New-Onset Atrial Fibrillation is an Independent Predictor of Mortality in Patients With Candidemia

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Research Article

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Abstract

Background: Candidemia, or invasive candidiasis infection, is prevalent in critically ill patients and significantly contributes to the mortality and morbidity of such patients. New-onset atrial fibrillation (NOAF) also occurs frequently in critically ill patients. However, the association between NOAF and candidemia is still uncertain. This study aims to determine whether NOAF could increase the mortality rate of critically ill patients who have candidemia.

Methods: We retrospectively identified NOAF in all patients who were admitted into a non-cardiac intensive care unit (ICU) and diagnosed as candidemia from January 2011 to March 2018. These patients were divided into 3 groups (NOAF, Prior AF, No AF). Clinical information and long-term outcome were collected and compared between three groups. Risk factors for these patients' short-term and long-term mortality were also analyzed.

Results: Ninety-two patients with candidemia were included from 2011 to 2018. Among these patients, 26 (28.3%) developed NOAF during their ICU hospitalization. Patients with NOAF had lower survival rate than those who never developed AF. The multivariate 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 an independent risk factor for 1 year mortality.

Conclusions: There was a high incidence of NOAF in patients with candidemia. In this study, we found NOAF was an independent predictor of in-hospital mortality and 1 year mortality after hospital discharge for patients with candidemia.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia found in critically ill patients [1–4]. Several critical medical or surgical conditions have been proven to be associated with cardiac arrhythmia. For patients in intensive care units, the development of atrial fibrillation can be triggered by fluid shift, neurohormonal disturbances or systemic inflammatory responses, and they are sometimes 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 representative of the critically ill category. Invasive fungal infections are a leading cause of ICU-associated infections and are also significantly predictors of mortality and morbidity in the critically ill [7–10]. *Candida* species have been reported as the most common cause of fungal diseases, and the incidence rate of candidemia in ICU patients is nearly 10 to 20 times greater than in 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 those patients with septic shock, candidemia is considered the clinical condition with the highest attributable mortality, ranging from 54%-66% [13–16].

Although previous studies have provided sufficient information to ascertain a relationship between candidemia and mortality or NOAF and mortality, no previous study has determined the epidemiology or predicted the mortality of candidemia patients who also have NOAF. Therefore, we retrospectively identified NOAF in all patients admitted to our ICU with candidemia and analyzed the effect of NOAF occurrence on patients' outcomes.

Materials And Methods

Study population

We retrospectively identified and analyzed all patients admitted to a non-cardiac ICU with candidemia, as reported by the microbiological department of Peking University People's Hospital in China from January 2011 to March 2018. Patients were categorized into 3 groups: 1) NOAF; 2) Prior AF; 3) No AF. The medical records of all patients were collected and reviewed. The data included the age, sex, height, weight, BMI, patient source (medical/surgical ward), underlying conditions (diabetes, hypertension, vascular disease, cerebral stroke, pneumonia, chronic renal dysfunction, and solid tumors), the worst laboratory data recorded within 3 days after admission to the ICU (hemoglobin level, temperature, serum total protein level, serum albumin level), the worst SOFA score recorded within 3 days after admission to the ICU and the CHA₂DS₂-VASc score. We also considered complications (heart failure and stroke), short-term outcome data (death in hospital, length of ICU stay, length of hospital stay, and duration of mechanical ventilation), and finally long-term outcome data (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 it was first detected by bedside telemetry and then confirmed by 12-lead ECG during hospitalization or pharmacologic therapy was initiated 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

The data were analyzed with SPSS software version 21.0. For continuous variables, we calculated the 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 to compare between multiple groups, and the LSD method was used for post-hoc comparison. For categorical variables, we used percentage 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 a prior history of AF before hospital admission. The baseline characteristics of these patients are shown in Table 1. Patients in the NOAF and Prior AF groups were older than the patients who did not have AF (mean age 74.04 ± 11.41 years and 81.29 ± 5.94 years vs. 67.12 ± 16.24 years). The NOAF and Prior AF patients had a higher occurrence of complications versus the No AF patients; the complications included heart failure (38.5% and 42.9% vs. 10.2%), and stroke (76.9% and 85.7% vs. 37.3%). The NOAF and Prior AF patients also had a higher CHA₂DS₂-VASc score versus the No AF patients (5.14 ± 2.12 and 3.65 ± 1.77 vs. 2.83 ± 1.81).

Distribution of Candida species

Distribution of *Candida* spp. in these patients is 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*.

AF status associated with increased mortality

Patients with prior AF and NOAF had a higher mortality rate than patients with no AF ($p=0.002$) (Figure 2). Over 80% of the patients with NOAF and all the patients with prior AF who were discharged from hospital died within 1 year, which is significantly higher than the mortality rate of survivors with no AF. According to the Kaplan-Meier univariate analysis, the overall average survival time is 22.9 months, the 6-month survival rate is 81.4%, the 1-year survival rate is 60.5%, and the 3-year survival rate is 44.2%. AF indicators have a significant impact on the survival rate of patients ($P<0.05$). And the survival rate of NOAF group was lower than that of No AF group (Figure 3).

In the 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 the 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 tumors and stroke were associated with 1 year mortality after discharge (Table 4). Furthermore, the logistic regression analysis indicated that NOAF was an independent risk factor for 1 year mortality (Table 5).

Discussion

The identification of prognostic factors that are associated with the outcomes of critically ill patients can be helpful to physicians in making treatment plans and discussing goals of care with patients and their relatives. In-hospital mortality is high in critically ill patients with candidemia, and its incidence increases

when these patients also have NOAF. Although much remains to be understood, heightened awareness and early intervention may help reduce the suffering of these patients.

The incidence of NOAF varies from 1% to 5% in regular inpatients [22, 23], 4.5% to 29.5% in mixed ICU patients [24], 8% to 10% in patients with sepsis, 6% to 22% in patients with severe sepsis [25-27], and 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 the incidence reported in previous studies on NOAF in critically ill patients (1.8% to 10%) and similar to the incidence for 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 major triggering factors for the development of AF in these patients[34, 35].

Compared with patients who have never developed AF, the duration of mechanical ventilation for patients with NOAF 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 the Kaplan-Meier univariate analysis and 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 a previous study, patients with NOAF had an increased risk of embolic stroke[36]. In our study, NOAF in patients with candidemia was associated with an increased risk of stroke compared with patients without AF. In the multivariate analysis, stroke was 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 incorporates congestive heart failure, hypertension, age (65-74 years, ≥ 75 years [doubled]), diabetes, previous stroke or TIA (doubled), vascular disease, and sex. It has been widely used for the assessment of thromboembolic risk and guiding antithrombotic therapy in patients with AF. Several studies have demonstrated that a higher CHA₂DS₂-VASc score is an independent predictor for mortality in patients with AF [40-44]. In our study, the CHA₂DS₂-VASc score was higher in patients with AF than those without AF, and multivariate analysis revealed that it was also a risk factor for in-hospital mortality, suggesting that the CHA₂DS₂-VASc score may be a prognostic factor associated with poor outcomes in critically ill patients with candidemia.

The SOFA score is used to determine the extent of a patient's organ dysfunction or failure. Unsurprisingly, the SOFA score was closely related to in-hospital mortality [40-44]. Anemia is a common clinical situation which could occur due to many factors, such as blood loss, nutritional deficiency, renal dysfunction, and inflammation. Similar to previous studies, patients with anemia had an increased rate of in-hospital

mortality in our study. This result reminded us that we should act quickly to treat anemia appropriately according to the cause.

Strengths and limitations

To our knowledge, this study is the first to demonstrate that NOAF is associated with in-hospital mortality and 1 year mortality in critically ill patients with candidemia, which suggests that NOAF may be considered as an important predictor of deterioration among these patients.

There are several limitations in our study. Firstly, these data were 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 was a single center study and the number of cases was relatively small, which limits the strength of our conclusions. Thirdly, the majority of patients with NOAF died within 1 year after discharge from hospital, so there was not enough data to assess long-term outcomes. Therefore, the results of our study might not be fully generalizable. Hence, 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, which includes short-term and long-term mortality in critically ill patients with candidemia. Further studies should involve larger, multicenter, prospective studies in order to obtain more accurate results that can assist clinicians in adjusting treatment plans and communicating 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 datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Peking University People's Hospital. Due to nature of retrospective study, this study would not interfere with patients who were enrolled, the study had got consent waiver from the Ethics Committee(No.20210608). Clinical information was obtained from electrical medical system and the authors guarantee patients' data confidentiality. All methods of this study were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no competing interests.

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None.

Authors' 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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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 stay	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 candidemia

Variable	Hospital Death		t/X ²	P
	No(n=44)	Yes(n=48)		
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≥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 Multivariate logistic regression model for in-hospital mortality

	B	S.E.	Wals	P	OR	OR95% C.I.	
						LL	UL
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 candidemia

Variable	Death within 1year after discharge		t/X ²	P
	No(n=25)	Yes(n=18)		
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 adission			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
Tempreture≤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 stsy	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 Multivariate 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

Figure 2

AF is associated with increased mortality in patients with candidemia

Figure 3

Kaplan-Meier univariate analysis