Multimorbidity and multiple causes of death in heart failure

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Abstract

Introduction Patients with heart failure (HF) usually have multiple comorbid conditions that interact with HF, either leading to its development, aggravating its progression or reducing the effectiveness of treatment. Although the prevalence of HF comorbidities has been studied, more evidence is needed on the strength of their independent association with HF and HF mortality.
Objective To examine the strength of association between HF and associated medical conditions.
Methods We analysed data from the Baker Biobank, encompassing 6530 adults aged between 18 and 69 years, collected between January 2000 and December 2011. Mortality was determined through linkage to the National Death Index. Medical conditions were self-reported by patients at enrolment to the Biobank. The strength of association between HF and co-occurring medical conditions as a cause of illness and death was assessed using multivariate logistic regression. Hazards of mortality were determined using Cox regression models.
Results Most HF patients (92.2%) had at least one additional medical condition. The most common comorbidities were hypertension, arrhythmia and dyslipidaemia. Coronary artery disease was the most common cause of death co-occurring with HF. HF patients had significantly higher odds of arrhythmia [odds ratio (OR) = 3.3; 95% confidence interval (CI): 2.7, 3.9]. Patients with kidney disease had 3 (95% CI: 2.1, 4.4) times higher odds of co-occurring HF as a cause of death compared to those without kidney disease. Patients with a history of HF had 3.6 (95% CI: 2.45, 5.24) times higher hazard of mortality from kidney disease.
Conclusion In multimorbidity analysis, other cardiovascular diseases had a strong association with HF. However, in multiple causes of death analysis, there was a strong association between kidney disease and HF.

Keywords Comorbidity · Registry · Mortality · Prognosis · Cardiovascular

Introduction

Heart failure (HF) is a major burden on patients and health systems in developed countries, and an emerging burden in developing countries (Sahle et al. 2016). There are about 38 million people with HF worldwide, with more than 10% of people aged 75 years and above in developed countries (Savarese and Lund 2017; Ponikowski et al. 2014; Vos et al. 2012). HF is responsible for a significant portion of health

expenditure in the developed world (Mozaffarian et al. 2016; Bui et al. 2011). Despite recent advances in pharmacological and device therapy, the mortality rate remains high, with only 50% of diagnosed patients surviving beyond five years after diagnosis (Tsutsui et al. 2007; Taylor et al. 2017b).

The prevalence of HF in the Australian population ranges between 1% and 2% (Sahle et al. 2016). As population-based estimates of HF prevalence and incidence in Australia are limited, the national burden of HF has been estimated using international prevalence rates. Recent estimates show that nearly half a million people aged 18 years or more had HF, representing 2.1% of the adult population. More than 150,000 admissions and about 1 million hospital days per annum are attributed to HF (Chan et al. 2016).

Heart failure commonly co-exists with other medical conditions, acting as either a disease modifier or a contributing factor. About three out of every four HF patients have at least one co-occurring medical condition (Lawson et al. 2018; Joyce et al. 2016). Although the pathophysiologic pathways leading to the development of HF are complex, the co-

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occurrence is mainly due to common (shared) risk factors, disease complications and treatment effects. These comorbid conditions affect both the progression and the outcome of HF in patients. This co-occurrence has negative impacts on morbidity, mortality and quality of life (van der Wal et al. 2017).

Despite the high rates of co-occurrence of HF with other medical conditions and evidence of impacts of the co-occurring conditions on morbidity and mortality, little is known about the strength of independent associations between HF and these conditions. Therefore, the objective of this study was to examine the strength of association between HF and co-occurring medical conditions and causes of death. Given that the guidelines for the management of patients with HF are based on a single-disease approach, evidence on the strength of association between HF and other conditions would inform innovative approaches that better support the management of these complex clinical cases to improve health outcomes and quality of life.

Methods

Data source

We used data collected as part of the Baker Biobank study. The Biobank data were collected between 2000 and 2011 from 6530 adults aged 18 to 69 years in Victoria, Australia. These data were linked to the Australian National Death Index (up to May 2018). Details of the methods used in the Biobank study have been reported elsewhere (Haregu et al. 2019).

Study variables

Medical history

A history of common cardiovascular diseases and other related medical conditions was collected using a questionnaire at the time of the study. Participants were asked about all the medical conditions they had. The history of some medical conditions, such as hypertension, obesity and dyslipidaemia, were supplemented by data from physical and biochemical measurements.

Causes of death

Both underlying and associated causes of death and date of death were obtained from the Australian National Death Index. ICD-10 codes were used to classify causes of death.

Co-occurrence

Any simultaneous existence of HF and co-existing medical conditions, including other cardiovascular diseases, stroke, diabetes, kidney disease, arthritis, dyslipidaemia, hypertension, asthma, retinopathy, cancer and mental health problems, either in the medical history or in the cause of death report, was considered as co-occurrence.

Hazards of mortality

Two forms of hazards of mortality were considered, namely, hazards of HF mortality among patients with a history of other medical conditions and hazards of mortality due to other causes of death among patients with a previous history of HF.

Data analysis

Co-occurrence rate

We described the co-occurrence rate of medical conditions among patients with HF (as a cause of illness) using prevalence rates. Similarly, the co-occurrence rate of other causes of death with HF (as a cause of death) was described using proportions.

Strength of association

The strength of association between HF and co-occurring medical conditions (as a cause of illness) was determined using logistic regression models. The strength of association between other causes of death and HF (as a cause of death) was also assessed using the same likelihood estimator.

Hazards of mortality

The hazards of HF mortality associated with co-occurring medical conditions and mortality associated with co-occurring medical conditions among patients with a history of HF were determined using Cox regression models.

Results

Study population

We included all 6530 Biobank study participants in this analysis. Of these, 63% were male and the average (standard deviation) age at recruitment was 57.4 (14.9) years. The median follow-up time was 12.8 years (interquartile range: 8.7, 15.4). Among the Biobank study population, 644 individuals had a previous history of HF. Analysis of linked data showed that 291 deaths among the Biobank population had HF mentioned as a cause of death, including in 105 deaths with a previous history of HF.

Co-occurrence rate

Our analysis of medical conditions in patients with HF showed that hypertension, arrhythmia and dyslipidaemia were the commonest co-occurring medical conditions. On the other hand, coronary artery disease was the main cause of death among deaths where HF was mentioned as a cause of death. The co-occurrence rates of HF and other medical conditions as causes of morbidity and mortality are shown in Fig. 1.

Cause of illness

Analysis of the strength of association between HF and co-occurring medical conditions showed that HF patients had 3.3 times higher odds of arrhythmia as compared to other patients. Patients with myocardial infarction were 2.7 times more likely to have a co-occurring HF. As shown in Fig. 2, stroke, valve disease, vascular disease, kidney disease, diabetes and obesity had a statistically significant association with HF. On the other hand, patients with dyslipidaemia and arthritis were unlikely to have HF as a co-occurring medical condition.

Cause of death

The analysis of the association between HF and other causes of death revealed that kidney disease had about three times higher odds of co-occurrence with HF. Atrial fibrillation, coronary artery disease and diabetes were the other causes of death that had a statistically significant association with HF

after adjustment for age, gender and other causes of death. On the other hand, cancer had a statistically significant negative association with HF (Table 1).

Hazards of heart failure mortality

In our analysis of hazards of HF mortality associated with co-occurring medical conditions, we found that patients with a history of HF had a 2.2 times higher hazard of mortality from kidney disease. A 53% increased hazard of mortality due to diabetes and myocardial infarction was also observed among patients with history of HF. Details of hazards of HF mortality among patients with a history of different medical conditions, after adjustment for age, gender and the factored medical conditions, are shown in Table 2.

Hazards of mortality among heart failure patients

During the follow-up period, a total of 105 patients with a previous history of HF have died. The hazard of all-cause mortality among HF patients was 2.45 [95% confidence interval (CI): 2.15,2.79]. The hazard of mortality related to arrhythmia was the highest. Hypertension, myocardial infarction and stroke did not constitute statistically significant hazards of mortality among patients with a history of HF. Table 3 shows the hazards of mortality among patients with HF and co-occurring conditions.
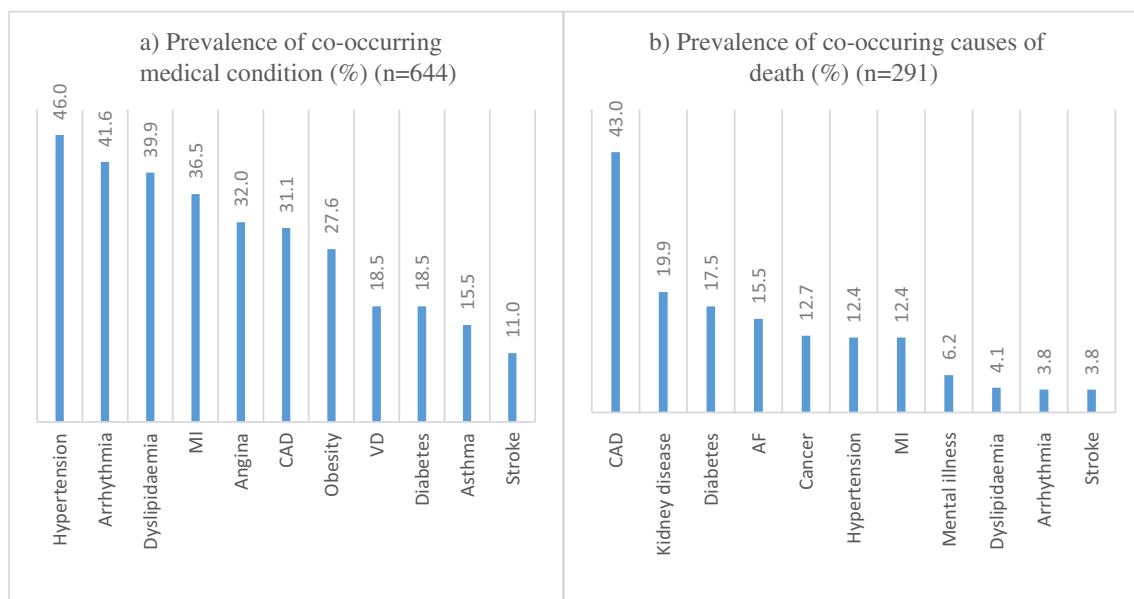
MI= Myocardial Infarction, CAD=Coronary Artery Disease, VD=Vascular Disease, AF=Atrial Fibrillation
Note: The numbers and percentages don't add up as many cases and deaths involvedmultiple conditions.

Fig. 1 Co-occurrence rate of medical conditions among cases and deaths
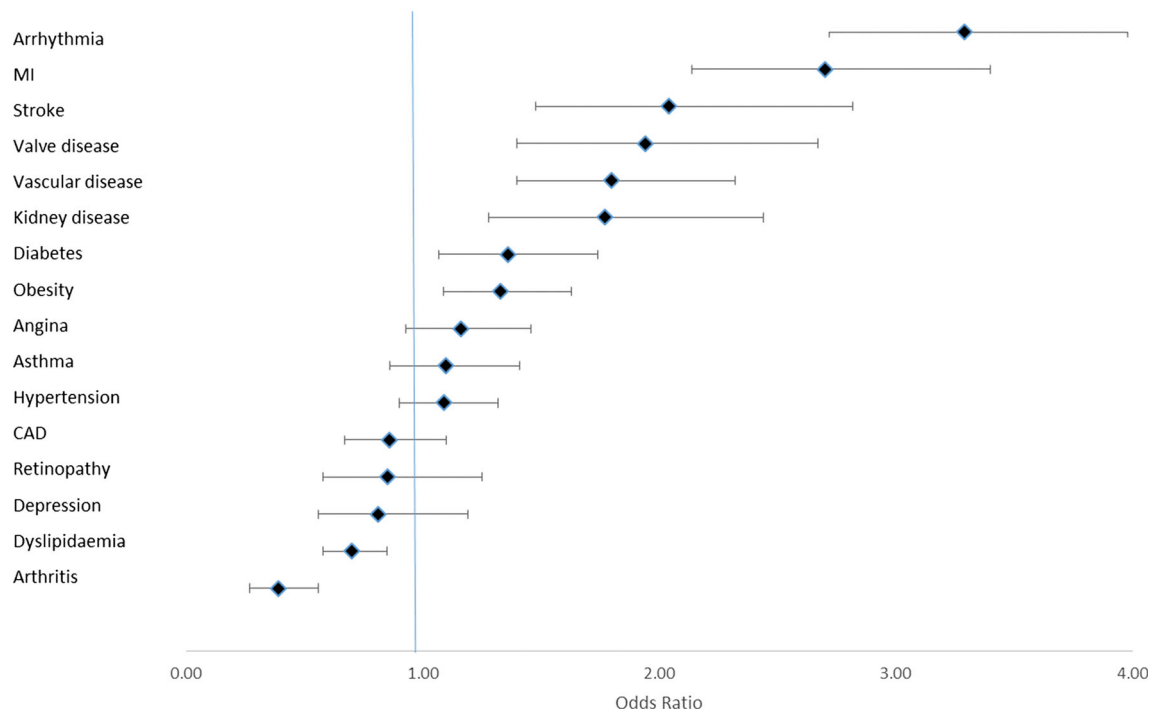
MI= Myocardial infarction, CAD=Coronary Artery Disease
Note: Odds ratios adjusted for gender, age and other medical conditions.

Fig. 2 Association between heart failure and co-occurring medical conditions (*n* = 6530 participants)

Discussion

Summary of the findings

This study showed that about 92% of patients with HF had at least one co-occurring medical condition. Hypertension was the most common (46%) co-occurring medical condition among patients with HF, while coronary artery disease was

Table 1 Association between heart failure and other co-occurring causes of death (*n* = 1584 deaths)

Cause of death	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Kidney disease	3.21 (2.24, 4.58)	3.03 (2.08, 4.42)*
Atrial fibrillation	2.56 (1.74, 3.77)	2.39 (1.56, 3.64)*
Coronary artery disease	1.93 (1.49, 2.51)	1.69 (1.27, 2.26)*
Diabetes	1.96 (1.38, 2.80)	1.53 (1.04, 2.26)*
Dyslipidaemia	1.94 (0.97, 3.86)	1.30 (0.57, 2.94)
Arrhythmia	1.45 (0.73, 2.90)	1.27 (0.62, 2.60)
Hypertension	1.53 (1.03, 2.28)	1.13 (0.70, 1.82)
Myocardial infarction	1.28 (0.87, 1.90)	0.88 (0.58, 1.35)
Stroke	0.82 (0.43, 1.58)	0.62 (0.31, 1.24)
Mental health problems	0.64 (0.39, 1.07)	0.58 (0.34, 0.99)*
Cancer	0.34 (0.23, 0.48)	0.36 (0.25, 0.52)*

n = total linked deaths, OR = odds ratio, CI = confidence interval

[a] Adjusted for gender, age and other causes of death

*Significant at 0.05 level

the most common (43%) cause of death among patients with history of HF. Arrhythmia and myocardial infarction had a stronger association with HF as compared to other conditions. In the multiple causes of death analysis, kidney disease was found to have a strong association with HF. Patients with kidney disease had a 54% higher hazard of mortality associated with HF. Patients with HF had a higher hazard of mortality related to arrhythmia.

Interpretation in the context of the literature

Many studies have reported that other cardiovascular diseases are the most common types of comorbid conditions in HF patients. However, an increase in the number of other medical conditions is more strongly associated with mortality (Manemann et al. 2016; Tromp et al. 2018). The findings of this study also showed that cardiovascular disease had a stronger association with HF in the multimorbidity analysis, and that kidney disease had a stronger association with HF in the multiple cause of death analysis.

A study on HF and multimorbidity in Australian general practice found that almost all HF patients had at least one and 53.4% had six or more other chronic conditions. The most common pair of co-occurring conditions among active patients with HF were hypertension and osteoarthritis (43.4%) (Taylor et al. 2017a). Similarly, this study showed that 92% of HF patients had at least one co-occurring medical condition.

Table 2 Hazards of heart failure mortality among patients with medical conditions

Gender (ref.: female)	HR from HF[a]	SE	z-Statistic	p-Value	95% CI	
Male	1.18	0.17	1.16	0.25	0.89	1.55
Age (ref.: < 40 years)						
40–59 years	1.48	0.57	1.01	0.31	0.69	3.15
60+ years	6.52*	2.41	5.09	0.00	3.17	13.44
Medical condition						
Heart failure	3.95*	0.55	9.83	0.00	3.01	5.20
Kidney disease	2.19*	0.39	4.36	0.00	1.54	3.11
Valve disease	1.76*	0.32	3.10	0.00	1.23	2.51
Vascular disease	1.72*	0.25	3.71	0.00	1.29	2.30
Diabetes	1.53*	0.22	2.95	0.00	1.15	2.04
Myocardial infarction	1.53*	0.23	2.81	0.01	1.14	2.06
Stroke	1.49*	0.27	2.21	0.03	1.05	2.13
Hypertension	1.32*	0.17	2.14	0.03	1.02	1.71
Obesity	1.27	0.17	1.80	0.07	0.98	1.66
Coronary artery disease	1.26	0.19	1.54	0.12	0.94	1.70
Arrhythmia	1.26	0.17	1.66	0.10	0.96	1.65
Angina	1.14	0.16	0.91	0.36	0.86	1.51
Retinopathy	1.11	0.23	0.50	0.61	0.74	1.66
Arthritis	0.99	0.18	−0.07	0.94	0.68	1.42
Asthma	0.77	0.14	−1.49	0.14	0.54	1.09
Depression	0.74	0.21	−1.06	0.29	0.43	1.29
Dyslipidaemia	0.67*	0.09	−3.10	0.00	0.52	0.86

HR = hazard ratio, HF = heart failure, SE = standard error, CI = confidence Interval

[a] Failure: HF deaths

*Significant at 0.05 level

As stated above, the most common co-occurring condition was cardiovascular disease.

Table 3 Hazards of mortality due to co-occurring conditions among heart failure patients

	HR (95% CI)[a]
Arrhythmia	7.76 (3.87, 15.54)*
Dyslipidaemia	4.27 (2.04, 8.94)*
Kidney disease	3.59 (2.45, 5.24)*
Diabetes	2.28 (1.56, 3.32)*
Atrial fibrillation	2.25 (1.43, 3.56)*
Coronary artery disease	1.91 (1.51, 2.41)*
Mental health problems	1.90 (1.13, 3.18)*
Hypertension	1.62 (0.98, 2.67)
Cancer	1.61 (1.22, 2.14)*
Myocardial infarction	1.50 (0.97, 2.30)
Stroke	0.63 (0.24, 1.62)
All causes	2.45 (2.15, 2.79)*

HR = hazard ratio, CI = confidence interval

[a] Adjusted for age, gender and history of medical conditions

*Significant at 0.05 level

A study in Olmsted County, Minnesota, showed that patients with HF experience a persistently high mortality and that a significant proportion of these deaths was from non-cardiovascular causes (Henkel et al. 2008). This is especially true for HF patients with preserved ejection fraction (Lee et al. 2011). However, the findings of this study indicated that both cardiovascular diseases and kidney disease are the major causes of death among patients with HF.

Coronary artery disease and hypertension are considered as the common causes of HF (Ziaeian and Fonarow 2016). In this study, coronary artery disease and hypertension also had higher rates of co-occurrence with HF. However, the adjusted association between these conditions and HF was relatively weaker. As our multimorbidity and cause of death analyses were cross-sectional in nature, it was not possible to ascertain the time sequence of occurrence of the co-occurring conditions.

Implications for policy, practice and research

The high prevalence of co-occurrence rates of medical conditions among HF patients suggests the need for comprehensive approaches in the management and phenotyping of patients

with HF. This is particularly important as the comorbid conditions are the main causes of readmission or death in a significant proportion of patients with HF.

The findings also suggest that other cardiovascular diseases have a strong association with HF. This implies the need for considering these conditions in the diagnosis and management of patients with HF. As co-occurring conditions could affect the effectiveness of treatment of HF and, conversely, treatment of HF may also affect the course of these conditions, an integrated approach to diagnosis and management is imperative.

Patients with kidney disease have higher hazards of mortality from HF. Given the reciprocal relationship between HF and kidney disease (Silverberg et al. 2004), this suggests the need for the prevention and proactive management of HF among these patients in order to reduce further complications and mortality.

On the other hand, higher hazards of mortality among HF patients are associated with arrhythmia and kidney disease. This implies the need for close monitoring of heart rhythm, lipid levels and renal function in patients with HF. The need for personalised care of HF patients needs to be considered.

Further research is also needed to substantiate evidence of the direction and pathways in the relationship between HF and the identified co-occurring medical conditions. In addition, cohort studies that can describe the progressive development of HF in patients with other cardiovascular diseases and vice versa are required. Evidence on the role of treatment in multimorbid cases would also be important.

Limitations of the study

Medical data were self-reported. Data on the duration of medical conditions and their degree of severity were not available. In this analysis, all medical conditions were treated at the same level, regardless of whether they were the index disease or comorbidity. Similarly, all causes of death were treated the same, regardless of underlying or associated cause of death. Hospital admission data were not included in the analysis.

Conclusions

In this analysis of multimorbidity, other co-occurring cardiovascular diseases and their risk factors had a strong association with heart failure (HF). However, while investigating multiple causes of death, kidney disease was found to have the strongest association with HF. Hazards of HF mortality were significantly higher among patients with kidney disease. Patients with HF had the highest hazards of mortality from arrhythmia, dyslipidaemia and kidney disease. Overall, the findings of this study described the prevalence of other medical conditions in patients with HF and the hazards of mortality from HF among patients with other medical conditions, and vice versa.

Compliance with ethical standards

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