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Postoperative Atrial Fibrillation and Flutter in Liver Transplantation: An Important Predictor of Early and Late Morbidity and Mortality

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Abbreviations:

AF: atrial fibrillation; AFL: atrial flutter; ALT: alanine aminotransferase; CAD: coronary artery disease; ECG: electrocardiogram; HCV: Hepatitis C, LT: liver transplant; MELD: model for end-stage liver disease; POAF: postoperative atrial fibrillation/flutter; UNOS: United Network for Organ Sharing.

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Abstract

Background

Postoperative atrial fibrillation/flutter (POAF) is the most common perioperative arrhythmia and may be particularly problematic after liver transplant (LT). This study is a single-center, retrospective analysis of POAF to determine its incidence following LT, identify risk factors, assess its impact on clinical outcomes, and summarize management strategies.

Methods

The records of all patients who underwent LT between 2010 and 2018 were reviewed. Extracted data included pre-LT demographics and cardiac evaluation, in-hospital post-LT cardiac events, early and late complications, and survival.

Results

Among 1011 patients, the incidence of post-LT POAF was 10.1%. Using binary logistic regression, pre-LT history of atrial fibrillation was the strongest predictor of POAF (Odds Ratio (OR) 6.7, Confidence Interval (CI) 2.0-22.6, p<0.001), followed by history of coronary artery disease (CAD) (OR 2.5, CI 1.1-5.8, p=0.03). Cardiac stress testing abnormality and CAD on cardiac catheterization were also associated with higher risk. Median time to POAF onset after LT was 3 days, with 72% resolving within 48 hours. POAF patients had greater hospital length of stay, death during the LT admission, and 90-day and 1-year mortality. POAF was an independent risk factor for post-LT mortality (OR 2.0, CI 1.3-3.0, p<0.01). Amiodarone was administered to 73% of POAF patients with no evidence of increased serum alanine aminotransferase levels.

Conclusion

POAF occurred in 10.1% of post-LT patients, with early onset and rapid resolution in most affected patients. POAF patients, however, had significant morbidity and mortality, suggesting that POAF is an important marker for worse early and late post-LT outcomes.

Background

Postoperative atrial fibrillation/flutter (POAF) is the most common perioperative arrhythmia (1). It occurs in 0.4-26% of non-cardiothoracic surgeries (2). Contemporary studies suggest that the presence of POAF is associated with higher in-hospital mortality and morbidity, as well as higher risk for stroke (3). Risk factors for developing POAF include older age, history of previous cardiac arrhythmias, presence of structural heart disease, electrolyte abnormalities, and type of surgery performed (1, 4). POAF most commonly develops between postoperative days 1 and 4, and it is generally self-limited with good response to intervention (1).

Liver transplant (LT) patients are theoretically at high risk of developing POAF given the presence of increased sympathetic flow, perioperative hemodynamic changes, and frequent use of vasopressors following surgery (2). In the immediate post-LT period, atrial fibrillation (AF) is particularly problematic as it can result in elevated central venous pressure and poor graft venous outflow (5). In addition, there has been a substantial increase in the number of LTs in older patients (>65 years) over the past decade (6). Since aging is an independent risk factor for the development of AF, an increase in the incidence of POAF post-LT is expected (7). Data regarding POAF following LT are scarce (8, 9).

The aims of this retrospective study in patients who underwent LT at a single, high-volume center were to 1) determine the incidence of new-onset POAF; 2) identify intrinsic and extrinsic risk factors associated with the development of POAF; 3) assess post-transplant clinical outcomes including hospital length of stay, readmission and early and late mortality; and 4) summarize the management of POAF, including the use of amiodarone in the setting of recent LT.

Methods

Study design and participants

This study reviewed all patients who underwent LT between January 1, 2010 and August 31, 2018 at Indiana University Hospital. Patients were surveyed for the development of AF and/or atrial flutter (AFL) post-LT. Data were combined for both AF and AFL since both arrhythmias frequently coexist in the same patient, and share similar risk factors and management strategies (10-12). POAF was defined as development of AF or AFL at any point postoperatively during the initial LT hospitalization in a patient who had no evidence of AF or AFL on preoperative electrocardiogram (ECG), regardless of history of pre-existing AF or AFL. Charts were independently reviewed by two investigators. Transplant and cardiology staff notes were reviewed for mention of AF or AFL. Presence of AF or AFL was confirmed by ECG and telemetry strips.

Demographic, clinical and outcome variables

Collected data included demographics (age, gender, race, body mass index, etiology of cirrhosis) and cardiac risk factors (pre-existing AF or AFL, hypertension, diabetes, personal history of coronary artery disease [CAD], family history of CAD, smoking history and pack-years). Model for end-stage liver disease (MELD) score and CHA_2DS_2-VASc score were calculated based on data collected prior to LT. Techniques for organ procurement, transplantation and immunosuppression have been reported previously by this center (13-15). All patients in this study received antibody-based immunosuppression induction with rabbit anti-thymocyte globulin. All patients were also initiated on tacrolimus therapy in a delayed fashion on post-

transplant day 2-4. Further adjustments to the immunosuppressive therapy were generally delayed until outpatient management by a transplant hepatologist.

Additional data were collected on preoperative and postoperative invasive and non-invasive testing modalities including coronary angiography, and stress and resting echocardiograms. All LT candidates at this center underwent extensive cardiac testing prior to listing for LT and this protocol and its results have been published previously (16). Patients were evaluated and listed for LT according to protocols established by our center and by the United Network for Organ Sharing (UNOS). Patients with active AF or AFL were not listed for transplant. Furthermore, any patient who developed AF or AFL while on the transplant list was made inactive until the arrhythmia was controlled through medications or ablation.

Length of hospital stay was calculated from the immediate postoperative transplant period until the date of discharge. Hospital readmission was recorded for any admission to the hospital within 90 days of the date of hospital discharge. Graft failure was defined as either the need for retransplantation or death from primary graft failure. Death follow-up was obtained by reviewing medical records, newspaper obituaries and death certificates, and by conducting phone interviews by social workers when necessary. A thorough cause of death analysis was completed for all patient deaths within 1 year of transplant. Long-term patient survival was analyzed using Cox regression analysis. Data regarding clinical management of AF and AFL were collected and interventions included the use of intravenous rate-control (esmolol, metoprolol, diltiazem) and antiarrhythmic (amiodarone, ibutilide) medications, and electrical cardioversion. The use of vasopressors (epinephrine, norepinephrine, phenylephrine) and inotropes (dobutamine, dopamine) at the time of POAF onset was also recorded.

Serum alanine aminotransferase (ALT) levels are a sensitive marker for drug toxicity in the transplant liver graft (17). To assess the potential toxicity of amiodarone to the newly transplanted liver, serum ALT levels were recorded daily in the immediate post-LT period (10 days) and then on days 14 and 30. ALT levels for patients who received amiodarone were compared to patients that did not.

Statistical analysis

Standard statistical testing was utilized for continuous and categorical variables, as indicated. Statistical significance was set at $p<0.05$. Binary logistic regression and Cox proportional hazards models were constructed for the occurrence of POAF and for patient survival analysis, respectively, using a direct entry technique. Co-variates were retained in the final models if the p-value for any variable was <0.10. Statistical testing was performed on SPSS software (IBM SPSS Statistics Version 25 IBM Corporation, Armonk, New York, USA). Use of center data for retrospective analysis has been reviewed and approved by the Institutional Review Board (Indiana University School of Medicine, study number 1011003619A010). The study protocol for this research conformed to the Declaration of Helsinki.

Results

Demographic and clinical characteristics

Data for a total of 1011 consecutive LT patients were included in this analysis. The cohort median MELD score was 22, age 57 years, body mass index 29 kg/m^2, with 67% males, and 90% identified as Caucasian (**Table 1**). The most common etiologies for cirrhosis were alcoholic liver disease (29%), followed by hepatitis C

(26%), and non-alcoholic fatty liver disease (24%). Twenty percent of patients had hepatocellular carcinoma at transplant. Regarding common cardiac risk factors, 2% had any prior history of AF or AFL, 30% were diabetic, 36% with hypertension, 50% with any history of tobacco use, 7% had a personal history of CAD and 37% with immediate family history of heart disease.

In this cohort, 102 (10.1%) patients had POAF, of which 8 (8%) had pre-existing history of AF or AFL. There were 7 patients with AFL only, compared to 83 with AF only, and 12 with both. All 7 (100%) patients with AFL only were alive at 1-year, compared to 64/83 (77%) in the AF only group and 10/12 (83%) in the AF and AFL group (p=0.33).

Bivariate analysis revealed that factors associated with POAF included higher MELD (p=0.01), older age (p<0.001), diabetes (p<0.01), history of AF or AFL (p<0.001) and history of CAD (p<0.001) (**Table 1**). The POAF and non-POAF groups did not differ with regard to diagnosis of hepatitis C or alcoholic liver disease, the presence of hepatocellular carcinoma, or if the transplant was a primary transplant or a re-do transplant. The POAF group had a higher incidence of non-alcoholic fatty liver disease compared to the non-POAF group (33% versus 22%, p=0.01).

A binary logistic regression model was constructed to obtain the predictors of POAF after LT (**Table 2).** Pre-LT history of AF or AFL was the strongest predictor of POAF (Odds Ratio (OR) 6.7, Confidence Interval (CI) 2.0-22.6, p<0.001), followed by history of CAD (OR 2.5, CI 1.1-5.8, p=0.03).

A review of pre-transplant cardiac testing is summarized in **Table 3**. Results were available for 95% of patients (95% and 92% for non-POAF and POAF patients, respectively). Cardiac stress test was normal in 66% of patients with POAF and 80% with no POAF (p=0.03). Similarly, 5-13% POAF patients had abnormalities on stress

testing in contrast to 3-10% of non-POAF patients (p=0.03). There were 69% of all patients who underwent cardiac catheterization, with POAF patients more likely to meet indication for this test (81% POAF versus 68% non-POAF, p<0.01). Patients with POAF had a higher incidence of documented non-obstructive or obstructive CAD on cardiac catheterization (29% and 13%, respectively) as compared to patients with no POAF (23% and 6%, respectively, p<0.01).

Clinical outcomes

Post-LT clinical outcomes, survival and cause of death analysis are summarized in **Table 4**. Compared to patients with no POAF, the POAF group had a longer average length of stay (18 days in POAF and 9 days in non-POAF, p<0.001) and a higher frequency of post-LT stay ≥ 30 days (30% POAF and 8% in non-POAF, p<0.001). There was no significant difference in the proportion of patients readmitted within 90 days from discharge (53% POAF versus 49% non-POAF, respectively, p=0.49). Patients with POAF had an 11% mortality rate during the transplant admission (compared to 3% non-POAF, p<0.001). Ninety-day and 1-year mortality rates in POAF group were 12% and 21% and were significantly higher than non-POAF group (4% and 6%, respectively, p<0.001 for both).

There were a total of 151 patient deaths during the study period (15% of total), a rate of 14% (n=125) in the non-POAF group compared to 25% (n=26) for POAF patients (p<0.01). Transplant-related complications, which included graft failure, were the most common cause of death (19%). Patients with POAF had a significantly higher rate of graft failure at 1 year, as compared to non-POAF group (non-POAF 6% and POAF 22%; p<0.001). Cox regression demonstrated that POAF was an independent risk factor for post-LT mortality (OR 2.0, CI 1.3-3.0, p<0.01) and

showed an 8-year patient survival difference of 82% (non-POAF) versus 64% (POAF) ($p<0.001$) (**Figure 1**).

POAF group: timing, management and clinical outcomes

A subgroup analysis of patients with POAF is summarized in **Table 5**. The median time post-LT to onset of first POAF episode was 3 days (range 0-45 days; interquartile range 2-6 days; mean 7 days (SE 1.0)). Eighty percent of patients had their first episode of POAF within 7 days of LT. Seventy-two percent of POAF resolved within 48 hours after onset, with a median time to resolution of 1 day (range 0-28 days; mean 2.7 days (SE 0.6)). Norepinephrine and vasopressin were the most commonly identified vasopressors being infused at the time of onset of POAF (38% and 35%, respectively). During the LT hospitalization, 38% had a documented recurrence of POAF after resolution of initial POAF episode, while no patients (0%) had evidence of POAF at the time of discharge. It is noted that 13% of patients with POAF died during the initial LT hospitalization, and 2 patients had documented unresolved AF or AFL prior to death. A total of 42% of patients had a follow-up ECG within 90 days following discharge, with 24% of patients having recurrence of AF or AFL at that time. It is not known if the follow-up ECG was performed for symptoms or as surveillance.

All POAF patients received standard inpatient treatment including rate control and maintenance therapy with calcium channel blockers and/or beta-blockers. Only 74 of the 102 patients with POAF (72%) received intravenous amiodarone. Common discharge cardiac medications for these patients included oral amiodarone, beta-blockers, and calcium channel blockers, though a large majority of POAF patients were not discharged on any of these medications. The median CHA_2DS_2-VASc

score for POAF patients was 2 (range 0-4; mean 1.7 (SE 0.1)). A total of 27% of POAF patients were discharged from the LT hospitalization on anticoagulation.

Serum electrolytes levels were monitored within 12 hours of the onset of POAF and included highest serum potassium (4.2 mEq/L (SE 0.06)), lowest serum potassium (3.9 mEq/L (SE 0.05)), and serum magnesium (2.0 mEq/L (SE 0.03)). Similarly, the highest and lowest central venous pressures within 12 hours of POAF onset were obtained and were 11 mmHg (SE 0.9) and 4 mmHg (SE 0.5), respectively.

Amiodarone toxicity

To assess the risk of amiodarone toxicity in post-LT POAF patients, serum ALT levels were compared between POAF patients who received intravenous amiodarone for treatment of POAF (n=74) and those who did not (n=28). There were no differences between the groups for peak ALT levels at all time points in the first 30 days post-transplant. These results suggest that the risk of amiodarone therapy to the newly transplanted liver graft is negligible (**Figure 2**).

Discussion

The incidence of POAF in the cohort presented in this study was 10.1%. This finding is similar to the incidence reported in a recent meta-analysis, where POAF was found to occur in 9% of post-LT patients (5). A recent systematic review explored the incidence and risk factors for POAF following general surgery (4). The incidence of POAF was reported to be 11% following abdominal surgeries. Risk factors identified for development of POAF included increased age and history of CAD. These results were consistent with our findings. In addition, results from the

preoperative cardiac workup showed that the incidence of POAF was higher in patients whose pre-transplant cardiac findings were suggestive of ischemia on stress test (p=0.03) and/or higher degree of coronary stenosis on cardiac catheterization (p<0.01).

In this study, we identified independent risk factors for POAF on multivariate analysis that were similar to well-established risk factors for development of AF in the general population such as age and diabetes (18). Interestingly, the incidence of POAF was significantly higher in patients with non-alcoholic fatty liver disease (33% vs. 22%, p=0.01). This finding can be explained by the fact that AF and non-alcoholic fatty liver disease share multiple risk factors for their development, such as obesity and insulin resistance (19). It is also worth mentioning that compared to patients <50 years of age, the incidence of POAF was 4.5 and 8 times higher in patient ≥50 years and ≥60 years, respectively. Since older patients are increasingly undergoing LT, the incidence of POAF is expected to increase (6). Among risk factors unique to LT patients, a higher MELD score was associated with an increased incidence of POAF. In a study conducted by Xia et al., it was found that patients with a higher MELD score had a more complicated perioperative course, increased preoperative comorbidities and higher vasopressors requirements (20). In our study, a higher MELD was associated with increased risk of POAF after adjusting for preoperative comorbidities and risk factors. Huang et al. showed that liver disease was an independent risk factor for the development of AF (21). These authors hypothesized that inflammatory and neurohormonal changes that occur with liver disease could contribute to the pathogenesis of AF. In addition, MELD was shown to be a strong predictor of new-onset AF, and higher scores were associated with increased risk of AF. These findings were also consistent with those of our study.

Pre-existing AF was reported in 2% of our cohort. In previous studies, Vannucci et al. reported the prevalence of AF in patients undergoing LT to be 2.5%, while Bargehr et al. found it to be 4.5% (8, 22). On the other hand, the prevalence of AF in the general population was reported to be 0.4-1% (23, 24). It was previously reported that the presence of cirrhosis could confer protection against AF due to associated decreased cardiac myocyte sensitivity to catecholamines, and to the accumulation of toxins with antiarrhythmic and/or anti-inflammatory properties that are otherwise cleared by a normally functioning liver (25, 26). However, and as mentioned earlier, newer studies suggest that the presence of liver disease could predispose to AF and confer an additional risk for its development (21).

POAF was significantly associated with worse outcomes in our study. Mortality rates at 90 days and 1 year were significantly worse when comparing the POAF and non-POAF groups (90-day mortality: 12% vs 4% and 1-year mortality: 21% vs 6%; $p<0.001$ for both). Similarly, Xia et al. found a significant increase in mortality rates at 1, 3 and 6 months in patients with POAF as compared to controls (1%, 20% and 24% for POAF group vs. 4%, 8% and 12% for non-POAF group; $p \leq 0.001$ for all). Furthermore, these authors report a significantly decreased survival for LT patients with POAF when followed over a period of 7 years (9). This finding was consistent with the results of our survival analysis. Cox regression showed an absolute 18% decrease in 8-year survival in POAF as compared to non-POAF group ($p<0.001$). The rate of graft failure at 1 year was significantly higher in the POAF versus the non-POAF group (22% vs. 6%, $p<0.001$). Similar findings were reported by Xia et al. at 1, 3 and 6 months following LT (17%, 25% and 28% for POAF group vs. 7%, 11% and 15% for non-POAF group; $p \leq 0.001$ for all) (9).

Another adverse outcome associated with POAF observed in our study included a longer duration of hospital stay as compared to non-POAF. Similar findings were also previously reported (27). A previous study showed that POAF was associated with a higher rate of intensive care unit readmission following LT (28). Our study analyzed the overall rate of readmission to the hospital, including but not limited to the intensive care unit, and showed that POAF was not associated with a higher readmission rate within 90 days of discharge. POAF can be associated with hemodynamic derangements, ventricular arrhythmias, cardiomyopathies and ischemic cardiac or cerebrovascular events (2). In our study, most POAF episodes were either self-limited or resolved with treatment. Therefore, increased mortality observed in POAF group was unlikely to be a direct complication of AF or AFL. However, development of POAF could reflect an overall poor physiologic status, and may be interpreted as a predictive or prognostic factor for cardiovascular complications rather than a causal factor (29).

The precise mechanisms for development of POAF following abdominal surgeries are not fully understood (30). One proposed mechanism suggests that the presence of derangements such as hypothermia, hypoxia, hypoglycemia and bleeding, as well as pain and hemodynamic derangements from surgery, can lead to myocardial injury and increased activation of the sympathetic system. These derangements, in addition to electrolyte disturbances (especially potassium and magnesium) and systemic inflammation, may predispose to POAF (2, 31). This proposed mechanism could provide insight into the pathophysiology of POAF and help to guide the physician in clinical management. As such, it is important to treat the aforementioned possible underlying factors when treating POAF. Recent studies also demonstrated decreased incidence of POAF with administration of antioxidants

(e.g. vitamin C, statins, N-acetylcysteine) during the perioperative period (32-34). These findings could lend support to the hypothesis that systemic inflammation following surgery contributes to development of POAF.

Most pharmacologic strategies for treating POAF have been studied for cardiothoracic surgeries, and there are no concrete guidelines for treatment of POAF in non-cardiothoracic surgeries (34). A large systematic review showed that the use of beta-blockers, on the day of or following a major non-cardiac surgery, was associated with a decreased 30-day all-cause mortality in patients with 2 or more Revised Cardiac Risk Index factors (35). The use of prophylactic beta-blockers has been studied following cardiac surgeries and was shown to decrease the rate of POAF (36). Some studies have shown that use of prophylactic amiodarone (oral or intravenous) decreased the incidence of POAF at the expense of increased risk of bradycardia and hypotension, particularly with intravenous doses of amiodarone exceeding 1 gram per day (36, 37) .

Hepatotoxicity is a well-established side effect of amiodarone. Acute liver toxicity from intravenous amiodarone was reported to be 13% in a prior study (38). However, our study showed no difference in daily ALT levels when used as a marker of toxicity between patients who received amiodarone for treatment of POAF and those who did not. Data regarding the safety and efficacy of either rate-control or anti-arrhythmic agents for the treatment of POAF post-LT and their long-term morbidity and mortality outcomes are still lacking.

A large study evaluated perioperative risk of stroke in patients with POAF following non-cardiothoracic surgeries. It was found that patients with POAF had cumulative rates of stroke of 1.5% (95% CI: 1.2%–1.8%) compared to 0.4% in non-POAF patients (95% CI: 0.3%–0. 4%) (3). Initiating antithrombotic therapy should be

considered if the initial episode of AF does not resolve within 24-48 hours of onset, or if the patient has had recurrent AF during that hospitalization (39). If any of these 2 criteria is met, antithrombotic therapy would be indicated in patients with CHA_2DS_2-VASc score ≥2. However, this complex decision should be weighed against the risk of bleeding. The decision to anticoagulate should directly involve the surgeon and should be clearly discussed and communicated with the patient and their family (1).

Limitations:

This is a retrospective study and is subject to the limitations of this study design. The study was performed in a highly-selective population since patients deemed high-risk for LT were generally denied listing. Furthermore, our study only investigated the preoperative risk factors which were associated with the development of POAF and intra- or postoperative risk factors were not considered. The association between POAF and immunosuppressive agents was not assessed in this study as all patients were on a standardized immunosuppression protocol. Only patients in the intensive care unit or patients on the general ward with cardiac risk factors or symptoms were continuously monitored on telemetry following LT surgery. Therefore, incomplete records of self-limiting or asymptomatic occurrence of POAF cannot be excluded.

Conclusion

This study showed that POAF is common following LT and is associated with increased morbidity and mortality. Early aggressive treatment of POAF may improve post-LT outcomes. We believe that more prospective studies are needed to further

understand the association of POAF with postoperative outcomes and to establish targeted treatment strategies, particularly in LT patients.

Figure and Table Legends

Table 1. Univariate and bivariate analysis of 1011 liver transplant patients, comparing those who did or did not have post-liver transplant atrial fibrillation/flutter.

Table 2. Binary logistic regression analysis for the predictors of post-liver transplant atrial fibrillation/flutter.

Table 3. Summary of pre-liver transplant cardiac testing, comparing patients who did or did not have post-liver transplant atrial fibrillation/flutter (n=1011).

Table 4. Post-liver transplant clinical outcomes, survival and cause of death analysis for 1011 study patients with 131 deaths (16%).

Table 5. Subgroup analysis of 102 liver transplant patients (of 1011) who developed postoperative atrial fibrillation and flutter (POAF).

Figure 1: Cox proportional hazards survival in post-liver transplant patients. POAF was an independent risk factor for post-LT mortality (OR 2.0, CI 1.3-3.0, $p<0.01$). Patient survival in the postoperative atrial fibrillation/flutter (POAF) group was significantly lower than that of the non-POAF group ($p<0.001$) after controlling for model for end-stage liver disease (MELD) score, tobacco use, hepatitis C infection (HCV+) and donor age (all $p<0.10$ in the final model).

Figure 2: Post-transplant alanine aminotransferase (ALT) levels in patients with postoperative atrial fibrillation/flutter (POAF) (n=102) who received amiodarone and those who did not. There was no significant difference in the ALT levels between the two groups ($p>0.10$ at all time points).

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Table 1. Univariate and bivariate analysis of 1011 liver transplant patients, comparing those who did or did not have post-liver transplant atrial fibrillation/flutter.

	Overall	No post-liver transplant atrial fibrillation or flutter	Post-liver transplant atrial fibrillation or flutter*	p-value
Number (%)	**1011 (100%)**	**909 (90%)**	**102 (10%)**	
MELD score	22 (6.6)			0.01
20 or less	45%	45%	33%	
21 to 29	43%	44%	47%	
30 and higher	12%	11%	20%	
Gender				0.17
Male	67%	66%	73%	
Female	33%	34%	27%	
Race				0.55
White	90%	90%	90%	
Black	5%	5%	3%	
Other	5%	5%	7%	
Age (years)	57 (10.6)			<0.001
Less than 30	4%	4%	0%	
30 to 39	5%	6%	1%	
40 to 49	14%	16%	3%	
50 to 59	38%	38%	34%	
60 and older	39%	36%	62%	
Body mass index (kg/m^2)	29.0 (6.1)			0.10
Less than 25.0	27%	27%	22%	
25.0 to 29.9	33%	35%	30%	
30.0 to 34.9	27%	26%	28%	
35.0 and higher	13%	12%	21%	
Graft number				0.43
First	97%	97%	99%	
Retransplant	3%	3%	1%	

Cardiac risk factors				
Diabetes mellitus				<0.01
No	70%	71%	57%	
Yes	30%	29%	43%	
Hypertension				0.65
No	64%	64%	62%	
Yes	36%	36%	38%	
Tobacco				0.22
Never	50%	49%	56%	
Current (at evaluation)	15%	16%	10%	
Former	35%	35%	34%	
Tobacco pack-year				0.65
None	50%	49%	54%	
1 to 20	27%	27%	29%	
20 to 40	16%	17%	12%	
>40	7%	7%	5%	
Patient history of atrial fibrillation/flutter				<0.001
No	98%	99%	92%	
Yes	2%	1%	8%	
Patient history of coronary artery disease				<0.001
No	93%	94%	83%	
Yes	7%	6%	17%	
Family history of coronary artery disease*				0.64
None	57%	56%	62%	
Immediate family (any)	37%	37%	32%	
Distant family only	6%	7%	6%	

* Includes 83 patients with atrial fibrillation alone, 7 with atrial flutter alone, and 12 with both.

** Many patients had more than one disease process simultaneously.

Table 2. Binary logistic regression analysis for the predictors of post-liver transplant atrial fibrillation/flutter.

		95% Confidence Interval for OR		
Co-variates	**Odds Ratio (OR)**	**Lower**	**Upper**	**p-value**
Model for end-stage liver disease (MELD) score at transplant	1.092	1.045	1.142	<0.001
Age at transplant	1.087	1.040	1.137	<0.001
Body mass index at transplant	1.062	1.001	1.127	0.05
History of diabetes	1.706	0.895	3.254	0.10
History of coronary artery disease	2.522	1.093	5.817	0.03
Pre-liver transplant history of atrial fibrillation or flutter	6.723	2.003	22.572	<0.001
Constant	0.000			<0.001

Table 3. Summary of pre-liver transplant cardiac testing, comparing patients who did or did not have post-liver transplant atrial fibrillation/flutter (n=1011).

Pre-liver transplant cardiac testing	Number (Overall percent of total)	NO post-liver transplant atrial fibrillation/flutter	Post-liver transplant atrial fibrillation/flutter	p-value
Number (%)	1011 (100%)	909 (90%)	102 (10%)	
Non-invasive stress testing	956 (95%)	864/909 (95%)	94/102 (92%)	0.26*
Normal	749 (78%)	80%	66%	0.03
Wall motion abnormalities	47 (5%)	5%	7%	
EKG changes without wall motion abnormalities	32 (3%)	3%	5%	
Non-diagnostic or equivocal	94 (10%)	10%	13%	
Normal nuclear test; no stress ECHO	30 (3%)	3%	7%	
Abnormal nuclear test	4 (<1%)	<1%	1%	
Cardiac catheterization	698/1011 (69%)	615/909 (68%)	83/102 (81%)	<0.01*
No catheterization indicated	313 (31%)	32%	19%	<0.01
Normal catheterization	394 (39%)	39%	39%	
Non-obstructive coronary artery disease	237 (23%)	23%	29%	
Obstructive coronary artery disease requiring intervention	67 (7%)	6%	13%	

* Compared to those who did not have non-invasive testing or cardiac catheterization

Table 4. Post-liver transplant clinical outcomes, survival and cause of death analysis for 1011 study patients with 131 deaths (16%).

	Overall	No post-liver transplant atrial fibrillation or flutter	Post-liver transplant atrial fibrillation or flutter	p-value
Number of study patients	**1011 (100%)**	**909 (90%)**	**102 (10%)**	
Hospitalization				
Length of hospital stay (days)	9	9	18	<0.001
Post-transplant stay 30 days or more	10%	8%	30%	<0.001
Readmission within 90 days of discharge	50%	49%	53%	0.49
Early death				
Death before discharge from transplant admission	4%	3%	11%	<0.001
Death within 90 days	5%	4%	12%	<0.001
Death within 1 year	8%	6%	21%	<0.001
Graft failure at 1 year	8%	6%	22%	<0.001
Cause of death analysis				
Number of deaths (% of total in study group)	151 (15%)	125 (14%)	26 (25%)	<0.01
Recurrence of hepatocellular carcinoma	10%	11%	4%	*
Other cancer	11%	12%	4%	
Infection / Sepsis	10%	9%	19%	
Transplant-related complications	19%	19%	19%	
Recurrence or progression of primary liver disease	12%	14%	4%	
Stroke or brain injury	3%	4%	0%	
Lung disease or injury, including aspiration	11%	9%	19%	
Renal failure	4%	5%	0%	

Other / Unknown	15%	15%	15%
Cardiac etiology	5%	2%	16%

* Unable to calculate p-value due to 12 cells with expected count less than 5 (60%).

Table 5. Subgroup analysis of 102 liver transplant patients (of 1011) who developed postoperative atrial fibrillation and flutter (POAF).

Number	102 (100%)
Days post-transplant to first POAF	
Mean (SE); Median (min-max)	7.0 (1.0); 3 (0-45)
Resolved within 48 hours?	72%
Days to resolution	
Mean (SE); Median (min-max)	2.7 (0.6); 1 (0-28)
Pressors infusing at onset of POAF	
Vasopressin	35%
Norepinephrine	38%
Dopamine	1%
Dobutamine	1%
Phenylephrine	2%
Epinephrine	1%
Recurrence of previously resolved POAF	
No recurrence during hospitalization	55%
Recurrence during hospitalization	38%
Persistent POAF (never resolved)	7%
Atrial fibrillation present on discharge*	0%
Died before discharge	13%
Post-transplant surveillance follow up EKG within 90 days of hospital discharge	
No follow up EKG	58%
Follow up EKG	42%
Atrial fibrillation on follow up surveillance EKG (among those receiving follow up EKG within 90 days)	
Yes	24%

No	76%
CHA_2DS_2-VASc score	
Mean (SE); Median (min-max)	1.7 (0.1); 2 (0-4)
Discharge medications	
Amiodarone	35%
Metoprolol/Carvedilol	30%
Diltiazem	8%
Anticoagulation (any)	27%
Clinical monitoring (median (SE))	
Peak serum potassium	4.2 (0.06)
Lowest serum potassium	3.9 (0.05)
Serum magnesium	2.0 (0.03)
Highest post-transplant central venous pressure	11 (0.9)
Lowest post-transplant central venous pressure	4 (0.5)

* Two patients died with atrial fibrillation/flutter prior to discharge