Predictor of enhanced mortality in patients with multimorbidity and atrial fibrillation in an acute hospital setting

I. Iñiguez Vázquez[1], M. Matesanz Fernández[1], E.M. Romay Lema[1], M.T. Seoane Pillado[2], R. Monte Secades[1], S. Pértega Díaz[2] and E. Casariego Vales[1]

From the [1] Department of Internal Medicine, Lucus Augusti University Hospital, 27003 Lugo, Spain and [2] Health Sciences Department, La Coruna University, 15006 La Coruña, Spain

Address correspondence to I. Iñiguez Vázquez, Department of Internal Medicine, Lucus Augusti University Hospital, Calle Doctor Ulises Romero, 1, 27003 Lugo, Spain. email: iria_inhiguez@hotmail.com

Abstract

Background. Patients with atrial fibrillation (AF) admitted to hospital commonly have comorbidities. Few studies have attempted to determine factors prognostic of mortality in hospitalized AF patients with multimorbidity.

Aim. To identify factors associated with mortality in hospitalized AF patients.

Design. Retrospective cohort study.

Methods. Patients with multimorbidity (≥2 chronic diseases), with or without AF, discharged from Lugo hospital (Spain) between 1 January 2000 and 31 December 2015. Data were extracted from hospital medical records.

Results. Of 74 220 patients (170 978 hospitalizations), 52 939 had multimorbidity (14 181 had AF; 38 758 no AF) and were included in our study. Patients with AF were older (mean ± standard deviation 78.6 ± 10.0 vs. 71.9 ± 14.2 years) and had a higher mortality rate (27.1 vs. 20.5%) than those without AF. Gender (female), age, stroke and congestive heart failure (CHF), but not AF, were independently associated with mortality. AF significantly increased the mortality risk in women [relative risk (RR) 1.091; 95% confidence interval (CI) 1.021–1.165; $P = 0.010$] and in those aged >80 years (RR 1.153; 95% CI, 1.1–1.2; $P < 0.001$). CHF independently increased the risk of mortality across all age groups (RR 1.496; 95% CI 1.422–1.574; $P < 0.001$).

Conclusions. Hospitalized patients with AF have a higher mortality rate than those without AF. The prognostic significance of AF changes with age and gender while CHF is associated with the greatest risk of death.

Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia encountered in routine clinical practice. It is associated with increased morbidity and mortality, both all-cause and cardiovascular.[1–10] In several studies conducted at a community level, the increase in mortality rate associated with AF varied depending on several factors.[11,12] Specifically, since the incidence of AF increases with age, mortality rates are expected to differ between age groups. Gender may also be a factor in mortality in patients with AF: the presence of AF has been associated with a 2-fold increase in mortality in women and only a 1.5-fold increase in men.[1,8,13,14] However, prognostic factors for mortality in patients with AF in the hospital setting (which is where most of the deaths occur) are unknown.

AF is a very common condition in the hospital setting,[15] where patients with multimorbidity may be admitted to various wards for different reasons related to the arrhythmia itself or to other causes. Beside this, it is rare for hospital in-patients to exclusively have AF. In fact, AF patients have been described as having greater multimorbidity than those of the same age without AF.[15–19] A limitation of these studies is that they were focussed on specific patient subgroups and not on the overall hospitalized AF population.[13,15] Indeed, there may be multiple factors associated with the increased risk of mortality in hospitalized AF patients, yet despite their potential importance, they have hardly been analysed.

For this reason, we conducted this study to assess the determinants of mortality in patients with multimorbidity, including those with AF, who were hospitalized in a general hospital in Spain.

Materials and methods

We conducted a retrospective cohort study at the Lugo Hospital, which has 879 beds and provides health care to 240 000 inhabitants. The general design of the study has been published previously.[20] Routine data for all patients admitted to the medical ward of Lugo Hospital

between 1 January 2000 and 31 December 2015 were used to identify patients with multimorbidity and AF, irrespective of the reason for the patient's hospital admission.

The data were derived from the basic minimum dataset collected for each patient who attends a hospital in Spain. This basic minimum dataset includes demographics, main diagnosis of admission and secondary diagnoses, comorbidities, diagnostic and therapeutic techniques, date of admission and discharge, outcome (discharge, transfer or death) and discharge pathway (home, another care centre etc.). All in-hospital deaths were recorded. In order to increase the accuracy of the data source, for each of the clinical records, the research team reviewed individually all of the patient's diagnoses, confirming and refining the available database.

Multimorbidity was defined as the presence of two or more chronic diseases in the same patient at the time of admission. For the purposes of this study, the chronic diseases were those included in the German Multicare Study, adapted to the hospital setting for use in this study (Table 1).[19]

Once patient eligibility had been confirmed, patient data were extracted into an anonymized database for analysis, using a numerical code as the patient identifier. The records were divided into two groups according to the presence or the absence of AF in the hospitalization report in the study period, and the incidence of in-hospital mortality compared in the two groups. As previously described,[22] the source of information is the minimum basic dataset from the hospital where the study was conducted. Since an individual patient may have been admitted more than once during the study period, two databases were built for the current analysis: the first array contained data to be analysed by hospitalization episode, and the second contained data to be analysed by patient.

This study was approved by the Galician Clinical Research Ethics Committee (2014/409). According to study design, informed consent was not required. The codes used to anonymize patient data were automatically generated using computer software and stored securely with the hospital's Clinical Documentation Service.

Statistical analysis

Baseline characteristics and hospital admissions data were summarized using descriptive statistics. The χ^2 test was used to compare qualitative variables and Student's *t*-test was used to compare quantitative variables in patients with versus without AF. The Kaplan–Meier method was used for the univariate survival analysis (probability of survival) and the log-rank test was used to compare survival curves. To estimate independent factors prognostic of mortality, a Cox proportional hazards model was used. In constructing the model, the initial selection was made for both clinical and statistical reasons, using variables that were significant at a *P*-value of <0.05 in the univariate analysis as well as variables that were not significant but clinically relevant and could alter the final result. The variables included in the maximum model were as follows: sex, age (stratified as <50, 51–60, 61–70, 71–80 and >80 years), sex (with women as the reference category), presence of stroke, presence of AF and presence of cardiac insufficiency. The categories were codified as dummy variables, using the first category as a reference. Relevant interaction factors were analysed, but not included in the final model since they did not significantly modify the likelihood of the response variable. We followed a backward procedure, taking into account the hierarchical principle and using the log-likelihood ratio test to assess goodness-of-fit and to compare models. The level of statistical significance was $P < 0.05$. The statistical software used was SPSS 19[23] and R 3.3.2 software (packages: ca, ade4, ggplot2).[24]

Results

Overall, 74 220 patients had 170 978 admissions to the Medical ward of Hospital Universitario Lucus Augusti between 1 January 2000 and 31 December 2015. Of these, 52 939 patients (115 498 admissions) had multimorbidity (71.3%), of whom 14 181 (26.8%) had AF. A total of 21

281 (28.7%) patients were excluded because they did not have multimorbidity, of whom 357 (1.7%) had AF.

Table 2 shows the characteristics of patients with multimorbidity with or without AF included in our analyses. Patients with AF (n = 14 181) had a higher in-hospital mortality rate (27.1%) than those without AF (n = 3858; 20.5%; $P < 0.001$; Table 2).

Figure 1 shows the probability of survival over time in hospitalized patients with AF and multimorbidity, regardless of the admission in which AF was diagnosed (n = 14 181), versus patients without AF (n = 38 758). There was no significant between-group difference in survival curves (P = 0.21). Nevertheless, we observed that survival was slightly higher in patients with AF versus those without; after the fifth year; however, the difference diminished and survival was higher in those patients without AF.

Table 3 shows the final model for the analysis of the independent factors affecting mortality in the total cohort of patients with multimorbidity. AF by itself was not a factor that independently influenced mortality in these patients. However, the presence of CHF was a significant risk factor for death [relative risk (RR) 1.027; 95% confidence interval (CI), 0.980–1.077; P = 0.267]. Furthermore, the risk of mortality was 1.2 times higher in men than in women (RR 1.203; 95% CI 1.159–1.248; P = 0.0001).

When the Cox proportional hazards analysis was repeated for each gender separately (Tables 4 and 5), factors influencing mortality differed between the sexes. In women, all the included variables were independent predictors of mortality (Table 4), whereas in men, neither AF nor stroke had independent prognostic value (Table 5). In contrast, increased age (RR 1.044; 95% CI 1.041–1.046; $P < 0.001$) and the presence of CHF (RR 1.408; 95% CI 1.308–1.515; $P < 0.001$) were statistically significant prognostic factors in both sexes.

Table 6 shows the results of the Cox model when patients were stratified by age. The risk of mortality associated with each of the variables included in the final model changed according

to the patient's age. None of the variables included in the model significantly modified the prognosis in younger patients (Table 6), but from the age of 51 years, the presence of AF had significant prognostic value. In individuals aged 51–70 years, AF presence was protective of survival. Between the ages of 71 and 80 years, its prognostic value became nonsignificant, but from age 81 onwards, AF was prognostic of mortality (RR 1.153; 95% CI 1.1–1.2; $P < 0.001$). The presence or absence of stroke followed a similar pattern with regard to age. In younger age groups, stroke had no independent prognostic value, until the age of 70 years, when it became an independent predictor or mortality. Finally, CHF was the most significant factor in the prognosis of these patients, with a significant effect on the risk of mortality from the age of 51 onwards **(**RR 1.589; 95% CI 1.5–1.7; $P < 0.001$). In all age groups, CHF was associated with the largest independent increased risk of mortality.

Discussion

This study shows that the profile of AF patients with multimorbidity requiring hospital admission is that of a sick elderly person, with more hospital admissions, longer average hospital stay and a higher risk of mortality than patients who do not have AF. The role played by AF as prognostic of mortality in patients with multimorbidity varies depending on sex and age.

This work shows that AF is protective regarding mortality until the age of 70 years. That is, in the age group of 50–70 years having AF not only does not increase the risk of death but it may even reduce it. There may be two possible reasons for this apparent contradiction. First, in younger age groups, the disease burden or the chance of developing serious complications from AF, such as CHF, is still very low.[14,21] Second, we believe that younger patients with AF are more likely to receive more monitoring and medical care than healthy people, and they are, therefore, more likely to have better disease control. Thus, it can be understood quite easily that

this group of patients have lower mortality rates. From the age of 70 years, AF is no longer protective, and it is only from the age of 80 years that AF becomes independently associated with an increased risk of mortality. That is, AF becomes a prognostic factor by itself only when the patient's health is significantly impaired and multiple comorbidities are present. AF is a marker of cardiovascular disease progression, to which many medical problems are related.

Regarding other prognostic factors, we observed that women and CHF from the age of 60 years, or stroke from the age of 70 years, significantly increased the probability of death. Note that CHF was independently associated with the greatest risk of death when all age groups were included.

We believe that Table 6 provides clinicians with a valuable clinical tool, allowing them to establish the prognosis of a patient with AF by their age over the range of 50–80 years old. Published studies on the role of AF in the risk of death by age group are contradictory. In general, these studies show that AF mortality risk is greater in elderly patients.[20,25] Other studies show no differences in the mortality risk between different age groups[26] or sexes,[27] or even show an increased risk of mortality in young women with AF.[1,8,11,28,29] These differences with our work may be explained by differences in the characteristics of patients with AF in those studies and the patients included in our study. However, since our study is the first to analyse AF patients admitted to the medical ward of a hospital, we think it offers a closer and more accurate insight into the clinical reality of hospitalized multimorbid patients.

We found that sex modifies the progression of patients with multimorbidity, including those with AF. This study showed that the risk of mortality in men is 1.2 times higher than in women. However, we note that, while all factors were independent predictors of mortality in women in our study, in men, only age and CHF were. That is, neither stroke nor AF itself were independent predictors of mortality in men. It seems that the higher risk of death in men than in women is probably due to reasons not directly related to AF. The reasons why AF is of

different prognostic value based on sex are not clear. It could be explained by differences in therapeutic approaches to the different sexes, e.g. a more conservative and less aggressive therapeutic approach to the treatment of AF in women,[30] by physiological and anthropomorphic differences between the sexes,[28,31–33] by genetic differences associated with the X chromosome,[34] or by the influence of sex hormones on cardiac conduction.[35] The development of new lines of research is required to determine more accurately the impact of these factors on mortality in AF patients.

Our study results support the need for individualized clinical management of patients with multimorbidity, including AF, based on their age and sex. For example, women and older patients require more intensive management of AF.

Therefore, AF can be considered one more aging-related factor and a clinical marker, which only at certain ages and in female patients is an independent predictor of a poor prognosis. AF-related conditions (e.g. CHF) and perhaps to a lesser extent, those caused by AF (e.g. stroke, thromboembolism), are what actually leads to a poor prognosis.

This study has several limitations. First, it only describes the features of adult patients hospitalized in a medical ward, so it is not possible to extend the results to patients admitted for surgical reasons. Second, the retrospective design could pose some doubts about the quality and veracity of clinical information included for analysis, since the source of the data was an administrative database. However, our study was conducted based on the clinical records made by treating physicians, and the subsequent coding was independently verified by researchers who are themselves experienced physicians. Finally, the data are from a single hospital in Spain. Results cannot necessarily be extrapolated to other geographic regions or to different sized hospitals; it would therefore be of interest if similar studies were conducted in other health districts in Spain.

Conclusions

In conclusion, hospitalized patients with multimorbidity and AF have a unique clinical profile and higher in-hospital mortality than those without AF. In patients with multimorbidity, AF by itself has no prognostic value until the age of 80 years, whereas CHF is an independent prognostic factor in all age groups. Regarding sex, all factors (AF, age, stroke and CHF) are independent predictors of mortality in women, whereas in men, only age and CHF are. The clinical management of AF patients should consider sex and age particularly regarding mortality risk.

Acknowledgements

We would like to thank Tracy Harrison of Springer Healthcare Communications who provided technical and native-English editing assistance. This medical writing assistance was funded by a fellowship from the FEMI Research Grants for Young Researchers 2018.

Conflict of interest: None declared.

References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998; 98:946–52.
2. Clavel-Ruipérez FG, Consuegra-Sánchez L, Félix Redondo FJ, Lozano Mera L, Mellado-Delgado P, Martínez-Díaz JJ, et al. Mortalidad y fibrilación auricular en el estudio FIACA: evidencia de un efecto diferencial según el diagnóstico al ingreso hospitalario. *Rev Esp Cardiol* 2018; 71:155–61.
3. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. *JAMA* 2011; 305:2080–7.
4. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, et al. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* 2007; 115:3050–6.

5. Nieuwlaat R, Prins MH, Le Heuzey JY, Vardas PE, Aliot E, Santini M, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. *Eur Heart J* 2008; 29:1181–9.
6. Pedersen OD, Brendorp B, Køber L, Torp-Pedersen C. Prevalence, prognostic significance, and treatment of atrial fibrillation in congestive heart failure with particular reference to the DIAMOND-CHF study. *Congest Heart Fail* 2003; 9:333–40.
7. Perez-Villacastin J, Perez Castellano N, Moreno Planas J. Epidemiology of atrial fibrillation in Spain in the past 20 years. *Rev Esp Cardiol (Engl Ed)* 2013; 66:561–5.
8. 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.
9. Vidaillet H, Granada JF, Chyou P, Maassen K, Ortiz M, Pulido JN, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med* 2002; 113:365–70.
10. Wong CK, White HD, Wilcox RG, Criger DA, Califf RM, Topol EJ, et al. Management and outcome of patients with atrial fibrillation during acute myocardial infarction: the GUSTO-III experience. Global use of strategies to open occluded coronary arteries. *Heart* 2002; 88:357–62.
11. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet* 2016; 388:1161–9.
12. Nguyen TN, Cumming RG, Hilmer SN. The impact of frailty on mortality, length of stay and re-hospitalisation in older patients with atrial fibrillation. *Heart Lung Circ* 2016; 25:551–7.
13. Andersson T, Magnuson A, Bryngelsson IL, Frøbert O, Henriksson KM, Edvardsson N, et al. All-cause mortality in 272, 186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *Eur Heart J* 2013; 34:1061–7.
14. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37:2893–962.
15. Gullón A, Suárez C, Díez-Manglano J, Formiga F, Cepeda JM, Pose A, et al. Características y tratamiento antitrombótico de los pacientes ancianos con fibrilación auricular no valvular hospitalizados en Medicina Interna. Registro NONAVASC. *Med Clin (Barc)* 2017; 148:204–10.
16. Chamberlain AM, Alonso A, Gersh BJ, Manemann SM, Killian JM, Weston SA, et al. Multimorbidity and the risk of hospitalization and death in atrial fibrillation: a population-based study. *Am Heart J* 2017; 185:74–84.
17. López Soto A, Formiga F, Bosch X, García Alegría J. García Alegría J, en representación de los investigadores del estudio ESFINGE. Prevalencia de la fibrilación auricular y factores relacionados en pacientes ancianos hospitalizados: estudio ESFINGE. *Med Clin (Barc)* 2012; 138:231–7.

18. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009; 104:1534–9.
19. Schafer I, Hansen H, Schon G, Maier W, Höfels S, Altiner A. The German MultiCare-study: patterns of multimorbidity in primary health care - protocol of a prospective cohort study. *BMC Health Serv Res* 2009; 9:145.
20. Díez-Manglano J. Factores determinantes de la mortalidad en la fibrilación auricular. *Rev Clin Esp* 2010; 210: 447.
21. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37:2129–200.
22. Iniguez Vazquez I, Monte Secades R, Matesanz Fernandez M, Romay Lema EM, Rubal Bran D, Casariego Vales E. Characteristics and temporal pattern of readmissions of patients with atrial fibrillation hospitalized in medical departments. *Rev Clin Esp* 2017; 217:309–14.
23. IBM Corp. *IBM Statistics for Windows*, Version 19.0. Armonk, NY, IBM Corp., 2010.
24. R Core Team. R: *A Language and Environment for Statistical Computing*. Vienna, Austria, R Foundation for Statistical Computing, 2013. http://www.R-project.org/.
25. Frost L, Engholm G, Husted MH. Decrease in mortality in patients with a hospital diagnosis of atrial fibrillation in Denmark during the period 1980-1993. *Eur Heart J* 1999; 20:1592–9.
26. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22:983–8.
27. Stortecky S, Buellesfeld L, Wenaweser P, Heg D, Pilgrim T, Khattab AA, et al. Atrial fibrillation and aortic stenosis: impact on clinical outcomes among patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 2013; 6:77–84.
28. Andrade JG, Deyell MW, Lee AYK, Macle L. Sex differences in atrial fibrillation. *Can J Cardiol* 2018; 34:429–36.
29. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016; 532:7013.
30. Riesgo A, Sant E, Benito L, Hoyo J, Miró O, Mont L, et al. Diferencias de género en el manejo de los pacientes con fibrilación auricular: análisis de base poblacional en un área básica de salud. *Rev Esp Cardiol* 2011; 64:233–6.
31. Cochet H, Mouries A, Nivet H, Sacher F, Derval N, Denis A, et al. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. *J Cardiovasc Electrophysiol* 2015; 26:484–92.

32. Liu XK, Jahangir A, Terzic A, Gersh BJ, Hammill SC, Shen WK. Age- and sex-related atrial electrophysiologic and structural changes. *Am J Cardiol* 2004; 94:373–5.
33. Tsai WC, Chen YC, Lin YK, Chen SA, Chen YJ. Sex differences in the electrophysiological characteristics of pulmonary veins and left atrium and their clinical implication in atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011; 4:550–9.
34. Ravn LS, Hofman-Bang J, Dixen U, Larsen SO, Jensen G, Hauno S, et al. Relation of 97T polymorphism in KCNE5 to risk of atrial fibrillation. *Am J Cardiol* 2005; 96:405–7.
35. Tsuneda T, Yamashita T, Kato T, Sekiguchi A, Sagara K, Sawada H, et al. Deficiency of testosterone associates with the substrate of atrial fibrillation in the rat model. *J Cardiovasc Electrophysiol* 2009; 20:1055–60.

Table 1. List of chronic diseases as suggested in the German Multicare study,[21] adapted to the hospital setting for use in the current study

Arterial hypertension or hypertensive cardiomyopathy	Alcohol dependence syndrome
Dyslipidaemia	Parkinson's disease and other movement disorders
Type 2 diabetes mellitus	Hypothyroidism
Atrial fibrillation or atrial flutter	Sleep apnoea
Congestive heart failure	Digestive system cancer
Ischemic heart disease	Alcoholic liver disease
Chronic obstructive pulmonary disease	Lung cancer
Anaemia	Other neoplasms
Stroke	Colorectal cancer
Dementia	Chronic enterocolitis
Valvular heart disease	Rheumatoid arthritis and its complications
Major depressive disorder	Lymphoma
Chronic kidney disease	Breast cancer
Obesity	Myeloma
Other mental disorders	Prostate cancer
Malnutrition	Non-alcoholic chronic liver disease

Table 2. Baseline patient's characteristics, patient's hospital admissions and patient's outcomes

		AF group (*n*=14 181)	Non-AF group (*n*=38 758)	*P*-value
		n (%)	*n* (%)	
Sex	Men	7108 (50.1)	21 786 (56.1)	<0.001
	Women	7073 (49.9)	16 972 (43.9)	
In-hospital death	No	10 333 (72.9)	30 794 (79.5)	<0.001
	Yes	3848 (27.1)	7964 (20.5)	
		Mean±SD	Mean±SD	
Age at first admission (years)		78.6±10.0	71.9±14.2	<0.001
No. of hospitalizations		3.1±2.9	2.2±2.4	<0.001
Time of stay (days)		35.1±37.3	25.2±33.2	<0.001
Time between admissions (days)		1685.1±1417.5	1456.0±1377.8	<0.001

AF, atrial fibrillation; No., number; SD, standard deviation.

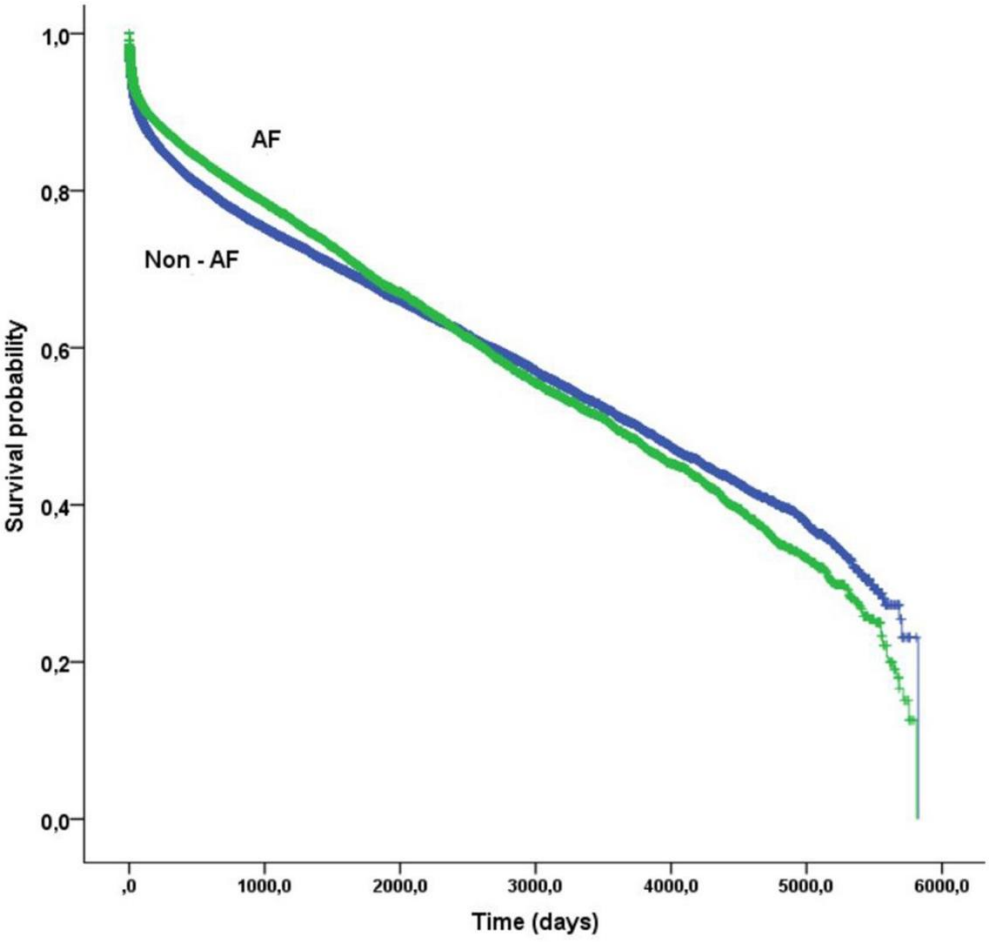

Figure 1. Kaplan–Meier survival curves for patients with atrial fibrillation (AF) and multi-morbidity compared with patients without AF (non-AF). $P = 0.21$ for the comparison.

Table 3. Final multivariate Cox model for risk of death among hospitalized patients with multimorbidity ($n = 52\ 939$)

Covariate	RR (95% CI)	*P*-value
Sex (ref: women)	1.203 (1.159–1.248)	<0.001
Age (1-year increment)	1.048 (1.046–1.050)	<0.001
AF (ref: no AF)	1.027 (0.980–1.077)	0.267
Stroke (ref: no stroke)	1.152 (1.081–1.229)	<0.001
CHF (ref: no CHF)	1.496 (1.422–1.574)	<0.001

AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; RR, relative risk.

Table 4. Final Cox model for women with multimorbidity ($n = 24\ 045$)

Covariate	RR (95% CI)	*P*-value
Age (1-year increment)	1.055 (1.052–1.059)	<0.001
AF (ref: no AF)	1.091 (1.021–1.165)	0.010
Stroke (ref: no stroke)	1.232 (1.124–1.351)	<0.001
CHF (ref: no CHF)	1.568 (1.460–1.648)	<0.001

AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; RR, relative risk.

Table 5. Final Cox model for men with multimorbidity ($n = 28\ 894$)

Covariate	RR (95% CI)	*P*-value
Age (1-year increment)	1.044 (1.041–1.046)	<0.001
AF (ref: no AF)	0.969 (0.905–1.037)	0.359
Stroke (ref: no stroke)	1.077 (0.985–1.179)	0.104
CHF (ref: no CHF)	1.408 (1.308–1.515)	<0.001

AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; RR, relative risk.

Table 6. Final Cox model for patients with multimorbidity by age group

Age group	≤50 years old (*n*=3718)		51–60 years old (*n*=5048)		61–70 years old (*n*=8866)		71–80 years old (*n*=16 608)		>80 years old (*n*=18 699)	
Covariate	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Sex (ref: women)	1.109 (0.9–1.4)	0.401	1.123 (0.9–1.3)	0.190	1.310 (1.2–1.5)	<0.001	1.263 (1.2–1.3)	<0.001	1.123 (1.0–1.2)	<0.001
AF (ref: no AF)	0.849 (0.4–1.9)	0.697	0.491 (0.3–0.7)	<0.001	0.664 (0.5–0.8)	<0.001	1.054 (0.9–1.1)	0.221	1.153 (1.1–1.2)	<0.001
Stroke (ref: no stroke)	0.468 (0.2–1.5)	0.191	0.747 (0.5–1.1)	0.190	0.870 (0.7–1.1)	0.199	1.124 (1.0–1.2)	0.045	1.301 (1.2–1.4)	<0.001
CHF (ref: no CHF)	1.008 (0.5–1.9)	0.980	1.441 (1.0–2.0)	0.032	1.566 (1.3–1.8)	<0.001	1.459 (1.3–1.6)	<0.001	1.589 (1.5–1.7)	<0.001

AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; ref, reference group; RR, relative risk.