of inflammatory mediators in the post-operative period (9,32), along with amplified sympathetic activity after surgery (33). Our study suggests that the substrate of AA in those patients is the recipient's left atrium, based on the lack of benefit of double lung transplant (in which complete surgical

pulmonary vein isolation is performed) compared with single lung transplant.

Multiple large multicenter studies have demonstrated that AAs are associated with both early and late mortality after CABG and heart transplantation (13,29-31,34-36). Patients with and without AAs had a survival difference that was evident early and increased with time (29). Our study demonstrated that certain patient characteristics are independent risk factors for early AAs after lung transplant. Careful monitoring of these patients for early AAs after surgery and consideration for anticoagulation therapy, if not contraindicated, may be beneficial. Anticoagulation therapy with warfarin has been associated with a reduction in risk of long-term mortality in CABG patients who developed AAs (29). Current American College of Chest Physicians and American College of Cardiology/American Heart Association guidelines (37) recommend the use of beta-blockers and amiodarone for the prevention and management of post-CABG AAs based on a few studies that have shown reduction in the incidence of arrhythmias and possible reduction in hospital cost with such medications (38-41). However, a recent study demonstrated similar outcomes and length of hospital stay in patients treated with rate versus rhythm control for post-cardiac surgery atrial fibrillation,

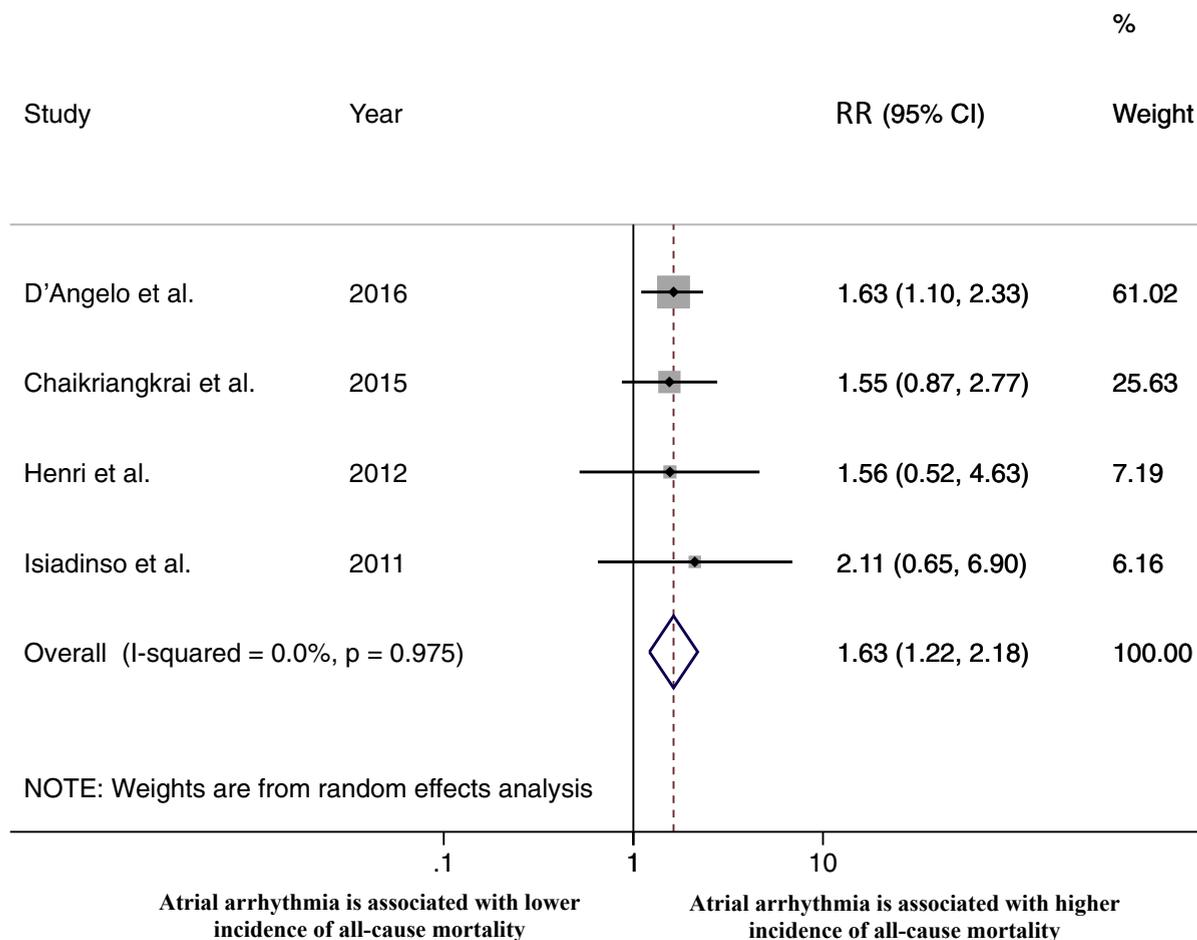
**FIGURE 3** Summary Unadjusted Risk Ratio of All-Cause Mortality by DerSimonian and Laird Random-Effects Model

Relative size of the data markers indicates the weight of the sample size from each study. AA = atrial arrhythmia; CI = confidence interval; RR = risk ratio.

with overall low incidence of persistent atrial fibrillation at 60 days after its onset (42). Additionally, there are anecdotal data on the benefit of statins and ranolazine for the prevention and management of post-cardiac surgery atrial fibrillation (43-46). Although the incidence of early post-lung transplant AAs is comparable to that after cardiac surgery, studies evaluating the best management strategies for early post-lung transplant AAs are lacking; therapeutic options for these patients have thus far been extrapolated from studies that addressed early AAs in post-CABG patients (7-10,14-17).

In the present meta-analysis, we only included studies that reported atrial fibrillation and/or atrial flutter post-lung transplant, mainly because of the difference in pathophysiology and management of

such AAs compared to other atrial tachyarrhythmia (e.g., atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, and atrial tachycardia). Both atrial fibrillation and flutter are associated with a higher risk of stroke, which is not the case for other AAs (47). Although establishing an association between early AAs and early/late stroke incidences is important in lung transplant recipients, most of the included studies did not report the outcome of stroke; thus, we were unable to analyze this endpoint. New-onset embolic stroke may have contributed to the increased risk of long-term mortality, as shown in similar post-CABG and heart transplant cohorts (13,29-31). At the same time, recent evidence has shown a significant association of atrial fibrillation with multiple comorbidities other than

**FIGURE 4** Summary Adjusted Risk Ratio of All-Cause Mortality by DerSimonian and Laird Random-Effects Model

Relative size of the data markers indicates the weight of the sample size from each study. Abbreviations as in Figure 3.

stroke, such as chronic kidney disease, congestive heart failure, ischemic heart disease, peripheral vascular disease, and sudden cardiac death, all of which might be contributing to the higher mortality incidence obvious in our patient population (47).

**STUDY LIMITATIONS.** To our knowledge, this review represents the largest cohort to date evaluating the impact of early AAs on post-lung transplant outcomes. However, this study has several limitations. As is the case with all observational studies, some confounders may have been unaccounted for; nonetheless, we conducted a secondary analysis using the adjusted effect size for all-cause mortality in an attempt to conduct a more robust association. The lack of data on important outcomes such as stroke

incidence and immediate post-operative length of stay after lung transplant hindered the evaluation of early AA association with these outcomes. Because we aimed to evaluate AA related to lung transplant, we limited our analysis to the studies that reported early post-operative AA; thus, the predictors and outcomes of late post-lung transplant AA were not examined. Also, the definition of early AAs was not consistent among all studies; however, both atrial fibrillation and flutter carry a similar long-term prognosis. Furthermore, studies exhibited a wide range of time to follow-up for all-cause mortality. Finally, the lack of patient level data limited establishing the impact of pre-operative medications (such as beta-blockers or calcium-channel blockers) on the incidence of post-lung transplant AA as well as the

impact of different antiarrhythmic medications and ablation techniques on the main outcome of all-cause mortality.

## CONCLUSIONS

Multiple risk factors were shown to correlate with a higher incidence of early post-operative AAs, which may have an additive association with increased risk of all-cause mortality and longer hospital stay. Further studies are needed to determine the best approach for early detection and management of such arrhythmias in an attempt to improve outcomes after lung transplantation.

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## PERSPECTIVES

### COMPETENCE IN MEDICAL KNOWLEDGE 1:

Early AAs occur commonly post-lung transplant and are associated with a significant increase in the incidence of post-lung transplant mortality.

### COMPETENCE IN MEDICAL KNOWLEDGE 2:

Older male patients with a history of smoking, restrictive lung disease, hypertension, coronary artery disease, hyperlipidemia, or LAD in trans-thoracic echocardiography carry a higher risk of developing early AAs after lung transplant.

### TRANSLATIONAL OUTLOOK:

Randomized clinical trials are required to assess the impact of early anti-coagulation and rhythm versus rate control strategies on various clinical outcomes including stroke and all-cause mortality after lung transplant.

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**KEY WORDS** atrial fibrillation, lung transplant, meta-analysis, mortality, outcomes, predictors

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**APPENDIX** For supplemental tables and figures, please see the online version of this article.