RESEARCH ARTICLE

The influence of atrial fibrillation on the mortality of incident ESRD patients undergoing maintenance hemodialysis

Hui-ling Hsieh1,2☯, Shih-chang Hsu3,4☯, Ho-shun Cheng5, Chun-you Chen6, Wen-cheng Huang3,4,7, Yuh-mou Sue1, Feng-yen Lin8,9, Chun-ming Shih6,9, Jaw-wen Chen10,11,12,13, Shing-jong Lin10,11,12,14,15, Po-hsun Huang10,11,14‡, Chung-te Liu1,7,8‡*

1 Division of Nephrology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, 2 Graduate Institute of Medical Science, National Defense Medical Center, Taipei, Taiwan, 3 Emergency Department, Department of Emergency and Critical Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, 4 Department of Emergency Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, 5 Division of Cardiology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, 6 Department of Radiation Oncology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, 7 Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, 8 Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, 9 Division of Cardiology and Cardiovascular Research Center, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan, 10 Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, 11 Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, 12 Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan, 13 Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan, 14 Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, 15 Board of Directors, Taipei Medical University, Taipei, Taiwan

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* 96320@w.tmu.edu.tw

Abstract

Background

Atrial fibrillation (AF) is highly prevalent, occurring in 1%–2% of the adult population, increasing the risk of stroke, and resulting in considerable healthcare costs. While stroke is a major complication of AF, end-stage renal disease (ESRD) patients also have a high risk of stroke, suggesting that AF is a possible risk factor for mortality of ESRD patients. However, whether the existence of AF at the initiation of hemodialysis predicts higher mortality risk of incident ESRD patients remains to be defined.

Methods

This retrospective cohort study was performed at Wanfang Hospital from January 2004 to May 2018. The end points were mortality of patients or the end of the study. Incident ESRD patients who were on maintenance hemodialysis for more than 3 months were eligible for inclusion. Cox proportional regression and Kaplan–Meier survival curves were used to determine the association between predictors and mortality. The association between AF and echocardiographic parameters, causes of death were also investigated.
Results

Of the 393 incident ESRD patients at initiation of hemodialysis, 57 (14.5%) had AF and the median age was 71 years. Patients with AF were significantly older; showed significantly higher C-reactive protein levels, more heart failure, chronic obstructive pulmonary disease and mortality. Multivariate Cox regression showed that AF had a hazard ratio of 4.1 (95% confidence interval: 2.4–7.0) for mortality. Age-specific analysis showed that AF was significantly associated with mortality in all age groups. Echocardiography measurements including ejection fraction and left ventricular hypertrophy (LVH) were similar in AF and non-AF patients. Cause-specific analysis showed that AF significantly associated with overall cardiovascular death and death due to acute myocardial infarction/coronary artery disease and sepsis.

Conclusions

AF at the initiation of hemodialysis predicts higher mortality risk of incident ESRD patients regardless of age. The systolic function and degree of LVH were similar in AF and non-AF patients. The association between AF and sepsis-related death suggested the role of systemic inflammation on the pathogenesis of AF.

Introduction

Atrial fibrillation (AF) is a common and complicated cardiac arrhythmia characterized by rapid and irregular atrial activation [1–3], which has a prevalence of around 1%–2% in the general population [4–6]. For the most part, AF remains silent and asymptomatic [7, 8]. Occasionally, the ventricular response becomes rapid and causes decompensated heart failure [9]. Regardless of the ventricular rate or the symptoms caused by AF, its disorganized atrial activation results in atrial thrombosis and increased risk of stroke [7–9]. In 2010, the number of annual incident cases was estimated at nearly 5 million [10]. With this high incidence, AF-related burden increased by 18.8% in men and 18.9% in women from 1990 to 2010 [10], leading to significantly increased cost of health care [9, 11–13]. Therefore, the management of AF has been an important issue.

In patients with end-stage renal disease (ESRD), the prevalence of AF is substantially higher than that of the general population, reaching as high as 3%–26.5% [14]. Furthermore, patients on hemodialysis have a higher incidence of AF, suggesting that uremia is associated with the pathogenesis of AF [15–16]. The annual report by the US Renal Data System stated that, in patients with CKD, the overall prevalence of cerebrovascular accident (CVA) was 16.1% and the 2-year survival of stage 4–5 CKD patients with CVA was 64.1%, suggesting a significant role of CVA in the outcome in this population [17]. Moreover, cardiovascular death is one of the leading causes of mortality among patients with ESRD [18–19]. These findings suggest that AF may have a causative role in the mortality of patients with incident ESRD, which remains to be defined to date.

As such, AF is a potential risk factor of mortality in patients with incident ESRD [20–22]. Nevertheless, whether AF predicts the mortality of incident ESRD patients remains to be clarified. To that end, we conducted a retrospective, longitudinal cohort study to investigate the predictive role of AF on the mortality of incident ESRD patients at the initiation of maintenance hemodialysis.
Materials and methods

Study design and subjects
The present study aimed to include incident ESRD patients on maintenance hemodialysis. Incident hemodialysis patients at Wan Fang Hospital, Taipei Medical University between January 2004 and May, 2018 were assessed for enrollment. Patients receiving maintenance hemodialysis, which was defined as those received maintenance hemodialysis for more than 3 months, were eligible for inclusion. Patients less than 20 years of age were excluded from analysis. This study was approved by the ethics committee and Institutional Review Board of Taipei Medical University (N201902034). Informed consent was waived by the ethics committee. The entire study was performed in accordance with the principles of the Declaration of Helsinki, as revised in 2000.

Measurement of covariates and outcomes
Baseline laboratory data and demographic profiles obtained at the initiation of maintenance hemodialysis were used for analysis. The diagnosis and the indication of hemodialysis was according to the discretion of the attending nephrologist. Other comorbidities were defined according to the International Classification of Disease, 10th Revision, clinical modification codes in the discharge diagnosis of the indexed hospitalization or clinic visiting. AF and HF were defined by the diagnosis on medical records made by cardiologists. Notably, patients with both paroxysmal and persistent AF were considered as AF patients in the present study.

The outcome was all-cause mortality. The period of mortality was defined by the time from hemodialysis initiation to mortality. The cause of death was based on the diagnosis of the indexed discharge summary made by the attending physician. Echocardiography was performed at baseline to evaluate ejection fraction (EF) and left ventricular hypertrophy (LVH). Echocardiographic diagnostic criteria of LVH were defined by the following guidelines: (1) normal heart size was defined as left ventricular mass (LVM) ≤ 115 g/m² in men and ≤ 95 g/m² in women and relative wall thickness (RWT) < 0.42; (2) concentric hypertrophy was defined as a LVM > 115 g/m² in men and > 95 g/m² in women and RWT > 0.42; (3) eccentric hypertrophy was defined as LVM > 115 g/m² in men and > 95 g/m² in women and RWT < 0.42; and (4) concentric remodeling was defined as LVM ≤ 115 g/m² in men and ≤ 95 g/m² in women and RWT > 0.42.

Statistical analysis
Continuous variables with normal distribution were reported as mean ± standard deviation, while continuous variables deviated from normal distribution were expressed as medians (25th and 75th percentiles). Categorical variables were reported as frequency and percentage. Comparisons of continuous variables were made by using a two-tailed t-test for unpaired samples or non-parametric methods, as appropriate. Comparisons of categorical variables were made using chi-squared test. The risk factors for mortality were analyzed using Cox proportional regressions and Kaplan-Meier (K-M) survival curve analysis. For multivariate Cox proportional regression, the potential risk factors of mortality were analyzed using univariate Cox proportional regression. Those with p values ≤ 0.2 in the univariate Cox proportional regression were included into the multivariable model. The association between predictors and outcomes in the Cox proportional regression model was expressed as hazard ratio (HR) and 95% confidence interval (CI). Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).
Results

Demographic and laboratory characteristics

Among the 393 incident ESRD patients, the median follow-up period was 46.6 months and the median age of the study subjects was 71 years. Overall, 200 (50.9%) patients were male and 57 (14.5%) patients had AF. By the end of the study, 138 (35.1%) patients had died. Patients with AF were older, of more male gender and more likely to have heart failure (HF), valvular heart disease (VHD), chronic obstructive pulmonary disease (COPD) and thyroid disease. More AF patients were using aspirin, while the use of clopidogrel and warfarin were not significantly different between AF and non-AF patients. Furthermore, patients with AF presented with significantly lower creatinine, higher Na, higher aspartate aminotransferase (AST), higher C-reactive protein (CRP) levels and higher circulating white blood cell (WBC) counts. The AF patients had insignificantly lower serum phosphorus levels and higher alanine aminotransferase (ALT) levels. Numbers of patients with chronic liver disease, CVA, diabetes mellitus, as well as serum levels of albumin, K, Ca, and parathyroid hormone, transferrin saturation, hemoglobin and platelets were similar between the groups. Notably, AF patients had significantly more mortality at the end of study, suggesting that AF is a potential risk factor for mortality of incident ESRD patients (Table 1).

AF and risk of mortality in incident ESRD patients

To investigate the association between AF and mortality in incident ESRD patients, AF and other potential risk factors were assessed by univariate Cox proportional regression and the predictors showing P values < 0.2 were enrolled into the multivariate analysis. Notably, serum creatinine level did not strongly correlate with residual renal function and was not included in the survival analysis. Higher WBC count signifies inflammation resembling CRP levels and was not included to avoid co-linearity of the regression model. Multivariate Cox proportional regression showed that age, CRP, presence of HF, COPD, and AF were significantly associated with mortality (Table 2). To confirm the influence of AF on mortality in incident ESRD patients, Kaplan-Meier (K-M) survival curve was used. This showed that AF patients had significantly higher mortality compared with non-AF patients (Fig 1). These findings showed that AF independently predicted mortality in incident ESRD patients.

Age and the impact of AF on the risk of mortality

To evaluate possible confounding effects of age on the association between AF and mortality, the patients were stratified by age into tertiles for analysis. The tertiles were ≤ 61 years, > 61 to ≤ 77 years, and > 77 years. The Cochrane-Armitage test showed that the oldest tertile had significantly more AF patients (Fig 2). However, Cox proportional regression analysis showed that AF was significantly associated with mortality in all age tertiles. This finding indicated that AF predicted the mortality in incident ESRD patients regardless of age (Fig 3).

Echocardiographic measurements in AF and non-AF incident ESRD patients

To investigate the underlying cause of the association between AF and mortality, pre-dialytic echocardiographic measurements were compared between AF and non-AF patients. Notably, in this part of analysis, only 205 patients with available echocardiographic reports were included. In the AF patients, 26 (53.06%) patients presented atrial fibrillation rhythm at the time of echocardiography examination. Overall, the echocardiography showed increased LVM and RWT, preserved EF, normal systolic and diastolic left ventricular diameter. The
echocardiographic measurements were not significantly different between AF and non-AF patients. These findings suggested that both groups exhibited LVH with preserved systolic function. Nonetheless, since atrial emptying/contraction ratio was not able to be measured in AF patient, diastolic dysfunction was not able to be evaluated in this group of patients. Regarding the type of LVH, AF patients showed more concentric LVH and less eccentric LVH compared to non-AF patients. Nonetheless, the distribution of the type of LVH were not significantly different between the two groups (Table 3).

Table 1. Baseline demographic and laboratory characteristics of the study population.

| Character     | Total (n = 393) | Non-AF (n = 336) | AF (n = 57) | P-value |
|---------------|----------------|------------------|------------|---------|
| Male (%)      | 200 (50.9%)    | 169 (50.3%)      | 31 (54.4%) | 0.55    |
| Age (years)   | 71 (57, 79)    | 69 (57, 78)      | 77 (71, 84)| <0.01*  |
| HF (%)        | 216 (55%)      | 175 (52.1%)      | 41 (71.9%) | <0.01   |
| VHD (%)       | 29 (7.38%)     | 18 (5.36%)       | 11 (19.30%)| <0.01   |
| CLD (%)       | 73 (18.6%)     | 63 (18.8%)       | 10 (17.5%) | 0.83    |
| COPD (%)      | 26 (6.6%)      | 15 (4.5%)        | 11 (19.3%) | <0.01   |
| CVA (%)       | 91 (23.2%)     | 79 (23.5%)       | 12 (21.1%) | 0.68    |
| DM (%)        | 259 (66%)      | 217 (64.6%)      | 42 (73.7%) | 0.18    |
| Thyroid disease (%) | 14 (3.56%) | 9 (2.68%) | 5 (8.77%) | 0.04 |
| Survival duration (months) | 46.6 (25.1, 74.4) | 52.2 (28.7, 80.2) | 18.7 (7.5, 35.3) | <.001 |
| Mortality (%) | 138 (35.1%)    | 110 (32.7%)      | 28 (49.1%) | 0.02    |
| Aspirin (%)   | 54 (13.74%)    | 39 (11.61%)      | 15 (26.32%)| <0.01   |
| Clopidogrel (%) | 20 (5.09%) | 16 (4.76%) | 4 (7.02%) | 0.51    |
| Warfarin (%)  | 2 (0.51%)      | 2 (0.6%)         | 0          | 0.56    |
| BUN (mg/dL)   | 110.6 ± 50.2   | 111.7 ± 49.7     | 104.3 ± 53.2| 0.31   |
| Cr (mg/dL)    | 9.1 (6.7, 11.7)| 7.3 (4.5, 8.7)  | <0.01*     |
| eGFR (mL/min/1.73 m²) | 4.6 (3.5, 6.8) | 4.4 (3.4, 6) | 6.5 (4.8, 8.9) | <0.01* |
| Albumin (g/dL)| 3.3 ± 0.6      | 3.3 ± 0.6        | 3.2 ± 0.6  | 0.81    |
| Na (mmol/L)   | 135.1±6.3      | 137.2±5.8        | 132±8.0   | 0.04    |
| K (mmol/L)    | 4.4 (3.8, 5.0) | 4.4 (3.8, 4.9)  | 4.5 (4.1, 5.1)| 0.25* |
| Ca (mg/dL)    | 7.9±1.6        | 7.9±1.2          | 7.9±1.0   | 0.92    |
| P (mg/dL)     | 5.9 (4.6, 7.6) | 6.4 (4.6, 7.8)  | 5.4 (4.2, 6.5) | 0.08* |
| PTH (pg/mL)   | 219 (94.5, 365)| 207 (94.5, 428) | 0.83*     |
| AST (U/L)     | 23 (17, 34)    | 22 (17, 32)      | 26 (20, 44) | <0.01* |
| ALT (U/L)     | 16 (12, 23)    | 16 (11, 23)      | 19 (15, 29) | 0.09    |
| Ferritin (ng/mL) | 296.6 (156.3, 551.9) | 286.8 (144.5, 547.3) | 375 (174.2, 635.7) | 0.34* |
| TSAT (%)      | 0.20 (0.15, 0.28) | 0.20 (0.15, 0.28) | 0.20 (0.15, 0.26) | 0.70* |
| CRP (mg/dL)   | 2.2 (0.5, 8.0) | 1.7 (0.5, 6.5)  | 6.1 (2.6, 13.2) | <0.01* |
| Hemoglobin (g/dL) | 8.5±1.7  | 8.5±1.7          | 8.8±1.8   | 0.15    |
| MCV (μm³)     | 90.5 (86.8, 93.9) | 90.5 (86.8, 93.8) | 90.3 (86.5, 95.5) | 0.92* |
| WBC (10³/μL)  | 8.2 (6.1, 10.5)| 8.0 (5.9, 10.4) | 9.0 (7.4, 11.0) | 0.02* |
| Neutrophil (%) | 77±12.2 | 77±12.2 | 76.6±13.5 | 0.78 |
| Platelet (10⁹/μL) | 172 (126, 231) | 173 (128.5, 233) | 163 (115, 223) | 0.56* |

AF, atrial fibrillation; HF, heart failure; VHD, Valvular heart disease; CLD, Chronic Liver Disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; PTH, Parathyroid hormone; AST, aspartate transaminase; ALT, alanine transaminase; TSAT, transferrin saturation; CRP, C-reactive protein; MCV, mean corpuscular volume; WBC, white blood cell. *Compared using the Exact Wilcoxon two-sample test

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Table 2. Risk factors for mortality in incident hemodialysis patients.a.

| Variable                   | Univariate |          |          |          | Multivariate |          |          |          |
|---------------------------|------------|----------|----------|----------|--------------|----------|----------|----------|
|                           | HR         | 95% CI   | P value  | HR       | 95% CI       | P-value  | HR       | 95% CI   |
| Age (per 10-year increment)| 1.8        | 1.6–2.2  | <0.01    | 1.6      | 1.4–1.9      | <0.01    |          |          |
| Na (per 10 mmol/L increment)| 1.1       | 0.8–1.5  | 0.49     |          |              |          |          |          |
| P (per 5 mg/dL increment) | 0.7        | 0.5–1.1  | 0.14     | 1.2      | 0.7–2.0      | 0.47     |          |          |
| AST (per 10 U/L increment)| 1.0        | 0.9–1.0  | 0.56     |          |              |          |          |          |
| Hemoglobin                | 1.0        | 0.9–1.2  | 0.38     |          |              |          |          |          |
| CRP (per 10 mg/dL increment)| 1.3       | 1.1–1.7  | 0.03     | 1.4      | 1.1–1.9      | 0.01     |          |          |
| Aspirin                   | 1.2        | 0.9–2.1  | 0.52     |          |              |          |          |          |
| HF                        | 1.8        | 1.3–2.7  | <0.01    | 1.7      | 1.1–2.7      | 0.01     |          |          |
| COPD                      | 3.7        | 2.2–6.5  | <0.01    | 2.3      | 1.2–4.5      | <0.01    |          |          |
| DM                        | 1.1        | 0.8–1.6  | 0.64     |          |              |          |          |          |
| VHD                       | 1.5        | 0.7–3.0  | 0.22     |          |              |          |          |          |
| Thyroid disease           | 3.5        | 1.6–7.4  | <0.01    | 2.2      | 0.8–5.7      | 0.11     |          |          |
| AF at baseline            | 4.6        | 2.8–7.1  | <0.01    | 4.1      | 2.4–7.0      | <0.01    |          |          |

HR, hazard ratio; P, phosphorus; PTH, Parathyroid hormone; AST, aspartate transaminase; ALT, alanine transaminase; HF, heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; VHD, Valvular heart disease AF, atrial fibrillation.

*a by multivariate Cox proportional regression

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Fig 1. Distribution of AF patients stratified by age tertiles. Statistics was performed using the Cochrane-Armitage test. The number of AF patients were 9 (6.82%), 20 (14.18%), and 28 (23.33%) in the age tertiles of age \( \leq 61 \), 61 < age \( \leq 77 \), and 77 < age, respectively. AF, atrial fibrillation.

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AF and cause of death in patients on maintenance hemodialysis

Of the 138 patients who had died by the end of study, the leading cause of death was sepsis (47.8%), followed by sudden cardiac arrest (28.2%) and acute myocardial infarction (AMI)/coronary artery disease (CAD, 9.4%). Among the causes of sepsis-related death, pneumonia was the most frequent type of infection, which was followed by soft-tissue infection and catheter infection. Notably, the number of death events due to CVA were similar in both group of patients (Table 4). The association between AF and mortality due to specific causes were examined using Cox proportional regression. In the multivariate Cox proportional regression (adjusted for age, presence of HF and COPD, serum albumin, Na and phosphorus), AF was significantly associated with overall cardiovascular death, death due to AMI/ CAD and sepsis (Fig 4).

Fig 2. HR of AF for mortality of incident hemodialysis patients stratified by age. Multivariate model was adjusted for presence of heart failure, chronic obstructive pulmonary disease, serum levels of albumin and phosphorus. HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation.

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Discussion

The main finding of the present study is that AF predicts the mortality in incident ESRD patients on maintenance hemodialysis. While AF may deteriorate heart failure, echocardiographic measurements, including LVM, RWT, and EF were similar between AF and non-AF patients in our study. Finally, in addition to increased risk cardiovascular death, AF was also associated with increased risk of sepsis-related death, suggesting the role of inflammation on the pathogenesis of AF.

One study based on US Renal Data System from 1992 to 2006 had demonstrated that the prevalence of AF among hemodialysis patients increased from 3.5% to 10.7% [23]. Another Taiwanese retrospective cohort study of 15,947 patients in 2016 showed that the incidence of AF was higher among hemodialysis patients [24]. In another study of 1,130 ESRD patients conducted in 2017, 26.9% of the cohort were noted to have AF during the study period [25]. In the present cohort, 14.5% of the incident ESRD patients had AF at the initiation of hemodialysis, confirming the high prevalence and incidence of AF in dialysis population. These findings suggest that uremia may have a role in the pathogenesis AF, but the mechanism remains to be investigated.
### Table 3. Pre-dialytic echocardiographic profiles of incident hemodialysis patients.

| Measurement (ref.) | Total (n = 205) | Non-AF (n = 156) | AF (n = 49) | P-value |
|-------------------|-----------------|-----------------|------------|---------|
| **Rhythm**        |                 |                 |            |         |
| Sinus rhythm (%)  | 179 (87.32%)    | 156 (100%)      | 23 (46.94%)| < .001  |
| AF rhythm (%)     | 26 (12.68%)     | 0               | 26 (53.06%)| < .001  |
| **IVS (6–12 mm)**| 13.1±2.3        | 13±2.3          | 13.3±2.1  | 0.43    |
| **LVEDD (36–52 mm)**| 48.8±7.9       | 48.9±8.0        | 48.5±7.9 | 0.72    |
| **LVPW (6–12 mm)**| 12.9±2.3        | 12.8±2.3        | 13.2±2.2 | 0.25    |
| **LV mass (67–162 g)**| 251.9 (195.3, 317) | 252.7 (188.7, 313.5) | 246.1 (209.3, 326) | 0.7* |
| **EF (≥55%)**    | 67 (58, 73)     | 67 (58, 73)     | 66 (56, 71) | 0.59* |
| **LVESD (20–36 mm)**| 31.2±8.6        | 31.2±8.7        | 31.4±8.2 | 0.84    |
| **RWT (0.22–0.42 cm)**| 0.52 (0.46, 0.61)| 0.53 (0.46, 0.61) | 0.52 (0.47, 0.6) | 0.59* |
| **LVMI (43–95 g/m²)**| 169.7±57        | 169.1±58.2      | 171.5±53.6| 0.80    |
| **BSA (n/a m²)** | 1.5±0.2         | 1.5±0.2         | 1.5±0.2  | 0.76    |
| **LVH by echocardiography** |         |                 |            |         |
| Normal            | 5 (2.4%)        | 4 (2.6%)        | 1 (2%)    | 1.00    |
| Concentric hypertrophy | 160 (77.7%) | 120 (76.4%)     | 40 (81.6%)| 0.43    |
| Eccentric hypertrophy | 26 (12.6%)  | 22 (14%)        | 4 (8.2%)  | 0.33    |
| Concentric remodeling | 15 (7.3%)    | 11 (7%)         | 4 (8.2%)  | 0.75    |

Ref, reference range; AF, atrial fibrillation; IVS, inter-ventricular septum; LVEDD, left ventricular end diastolic diameter; LVPW, left ventricular Posterior wall; LV mass, left ventricular mass; EF, ejection fraction; LVESD, left ventricular end systolic diameter; RWT, relative wall thickness; LVMI, left ventricular mass index; BSA, body surface area; LVH, left ventricular hypertrophy.

*Compared using the Exact Wilcoxon two-sample test.

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### Table 4. Causes of death in patients on maintenance hemodialysis.

| Cause of death       | Total (n = 138) | Non-AF (n = 110) | AF (n = 28) | P-value |
|----------------------|-----------------|-----------------|------------|---------|
| AMI/CAD              | 13 (9.4%)       | 9 (8.2%)        | 4 (14.3%)  |         |
| Sudden cardiac arrest| 39 (28.2%)      | 33 (30%)        | 6 (21.4%)  |         |
| Sepsis               | 66 (47.8%)      | 51 (46.4%)      | 15 (53.6%) |         |
| Pneumonia            | 41 (29.7%)      | 30 (27.3%)      | 11 (39.3%) |         |
| Catheter infection   | 6 (4.3%)        | 5 (4.5%)        | 1 (3.6%)   |         |
| Soft-tissue infection| 9 (6.5%)        | 7 (6.4%)        | 2 (7.1%)   |         |
| Intra-abdominal infection | 4 (2.9%) | 4 (3.6%)        | 0          |         |
| Renal necrosis       | 1 (0.7%)        | 1 (0.9%)        | 0          |         |
| Urinary tract infection| 2 (1.4%)       | 2 (1.8%)        | 0          |         |
| Infective endocarditis | 2 (1.4%)      | 2 (1.8%)        | 0          |         |
| Other causes*        | 20 (14.4%)      | 17 (15.5%)      | 3 (10.7%)  |         |
| Trauma               | 1 (0.7%)        | 1 (0.9%)        | 0          |         |
| Hypovolemic shock    | 4 (2.9%)        | 3 (2.7%)        | 1 (3.6%)   |         |
| Heart failure        | 2 (1.4%)        | 2 (1.8%)        | 0          |         |
| Cerebrovascular events| 5 (3.6%)       | 4 (3.6%)        | 1 (3.6%)   |         |
| Malignancy           | 3 (2.2%)        | 3 (2.7%)        | 0          |         |
| Hyperkalemia         | 5 (3.6%)        | 3 (2.7%)        | 2 (7.1%)   |         |

AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease.

*trauma, hypovolemic shock, congestive heart failure, cerebrovascular events, malignancy and hyperkalemia.

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While a previous 9-year cohort study in Japan showed that DM was highly associated with all-cause mortality in patients undergoing hemodialysis (adjusted HR: 2.39; p < 0.001) [26], the present study showed that DM was not significantly associated with the risk of mortality. This discrepancy may result from the difference in race, glucose control status or relative short study period of the present study.

In the non-dialysis population, the incidence of stroke in AF patients ranges 5.9–9.0 per 100 patient-years [27]. In contrast, a large cohort study based on data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that in hemodialysis patients with AF, the incidence of stroke was 3.4 per 100 patient-years, which was plausibly lower than that of the non-dialysis population [28]. In the present study that exclusively enrolled hemodialysis patients, CVA events were also rare. In support of our finding, a recent systemic review showed that, for AF patients who were on hemodialysis, warfarin did not reduce the risk of stroke, but rather increased the risk of bleeding [29]. Indeed, the data from DOPPS also showed that in AF patients who were on hemodialysis and were > 75 years of age, the use of
warfarin was associated with increased risk of stroke [28]. Altogether, these findings suggest that the use of anti-coagulation therapy should be reconsidered in ESRD patients with AF.

In our study, echocardiography measurements, including systolic function and degree of LVH were similar between AF and non-AF patients. While more AF patients were diagnosed as having HF, the EF measured by echocardiography was not significantly different from non-AF patients. One explanation may be that the AF patients experienced more diastolic heart failure with preserved EF. Nevertheless, due to the reason that atrial emptying/contraction ratio was not measurable in AF patients, it is difficult to evaluate the degree of diastolic dysfunction this group of patients.

In non-dialysis patients who experienced AMI, AF is a common complication associated with adverse outcomes [30, 31]. Also, non-dialysis patients with pre-existing AF have increased risk of AMI [32]. In the present study, significantly higher risk of CV death was noted in incident hemodialysis patients with AF, suggesting a similar risk imposed by AF in dialysis population.

AF resulted from electrophysiological abnormalities of atrial tissue, which was stimulated by several pathogenic factors such as systemic inflammation [33,34]. In accordance with this point of view, previous studies also showed that in patients with severe sepsis, new-onset or precipitated AF are frequently seen and are associated with adverse outcomes [35, 36]. On the other hand, it had also been reported that AF was associated with increased mortality in patients with pneumonia [37, 38]. The present study showed that in incident ESRD patients, AF significantly associated with sepsis-related death and that CRP was associated with risk of mortality. Both findings supported the role of systemic inflammation on the pathogenesis of AF.

The limitations of the present study included retrospective design with various uncontrolled factors, relatively small sample size, unavailable information on volume status and heart rate on the time of echocardiography. On the other hand, the strengths of our study include complete laboratory data, detailed echocardiography measurements and accurately confirmed causes of death in analysis.

In conclusion, AF is an independent predictor for mortality in incident ESRD patients irrespective of age. Cause-specific analysis showed that AF was associated with cardiovascular and sepsis-related mortality in patients on maintenance hemodialysis. While AF may deteriorate HF, systolic function and degree of LVH were not significantly different in AF and non-AF patients. Finally, the association between AF and sepsis-related mortality suggest the role of systemic inflammation on the pathogenesis of AF.

Supporting information

S1 Dataset.
(XLSX)

Author Contributions

Conceptualization: Hui-ling Hsieh, Shih-chang Hsu, Ho-shun Cheng, Chun-you Chen, Jaw-wen Chen, Po-hsun Huang, Chung-te Liu.

Data curation: Hui-ling Hsieh, Shih-chang Hsu, Chun-you Chen, Chung-te Liu.

Formal analysis: Shih-chang Hsu, Chung-te Liu.

Methodology: Chung-te Liu.

Project administration: Chung-te Liu.
Supervision: Wen-cheng Huang, Yuh-mou Sue, Feng-yen Lin, Chun-ming Shih, Jaw-wen Chen, Shing-jong Lin, Po-hsun Huang, Chung-te Liu.

Writing – original draft: Chung-te Liu.

Writing – review & editing: Chung-te Liu.

References

1. Shah SR, Luu SW, Calestino M, David J, Christopher B. Management of atrial fibrillation-flutter: up-to-date guideline paper on the current evidence. J Community Hosp Intern Med Perspect. 2018; 8:269–75. https://doi.org/10.1080/20009666.2018.1514932 PMID: 30357020

2. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: The Framingham heart study. Circulation. 2004; 110:1042–46. https://doi.org/10.1161/01.CIR.0000140263.20897.42 PMID: 15313941

3. Heeringa J, Van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006; 27:949–53. https://doi.org/10.1093/eurheartj/ehi825 PMID: 16527828

4. Chiang CE, Wu TJ, Ueng KC, Chao TF, Chang KC, Wang CC, et al. 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. J Formos Med Assoc. 2016; 115:893–952. https://doi.org/10.1016/j.jfma.2016.10.005 PMID: 27890386

5. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. JAMA. 2001; 285:2370–75. https://doi.org/10.1001/jama.285.18.2370 PMID: 11343485

6. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest. 2012; 142;E49–98. https://doi.org/10.1378/chest.11-2886 PMID: 22459778

7. Esato M, Chun YH, An Y, Ogawa H, Wada H, Hasegawa K, et al. Clinical impact of asymptomatic presentation status in patients with paroxysmal and sustained atrial fibrillation: The Fushimi AF registry. Chest. 2017; 152:1266–75. https://doi.org/10.1016/j.chest.2017.08.004 PMID: 28823813

8. Glotzer TV, Ziegler PD. Silent atrial fibrillation as a stroke risk factor and anticoagulation indication. Can J Cardiol. 2013; 29:S14–S23. https://doi.org/10.1016/j.cjca.2013.03.023 PMID: 23790594

9. Kirchhof P, Benussi S, Kotecha D, Ahrsson A, Tarata D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38):2893–2962. https://doi.org/10.1093/eurheartj/ehw210 PMID: 27567408

10. Chugh SS, Hwangveld R, Narayan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014; 129;837–47. https://doi.org/10.1161/CIRCULATIONAHA.113.005119 PMID: 24345399

11. Wodchis WP, Bhatia RS, Leblanc K, Meshkat N, Morra D. A review of the cost of atrial fibrillation. Value Health. 2012; 15:240–48. https://doi.org/10.1016/j.jval.2011.09.009 PMID: 22433754

12. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002; 113:359–64. https://doi.org/10.1016/S0002-9343(02)01236-6 PMID: 12401529

13. Vermond RA, Geelhoed B, Verweij T, Tielenman RG, Van der Harst P, Hillege HL, et al. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. J Am Coll Cardiol. 2015; 66:1000–7. https://doi.org/10.1016/j.jacc.2015.06.1314 PMID: 26314526

14. Königsbürgge O, Lorenz M, Aunger M, et al. Venous thromboembolism and vascular access thrombosis in patients with end-stage renal disease on maintenance hemodialysis: cross-sectional results of the Vienna investigation of atrial fibrillation and thromboembolism in patients on hemodialysis (VIVALDI). Thromb Res. 2017; 158;59–64. https://doi.org/10.1016/j.thromres.2017.08.011 PMID: 28838224

15. Liao JNC, Chao TF, Liu CJ, Wang KL, Chen SJ, Lin YJ, et al. Incidence and risk factors for new-onset atrial fibrillation among patients with end-stage renal disease undergoing renal replacement therapy. Kidney Int. 2015; 87:1209–15. https://doi.org/10.1038/ki.2014.393 PMID: 25587708

16. Goldstein BA, Arce CM, Hlatky MA, Turakhia M, Setoguchi S, Winkelmayer WC. Trends in the incidence of atrial fibrillation in older patients initiating dialysis in the United States. Circulation. 2012; 126;2283–2301. https://doi.org/10.1161/CIRCULATIONAHA.112.099606 PMID: 23032326
17. Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2017; 69: A7–A8. https://doi.org/10.1053/ajkd.2016.12.004 PMID: 28236831
18. Sud M, Tangri N, Pintilie M, Levey AS, Naimark D. Risk of end-stage renal disease and death after cardiovascular events in chronic kidney disease. Circulation. 2014; 130:458–65. https://doi.org/10.1161/CIRCULATIONAHA.113.010706 PMID: 24899688
19. Genovesi S, Porcu L, Luise MC, Riva H, Nava E, Contaldo G, et al. Sudden death in end stage renal disease: comparing hemodialysis versus peritoneal dialysis. Blood Purif. 2017; 44:77–88. https://doi.org/10.1159/000464347 PMID: 28365692
20. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016; 354: i4482. https://doi.org/10.1136/bmj.i4482 PMID: 27599725
21. Bansal N, Xi E, Tao K, et al.; CRIC Study. Atrial fibrillation and risk of ESRD in adults with CKD. Clin J Am Soc Nephrol. 2016; 11:1189–96. https://doi.org/10.2215/CJN.0121106.2015 PMID: 28684256
22. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. Eur Heart J. 2009; 30:1038–45. https://doi.org/10.1093/eurheartj/ehn579 PMID: 19109347
23. Violi F, Soliman EZ, Pignatelli P, Pastori D. Atrial fibrillation and myocardial infarction: A systematic review and appraisal of pathophysiologic mechanisms. J Am Heart Assoc. 2016; 5:pii:e003347. https://doi.org/10.1161/JAHA.116.003347 PMID: 27208001
24. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 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. Circulation. 2014; 30:199–267.
25. Yamashita Y, Takagi D, Hamatani Y, Iguchi M, Masunaga N, Esato M, et al. Clinical characteristics and outcomes of dialysis patients with atrial fibrillation: the Fushimi AF Registry. Heart Vessels. 2016; 31:2025–2034. https://doi.org/10.1007/s00380-016-0818-x PMID: 26973346
26. Lau YC, Lip GYH. Atrial fibrillation during sepsis: a determinant of long-term outcomes? Chest. 2014; 146:1138–40. https://doi.org/10.1378/chest.14-0986 PMID: 25367462
36. Walkey AJ, Quinn EK, Winter MR, McManus DD, Benjamin EJ. Practice patterns and outcomes associated with use of anticoagulation among patients with atrial fibrillation during sepsis. JAMA Cardiol. 2016; 1:682–90. https://doi.org/10.1001/jamacardio.2016.2181 PMID: 27487456

37. Gamst J, Christiansen CF, Rasmussen BS, Rasmussen LH, Thomsen RW. Pre-existing atrial fibrillation and risk of arterial thromboembolism and death following pneumonia: a population-based cohort study. BMJ Open. 2014; 4:e006486. https://doi.org/10.1136/bmjopen-2014-006486 PMID: 25398678

38. Zhu J, Zhang X, Shi G, Yi K, Tan X. Atrial fibrillation is an independent risk factor for hospital-acquired pneumonia. PLOS ONE. 2015; 10: e0131782. https://doi.org/10.1371/journal.pone.0131782 PMID: 26204447