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Heart failure and dementia: survival in relation to types of heart failure and different dementia disorders

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Aims Heart failure (HF) and dementia frequently coexist, but little is known about their types, relationships to each other and prognosis. The aims were to (i) describe patients with HF and dementia, assess (ii) the proportion of specific dementia disorders in types of HF based on ejection fraction and (iii) the prognostic role of types of HF and dementia disorders.

Methods and results The Swedish Heart Failure Registry (RiksSvikt) and The Swedish Dementia Registry (SveDem) were record-linked. Associations between dementia disorders and HF types were assessed with multinomial logistic regression and survival was investigated with Kaplan–Meier analysis and multivariable Cox regression. We studied 775 patients found in both registries (55% men, mean age 82 years). Ejection fraction was preserved in 38% of patients, reduced in 34%, and missing in 28%. The proportions of dementia disorders were similar across HF types. Vascular dementia was the most common dementia disorder (36%), followed by other dementias (28%), mixed dementia (20%), and Alzheimer disease (16%). Over a mean follow-up of 1.5 years, 76% of patients survived 1 year. We observed no significant differences in survival with regard to HF type ($P = 0.2$) or dementia disorder ($P = 0.5$). After adjustment for baseline covariates, neither HF types nor dementia disorders were independently associated with survival.

Conclusions Heart failure with preserved ejection fraction was the most common HF type and vascular dementia was the most common dementia disorder. The proportions of dementia disorders were similar across HF types. Neither HF types nor specific dementia disorders were associated with survival.

Keywords Dementia • Alzheimer disease • Vascular dementia • Heart failure • Preserved ejection fraction • Reduced ejection fraction • Survival • Registry

Introduction

Since 1977, when the term 'cardiogenic dementia' was introduced,[1] cardiovascular diseases and risks have been recognized as factors contributing to the development of, and coexisting with, dementia as well as targets for its prevention.[2–4] Specifically, heart failure (HF) has been suggested as a risk factor for dementia. However, in the elderly, HF and dementia frequently coexist and the precise underlying mechanisms remain difficult to disentangle.[5,6]

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Patients suffering from heart failure with reduced ejection fraction (HFREF) represent a group to which the most attention has been paid and for which the most therapeutic evidence has been accumulated.[7] Heart failure with preserved ejection fraction (HFPEF) has been increasingly recognized as equally common and serious as HFREF.[5] Most literature suggests that HFREF is associated with greater mortality compared with HFPEF,[8] although this remains controversial.[9] It has been argued that exclusion of patients with missing information on ejection fraction could have led to the inconsistency of these results.10 Aging and comorbidities may play an important role in the development of HFPEF,[11] which is expected to become the predominant type of HF in the future.[12]

Advanced age is the major risk factor for dementia, a syndrome characterized by progressive loss of cognitive capabilities and independence. Alzheimer disease (AD) is the most common dementia disorder overall and, to date, its cause is unknown, and there is no disease-modifying treatment. Dementia that develops as a consequence of cerebral infarctions or haemorrhages is termed vascular dementia[13] and is regarded as the second most common dementia disorder.[14] Alzheimer disease may also coexist with vascular pathology; this is termed mixed dementia.[15] A recent study suggested that AD patients have a higher survival rate than individuals diagnosed with other dementia disorders.[16]

Limited research on associations between HF types and dementia disorders has been performed and the prognostic impact of specific dementia disorders in HF and vice versa is unknown. We aimed to (i) describe patients suffering from both HF and dementia, (ii) determine the associations between specific dementia disorders and HF types, and (iii) assess survival in different HF types and dementia disorders.

Methods

Patients and registries

The Swedish Heart Failure Registry (RiksSvikt) and The Swedish Dementia Registry (SveDem) were linked based on a unique identification number and patients found in both registries (775 individuals) were used in this study. RiksSvikt is a national registry that aims to assess and improve the quality of care and provide systematic research in HF in Sweden (http://www.rikssvikt.se)[17] and included 55 313 individuals who were registered from 2000 to 2013 at discharge from hospital or outpatient visit. The Swedish Dementia Registry (SveDem) is a national registry for monitoring and improvement of the quality of dementia care in Sweden (http://www.svedem.se).[18] It included 36 354 patients who were newly diagnosed with dementia from 2007 to 2013. Data on death was obtained from The Swedish Population Registry. Subjects were followed from the date they were registered into the second registry until their death or October 14, 2013. This study complies with the Declaration of Helsinki and was approved by regional ethical review board in Stockholm. Patients were informed of entry into the registries and allowed to decline participation.

Heart failure

The inclusion criterion for registration into RiksSvikt is presence of HF judged by a clinician. HFPEF was defined as ejection fraction $\geq$40%. An ejection fraction between 40% and 50% might not be considered normal or preserved, but all therapy data comes from patients with ejection fraction $\leq$40%; therefore the 40% cut-off was chosen. heart failure with missing ejection fraction (HFMEF) was defined when the value of ejection fraction was absent in RiksSvikt.

Dementia

The inclusion criterion for registration into SveDem is newly diagnosed dementia according to The International Classification of Diseases version 10 (ICD 10).[19] Patients were diagnosed with one of the following dementia disorders: AD, mixed dementia, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease dementia, unspecified dementia (if the diagnosis is not ascertained or necessary investigations have not been performed), or other types. For this study patients were divided into four groups: AD, mixed dementia, vascular dementia, and other dementias (including the remaining dementia disorders).

Clinical characteristics

Variables about baseline medical history, the use of drugs and results of clinical and laboratory tests come from information collected in RiksSvikt or SveDem. For multivariable analysis of associations between dementia disorders and types of HF as well as multivariable analysis of predictors of death, 23 clinically relevant variables were selected for adjustment (*Table 1*). Total number of drugs was used as a proxy for overall comorbidity.[20]

Statistical analysis

Mean ($\pm$ standard deviation) and percentages were used to describe continuous and categorical variables, respectively. Multinomial logistic regression was performed to find associations between specific dementia disorders and types of HF; odds ratios with 95% confidence intervals (CIs) were calculated. Survival was analysed by Kaplan–Meier analysis and log-rank tests. Cox proportional hazards regression models were used to estimate hazard ratio and 95% CI for clinical characteristics for all-cause mortality as outcome. A two-tailed *P*-value of <0.05 was considered statistically significant. Data was analysed using the Statistical Package for the Social Sciences software version 22 (SPSS; IBM Corporation, Armonk, NY, USA).

Results

Characteristics of patients

A total of 775 patients were found in both RiksSvikt and SveDem. *Table 1* shows their baseline characteristics. They were on average 82 years old when they were entered into the second registry (age ranged from 56 to 96 years). Most of the patients (75%) were registered into SveDem after RiksSvikt (range 1 day to 11 years), while the opposite occurred in 25% of patients (range 1 day to 5 years). Men represented 55% of the whole study population. The majority of patients were recorded into RiksSvikt at discharge from an inpatient stay (66%), while outpatient registrations accounted for 34%. Specialists at memory clinics registered 64% of patients into SveDem, while 36% were entered by primary care physicians.

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Table 1 Characteristics of patients

Patients with heart failure and dementia ($n = 775$)			Missing (%)
Age, years		81.8 ± 6.4	0
Gender	Male	427 (55.0)	
	Female	348 (45.0)	
Type of heart failure	Preserved ejection fraction	292 (37.7)	
	Reduced ejection fraction	264 (34.1)	
	Missing ejection fraction	219 (28.3)	
Dementia disorder	Alzheimer disease	122 (15.7)	
	Mixed dementia	155 (20.0)	
	Vascular dementia	277 (35.7)	
	Other dementias	221 (28.5)	
Civil status	Married/cohabiting	390 (50.3)	4.9
	Single	347 (44.8)	
Living arrangements	Independent	688 (88.8)	0.1
	Other (institution)	86 (11.1)	
Location of RiksSvikt registration	Inpatient	509 (65.7)	0
	Outpatient	266 (34.3)	
Location of SveDem registration	Primary care unit	282 (36.4)	0
	Specialist centre	493 (63.6)	
Planned heart failure follow-up specialty	Specialty care (cardiology or internal medicine)	283 (36.5)	9.9
	Other (other specialty, geriatrics)	389 (50.2)	
	Primary care	26 (3.4)	
Planned follow-up at nurse-based heart failure clinic		195 (25.2)	0
Functional examination and laboratory	Systolic blood pressure	130.6 ± 20.6	1.2
	Heart rate	74.8 ± 15.6	5.8
	Haemoglobin (g/L)	130.7 ± 16.4	0
	Glomerular filtration rate (mL/min)	60.6 ± 26.0	0
	Mini Mental State Examination	21.1 ± 4.9	7.4
Comorbidities and drugs	Ischaemic heart disease	402 (51.9)	6.2
	Atrial fibrillation	457 (59.0)	0.8
	Diabetes mellitus	177 (22.8)	1.9
	RAS antagonists	570 (73.5)	0.9
	Beta blockers	624 (80.5)	0.8
	Diuretics	614 (79.2)	0.9
	Anticoagulants	280 (36.1)	1.1
	Cholinesterase inhibitors	198 (25.5)	3.2
	Memantine	66 (8.5)	4.1
	Total number of drugs	8.1 ± 3.2	17.1

RAS, renin–angiotensin system.
Data presented as mean ± standard deviation or frequency (%).
Glomerular filtration rate was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) formula. RAS antagonists include angiotensin converting enzyme inhibitors and angiotensin receptor blockers. All these 23 variables were used for multivariable analysis in logistic regression models (*Tables 2* and *3*).

HF types

The most common type of HF was HFPEF (292 patients, 38%), while 264 patients (34%) suffered from HFREF; ejection fraction was missing in 219 cases (HFMEF 28%). Atrial fibrillation was the most common cardiovascular comorbidity among patients with HF and dementia (59%). The patients used an average of eight drugs. Beta blockers were prescribed to 81% of patients and renin–angiotensin system antagonists to 74%.

Dementia disorders

Figure 1A shows distribution of dementia disorders overall and in different HF types. The most common dementia disorder was vascular dementia ($n = 277$, 36%). Patients with other dementias were in the second most frequent group ($n = 221$, 28%), followed by mixed dementia in 155 patients (20%) and AD in 122 individuals (16%). Other dementias grouped 186 individuals with unspecified dementia (24%), eight patients suffering from dementia with Lewy bodies, six from frontotemporal dementia, six from Parkinson disease dementia, and 15 other types of dementia.

There were small differences in the frequency of dementia disorders across all HF types (*Figure 1B*). The highest proportion of patients diagnosed with vascular dementia occurred in the HFREF group (38% vs. 35% in HFPEF vs. 34% in HFMEF). Patients suffering from HFREF had also the lowest frequency of AD (14% vs. 16% in HFPEF vs. 18% in HFMEF).

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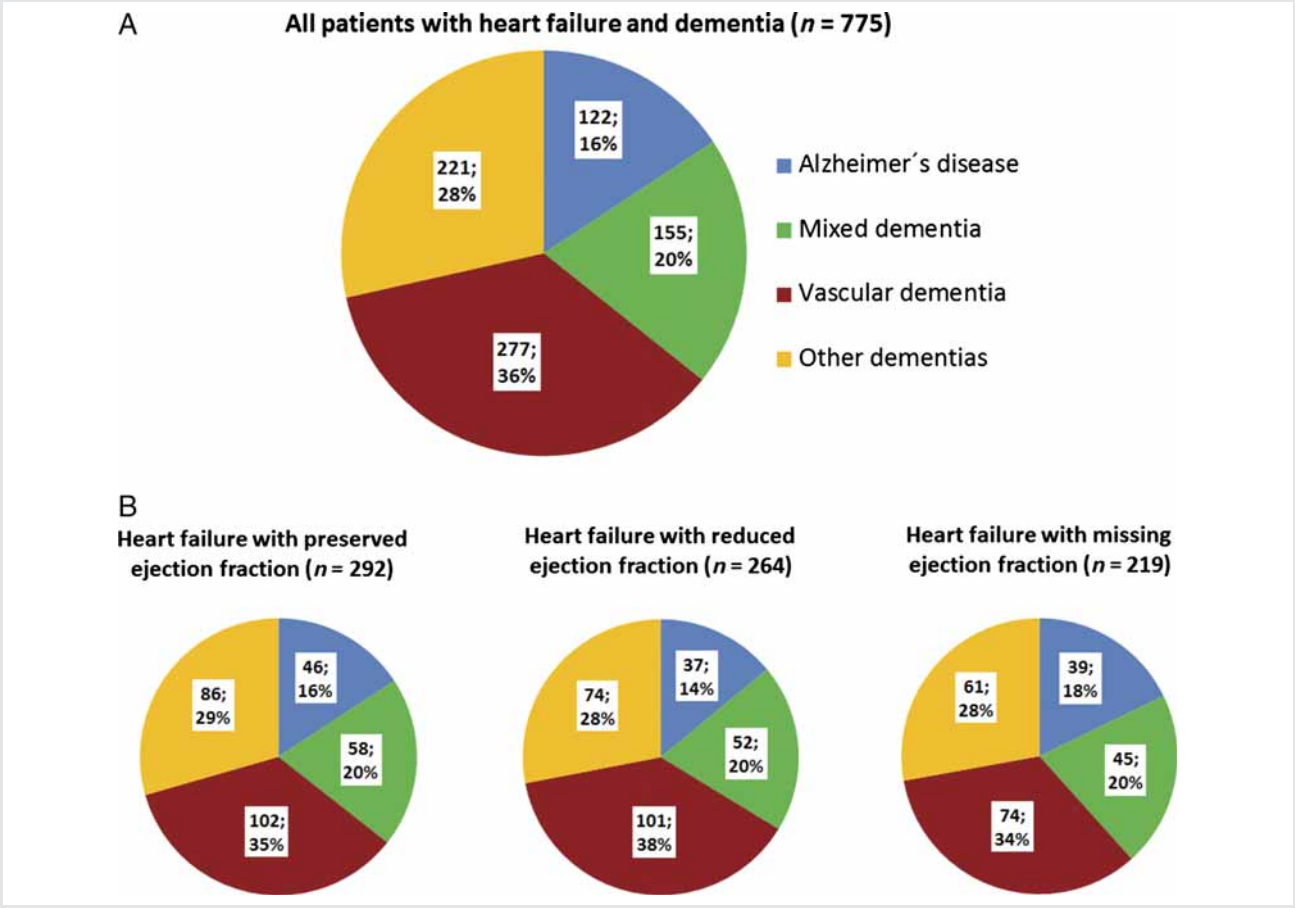

Figure 1 (A) Proportions of dementia disorders in all patients with heart failure and dementia and (B) in heart failure with preserved ejection fraction, reduced ejection fraction, and missing ejection fraction separately.

Associations between dementia disorders and HF types

Table 2 presents odds ratios for associations between dementia disorders and types of HF. For example, on crude analysis, the odds ratio for association between vascular dementia and HFREF was 1.23 (95% CI = 0.74–1.06). When adjusted for selected baseline characteristics, the odds ratio was 1.23 (95% CI = 0.70–2.14) and after adjusting for all covariates it was 1.38 (95% CI = 0.59–3.26). None of the associations between dementia disorders and types of HF reached statistical significance.

Survival

The patients were followed-up for an average of 1.5 years (range 1–2238 days) and there were 264 deaths per 1000 person-years. One-year survival rate was 76% for the whole population and their median estimated survival time reached 943 days.

Figure 2A shows survival according to HF type. Individuals with HFMEF had the lowest 1-year survival rate (72% vs. 79% in HFPEF vs. 76% in HFREF) and the lowest median estimated survival time (874 days vs. 998 days in HFPEF vs. 1016 days in HFREF). However, using a log-rank test, we did not find any statistically significant difference in survival according to types of HF ($P = 0.221$).

Figure 2B shows survival stratified by dementia disorders. The AD patients had the highest 1-year survival rate (80% vs. 74% in mixed dementia vs. 75% in vascular dementia vs. 77% in other dementias). The longest median estimated survival time has been found in other dementias (1093 days vs. 897 days in AD vs. 1016 days in mixed dementia vs. 876 days in vascular dementia). Using a log-rank test we again did not find any statistically significant difference regarding survival among different dementia disorders (0.488).

Table 3 presents hazard ratios for all-cause mortality. On crude analysis, in comparison with HFPEF, HFMEF was associated with a hazard ratio of 1.27 (95% CI = 0.96–1.67) and HFREF with a hazard ratio of 1.06 (95% CI = 0.81–1.39). When adjusted for dementia disorders and selected baseline characteristics, a similar trend occurred, with HFMEF having a hazard ratio of 1.14 (95% CI = 0.85–1.53) and HFREF having a hazard ratio of 1.00 (95% CI = 0.75–1.33). After complete adjustment for all covariates, the hazard ratio for HFMEF was 1.03 (95% CI = 0.65–1.63) and 1.40 (95% CI = 0.94–2.10) for HFREF.

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Table 2 Odds ratios with 95% confidence intervals for associations between specific dementia disorders and different types of heart failure

	Heart failure and preserved ejection fraction ($n = 292$)	Heart failure and reduced ejection fraction ($n = 264$)	Heart failure and missing ejection fraction ($n = 219$)
Crude analysis			
Alzheimer disease	Reference	Reference	
Mixed dementia		1.115 (0.629–1.975)	0.915 (0.514–1.630)
Vascular dementia		1.231 (0.737–2.056)	0.856 (0.508–1.441)
Other dementias		1.070 (0.628–1.823)	0.837 (0.488–1.433)
Adjusted for age, gender, Mini Mental State Exam, haemoglobin, and glomerular filtration rate			
Alzheimer disease	Reference	Reference	
Mixed dementia		1.201 (0.647–2.228)	0.791 (0.427–1.467)
Vascular dementia		1.227 (0.703–2.143)	0.790 (0.454–1.374)
Other dementias		1.197 (0.669–2.140)	0.698 (0.390–1.251)
Complete adjustment*			
Alzheimer disease	Reference	Reference	
Mixed dementia		1.856 (0.814–4.234)	0.782 (0.331–1.848)
Vascular dementia		1.383 (0.586–3.264)	0.564 (0.232–1.367)
Other dementias		2.273 (0.994–5.196)	0.888 (0.378–2.086)

*Adjusted for all variables in *Table 1*.

When compared with AD, patients with vascular dementia had a hazard ratio of 1.17 (95% CI = 0.84–1.65) on crude analysis. This trend remained after adjusting for covariates. After complete adjustment, the hazard ratio for vascular dementia was 1.18 (95% CI = 0.64–2.17). Overall, statistical significance was not reached in any analysis.

Discussion

In this registry-based study of patients with HF and dementia, we found that (i) HFPEF was the most common HF type and vascular dementia the most common dementia disorder, (ii) that dementia disorder did not affect HF type or vice versa, and (iii) that 1-year survival rate was 76% overall with no difference according to HF type or dementia disorder.

Characteristics of patients

Patients in our study population were on average 82 years old when they were diagnosed with HF and dementia. They were older than HF patients and dementia patients in general. Patients with HF are on average 74 years old when they are registered into RiksSvikt[21] and patients with dementia are on average 79 years old at the time of registration into SveDem.[22]

The majority of the patients were men (55%). The proportion of males was the highest within the youngest patients and was decreasing with advanced age, which is in line with a known pattern among HF patients.[23] Female gender is more common in the general population of dementia patients, however, the predominant dementia disorder is AD, which is associated with female gender.[22]

Not surprisingly given the great age, the most common type of HF was HFPEF. Decreased cerebral perfusion owing to HF accompanied by maladaptive neurohormonal activation and a systemic inflammatory state are suggested to contribute to the disruption of the neurovascular unit and to dementia.[5] Given the multifactorial nature of the HF syndrome and the numerous physiological similarities between HFPEF and HFREF, HFPEF is likely as relevant for the development of dementia, even though causality cannot be established.[5]

A large proportion of patients had missing information on the level of ejection fraction (28%), which implies down-prioritization of diagnostic and follow-up investigations and most likely concurrently lower ambition in initiating and optimizing evidence-based treatment of HF.

In agreement with previous research,[24] we found that vascular dementia was the most common dementia disorder in the whole HF population, accounting for 36% of the cases. Hjelm and colleagues[24] reported that HF patients had a significantly higher prevalence of vascular dementia, but not AD. Conversely, Qiu *et al.*[25] emphasized the importance of HF in the development also of AD. In the present study, vascular dementia was the most frequent dementia disorder across all types of HF. We observed a trend that vascular dementia was slightly more common in HFREF, while AD accounted for a smaller proportion in this HF subgroup, which if confirmed could be consistent with more vascular disease in HFREF and higher age in HFPEF; however, this difference did not reach statistical significance.

The second most common dementia disorder was unspecified dementia and accounted for 24% of cases. Advanced age and frailty of these patients could explain a high proportion of rather undiagnosed subjects. They may be difficult to diagnose because of their frailty or may be believed not to benefit from advanced diagnostic work-up to unveil the aetiology of dementia.

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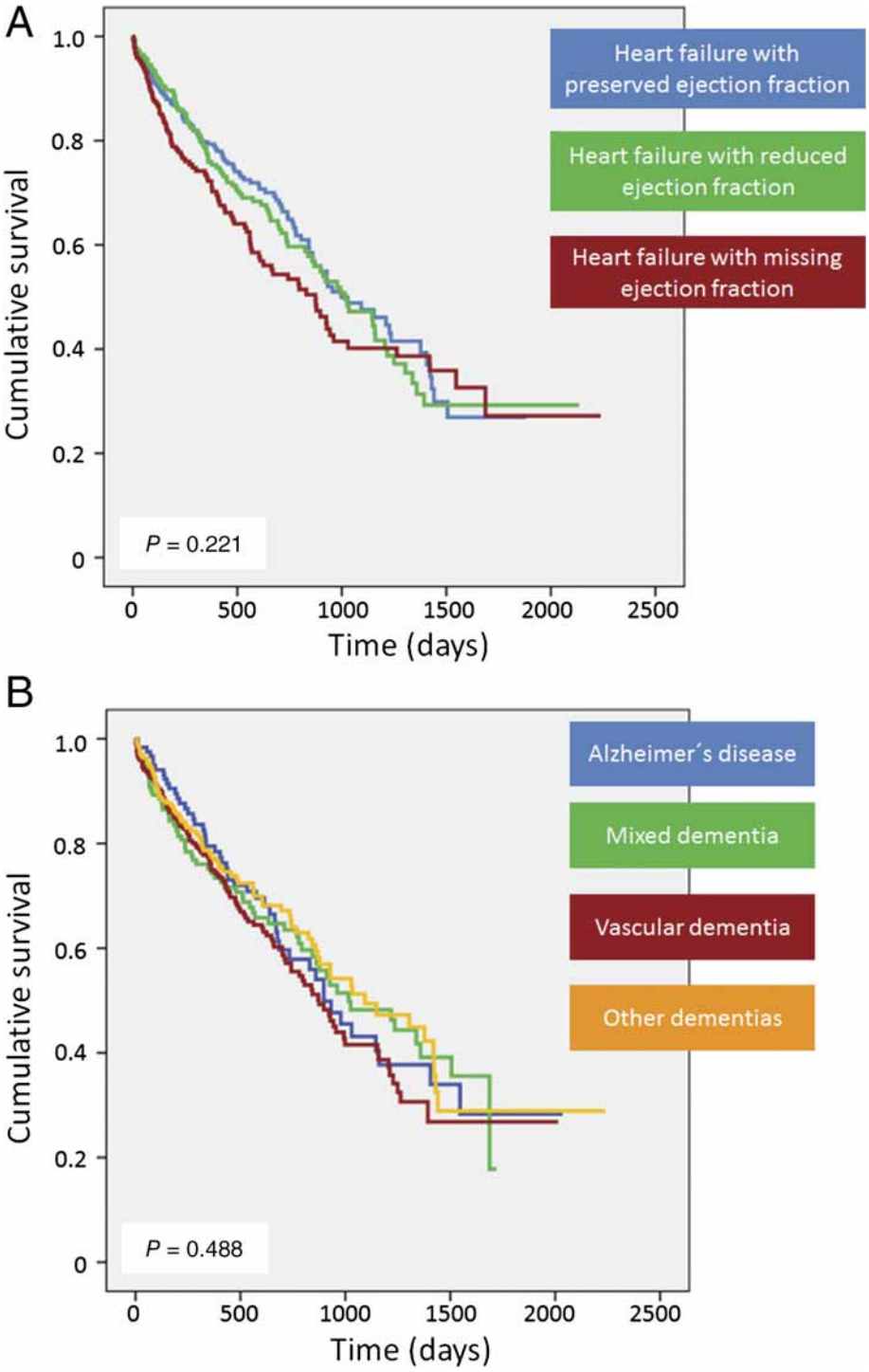

Figure 2 Kaplan–Meier estimates of the cumulative survival of patients with heart failure and dementia, according to (A) heart failure type and (B) dementia disorder. *P*-values are from log-rank test.

Survival

The 1-year survival rate of patients in the present study population was 76%, varying between 72% in HFMEF and 79% in HFPEF and between 74% in mixed dementia and 80% in AD. In a general HF population in Sweden, 1-year survival rate is about 80%[21], suggesting that dementia not only may contribute to the development of incident HF but it may also contribute to worse prognosis in prevalent HF.

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Table 3 Multivariable analysis for death by Cox regression

	Hazard ratio (95% confidence interval)	*P*-value
Types of heart failure: crude analysis		
Heart failure with preserved ejection fraction	Reference	
Heart failure with reduced ejection fraction	1.064 (0.812–1.394)	0.652
Heart failure with missing ejection fraction	1.268 (0.962–1.670)	0.092
Dementia disorders: crude analysis		
Alzheimer disease	Reference	
Mixed dementia	1.014 (0.699–1.471)	0.942
Vascular dementia	1.176 (0.842–1.645)	0.342
Other dementias	0.952 (0.666–1.361)	0.786
Types of heart failure and dementia disorders adjusted for each other		
Heart failure with preserved ejection fraction	Reference	
Heart failure with reduced ejection fraction	1.054 (0.804–1.382)	0.702
Heart failure with missing ejection fraction	1.271 (0.964–1.674)	0.089
Alzheimer disease	Reference	
Mixed dementia	1.012 (0.697–1.468)	0.952
Vascular dementia	1.190 (0.851–1.665)	0.310
Other dementias	0.963 (0.673–1.378)	0.837
Adjusted for age, gender, Mini Mental State Exam, haemoglobin and glomerular filtration rate and dementia and heart failure subtype respectively		
Heart failure with preserved ejection fraction	Reference	
Heart failure with reduced ejection fraction	0.998 (0.748–1.332)	0.991
Heart failure with missing ejection fraction	1.137 (0.845–1.529)	0.397
Alzheimer disease	Reference	
Mixed dementia	1.009 (0.681–1.495)	0.964
Vascular dementia	1.267 (0.890–1.805)	0.189
Other dementias	0.841 (0.572–1.236)	0.379
Complete adjustment*		
Heart failure with preserved ejection fraction	Reference	
Heart failure with reduced ejection fraction	1.403 (0.936–2.102)	0.101
Heart failure with missing ejection fraction	1.028 (0.648–1.628)	0.908
Alzheimer disease	Reference	
Mixed dementia	0.870 (0.488–1.551)	0.636
Vascular dementia	1.182 (0.643–2.171)	0.591
Other dementias	1.018 (0.564–1.837)	0.952

*Adjusted for all variables in *Table 1*.

As suggested, missing information on ejection fraction may reflect a reduced level of ambition from physicians towards diagnostic work-up or care of patients, perhaps because of frailty and/or comorbidities, and has therefore been suggested as a marker of adverse outcomes.[10] We observed a trend that patients with HFMEF may have had a higher risk of death when compared with HFPEF, but this did not remain after adjustment for all covariates. Similarly, patients with HFREF seemed to have higher risks in comparison with HFPEF, but this failed to reach statistical significance.

Alzheimer disease has been suggested as the least deadly dementia disorder,[16] even though there is conflicting evidence as to whether mortality differs between dementia disorders,[26,27] varying based on cohort, study design and the length of follow-up. We observed that AD patients had the highest 1-year survival rate among all dementia disorders (80%). The occurrence of deaths during the first year was rather lower in AD, which seemed balanced with a relatively higher number of deaths during the next years, reflecting the more continuously progressive character of AD. In contrast, individuals diagnosed with mixed and vascular dementia had lower 1-year survival rates (74% and 75%, respectively). However, we did not find any statistically significant differences in the survival time among patients with different dementia disorders.

Limitations and strengths

Our study has several limitations. The diagnoses of dementia and HF were based on clinical judgment and not adjudicated. The accuracy of the dementia diagnoses has not been examined and confirmed by pathological examination. It needs to be acknowledged that the diagnosis of a dementia disorder is often set based on the past history of cardiovascular diseases and this circularity problem represents a limitation to our research.

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In addition, bias related to patient population, patient selection and reporting cannot be ruled out as the data is derived from a registry in which participation can be declined and the coverage and completeness of registrations may differ from site to site. Although many hospitals and primary care units report to the registries, neither RiksSvikt nor SveDem have a complete coverage throughout Sweden; this fact does not allow us to determine the prevalence or incidence of dementia in HF or include a control group of dementia-free subjects.

Conclusion

In this study of the nationwide RiksSvikt and SveDem, HFPEF was the most common type of HF and vascular dementia was the most common dementia disorder. We did not observe any statistically significant associations between dementia disorders and HF types or any statistically significant associations between HF type or dementia disorder and survival.

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