Internal and Emergency Medicine (2019) 14:71–76
https://doi.org/10.1007/s11739-018-1950-7

IM - ORIGINAL

Risk of new-onset atrial fibrillation among heart, kidney and liver transplant recipients: insights from a national cohort study

Wei-Syun Hu[1,2] · Cheng-Li Lin[3]

Received: 2 May 2018 / Accepted: 13 September 2018 / Published online: 25 September 2018

Abstract

The objective of the study was to explore the incidence of atrial fibrillation (AF) in various populations of patients with organ transplantation (OT). We used a large national data set from Taiwan to investigate the incidence of AF after OT. Frequency matching method used to match controls: OT patients were 4:1. Kaplan–Meier analyses with the use of the Aalen–Johansen estimator was employed for estimating the cumulative incidences of new-onset AF. The Fine–Gray competing risks model was also employed to analyze the risk of AF for the OT cohort compared with the non-OT cohort. 6955 OT patients and 27,820 controls were included in this study. OT did lead to a 3.09-fold risk for AF [95% confidence interval (CI) = 2.07–4.62], especially in the subgroup of female gender [adjusted subhazard ratio (aSHR) = 6.66, 95% CI = 3.85–11.5], age ≤ 49 years (aSHR = 8.19, 95% CI = 3.99–16.8) and without comorbidity (aSHR = 4.61, 95% CI = 2.71–7.87). Moreover, liver recipients tended to be more likely to develop new-onset AF among those OT patients (aSHR = 4.07, 95% CI = 2.63–6.30) as compared to the controls. This study demonstrates an increased incidence of AF after OT. Heightened awareness and clinician vigilance are warranted to facilitate early diagnosis and improved outcomes.

Keywords Atrial fibrillation · Cohort · Competing risk analysis · Organ transplantation

Introduction

Organ transplantation (OT) is a standard procedure for patients with end stage organ failure [1–5]. Despite robust improvement of surgical techniques and post-procedure multidiscipline care, the morbidity and mortality remain high [1–5]. Such patients are susceptible to adverse cardiovascular outcomes; indeed, patients with OT are at higher risk of incident atrial fibrillation (AF), and OT patients with AF are again at elevated risk of ischemic stroke and other cardiovascular events [6–10]. As a preventive medical point of view, a study of AF risk in patients with various types of OT including heart, kidney and liver is worthwhile and of clinical relevance [6–10]. Hence, we conducted this retrospective cohort study from the well-validated Taiwan registries with the use of matching method and the Fine–Gray competing risks model to examine the risk of AF in patients with OT and to explore the subgroup analysis [11].

✉ Wei-Syun Hu
weisyunhu@gmail.com

1 School of Medicine, College of Medicine, China Medical University, Taichung 40402, Taiwan

2 Division of Cardiovascular Medicine, Department of Medicine, China Medical University Hospital, 2, Yuh-Der Road, Taichung 40447, Taiwan

3 Management Office for Health Data, China Medical University Hospital, Taichung 40447, Taiwan

Methods

Data sources

We conducted a retrospective nationwide longitudinal cohort study by analyzing the National Health Insurance Research Database (NHIRD) of the National Health Insurance (NHI) program in Taiwan [12]. This NHI program was implemented in March 1995 and covers 99% of the 23 million residents in Taiwan [12]. Details of the program can be found in previous studies [13, 14]. For this cohort study, we used a subset of the NHIRD containing health-care data including files of the Registry for Catastrophic Illness Patient Database (RCIPD), inpatients claims, and Registry of Beneficiaries. Diseases were coded according to the International Classification of Disease, Ninth Revision, Clinical Modification

(ICD-9-CM). The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

Study participants

The study subjects receiving an OT were identified in the RCIPD between January 1, 2000 and December 31, 2010, including heart (ICD-9-CM code V42.1), kidney (ICD-9-CM code V42.0) and liver transplantation (ICD-9-CM V42.7 code). The date of receiving an OT is defined as the index date. We excluded patients with AF (ICD-9-CM code 427.31) before the index date, those who were younger than 20 years, or lacking gender and age data. For each OT patient, we randomly selected four non-OT patients form the same study period, using the same exclusion criteria and frequency matching with the OT cohort for gender and age (every 5-year span) to construct the non-OT cohort.

Outcome definition and comorbidities

The first diagnosis of AF from hospitalization records between 2000 and 2011 is identified as the study end point. All subjects were followed up until the occurrence of the study end point or censored because of death, withdrawal from the NHI program, or until December 31, 2011 (whichever occurred first). We also incorporated inpatient diagnosis records to ascertain the baseline comorbidities, namely hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary heart disease (CHD) (ICD-9-CM codes 410–414), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, 496), peripheral arterial occlusive disease (PAOD) (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, 447.9), chronic kidney disease (CKD) (ICD-9-CM code 585), hyperthyroidism (ICD-9-CM codes 242, 376.21), sleep disorders (ICD-9-CM codes 307.4, 780.5), gout (ICD-9-CM code 274), cancer (ICD-9-CM codes 140–208), and stroke (ICD-9-CM codes 430–438).

Statistical analysis

The distributions of baseline characteristics (gender, age, and comorbidities) were compared between the cohorts with and without OT by Chi-square test (for categorical variables) and by *t* test (for continuous variables). The follow-up times were used to estimate the incidence density rates of AF in both cohorts. For estimating the cumulative incidence of AF in the OT and the non-OT cohorts, we performed the Kaplan–Meier analyses using the Aalen–Johansen estimator, which considered death events as the competing risk [15]. After accounting for the competing risk of death, the risk of AF for the OT cohort compared with the non-OT cohort was expressed as crude and adjusted subhazard ratios (SHRs) with 95% confidence intervals (CIs) using univariable and multivariable models, which extended the standard Cox proportional hazard regression model. The confounders including age, gender, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, CHD, COPD, PAOD, CKD, hyperthyroidism, sleep disorders, gout, cancer, and stroke were adjusted in the multivariable models. Mortality for patients who have AF was subsequently compared between the OT and the non-OT cohorts. All statistical analyses were performed using SAS 9.4 statistical software (SAS Institute, Inc., Cary, N.C., USA).

Results

Table 1 shows that the two study cohorts are similar in the distributions of gender and age. Most of the study patients are men (60.9%) and age ≤ 49 years (53.5%). The mean age in the OT cohort and non-OT cohort is 47.7 (standard deviation【SD】 = 11.3) and 47.7 (SD = 11.4) years, respectively. The OT patients are more likely to have hypertension, diabetes mellitus, hyperlipidemia, CHD, COPD, PAOD, CKD, hyperthyroidism, sleep disorders, gout, cancer, and stroke than the non-OT patients.

The cumulative incidence of new-onset AF is significantly higher for the OT patients than for the non-OT patients after accounting for death as the competing risk (Fig. 1).

The overall incidence density rate of AF is approximately 4.42 times higher in the OT cohort than in the non-OT cohort (3.86 vs. 0.82 per 1000 person-years) (Table 2). Compared to the non-OT cohort, the adjusted SHR (aSHR) of AF in the OT cohort is 3.09 (95% CI = 2.07–4.62). In gender-stratified analysis, the incidence of AF in the OT cohort is higher than that in the non-OT cohort, and the risk of AF is significantly higher in females (aSHR = 6.66, 95% CI = 3.85–11.5) than in males (aSHR = 1.82, 95% CI = 1.04–3.17). The age-stratified analysis shows that the incidence of AF increases with increase in age in both cohorts. However, the age-stratified risk of AF for the OT cohort relative to the non-OT cohort is the greatest for those age 49 years or younger (aSHR = 8.19; 95% CI = 3.99–16.8). In comorbidity-stratified analysis, the incidence of AF in the OT cohort is higher than that in the non-OT cohort, and the risk is higher in those without comorbidity (aSHR = 4.61, 95% CI = 2.71–7.87) than in those with comorbidity (aSHR = 1.84, 95% CI = 1.27–2.68). In the interaction analysis, gender, age, and comorbidity significantly modify the association between OT and AF (all *p* values for interactions are < 0.05).

Table 3 represents the calculated aSHRs of AF according to various subtypes of OT. Compared with the non-OT subjects, the risk of new-onset AF is not significant

Table 1 Demographic characteristics and comorbidities in patients with and without organ transplant

	Organ transplant recipients		*p* value
	No	Yes	
	(*N* = 27,820)	(*N* = 6955)	
Gender			0.99
Women	10,884(39.1)	2721(39.1)	
Men	16,936(60.9)	4234(60.9)	
Age stratified			0.99
≤49	14,892(53.5)	3723(53.5)	
50–64	11,656(41.9)	2914(41.9)	
≧65	1272(4.57)	318(4.57)	
Age, mean ± SD[#]	47.7 ± 11.4	47.7 ± 11.3	0.89
Comorbidity			
Hypertension	1345(4.83)	3613(52.0)	< 0.001
Diabetes mellitus	893(3.21)	1308(18.8)	< 0.001
Hyperlipidemia	494(1.78)	652(9.37)	< 0.001
CHD	563(2.02)	751(10.8)	< 0.001
COPD	189(0.68)	113(1.62)	< 0.001
PAOD	27(0.10)	74(1.06)	< 0.001
Chronic kidney disease	115(0.41)	3568(51.3)	< 0.001
Hyperthyroidism	67(0.24)	49(0.70)	< 0.001
Sleep disorders	175(0.63)	167(2.40)	< 0.001
Gout	256(0.92)	468(6.73)	< 0.001
Cancer	556(2.00)	858(12.3)	< 0.001
Stroke	523(1.88)	341(4.90)	< 0.001

Chi-Square test;[#]two sample *t* test

SD standard deviation, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *PAOD* peripheral artery occlusive disease

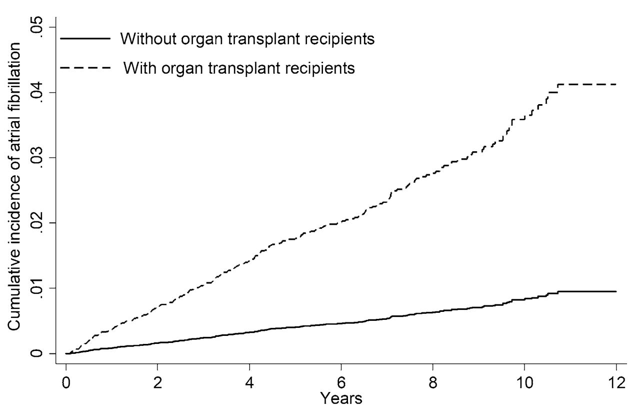

Fig. 1 Cumulative incidence curves of new-onset AF for groups with and without organ transplantation

for heart recipients (aSHR = 1.91, 95% CI = 0.67–5.47). Compared with the non-OT cohort, those undergoing liver transplantation are 4.07-fold more likely to develop AF (95% CI = 2.63–6.30), followed by those receiving kidney transplantation (aSHR = 2.34, 95% CI = 1.29–4.23).

The mortality rates for patients who have AF with and without OT are shown in Table 4. The risk of mortality after AF is lower for OT patients relative to those without OT, with an adjusted HR of 0.33 (95% CI = 0.09–1.29).

Discussion

This is a large-scale retrospective analysis based on the Catastrophic Illnesses Patient Database in Taiwan to assess the association between OT and incident AF. The main results are (1) 1.96% of the 6955 patients with OT in the registry have a diagnosis of AF; (2) OT is associated with higher AF incidence, with an increasing subhazard ratio while incorporating mortality as a competing risk; (3) the association is stronger in patients of female gender, younger age and without comorbidity; (4) liver transplantation appears to be more strongly associated with a higher incidence of AF.

The strength of this report is that it takes advantage of the large, population-based sample of the Taiwanese National Health System [12]. In addition, the study methods are valid, and the statistical analysis plan with the use of the Fine–Gray competing risks methodology is particularly suited for this population [11, 15].

AF is a commonly encountered complication of OT [6–10]. The occurrence of AF after OT indicates that the patients are more likely to develop adverse clinical events and it does affect patient care strategies in clinical practice [6–10]. Classifying patients according to a diagnosis of AF is commonly done in cardiology research, and the CHA_2DS_2-VASc score is useful because it allows clinicians to identify AF patients at high risk for stroke, in whom anticoagulation should be initiated [16, 17]. However, compared with other acute health problems such as stroke and acute myocardial infarction, chronic AF may often be ignored by patients or physicians, since it is frequently asymptomatic for many years. Hence, to address this important issue, the underlying database—a huge nationwide sample of patients—may be adequate as a source for detecting the onset of new AF [12]. We find a statistically significant positive association between OT and incident AF. It seems that the association is stronger in women than in men, in young adults than in aged adults, and in subjects without comorbidity rather than with comorbidity. The presented results should still be validated in further prospective research given the small number of AF events in the subgroup analysis.

In this investigation, we find a strong association between OT and post-operative AF. Etiologies and risk factors for AF in this population differ from those typical in a general population [6–10]. Possible explanations and underlying mechanisms in the association are: either surgery

Table 2 Comparison of incidence and subhazard ratio of new-onset atrial fibrillation between patients with and without organ transplant stratified by gender, age, and comorbidity

	Organ transplant recipients						Crude SHR (95% CI)	Adjusted SHR[†] (95% CI)
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]		
All	128	156,916	0.82	136	35,253	3.86	4.42 (3.47, 5.63)***	3.09 (2.07, 4.62)***
Gender								
Women	40	65,451	0.61	62	15,067	4.12	6.38 (4.29, 9.49)***	6.66 (3.85, 11.5)***
Men	88	91,466	0.96	74	20,187	3.67	3.53 (2.59, 4.81)***	1.82 (1.04, 3.17)*
p for interaction								0.03
Stratify age								
≤49	20	91,899	0.22	66	21,331	3.09	13.5 (8.17, 22.2)***	8.19 (3.99, 16.8)***
50–64	76	58,946	1.29	63	12,652	4.98	3.58 (2.57, 5.00)***	2.71 (1.55, 4.75)***
≧65	32	6072	5.27	7	1269	5.51	0.95 (0.42, 2.16)	0.70 (0.23, 2.16)
p for interaction								<0.001
Comorbidity[‡]								
No	92	143,556	0.64	16	4995	3.20	4.92 (2.90, 8.36)***	4.61 (2.71, 7.87)***
Yes	36	13,361	2.69	120	30,258	3.97	1.49 (1.02, 2.17)*	1.84 (1.27, 2.68)**
p for interaction								<0.001

Crude SHR crude subhazard ratio

*$p<0.05$, **$p<0.01$, ***$p<0.001$

Rate[#], incidence rate, per 1000 person-years; Adjusted SHR[†]: multivariable analysis including gender, age, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral arterial occlusion disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, cancer, and stroke (Death was also added in the model to measure adjusted SHR)

Table 3 Incidence rates and subhazard ratios of new-onset atrial fibrillation for the organ transplant recipient cohort relative to the non-organ transplant recipient cohort

Variables	*N*	Event	Person-years	Rate[†]	Crude SHR (95% CI)	Adjusted SHR[†] (95% CI)
Atrial fibrillation						
Without organ transplant	27,820	128	156,916	0.82	1(Reference)	1(Reference)
Organ transplant recipients						
Subgroups						
Heart	476	7	1874	3.73	3.88 (1.82, 8.29)***	1.91 (0.67, 5.47)
Kidney	4398	98	26,029	3.77	4.41 (3.38, 5.76)***	2.34 (1.29, 4.23)**
Liver	2081	31	7350	4.22	4.59 (3.11, 6.79)***	4.07 (2.63, 6.30)***

**$p<0.01$, ***$p<0.001$

Rate[†], incidence rate, per 1000 person-years; crude SHR, crude subhazard ratio; Adjusted SHR[†]: multivariable analysis including gender, age, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral arterial occlusion disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, cancer, and stroke (Death was also added in the model to measure adjusted SHR)

and anesthesia-related factors, for example, hemodynamic instability, stress hormone secretion, autonomic dysfunction, electrolyte abnormality, fluid status, hypercoagulable status, or host-related factors, such as immunocompromised setting, underlying medical comorbidities, and the use of immunosuppressive agents [6–10]. Heightened awareness and clinician vigilance are warranted to facilitate early diagnosis and improved outcomes.

Limitations

First, the use of administrative claims codes is potentially a major limitation and should be acknowledged. Some investigators may doubt the completeness of ICD coding and the accuracy of the diagnostic codes. However, our study is from well-validated Taiwan registries to provide

Table 4 Mortality rate of atrial fibrillation for patients with organ transplant compared with those without organ transplant

	Organ transplant recipients	
	No	Yes
Atrial fibrillation (*N*)	128	136
Death (*N*)	16	18
Mortality rate (%)	12.5	13.2
Mean followed time ± SD (years)	2.23 ± 1.80	4.25 ± 2.90
Crude HR (95% CI)	1 (Reference)	0.49 (0.24, 1.02)
Adjusted HR† (95% CI)	1 (Reference)	0.33 (0.09, 1.29)

Crude HR crude hazard ratio

Adjusted HR†: multivariable analysis including gender, age, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral arterial occlusion disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, cancer, and stroke

a large study power [18, 19]. Second, there is no way to manually verify the existence of AF in the population. Hence, there may have been some underestimation if a diagnosis code of AF was not recorded in spite of a clinical event. Third, the absence of detailed clinical and personal health-associated behaviors affecting the results of the study is possible. Fourth, even after multivariate adjustment, there likely remain significant confounders accounting for the differences between OT recipients and controls. Finally, this study is a retrospective observational one, data were self-adjudicated, and there was no external adjudication of events.

Conclusion

This study demonstrates an increased incidence of AF after OT. Heightened awareness and clinician vigilance are warranted to facilitate early diagnosis and improved outcomes.

Acknowledgements This study was supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW107-TDU-B-212-123004).

Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

References

1. Health Resources and Services Administration: Organ procurement and transplant network database (2013). Available at. http://optn.transplant.hrsa.gov/. Accessed 20 Oct 2013
2. Bertoux F, On behalf of the EBPG Expert Group on Renal Transplantation (2002) European best practice guidelines on renal transplantation. Part 2. Nephrol Dial Transplant 17(Suppl 4):1–67
3. Lindenfeld J, Miller GG, Shakar SF, Zolty R, Lowes BD, Wolfel EE, Mestroni L, Page RL 2nd, Kobashigawa J (2004) Drug therapy in the heart transplant recipient. Part I: cardiac rejection and immunosuppressive drugs. Circulation 110(24):3734–3740
4. American Society of Transplantation (2001) In: Norman DJ, Turka LA (eds) Primer on transplantation, vol 2. Wiley, New York, p 732
5. Busuttil RW (2005) In: Busuttil W, Klintmalm GB (eds) Transplantation of the liver, vol 2. Sounders, Philadelphia, p 1485
6. Xia VW, Worapot A, Huang S, Dhillon A, Gudzenko V, Backon A, Agopian VG, Aksoy O, Vorobiof G, Busuttil RW, Steadman RH (2015) Postoperative atrial fibrillation in liver transplantation. Am J Transplant 15(3):687–694
7. Lentine KL, Schnitzler MA, Abbott KC, Li L, Xiao H, Burroughs TE, Takemoto SK, Willoughby LM, Gavard JA, Brennan DC (2006) Incidence, predictors, and associated outcomes of atrial fibrillation after kidney transplantation. Clin J Am Soc Nephrol 1(2):288–296
8. Abbott KC, Reynolds JC, Taylor AJ, Agodoa LY (2003) Hospitalized atrial fibrillation after renal transplantation in the United States. Am J Transplant 3(4):471–476
9. Thajudeen A, Stecker EC, Shehata M, Patel J, Wang X, McAnulty JH Jr, Kobashigawa J, Chugh SS (2012) Arrhythmias after heart transplantation: mechanisms and management. J Am Heart Assoc 1(2):e001461
10. Pavri BB, O'Nunain SS, Newell JB, Ruskin JN, William G (1995) Prevalence and prognostic significance of atrial arrhythmias after orthotopic cardiac transplantation. J Am Coll Cardiol 25(7):1673–1680
11. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496–509
12. Database NHIR (2007) Taiwan. http://nhird.nhri.org.tw/en/index.html. Accessed 10 May 2017
13. Hu WS, Lin CL (2017) Comparison of CHA2DS2-VASc, CHADS2 and HATCH scores for the prediction of new-onset atrial fibrillation in cancer patients: a nationwide cohort study of 760,339 study participants with competing risk analysis. Atherosclerosis 266:205–211
14. Hu WS, Lin CL (2018) CHA2DS2-VASc score for prediction of ischemic stroke in patients with systemic lupus erythematosus without atrial fibrillation. Lupus 27(8):1240–1246
15. Gooley TA, Leisenring W, Crowley J, Storer BE (1999) Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 18(6):695–706
16. 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) 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 64(21):e1–e76
17. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, ESC Committee for Practice Guidelines (CPG) (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010

ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 33(21):2719–2747
18. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH (2014) Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol 24(6):500–507
19. Cheng CL, Chien HC, Lee CH, Lin SJ, Yang YH (2015) Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. Int J Cardiol 15(201):96–101