The Impact of New-Onset Atrial Fibrillation on Short-Term and Long-Term Mortality of Critically Ill Patients with Candidemia

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Research Article

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Abstract

Background: Both new-onset atrial fibrillation (NOAF) and candidemia occurred frequently in critically ill patients, which are associated with poor outcomes. But, the association between NOAF and critically ill patients with candidemia is still uncertain. This study is try to identify the impact of NOAF on short-term and long-term mortality of critically ill patients with candidemia.

Methods: We retrospectively identified NOAF in all patients with candidemia admitted to a non-cardiac intensive care unit (ICU) from January 2011 to March 2018 in a teaching hospital. We categorized these patients into 3 groups (NOAF, Prior AF, No AF) and compared clinical information between groups. Risk factors for these patients' short-term and long-term mortality were also analyzed.

Results: Ninety-two patients with candidemia were identified from 2011 to 2018. Among these patients, 26 (28.3%) developed NOAF during their hospital stay. The multivariable logistic regression analysis indicated that stroke, anemia, Sequential Organ Failure Assessment (SOFA) score and NOAF were independent risk factors for in-hospital mortality and NOAF was also the independent risk factor for 1 year mortality.

Conclusions: There was a high incidence of NOAF in critically ill patients with candidemia, which was associated with in-hospital mortality and 1 year mortality after hospital discharge. Further multicenter studies should be conducted to help confirm this relationship and to find effective interventions that reduce short-term and long-term mortality.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia found in postoperative and critically ill patients[1–4]. Several critical medical or surgical conditions have been proved to be associated with this cardiac arrhythmia. In intensive care unit, the development of atrial fibrillation can be triggered by fluid shift, neurohormonal disturbances, systemic inflammatory responses and sometimes be viewed as a response to physiological stress[5]. NOAF is both a marker of disease severity as well as a likely contributor to poor outcomes[6, 7].

Patients with fungal infections are a representative category of critically ill. Invasive fungal infection is a leading cause of ICU-associated infection and also a significantly predictor to mortality and morbidity in the critically ill[7–10]. *Candida* species has been reported as the most common cause of fungal disease, and the incidence rate of candidemia in ICU is nearly 10 to 20 times more than non-ICU patients[11, 12]. Patients with candidemia often have serious underlying diseases and the crude mortality is extremely high ranging from 36–63%[13–16]. Moreover, among these patients with septic shock, candidemia is considered the clinical condition with the highest attributable mortality, ranging from 54%-66%[13–16].

Although available evidence provides enough information regarding a relationship between candidemia or NOAF and mortality, separately. But no previous study has determined the epidemiology and outcome

of NOAF in candidemia patients. Therefore, the clinical importance of candidemia-associated NOAF is a matter of ongoing uncertainty. Therefore, we retrospectively identified NOAF in all patients admitted to our ICU with candidemia and analyzed its effect on patients' outcome.

Materials And Methods

Study population

We retrospectively identified and analyzed all patients admitted to a non-cardiac ICU with candidemia reported by the microbiological department of Peking University People's Hospital in China from January 2011 to March 2018. We investigated NOAF following candidemia hospitalization and categorized patients into 3 groups: 1) NOAF; 2) Prior AF; 3) No AF. The medical records of all patients were reviewed and the following information was collected: age, sex, height, weight, BMI, patient source (medical/surgical ward), underlying conditions (diabetes, hypertension, vascular disease, cerebral stroke, pneumonia, chronic renal dysfunction, solid tumor), the worst laboratory data within 3 days after admission to the ICU (hemoglobin level, temperature, serum total protein level, serum albumin level) and the worst SOFA score within 3 days after admission to the ICU and CHA₂DS₂-VASc score, complications including heart failure and stroke, short-term outcome data including death in hospital, length of ICU stay, length of hospital stay, and duration of mechanical ventilation, long-term outcome including death within 3 years after hospital discharge.

Definitions

We defined candidemia as the isolation of *Candida* species from at least one blood culture in patients with symptoms or signs of a systemic infection. NOAF was categorized if first detected by bedside telemetry and confirmed by 12-lead ECG during hospitalization or initiated pharmacologic therapy without previous AF. Anemia was defined as a hemoglobin level < 70 g/l. Hypoproteinemia was defined as a total protein level < 60 g/dl or serum albumin level < 25 g/dl.

Statistical analysis

Data were analyzed with SPSS software version 21.0. For continuous variables, we used means with SDs. We compared independent groups using the *t* test, and paired groups using paired sample *t* test; One-way analysis of variance was used for comparison between multiple groups, and LSD method was used for post-hoc comparison. For categorical variables, we used percents and counts. The count data were described by case number (*n*), and the difference between groups was tested by the Chi-square test. Factors with a *p* < 0.05 in univariate tests were analyzed with a binary logistic regression model to identify the independent risk factors. The difference was statistically significant when *p* < 0.05.

Results

Incidence of new-onset atrial fibrillation and baseline characteristics

Ninety-two patients with candidemia were identified over a 7-year period from 2011 to 2018. Among these patients with candidemia, 26 (28.3%) developed NOAF during their hospital stay and 7 (7.6%) had AF history before hospital admission. Baseline characteristics of these patients are shown in table 1. Patients in NOAF and prior AF groups were older than no AF patients (mean age 74.04 ± 11.41 years and 81.29 ± 5.94 years vs. 67.12 ± 16.24 years), and more easier to complicate with heart failure (38.5% and 42.9% vs. 10.2%), stroke (76.9% and 85.7% vs. 37.3%). Patients with prior AF and NOAF also had a higher CHA₂DS₂-VASc score (5.14 ± 2.12 and 3.65 ± 1.77 vs. 2.83 ± 1.81).

Distribution of Candida species

Distribution of Candida spp. of these patients was shown in Figure 1. *Candida albicans* was the most prevalent fungal species in patients with or without AF, followed by *Candida parapsilosis*, *Candida glabrata* and *Candida tropicalis*.

Risk factors for short-term and long-term outcomes

Compared with patients never developed AF, patients with NOAF or prior AF had a longer mechanical ventilation time (33.69 ± 34.46 days and 15.43 ± 12.87 days vs. 13.71 ± 26.22 days) and higher in-hospital death rate (73.1% and 85.7% vs. 39%). And 85.7% of these patients with POAF and all patients with prior AF who survived when discharged from hospital died within 1 year, which is extremely higher than survivors with no AF.

In univariate analysis, in-hospital mortality was associated with cerebral stroke, heart failure, stroke, anemia, CHA₂DS₂-VASc score, SOFA Score, new-onset AF and total mechanical ventilation days as shown in Table 2. In logistic regression analysis, stroke, anemia, SOFA score and NOAF were independent risk factors for in-hospital mortality (Table 3).

For long-term outcome, the univariate analysis showed that NOAF, hypertension, solid tumor and stroke were associated with 1 year mortality after discharge (Table 4). And the logistic regression analysis indicated that NOAF was the independent risk factor for 1 year mortality (Table 5).

Discussion

Identification of prognostic factors associated with the outcomes of critically ill patients can be helpful to physicians in making treatment plan and discussing goals of care with patients and their relatives. In-hospital mortality is high in critically ill patients with candidemia, and its incidence rise when these patients complicated with NOAF. Although much remains to be understood, heightened awareness and early intervention may help reduce the burden among these patients.

The incidence of NOAF varies from 1 to 5% in regular inpatients[22, 23], 4.5% to 29.5% in mixed ICU[24], 8% to 10% inpatients with sepsis, 6% to 22% in patients with severe sepsis[25-27], 23% to 44% in patients with septic shock[28-30]. In our study, we demonstrated that 28.3% of all patients with candidemia

developed NOAF which is much higher than previous study about NOAF in critical ill patients (1.8% to 10%) and similar with patients with septic shock[31-33]. This increasing incidence may support the hypothesis that a systemic inflammatory response, increased physiological stress and autonomic dysfunction are the major triggering factors for AF developing in these patients[34, 35].

Compared with patients who never developed AF, the mechanical ventilation time in patients with POAF was significantly prolonged, which translated into more resource utilization and higher costs. Patients with NOAF also had an extremely high in-hospital mortality rate (73.1%) and 1 year mortality rate after discharge from hospital (85.7%). In multivariate logistic regression analysis, NOAF was significantly associated with higher in-hospital mortality and 1 year mortality in patients with candidemia, which indicated that NOAF could be a predictor for poor outcomes of these patients.

According to previous study, Patients with NOAF had an increased risk of embolic stroke[36]. In our study, NOAF in patients with candidemia is associated with an increased risk of stroke compared with patients without AF. In multivariable analysis, stroke is also associated with in-hospital mortality. The possible explanations are that AF could cause embolic and ischaemic stroke which could be attributable to haemodynamic instability and biochemical disturbances and lead to clinical deterioration and death[37-39].

The CHA₂DS₂-VASc score which include congestive heart failure; hypertension; age (65-74 years, ≥ 75 years [doubled]); diabetes; previous stroke or TIA (doubled); vascular disease; and sex has been widely used for the assessment of thromboembolic risk and guiding antithrombotic therapy in patients with AF. Several studies have demonstrated that the higher CHA₂DS₂-VASc score is an independent predictor for mortality in patients with AF[40-44]. In our study, CHA₂DS₂-VASc score was higher in patients with AF than those without AF and also a risk factor for in-hospital mortality even following a multivariate analysis, suggesting that CHA₂DS₂-VASc score may be a prognostic factor associated with the poor outcome in critically ill patients with candidemia.

Unsurprisingly, SOFA score as a organ dysfunction or failure evaluating system was closely related to in-hospital mortality[40-44]. Anemia is a common clinical situation which could due to many factors including blood loss, nutritional deficiency, renal dysfunction, inflammation and so on. Same as previous studies, patients with anemia had an increased in-hospital mortality in our study. This result reminded us that we should correct anemia appropriately according to the cause.

Strengths and limitations

To our knowledge, this study is the first to demonstrate that NOAF was associated with in-hospital mortality and 1 year mortality in critically ill patients with candidemia, which suggested that NOAF maybe considered an important predictor of deterioration among these patients. There are several limitations in our study. Firstly, these data was retrospectively collected, and it is possible that the number of prior-AF cases may be inaccurate as many patients may have asymptomatic AF. Secondly, this is a single center study. The number of cases is relatively small making our conclusion not sufficient. Thirdly, majority of

patients with NOAF died within 1 year after discharge from hospital, so there is insufficient data to assess long-term outcome. Therefore, the result of our study might not be fully generalizable, so a multicenter prospective, randomized controlled trial should be conducted to overcome these limitations.

Conclusions

Our study identified an important novel association between NOAF and poor outcomes including short-term and long-term mortality in critically ill patients with candidemia. Further studies should involve larger, multicenter, prospective studies to get more accurate result and help the clinicians to adjust the treatment plan and communicate with patients and their relatives.

Abbreviations

NOAF: New-onset atrial fibrillation

AF: Atrial fibrillation

ICU: Intensive care unit

BMI: Body mass index

COPD: Chronic obstructive pulmonary disease

SOFA: Sequential Organ Failure Assessment score

Declarations

Availability of data and materials

The dataset used and analyzed in our study are available from the corresponding author on reasonable request.

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Contributions

YZA designed this study and revised the manuscript for important intellectual content; ZLX and AQD collected and analysed the data and ZLX drafted this manuscript. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Peking University People's Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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Tables

Table 1 : Baseline characteristics of patients with candidemia by AF status

Variable	Atrial Fibrillation			F/X ²	P
	No AF	New-onset AF	Prior AF		
Age	67.12±16.24	74.04±11.41	81.29±5.94	4.277	0.017
Gender				0.726	0.695
Male	39(66.1)	15(57.7)	5(71.4)		
Female	20(33.9)	11(42.3)	2(28.6)		
Height(cm)	166.44±7.46	164.35±8.42	168.86±8.23	1.149	0.322
Weight(kg)	64.05±12.32	59.88±9.44	64.71±8.40	1.312	0.274
BMI	23.04±3.73	22.27±3.94	22.66±1.95	0.390	0.679
Hospital admission				2.605	0.272
Medical ward	16(27.1)	9(34.6)	4(57.1)		
Surgical ward	43(72.9)	17(65.4)	3(42.9)		
Comorbid conditions					
Hypertension	27(45.8)	12(46.2)	5(71.4)	1.733	0.421
Diabetes	19(32.2)	7(26.9)	4(57.1)	2.172	0.338
Vascular Disease	15(25.4)	6(23.1)	3(42.9)	1.059	0.589
Cerebral Stroke	16(27.1)	8(30.8)	4(57.1)	2.448	0.294
Pneumonia	21(35.6)	14(53.8)	6(85.7)	7.996	0.018
Hematological disease					
Chronic renal dysfunction	14(23.7)	3(11.5)	3(42.9)	3.526	0.171
Solid tumor	24(40.7)	10(38.5)	2(28.6)	0.406	0.816
Heart Failure	6(10.2)	10(38.5)	3(42.9)	10.709	0.005
Stroke	22(37.3)	20(76.9)	6(85.7)	15.597	0.000
Laboratory data					
Anemia	21(35.6)	11(42.3)	3(42.9)	0.417	0.812
Temperature≥38°C	48(81.4)	23(88.5)	7(100.0)	3.112	0.211
Hypoproteinemia	53(89.8)	26(100.0)	7(100.0)	2.683	0.272
CHA ₂ DS ₂ -VASc score	2.83±1.81	3.65±1.77	5.14±2.12	5.987	0.004
SOFA Score	8.85±4.83	9.31±4.21	11.00±3.06	0.720	0.489

Short-term Outcome(days)					
Hospital length of stay	50.73±40.93	64.38±31.38	55.00±35.49	1.158	0.319
Total ICU length of stsy	32.80±35.09	52.65±37.25	45.57±35.94	2.895	0.061
Mechanical ventilation	13.71±26.22	33.69±34.46	15.43±12.87	4.623	0.012
Hospital Death	23(39.0)	19(73.1)	6(85.7)	12.431	0.002
Long-term Outcome					
1 year	11(31.4)	6(85.7)	1(100.0)	8.088	0.006
2 year	3(12.0)	0(0.0)	0	0.250	1.000
3 year	4(19.0)	0(0.0)	0	0.412	1.000

Abbreviations: CI: confidence interval; AF: Atrial fibrillation; SOFA score: Sequential Organ Failure Assessment score; ICU: Intensive care unit.

Table 2 Baseline characteristics for in-hospital mortality of patients with candedimia

Variable	Hospital Death		t/ χ^2	P
	No	Yes		
Age	68.18±16.08	71.96±13.93	-1.207	0.231
Gender			0.116	0.733
Male	29(65.9)	30(62.5)		
Female	15(34.1)	18(37.5)		
Height(cm)	166.59±8.30	165.52±7.38	0.655	0.514
Weight(kg)	64.66±13.23	61.33±9.23	1.386	0.170
BMI	23.23±4.18	22.39±3.13	1.088	0.280
Hospital admission			0.153	0.696
Medical ward	13(29.5)	16(33.3)		
Surgical ward	31(70.5)	32(66.7)		
Comorbid conditions				
Hypertension	17(38.6)	27(56.3)	2.854	0.091
Diabetes	13(29.5)	17(35.4)	0.360	0.548
Vascular Disease	8(18.2)	16(33.3)	2.733	0.098
Cerebral Stroke	8(18.2)	20(41.7)	5.980	0.014
Pneumonia	17(38.6)	24(50.0)	1.200	0.273
Hematological disease				
Chronic renal dysfunction	7(15.9)	13(27.1)	1.685	0.194
Solid tumor	16(36.4)	20(41.7)	0.271	0.603
Heart Failure	5(11.4)	14(29.2)	4.440	0.035
Stroke	13(29.5)	35(72.9)	17.306	0.000
Laboratory data				
Anemia	12(27.3)	23(47.9)	4.151	0.042
Temperature $\geq$ 38°C	35(79.5)	43(89.6)	1.793	0.181
Hypoproteinemia	41(93.2)	45(93.8)	0.012	0.912
CHA ₂ DS ₂ -VASc score	2.68±1.79	3.75±1.91	-2.764	0.007
SOFA Score	6.59±3.76	11.48±3.93	-6.082	0.000

New-onset AF	7(15.9)	19(39.6)	6.346	0.012
Hospital length of stay	50.52±38.73	58.94±37.65	-1.056	0.294
Total ICU length of stay	31.50±29.00	46.60±41.22	-2.046	0.044
Total mechanical ventilation days	11.70±21.87	26.63±33.33	-2.558	0.012

Abbreviations: CI: confidence interval; AF: Atrial fibrillation; SOFA score: Sequential Organ Failure Assessment score; ICU: Intensive care unit.

Table 3☐Multivariable logistic regression model for in-hospital mortality

	B	S.E,	Wals	P	OR	OR95% C.I.	
						☐☐	☐☐
Cerebral Stroke	1.854	1.142	2.638	0.104	6.387	0.682	59.854
Heart Failure	-0.386	0.990	0.152	0.696	0.680	0.098	4.727
Stroke	1.789	0.760	5.545	0.019	5.981	1.350	26.503
Anemia	1.501	0.738	4.139	0.042	4.487	1.056	19.054
CHA ₂ DS ₂ -VASc score	0.111	0.261	0.183	0.669	1.118	0.671	1.864
SOFA score	0.376	0.100	14.129	0.000	1.456	1.197	1.772
New-onset AF	1.630	0.792	4.231	0.040	5.105	1.080	24.130
Total ICU length of stay	0.020	0.012	2.848	0.091	1.021	0.997	1.045
Total mechanical ventilation days	-0.001	0.016	0.005	0.946	0.999	0.967	1.031

Abbreviations: CI: confidence interval; AF: Atrial fibrillation; SOFA score: Sequential Organ Failure Assessment score; ICU: Intensive care unit.

Table 4☐ Baseline characteristics for 1 year mortality of patients with candedimia

Variable	Table 1		t/X ²	P
	No	Yes		
Age	66.44±17.43	71.28±14.22	-0.968	0.339
Gender			2.185	0.139
Male	14(56.0)	14(77.8)		
Female	11(44.0)	4(22.2)		
Height(cm)	165.48±8.91	167.83±7.55	-0.909	0.369
Weight(kg)	65.44±12.37	62.83±14.56	0.633	0.530
BMI	23.82±3.95	22.23±4.47	1.229	0.226
Hospital admission			0.497	0.481
Medical ward	8(32.0)	4(22.2)		
Surgical ward	17(68.0)	14(77.8)		
Hypertension	13(52.0)	4(22.2)	3.882	0.049
Diabetes	7(28.0)	5(27.8)	0.000	0.987
COPD				
Vascular Disease	3(12.0)	5(27.8)	0.836	0.360
Cerebral Stroke	5(20.0)	3(16.7)	0.000	1.000
Pneumonia	8(32.0)	9(50.0)	1.418	0.234
Hematological disease				
Chronic renal dysfunction	4(16.0)	3(16.7)	0.000	1.000
CVVH				
Solid tumor	7(28.0)	12(66.7)	6.344	0.012
Heart Failure	1(4.0)	4(22.2)	1.841	0.175
Stroke	4(16.0)	9(50.0)	5.736	0.017
Laboratory data				
Anemia	7(28.0)	5(27.8)	0.000	0.987
Temperature≥38°C	20(80.0)	14(77.8)	0.000	1.000
Hypoproteinemia	23(92.0)	17(94.4)	0.000	1.000
CHA ₂ DS ₂ -VASc score	2.68±1.93	2.78±1.63	-0.175	0.862

SOFA Score	5.84±3.58	7.72±3.92	-1.635	0.110
New-onset AF	1(4.0)	6(33.3)	4.630	0.031
Hospital length of stay	59.16±43.72	40.78±28.08	1.564	0.125
Total ICU length of stay	37.36±32.88	24.56±21.73	1.439	0.158
Total mechanical ventilation days	13.08±25.28	10.44±17.18	0.383	0.704

Abbreviations: CI: confidence interval; AF: Atrial fibrillation; SOFA score: Sequential Organ Failure Assessment score; ICU: Intensive care unit.

Table 5 Multivariable logistic regression model for 1 year mortality after discharge

	B	S.E.	Wals	P	OR	95% C.I.	
New-onset AF	2.528	1.276	3.926	0.048	12.526	1.028	152.682
Hypertension	-0.944	0.820	1.326	0.249	0.389	0.078	1.940
Solid tumor	0.848	0.790	1.152	0.283	2.336	0.496	10.996
Stroke	0.769	0.856	0.807	0.369	2.157	0.403	11.542

Abbreviations: CI: confidence interval; AF: Atrial fibrillation.

Figures

Figure 1

Distribution of candida spp. of these patients by AF status