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Original Article

Risk of incident atrial fibrillation after a prior critical illness: A retrospective cohort study

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ABSTRACT

Objective: This investigation aimed at assessing the issue of incident atrial fibrillation (AF) associated with acute critical illness.

Methods: The study came from Taiwan and used that nation's Longitudinal Health Insurance Database 2000. Using propensity score matching, multivariable adjustment and competing risk methods, the correlations between the new-onset AF and critical illness (septicemia/septic shock, acute myocardial infarction【AMI】, hemorrhagic stroke and ischemic stroke) were investigated.

Results: This study consisted of 46470 patients in the critical illness cohort, 618998 persons in the general population cohort. Additionally, 37,060 critically ill patients were matched with 37060 control patients based on propensity score methods. Compared with general population cohort, patients with septicemia/septic shock were 3.12-fold more likely to develop AF (95% confidence interval【CI】= 2.88–3.39), followed by patients with ischemic stroke (adjusted hazard ratio【aHR】= 1.96, 95% CI = 1.80–2.14), patients with AMI (aHR = 1.62, 95% CI = 1.32–2.00) and patients with hemorrhagic stroke (aHR = 1.46, 95% CI = 1.13–1.88). In addition, after controlling for the confounding factors and the competing risk of death, the critical illness cohort still exhibited a significantly higher risk of AF than the general population cohort (adjusted subhazard ratio [aSHR] = 2.66, 95% CI = 2.49–2.84).

Conclusions: Our study explored incident AF among patients with critical illness in their medical history. Patients with septicemia/septic shock were at the highest risk of developing new-onset AF among these critically ill patients.

1. Introduction

Emerging role of atrial fibrillation (AF) and its clinical implications for the associated complications, such as stroke, thromboembolism and cardiac failure resulting in early death has been recognized; indeed, the increasing importance of AF in the globalized world has been established [1–4].

Patients with acute critical illness had a greater risk of new-onset AF than the general population and the underlying mechanistic pathways of this phenomenon seemed majorly through stress reaction, autonomic dysfunction, neuroendocrine imbalance and inflammatory response [5–12]. Indeed, incident AF in acute critical illness is a field that has recently attracted a significant clinical and research interest because management of new-onset AF in individuals with acute critical illness, such as septicemia/septic shock, acute myocardial infarction (AMI), ischemic stroke and hemorrhagic stroke is of great challenge since the pharmacologic strategy for these fragile patients is somewhat difficult in terms of the benefits and risks of the administration of anticoagulation therapy [5–12].

Although the stronger association of critical illness with new-onset AF has been well-studied; to the best of our knowledge, there is no data in literature specifically exploring the issue of comparison of incidence and risk of AF in patients with different specified critical illness with those without critical illness. Hence, this investigation aimed at assessing the issue of incident AF in patients surviving acute critical illness with propensity score method, multivariate adjustment and competing risk analysis.

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Table 1
Demographic characteristics and comorbidities in subjects with and without critical illness with and without propensity score matching analysis.

Variable	Without propensity score matching		*p*-value	With propensity score matching		Standardized mean differences[b]
	Critical illness			Critical illness		
	No	Yes		No	Yes	
	N = 618998	*N* = 46470		*N* = 37060	N = 37060	
Age, year			< 0.001			
≤49	446599(72.2)	7839(16.9)		5723(15.4)	7156(19.3)	0.102
50–64	117991(19.1)	12149(26.1)		11096(29.9)	10425(28.1)	0.04
65+	54408(8.79)	26482(57.0)		20241(54.6)	19479(52.6)	0.041
Mean ± SD[a]	42.1 ± 14.9	65.6 ± 15.5	< 0.001	64.7 ± 14.4	63.9 ± 15.5	0.05
Sex			< 0.001			
Female	312856(50.5)	19506(42.0)		15786(42.6)	15954(43.1)	0.01
Male	306142(49.5)	26964(58.0)		21274(57.4)	21106(57.0)	0.01
Comorbidity						
Hypertension	90970(14.7)	31638(68.1)	< 0.001	26306(71.0)	24840(67.0)	0.09
Diabetes mellitus	24279(3.92)	12349(26.6)	< 0.001	9292(25.1)	9129(24.6)	0.01
Hyperlipidemia	67340(10.9)	15055(32.4)	< 0.001	12981(35.0)	12190(32.9)	0.05
CHD	19259(3.11)	9663(20.8)	< 0.001	7359(19.9)	7119(19.2)	0.02
COPD	29924(4.83)	11089(23.9)	< 0.001	7890(21.3)	7792(21.0)	0.01
PAOD	5470(0.83)	2341(5.04)	< 0.001	1709(4.61)	1694(4.57)	0.002
Chronic kidney disease	4141(0.67)	3791(8.16)	< 0.001	2077(5.60)	2195(5.92)	0.01
Hyperthyroidism	7739(1.25)	486(1.05)	< 0.001	385(1.04)	395(1.07)	0.003
Sleep disorders	76460(12.4)	11713(25.2)	< 0.001	9536(25.7)	9092(24.5)	0.03
Gout	33514(5.41)	7734(16.6)	< 0.001	6229(16.8)	5869(15.8)	0.03
Lower leg fracture or surgery	7652(1.24)	2602(5.60)	< 0.001	1605(4.33)	1672(4.51)	0.01
Cancer	8021(1.30)	4890(10.5)	< 0.001	2936(7.92)	2902(7.83)	0.003
Medication						
Norepinephrine	201(0.03)	3534(7.60)	< 0.001	176(0.47)	410(1.11)	0.07
Dopamine	1674(0.27)	10098(21.7)	< 0.001	1421(3.83)	2211(5.97)	0.10
Dobutamine	202(0.03)	818(1.76)	< 0.001	147(0.40)	231(0.62)	0.03
Mean CHA2DS2-VASc score (SD)	0.82 ± 0.91	3.39 ± 1.90	< 0.001	2.30 ± 1.40	3.37 ± 1.91	0.64
Mean follow-up years (SD)	6.45 ± 3.19	3.71 ± 3.37	< 0.001	5.67 ± 3.14	4.26 ± 3.35	0.44

Chi-Square Test.
SD denotes standard difference.
CHD denotes coronary heart disease.
COPD denotes chronic obstructive pulmonary disease.
PAOD denotes peripheral artery occlusive disease.
[a] T-Test
[b] A standardized mean difference of ≤0.10 indicates a negligible difference between the two cohorts.

2. Methods

2.1. Data source

We designed a retrospective cohort study using the Longitudinal Health Insurance Database2000 (LHID2000) of Taiwan's National Health Insurance (NHI) program. The NHI program, launched in March 1995, has covered nearly 99% of Taiwanese people at the end of 2015 [13]. In brief, the LHID2000 contained all the original claim data of 1000000 individuals randomly sampled from the 2000 Registry for Beneficiaries. The NHI program and LHID2000 have been described in detail in previous investigations [14,15]. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115).

2.2. Sampled participants

This study identified patients aged ≥20 years with newly diagnosed acute critical illness, including septicemia/septic shock (ICD-9 codes 038,785.52, AMI (ICD-9 code 410), hemorrhagic stroke (ICD-9 code 430-432) and ischemic stroke (ICD-9 code 433-438) between January 1, 2000 and December 31, 2010. The diagnosis date of acute critical illness was defined as the index date. We excluded patients who had a medical history with AF (ICD-9 code 427.31).

Individuals aged ≥20 years in LHID2000 with neither acute critical illness nor AF were defined as non-critical illness general population cohort. To minimize the selection bias, additional critical illness and control cohorts were 1:1 matched by propensity score [16]. The propensity score was calculated by a logistic regression to estimate the probability of the disease status, given the baseline variables, including age, sex, and comorbidities of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral arterial occlusive disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer and medications of Norepinephrine, Dopamine and Dobutamine.

2.3. Outcome measurements

All enrolled individuals were followed up until the occurrence of incident AF, death, withdrawal from the NHI program or until the end of 2011 (whichever came first).

2.4. Statistical analysis

Demographic characteristics and the prevalence of comorbidities were compared between the critical illness cohort and general population cohorts; and Chi-square test was used for categorical variables whereas *t*-test was used for continuous variables. Comparisons between the critical illness cohort and the propensity score matching non-critical illness cohort were examined by the standardized difference. A standardized difference of ≤0.10 is thought to be a negligible difference [17]. To assess the difference in the cumulative incidence curves for AF

between critical illness and general population cohorts, the Kaplan-Meier analysis and log-rank test were applied. The incidence density rate of AF was calculated as the number of AF events divided by the sum of follow-up time (per 1000 person-years). Uni- and multi- variable Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of incident AF associated with critical illness as compared to the non-critical illness cohort with and without propensity score matching. For further analysis, we assessed the effects of different subtypes of critical illness on the risk of developing AF compared with the general population cohort. In addition, the subhazard ratios (SHRs) and 95% CIs of AF were also measured while considering death as a competing risk [18]. SAS statistical package (version 9.4; SAS Institute Inc., Cary, NC, USA) was used to conduct the statistical analysis. R software was used to plot the cumulative incidence curves for AF. The statistical significance was defined as a two-tailed P value < 0.05.

3. Results

3.1. Baseline characteristics

This study consisted of 46470 patients in the critical illness cohort, 618998 persons in the general population cohort (Table 1). Compared with the general population cohort, the critical illness cohort was older, had more men and were more prevalent with comorbidities and medications. The mean CHA_2DS_2-VASc score in the critical illness cohort and in the general population cohort was 3.39 ± 1.90 and 0.82 ± 0.91, respectively. The mean follow-up periods for incident AF in critical illness and general population cohorts were 3.71 ± 3.37, and 6.45 ± 3.19 years, respectively. Additionally, 37,060 critical illness patients were matched with 37,060 control patients based on propensity score methods. The critical illness cohort and the propensity score matching non-critical illness cohort were similar in the distributions of age, sex, comorbidities and medications.

3.2. Incidence and HR of AF

Fig. 1 showed that the cumulative incidence curve of new-onset AF was significantly higher in the critical illness cohort than that in the general population cohort by 10.0% (log rank test $P < 0.001$) at the end of follow-up. The overall incidence density of AF was higher in the critical illness cohort than in the general population cohort (11.1 vs. 0.80 per 1000 person-years) (Table 2). Compared with general population cohort, the adjusted HR (aHR) of AF was 2.32 (95% CI = 2.17–2.48) for the critical illness cohort. The incident AF was 2.25-fold greater in the critical illness cohort (10.0 per 1000 person-years, event = 1585) than the propensity score matching non-critical illness cohort (4.37 per 1000 person-years, $n = 919$). The risk of AF in the critical illness cohort was 2.38-fold higher than in the propensity score matching non-critical illness cohort (95% CI = 2.19–2.58) after adjusting for the confounders.

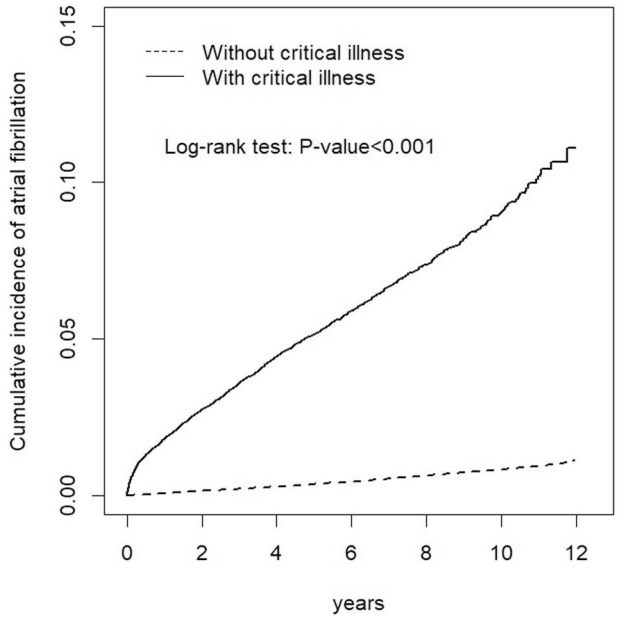

Fig. 1. Cumulative incidence curves of new-onset atrial fibrillation for groups with and without critical illness without propensity score matching.

3.3. Subtype analysis

Compared with general population cohort, patients with septicemia/septic shock were 3.12-fold more likely to develop AF (95% CI = 2.88–3.39), followed by patients with ischemic stroke (aHR = 1.96, 95% CI = 1.80–2.14), patients with AMI (aHR = 1.62, 95% CI = 1.32–2.00) and patients with hemorrhagic stroke (aHR = 1.46, 95% CI = 1.13–1.88) (Table 3).

3.4. Sensitivity analysis

The results of the univariable and multivariable competing-risk regression models of the risk of AF were shown in Table 4. In the univariable model, the crude SHR of developing AF for critical illness patients was 3.72 (95% CI = 3.50–3.95) compared to the general population cohort. After controlling for the covariates and the competing risk of death, the critical illness cohort still exhibited a significantly higher risk of AF than the general population cohort (adjusted SHR [aSHR] = 2.66, 95% CI = 2.49–2.84).

3.5. Incidence and HR of AF, according to follow-up period, in the subtype critical illness patients compared with the propensity score matching control patients

The aHR of AF was significantly higher in the first year of follow-up (aHR = 5.10, 95% CI = 3.84–6.76) in the septicemia/septic shock cohort compared to the propensity score matching non-critical illness cohort, and reduced with increasingly longer period to 2.92 (95%CI = 2.18–3.91) for 3–5 years of follow-up (Table 5). The risk remained for > 5 years of follow-up (aHR = 2.73, 95% CI = 2.16–3.46). Similar results were observed in the ischemic stroke cohort compared to the propensity score matching non-critical illness cohort.

Most new-onset AF occurred in ≦1 years of follow-up in the AMI cohort compared to the propensity score matching non-critical illness cohort (aHR = 2.90, 95% CI = 1.46–5.73). Similar results were observed in the hemorrhagic stroke cohort compared to the propensity score matching non-critical illness cohort.

4. Discussions

This study demonstrated the relationship of different subtypes of acute critical illness with new-onset AF incidence with propensity matching, multivariate adjustment and competing risk methods. Subjects with septicemia/septic shock were found to be more likely to develop incident AF as compared to other acute critical illnesses.

The major strengths of the study included its large numbers, long follow-up duration and the rigorous statistical analysis methods using the nation's database from Taiwan which potentially could add additional evidence linking critical illness and AF from the view point of clinical aspect [13–18].

The burden of AF on cardiovascular morbidity and mortality is huge; the $CHADS_2$ score and its updated version, the CHA_2DS_2-VASc score, are clinical prediction rules for estimating the risk of stroke in

Table 2
Incidence density rates and hazard ratios of atrial fibrillation for patients with critical illness compared to those without critical illness according to types of matching between study cohorts.

	Without propensity score matching		With propensity score matching	
	Critical illness		Critical illness	
	No	Yes	No	Yes
	(N = 618998)	(N = 46470)	(N = 37060)	(N = 37060)
Person-years	3994661	172310	210305	157876
Atrial fibrillation				
Event	3178	1907	919	1585
Rate #	0.80	11.1	4.37	10.0
Crude HR* (95% CI)	1(Reference)	13.8(13.0,14.6)***	1(Reference)	2.25(2.08, 2.45)***
Adjusted HR†(95% CI)	1(Reference)	2.32(2.17, 2.48)***	1(Reference)	2.38(2.19, 2.58)***

Rate#, incidence rate, per 1000 person-years; Crude HR*, crude hazard ratio; Adjusted HR†: multivariable analysis including age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral artery occlusive disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer, and medications of Norepinephrine, Dopamine, and Dobutamine.
*** $p < 0.001$.

Table 3
Incidence density rates and hazard ratios of atrial fibrillation for patients with various subtypes of critical illness compared to those without critical illness without propensity score matching.

Variable	Event	Person-years	Rate#	Crude HR(95% CI)	Adjusted HR† (95% CI)
Atrial fibrillation					
Critical illness					
None	3178	3994661	0.80	1(Reference)	1(Reference)
Septicemia/septic shock	1028	68384	15.0	18.6(17.3, 20.0)***	3.12(2.88, 3.39)***
Acute myocardial infarction	97	12181	7.96	9.99(8.16, 12.2)***	1.62(1.32, 2.00)***
Hemorrhagic stroke	60	14536	4.13	5.18(4.01, 6.68)***	1.46(1.13, 1.88)**
Ischemic stroke	722	77208	9.35	11.8(10.9, 12.8)***	1.96(1.80, 2.14)***

Rate#, incidence rate, per 1000 person-years; Crude HR, crude hazard ratio; Adjusted HR†: multivariable analysis including age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral artery occlusive disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer, and medications of Norepinephrine, Dopamine, and Dobutamine.
** $p < 0.01$.
*** $p < 0.001$.

patients with non-rheumatic AF [19–22]. In addition, the prognostic stratification of incident AF in critically ill patients has been widely explored; however, management approach to subjects with new-onset AF in patients who survived critical illness is challenging since critical illness patients are very heterogeneous with regard to the wide disparity of the manifestations of thrombosis or bleeding, or even in combination [5–12].

Table 4
Risk of atrial fibrillation for patients with critical illness compared to those without critical illness using the competing-risks regression models without propensity score matching.

	Competing-risks regression models	
	Critical illness	
	No	Yes
	(N = 618998)	(N = 46470)
Atrial fibrillation		
Crude SHR (95% CI)	1(Reference)	3.72(3.50, 3.95)***
Adjusted SHR† (95% CI)	1(Reference)	2.66(2.49, 2.84)***

†: Multivariable analysis including age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral artery occlusive disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer, and medications of Norepinephrine, Dopamine, and Dobutamine (death was also added in the model to measure adjusted subhazard ratio.
*** p < 0.001.

Although the connection between critical illness and incident AF has been established and the association is thought to be mediated by immune response, inflammatory system and the dysregulation of neuroendocrine system [5–12], there is no information concerning the incidence of AF in these patients in the follow-up period. A relative impact of each critical illness on the development of new-onset AF might be different depending on the differential effects of the underlying signaling pathways. Based on this rationale for exploring this hypothesis with robust statistical methods approach [16–18], we found that among critically ill patients, those with septicemia/septic shock tended to carry a higher rate of incident AF than other cardiac and cerebrovascular diseases, such as AMI, ischemic stroke and hemorrhagic stroke and the risk remained for > 5 years of follow-up; implying that the mechanisms responsible for AF occurrence in the acute phase of sepsis can continue their action beyond the time of this disease. Future works to confirm our observations and to provide more extensive information on the causal mechanisms responsible for the association with the development of new-onset AF in different subtypes of critical illness are motivated.

4.1. Limitations

Our study might be faulted by the following considerations. First, use of a single ICD-9 code to evaluate for the presence of AF is likely to have a low sensitivity, especially given the known difficulties in

Table 5
Incidence density rates and hazard ratios of atrial fibrillation, according to follow-up period, in the subtype critical illness patients compared with the propensity score matching control patients.

Variables	Septicemia/septic shock						Crude HR (95% CI)	Adjusted HR† (95% CI)
	No *N* = 15,860			Yes *N* = 15,860				
	Event	PY	Rate#	Event	PY	Rate#		
Follow-up period								
≦1	60	15,545	3.86	275	12,772	21.5	5.38(4.07, 7.12)***	5.10(3.84, 6.76)***
1–3	98	27,485	3.57	203	18,903	10.7	3.01(2.36, 3.83)***	2.91(2.27, 3.72)***
3–5	72	20,647	3.49	135	12,697	10.6	3.04(2.28, 4.05)***	2.92(2.18, 3.91)***
> 5	124	28,549	4.34	172	14,547	11.8	2.77(2.20, 3.49)***	2.73(2.16, 3.46)***
	Acute myocardial infarction						Crude HR (95% CI)	Adjusted HR† (95% CI)
	No *N* = 2156			Yes N = 2156				
	Event	PY	Rate#	Event	PY	Rate#		
Follow-up period								
≦1	13	2132	6.10	33	1907	17.3	2.77(1.46, 5.26)**	2.90(1.46, 5.73)**
1–3	18	3714	4.85	15	3061	4.90	1.00(0.50, 1.99)	1.14(0.54, 2.40)
3–5	11	2532	4.34	10	2093	4.78	1.10(0.47, 2.59)	1.37(0.54, 3.48)
> 5	19	3007	6.32	13	2537	5.12	0.81(0.40, 1.64)	0.94(0.44, 2.02)
	Hemorrhagic stroke						Crude HR (95% CI)	Adjusted HR† (95% CI)
	No *N* = 3162			Yes N = 3162				
	Event	PY	Rate#	Event	PY	Rate#		
Follow-up period								
≦1	15	3135	2.23	15	2630	5.70	2.53(1.03, 6.20)*	2.68(1.07, 6.69)*
1–3	13	5613	2.32	17	4239	4.01	1.73(0.84, 3.55)	1.97(0.94, 4.14)
3–5	11	4138	2.66	6	3084	1.95	0.73(0.27, 1.98)	0.83(0.30, 2.31)
> 5	21	5661	3.71	18	3860	4.66	1.26(0.67, 2.37)	1.33(0.70, 2.51)
	Ischemic stroke						Crude HR (95% CI)	Adjusted HR† (95% CI)
	No N = 15,178			Yes N = 15,178				
	Event	PY	Rate#	Event	PY	Rate#		
Follow-up period								
≦1	66	14,965	4.41	220	14,078	15.6	3.50(2.66, 4.61)***	3.47(2.64, 4.58)***
1–3	115	26,593	4.32	183	22,980	7.96	1.84(1.45, 2.32)***	1.91(1.51, 2.42)***
3–5	90	19,770	4.55	110	16,318	6.74	1.48(1.12, 1.96)**	1.54(1.17, 2.04)**
> 5	138	26,480	5.21	146	20,195	7.23	1.40(1.11, 1.76)**	1.42(1.12, 1.80)**

Rate#, incidence rate, per 1000 person-years; Crude HR, crude hazard ratio; Adjusted HR†: multivariable analysis including age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, chronic obstructive pulmonary disease, peripheral artery occlusive disease, chronic kidney disease, hyperthyroidism, sleep disorders, gout, lower leg fracture or surgery, cancer, and medications of Norepinephrine, Dopamine, and Dobutamine.

* $p < 0.05$.

** $p < 0.01$.

*** $p < .001$.

diagnosing paroxysmal and asymptomatic forms of this disease. Second, the information on essential confounding factors, including body mass index, smoking history, alcohol consumption and family history of AF were missing in this study.

Third, other surgical critical disorders, such as trauma, burn injury and major surgery were not included in this analysis. Fourth, due to the limitations of this national dataset, specific functional/clinical parameters able to predict AF in patients in specific critical clinical status; and echocardiographic markers of structural heart disease able to predict new onset AF in critically ill patients were not attempted. Hence, classifying specific subgroups at risk in order to better understand the clinical determinants of incident AF is not possible, which might limit this survey from the pathophysiological point of view and also in terms of the clinical inference on the prognosis. Finally, since the data are originated from an Asian cohort and then our results probably not generalizable to other races.

5. Conclusions

The current study reported incident AF in survivors of critical illness with solid methodology approach. Among critically ill patients, those with septicemia/septic shock carried the highest risk of incident AF.

Disclosure

None.

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