〈Regular Article〉

Clinical factors for mortality in very elderly patients with atrial fibrillation

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ABSTRACT **Background and aim**: There is limited information available about the cause of death of very elderly patients with atrial fibrillation aged ≥ 85 years. The aim of this study was to clarify the cause of death and clinical risk factors for very elderly patients with AF ≥ 85 years.

Method; A total of 1,196 patients with AF registered in the KIBIDAN-GO registry at Kawasaki Medical School between 2002 and 2017, were retrospectively studied. We divided the patients into 2 groups (age < 85 years and age ≥ 85 years old) and compared the cause of death and clinical risk factors for death between the 2 groups.

Results: During the follow-up period (median follow-up period was 4360 days), 239 patients (20%) died. The main cause of death was non-CV disease in both groups. The multivariate Cox regression analysis showed that body mass index (BMI) [hazard ratio (HR); 0.55, 95% confidence interval (CI) (0.33-0.87), p = 0.01], hemoglobin (HR 0.93, 95% CI (0.87-0.98), p = 0.02), and anticoagulants [HR 1.4, 95% CI (1.04-1.63), p = 0.04] were associated with all-cause death in patients aged < 85 years old. On the other hand, BMI [HR 0.55, CI 95% (0.55-0.63), p = 0.01] and chronic kidney disease (CKD) (HR 1.87, 95% CI (1.10-1.80), p = 0.04) were associated with all-cause death in patients aged ≥ 85 years.

Conclusions: In very elderly patients with AF, the main cause of death was non-CV disease, and CKD and BMI were significantly associated with all-cause death.

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Key words：Atrial fibrillation, Very elderly, Mortality, Chronic kidney disease, Low body mass index

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and independently increases the risk of all-cause mortality[1-4]. Patients with AF had a 1.5-4 fold increased risk of all-cause death compared with the general population[5].

According to the Ministry of Health, Labor and Welfare's vital statistics in 2021 in Japan, the annual age-specific mortality rate for population aged ≥ 85 years was 22%[6]. In Japan, the aging of the population and the high mortality of the elderly are problems for the health care economy.

The prevalence rate of AF increases with age, and elderly patients with AF are likely to have a greater

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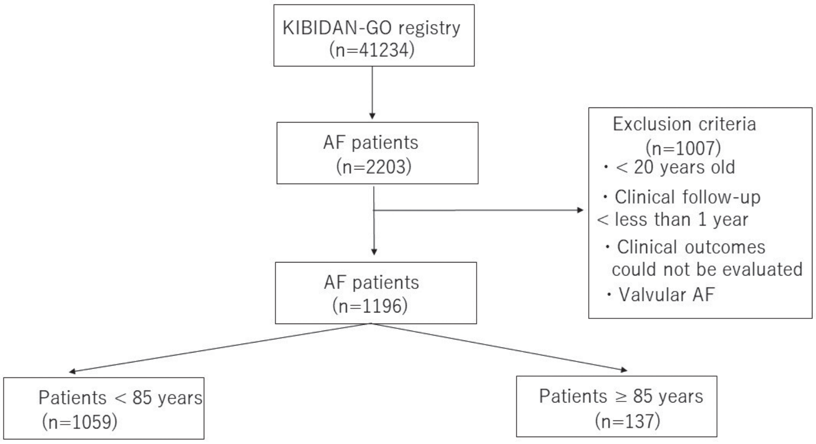


Fig. 1. Study flow chart in the present study. AF; atrial fibrillation

number of comorbidities. Therefore, these elderly patients with AF need to be managed adequately.

Several recent reports have shown that the main cause of death in patients with AF, including elderly patients, is non-cardiovascular (CV) death[7−10]. However, little information is available about clinical factors for all-cause death in very elderly patients with AF aged ≥ 85 years. The aim of this study was to investigate the cause of death in very elderly patients with AF to identify factors associated with all-cause death and clarify the difference from patients aged < 85 years.

METHODS

Study population

This study was a single-center, observational, retrospective study. Among patients with AF in our hospital and registered in the institutional KIBIDAN-GO (Kawasaki BioImaging DAtabase for loNg term cardiovascular proGnOsis) database from January 2002 to December 2017, 2,203 consecutive AF (paroxysmal, persistent or permanent) patients were enrolled. Patients < 20 years old, valvular AF[11] and patients with only one clinical follow-up were excluded. Patients were also excluded if their clinical outcomes could not be evaluated. Finally, we analyzed 1,196 patients with AF with more than 1 year of prognostic information (age range 25-101 years old). We divided the patients into 2 groups according to their age (age < 85 years and age ≥ 85 years; very elderly) when AF was confirmed by the oldest 12-lead electrocardiogram. The study flow chart is shown in Fig. 1. All-cause death consisted of CV death [(heart failure, acute coronary syndrome, vascular (aortic dissection and acute vascular occlusion), stroke (subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage and ischemic cerebral infarction), arrhythmia (ventricular fibrillation, ventricular tachycardia)] and non-CV death (infection, cancer, others) and undetermined causes. This study complied with the Declaration of Helsinki and was approved by the institutional review board of Kawasaki Medical School (IRB number: 6045-00).

Criteria for atrial fibrillation and other risk factors

All study patients were diagnosed as presenting AF that was confirmed based on 12-lead ECG with at least 30 seconds consecutive beat examinations performed. Heart failure was defined according to the Framingham Heart Study criteria[12]. Hypertension was defined as a history of a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure > 90 mmHg, or the use of antihypertensive therapy. Dyslipidemia was defined as a fasting total cholesterol concentration ≥ 220 mg/dl, or the use of antihyperlipidemic therapy. Diabetes mellitus was defined as a fasting plasma glucose concentration ≥ 126 mg/dl or HbA1C ≥ 6.5% or the use of antidiabetic therapy. Chronic kidney disease (CKD) was diagnosed as an estimated glomerular filtration rate < 60 mL/min/m^2. Stroke included subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage and ischemic cerebral infarction.

Statistical Analysis

Continuous variables are expressed as the median and interquartile range. Categorical variables are presented as numbers and percentages and were compared using the $\chi 2$ test when appropriate; otherwise, we used Fisher's exact test. Long-term survival was evaluated by Kaplan-Meier survival analysis. A Cox regression model was used on potential confounders to identify factors associated with all-cause death. P values less than 0.05 were considered statistically significant. All statistical analyses were performed using the SAS software program, version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

The baseline characteristics of the study population are shown in Table 1. The median patient age was 73 years old, and 56% of the patients were male. The median patients BMI was 22.0 (22.9 in patients aged < 85 years and 16.8 in patients age ≥ 85 years). The median CHADS2 score[12] was 2. BMI was significantly lower in patients aged ≥ 85 years group than in those aged < 85 years group. The prevalence of CKD was significantly higher in patients aged ≥ 85 years group than in those aged < 85 years group. Laboratory data are shown in Table 2. Estimated glomerular filtration rate (eGFR) and hemoglobin were significantly lower in patients

Table 1. Baseline clinical characteristics of the two groups

	All (n = 1196)	< 85 years (n = 1059)	≥ 85 years (n = 137)	p value
Age (years)	74.7 ± 10	71 ± 9	87 ± 4	< 0.01
Male gender, n (%)	664 (56)	601 (57)	63 (46)	< 0.01
Height (cm)	157 ± 8	159 ± 8	152 ± 9	< 0.01
Weight (kg)	58 ± 10	59 ± 13	51 ± 9	< 0.01
BMI (kg/m^2)	22.9 ± 3	23.8 ± 4.3	21.9 ± 3.5	< 0.01
Heart rate (bpm)	72 ± 18	72 ± 12	73 ± 11	0.86
LVEF (%)	57 ± 11	57 ± 12	57 ± 11	0.97
$CHADS_2$ score	2.1 ± 1.1	2.1 ± 1.2	2.4 ± 1.1	0.04
Hypertension, n (%)	721 (60)	656 (62)	65 (47)	< 0.01
Diabetes, n (%)	331 (28)	307 (29)	24 (18)	0.10
Dyslipidemia, n (%)	373 (31)	344 (32)	29 (21)	< 0.01
Chronic kidney disease, n (%)	168 (14)	137 (13)	31 (23)	< 0.01
Dialysis, n (%)	54 (4.5)	53 (5)	1 (0.7)	< 0.01
Cancer, n (%)	319 (26)	280 (26)	39 (28)	0.62
COPD, n (%)	104 (8.7)	96 (9.1)	8 (5.8)	0.210
History of heart failure, n (%)	412 (34)	357 (33)	55 (40)	0.01
History of stroke, n (%)	163 (14)	144 (14)	19 (14)	0.93
History of IHD, n (%)	63 (5.2)	56 (5.2)	7 (5.1)	0.14
PCI, n (%)	41 (3.4)	35 (3.3)	6 (4.4)	0.53
CABG, n (%)	22 (1.8)	21 (2.0)	1 (0.7)	0.25
RFCA, n (%)	40 (3.3)	40 (3.7)	0 (0)	−

Abbreviation; LVEF, left ventricular ejection fraction, IHD, ischemic heart disease, PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting, RFCA, radiofrequency catheter ablation. Continuous data are presented as mean ± standard deviation (SD)

Table 2. Laboratory data of the two groups

	All (n = 1196)	< 85 years (n = 1059)	≥ 85 years (n = 137)	p value
Total cholesterol (mg/dL)	169 ± 55	167 ± 54	157 ± 64	0.06
LDL-cholesterol (mg/dL)	89 ± 46	91 ± 45	79 ± 54	< 0.01
HDL-cholesterol (mg/dL)	42 ± 22	43 ± 21	36 ± 24	< 0.01
HbA1C (%)	5.4 ± 2.2	5.7 ± 2.0	5.3 ± 2.2	< 0.01
Hemoglobin (g/dL)	11 ± 3.0	12 ± 3.0	10 ± 4.0	0.01
Creatinine (mg/dL)	1.2 ± 1.2	1.1 ± 0.8	1.5 ± 1.2	< 0.01
eGFR (ml/min/1.73m^2)	53 ± 29	57 ± 33	30 ± 21	< 0.01
BNP (pg/mL)	375 ± 652	354 ± 510	395 ± 423	0.54
CRP (mg/dL)	1.1 ± 2.4	1.0 ± 2.5	1.8 ± 3.5	< 0.01
Uremic acid (mg/dL)	5.8 ± 2.5	5.9 ± 2.4	5.5 ± 3.0	0.26
CK (IU/L)	153 ± 546	173 ± 973	160 ± 402	0.40
BUN (mg/dL)	21 ± 15	21 ± 14	25 ± 18	0.03

Abbreviation; eGFR, estimated glomerular filtration rate, BNP, brain natriuretic peptide, CRP, C-reactive protein, CK, creatine kinase, BUN, blood urea nitrogen. Continuous data are presented as mean ± standard deviation (SD)

Table 3. Medications of the two groups

	All (n = 1196)	< 85 years (n = 1059)	≥ 85 years (n = 137)	p value
Oral anticoagulants, n (%)	869 (72)	807 (76)	52 (38)	< 0.01
Warfarin, n (%)	601 (69)	554 (69)	47 (90)	< 0.01
DOAC, n (%)	258 (30)	253 (31)	5 (10)	< 0.01
ARB, n (%)	431 (36)	392 (37)	39 (28)	0.05
ACE-I, n (%)	332 (28)	303 (29)	29 (21)	0.06
CCB, n (%)	456 (38)	414 (39)	42 (31)	0.05
Beta-blocker, n (%)	534 (45)	487 (46)	47 (34)	0.01
Diuretic, n (%)	467 (39)	426 (40)	41 (30)	0.05
Statin, n (%)	410 (34)	376 (36)	34 (25)	0.02
Antiarrhythmia drug, n (%)	218 (18)	201 (19)	17 (12)	0.06

Abbreviation; DOAC, direct oral anticoagulants ARB, angiotensin receptor antagonist, ACE-I angiotensin converting enzyme-inhibitor, CCB, calcium channel blocker

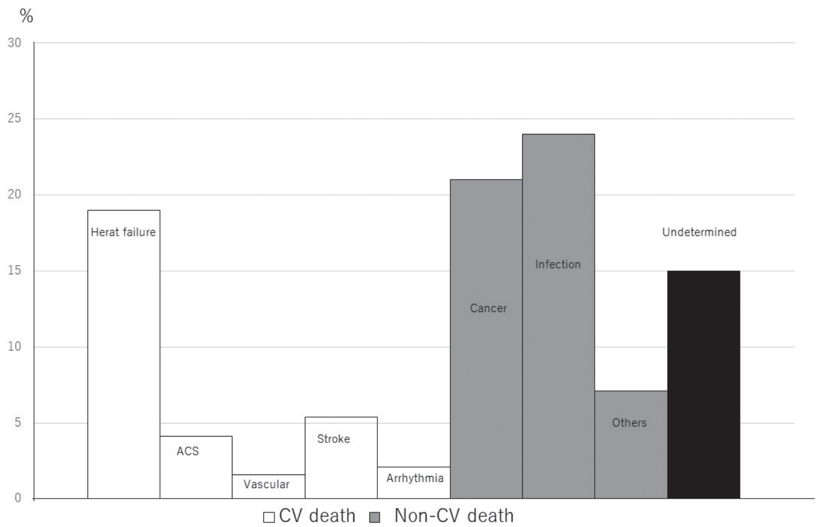


Fig. 2. All-causes of death in the present study. The main cause of death was infection, followed by cancer and heart failure.

Table 4. Causes of death

	All (n = 1196)	< 85 years (n = 1059)	≥ 85 years (n = 137)	p value
All-cause death, n (%)	239 (20)	180 (17)	59 (43)	< 0.01
CV death, n (%)	**80 (33)**	**61 (34)**	**19 (32)**	**0.81**
Heart failure, n (%)	48 (19)	34 (19)	14 (24)	0.43
ACS, n (%)	10 (4.1)	9 (5.0)	1 (1.7)	0.02
Vascular, n (%)	4 (1.6)	3 (1.7)	1 (1.7)	0.45
Stroke, n (%)	13 (5.4)	11 (6.1)	2 (3.4)	0.40
Ischemia, n (%)	5 (2.1)	5 (2.8)	0 (0)	–
Hemorrhage, n (%)	8 (3.3)	6 (3.2)	2 (3.4)	0.75
Arrhythmia, n (%)	5 (2.1)	4 (2.2)	1 (1.7)	0.80
Non-CV death, n (%)	**124 (52)**	**89 (49)**	**35 (59)**	**0.81**
Cancer, n (%)	49 (21)	37 (21)	12 (20)	0.97
Infection, n (%)	58 (24)	36 (20)	22 (37)	< 0.01
Others, n (%)	17 (7.1)	16 (8.9)	1 (1.7)	0.03
Undetermined, n (%)	35 (15)	30 (17)	5 (8.5)	0.10

Abbreviation; CV, cardiovascular, ACS, acute coronary syndrome

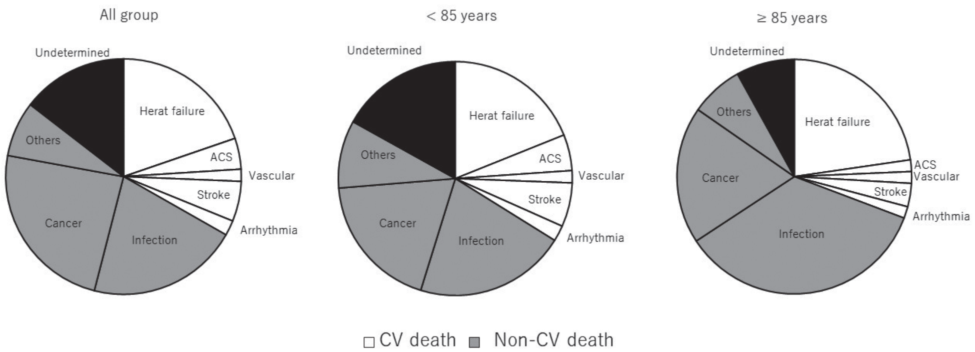
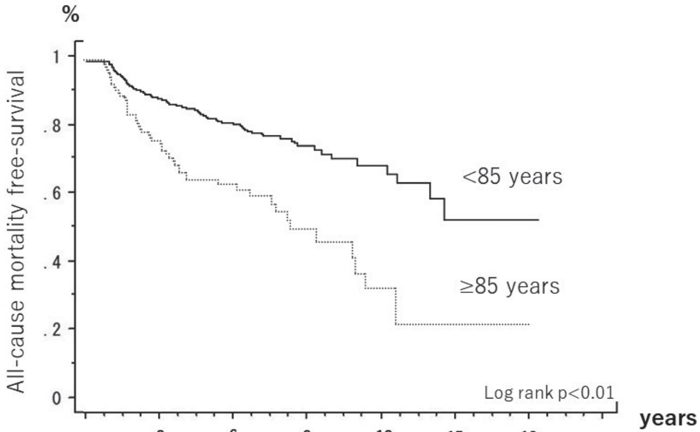


Fig. 3. Causes of death between the 2 groups categorized across age. The main cause of death was heart failure, followed by infection and cancer in patients aged < 85 years. On the other hand, the main cause of death was infection, followed by heart failure and cancer in patients aged ≥ 85 years.

aged ≥ 85 years group than in those aged < 85 years. Table 3 shows medications at baseline. Eight hundred sixty-nine patients (72%) were prescribed oral anticoagulants (OACs) [(69%, warfarin, 30% direct oral anticoagulants (DOACs)].

During the follow-up period (median;4360 days), a total of 239 (20%) patients died [n = 80, CV death; heart failure (19%), acute coronary syndrome (4.1%), peripheral vascular disease (1.6%), arrhythmia (2.1%), stroke (5.4%), n = 124, non-CV death; cancer (21%), infection (24%), others (7.1%) and undetermined (15%)] (Table 2 and Fig. 2). For all-cause death, 17% of patients aged < 85 years died, and 43% of patients aged ≥ 85 years died.

The main cause of death was cancer (21%), followed by infection (20%) and heart failure (19%) in patients aged < 85 years. On the other hand, the main cause of death was infection (37%), followed by heart failure (24%) and cancer (20%) in patients aged ≥ 85 years. Death due to stroke was 6.1% (age < 85 years) and 3.4% (age ≥ 85 years), respectively (Table 4). The causes of death varied widely in each group and are summarized in Fig. 3. Kaplan-Meier curves showed long-term survival was significantly lower in patients aged ≥ 85 years than those patients aged < 85 years (Log rank: p < 0.001) (Fig. 4). Fig. 5 shows the Cox regression analyses for cause of death in each age group. Low body mass index



Number of subjects at risk		3	6	9	12	15	18
Aged < 85 years	1059	1002	950	920	884	879	879
Aged ≥85 years	137	111	91	86	79	78	78

Number of events							
Aged < 85 years	0	57	52	30	36	5	0
Aged ≥85 years	0	26	20	5	7	1	0

Fig. 4. Cox regression analyses for all-cause death. (A) < 85 years, (B) ≥ 85 years.
Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs) in the multivariate model for study patients. BMI, body mass index. CKD, chronic kidney disease. COPD, chronic obstructive pulmonary disease.

(BMI), OAC and hemoglobin were associated with all-cause death in patients aged < 85 years (A). On the other hand, BMI and CKD were associated with all-cause death in patients aged ≥ 85 years (B).

DISCUSSION

This study clarified the causes of death and clinical factors for all-cause death in very elderly patients with AF aged ≥ 85 years. The principal findings in the present study are as follows. 1) The main cause of death was non-CV death. 2) A clinical factor for all-cause death was different between the 2 groups. 3) BMI and CKD were associated with all-cause death in patients aged ≥ 85 years.

Cause of death in very elderly patients with AF

The main cause of death was non-CV disease, including cancer, followed by infection in patients aged ≥ 85 years. On the other hand, the main cause of CV death was heart failure, followed by stroke in patients aged ≥ 85 years. These results were consistent with previous reports[8, 10, 14–16]. These results of our study showed that among patients aged ≥ 85 years, although non-CV death was increased and became the main cause of death, not only non-CV death but also CV death, especially heart failure, should be addressed as a major cause of death in patients aged ≥ 85 years. According to the Ministry of Health, Labor and Welfare's vital statistics in 2021 in Japan, the annual age-specific mortality rate for population aged < 85 years was 0.65%, while the those of aged ≥ 85 years was 22%[6]. Our present study, the annual age-specific mortality for population aged < 85 years was 1.5%, while the those of aged ≥ 85 years was 3.9%. These differences in mortality are because our study is a hospital-based study. Our study suggests that patients aged < 85 years with AF may have higher mortality than those patients without AF and a top 5 of the main causes of death for patients aged ≥

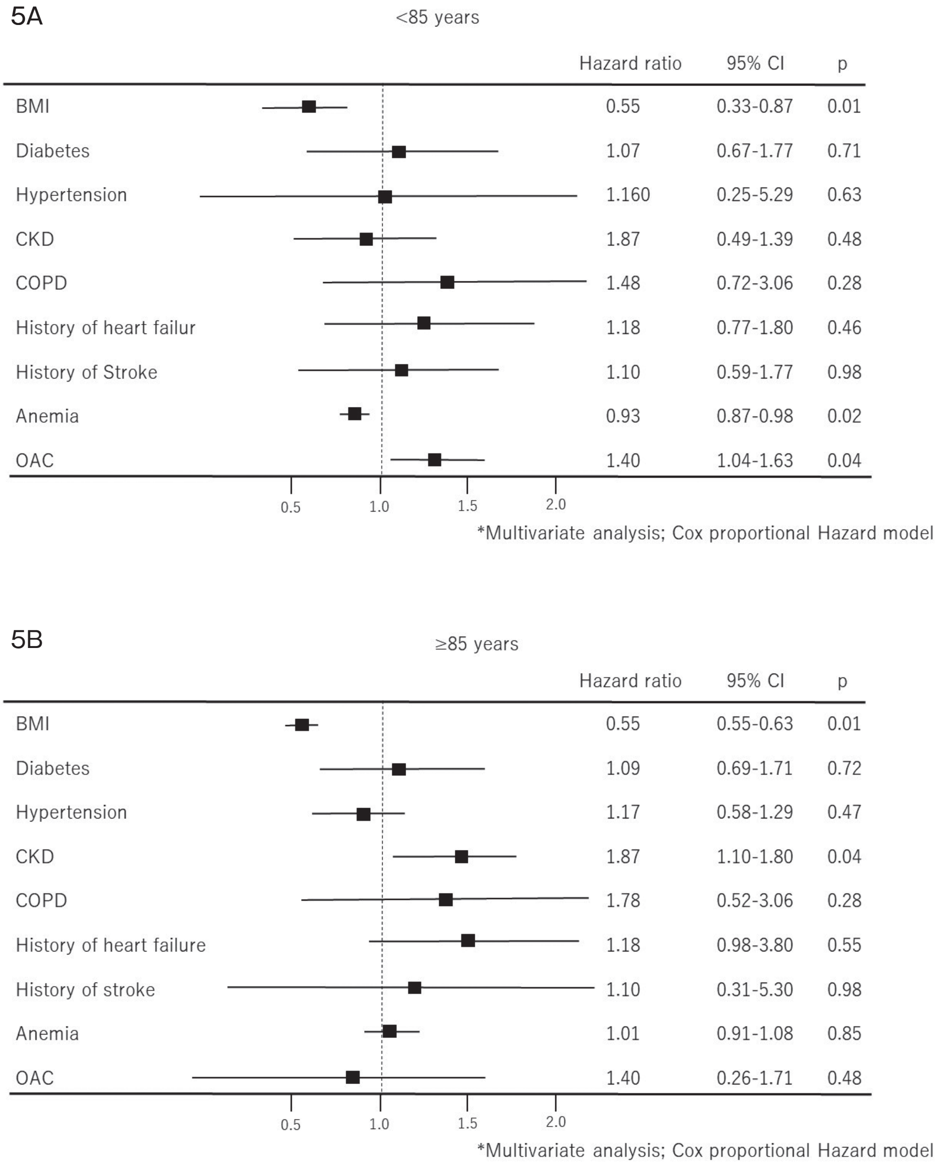


Fig. 5. Kaplan-Meier survival-free survival curves showing a significantly lower survival rate in the patients aged ≥ 85 years group than in those aged < 85 years group.

85 years were senility, followed by heart disease, cancer, cerebrovascular disease, and pneumonia. On the other hand, in our study, a top 5 of the main causes of death were pneumonia, followed by heart disease, cancer, cerebrovascular disease, and others. The differences in the main cause of death could be related to that the present study was a hospital-based study.

In addition, we divided the patients into 3 groups (patients aged < 65 years group, patients aged 65-84 years group and patients aged ≥ 85 years) and analyzed the cause of death among the 3 groups. The main cause of death was heart failure in patient aged < 65 years group, the main cause death was infection in patients aged 65-84 and patients aged ≥ 85 years group. A cancer was not the main cause of death in all 3 groups. However, a clinical factor for all-cause death was different between 3 groups. BMI and CKD were independent predictors of all-cause mortality in patients aged < 65 and patients aged ≥ 85years. On the other hand, anemia, BMI, use of OAC, CKD, history of heart failure and COPD were independent predictors of all-cause mortality in patients aged 65-84 years. BMI was a clinical factor related to all-cause death in all aged groups and CKD in patients aged < 65 and ≥ 85 years. These results might be due to dialysis patients were more frequently observed in the patients aged < 65 years group.

In the present study suggested that although the causes of death were infection, heart failure and cancer in all age groups, the clinical factor for all-cause mortality differed among the age groups.

Impact of CKD on very elderly patients with AF

CKD was one of the clinical factors for all-cause death in the present study. Many elderly patients have CKD as an underlying disease (approximately 36%), and more than 40% are over 80 years old[17, 18]. In addition, it was reported that AF was associated with greater risks of subsequent renal function decline in patients with CKD[19]. Moreover, these patients tend to be polypharmacy for their multimorbidity, which can further cause renal dysfunction. Catheter ablation was expected to reduce the number of prescriptions in these patients. Although it has been reported that recovery to sinus rhythm by catheter ablation was effective for improving renal function in patients with AF[20], there was an opinion that catheter ablation for elderly patients has some problems, such as long-term recurrence rates and complications[21]. Therefore, elderly patients with AF who cannot benefit from catheter ablation could be selected with medical therapy only.

CKD was associated with an increased risk of stroke and mortality in patients with AF[22]. A recent study reported that the absolute benefit of OACs was the highest in very elderly patients with AF[23].

The influence of OACs in patients with polypharmacy is still unknown. A previous report showed that the concomitant use of nonsteroidal anti-inflammatory drugs and warfarin, which are frequently used in elderly patients, increases the risk of bleeding by suppressing platelet activity[24]. In fact, many doctors are hesitant to prescribe DOACs to elderly patients because they recognize risk factors for bleeding, such as CKD, hemorrhage history, polypharmacy and frailty in clinical practice[25].

In the present study, although the use of OACs was significantly lower in patients aged ≥ 85 years than in those aged < 85 years, there was no significant difference in the death rate from stoke in either group. In contrast, the use of OAC and anemia were associated with all-cause death in patients aged < 85 years. The reason is that younger patients are more likely to use anticoagulants. As a result, these patients had anemia complicated by bleeding. However, patients aged < 85 years, other deaths among non-cardiovascular deaths were significantly higher than in those aged ≥ 85. Therefore, the use of OACs might be associated with non-stroke death, such as cancer and infection related bleeding, rather than stroke death in patients aged < 85 years.

Impact of BMI and mortality on very elderly patients with AF

Our result showed that high BMI was associated with lower mortality in patients aged ≥ 85 yeas. The association between BMI and all-cause mortality has been widely reported[26−30]. The mean BMI was 21.9 in patients aged ≥ 85 years, and 24% of patients had a high BMI (> 18.5) in our study. Bhaskaran *et al* reported that BMI had J-shaped associations with mortality and most specific causes of death and that higher BMI (18-22) was associated with decreased mortality risk[31].

Study limitations

The results of the present study have several limitations. First, this study may be weakened by the small population size, single-center and hospital-based study. Therefore, the results cannot be generalized. Second, the mortality rate might be underestimated because patients without a clinical follow-up for more than 1 year were excluded from our study. Third, statistical analysis was based only on data at the time of study enrollment. Thus, we did not consider changes in treatments such as medication, and cardiac ablation during the follow-up periods. Forth, for patients aged < 85 years, patients background needs consideration, since the age range was wide from 20 to 84 years old.

Fifth, the classification (paroxysmal, persistent, permanent) of AF was not distinguished in this study. Last, there were no data available in comparison to patients without AF in the present study.

CONCLUSIONS

The main cause of death was non-CV death regardless of age in patients with AF. The clinical factors associated with death differed between patients aged < 85 and ≥ 85 years. In very elderly patients with AF, CKD and BMI were associated with all-cause death.

DISCLOSURES

There is nothing to disclose for all authors.

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