Association of heart failure with multimorbidity and socioeconomic status

Scholten, Mia

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MIA SCHOLTEN
DEPARTMENT OF CLINICAL SCIENCES MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

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MIA SCHOLTEN is a specialist in General Medicine, Cardiology and Internal Medicine, working at Victoria Vård & Hälsa in Malmö. This thesis an epidemiological study dealing with association of heart failure with multimorbidity and socioeconomic status. The findings of this thesis could enable new approaches to reduce the prevalence of heart failure and its complications.

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Mia Scholten, MD

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Abstract:

Heart failure (HF) arises frequently as a complication of other cardiovascular diseases and is subsequently associated with multimorbidity. HF is also strongly associated with socioeconomic deprivation. Analyzing the prevalence of HF in relation to age, gender, multimorbidity and socioeconomic status (SES) could provide new strategies for the prevention of HF and its complications. This thesis was based on four papers. Papers I and II analyzed the disparities of HF in relation to age, gender, multimorbidity and SES in southern Sweden. Paper III analyzed the associations between HF and malignancies in southern Sweden. Paper IV evaluated the risk for cardiovascular-related readmission within 100 days after discharge in HF patients depending on their comorbidities. **Results**: In Papers I-III, HF had an increased OR with advancing age and multimorbidity level. HF was strongly associated with socioeconomic deprivation, especially in women. Men had a higher OR of HF in all age groups and multimorbidity levels than women. HF patients had an increased OR for malignancies compared to the general population and socioeconomically deprived populations, but a lower OR when compared with multimorbidity. In Paper IV, HF patients with chronic kidney disease, atrial fibrillation or chronic obstructive pulmonary disease had an increased risk for cardiovascular-related readmission within 100 days after discharge, but with a low predictive value. **Conclusion**: HF had a strong association with multimorbidity and socioeconomic deprivation. Men had a higher mean probability of HF than women independent of age, multimorbidity level and SES. HF was associated with a higher risk for malignancies than the general population and socioeconomically deprived population, but a lower risk when compared with the multimorbid population. Chronic kidney disease, atrial fibrillation and chronic obstructive pulmonary disease had only a low impact on the risk for cardiovascular-related readmissions in HF patients in relation to cardiovascular events.

Key words: heart failure, socioeconomic status, malignancy, multimorbidity, readmission, comorbidity, primary health care centre, odds ratio

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Table of Contents

Abstract

Heart failure (HF) arises frequently as a complication of other cardiovascular diseases and is subsequently associated with multimorbidity. HF is also strongly associated with socioeconomic deprivation. Analyzing the prevalence of HF in relation to age, gender, multimorbidity and socioeconomic status (SES) could provide new strategies for the prevention of HF and its complications.

This thesis was based on four papers. Papers I and II analyzed the disparities of HF in relation to age, gender, multimorbidity and SES in southern Sweden. Paper III analyzed the associations between HF and malignancies in southern Sweden. Paper IV evaluated the risk for cardiovascular-related readmission within 100 days after discharge in HF patients depending on their comorbidities.

Results: In Papers I-III, HF had an increased OR with advancing age and multimorbidity level. HF was strongly associated with socioeconomic deprivation, especially in women. Men had a higher OR of HF in all age groups and multimorbidity levels than women. HF patients had an increased OR for malignancies compared to the general population and socioeconomically deprived populations, but a lower OR when compared with multimorbidity. In Paper IV, HF patients with chronic kidney disease, atrial fibrillation or chronic obstructive pulmonary disease had an increased risk for cardiovascular-related readmission within 100 days after discharge, but with a low predictive value.

Conclusion: HF had a strong association with multimorbidity and socioeconomic deprivation. Men had a higher mean probability of HF than women independent of age, multimorbidity level and SES. HF was associated with a higher risk for malignancies than the general population and socioeconomically deprived population, but a lower risk when compared with the multimorbid population. Chronic kidney disease, atrial fibrillation and chronic obstructive pulmonary disease had only a low impact on the risk for cardiovascular-related readmissions in HF patients in relation to cardiovascular events.

Populärvetenskaplig sammanfattning

Hjärtsvikt är ofta ett kroniskt tillstånd som är svårt att bota. Tack vare förebyggande satsningar på bättre livsstil och behandlingsmetoder har patienter med hjärtsvikt fått bättre överlevnad jämfört med tidigare. Totalt har hjärtsvikt dock ökat till ca 64 miljoner bland världens befolkning, vilket utgör den snabbast växande kardiovaskulära sjukdomen globalt. Bland äldre från 65 år är hjärtsvikt den vanligaste diagnosen i höginkomstländer och anledningen till sjukhusinläggning. Dålig livskvalitet hos hjärtsviktspatienterna är den vanligaste orsaken till hjärtsjukvård, vilket innebär minst dubbelt så hög sjukvårdskostnad som den allmänna befolkningen. Sjukvården har en stor arbetsbörda för att ta hand om denna kroniska sjukdom som är associerad med dålig livskvalitet och hög dödlighet. Femårs mortaliteten hos patienter med hjärtsvikt är mer än dubbel så hög jämfört med den allmänna populationen.

Nästan alla invånare i Sverige är listade på en vårdcentral som oftast ligger i närheten av deras bostad. Olika individer har olika grad av sjukvårds- och omvårdnadsbehov. Behoven för de listade patienterna och sammansättningen av patienter listade på en vårdcentral (case-mix) kan variera på grund av de lokala förhållandena där vårdcentralen fysiskt verkar (socioekonomisk position). I primärvårdens uppdrag ingår att fokusera på individens behov snarare än enskilda sjukdomar, varför det är av intresse att öka kunskapen om samsjuklighet och multisjukdom hos patienterna. Eftersom hjärtsvikt är slutstadium av många kardiovaskulära sjukdomar och delar riskfaktorer med många kroniska sjukdomar är den starkt förknippad med multisjukdom. Multisjukdom definieras som samtidig förekomst av minst två kroniska sjukdomar hos samma individ. En del hjärtsviktspatienter är allvarligt sjuka och har ett stort vårdbehov som kräver resurser inom primärvården. Stort fokus ligger på att förbättra den medicinska vården av hjärtsvikt och särskilda vårdförlopp (Standardiserat vårdförlopp). Många vårdcentraler har byggt upp hjärtsviktsmottagningar som framför allt fokuserar på hjärtsjukdomens medicinska behandling.

Socioekonomisk utsatthet är en av de viktigaste riskfaktorerna till hjärtsvikt. Andra kända riskfaktorer till hjärtsvikt som DM, rökning, hypertoni, fysisk inaktivitet och hyperlipidemi förklarar endast en del av den ökade förekomsten av hjärtsvikt i den socioekonomiskt utsatta populationen. Män drabbas i större utsträckning av systolisk hjärtsvikt till följd av ischemisk hjärtsjukdom och har tidigare sjukdomsdebut och högre mortalitet jämfört med kvinnor. Diastolisk hjärtsvikt är däremot dubbelt så vanligt hos kvinnor än hos män, och har oftast hypertoni och klaffel som bakomliggande orsak. Generellt tenderar kvinnor med hjärtsvikt att ha förmaksflimmer, DM, hypertoni, anemi, järnbrist, njursjukdom, artrit, depression och sköldkörtelsjukdomar som samsjukligheter.

Flera studier har påvisat ökad förekomst av cancer hos patienter med hjärtsvikt och DM. Alla dessa tre tillstånd har en gemensam inflammatorisk profil och påverkar varandra i viss utsträckning. Även deras riskfaktorer överlappar varandra med bl.a. övervikt, rökning, fysisk inaktivitet och socioekonomisk utsatthet. Dock förekommer endemiska skillnader mellan förekomst av hjärtsvikt, DM och cancer beroende på miljöfaktorer, kostvanor, ärftlighet och livsstil etc. Prognosen för hjärtsvikt är för närvarande sämre jämfört med många cancerformer. En tidigt ställd diagnos är en förutsättning för att i rätt tid inleda lämplig behandling, förbättra livskvalitet och minska risken för komplikationer.

I delarbete I - III har vi studerat skillnader i förekomst av hjärtsvikt i relation till ålder, kön, SES och multisjukdom inkl. cancer. Utifrån dataregister från Region Skånes databas som innehåller information om ålder, kön och diagnoser hos Skånes befolkning under 2015 kunde vi analysera dessa skillnader. Hjärtsvikt var associerad med socioekonomisk utsatthet. Mellan 40 och 80 års ålder var förekomsten av hjärtsvikt ungefär dubbelt så hög i den mest socioekonomiskt utsatta gruppen jämfört med den mest priviligierade gruppen. Nästan alla hjärtsviktspatienter (99,07%) var dessutom multisjuka. Förekomsten av hjärtsvikt ökade med stigande ålder och grad av multisjukdom. Män hade högre förekomst av hjärtsvikt än kvinnor oavsett ålder, multisjukdom och SES. Mellan den mest socioekonomiskt priviligierade och utsatta gruppen fanns det större skillnad på förekomst av hjärtsvikt hos kvinnor än hos män. Kvinnor hade högre förekomst av multisjukdom oavsett ålder och SES, men lägre andel hjärtsvikt jämfört med män. Hjärtsvikt var associerad med cancer, i synnerhet hematologiska maligniteter. Multisjukdom var en viktigare faktor för cancer än hjärtsvikt, till skillnad från socioekonomisk utsatthet. Män hade högre OR för cancer jämfört med kvinnor, i synnerhet bland de multisjuka.

I delarbete IV har vi analyserat risken för kardiovaskulär relaterad återinläggning inom 100 dagar efter utskrivningen beroende på samsjukligheter hos hjärtsviktspatienterna. Studiepopulationen bestod av 5029 hjärtsviktspatienter i Region Halland som blev återinlagda mellan 2017 - 2019. Resultaten visade att hjärtsviktspatienter med förmaksflimmer, perifer arteriell sjukdom, DM, kronisk obstruktiv lungsjukdom eller kronisk njursjukdom hade högre risk för kardiovaskulär relaterad återinläggning inom 100 dagar efter utskrivning. Både DM och perifer arteriell sjukdom förlorade sin betydelse när vi justerade dessa sjukdomar i samma modell. Genom att jämföra individuell sjuklighetsgrad med logistisk regression och Rasch analys har inte påvisat någon statistisk signifikant skillnad, men det prediktiva värdet var lågt, vilket innebär att andra faktorer har större betydelse för kardiovaskulär relaterad återinläggning inom 100 dagar efter utskrivningen, möjligtvis i kombination med dessa samsjukligheter.

Det är motsägelsefullt att hjärtsvikt hade stark koppling till cancer och låg SES, samtidigt som den socioekonomiskt mest utsatta gruppen hade 35% lägre risk för solida cancertumörer jämfört med den socioekonomiskt mest priviligierade

gruppen. Socialstyrelsen rapporterade nyligen att populationen med hög SES och cancer hade bättre överlevnad jämfört med populationen med låg SES och cancer, vilket delvis beror på att den priviligierade gruppen har större förmåga att ta till sig hälsorelaterad information. Genom att kartlägga cancerformer hos befolkningen tillhörande olika SES och jämföra cancerformer hos patienter med eller utan hjärtsvikt skulle kunna förtydliga dessa skillnader i överlevnad. En del kroniska sjukdomar har större betydelse för cancerutveckling än andra, varför det är angeläget att analysera vilka samsjukligheter som hjärtsviktspatienterna har.

Resultaten i denna avhandling har ökat våra kunskaper om hjärtsvikt, vilket kan bidra till förebyggande interventioner för att minska patientlidande och sjukvårdsbördan.

List of Papers

Paper I

Scholten M, Midlöv P, Halling A: Disparities in prevalence of heart failure according to age, multimorbidity level and socioeconomic status in southern Sweden: a cross-sectional study

Paper II

Scholten M, Midlöv P, Halling A: Disparities in prevalence of heart failure between men and women according to age, multimorbidity level and socioeconomic status in southern Sweden: a cross-sectional study

Paper III

Scholten M, Halling A: Associations of heart failure to prevalence of haematologic- and solid malignancies in southern Sweden: a cross-sectional study

Paper IV

Scholten M, Davidge J, Agvall Björn, Halling A: Comorbidities in heart failure patients that predict cardiovascular readmissions within 100 days - an observational study

Author's contribution to the papers

Paper I

Dr. Mia Scholten contributed with data collection, data analysis, writing and editing the manuscript. Professor Patrik Midlöv provided critical comments and feedback on the manuscript. Professor Anders Halling was involved in data collection, design of the study, data analysis, editing the manuscript and student supervision.

Paper II

Dr. Mia Scholten contributed with data collection and analysis, writing and editing the manuscript. Professor Patrik Midlöv provided critical comments and feedback on the manuscript. Professor Anders Halling was involved in data collection, design of the study, data analysis, editing the manuscript and student supervision.

Paper III

Dr. Mia Scholten contributed with data collection and analysis, writing and editing the manuscript. Professor Anders Halling was involved in data collection, design of the study, data analysis, editing the manuscript and student supervision.

Paper IV

Dr. Mia Scholten contributed with data collection and analysis, writing and editing the manuscript. Dr. Jason Davidge and Dr. Björn Agvall have contributed with data collection and analysis, and editing the manuscript. Professor Anders Halling was involved in data collection and analysis, design of the study, editing the manuscript and student supervision.

Abbreviations

AUC	area under curve
CI	Confidence Interval
CKD	chronic kidney disease
CNI	Care Need Index
COPD	chronic obstructive pulmonary disease
CRT	cardiac resynchronization therapy
CVI	cerebrovascular insult
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate (ml/min)
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFmrEF	heart failure with mildly reduced ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
ICD 10	International Classification of Diseases and Related Health Problems, 10th revision
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MM	multimorbidity
NYHA	New York Heart association
NT-proBNP	N-terminal-pro Brain Natriuretic Peptide
OR	odds ratio
PAD	peripheral artery disease
PHC	primary health care centre
ROC	Receiver operating characteristic
SES	socioeconomic status
TAPSE	tricuspid annular plane systolic excursion

Introduction

The heart is the most important organ responsible for circulation in the whole body. During the lifetime, the heart undergoes changes depending on heredity and comorbidities. Some changes evolve primarily in the heart, like myocardial infarction due to coronary atherosclerosis, ventricular hypertrophy owing to chronic aorta stenosis and bradycardia due to atrioventricular blocks, whilst some changes may be complications of pathological conditions arising from elsewhere in the body. For example, electrolyte imbalance may cause fatal arrhythmias, septicaemia may develop endocarditis, aorta dissection may cause heart tamponade and subsequent sudden death, etc.

The definition of HF is typical symptoms due to reduced cardiac output to supply the circulatory system at rest or during activity [1]. HF develops when the heart fails to relax properly during diastole or contract normally during systole as a consequence of structural or functional impairment [2]. The aetiology of HF varies geographically, with coronary artery disease and hypertension as the main factors in Western countries. Other common diseases underlying HF are valvular heart disease, cardiomyopathy, infection, arrhythmia, congenital heart disease, endocardial disease, pericardial disease, neuromuscular disease, obstructive sleep apnoea, metabolic, infiltrative and storage disorders, as well as excess alcohol use, radiotherapy and cardiotoxic drugs [1-3]. Hyperuricaemia or gout is also associated with increased incidence of HF, most likely contributed by diuretic treatment and shared risk factors like myocardial infarction and metabolic syndrome [4], likewise rheumatoid arthritis, which is independent of coronary artery disease [5].

Diagnosis of heart failure

The typical symptoms of HF are fatigue, breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance and peripheral oedema, usually accompanied by pulmonary crackles and elevated jugular venous pressure [1]. The diagnosis of HF is usually made clinically, but providing individual treatment requires further identification of the aetiology of the cardiac dysfunction.

According to the European Society Guidelines for HF 2021, natriuretic peptides are recommended as an initial investigation in patients with typical symptoms of HF

[1]. The N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is a prohormone with a 76 amino acid N-terminal inactive protein secreted by cardiomyocytes in the heart ventricles as a response to blood overload. This biomarker is conventionally used to evaluate the degree of HF and to differentiate between causes of dyspnoea due to HF from other conditions exhibiting dyspnoea [1]. Elevated natriuretic peptide levels support the diagnosis of HF, but normal levels do not exclude a diagnosis of HFmrEF or HFpEF. Diagnosing these HF subtypes requires further investigation with hemodynamic measurement of left ventricular filling pressure [2].

Echocardiography is the most convenient examination for assessment of cardiac morphology and function like chamber size, left ventricular hypertrophy, hypokinesia, dyskinesia, right ventricular function, pulmonary hypertension, valvular heart disease and diastolic function. Cardiac magnetic resonance imaging is increasingly used for myocardial characterisation and a more accurate estimation of LVEF [6].

Blood tests including iron status, fasting glucose, HbA1c, urea, electrolytes, lipids, liver and thyroid function, full blood count and creatinine are recommended as basic investigations for comorbidities. A 12-lead electrocardiogram and chest radiography could also guide potential therapy.

Epidemiology of heart failure

Data on the global incidence, prevalence and mortality of HF are scarce and unreliable [7]. Available literature about HF epidemiology is derived mostly from high-income countries. Although the incidence and prevalence of HF have decreased during recent decades, the total number of HF cases has increased steadily due to global ageing and population growth [8]. The progressive burden of HF globally was estimated to be approximately 64 million people in 2017, which challenges health care systems [9]. The prevalence of HF varies worldwide due to different diagnosis criteria and underdiagnosed cases, in particular HFpEF. This HF subtype constitutes up to 76% of the unrecognized cases of HF because their unspecific symptoms are easily misinterpreted as deconditioning, obesity, ageing or lung disease [10].

HF corresponds to the fastest growing cardiovascular condition globally, mostly as a complication of other cardiovascular diseases, but can also underly illnesses such as impaired kidney function or cancer [11-13]. Around 2% of all adults are diagnosed with HF in Western countries, where this diagnosis is the most common in people from 65 years of age. HF is also the leading reason for hospital admission in elderly, entailing enormous burden on the health care systems.

A cohort study between 1998 - 2017 was conducted in the UK to identify the incidence of HF. Beyond an increasing prevalence of comorbidities annually, high BMI and tobacco consumption, the most socioeconomically deprived population was diagnosed with HF five years earlier than the most affluent [14]. South Asians and the black group were around 6 vs 9 years younger than whites at HF diagnosis. Even the common comorbidities in HF patients were more prevalent in South Asians and the black group than in the white group, like hypertension and DM [14]. The hospitalisation and mortality rate for HF patients also varies with ethnicity [15]. A Swedish cohort study reported the highest incidence of HF among first-generation immigrants from Iraq and Bosnia, probably due to their high incidence of coronary heart disease and socioeconomic deprivation [16]. Since our study participants represent a heterogeneous population comprised of a substantial number of immigrants with origin from all continents in the world, we expect racial disparities in the incidence and outcome of HF.

In general, men were diagnosed with HF five years earlier than women, probably due to their higher prevalence of ischaemic heart disease [14]. Women have a lower incidence of HF with the most remarkable difference in incidence of HFrEF - they are 65% less likely to develop HFrEF than men [17]. On the other hand, women have significantly higher odds for HFpEF than men, which is a supposedly underdiagnosed condition because even the people at high risk for HFpEF are frequently asymptomatic [18, 19]. Men are predisposed to macrovascular coronary artery disease and myocardial infarction causing HFrEF, whereas women predominately have coronary microvascular dysfunction/endothelial inflammation causing HFpEF [4, 27-29]. Women are more susceptible to postpartum cardiomyopathy and Takotsubo cardiomyopathy [13]. The cardiotoxicity of chemotherapy used for breast cancer treatment is also recognized as a risk factor for non-ischaemic cardiomyopathy in women [20]. In conclusion, women with HFrEF commonly have a higher prevalence of non-ischaemic cardiomyopathy [28, 29], better overall survival and lower risk for hospitalization if compared with men, regardless of EF [4, 33].

Complications of heart failure

Several studies have shown the increased risk of cancer development in HF patients, who experience a worse prognosis compared with cancer patients without HF [21, 22]. Hasin et al. reported that the risk of cancer development increased over time from two years after HF diagnosis, and the incidence of subsequent cancer diagnosis was approximately 70% higher among patients with HF than non-HF controls. Their mortality rate was 56% higher compared to the HF patients who did not develop cancer, probably secondary to limited treatment possibilities and an accelerated burden of complications from the combination of HF and cancer [23]. These two

diseases share many risk factors, such as ageing, smoking and metabolic syndrome [24]. The pathophysiological mechanisms leading to cancer development in HF patients include inflammation, oxidative stress, neuro-hormonal activation and a dysfunctional immune system. This combination of shared mechanisms and risk factors may underlie the rising prevalence of malignancies in HF patients [24].

HF shares many risk factors with common comorbidities, which subsequently result in various degrees of disability and the need for hospitalization. Despite current therapy, the mortality and HF readmission rates within 60 - 90 days after HF discharge approach 15% and 30%, respectively. This early post-discharge period has been coined as a 'vulnerable phase' and accounts for enormous costs annually on HF care [25]. The pathophysiology causing these complications might be associated with persisting filling pressure elevation at the time of discharge and subsequent deterioration of post-discharge haemodynamics. A prior study reported a high risk of clinical events following HF hospitalisation secondary to low up-titration and early discontinuation of guideline-directed medical therapy in three countries with different health care systems and economies (Sweden, UK and US) [26]. These events involved HF hospitalisation or death, which ranged from 40.0 to 86.9 per 100 patient-years across all treatment groups, including ACEi, ARB, beta-blockers, MRA and ARNI [26]. Thus, intensive initiation of HF treatment during the 'vulnerable phase' could reduce the rates of early readmission and mortality [27].

Mortality of heart failure

HF death has increased following the pandemic burden of HF patients. The prognosis of HF patients depends on their treatments and comorbidities, which is comparable with some cancers [28]. Prior studies reported the higher the LVEF, the better the survival rate [29, 30]. However, Davidge et al. revealed no difference in all-cause mortality among the HF subtypes, but patients receiving beta-blockers combined with ACEi had an almost 50% reduction in the mortality rate [31]. Advancing age, elevated NT-proBNP, severe renal impairment (eGFR < 30 mL/min/1.73 m2), as well as the common comorbidities (hypertension, COPD, valvular heart disease, ischaemic heart disease, DM, cerebrovascular insult and atrial fibrillation), had an increased HR for all-cause mortality, meanwhile, no difference in mortality was observed between the genders [31]. A total of 43% of this cohort were not diagnosed with any HF subtype that had a significantly higher mortality, HR 1.27 (95% CI 1.17 - 1.37), possibly as a result of inadequate treatment of HF according to the guidelines [31]. Other non-vascular conditions associated with increased mortality in HF patients are sleep apnoea and hyperuricaemia, which increase with progressive serum uric acid level [32-34].

The mortality rate of HF varies depending on the study population. Younger patients with fewer comorbidities and stable outpatients had a lower mortality rate than those HF patients with frequent hospitalisations [35, 36]. Higher age at admission was associated with an increased mortality rate in HF patients, most likely due to a higher comorbidity burden [37]. The cause of death in HF patients has changed over time. Two decades ago, a Canadian prospective study reported that 66% of HF patients died of cardiovascular causes, of whom 70% had HFrEF and 45% had HFpEF [38]. During recent years, cardiovascular deaths in HF patients have decreased at the cost of a dramatic increase in non-cardiovascular deaths, chiefly reflecting an increase in cancer-related deaths [39].

The mortality of HF also varies with the national income level. High-income countries had the lowest age- and sex- standardised mortality rates followed by an increasing mortality rate depending on decreasing national income level. This correlation between mortality rate and national income level persisted after further adjustment for clinical characteristics: BMI, DM, COPD, tobacco consumption, impaired kidney function, NYHA class, HF duration >1 year, HF aetiology (ischaemic, dilated, rheumatic valvular, non-rheumatic valvular, other), in-patient recruitment, education level, chronic HF treatments (beta-blocker, ACEi, MRA, ICD) [40]. Even the short-term mortality rate rose continuously with decreasing national income levels in HF patients for both all-cause hospitalisation and HF hospitalisation. The HF patients in high-income countries had also the lowest proportion of cardiovascular deaths compared to the countries with lower income levels [40].

An American review has recently reported that people with low SES were more vulnerable as regards a higher incidence of HF, HF hospitalisations, readmissions and mortality compared to their counterparts with high SES [41]. These worse outcomes were supposedly attributed to a higher incidence of risk factors for HF in the socioeconomically deprived population, including hypertension, smoking, DM and obesity [42]. Tailored multifaceted approaches to optimise care coordination, discharge planning, targeted interventions for HF follow-up care and medication adherence have been shown to improve their outcomes in socioeconomically deprived populations [43, 44].

Treatment of left ventricular heart failure

The treatment of HF is primarily oriented on the comorbidities underlying HF. If HFrEF is still symptomatic, the following treatments are recommended to reduce the mortality rate, either cardiovascular or all-cause mortality. All treatment strategies aim to achieve reduced mortality and complications, improve the quality

of life and functional capacity, and prevent recurrent hospitalisations due to exacerbation of HF.

Physical conditioning is recommended to improve the quality of life and exercise capacity leading subsequently to reduced all-cause and HF hospitalisations [45]. Besides non-pharmacologic interventions, pharmacotherapy with ACE-I or an ARNI, beta-blockers, MRA and sodium-glucose cotransporter 2 inhibitors are the cornerstones of treatment for HFrEF. These drugs have evidence to improve survival and reduce the symptoms and risk of HF hospitalisations in patients with HFrEF with the most beneficial effect when used in conjunction [46-50]. Beta-blockers are given to HF patients at a low dose in a clinically stable and euvolemic phase and gradually up-titrated to the maximum tolerated dose. ARNI is recommended in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with ACE-I or ARB. ARBs are recommended for HF patients who do not tolerate ACE-I or ARNI [1]. Diuretics are prescribed for HF patients with congestion to achieve and maintain euvolaemia.

HF patients with an LVEF $\leq$ 35% and receiving $\geq$ 3 months of optimal medical therapy but still symptomatic (NYHA class II–III) are considered for ICD implantation to reduce their risk of sudden death and all-cause mortality, if they have a life expectancy of more than one year with good functional status [51]. Patients with HFrEF and sinus rhythm with a QRS duration $\geq$ 150 ms can be considered for cardiac resynchronisation therapy with a pacemaker or defibrillator (CRT-P/CRT-D), even those with left bundle branch block with QRS duration $\geq$ 130 ms [52]. CRT in these patients has documented enhanced quality of life, improved cardiac function, reduced morbidity and mortality [52, 53]. For those HF patients who, despite optimal medical therapy belong to NYHA class IV, ICD is indicated to bridge the treatment with CRT, LVAD or cardiac transplantation [54-58].

LVAD should be considered if they are refractory to optimal medical and device therapy. Special circumstances are required for these patients including living together with a caregiver who is capable of assisting the patient with the equipment. In the absence of right ventricular dysfunction and/or severe tricuspid regurgitation and other major contraindications like infection, oral anticoagulation, ventricular arrhythmias or renal failure, they should have at least one of the following [1]:

- Low LVEF < 25% or having peak oxygen consumption < 12 mL/kg/min and/or < 50% predicted value, or unable to exercise for HF
- $\geq$ 3 HF hospitalisations during the last year without an obvious cause.
- Continuous need for intravenous inotropic therapy or mechanic circulatory support.
- Reduced perfusion causing progressive end-organ dysfunction without low ventricular filling pressure.

People with advanced HF (NYHA class IIIB or IV) without other therapeutic options except for LVAD are eligible for heart transplantation if the contraindications are excluded [59, 60].

The recommended treatment of HFmrEF is diuretics and sodium-glucose cotransporter 2 inhibitors to reduce hospitalisations or cardiovascular death [61]. ACE-I or an ARNI, beta-blockers, MRA could also be considered in selected patients with HFmrEF [62]. For patients with HFpEF, management is focused on the aetiology and comorbidities besides treatment with diuretics and sodium-glucose cotransporter 2 inhibitors [62, 63].

Treatment of right ventricular heart failure

Right ventricular failure may also contribute to impaired LV filling thus causing reduced systemic cardiac output. Right ventricular failure typically exhibits systemic venous congestion requiring diuretics, but low cardiac output and haemodynamic instability due to arterial hypotension indicate treatment with inotropes in combination with norepinephrine [64].

Primary prevention of heart failure

Some risk factors are acknowledged as common comorbidities of HF, i.e. hypertension, DM, coronary artery disease and hyperlipidaemia. Antihypertensive therapy could prevent or delay HF diagnosis and reduce HF hospitalisations [65]. Using sodium-glucose-cotransporter 2 inhibitors for patients with DM and cardiovascular disease or at high risk of cardiovascular disease is an evident strategy to prevent HF hospitalisations [66]. Statins should be generously prescribed to people with, or at high risk of cardiovascular disease, which also have a preventive effect on HF development and hospitalisations [67, 68].

A Swedish prospective study reported a significantly reduced risk for HF in physically active women compared to non-active, and an increase in BMI from overweight ($25 \leq \text{BMI} < 30$) to obese ($\text{BMI} \geq 30$) almost doubled their risk for HF [69]. Thus, non-pharmacological preventive strategies like physical activity, healthy diet, reduced obesity, alcohol consumption and cigarette smoking are widely recommended to the whole population including those at high risk of HF [70-73].

Aims

The aim of the study was to determine the associations of HF with age, gender, SES and multimorbidity, including malignancies, of the patients listed at PHCs in southern Sweden. We also evaluated the risk for cardiovascular-related readmissions within 100 days after discharge due to common comorbidities in HF patients.

The specific aims of each paper were following:

Paper I: To study the prevalence of HF in relation to age, MM and SES of the population listed at PHCs in southern Sweden.

Paper II: To analyze the disparities in prevalence of HF between men and women according to age, MM level and SES of the population listed at PHCs in southern Sweden.

Paper III: To study the associations between HF and the prevalence of haematologic- and solid malignancies in southern Sweden.

Paper IV: To study the comorbidities in HF patients that predict cardiovascular-related readmission within 100 days after discharge.

Ethical consideration

The study protocols of Papers I – III were approved by the regional Ethical Review Board at Lund University, with application No 2018/778. The studies started after this approval. Anonymized data of the present study were retrieved from the Scania County Council for research purposes. Since only anonymized data were available, the study participants could not be asked for consent to participate. Instead, they were provided for active refusal of participation after publishing information about the planned study in the Swedish local newspaper "Sydsvenskan". Except for the description of the study, this advertisement contained information on how to contact the research manager (first author) for the possibility of active refusal.

Paper IV was approved by The Swedish Ethical Review Authority, Stockholm Department 2 Medicine under registration number 2020-00455. Pseudonymized data were provided by the County Council in Region Halland.

The requirement for informed consent was waived after approval from the Swedish Ethical Review Authority, Stockholm Department 2 Medicine and Lund University since all results were published at a group level and could not be traced to any study participant. All methods in our studies complied with relevant guidelines and regulations as stated in the Declaration of Helsinki. These epidemiologic studies did not involve any biological material from the study participants and were not associated with any medical risk during the study procedure.

Definitions and terminology

Heart failure

HF is a clinical syndrome consisting of cardinal symptoms including dyspnoea, oedema, fatigue, confusion, weight changes, reduced appetite, nausea and increased heart rate, usually accompanied by signs, e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema. It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise [1].

The New York Heart Association's (NYHA) classification is related to the severity of symptoms [1].

NYHA Classifications I - IV:

I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).

II. Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in undue fatigue, palpitation, dyspnoea.

III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes undue fatigue, palpitation, or dyspnoea.

IV. Unable to carry on any physical activity without discomfort. Symptoms of HF at rest can be present. If any physical activity is undertaken, discomfort increases.

HF is categorised as right-sided HF affecting the right side of the heart and left-sided HF affecting the left side of the heart. When both sides are affected, biventricular HF is established. Left-sided HF is practically divided into subtypes depending on the ejection fraction: HF with preserved ejection fraction (HFpEF), mildly reduced ejection fraction (HFmrEF) or reduced ejection fraction (HFrEF) [1]:

- People with HF symptoms and structural and/or functional cardiac abnormalities and/or elevated natriuretic peptides, although when LVEF ≥50%, have HFpEF.

- LVEF between 41% and 49% are classified as *mildly* reduced LV systolic function, i.e. HFmrEF.
- Patients with HFrEF have a significant reduction in left ventricular systolic function, LVEF ≤ 40%.

The diagnosis of right ventricular function is commonly performed using echocardiography, which determines either the quantitative fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) or Doppler tissue imaging-derived systolic S′ velocity of the tricuspid annulus. FAC < 35% or TAPSE < 17 mm indicates right ventricular systolic dysfunction, meanwhile a systolic annular velocity < 9.5 cm/s predicts right ventricular dysfunction [74].

Multimorbidity

People with more comorbidities have an increased risk for HF development [75]. On the other hand, HF is also strongly associated with comorbidities, more than other cardiovascular conditions like PAD, coronary heart disease and cerebrovascular disease [76]. Due to population ageing and an increasing comorbidity burden, more people live with MM worldwide, but the demography has various patterns [77, 78]. The criterium of MM is two or more chronic conditions in the same individual. Comorbidities are often intimately linked to each other because they share risk factors and pathophysiological pathways, e.g. people with ischaemic heart disease have a higher risk for HF development [79].

A European cross-sectional study listed the most common combinations of chronic diseases in the multimorbid population from 50 years of age to compare between the genders. Men had a higher prevalence of comorbidities associated with high mortality rate than women, i.e. DM, heart attack, COPD, cancer, even though the women had a higher total prevalence of MM than men [77, 80-83]. MM was also closely associated with increasing age, BMI and socioeconomic deprivation, besides low quality of life, disability, loneliness and small social network [77, 84]. Many of these risk factors are preventable in both socio-environmental and physical aspects. Thus, MM is probably a response to physiological strains and socio-cultural environment within an individual. The chronic diseases are expected to have a mutual impact on each other: disability may cause loneliness and loneliness might result in further disability. The prevalence of MM has also large variability in European countries and between countries in the same region. MM was most prevalent in Poland, Czech Republic and Portugal, contrasting the lowest prevalence in Switzerland, Denmark and Sweden. Generally, the prevalence of MM was shown

to be related to the physical and sociodemographic characteristics of the population. [77].

Even a rising trend has been observed in the prevalence of MM in low- and middle-income countries. Asia has the most populations in the world that are diagnosed with HF many years earlier than European countries, but still accompanied by a high comorbidity burden and worse outcomes [85, 86]. Significant differences were also observed in the HF registries among Asian regions in comparison with Western countries regarding age, BMI, gender and comorbidities including hypertension, cancer, CKD, DM, atrial fibrillation, coronary artery disease and COPD [87].

People with MM have an increased risk for premature death and account for a substantial burden for health care requiring more frequent hospitalisations with longer lengths of hospital stay, and comprise 78% of all consultations in primary care in high-income countries [88, 89]. An increasing number of comorbidities indicates polypharmacy, which may also contribute to the development of MM. For example, oral steroids prescribed for polymyalgia rheumatica may cause DM, cataracts and osteoporosis as additional chronic conditions. Simultaneous administration of Non-Steroidal Anti-inflammatory medication for arthritis may cause gastrointestinal bleeding. Thus, increasing polypharmacy and complexity of the chronic conditions may have a mutual impact on each other, which subsequently results in worse outcomes and prognoses.

In this context, to prevent and heal a single disease could implicate less development of comorbidities as many conditions are strongly clustered to each other. A strategy for medical education, research and organisation is required to consider the different patterns of MM and individual physical and socioeconomic conditions.

Socioeconomic status

Socioeconomic injustice is a driver of health inequalities. Health inequalities at the population level are not primarily produced by individual behaviour, but rather a matter of the wider cultural environments, social and economic circumstances in which we are born, grow, live, work and age [90]. Health inequality is usually a consequence of the systematic differences in health that exist between areas or groups, social classes, for example by gender, age, race or place. Since they are socially produced, they are potentially preventable. Furthermore, inequalities in health are not restricted to differences between the most socioeconomically privileged and deprived groups but exist across the entire social gradient: the lower the social position, the worse the health. Health inequalities are universal and implicate higher rates of morbidity and mortality in lower SES [90, 91].

Health inequalities represent a pressing societal and policy issue as these result in unnecessary premature deaths, entailing large economic costs as a consequence of higher health care burden and lower productivity [92]. Reducing the socioeconomic gradient in health therefore requires measures that affect all of us, and not only the most socioeconomic deprived people. Populations with high vulnerability to illness are even more disadvantaged than can be determined by a disease-by-disease approach because of the way morbidity clusters in these groups, which requires more resource consumption than the total costs for different diseases [93].

We applied the term Care Need Index (CNI) [94] to divide the PHCs into 10 groups depending on their socioeconomic status. CNI is based on different measures within each group, which in our study characterised the patients listed at different PHCs in Scania. Those patients listed at PHCs belonging to the most socioeconomically affluent population were assigned to the CNI 1 percentile; those patients listed at PHCs belonging to the most deprived population were assigned to the CNI 10 percentile [94].

The socioeconomic variables for CNI are comprised of:

- Age over 65 years and living alone
- Foreign born (Eastern Europe, Asia, Africa and South America)
- Unemployed between 16 - 64 years
- Parent living with children aged 17 or younger
- Individuals from one year who moved into this area
- Low education between 25 - 64 years
- Age younger than five years

Methods

Study design: Paper I - III had a cross-sectional design and were register-based, descriptive and non-interventional. Paper IV was an observational study.

Data collection and study population

Paper I - III

The study population was comprised of almost one million inhabitants from 20 years onwards living in Scania in the last week of 2015. The Scania County Council health care register contained anonymised information about the study participants including age, gender, SES and diagnostic data.

The data were collected concerning diagnoses at each consultation at all health care centres in both primary- and secondary health care. A total of 152 PHCs were in operation in Scania during 2015. On average, 8,587 patients (95% CI 7971.49 - 9292.88) were listed including 133 patients with HF (95% CL 122.60 to 143.80) at each PHC. The study population was divided into age groups 20 to 80, enclosing 10-year intervals in each age group: the age group 40 included inhabitants aged 40 to 49, the age group 60 included inhabitants aged 60 to 69, and so on. The age group 80 covered all inhabitants aged 80 years onwards. MM was estimated by compiling the number of chronic conditions in every patient. To study the degree of MM in relation to other variables, the multimorbid population was categorised into groups MM0 (less than two chronic conditions), MM1 (two to four chronic conditions), MM2 (five to nine chronic conditions), and MM3 (10 chronic conditions or more).

Diagnoses were recorded in accordance with the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD 10) (Paper III, Appendix Table 1). The diagnosis code I50 encompassed all subtypes of HF. The prevalence and ORs of MM, general population, HF, DM, haematologic- and solid malignancies were analysed separately.

Paper IV

The study participants were recruited if they obtained an ICD -10 diagnosis between 2013 -2020 including HF, hypertension, DM, ischaemic heart disease, PAD, acute myocardial infarction, CVI, atrial fibrillation, CKD, valvular heart disease, COPD (Paper IV, Appendix Table 1). Only the first hospitalisation of each patient was included if patients were admitted to hospital more than once during the study period. The registration of readmission during the 100 day-study period was performed if the readmission was caused by a cerebrovascular disease (Paper IV, Appendix Figure).

Study procedures

Paper I and II

We applied the term Care Need Index (CNI) [94] to divide the PHCs into 10 groups depending on their SES. CNI is based on different measures of a group, in this case characterising all patients listed at different PHCs in Scania. Those patients listed at PHCs belonging to the most socioeconomically affluent percentile were categorised to CNI 1, and those patients listed at PHCs belonging to the most deprived percentile were categorised to CNI 10 [94].

Paper III

The prevalence of haematologic- and solid malignancies was analysed separately stratifying for genders, age groups and MM levels. Multivariable logistic regression was used to determine the associations between different variables in more complex models. We compared the ORs for haematologic- and solid malignancies using the following variables: age, gender, HF, DM, SES and MM levels.

Paper IV

A population-based retrospective study with 5,029 study participants having a diagnosis of HF and 10 common comorbidities was conducted in Region Halland. The participants were admitted and discharged during 2017 - 2019. Competing risk regression was applied to estimate the HR of the 10 comorbidities for cardiovascular-related readmission within 100 days after discharge. The 10 comorbidities were utilised for a composite measure to construct dichotomous indicator variables and Rasch analysis to evaluate their individual comorbidity level. Logistic regression generated ROC and AUC to analyse how well the model

explained the probability of readmission within 100 days after discharge or death in these HF patients according to their individual comorbidity level.

Statistical analyses

We analysed data from 981,388 (about a tenth of the Swedish population) citizens aged 20 years and older living in Scania in 2015.

Descriptive analyses were performed using frequencies, percentages and cross-tabulations. Chi-squared-test was used to calculate the p-values and the limit for statistical significance was a P-value < 0.05. Associations between the variables were calculated using univariate and multivariate statistics. The figures only exhibited the linear predictions of the fully adjusted models. Delta-method was applied to calculate the predicted mean probability of HF as average marginal effects and contrasts.

Paper I: The mean probability of HF was analysed between all CNI groups and different MM levels.

Paper II: The mean probability of HF was estimated in relation to MM levels, genders and CNI percentiles.

Paper III: Multivariate logistic regression was performed to analyse the probability for haematologic- and solid malignancies in relation to age, gender, SES, MM levels, HF and DM.

Paper IV: We compared the prevalence of 10 common comorbidities in relation to age groups, HF subtypes and levels of their renal function. Competing risk regression was applied to estimate the HR in 10 common comorbidities for readmission within 100 days after discharge. The HR was stratified for age, gender, HF subtype, levels of NT-proBNP and renal function. Considering the substantial comorbidity overlap within HF patients, the comorbidities with statistically significant HR were adjusted in the same model to compare with the HRs for these comorbidities separately.

STATA version 16.0, 17.0 and 18.0 (Stata Corporation, Texas, USA) were used for statistical analyses and artworks.

Cross-tabulations

A cross-tabulation is used to exhibit the relationship between two or more variables. Different variables are placed on the x-axis and the y-axis enabling the analysis of their underlying relationships within the survey results.

Logistic regression

Logistic regression is widely used in various fields, including social sciences, machine learning and most medical fields. The goal of logistic regression is to use the dataset to create a predictive model of the outcome variable. Logistic regression is used to calculate the OR for measurement of being a case in the exposed group divided by the odds in the unexposed group. Binary variables (dependent variables with two categories) are widely used in statistics to model the probability of a certain event taking place. Binary variables can be generalised to categorical variables when there are more than two possible values, and binary logistic regression generalises to multinomial logistic regression.

Multinomial logistic regression was frequently applied in our study to compare the associations of different variables in relation to each other. In Paper I, logistic regression was applied to estimate the association between HF and SES, age and MM. In Paper II, we used logistic regression to further analyse the disparities in mean probability of HF between the genders. In Paper III, logistic regression was conducted to calculate the associations between HF and malignancies stratifying for age, MM, gender and SES.

Delta-method

The Delta method is applied to derive the asymptotic distribution of a random variable. It is a conventional method from the early 20th century and is usually utilised to derive standard errors and confidence intervals for functions of parameters whose estimators are asymptotically normal [95].

In Paper I, the Delta method was applied to exhibit the differences in mean probability of HF between the MM levels and CNI percentiles, respectively.

In Paper II, the Delta method was used to compare the mean probability of HF between the genders stratifying for CNI percentiles and MM levels.

Chi-squared test

The chi-squared distribution is primarily utilised for hypothesis testing and, to a lesser extent, for confidence intervals for population variance when the underlying distribution is normal. For hypothesis tests, the sampling distribution approaches the normal distribution as the sample size increases. Chi-squared test is also widely used because it turns up as the large sample distribution of generalised likelihood ratio tests, which commonly provide the highest power to reject the null hypothesis.

However, the normal and chi-squared approximations are only valid asymptotically. Because the test statistic is asymptotically normally distributed, provided the sample size is sufficiently large, the distribution used for hypothesis testing may be approximated by a normal distribution.

Considering our large study population, we applied Chi-squared test to determine whether there is a statistical significance between the expected prevalence and the observed prevalence (Paper III).

Competing risks regression

Competing risk arises when more than one possible outcome is possible during follow-up for survival data, and the occurrence of an outcome can preclude the outcome of interest. In other words, individuals experiencing the competing risk event in a competitive analysis have no probability of experiencing the event of interest [96].

Cumulative incidence derived from Kaplan-Meier estimator is always larger than that obtained by counting for competing risks. In Kaplan-Meier estimation, an individual is removed from the risk set when the individual experiences a competing event. Within the competing risk framework, the individual is an event in the calculation of overall survival probability. Therefore, the overall survival of any event is lower when competing risks are considered.

In Paper IV, competing risks regression was utilised instead of Cox proportional hazard regression to achieve higher accuracy, because using competing risks regression factored in the high mortality rate within the study population [97].

ROC curve

ROC (Receiver operating characteristic) is a graphical plot illustrating the performance of a binary classifier model or multiclass classification at varying threshold values. The ROC curve demonstrates how well the prediction correlates with a plot of the true positive rate against the false positive rate at each threshold setting. The true positive rate defines how many correct positive results occur among all positive samples available during the test. Meanwhile, the false positive rate defines how many false positive results occur among all negative samples available during the test. A ROC space is defined by a false positive rate and a true positive rate, which depicts relative trade-offs between true positive and false positive. The diagonal divides the ROC space sharing the points above the diagonal, representing good classification results (better than random), from the points below

the diagonal, representing bad results (worse than random). The best possible prediction is the point in the upper left corner (0.1) of the ROC space, representing 100% sensitivity and specificity. AUC (area under the curve) is estimated as the value of the prediction, and the predicted value diminishes if the prediction approaches the random classifier (diagonal).

In Paper IV, competing risk regression was applied to predict the risk for cardiovascular- related readmission within 100 days after discharge, using 10 common comorbidities as variables. The individual comorbidity level was calculated with logistic regression and Rasch analysis and demonstrated in ROC as AUC.

Rasch analysis

A Rasch model represents the structure fitted for data in order to obtain measurements from the data, i.e. it provides a criterion for successful measurement. The Rasch model provides diagnostic information regarding how well the criterion is met and how well items or questions on assessments work to measure the ability or trait. In the Rasch model, the probability of a correct response is modelled as a logistic function of the difference between the person and item parameter. For example, item parameters represent the difficulty of items in educational tests, while person parameters represent the ability of people who are assessed. High probability of a correct response on that item is expected if a person's ability is high in relation to the difficulty of an item. When a person's ability is equal to the difficulty of the item, by definition, there is a 0.5 probability of a correct response in the Rasch model. The Rasch model is applicable in different areas including market science, educational research, agriculture and health science.

In Paper IV, we applied Rasch analysis to estimate the individual comorbidity level.

Results

I´m no special *talent. I´m only passionately curious.*
- Albert Einstein

Paper I

A total of 2.06% (20,193 patients) of the study population had HF. The prevalence was low, under 40 years of age in the whole study population but increased consistently at least twofold in all age groups and CNI percentiles from age group 30. Among the elderly population from 80 onwards, the prevalence of HF was 17.31% (Paper I, Table 1). The socioeconomically deprived population was more likely to have a younger population under 40 years of age, contrasting the affluent population who were dominated by individuals of middle age onwards. Only 33.25% were 50 years and older in the population belonging to the most deprived CNI percentile, which was lower than other CNI percentiles in the study population (Paper I, Table 1).

38.40% (377,161 patients) of the study population had MM and the prevalence was correlated to the individual SES. The people belonging to the most socioeconomically deprived CNI percentile had the highest prevalence of MM between 40 - 60 years, meanwhile the socioeconomically most affluent CNI percentile had the highest prevalence of MM from 60 years onwards when compared to other CNI percentiles. Independent of SES, the prevalence of MM increased progressively with advancing age: the age group 20 had 14.89% MM, which increased to 86.22% in the age group 80 (Paper I, Table 1). Almost all HF patients (99.07%) fulfilled the criteria for MM, but only 5.30% (20,005 patients) of the multimorbid people had HF (Paper I, Table 1). The MM1 (2 - 4 chronic conditions) group included 1.49% patients with HF, the MM2 (5 - 9 chronic conditions) group included 11.16% patients with HF, and the MM3 (>10 chronic conditions) group included 39.28% patients with HF. The predicted mean probability of HF adjusted for age and MM level is shown in Paper I, Figure 1. Although the prevalence of HF increased consistently with advancing MM level, most of the HF patients (58.18%, 11,748 patients) belonged to the MM2 group, followed by the MM3 group comprising 21.70% (4,382 patients) of all HF patients. Only 19.19% (3,875 patients) of all HF patients belonged to the MM1 group. Notably, the MM1 group

had a total of 260,764 patients, the MM2 group had 105,241 patients and the MM3 group had 11,156 patients.

The mean probability of HF was strongly correlated to individual SES (Paper I, Figure 2). The prevalence of HF in the socioeconomically most deprived CNI percentile was estimated to be approximately double as high as in the most affluent CNI percentile between 40 and 80 years of age (Paper I, Table 1). Even significant disparities in the probability of having HF were observed when comparing the most deprived CNI percentile with other CNI percentiles of the PHCs, although at much lower levels (Figure 1). The individuals belonging to the most deprived CNI percentile had the highest prevalence of HF from age group 40, which persisted when their prevalence of MM was lower than other CNI percentiles from 70 years of age. For comparison, the most socioeconomically affluent CNI percentile had a relatively low prevalence of HF in most age groups, even from age group 60 as their prevalence of MM became higher than the more deprived CNI percentiles (Paper I, Table 1). The prevalence of HF had a different correlation to SES when compared with MM, although both were strongly associated with ageing (Paper I, Table 1).

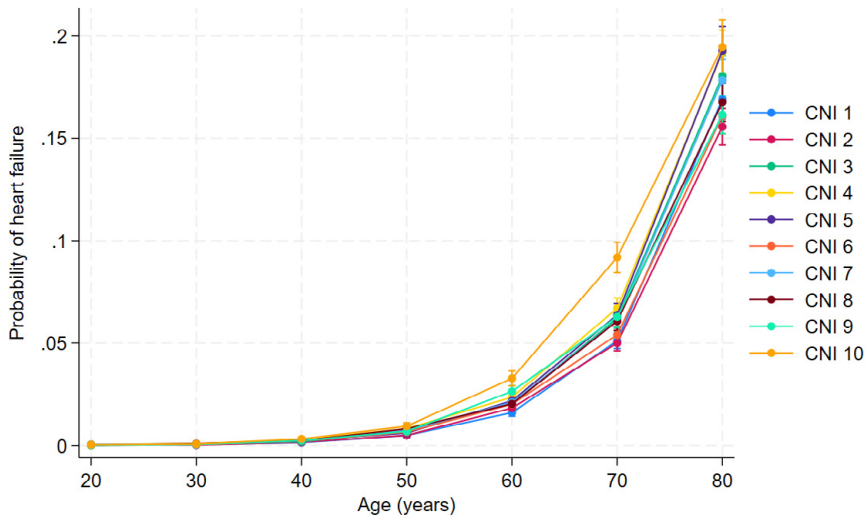

Figure 1. The predicted mean probability of heart failure adjusted for all CNI (Care Need Index) percentiles adjusted for age with 95% confidence intervals, using Delta-Method.

Paper II

Of the 981,383 study participants, 50.85% were women and 49.15% were men. The women had a lower prevalence of HF than men (1.93% vs 2.19%). Men had an increased OR for HF, 1.70 (95% CI 1.65–1.75), when compared to women. The difference in prevalence and mean probability of HF between the genders persisted in all age groups and became increasingly obvious with advancing age and reached 3.01% vs 0.03 in the age group 80 (Paper II, Figure 1). Men had also a higher prevalence of HF in all MM levels than women with an increasing difference in probability of having HF from MM1 to MM3 (Paper II, Figure 2). Using women as reference, the predicted mean probability of HF as a comorbidity in men was 0.06 (95% CI 0.05 − 0.06) in the age group 70 at MM2 level (5-9 chronic conditions), and 0.10 (95% CI 0.07 − 0.13) at MM3 level (>10 chronic conditions).

The women had a higher prevalence of MM than men (42.82% vs 33.89%), which was observed in all age groups and CNI percentiles, but their prevalence of HF was consistently lower if compared to men. Independent of SES, women also had a lower prevalence of HF among the multimorbid patients than men (Paper II, Table 1).

In the whole study population, women belonging to the socioeconomically most affluent CNI percentile had the lowest prevalence (1.55%) of HF, contrasting men belonging to the most deprived CNI percentile had the highest mean probability of HF. Men listed at the PHCs with the most deprived CNI percentile had the highest prevalence of HF between 50 to 80 years of age, whereas the women belonging to this CNI percentile had the highest prevalence of HF from 60 years onwards, if compared to the more affluent CNI percentiles (Paper II, Table 1). Women had a more pronounced disparity in probability of HF between the most affluent and deprived CNI percentile than men, especially in the age group 80 where the disparity was estimated to be 14 times higher compared to men (Paper II, Figure 3).

Women had a lower predicted mean probability of HF than men and the difference increased with advancing age in most CNI percentiles. Most values of the difference in probability from age group 50 were statistically significant except in the CNI percentile 7 and 10, where the elderly from 80 years had no difference in mean probability of having HF between the genders (Paper II, Figure 4).

Paper III

The prevalence of HF in the study population was 2.06%, of whom 28.04% had DM as a comorbidity. A total of 0.39% of the study population had haematologic malignancies and 4.97% had solid malignancies (Paper III, Table 1), which was lower if compared to the people with HF (1.73% had haematologic malignancies and 16.60% had solid malignancies). Although the total prevalence of DM was more

than three times higher than HF (6.50%), their prevalence of haematologic- and solid malignancies was only 0.83% and 10.47%, respectively (Paper III, Table 1). The HF patients in the MM1 and MM2 groups (with 2 - 9 chronic conditions) had a higher prevalence of haematologic malignancies compared to the general population, but not the HF patients belonging to the MM3 group (having 10 chronic conditions or more). Regarding solid malignancies, HF patients had a lower prevalence than the general population with MM of all levels (Paper III, Table 1).

When HF was adjusted for age and gender, the OR for haematologic malignancies was 1.69 (95% CI 1.51 - 1.90), and the OR for solid malignancies was 1.21 (95% CI 1.16 - 1.26) (Paper III, Model B, Tables 2 and 3). When DM was added to the multivariate logistic regression, these ORs decreased slightly. No statistical significance was observed for the probability of having haematologic malignancies in DM patients, but they had an increased OR for solid malignancies, 1.07 (95% CI 1.04 - 1.10), when adjusted for HF, age and gender (Paper III, Model C, Tables 2 and 3). SES had no striking impact on the ORs of HF and DM when added into Model D, nor on the ORs for haematologic malignancies (Paper III, Model D, Table 2 and 3). However, the risk for solid malignancies reduced largely with increasing socioeconomic deprivation, resulting in a 35% lower risk in the most socioeconomically deprived CNI-percentile compared to the most affluent CNI-percentile (Paper III, Model D, Tables 2 and 3). The ORs of gender, age and SES remained statistically significant when MM was further adjusted into Model E, meanwhile HF and DM lost their significance for both haematologic- and solid malignancies (Paper III, Tables 2 and 3).

The ORs for solid malignancies were lower than the ORs for haematologic malignancies in the multimorbid patients at all levels (Paper III, Model E, Tables 2 and 3). Both haematologic- and solid malignancies had an increasing OR with advancing age, but MM had a higher probability for haematologic malignancies than all age groups (Paper III, Model E, Table 2). Compared to solid malignancies, only the multimorbid patients belonging to the MM3 group (10 chronic conditions or more), with HF and DM included, had a higher OR than all age groups (Paper III, Model E, Table 3). Women had a lower probability for both haematologic- and solid malignancies than men, which was highlighted when further adjusted for MM (Paper III, Tables 2 and 3).

Paper IV

This study included 10 common comorbidities in HF patients and their prevalence of atrial fibrillation was 58%, PAD 5%, CVI 16%, valvular heart disease 21%, hypertension 75%, ischaemic heart disease 46%, acute myocardial infarction 19%, CKD 23%, DM 26% and COPD 18% (Paper IV, Table 1). Only a few of the HF

patients with atrial fibrillation, ischaemic heart disease, PAD, CVI, valvular heart disease, acute myocardial infarction, hypertension, CKD, DM or COPD as comorbidity were younger than 50 years of age (Paper IV, Table 1). The majority of the HF patients with the comorbidities acute myocardial infarction (61%), DM (64%), COPD (67%), ischaemic heart disease (71%), PAD (74%), valvular heart disease (75%), hypertension (75%), atrial fibrillation (77%), CKD (77%) or CVI (80%) were even older than 75 years of age (Paper IV, Table 1).

Of these 10 common comorbidities in HF patients, only atrial fibrillation (HR 1.22, 95% CI 1.09 - 1.37), COPD (HR 1.17, 95% CI 1.03 - 1.34), CKD (HR 1.29, 95% CI 1.12 - 1.48), PAD (HR 1.28, 95% CI 1.03 - 1.61) or DM (HR 1.13, 95% CI 1.00 -1.27) had an increased HR for cardiovascular-related readmission within 100 days after discharge (Paper IV, Table 2). When adjusting the HF patients with atrial fibrillation, COPD, CKD, PAD or DM simultaneously, DM and PAD lost their significance for increased risk of readmission, but not the comorbidities CKD, atrial fibrillation or COPD.

The most prevalent comorbidity causing an increased risk for readmissions in our study was atrial fibrillation (58%) (Paper IV, Tables 1 and 2). Although hypertension was the most prevalent comorbidity in HF patients (75%), they had no increased risk for cardiovascular-related risk for readmissions within 100 days after discharge. Neither CVI nor valvular heart disease as a comorbidity in HF patients had any increased risk for readmissions (Paper IV, Tables 1 and 2). Coronary artery disease is depicted as the predominant risk factor in more than 50% of HF patients in North America and Europe [41], but the patients with ischaemic heart disease or acute myocardial infarction did not exhibit any increased risk for cardiovascular-related readmission within 100 days after discharge in our study. Nonetheless, PAD accounted for the smallest patient group of comorbidities, constituting only 5% of HF patients, and was associated with an increased risk for readmissions (Paper IV, Tables 1 and 2). A prior study provided a more extensive description of this study population, please see Table 1 in this article [97].

All comorbidities were used as dichotomous indicator variables, or by constructing a comorbidity measure of the 10 comorbidities using Rasch analysis for calculation with models of increasing complexity using logistic regression. Similar values were obtained as results of ROC analysis after the univariate logistic regression using the comorbidities as dichotomous indicator variables (0.57; 95% CI 0.55 - 0.59) (Paper IV, xb1, Figure 1) comparing Rasch analysis to estimate individual comorbidity level (0.56; 95% CI 0.54 - 0.57) (Paper IV, xb1, Figure. 2). After adding the variables NT-proBNP and renal function into the logistic regression or Rasch analysis, the AUC was significantly improved (Paper IV, xb5, xb6, Figure 1 and 2). Despite ROC analysis after the most complete models, both logistic regression with the comorbidities as dichotomous indicator variables and Rasch analysis resulted in low values with AUC of 0.63 (95% CI 0.61 - 0.64) and 0.62 (95% CI 0.60 - 0.64), respectively (Paper IV, xb6, Figure 1 and 2).

Discussion

Prior epidemiologic studies have consistently shown that societal advantages and disadvantages entail consequences on public health. Identifying societal characteristics and the SES-related pattern of disease has been an urgent issue for social epidemiologists. In this thesis, we have analysed the epidemiology of HF and its association with MM and SES. A growing and ageing population challenges the health care system to provide care programs for the management of this ever-increasing patient category with HF and surrounding MM. Hopefully, we have gained knowledge in this area enabling novel approaches to improve the quality of life and outcomes in the general population.

Paper I

We have shown an increased probability of HF in relation to advancing age, MM level and socioeconomic deprivation. Although both HF and MM are strongly associated with advancing age, they have different correlations to individual SES. The most pronounced disparity in prevalence of HF was observed between 40 and 80 years: the most socioeconomically deprived CNI percentile had approximately double as high as the most affluent CNI percentile. The differences in probability of having HF between the most socioeconomically deprived CNI percentile and other CNI percentiles were less prominent.

The population listed at PHCs with socioeconomically deprived CNI percentiles had a low average age compared to the affluent population. The most socioeconomically deprived CNI percentile had the highest prevalence of HF from 40 years of age and the lowest proportion of the population (33.25%) from 50 years if compared to the more affluent CNI percentiles, which indicates that they were probably affected by diseases with higher mortality if compared to the affluent population.

An American cohort study revealed an increased risk for HF incidence during the life course for socioeconomically deprived people, but low SES as a risk factor was more significant for HF development during mid-to-older adulthood [98]. This phenomenon could explain our findings of the highest prevalence of HF from 40 years onwards in the most socioeconomically deprived CNI percentile. Since HF usually arises in the elderly as a complication of organ damage across decades,

socioeconomic deprivation is supposed to have a rather indirect impact on HF development, for example by influencing physical inactivity, poor diet and smoking in youth. The same cohort reported also a higher incidental risk of HF in blacks compared with whites within the same SES levels [98], which could also explain our results as immigrants are generally more socioeconomically disadvantaged than natives in Sweden.

Almost all HF patients were concomitantly multimorbid in our study. This strong association between HF and MM probably emerged from pathophysiological pathways of the comorbidities in HF patients, which might deserve a perpetuating factor. A population-based cohort study enrolling four million participants has shown that HF patients with three or more chronic comorbidities increased from 68% in 2002 to 87% in 2014, which can be partly explained by the enhanced lifespan in HF patients due to improved management [99]. An increased comorbidity burden, regardless of being cardiovascular or not, in turn, could deteriorate HF and survival [100, 101], which is congruent with our findings as the multimorbid patient groups diminished with increasing MM level, possibly due to an increasing mortality rate.

Paper II

Men had a higher prevalence of HF than women, 2.19% (10,563 patients) vs 1.93% (9630 patients), respectively. Men had a higher mean probability of HF at all age groups and MM levels than women, which became more obvious with advancing age and MM level. Even among the multimorbid population, women had a lower prevalence of HF than men in all CNI percentiles. HFpEF is the subtype incorporated with the highest prevalence of misclassification among all HF subtypes [10], which is also the subtype affecting women to a greater extent than men. This underdiagnosed subtype could partly explain the difference in HF prevalence between the genders in our study.

Women listed at the PHCs belonging to the most affluent CNI percentile had the lowest prevalence in the whole study population, in contrast to men listed at the PHCs with the most deprived CNI percentile having the highest mean probability of HF.

The discrepancy in mean probability of HF between the most affluent and deprived CNI percentile was more pronounced among women compared to men, suggesting socioeconomic deprivation constitutes a more important predictor for HF in women than men. According to the Swedish Heart Failure Registry, women with HF were largely more socioeconomically deprived when compared with men, which is accompanied by differences in use of care and therapy adherence [102], but our results were still convincing concerning the disparities between the genders and SES.

The Swedish Heart Failure Registry population was comprised of 42,987 patients, 37% were females, who were older and more symptomatic than men [103]. 55% of the HFpEF patients were women and 45% were men; 39% of the HFmrEF patients were women and 61% were men; only 29% of the HFrEF patients were women and 71% were men. After adjustments, women had a significantly lower mortality rate than men across all HF subtypes, particularly at lower EF percentages [103]. Men with HF had a higher prevalence of DM and ischaemic heart diseases as comorbidities than women, which are also associated with an increased mortality rate [103-105]. Other studies presented different sets of comorbidities with various effects on the incidence of HF and mortality rate in men and women, e.g. the combination of anaemia and coronary artery disease with either DM or hypertension had a higher relative mortality risk in HF patients compared with the combination of three comorbidities, hypertension, anaemia, and atrial fibrillation [101, 106]. In accordance with our data, women had a higher prevalence of MM, but a lower prevalence of HF and a larger proportion of elderly over 80 years than men, regardless of SES.

A British trial over two decades also reported that men with HF had a higher prevalence of comorbidities associated with worse survival including atrial fibrillation, stroke, COPD, ischaemic heart disease, DM and cancer compared to women, who had a higher prevalence of asthma, obesity, osteoarthritis, hypertension, depression and anaemia [14, 107]. People in the socioeconomically most deprived group were four years younger than the most affluent group at HF diagnosis and had a significantly higher prevalence of most comorbidities, in particular obesity, IHD, COPD and DM. Compared to the most affluent group, this group also had more smokers and a higher prevalence of the most established risk factor for HF - namely IHD [14, 108].

Other factors underlying our results might be the effect of sex-based differences in the physiology of the cardiovascular system and the progression of cardiovascular disease depending on sex hormones [103]. Oestrogen is considered to have a cardioprotective effect, possibly causing the sex-based differences in cardiac physiology. However, this sex difference in cardiac physiology was attenuated when comparing postmenopausal women with age-matched men, which could explain our results that women are generally older at HF diagnosis [109]. Men with chronic HF and typical cardiovascular risk factors, i.e. metabolic syndrome with DM, are prone to develop testosterone deficiency, which subsequently is associated with increased hospitalizations and mortality [110].

Paper III

Compared to the general population, people with HF had an increased OR of 1.69 (95% CI 1.51 - 1.90) for haematologic malignancies and 1.21 (95% CI 1.16 - 1.26) for solid malignancies, when adjusted for gender and age. This difference in OR between haematologic and solid malignancies in HF patients might be attributed to a stronger dependence on cardiac output and blood supply in the bone marrow than the rest of the body. When MM was added to the more complex multivariate models, MM had a steeply rising OR with advancing MM level, which attenuated the increased risk of HF and DM for haematologic- and solid malignancies to null value. These results emphasize the close relationship between MM and malignancies contributed by both HF and DM in our study. After all, the MM1 group had higher ORs for haematologic malignancies and solid malignancies than HF and DM adjusted together, probably due to combination with other chronic conditions.

Both haematologic and solid malignancies had a rising OR with advancing age, but decreased dramatically after adjustment for MM. For haematologic malignancies, advancing age lost its significance completely compared to MM, meanwhile only the MM3 level, including HF and DM, was a more important factor than advancing age for solid malignancies. Among the multimorbid population, only those with HF belonging to MM1 and MM2 levels had a higher prevalence of haematologic malignancies compared to the general population, meanwhile the HF patients belonging to MM3 group had a lower prevalence. As the MM3 group was the smallest patient group in the multimorbid population, we hypothesise that the HF patients, which belonged to MM1 and MM2 levels, developed more haematologic malignancies due to their lower mortality rate compared to the MM3 group.

The people with HF or DM had a higher prevalence of haematologic- and solid malignancies than the general population, meanwhile the multimorbid population had a higher prevalence of solid malignancies than the people with HF or DM. Although the total prevalence of DM (6.50%) was approximately three times higher than HF (2.06%), the HF patients had a higher prevalence of both haematologic- and solid malignancies than the people with DM. Although 28.04% of the HF patients had DM, the OR for solid malignancies decreased negligibly when further adjusted for DM. A meta-analysis recruiting about a half million HF patients, with 27.58% DM as comorbidity, was carried out to estimate their incidence of cancer. Compared to the patients without HF, who only had 14.49% DM, the HF group had HR 1.43 for cancer, 1.63 for haematological cancer, 1.28 for breast cancer, 1.89 for lung cancer and 1.32 for colorectal cancer, but no difference was observed in the incidence of prostate cancer between these groups [112]. Interestingly, these values did not change significantly when comparing the follow-up time between less than five years or at least five years, neither the sample size lower than 100,000 or at least 100,000. Consistent with our results, DM possibly had a potential positive

effect on the incidence of cancer among HF patients [112]. The prevalence of DM in HF patients and the increased risk for cancer were also representative of our data.

The socioeconomically affluent CNI percentiles had a significantly higher risk for solid malignancies than the most deprived CNI percentile when adjusted for gender, age, HF, DM and MM. A retrospective British cohort study enrolled HF patients of different ethnicities (91% whites, 1.7% South Asia and 1% black). The most socioeconomically affluent group had a higher annual growth rate of cancer than the most deprived group. The white group had a significantly higher prevalence of cancer, followed by the black group and South Asian group [14]. This combined disparity reliant on SES and ethnicity might also explain the findings in our study.

The increased prevalence of malignancies in HF patients might be multifactorial and bidirectional. Both conditions are characterised by oxidative stress and inflammatory activity with a detrimental effect on each other [113, 114]. Suggesting their common risk factors and overlap in metabolic pathways, HF is one of the most reported incident comorbidities after a cancer diagnosis. The incidence of HF increased with time and was much higher at five years after cancer diagnosis compared to matched controls [115]. An increased risk of HF was observed in survivors of non-Hodgkin lymphoma, leukaemia, multiple myeloma, breast, bladder and kidney cancer, supposedly contributed by cancer treatments [20]. Haematologic, oesophageal, kidney, lung and ovarian cancer were associated with over 50% increment in risk of HF development, which might be caused by some specific mutations in hematopoietic cells [115, 116]. Due to earlier cancer detection and improved management, the amount of cancer survivors has increased, which is a challenge for the health care system as the survivors experience an enhanced risk for MM. MM was up to three times more common among cancer survivors than the general population, especially in ethnic minority groups and socioeconomically deprived individuals [117].

Different comorbidities in HF patients may account for various significance on cancer development, e.g. hypertension was reported to have an 11% higher risk for colorectal cancer and a 7% higher risk for breast cancer [118]. A Danish cohort reported that atrial fibrillation, as a common comorbidity in HF patients, was associated with a 19.1% incidence of cancer in women and 23.3% in men within 12 years after atrial fibrillation diagnosis. This cohort even uncovered men had a higher prevalence of cancer than women in general (22.3% vs.18.9%), which is in line with our results [119]. Coronary artery disease had more than doubled higher risk for cancer and mortality when compared with those patients without atherosclerotic cardiovascular diseases [120]. The co-occurrence of coronary artery disease, considered the main aetiological factor of HF, and HF might implicate an increased risk for cancer development exceeding the total risk of these conditions if existed separately [108]. Our findings presented an increasing probability for malignancies with advancing MM level, which could be a consequence of HF or more likely interactions between the included chronic conditions.

Paper IV

The HF patients who were admitted to hospital were under surveillance for 100 days post-discharge to determine whether common comorbidities affected their risk of cardiovascular-related readmission. From a total of 10 comorbidities adjusted in the same model, only the comorbidities CKD, atrial fibrillation DM, PAD or COPD had an increased HR, independent of age, gender, HF subtype and renal function. DM and PAD lost their significance for readmission after adjustment for these five comorbidities in the same model, which demonstrated the importance of atrial fibrillation, CKD or COPD for their increased risk of cardiovascular-related readmission. Logistic regression, with comorbidities as dichotomous indicator variables used for ROC analysis, resulted in similar values for individual comorbidity level as Rasch analysis, although both with low predictive value.

Atrial fibrillation and HF predispose each other and share many risk factors and pathophysiology, causing increased morbidity and mortality [121, 122]. The Swedish Heart Failure registry showed that the prevalence of atrial fibrillation in HF patients ranged between 53% - 65% depending on HF subtype, and atrial fibrillation increased their risk of HF hospitalisations, CVI and mortality independent of the ejection fraction, which is comparable with our findings [123]. The high prevalence of CVI (80%) in the elderly over 75 years among our study participants is supposedly a consequence of the high prevalence of atrial fibrillation and HF combined.

HF patients with CKD may have elevated NT-proBNP caused by CKD and cannot be evaluated regarding their decompensation. CKD, defined as an estimated glomerular filtration rate $\leq$ 60 mL/min.1.73 m^2, itself may cause fluid overload indicating hospital admissions. HF patients with CKD had an increased risk for readmission probably because they are refractory to the conventional HF treatment. ACEi and diuretics may worsen kidney function and electrolyte balance. Instead, peritoneal dialysis, high-dose iron, cardiac resynchronisation therapy and sodium-glucose cotransporter inhibitor therapy are recommended to reduce HF hospitalisations [125]. HF patients with CKD in the Swedish Heart Failure Registry have shown an increased mortality rate than those HF patients without CKD, in particular the subtypes HFrEF and HFmrEF [124].

PAD was the smallest group of comorbidities in our study, comprising only 5% of the HF patients and had an increased risk for cardiovascular-related readmissions within 100 days after discharge. An international trial included HF patients with PAD, who had an increased risk for HF hospitalizations, mortality, myocardial infarction and stroke, compared to the HF patients without PAD [126]. PAD in these HF patients was mostly one symptom of their atherosclerotic cardiovascular disease, combined with smoking and prevalent DM, they had an increased risk of cardiovascular-related hospitalisations [126]. A multinational trial uncovered HF

readmission incidence was relatively low in PAD, coronary artery disease and cerebrovascular disease within the first 100 days after discharge, but increased substantially during the follow-up time and reached 2.9% at three years in the PAD group, followed by 1.4% in the coronary artery disease group and 0.9% in the cerebrovascular disease group. Within the patient group affected by ischaemic heart disease, the incidence of HF readmission increased with advancing symptomatic coronary atherosclerotic burden [127]. These results are convincing about the different symptoms correlated to various degrees of atherosclerosis, which facilitate the interpretation of our findings.

The increased risk of cardiovascular-related readmission could even be attributed to the total comorbidity burden or specific combinations of comorbidities in HF patients. A retrospective study reported an increased risk for HF readmission with the time from index hospitalization, even though the difference was small between 90 days and 180 days after discharge [128]. This risk for HF readmission rose continuously with elevated comorbidities burden including DM, COPD, CKD, hypertension, PAD etc. The ROC curve and AUC mainly based on these comorbidities at 90 days after discharge resulted in similar values (0.58) compared with our results [128].

The American National Readmission Database analysed the aetiologies and predictors of 30-day readmission in HF patients. 85% of HF patients were readmitted once within 30 days after discharge [129]. The most prevalent comorbidity in the readmitted HF patients was atrial fibrillation 45.6%, followed by IHD 39.9%, COPD 34.9%, DM 32.1%, anaemia 31.5%, CKD 28.5%, hypertension 23.8% and PAD 7%. Smokers and high comorbidity burden were also common in these readmitted HF patients [129]. Most of the readmissions were cardiovascular-related with HF as the most common aetiology. Similar to our findings, the high comorbidity burden, especially atrial fibrillation, COPD, CKD, IHD and anaemia belonged to the independent predictors of 30-day readmission, likewise male sex, low SES and nonelective admissions [129].

Strengths and limitations

This doctoral thesis presents several strengths. All HF patients included in this study were diagnosed following the diagnosis criteria for HF according to ESC (European Society of Cardiology) guidelines. Our results were representative although similar studies in other Western countries had a much longer follow-up time and larger study group [112]. Sweden has a reliable register system using social security numbers enabling the characterization of the study population and detecting their contact with the health care system. Sweden's health care system applies the International Statistical Classification of Diseases and Related Health Problems 10th

Revision (ICD-10) for diagnosis, which facilitates our research procedure. The Swedish population is not limited by their individual health insurance plan regarding investigation and treatment options.

The studies in this doctoral thesis have plenty of limitations. We did not stratify the MM level in different CNI percentiles, which might further highlight our findings regarding socioeconomic deprivation. The severity of all diagnoses included in MM could also explain the disparities in the analyzed variables in our study population. Patients may have various attitudes regarding physical examination and adherence to treatments depending on many factors, which affect our results. A considerable part of our study population were immigrants from most countries in the world, but no ethnic differences were considered regarding their diagnoses in relation to age, gender and SES. The time at diagnosis of HF and malignancies was not registered, which could gain our knowledge of their causal relation.

This doctoral thesis contains population-based studies carried out in southern Sweden, which possibly has a limited validity when extrapolated to populations with characteristics different from this study population. As SES poses a dynamic factor, the cross-sectional design of this survey did not allow us to investigate the reversibility of SES and the outcomes in all MM accordingly. For many years, Swedish hospitals have had limited resources for admission and surveillance of patients, including HF patients, who are frequently treated as outpatients instead. Some patients are listed at PHCs outside of their neighbourhood, which could affect our data on SES.

Conclusion

Paper I

Almost all HF patients had MM. The mean probability of HF increased with advancing age and MM level. The patients listed at the socioeconomically most deprived CNI percentile had the lowest proportion of individuals older than 50 years of age and the highest probability of HF compared to the more affluent population in our study. The most deprived CNI percentile had the highest prevalence of HF from 40 years of age and was double as high as the most affluent CNI percentile until 80 years of age. The size of each MM group diminished with advancing MM level, probably due to a rising mortality rate. HF is convincingly one of many conditions associated with socioeconomic deprivation and high mortality.

Paper II

Men had a higher mean probability of HF than women, regardless of age and MM level. This disparity increased with advancing age and MM level. Women in the socioeconomically most affluent group had the lowest mean probability in the entire study population, contrasting men belonging to the most deprived group, who had the highest mean probability of HF. The disparity of mean probability of HF between the socioeconomically most affluent and deprived group was more obvious in women than men, indicating socioeconomic deprivation as a stronger predictor for HF in women than men. Women had a higher prevalence of MM than men in all age groups, but men had a higher prevalence of HF among the multimorbid population, regardless of SES.

Paper III

People with HF had an increased risk for malignancies, haematologic malignancies in particular. Men had a higher probability for malignancies than women, especially after adjustment for MM. Unlike socioeconomic deprivation, MM was a stronger predictor for both haematologic- and solid malignancies than HF. Advancing MM

level presented a substantial increment in association with malignancies. Increasing socioeconomic deprivation was largely associated with decreasing probability for solid malignancies with the greatest difference between the most affluent and deprived CNI percentile.

Paper IV

The HF patients with comorbidities CVI, valvular heart disease, hypertension, ischaemic heart disease or acute myocardial infarction had no increased risk for cardiovascular-related readmission within 100 days after discharge. HF patients with comorbidities DM or PAD lost their significance for readmission when adjusting for atrial fibrillation, CKD and COPD in the same model. Measures of individual comorbidity level using logistic regression or Rasch analysis did not show any statistically significant difference, but their predictive value was low. Other factors might be stronger predictors for cardiovascular-related readmission within 100 days after discharge in HF patients, possibly in combination with the comorbidities atrial fibrillation, CKD and COPD.

Future research

You never realize what was done, but only see what is still to do.
-Marie Curie

The high prevalence of MM in people with HF underlines HF as rather a systemic disease affecting multiple organ systems than only the heart. The Swedish health care system is moving the main part of health care from secondary health care towards primary health care, which is facing a progressive expansion of patients with MM and HF in the future. Both HF and malignancies are leading causes of morbidity and mortality worldwide. Global health care has to meet the coming epidemic of these patients with new strategies.

Our access to large databases including individual diagnosis-based registers provides an excellent opportunity to conduct population-based research. To analyse all comorbidities included in MM and stratifying for MM level would further explicate their associations with HF. A special emphasis on cancer is recommended because it is expected to become the leading cause of mortality globally in a few years. Our results uncovered that HF was associated with malignancies and low SES contradicted by the fact that socioeconomically deprived individuals had fewer malignancies than the affluent population. Recently, the Swedish Social Welfare Board reported that the number of survivors five years after their cancer diagnosis has increased, and the socioeconomically most affluent population had the best survival, in contrast to the most deprived population which had the worst survival. Generally, the mortality of preventable conditions in the socioeconomic deprived population is twice as high as in the affluent population, which is partly due to their difference in health literacy. Thus, the comparison between the types of malignancies in people, with and without HF, could guide us to the next research topic. To characterise the malignancies in the socioeconomically affluent population and deprived population could also boost our knowledge in this area.

Another research topic of interest is the difference between the HF subtypes in relation to SES and prevalence of malignancies. Racial disparities regarding HF and MM are also a pertinent issue in Swedish society. To define stronger risk factors of HF admission than comorbidities would benefit HF patients in terms of improved quality of life and survival, which could reduce the global burden of health care as well.

In respect of the ever-growing pandemic burden of HF and its implications, all new knowledge in this area would facilitate the management of this disseminating health problem.

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Paper I

BMJ Open

Disparities in prevalence of heart failure according to age, multimorbidity level and socioeconomic status in southern Sweden: a cross-sectional study

Mia Scholten , Patrik Midlöv , Anders Halling

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Center for Primary Health Care Research, Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

Correspondence to
Dr Mia Scholten;
mia.scholten@med.lu.se

ABSTRACT

Objective The aim of this study was to compare the prevalence of heart failure (HF) in relation to age, multimorbidity and socioeconomic status of primary healthcare centres in southern Sweden.

Design A cross-sectional study.

Setting The data were collected concerning diagnoses at each consultation in all primary healthcare centres and secondary healthcare in the southernmost county of Sweden at the end of 2015.

Participants The individuals living in southern Sweden in 2015 aged 20 years and older. The study population of 981 383 inhabitants was divided into different categories including HF, multimorbidity, different levels of multimorbidity and into 10 CNI (Care Need Index) groups depending on the socioeconomic status of their listed primary healthcare centre.

Outcomes Prevalence of HF was presented according to age, multimorbidity level and socioeconomic status. Logistic regression was used to further analyse the associations between HF, age, multimorbidity level and socioeconomic status in more complex models.

Results The total prevalence of HF in the study population was 2.06%. The prevalence of HF increased with advancing age and the multimorbidity level. 99.07% of the patients with HF fulfilled the criteria for multimorbidity. The total prevalence of HF among the multimorbid patients was only 5.30%. HF had a strong correlation with the socioeconomic status of the primary healthcare centres with the most significant disparity between 40 and 80 years of age: the prevalence of HF in primary healthcare centres with the most deprived CNI percentile was approximately twice as high as in the most affluent CNI percentile.

Conclusion The patients with HF were strongly associated with having multimorbidity. HF patients was a small group of the multimorbid population associated with socioeconomic deprivation that challenges efficient preventive strategies and health policies.

Strengths and limitations of this study

- ► Our large cohort with almost 1 million inhabitants included 20 193 patients with heart failure and 377 161 patients with multimorbidity in southern Sweden, which increases the validity of our results.
- ► The data were based on clinical diagnoses registered by physicians, rather than self-reported data, which eliminated any recall bias.
- ► Many patients have diagnoses that are usually neglected by the patients and staff in the healthcare, because these do not impair their quality of life or prognosis, which constitutes a consistent error source to our statistics.
- ► As heart failure has none-specific symptoms at the onset, we suspect that many people were underdiagnosed regarding this condition.
- ► We had no data on the quality of healthcare in the neighbourhood.

INTRODUCTION

Heart failure (HF) and multimorbidity (MM) are leading causes of morbidity, hospitalisations, disability and death in Western countries.[1 2] The prevalence of HF and MM increases with age and the cost of care and treatment constitutes a considerable burden on primary healthcare and on healthcare as a whole.[1] In high-income countries, HF is the most common diagnosis in hospitalised elderly patients aged >65 years.[2] In Sweden, 31% of medical expenditures were spent for HF patients with reduced ejection fraction (HFrEF) in primary healthcare, 29% for primary cardiac hospitalisations and 40% were for non-cardiac hospitalisations.[3]

HF is classified into three major groups: HF with reduced EF (HFrEF), HF with midrange EF (HFmrEF), and HF with preserved ejection fraction (HFpEF).[4] All subtypes of HF have the same clinical phenotype,[5] but different pathophysiology and prognosis.[6] The systolic failure or HFrEF (or systolic dysfunction) is established when the left ventricle loses its ability to contract normally, resulting in EF <40%. The heart cannot pump with enough force to push enough blood into the circulation. HFrEF develops usually in response to larger-scale myocyte loss/dysfunction, with the most common aetiologies

including acute myocardial infarction, genetic abnormalities, myocarditis or toxin effects (eg, alcohol or chemotherapy).[7] Diagnosis of systolic dysfunction is easier than the diagnosis of diastolic dysfunction due to the objective finding of reduced ejection fraction. HFmrEF shares features with both HFrEF and HFpEF, including the aetiology, symptomatology, age of the patients and comorbidities.[8] Four diagnostic criteria are simultaneously required for HFmrEF: symptoms with or without signs of HF, LVEF of 40%–49%. Elevated natriuretic peptides, and relevant structural heart disease: left ventricle hypertrophy or left atrial enlargement or diastolic dysfunction.[9] HFpEF or diastolic HF (or diastolic dysfunction) is established when the left ventricle loses its ability to relax normally, because the muscle has become stiff. The heart cannot properly fill with blood during the resting period between each beat. The pathophysiological derangements in HFpEF include concentric remodelling, ventricular-vascular stiffening and loss of ventricular-vascular reserve function are resulted from chronic pressure overload due to arterial hypertension.[10] Diastolic HFpEF with LVEF ≥50%, and is preferably found among elderly, women, and patients with diabetes mellitus and hypertension.[11–14]

Beside the risk factors like physical inactivity, obesity, chemotherapy, heritability and hyperlipidaemia, which increases the incidence of HF, the incidence also varies with the patient's socioeconomic status (SES).[15–20] Higher income has previously been associated with a lower risk of developing HF.[21] Moreover, the risk factors for HF, such as hypertension and coronary heart disease, also vary with SES.[22] HF is often a chronic complication of other cardiovascular comorbidities, particularly ischaemic heart disease, atrial fibrillation and valve dysfunctions.[23] Due to improved medical management, the age-adjusted incidence and prevalence of HF are decreasing, and the HF patients have got prolonged life expectancy.[1] Consequently, the absolute number of patients with HF has drastically increased, secondary to global ageing, as well as general population growth.[24] Although reliable estimates for middle-income and low-income nations are lacking, evidence from the current literature suggests that HF is the fastest growing cardiovascular condition globally.[25 26]

The aetiology of HF is diverse and varies geographically worldwide: High-income countries are disproportionally affected by ischaemic heart disease and COPD (chronic obstructive pulmonary disease) compared with low-income countries, which in turn are primarily affected by hypertensive heart disease, rheumatic heart disease, cardiomyopathy and myocarditis.[27] More than two-thirds of all cases of HF can be attributed to four underlying conditions: ischaemic heart disease, COPD, hypertensive heart disease and rheumatic heart disease.[1]

HF is often a chronic condition with insidious symptoms at the onset, which could make early and accurate diagnosis difficult. The diagnosis of HF requires three criteria to be fulfilled: typical clinical symptoms, such as dyspnoea, fatigue, exertional intolerance and oedema of the lower body, elevated BNP value and objective findings of impaired cardiac function on echocardiography, myocardial scintigraphy, magnet resonance tomography or other imaging.[13]

The aim of this study was to compare the prevalence of HF in relation to age, MM level and SES of primary healthcare centres in southern Sweden.

METHODS

Setting and study population

Most residents in Sweden are listed at a primary healthcare centre, either a public or private healthcare centre. Scania is the southernmost county of Sweden with around 1.3 million inhabitants during 2015.[28] Approximately one-quarter of the study population were born abroad.[29] The biggest city in Scania is Malmö with about 320 000 inhabitants during 2015, ranked as the third largest city in Sweden.[28] About one-third of the residents in Malmö were born abroad representing most countries in the world.[30] Almost half of the residents in Malmö (48.40%) were under 35 years during 2015.[31] The study population comprised individuals aged 20 years and older living in Scania during the last week of 2015. This age cut-off was chosen because the types of HF affecting children and younger people are pathologically distinct from those found in older adults.

The study population was divided into age groups: 20, 30, 40, 50, 60, 70, 80+. The age group 20 included inhabitants aged 20 to 29 years, the age group 30 included inhabitants aged 30–39 years and so on. The age group 80+ included all inhabitants from 80 years and over.

Data source and measurements

The data used in this study was retrieved from the County Council healthcare register in Scania that contains anonymised registry information from the study population, including age, gender, SES and diagnostic data in the last week of 2015.

The data were collected concerning diagnoses at each consultation in all primary healthcare centres and secondary healthcare. Diagnoses were recorded according the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD 10). HF was diagnosed following the diagnosis criteria for HF according to ESC (European Society of Cardiology) guidelines and recorded as I50, which comprised all subtypes of HF. Totally 152 primary healthcare centres were operating during 2015 in Scania, with on average 8587 listed patients (95% CI 7971.49 to 9292.88) including 133 patients with HF (95% CL 122.60 to 143.80) at each primary healthcare centre.

Multimorbidity

MM was defined as coexistence of two or more chronic conditions in the same person, independently if cardiovascular or not. To measure MM, we used a method to identify chronic conditions developed by Calderón-Larrañaga *et al* at the Ageing Research Centre in Stockholm.[32] They

analysed the full list of ICD-10 codes on a four-digit level to define if a diagnosis is chronic or not in an elderly population. To determine if a condition is chronic or not the following key features were identified and discussed concerning their pertinence and suitability in older populations: duration, course, reversibility, treatment and consequences. They were then grouped into 60 groups of chronic conditions if their duration exceeded 3 months. We applied their definition and list of chronic conditions to estimate the MM in our study population. All information about diagnoses was obtained from electronic medical record database in the county council in Scania. MM was then estimated by counting the number of chronic conditions in each patient. To study the MM level in relation to the prevalence of HF, the patients were further divided into groups MM0 (less than 2 chronic conditions), MM1 (2–4 chronic conditions), MM2 (5–9 chronic conditions) and MM3 (10 chronic conditions or more).

Socioeconomics

We used the term Care Need Index (CNI)[33] to divide the primary healthcare centres into 10 groups depending on their SES. CNI is based on different measures of a group, in this case the patients listed to different primary healthcare centres in Scania. CNI 1 was assigned to those patients listed at primary healthcare centres who belonged to the most socioeconomically affluent percentile, and CNI 10 was assigned to those patients listed at primary healthcare centres who belonged to the most socioeconomically deprived percentile.[33]

Statistical analyses

We analysed data from 981 383 (about a tenth of the Swedish population) inhabitants aged 20 years and older living in Scania during the last week of 2015. Associations between the variables were studied using univariate and multivariate statistics.

We used frequencies, percentages and cross tabulations for descriptive analysis. Logistic regression was used to analyse the associations between the univariate and multivariate models. Only the linear predications of the fully adjusted models were shown in the figures.

A p <0.05 was considered statistically significant. The predicted mean probability of HF was calculated as average marginal effects using the Delta-method.

We used STATA V.16.0 and V.17.0 (Stata) for statistical analyses.

Patient and public involvement

Data in this study are based on anonymised information provided by the County Council of Scania.

The study participants were not involved in the recruitment to the study by themselves. Due to the requirement of anonymised data, each individual could not be asked for consent to participate; active refusal of participation was instead applied. This was done by publishing information about the planned study in the Swedish local newspaper 'Sydsvenskan'. The advertisement outlined the study and contained information on how to contact the research manager (first author) to opt out of the study. The study results are published anonymised in group level, and cannot be disseminated to every study participant.

RESULTS

The total prevalence of HF in the study population was found to be 2.06% (20193 patients) in 2015. HF was a rare disease under 40 years of age in the whole study population, but the prevalence increased at least twofold in all age groups and CNI percentiles from 30 years of age onwards and reached 17.31% in the age group 80+ (table 1). The individuals listed at primary healthcare centres with deprived CNI percentiles were more likely to have a higher proportion of individuals younger than 40 years and the opposite was true for primary healthcare centres with affluent CNI percentiles. The primary healthcare centres with the most deprived CNI percentile had the lowest proportion of population from middle age, only 33.25% were 50 years and older, whereas the affluent CNI percentiles were likely to be dominated by individuals from 50 years and over (table 1).

MM was present in 38.40% (377161 patients) of the study population and followed different patterns according to age groups and CNI percentiles of the primary healthcare centres (table 1). HF was strongly correlated to MM: 99.07% of the patients with HF fulfilled the criteria for MM, independently of the age at their diagnosis. The prevalence of MM increased steadily with advancing age, from 14.89% in the age group 20 to 86.22% in the age group 80+ (table 1). The prevalence of HF increased consistently with the MM level: the MM1 (2–4 chronic conditions) group had 1.49% patients with HF, the MM2 (5–9 chronic conditions) group had 11.16% patients with HF and the MM3 (>10 chronic conditions) group had 39.28% patients with HF. The total prevalence of HF among the multimorbid patients was only 5.30% (20005 patients) (table 1). The predicted mean probability of HF adjusted for age and MM level is shown in figure 1.

If we consider the prevalence of HF in different MM levels: 19.19% (3875 patients) of all patients with HF belonged to the MM1 group, 58.18% (11748 patients) belonged to the MM2 group and 21.70% (4382 patients) belonged to the MM3 group. The MM2 group as a whole was more than nine times larger than the MM3 group (105 241 vs 11 156 patients).

The prevalence of HF had a strong correlation with the SES of the primary healthcare centres (figure 2). The most significant disparity was between 40 and 80 years of age: the prevalence of HF in primary healthcare centres with the most deprived CNI percentile was significantly increased and approximately twice as high as in the most affluent CNI percentile (table 1). Although at much lower levels, significant disparities in prevalence of HF could be observed when comparing the most deprived

Table 1 Prevalence of heart failure (HF) and multimorbidity (MM) in all age groups and CNI percentiles

			HF							
			No MM		Yes MM					
CNI percentiles	Age	N	No	Yes	No	Yes	MM (%)	HF (%)	HF with MM (%)	MM with HF (%)
CNI 1	20	12 866	10 842	2020	1	3	15.72	0.03	75.00	0.15
	30	17 890	14 347	3533	2	8	19.79	0.06	80.00	0.23
	40	24 753	18 672	6047	3	31	24.55	0.14	91.18	0.51
	50	17 806	11 062	6656	5	83	37.85	0.49	94.32	1.23
	60	19 358	7857	11 190	5	306	59.39	1.61	98.39	2.66
	70	13 345	2894	9769	5	677	78.28	5.11	99.27	6.48
	80	5 614	610	4055	1	948	89.12	16.90	99.89	18.95
CNI 2	20	16 173	13 755	2411	1	6	14.94	0.04	85.71	0.25
	30	16 095	12 861	3230	0	4	20.09	0.02	100.00	0.12
	40	20 750	15 497	5220	0	33	25.32	0.16	100.00	0.63
	50	18 892	11 602	7196	2	92	38.58	0.50	97.87	1.26
	60	19 729	8378	10 990	6	355	57.50	1.83	98.34	3.13
	70	12 752	3090	9024	5	633	75.73	5.00	99.22	6.55
	80	6 278	833	4468	2	975	86.70	15.56	99.80	17.91
CNI 3	20	16 970	14 424	2540	1	5	15.00	0.04	83.33	0.20
	30	15 252	12 212	3030	0	10	19.93	0.07	100.00	0.33
	40	16 596	12 045	4520	1	30	27.42	0.19	96.77	0.66
	50	14 638	8843	5693	2	100	39.58	0.70	98.04	1.73
	60	15 383	6310	8760	4	309	58.95	2.03	98.72	3.41
	70	10 056	2269	7163	4	620	77.40	6.21	99.36	7.97
	80	5 553	649	3903	8	993	88.17	18.03	99.20	20.28
CNI 4	20	14 112	11 835	2271	3	3	16.11	0.04	50.00	0.13
	30	13 429	10 665	2753	1	10	20.57	0.08	90.91	0.36
	40	15 769	11 417	4309	1	42	27.59	0.27	97.67	0.97
	50	14 658	8622	5915	3	118	41.16	0.83	97.52	1.96
	60	14 826	6017	8459	7	343	59.37	2.36	98.00	3.90
	70	9 409	2221	6558	0	630	76.39	6.70	100.00	8.76
	80	5 122	646	3493	6	977	87.27	19.19	99.39	21.86
CNI 5	20	12 796	10 794	2000	1	1	15.64	0.02	50.00	0.05

Continued

Table 1 Continued

			HF							
			No MM		Yes MM					
CNI percentiles	Age	N	No	Yes	No	Yes	MM (%)	HF (%)	HF with MM (%)	MM with HF (%)
	30	13 168	10 455	2706	0	7	20.60	0.05	100.00	0.26
	40	13 879	10 028	3816	2	33	27.73	0.25	94.29	0.86
	50	12 142	7171	4897	2	72	40.92	0.61	97.30	1.45
	60	11 723	4870	6597	3	253	58.43	2.18	98.83	3.69
	70	7 333	1704	5162	0	467	76.76	6.37	100.00	8.30
	80	4 178	489	2884	3	802	88.22	19.27	99.63	21.76
CNI 6	20	18 134	15 365	2766	0	3	15.27	0.02	100.00	0.11
	30	15 745	12 638	3099	2	6	19.72	0.05	75.00	0.19
	40	18 285	13 316	4928	2	39	27.16	0.22	95.12	0.79
	50	16 530	9833	6588	2	107	40.50	0.66	98.17	1.60
	60	16 438	6943	9163	5	327	57.73	2.02	98.49	3.45
	70	11 457	2667	8171	4	615	76.69	5.40	99.35	7.00
	80	6 894	940	4845	6	1103	86.28	16.09	99.46	18.54
CNI 7	20	18 045	15 624	2411	1	9	13.41	0.06	90.00	0.37
	30	14 656	11 977	2669	1	9	18.27	0.07	90.00	0.34
	40	14 400	10 590	3777	2	31	26.44	0.23	93.94	0.81
	50	12 597	7597	4907	4	89	39.66	0.74	95.70	1.78
	60	13 119	5696	7147	5	271	56.54	2.10	98.19	3.65
	70	8 930	2194	6193	1	542	75.42	6.08	99.82	8.05
	80	5 569	788	3788	5	988	85.76	17.83	99.50	20.69
CNI 8	20	22 405	18 803	3597	1	4	16.07	0.02	80.00	0.11
	30	21 019	16 659	4341	0	19	20.74	0.09	100.00	0.44
	40	19 268	13 828	5395	2	43	28.22	0.23	95.56	0.79
	50	17 755	10 435	7175	7	138	41.19	0.82	95.17	1.89
	60	17 014	7233	9435	3	343	57.47	2.03	99.13	3.51
	70	10 651	2616	7388	4	643	75.40	6.07	99.38	8.01
	80	6 039	838	4189	7	1005	86.01	16.76	99.31	19.35
CNI 9	20	23 116	19 785	3328	1	2	14.41	0.01	66.67	0.06
	30	21 531	17 553	3967	2	9	18.47	0.05	81.82	0.23

Continued

Table 1 Continued

			HF						
			No MM		Yes MM				
CNI percentiles	Age	N	No	Yes	No	Yes	MM (%)	HF (%)	HF with MM (%)	MM with HF (%)
	40	16 388	12 072	4277	1	38	26.33	0.24	97.44	0.88
	50	14 812	8881	5828	2	101	40.03	0.70	98.06	1.70
	60	12 646	5696	6616	2	332	54.94	2.64	99.40	4.78
	70	8 915	2342	6013	4	556	73.68	6.28	99.29	8.46
	80	6 064	1042	4043	8	971	82.68	16.14	99.18	19.37
CNI 10	20	26 259	22 707	3542	2	8	13.52	0.04	80.00	0.23
	30	21 295	17 348	3931	1	15	18.53	0.08	93.75	0.38
	40	15 007	10 531	4428	4	44	29.80	0.32	91.67	0.98
	50	12 602	7145	5338	0	119	43.30	0.94	100.00	2.18
	60	9 304	4061	4938	3	302	56.32	3.28	99.02	5.76
	70	5 751	1643	3580	2	526	71.40	9.18	99.62	12.81
	80	3 450	662	2117	2	669	80.75	19.45	99.70	24.01
All CNI percentiles	20	180 876	153 934	26 886	12	44	14.89	0.03	78.57	0.16
	30	170 080	136 715	33 259	9	97	19.61	0.06	91.51	0.29
	40	175 095	127 996	46 717	18	364	26.89	0.22	95.29	0.77
	50	152 432	91 191	60 193	29	1019	40.16	0.69	97.23	1.66
	60	149 540	63 061	83 295	43	3141	57.80	2.13	98.65	3.63
	70	98 599	23 640	69 021	29	5909	75.99	6.02	99.51	7.89
	80	54 761	7497	37 785	48	9431	86.22	17.31	99.49	19.97
	Total	981 383	604 034	357 156	188	20 005	38.43	2.06	99.07	5.30

MM (%)=total prevalence of MM.
HF (%)=total prevalence of HF.
HF with MM (%)=prevalence of HF with MM.
MM with HF (%)=prevalence of MM with HF.
CNI, Care Need Index.;

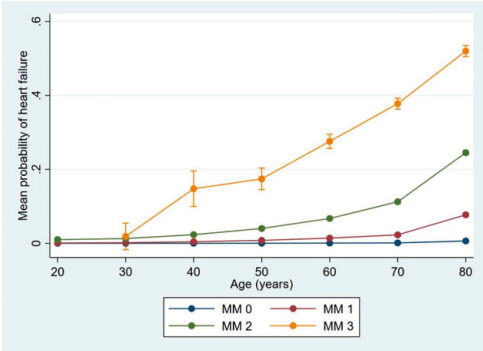

Figure 1 The predicted mean probability of heart failure adjusted for different age groups and multimorbidity levels with 95% CIs using delta methods. MM0, less than 2 chronic conditions (not multimorbid); MM1, 2–4 chronic conditions; MM2, 5–9 chronic conditions; MM3, 10 or more chronic conditions.

CNI percentile with other CNI percentiles of the primary healthcare centres. The primary healthcare centres with the most deprived CNI percentile had the highest prevalence of HF from 40 years of age, although their prevalence of MM was lowest from 70 years of age. In contrast, the prevalence of HF in the most affluent CNI percentile remained relatively low in most age groups, even from 60 years of age as their prevalence of MM became highest (table 1). Only 4.58% of the multimorbid individuals belonging to this CNI percentile had HF, which was lowest compared with the more deprived CNI percentiles. The association between the prevalence of HF and CNI percentiles followed different patterns compared with MM as shown in table 1.

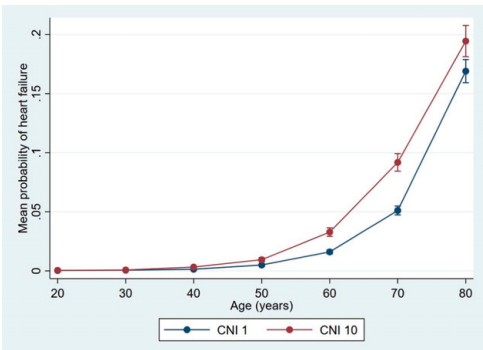

Figure 2 Disparities in the predicted mean probability of heart failure adjusted for age between the most affluent (CNI 1) and deprived (CNI 10) CNI percentile with 95% CIs using delta methods. CNI, Care Need Index.

DISCUSSION

The total prevalence of HF was about 2% in Scania during 2015, which was the same as the prevalence in Sweden and other Western countries.[34 35] HF was a rare disease under 40 years of age and increased substantially with advancing age. 99.07% of the patients with HF in our study population had MM, which could be explained by the diagnosis HF mostly constitutes a complication of other cardiovascular conditions.[23 36] MM was present in 38.40% of the study population, but included only 5.30% patients with HF. The high prevalence of MM could be explained by the socioeconomic difference within the study population and the considerable part of elderly with high prevalence of MM. With increasing MM level, the prevalence of HF increased from 1.49% in the MM1 (2–4 chronic conditions) group to 39.28% in the MM3 (more than 10 chronic conditions) group. The MM3 group had fewer patients, but a higher prevalence of HF than the MM2 group, which makes us to believe that the MM3 group had a higher mortality in general.

Most primary healthcare centres are public and organised similarly irrespective of CNI. The socioeconomic boundaries are quite sharp and agree with uptake areas of the different primary healthcare centres. The CNI category was an average socioeconomic level of the patients listed at the primary healthcare centres.

The prevalence of HF also had a strong association with the SES of primary healthcare centres with the most significant disparity between 40 and 80 years of age: the prevalence of HF in primary healthcare centres with the most deprived CNI percentile was approximately twice as high as in the most affluent CNI percentile. The fact that the prevalence of HF was highest from 40 years of age in the most deprived CNI percentile of primary healthcare centres indicates that HF is a disease associated with socioeconomic deprivation. The correlation was assessed visually as the difference in prevalence of HF was obvious between the most affluent and deprived CNI percentiles.

The individuals listed at primary healthcare centres with deprived CNI percentiles were more likely to have high proportion of inhabitants younger than 40 years, and the opposite wastrue for primary healthcare centres with affluent CNI percentiles. The primary healthcare centres with the most deprived CNI percentile had the lowest proportion of population (33.25%) from 50 years and the highest prevalence of HF from 40 years of age compared with the more affluent population, which makes us to suspect that they suffered from SES related MM with worse prognosis, including HF.

HF is common in multimorbid patients with COPD,[37] with prevalence in 33.2% of women and 35.7% of men over 80 years of age.[38] In most countries, low SES is associated with higher prevalence of COPD and mortality.[39] The estimated mortality in patients with COPD and coexisting HF was seven times higher than in patients with COPD alone, thus the patients with these two conditions were reported with the highest mortality among patients hospitalised with COPD exacerbation.[40] Other conditions with

high impact on mortality in patients with HF including stroke, renal disease and diabetes mellitus,[41] are strongly associated with low SES as well.[42–44]

With respect to the global burden of ischaemic heart disease, the incidence of acute myocardial infarction worldwide is highest in Eastern Europe and Central Asia.[45] Compared with the Swedish population, the first-generation immigrants from Iraq and Bosnia had the highest incidence of HF, probably due to a higher incidence of coronary heart disease.[4] When this incidence of HF was further adjusted for SES, marital status and educational level, the HR for HF raised significantly compared with the immigrants from other countries. As many of these immigrants are socioeconomically highly disadvantaged in Sweden, these results support our findings. Interestingly, the HF risk pattern among the second-generation immigrants in most cases differed only marginally compared with their Swedish counterparts, indicating that their risk factor is not purely genetic, rather responsive to other factors.[4]

A similar study in Scotland revealed that older people typically have more morbidities with lower functional status, whereas younger people are more often affected by combinations physical and mental health disorders. Except that the most affluent population being on average 2–5 years older at onset of morbidity (dependent on the disorder), conditions like coronary heart disease, diabetes mellitus, COPD, depression, painful disorders or cancer were more common in people living in deprived areas.[46] This could explain that people in the affluent areas suffered from MM with less disability and had better prognosis.

We do not know if MM causes socioeconomic deprivation or if low SES causes MM. There is presumably an impact in both directions. Many people with MM do retire earlier, and have more socioeconomic consequences than the working population. Statistically, this group degrades in the SES, which even may influence their family members. On the other hand, many people in the deprived areas have to accept a job which is more health challenging, and become multimorbid many years earlier than the affluent population.

Strengths and limitations

Our study has a number of strengths. Our large cohort with almost 1 million inhabitants included all patients with HF and MM in Scania during the study period, which increases the validity of our results. The outcome data were based on clinical diagnoses registered by physicians, rather than self-reported data, which eliminated any recall bias. Our findings have similarities with correlative studies in other countries,[21 23] which increases the credibility of our results.

This study has certain limitations. We had no data on several risk factors for HF, such as smoking, obesity or physical inactivity. However, some prior works on SES and HF had adjusted for smoking and physical inactivity and still found an independent association.[21] We had no results of echocardiography, and thus could not analyse the subtypes of HF in our study population. As HF has none-specific symptoms at the onset, we suspect that many people were underdiagnosed regarding this condition. Those patients with HF belonging to the MM0 group were probably underdiagnosed as well, because HF usually constitutes a complication of other diseases or treatments. Many patients have diagnoses that are usually neglected by the patients and staff in the healthcare, because these do not impair their quality of life or prognosis, which constitutes a consistent error source to our statistics. We had no data on the severity of HF and other conditions, which have high impact on the mortality. We had no data on the quality of healthcare in the neighbourhood. Our results could be more accurate if the age group 80+ were divided into age group 80 and 90+, and analysed separately.

CONCLUSION

The prevalence of HF was strongly associated with MM, with increasing prevalence of HF with MM level. The patients listed at primary healthcare centres with the most socioeconomic deprived CNI percentile had a significantly elevated risk of developing HF and probably MM with worse prognosis, which resulted in the lowest proportion of population from 50 years compared with the more affluent population in our study. HF patients was a small group of the multimorbid population associated with socioeconomic deprivation that challenges efficient preventive strategies and health policies.

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Contributors In accordance with the Vancouver Protocol, AH was involved in data collection, design of the study, data analysis, editing the manuscript and student supervision. MS contributed with data collection, data analysis, writing and editing the manuscript. PM provided critical comments and feedback on the manuscript. AH acts as a gaurantor for this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The regional Ethical Review Board at Lund University (application no. 2018/778) approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. Scania County council provided anonymised data of the study population, which is confidential and not available for open access according to the Swedish law.

ORCID iDs
Mia Scholten http://orcid.org/0000-0002-3519-0129
Patrik Midlöv http://orcid.org/0000-0002-5871-8731
Anders Halling http://orcid.org/0000-0002-1035-7586

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Paper II

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RESEARCH ARTICLE

Disparities in prevalence of heart failure between the genders in relation to age, multimorbidity and socioeconomic status in southern Sweden: a cross-sectional study

Mia Scholten, Patrik Midlöv and Anders Halling

Center for Primary Health Care Research, Department of Clinical Sciences, Malmö, Lund University, Sweden

ABSTRACT

Objective: Prior studies have reported that heart failure typically affects elderly, multimorbid and socioeconomically deprived men. Women with heart failure are generally older, have a higher EF (ejection fraction) and have more heart failure-related symptoms than men. This study explored the disparities in the prevalence of heart failure between men and women in relation to age, multimorbidity level and socioeconomic status of the population in southern Sweden.
Design: A register-based, cross-sectional cohort study.
Design: Setting and subjects: The inhabitants from 20 years of age onwards ($N = 981,383$) living in southern Sweden in 2015.
Design: Main outcome measure: Prevalence and mean probability of having heart failure in both genders. CNI (Care Need Index) percentiles depend on the socioeconomic status of their listed primary healthcare centres.
Results: Men had a higher OR for HF – 1.70 (95% CI 1.65–1.75) - than women. The probability of men having heart failure increased significantly compared to women with advancing age and multimorbidity levels. At all CNI levels, the multimorbid patients had a higher prevalence of heart failure in men than in women. The disparity in the mean probability of heart failure between the most affluent and deprived CNI percentile was more apparent in women compared to men, especially from 80 years.
Conclusions: The prevalence of heart failure differs significantly between the genders. Men had an increasing mean probability of heart failure with advancing age and multimorbidity level compared to women. Socioeconomic deprivation was more strongly associated with heart failure in women than in men.
The probability of having heart failure differs between the genders in several aspects.

KEY POINTS

- Independently of socioeconomic status, men had a higher prevalence of heart failure than women among the multimorbid patients.
- The mean probability of men having heart failure increased significantly compared to women with advancing age and multimorbidity level.
- Socioeconomic status was more strongly associated with heart failure in women than in men.

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Introduction

HF represents a global health problem that has a high impact on healthcare resources and affects approximately 26 million adults worldwide [1]. HF is one of the leading causes of morbidity and mortality among elderly individuals, and the mortality rate remains high despite the implementation of new treatment strategies. With increased life expectancy, combined with innovative treatments for cardiovascular comorbidities, HF is a major burden for healthcare services in many high-income countries.

HF presents with similar symptoms in both men and women. However, females are generally older and have a higher EF (ejection fraction) have and more HF-related symptoms than men [1]. Three criteria are required for the diagnosis of HF: typical clinical

CONTACT Mia Scholten Mia.Scholten@med.lu.se Center for Primary Health Care Research, Department of Clinical Sciences, Malmö Lund University, Sweden

symptoms, such as dyspnoea, fatigue, exertional intolerance and oedema of the lower body; objective findings of elevated BNP value; and impaired cardiac function on echocardiography, myocardial scintigraphy, magnet resonance tomography or other imaging [2].

HF is classified as HFrEF (heart failure with reduced ejection fraction), HFmrEF (heart failure with mildly reduced ejection fraction), and HFpEF (heart failure with preserved ejection fraction). All subtypes of HF have the same clinical symptoms, but different pathophysiology and prognosis. HFrEF is established when the left ventricle loses its ability to contract normally, whereas HFpEF is established when the left ventricle loses its ability to relax normally. HFmrHF has a mixture of characteristics from both HFrEF and HFpEF regarding aetiology, pathophysiology and comorbidities [3]. The symptoms of HF are usually not specific like wheezing, coughing, and shortness of breath, which can be misinterpreted as bronchial asthma and can delay the diagnosis of cardiac asthma caused by congestive HF [4]. Women have double the risk for incident HFpEF and are more likely to have a background of hypertension and valve dysfunctions as HF aetiologies compared to men [1,5]. Men are predisposed to HFrEF with ischaemic aetiology and have an earlier onset of HFrEF and a higher mortality rate compared to women [6]. Although cardiovascular risk factors predispose both genders to HFrEF, diabetes and obesity significantly increase the risk of HFrEF in women compared to men. Generally, it is observed that female HF patients tend to have more comorbidities such as atrial fibrillation, diabetes, hypertension, anaemia, iron deficiency, renal disease, arthritis, depression, and thyroid abnormalities [1].

Multimorbidity is common in all subtypes of HF, but slightly more severe in HFpEF. A majority of deaths in patients with HFpEF are cardiovascular-related, but the proportion of non-cardiovascular related deaths is higher in patients with HFpEF than HFrEF [7].

Low socioeconomic status is one of the most common predictors of morbidity and premature mortality in the world, even when taking traditional risk factors into consideration [8], not least for the morbidities that contribute most to the mortality rate, i.e. cancer and cerebrovascular diseases [9, 10]. Prior studies reported inequalities in HF risk according to neighbourhood, socioeconomic deprivation, education and occupational social class. Notably, the increased HF risk in the socioeconomically deprived population was only partly influenced by established cardiovascular risk factors, including hypertension, hyperlipidaemia, diabetes, smoking, and physical inactivity [11–16]. Marital status is also one of the important socioeconomic factors; living alone is often associated with a lower income. Unmarried men have double the age-adjusted relative mortality risk and higher incidence of HF compared to their married counterparts. There is a continuous gradient in Western countries, including Sweden, between cardiovascular morbidity and mortality and socioeconomic status (SES), with higher SES being more favourable [17–20]. The aim of this study was to explore the disparities in the prevalence of HF between men and women in relation to age, multimorbidity level and socioeconomic status of the population listed at primary healthcare centres in southern Sweden.

Material and methods

Setting and study population

Most residents in Sweden are listed at a primary healthcare centre. Scania is the southernmost county of Sweden and had approximately 1.3 million inhabitants in 2015. The whole study population was recruited from Scania. The biggest city in Scania is Malmö, which is Sweden's third largest city, and had approximately 320,000 inhabitants during the study period. In 2015, about a third of the residents in Malmö were born abroad with most countries in the world being represented, whilst approximately 25% of the whole study population were born abroad [21]. Almost half of the inhabitants (48.40%) in Malmö were under 35 years of age in 2015 [22].

The study population was divided into age groups from 20 to 80. The age group 20 included all individuals between 20 to 29 years, the age group 40 included all individuals between 40 to 49 years, and so on. The age group 80 included all individuals aged 80 years and older. Gender was categorised as female and male.

Data source and measurements

The data we used in this study were retrieved from the Scania County Council healthcare register which contains anonymised registry information from the population, including age, gender, socioeconomic status and diagnostic data. Data were collected concerning diagnoses at each consultation in both primary and secondary health care. Diagnoses were recorded according to the International Statistical Classification of Diseases and Related Health Problems version 10

(ICD 10). HF was identified if the diagnosis code I50 was recorded, which comprised all subtypes of HF. A total of 152 primary healthcare centres were in operation in Scania during 2015, with an average of 8587 listed patients (95% CI 7971 – 9292) including 133 patients with HF (95% CI 122 – 143) at each primary healthcare centre.

Multimorbidity

To measure multimorbidity we used a method developed by A Calderòn-Larrañaga et al. at The Aging Research Centre in Stockholm [23]. They analysed the full list of ICD-10 codes on a four-digit level to define if a diagnosis is chronic or not in an elderly population. A disease or condition was considered to be chronic if it had a prolonged duration and either (a) left residual disability or worsening quality of life or (b) required a long period of care, treatment, or rehabilitation. This measure of multimorbidity was designed for persons older than 60 years and was based on a clinical assessment of medical diagnoses by specialists in geriatrics and family medicine.

To determine if a condition is chronic or not the following key features were identified and discussed concerning their pertinence and sustainability: duration, course, reversibility, treatment, and consequences. The diagnoses were then grouped into 60 chronic disease categories, which is the most comprehensive list of chronic conditions for measuring multimorbidity thus far. The broad scope of diagnoses included conditions such as blood diseases, lens diseases, chromosomal abnormalities, chronic infectious diseases, chronic ulcers of the skin, allergies, autoimmune and connective tissue diseases, glaucoma, multiple sclerosis, peripheral neuropathy, venous and lymphatic disorders etc. We applied their definition and list of chronic conditions to estimate multimorbidity in the study population. Multimorbidity was then estimated by counting the number of chronic conditions in each patient. All diagnoses from the last week of 2015 were obtained from the electronic medical record database in Scania County Council. Those individuals who had at least two of these chronic conditions were considered multimorbid. To study the degree of multimorbidity in relation to the prevalence of HF, the patients were then further divided into groups MM0 (less than two chronic conditions), MM1 (two to four chronic conditions), MM2 (five to nine chronic conditions), and MM3 (ten chronic conditions or more).

Socioeconomics

We used the term Care Need Index (CNI) [24] to divide the primary healthcare centres into 10 groups depending on their socioeconomic status. CNI is based on different measures of a group, which in our study were the patients listed at different primary healthcare centres in Scania. CNI 1 percentile was assigned to those listed patients at primary healthcare centres that belonged to the most socioeconomically affluent population; CNI 10 percentile was assigned to those

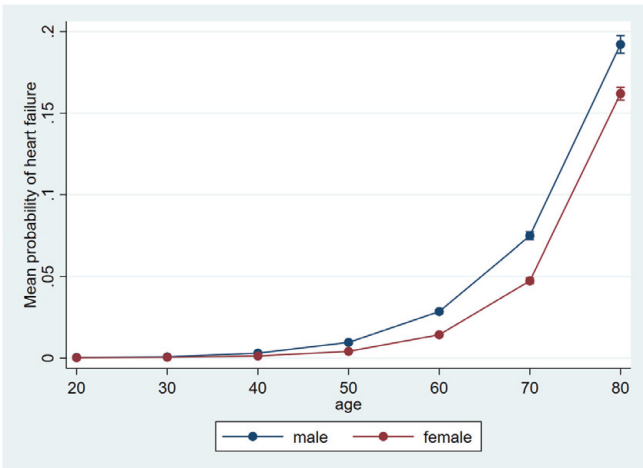

Figure 1. The mean probability of heart failure in women and men adjusted for age with 95% confidence intervals, using Delta method.

Table 1. Prevalence of heart failure and multimorbidity in all age groups and CNI (Care Need Index) percentiles, and prevalence of heart failure in the multimorbid patients in women and men.

	Women					Men				
	HF		MM			HF		MM		
CNI percentiles	N	%	N	%	HF/MM %	N	%	N	%	HF/MM %
CNI 1										
age										
20	2	0.03	1243	20.29	0.16	2	0.03	780	11.57	0.26
30	4	0.04	2403	25.01	0.17	6	0.07	1138	13.74	0.53
40	9	0.07	3670	29.55	0.25	25	0.20	2408	19.53	1.04
50	20	0.23	3669	41.58	0.55	68	0.76	3070	34.18	2.21
60	102	1.01	6059	60.10	1.68	209	2.25	5437	58.61	3.84
70	240	3.53	5317	78.20	4.51	442	6.75	5129	78.35	8.62
80	507	15.13	2987	89.14	16.97	442	19.53	2016	89.09	21.92
CNI 2										
age										
20	3	0.04	1538	19.00	0.20	4	0.05	879	10.88	0.46
30	1	0.01	2091	25.06	0.05	3	0.04	1143	14.74	0.26
40	9	0.09	3134	29.68	0.29	24	0.24	2119	20.79	1.13
50	29	0.30	4057	42.23	0.71	65	0.70	3231	34.80	2.01
60	127	1.26	5767	57.43	2.20	234	2.42	5578	57.58	4.20
70	257	3.89	5017	75.97	5.12	381	6.20	4640	75.47	8.21
80	548	14.66	3221	86.17	17.01	429	1.89	2222	87.48	19.31
CNI 3										
age										
20	1	0.01	1609	19.48	0.06	5	0.06	936	10.75	0.53
30	6	0.08	1977	25.55	0.30	4	0.05	1063	14.15	0.38
40	7	0.08	2763	33.23	0.25	24	0.29	1787	21.58	1.34
50	35	0.47	3216	43.37	1.09	67	0.93	2577	35.68	2.60
60	95	1.22	4660	59.70	2.04	218	2.88	4409	58.19	4.94
70	253	4.71	4176	77.72	6.06	371	7.92	3607	77.02	10.29
80	586	16.81	3059	88.76	18.93	415	20.09	1801	87.17	23.04
CNI 4										
age										
20	1	0.01	1486	21.10	0.07	5	0.07	788	11.15	0.63
30	7	0.10	1754	25.99	0.40	4	0.06	1009	15.10	0.40
40	9	0.12	2577	33.12	0.35	34	0.43	1774	22.21	1.92
50	36	0.49	3261	44.59	1.10	85	1.16	2772	37.74	3.07
60	105	1.45	4297	59.38	2.44	245	3.23	4505	59.36	5.44
70	252	5.34	3601	76.28	7.00	378	8.06	3587	76.51	10.54
80	560	18.06	2708	87.33	20.68	423	20.93	1762	87.18	24.01
CNI 5										
age										
20	0	0.00	1301	20.53	0.00	2	0.03	700	10.84	0.29
30	3	0.05	1788	27.37	0.17	4	0.06	925	13.94	0.43
40	11	0.16	2244	33.36	0.49	24	0.34	1605	22.44	1.50
50	18	0.30	2680	45.06	0.67	56	0.90	2289	36.96	2.45
60	76	1.31	3443	59.26	2.21	180	3.04	3407	57.62	5.28
70	183	4.86	2866	76.06	6.39	284	7.97	2763	77.50	10.28
80	451	17.31	2306	88.49	19.56	354	22.52	1380	87.79	25.65
CNI 6										
age										
20	1	0.01	1698	19.47	0.06	2	0.02	1071	11.38	0.19
30	2	0.03	1989	25.51	0.10	6	0.08	1116	14.04	0.54
40	13	0.14	2942	32.42	0.44	28	0.30	2025	21.99	1.38
50	41	0.50	3620	43.99	1.13	68	0.82	3075	37.05	2.21
60	127	1.54	4781	57.80	2.66	205	2.51	4709	57.67	4.35
70	272	4.43	4709	76.71	5.78	347	6.53	4077	76.66	8.51
80	642	14.73	3768	86.46	17.04	467	18.41	2180	85.96	21.42
CNI 7										
age										
20	3	0.04	1484	17.44	0.20	7	0.07	936	9.82	0.75
30	4	0.06	1659	23.86	0.24	6	0.08	1019	13.23	0.59
40	12	0.17	2226	31.61	0.54	21	0.29	1582	21.50	1.33
50	27	0.43	2705	42.79	1.00	66	1.05	2291	36.51	2.88
60	91	1.37	3809	57.17	2.39	185	2.87	3609	55.90	5.13
70	229	4.74	3651	75.57	6.27	314	7.66	3084	75.24	10.18
80	605	17.12	3025	85.62	20.00	388	19.06	1751	86.00	22.16
CNI 8										
age										
20	2	0.02	2390	20.33	0.08	3	0.03	1211	11.37	0.25
30	3	0.03	2778	26.73	0.11	16	0.15	1582	14.89	1.01

(*continued*)

Table 1. Continued.

	Women					Men				
	HF		MM			HF		MM		
CNI percentiles	N	%	N	%	HF/MM %	N	%	N	%	HF/MM %
40	14	0.15	3224	33.45	0.43	31	0.32	2214	22.99	1.40
50	50	0.54	4139	44.86	1.21	95	1.11	3174	37.21	2.99
60	114	1.28	5235	58.71	2.18	232	2.86	4543	56.10	5.11
70	269	4.58	4450	75.77	6.04	378	7.91	3581	74.95	10.56
80	625	15.58	3464	86.36	18.04	387	19.08	1730	85.31	22.37
CNI 9										
age										
20	0	0.00	2194	18.32	0.00	3	0.03	1136	10.20	0.26
30	4	0.04	2411	23.78	0.17	7	0.06	1565	13.74	0.45
40	10	0.13	2468	31.44	0.41	29	0.34	1847	21.64	1.57
50	29	0.41	3185	44.51	0.91	74	0.97	2744	35.84	2.70
60	117	1.82	3661	56.87	3.20	217	3.49	3287	52.94	6.60
70	253	5.16	3687	75.18	6.86	307	7.65	2882	71.85	10.65
80	626	15.47	3344	82.63	18.72	353	17.50	1670	82.80	21.14
CNI 10										
age										
20	6	0.04	2311	17.06	0.26	4	0.03	1239	9.75	0.32
30	6	0.06	2334	24.46	0.26	10	0.09	1612	13.72	0.62
40	18	0.26	2601	37.30	0.70	30	0.37	1907	23.46	1.57
50	29	0.49	2879	48.68	1.01	90	1.35	2578	38.55	3.49
60	130	2.80	2712	58.50	4.79	175	3.75	2528	54.16	6.92
70	260	8.20	2319	73.13	11.21	268	10.39	1787	69.26	15.00
80	443	19.24	1891	82.15	23.43	228	19.86	895	77.96	25.47

HF = heart failure.
MM = Multimorbidity.
N = number of patients.

patients listed at primary healthcare centres that belonged to the most deprived population [24].

Statistical analyses

We used frequencies, percentages and cross-tabulations for descriptive analysis. Multivariable logistic regression was used to analyse the multivariate models. Only the linear predictions of the fully adjusted models are shown in the figures. A p-value of < 0.05 was considered statistically significant. The predicted mean probability of HF was calculated as average marginal effects and contrasts using the Delta-method. The Delta-method is a statistical method, which we used to calculate the mean probability of HF in different categories [25]. We used STATA version 16.0 and 17.0 (Stata Corporation, Texas, USA) for statistical analyses and to create the artwork.

Results

We analysed data from 981,383 inhabitants (about a tenth of the Swedish population) aged 20 years and older living in Scania in the last week of 2015. The study population consisted of 50.85% women and 49.15% men. The total prevalence of HF was 1.93% (9,630 patients) in women and 2.19% (10,563 patients) in men. Men had a higher odds ratio for HF – 1.70 (95% CI 1.65–1.75) - than women. Men had a higher prevalence and mean probability of HF than women across all age groups, and the difference in prevalence and mean probability of HF between the genders increased continuously with advancing age. In the age group 80, the difference in prevalence reached 3.01% and the mean probability was 0.03 between the genders (Figure 1).

The total prevalence of multimorbidity was 42.82% in women (213,685 patients) and 33.89% in men (163,470 patients) in 2015. The women had a higher prevalence of multimorbidity in all age groups and CNI percentiles, but included a lower prevalence of HF, when compared to men. Men had also a higher prevalence of HF among the multimorbid patients than women in all CNI percentiles (Table 1).

Men had a higher mean probability of HF in all multimorbidity levels and the difference increased with each multimorbidity level, except the MM0 group, when compared to women. The predicted mean probability of HF as a comorbidity in men belonging to the age group 70 was 0.06 (95% CI $0.05 - 0.06$) in the MM2 (5-9 chronic conditions) group, and 0.10 (95% CI $0.07 - 0.13$) in the MM3 (>10 chronic conditions) group, if compared to women as reference (Figure 2).

The women listed at the primary healthcare centres with the most affluent CNI percentile had the lowest

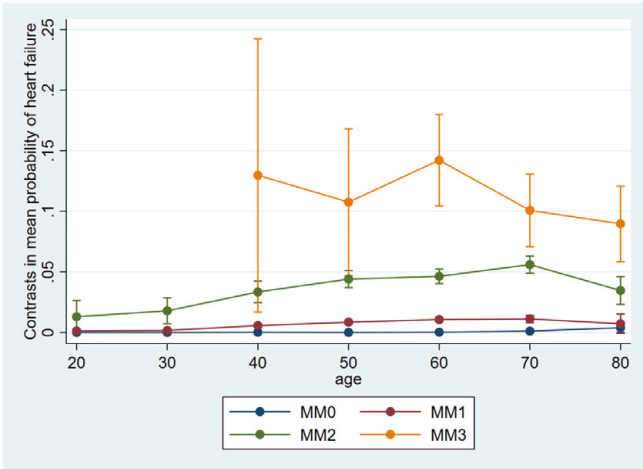

Figure 2. The difference in mean probability of heart failure between the genders with increasing level of multimorbidity used women as reference with 95% confidence intervals, using Delta method. MM0 = less than two conditions (not multimorbid); MM1 = 2-4 chronic conditions; MM2 = 5-9 chronic conditions; MM3 = more than 10 chronic conditions.

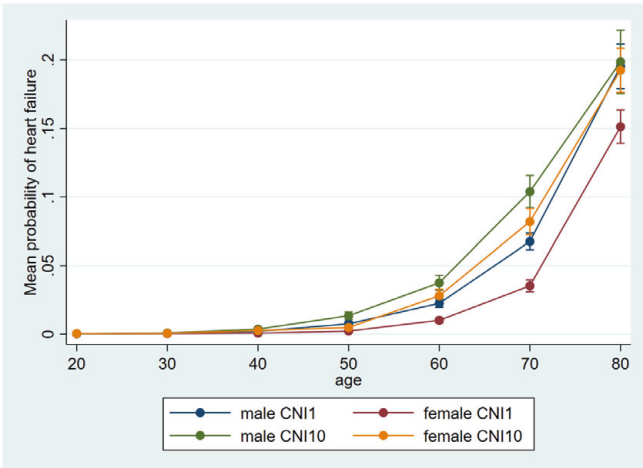

Figure 3. Disparities in mean probability of heart failure between the genders in the most affluent and deprived CNI (Care Need Index) percentile with 95% confidence intervals, using Delta method.

prevalence of HF in the whole study population. The men listed at the primary healthcare centres with the most deprived CNI percentile had the highest prevalence of HF between 50 to 80 years of age, while the women belonging to this CNI percentile had the highest prevalence of HF from 60 years of age, if compared to the more affluent CNI percentiles (Table 1). The disparity in the mean probability of HF between the most affluent and deprived CNI percentile was more apparent in women compared to men (Figure 3). The most obvious disparity was observed in the HF patients from 80 years: Women had about a 14 times

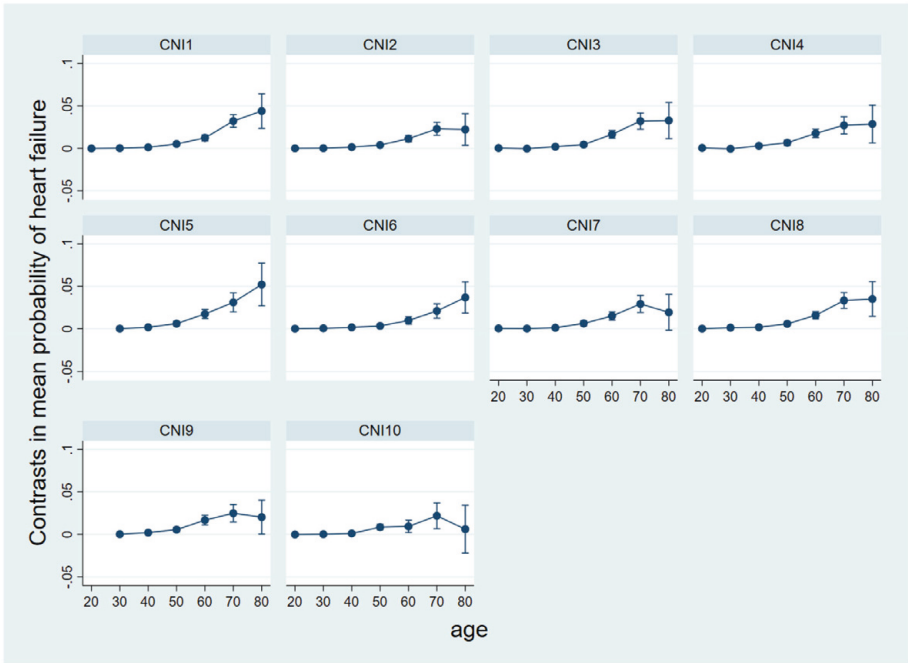

Figure 4. The difference in mean probability of heart failure in all age groups and CNI (Care Need Index) percentiles between the genders used women as reference with 95% confidence intervals, using Delta method.

higher disparity of mean probability of HF than men between the most affluent and deprived percentile (Figure 3).

Men had an increasing mean probability of HF and confidence interval with advancing age compared to women in most CNI percentiles. Most values were statistically significant from 50 years of age with the exception of the age group 80 in CNI percentiles 7 and 10, indicating no difference in mean probability of having HF between the genders in these groups (Figure 4).

Discussion

The total prevalence of HF was 1.93% (9,630 patients) in women and 2.19% (10,563 patients) in men. Men had a higher OR for HF – 1.70 (95% CI 1.65–1.75) - than women. The mean probability of men, compared to women, having HF increased significantly with advancing age and multimorbidity level. The women had a higher prevalence of multimorbidity in all age groups and CNI percentiles, but a lower prevalence of HF, when compared to men. Men had also a higher prevalence of HF among the multimorbid patients than women in all CNI percentiles. The disparity in the mean probability of having HF between the most affluent and deprived CNI percentile was more apparent in women, which suggests that socioeconomic deprivation was more strongly associated with HF in women than in men. Growing evidence supports the cardioprotective effect of oestrogen [26], which could explain the lower prevalence of HF in women within each CNI percentile, although our results indicate that socioeconomic deprivation was independently associated with HF as well as gender and multimorbidity.

Strengths and weaknesses of the study

The main strength of this study was the large study population comprising almost one million inhabitants, corresponding to about 10% of the Swedish population. HF is known to be strongly associated with advancing age, but our results even analysed a crude difference between the genders having HF in relation to multimorbidity level and socioeconomic status.

This study has several limitations. All patients with the diagnosis code I50 were included, which did not distinguish the subtypes of HF characterised by

different aetiologies and multimorbidity levels. Since HF might appear with non-specific symptoms, we suspect that this condition is underdiagnosed. In particular, HFpEF, is more difficult to diagnose than HFrEF, due to a lack of objective findings of reduced ejection fraction during echocardiography.

We have no data on the severity of HF, which is an important factor regarding the outcome and mortality. Furthermore, we had no access to many risk factors of HF, such as heredity, congenital heart disease, drug abuse or obesity. The data on comorbidities with a high impact on mortality were also lacking. Many patients were most likely underdiagnosed concerning the conditions, which had no impact on their quality of life or prognosis, thus resulting in a lower prevalence of multimorbidity and multimorbidity levels. The low availability of cardiologic consultations in primary health care could influence the treatment outcome and the prognosis of HF. We had no data on the quality of health care in the neighbourhood.

Findings in relation to other studies

Our findings have similarities with studies conducted in other countries [27,28], which increases the credibility and validity of our results. A prior study reported that men were approximately five years younger than women at the time of HF diagnosis [27]. Some improvements for men have been observed, probably due to improved primary coronary interventions, but this sex difference persisted over time and is still consistent with our findings [29]. An American epidemiologic cohort study also reported that HF is far more prevalent in men than women across all age groups from the age of 20, with more apparent differences among elderly people [28]. Various chronic disorders tend to coexist and predominate as possible etiologies for HF including coronary disease, hypertension, and diabetes mellitus [30]. All these disorders are associated with socioeconomic deprivation [31], which contributes to increased multimorbidity levels as well.

With the prevention of cardiovascular diseases, obesity and smoking [32], HF occurs later in their life but still affects mostly male, elderly, multimorbid and socioeconomically deprived individuals [33]. It is most likely a complex pathway between socioeconomic deprivation and disparities in the prevalence of HF between the genders. Further studies are warranted to investigate the specific risk factors for HF and multimorbidity associated with age, gender and socioeconomic deprivation to improve general health. The more we learn about the risk factors and diagnoses constituting multimorbidity, the more we can improve public health. Multimorbidity is most likely a continuous scale of interactive chronic disorders rather than single diagnoses. Analyzing the composition of multimorbidity in HF patients should be the next step towards increased knowledge about their risk factors. Our data revealed a high prevalence of multimorbidity in young women, who could have diagnoses such as thyroid disease, asthma and psychiatric disorders, which are common chronic disorders in young people [34]. Socioeconomic inequality is a political issue and is known to have health consequences. Healthcare staff could offer more preventive strategies for the socioeconomically deprived population, in order to diminish this inequality indirectly.

Meaning of the study and conclusions

The prevalence of HF differs significantly between the genders. Men had an increasing mean probability of HF with advancing age and multimorbidity level compared to women. HF constitutes one of the SES-related conditions and most likely worsens the prognosis of multimorbid patients. Standardized pathways should be implemented nationally to diagnose and provide care for HF patients in primary health care. Prevention of socioeconomic inequality could be an important approach to reducing the prevalence of HF, especially in women.

Acknowledgements

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Consent for publication

Not applicable.

Statement of ethics

Data in the present study are based on anonymised information provided by Scania County Council. They provided anonymised information for research purposes once the study had been approved by the Ethics Committee at Lund University (application no. 2018/778). All analyses were performed in accordance with relevant guidelines and regulations.

Due to the requirement for anonymised data, each individual could not be asked for consent to participate; the active refusal of participation was instead applied. This was done by publishing information about the planned study in the Swedish local newspaper "Sydsvenskan". The

advertisement outlined the study and contained information on how to contact the research manager (first author) to opt out of the study.

Disclosure statement

The authors declare that they have no competing interests.

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ORCID

Mia Scholten http://orcid.org/0000-0002-3519-0129
Patrik Midlöv http://orcid.org/0000-0002-5871-8731
Anders Halling http://orcid.org/0000-0002-1035-7586

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Paper III

PLOS ONE

RESEARCH ARTICLE

Associations of heart failure to prevalence of haematologic- and solid malignancies in southern Sweden: A cross-sectional study

Mia Scholten*, Anders Halling

Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden

* Mia.Scholten@med.lu.se

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Abstract

Background

Heart failure (HF) and cancer are common diseases among the elderly population. Many chronic diseases, including diabetes mellitus (DM), share risk factors and increase the incidence of HF and cancer. The aim of this study was to investigate if there was an association between HF and the prevalence of haematologic- and solid malignancies.

Methods

The study population was comprised of almost one million adults living in southern Sweden in 2015. All participants were divided into seven age groups from 20 and onwards, and 10 percentiles according to their socioeconomic status (SES). All data concerning diagnoses from each consultation in both primary- and secondary health care were collected during 18 months. The prevalence of haematologic and solid malignancies was measured separately for men and women, age groups, SES and multimorbidity levels. Multivariable logistic regression was used to determine the associations between HF and the probability of having haematologic- and solid malignancies in more complex models including stratifying variables.

Results

People with HF had a higher prevalence of haematologic- and solid malignancies than the general population, but a lower prevalence of solid malignancies than the multimorbid population. The people with HF had an increased OR for haematologic malignancies, 1.69 (95% CI 1.51–1.90), and solid malignancies, OR 1.21 (95% CI 1.16–1.26), when adjusted for gender and age. In more complex multivariate models, multimorbidity explained the increased OR for haematologic- and solid malignancies in people with HF. Increasing socioeconomic deprivation was associated with a decreased risk for solid malignancies, with the lowest risk in the most socioeconomically deprived CNI-percentile.

Conclusions

HF was shown to be associated with malignancies, especially haematologic malignancies. Multimorbidity, however, was an even more important factor for both haematologic- and

solid malignancies than HF in our study, but not socioeconomic deprivation. Further research on the interactions between the chronic conditions in people with HF is warranted to examine the strength of association between HF and malignancies.

Introduction

HF and cancer are common diseases among the elderly population. Many chronic diseases, including DM, share risk factors such as sedentary lifestyle, genetics, obesity and tobacco smoking, which are also known risk factors for HF and cancer [1–3]. HF is mostly a complication or end stage of other cardiovascular diseases (CVD) and is strongly associated with multimorbidity. Results from our previous study of this population have shown that almost all (99.07%) adult people with HF had multimorbidity [4]. Furthermore, patients in the most socioeconomically deprived percentile were affected by HF many years earlier than patients in the more socioeconomically affluent percentiles [4]. People with HF due to ischaemic heart disease have been reported to have a higher incidence of cancer compared to HF due to other aetiologies [5]. Chronic diseases such as hypertension and DM have also been shown to be associated with an increased risk for cancer [6,7].

Cancer and CVD are both associated with a high mortality rate. Around 15% of the global death burden is due to cancer and 30% is a result of CVD [8]. Both HF and cancer have been linked to increased chronic inflammation and oxidative stress, which play central roles in the pathophysiology of both diseases [2]. Several studies have provided evidence that the progression of either HF or cancer is linked to enhanced tissue inflammation [9,10]. In addition, it has been speculated that radiation, epigenetic mechanisms and regenerative signalling are all potential links to both HF and cancer [11]. RAAS activation—a common response to HF—has been shown to be strongly associated with an increase in tumour angiogenesis, angiogenetic factor expression, invasiveness and metastasis leading to a poor prognosis [12]. Treatment of HF with angiotensin receptor blockers (ARBs) or ACE inhibitors (ACEi) has been hypothesised to reduce the risk for cancer based on data derived from both the SOLVD and CHARM studies [13]. A Danish study enrolling 9,307 people with HF (predominantly with left ventricular ejection fraction $< 45\%$) showed a higher incidence rate of malignancies compared to the general population [14].

DM, which is a common comorbidity in people with HF, represents a risk factor for cancer, particularly hepatocellular, hepatobiliary, pancreas, breast, ovarian, endometrial, and gastrointestinal cancers [15]. Between 8% and 18% of individuals with diagnosed cancer also have DM as a comorbidity [15]. Moreover, there is evidence showing that DM is associated with higher cancer mortality [16,17]. Although the links between DM and cancer are not yet completely understood, biological mechanisms such as increased bioactivity of insulin-like growth factor 1, chronic inflammation, oxidative stress, dysregulations of sex hormones, direct effects of excess glucose and insulin signalling are most likely involved [18–21].

In this study, we aimed to investigate if there was an association between HF and the prevalence of haematologic- and solid malignancies. DM, as a common comorbidity in people with HF, was also analysed to study its impact on the association between HF and the probability of having haematologic- and solid malignancies.

Materials and methods

Setting and study population

Scania is the southernmost county of Sweden and had approximately 1.3 million inhabitants in 2015 [22]. The biggest city in Scania is Malmö, which had about 320,000 inhabitants during the study period, and is ranked as the third largest city in Sweden [22]. About a third of the residents in Malmö were born abroad with most countries in the world being represented [23], whilst approximately 25% of the whole study population were born abroad [24]. Almost half of the inhabitants (48.40%) in Malmö were under 35 years of age in 2015 [25].

This is a cross-sectional study, which included all inhabitants from the age of 20 and older living in Scania during the last week of 2015. This age cut-off was chosen because children and younger people tend to have subtypes of HF with other aetiologies than those found in older adults. The study population was divided into seven age groups, ranging from 20 to 80. The age group 20 included all individuals from 20 to 29 years, and the age group 50 included all individuals from 50 to 59 years, and so on. The age group 80 included all individuals aged 80 and older. The general population was comprised of all the participants in our study.

Data source and measurements

Most residents in Sweden are listed at a primary health care centre (PHC). A total of 152 PHCs were in operation during 2015 in Scania, with an average of 8587 listed patients (95% CI 7971–9293) at each PHC. The data we used in this study were retrieved from the Scania County Council health care register that contains anonymised registry information from 981,383 (about a tenth of the Swedish population) inhabitants, including age, gender, socioeconomic status and diagnostic data. **This database has a good quality because all patient data are included from both private and public health care, which is also a part of the Swedish national patient register.** During a period of 18 months (July 2014—December 2015), we collected all data concerning diagnoses from each consultation in both primary- and secondary health care. Diagnoses were recorded according to the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD 10) (Appendix Table 1 in S1 Appendix).

Socioeconomics

We used the term Care Need Index (CNI) [26] to divide the PHCs into 10 percentiles depending on their socioeconomic status. CNI is based on different measures of a group, which in this case was the patients listed at different PHCs in Scania. CNI 1 was assigned to those patients listed at PHCs that belonged to the most socioeconomically affluent percentile, and CNI 10 was assigned to those patients listed at PHCs that belonged to the most socioeconomically deprived percentile [26].

Multimorbidity

Multimorbidity is defined as the simultaneous coexistence of two or more chronic conditions in the same person [27]. To measure multimorbidity, we used a method to identify chronic conditions developed by A Calderòn-Larrañaga *et al.* at the Aging Research Centre in Stockholm [27]. They analysed the full list of ICD-10 codes on a four-digit level to define if a diagnosis is chronic or not in an elderly population. To determine if a condition is chronic or not the following key features were identified and discussed concerning their pertinence and suitability in older populations: duration, course, reversibility, treatment, and consequences. They were then grouped into 60 chronic disease categories [27]. We applied their definition and list

of chronic conditions to estimate multimorbidity in our study population. Multimorbidity was then calculated by counting the number of chronic conditions in each patient. To study the degree of multimorbidity, the patients were further divided into groups MM0 (less than two chronic conditions), MM1 (two to four chronic conditions), MM2 (five to nine chronic conditions) and MM3 (10 chronic conditions or more).

Statistical analyses

The study population was divided into HF-, DM patients and the general population with and without haematologic- respective solid malignancies, which were further stratified according to gender, age and multimorbidity level. We used frequencies, percentages and cross-tabulations for descriptive analysis and Chi-square-test to calculate the p-values. A p-value ≤ 0.05 was considered to be statistically significant. A p-value between 0.01 and 0.05 was considered to be a low level of significance; between 0.001 and 0.01 as a middle level of significance; and ≤ 0.001 as a high level of significance. Multivariate logistic regression of increasing complexity (Models A—E) was used to analyse the associations between HF and the probability of having haematologic-respective solid malignancies. The different variables in Model A—E are listed in Appendix Table 2 in S1 Appendix. All statistical analyses were performed with STATA version 17.0 (Stata Corporation, Texas, USA).

Ethics

Data in the present study are based on anonymised information provided by the Scania County Council. They provided anonymised information for research purposes once the study had been approved by the Ethics Committee at Lund University. We confirm that all analyses of the human data were performed in accordance with relevant guidelines and regulations as stated in the Declaration of Helsinki.

The study participants were not involved in the recruitment to the study by themselves. Due to the requirement concerning anonymised data, each individual could not be asked for consent to participate; active refusal of participation was instead applied. This was done by publishing information about the planned study in the Swedish local newspaper "Sydsvenskan". The advertisement outlined the study and contained information on how to contact the research manager (first author) to opt out of the study. The regional Ethical Review Board at Lund University approved the study (application no. 2018/778), which deemed the informed consent process as unnecessary, since the study results are published anonymised on a group level, and cannot be traced to every study participant.

Results

The total prevalence of HF in the study population was 2.06%, of whom 28.04% also had DM. A total of 0.39% of the study population had haematologic malignancies and 4.97% had solid malignancies (Table 1). The prevalence of haematologic malignancies in people with HF was 1.73% and for solid malignancies, it was 16.60%. The total prevalence of DM was 6.50% in the study population, but the prevalence of haematologic- (0.83%) and solid malignancies (10.47%) was lower compared to the people with HF (Table 1). The people with HF having 2–9 chronic conditions had a higher prevalence of haematologic malignancies compared to the general population, but not the people with HF having 10 comorbidities or more. People with HF had a lower prevalence of solid malignancies than the general population with multimorbidity of all levels (Table 1).

People with HF had an increased OR for haematologic malignancies, OR 1.69 (95% CI 1.51–1.90), and solid malignancies, OR 1.21 (95% CI 1.16–1.26) when adjusted for age and

Table 1. Prevalence of haematologic- and solid malignancies in the general population compared to patients with heart failure or diabetes mellitus.

	General population					Haematologic malignancies						Solid malignancies					
		Heart failure		Diabetes mellitus		General population		Heart failure		Diabetes mellitus		General population		Heart failure		Diabetes mellitus	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Gender																	
men	482355	2.19	10563	7.57	36516	0.43	2055	1.92	203	0.94	345	5.13	24757	19.41	2051	11.60	4236
women	499028	1.93	9630	5.45	27210	0.36	1802	1.52	146	0.67	181	4.61	23018	13.51	1301	8.95	2436
p-value*									NS		< 0.001				< 0.001		< 0.001
Age (years)																	
20–29	180876	0.03	56	0.76	1373	0	0	0	0	0	0	0.45	818	0	0	0.51	7
30–39	170080	0.06	106	1.28	2175	0.09	152	0.94	1	0.23	5	0.80	1367	1.89	2	1.47	32
40–49	175095	0.22	382	3.02	5288	0.15	268	1.05	4	0.26	14	1.59	2783	3.14	12	2.29	121
50–59	152432	0.69	1048	6.94	10586	0.29	445	1.43	15	0.46	49	3.56	5422	5.92	62	4.28	453
60–69	149540	2.13	3184	12.52	18718	0.68	1021	1.79	57	0.74	138	8.67	12961	11.78	375	9.41	1762
70–79	98599	6.02	5938	17.28	17037	1.15	1136	1.92	114	1.20	204	15.00	14793	17.75	1054	16.06	2736
≥ 80	54761	17.31	9479	15.61	8549	1.33	728	1.67	158	1.36	116	17.59	9631	19.49	1847	18.26	1561
p-value*									< 0.001		< 0.001				< 0.001		< 0.001
Multimorbidity level**																	
0–1	604221	0.03	188	0.53	3190	0.07	451	0	0	0	0	1.03	6218	0	0	0	0
2–4	260764	1.49	3875	9.51	24788	0.58	1502	0.75	29	0.33	82	7.73	20165	6.37	247	4.84	1199
5–9	105241	11.16	11748	28.95	30463	1.52	1603	1.73	203	1.02	312	17.49	18410	17.08	2007	13.85	4218
≥ 10	11156	39.28	4382	47.37	5285	2.70	301	2.67	117	2.50	132	26.73	2982	25.06	1098	23.75	1255
p-value*									< 0.001		< 0.001				< 0.001		< 0.001

*p-value of proportion of haematologic- and solid malignancies according to heart failure or diabetes mellitus.

**Multimorbidity level = number of chronic conditions.

N = total number of individuals; NS = Not significant, P > 0.05.

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gender (Model B, Tables 2 and 3). These ORs decreased slightly when further adjusted for DM. DM had no significance for the probability of having haematologic malignancies, but an increased probability for solid malignancies, OR 1.07 (95% CI 1.04–1.10), when adjusted for HF, age and gender (Model C, Tables 2 and 3). The ORs of HF and DM did not change significantly when further adjusted for SES. Increasing socioeconomic deprivation was associated with a decreased risk for solid malignancies. The most socioeconomically deprived CNI percentile had a 35% lower risk for solid malignancies than the most socioeconomically privileged CNI-percentile (Model D, Tables 2 and 3). When multimorbidity was added in Model E, the ORs of HF and DM disappeared for both haematologic- and solid malignancies (Model E, Tables 2 and 3).

The ORs for haematologic malignancies exceeded the ORs for solid malignancies in the multimorbid patients of all levels (Model E, Tables 2 and 3). The probability for both haematologic- and solid malignancies increased with advancing age, but multimorbidity had a higher significance for the probability of haematologic malignancies than all age groups (Model E, Table 2). Meanwhile, only the multimorbid patients with 10 chronic conditions or more, including HF and DM, had a higher significance for the probability of solid malignancies than all age groups (Model E, Table 3). Men had a higher OR for both haematologic- and solid malignancies than women, which increased further when adjusted for multimorbidity (Tables 2 and 3).

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for haematologic malignancies in different categories.

	Model A	Model B	Model C	Model D	Model E
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender					
men	1.31 (1.23–1.40)	1.30 (1.22–1.38)	1.30 (1.22–1.38)	1.30 (1.21–1.38)	1.45 (1.36–1.54)
women	1	1	1	1	1
Age (years)					
20–29	1	1	1	1	1
30–39	1.51 (1.18–1.93)	1.51 (1.18–1.93)	1.51 (1.18–1.93)	1.50 (1.17–1.92)	1.32 (1.03–1.69)
40–49	2.59 (2.07–3.23)	2.58 (2.06–3.23)	2.58 (2.06–3.23)	2.54 (2.03–3.18)	1.86 (1.49–2.33)
50–59	4.94 (4.00–6.11)	4.92 (3.98–6.08)	4.91 (3.97–6.06)	4.85 (3.93–5.99)	2.66 (2.14–3.29)
60–69	11.64 (9.54–14.21)	11.47 (9.39–14.00)	11.41 (9.34–13.93)	11.22 (9.18–13.71)	4.46 (3.63–5.47)
70–79	19.86 (16.28–24.21)	19.04 (15.61–23.23)	18.91 (15.49–23.08)	18.59 (15.23–22.71)	5.38 (4.37–6.62)
≥ 80	23.61 (19.26–28.93)	21.04 (17.13–25.85)	20.93 (17.03–25.72)	20.69 (16.83–25.43)	5.07 (4.09–6.28)
Heart failure		1.69 (1.51–1.90)	1.68 (1.50–1.89)	1.69 (1.50–1.90)	0.94 (0.83–1.06)
Diabetes mellitus			1.04 (0.95–1.15)	1.05 (0.95–1.15)	0.56 (0.51–0.61)
Socioeconomic percentile					
1 (highest)				1	1
2				0.97 (0.85–1.10)	1.01 (0.89–1.15)
3				0.99 (0.87–1.13)	1.00 (0.88–1.14)
4				0.91 (0.79–1.04)	0.91 (0.79–1.04)
5				0.93 (0.81–1.08)	0.95 (0.82–1.09)
6				0.88 (0.77–1.00)	0.91 (0.80–1.04)
7				0.94 (0.82–1.08)	0.99 (0.86–1.13)
8				0.93 (0.82–1.06)	0.97 (0.85–1.10)
9				0.82 (0.72–0.95)	0.89 (0.78–1.03)
10 (lowest)				0.86 (0.74–1.00)	0.94 (0.80–1.09)
Multimorbidity level*					
0–1					1
2–4					5.44 (4.87–6.07)
5–9					11.95 (10.62–13.46)
≥ 10					21.41 (18.10–25.33)

*Multimorbidity level = number of chronic conditions.

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Discussion

The total prevalence of HF was 2.06% and for DM it was 6.50% in the study population. Both conditions had a higher prevalence of haematologic- and solid malignancies than the general population, but a lower prevalence of solid malignancies than the multimorbid population. Although the total prevalence of DM was approximately three times higher than HF, the DM patients had a lower prevalence of both haematologic- and solid malignancies than the people with HF. In spite of the high prevalence of DM in people with HF (28.04%), they had only slightly decreased ORs when further adjusted for DM. When multimorbidity was adjusted together with HF and DM, the ORs of HF and DM disappeared for both haematologic- and solid malignancies. These results highlight the strong association between multimorbidity and malignancies contributed by both HF and DM in our study. Nevertheless, only these two conditions together did not explain the increased probability for haematologic- or solid malignancies in the MM1 group as the ORs were 5.44 (95% CI 4.87–6.07) and 4.78 (95% CI 4.64–4.93),

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for solid malignancies in different categories.

	Model A	Model B	Model C	Model D	Model E
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender					
men	1.28 (1.26–1.31)	1.28 (1.25–1.30)	1.27 (1.25–1.30)	1.27 (1.25–1.30)	1.42 (1.39–1.45)
women	1	1	1	1	1
Age (years)					
20–29	1	1	1	1	1
30–39	1.78 (1.63–1.94)	1.78 (1.63–1.94)	1.78 (1.63–1.94)	1.76 (1.61–1.92)	1.58 (1.44–1.72)
40–49	3.55 (3.28–3.84)	3.55 (3.28–3.84)	3.54 (3.28–3.83)	3.43 (3.18–3.71)	2.64 (2.44–2.86)
50–59	8.12 (7.54–8.74)	8.11 (7.53–8.73)	8.07 (7.50–8.69)	7.85 (7.29–8.45)	4.73 (4.39–5.10)
60–69	20.96 (19.52–22.50)	20.86 (19.43–22.40)	20.69 (19.27–22.22)	19.93 (18.56–21.40)	9.20 (8.55–9.89)
70–79	39.23 (36.55–42.11)	38.75 (36.10–41.60)	38.31 (35.69–41.14)	36.85 (34.31–9.57)	12.91 (12.00–13.88)
≥ 80	48.18 (45.29–52.32)	47.01 (43.72–50.56)	46.58 (43.31–50.09)	45.20 (42.03–48.62)	13.48 (12.51–14.53)
Heart failure		1.21 (1.16–1.26)	1.20 (1.15–1.24)	1.20 (1.16–1.25)	0.69 (0.66–0.72)
Diabetes mellitus			1.07 (1.04–1.10)	1.08 (1.05–1.11)	0.58 (0.57–0.60)
Socioeconomic percentile					
1 (highest)				1	1
2				0.94 (0.91–0.97)	0.98 (0.94–1.01)
3				0.85 (0.82–0.89)	0.86 (0.82–0.89)
4				0.86 (0.83–0.90)	0.86 (0.83–0.90)
5				0.85 (0.81–0.89)	0.86 (0.82–0.90)
6				0.83 (0.80–0.86)	0.85 (0.81–0.88)
7				0.88 (0.84–0.91)	0.91 (0.88–0.95)
8				0.86 (0.83–0.90)	0.89 (0.85–0.92)
9				0.77 (0.74–0.81)	0.83 (0.80–0.87)
10 (lowest)				0.65 (0.62–0.69)	0.70 (0.67–0.74)
Multimorbidity level*					
0–1					1
2–4					4.78 (4.64–4.93)
5–9					9.13 (8.83–9.44)
≥ 10					16.04 (15.18–16.95)

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respectively. These findings indicate that both HF and DM contributed to the increased probability of haematologic and solid malignancies but, in combination with other chronic conditions, might be even stronger risk factors.

People with HF had a higher probability for haematologic than solid malignancies when adjusted for age and gender, thus suggesting a stronger association between HF and haematologic malignancies than solid malignancies. Even multimorbidity of all levels, including HF and DM, had higher ORs for haematologic than solid malignancies, indicating that multimorbidity was a more important factor for haematologic malignancies in our study. The more socioeconomically deprived CNI percentiles had a significantly lower risk for solid malignancies than the most socioeconomic privileged CNI-percentile. These findings could be explained by a lower adherence to screening guidelines in the socioeconomically deprived population resulting in a later diagnosis [28,29].

When stratifying for multimorbidity levels, only the people with HF having 2–9 chronic conditions had a higher prevalence of haematologic malignancies compared to the general population, but not the people with HF having 10 comorbidities or more. A previous study

reported a lower prevalence of people with HF having10 chronic conditions or more than those belonging to the MM2 group [4], who presumably developed fewer malignancies due to their high mortality rate.

The multimorbid patients, including HF and DM, had a higher OR for haematologic malignancies than all age groups. For solid malignancies, only the multimorbid patients with 10 chronic conditions or more had a higher OR than all age groups. These findings indicate that multimorbidity was a more important factor for haematologic malignancies independent of age, meanwhile multimorbidity with 10 chronic conditions or more, including HF and DM, was a more important factor for solid malignancies independent of age.

People with HF are characterised by reduced overall perfusion and chronic inflammation, which could contribute to cancer development [2]. On the other hand, some specific mutations in haematologic malignancies could also cause HF development [30]. Another plausible explanation is HF in these patients may constitute a complication of cancer treatment [31,32]. A retrospective study revealed that the probability of incurring doxorubicin-induced HF was related to the total dose of doxorubicin administered: the higher the cumulative amount of administered drug, the more increased risk for HF. An increase in drug-related HF was also observed with advancing patient age, independent of performance status, gender, race, and tumour type [32].

A meta-analysis including around four million DM patients and 10,516 leukaemia patients reported a 3.48-fold relative risk of leukaemia within the first year of type 2 DM diagnosis than the population with normal glucose values. The incidence of leukaemia was also significantly increased in patients with type 2 DM for 1–10 years. After 10 years of the DM diagnosis, the relative risk of leukaemia declined to the level of the general population among these patients [33]. These findings could be explained by a normalisation of fasting serum glucose levels in the DM patients by anti-diabetic treatment many years after diagnosis, which prevents the development of hyperglycaemia-induced leukaemia [34]. A comprehensive meta-analysis regarding type 2 DM and the risk of developing cancer has shown that the presence of DM is associated with a 10% increase in the relative risk (RR) of developing cancer (RR, 1.10; 95% CI 1.04–1.17) [20], and the hazard ratio for cancer incidence was 1.76, (95% CI 1.71–1.81, $P < 0.001$), for people with HF [35]. These results are comparable with the DM patients in our study, who had no significance for haematologic malignancies, but an increased probability for solid malignancies, although less than the people with HF.

In a prospective cohort study, which included almost 300,000 participants from seven European countries, middle-aged and free of cancer, CVD, and DM [1]. Cox regression was used to calculate hazard ratios of developing multimorbidity in relation to body mass index (BMI), smoking status, physical activity, alcohol intake, adherence to the Mediterranean diet, and their combination as a healthy lifestyle index score. During a median follow-up of 11 years, 1.11% of the participants developed multimorbidity including cancer and cardiometabolic diseases [1]. A healthy lifestyle was inversely associated with multimorbidity. After a diagnosis of DM, the 10-year risks of multimorbidity were 30% for men and 18% for women with healthy lifestyles. For unhealthy lifestyles, the figures were 40% for men and 25% for women, respectively. After a diagnosis of CVD, the 10-year risks of multimorbidity were slightly lower than the DM patients but were comparatively higher than the cancer patients [1]. The importance of these common risk factors for lifestyle-related multimorbidity could, in part, explain the results of our study.

Another cross-sectional study reported a prevalence of 9% having any type of cancer and 38% multimorbidity [36]. Respiratory conditions and arthritis were statistically significantly associated with having all-site cancer, with OR 1.3 (95% CI 1.1–1.6) and OR 1.5 (95% CI 1.2–1.8), respectively. Multimorbidity was statistically significantly associated with having all-site

cancer (OR 1.4, 95% CI 1.2–1.7), cervical cancer (OR 2.6, 95% CI 1.2–5.4), and bladder cancer (OR 2.8, 95% CI 1.0–7.6) [36]. These results suggest that various cancer types are differently associated with various chronic conditions, and most likely composition of multimorbidity, which could explain the substantial increase of OR with advancing multimorbidity level in our study.

The estimated cancer deaths are expected to overcome those for ischaemic heart disease, with a 2.08-fold increase (1.76-fold for the increase in ischaemic heart disease) by the year 2060. Thus, cancer will become the leading cause of mortality globally immediately after 2030 [37]. Prevention of cancer is therefore a pressing issue. Our study revealed new factors associated withmalignancies, but the pathophysiology in these patient groups is still elusive and has to be explored in further studies.

Strengths and limitations

We have analysed the difference in the prevalence of haematologic- and solid malignancies between the general population and patients with two common chronic diseases. The difference in prevalence between the general population and these patient groups had a high level of statistical significance in all age groups and multimorbidity levels. We used multivariable logistic regression to compare the ORs of different variables in relation to each other to determine their significance for haematologic- and solid malignancies. Our findings have similarities with corresponding studies in other countries, which improves the validity and credibility of this study. The study population was heterogeneous comprising adults from many nationalities, which reduces the probability of consanguinity and its consequences for health.

We had no data on the hereditary forms of common solid malignancies, like breast cancer, colorectal cancer and prostate cancer. Data on heredity in our study could even influence the variables gender, age, HF, DM and multimorbidity level, but not socioeconomic status. We had no data on the subtypes of HF, which have different impacts on the complications and outcomes for these patients. The data on comorbidities in the people with HF were lacking as well, which might have stronger associations with haematologic- or solid malignancies than HF. Many haematologic- and solid malignancies affect individuals under 20 years of age more frequently than elderly individuals, which could influence our statistics radically if they were included. Some malignancies are asymptomatic or cause non-specific symptoms during the first year, which usually result in a diagnosis delay. According to current diagnosis rules, only the cancer patients receiving treatments were assigned the diagnosis categories C or D. Thus, cancer patients without current treatments might be underdiagnosed, for example, those with low malignancy or end-stage cancer. The treatments of the examined people with HF and DM could be suboptimal and result in a worse outcome and earlier complications. This was a cross-sectional study, which could have divergent results than a cohort study. Our results are largely based on administrative data and the strength of the association between HF and malignancies remains unclear.

Conclusions

HF was shown to be associated with malignancies, especially haematologic malignancies. DM explained only a small part of the increased probability for solid malignancies in the people with HF, but contributed to the increased probability for haematologic- and solid malignancies in the multimorbid population together with HF. Multimorbidity was a more important factor for both haematologic- and solid malignancies than HF in our study, but not socioeconomic deprivation. We hypothesise that interactions between chronic conditions are stronger risk factors for malignancies than individual diseases in people with multimorbidity. As most

people with HF have multimorbidity, further research is warranted to examine the strength of the association between HF and malignancies.

Supporting information

S1 Checklist. STROBE statement—Checklist of items that should be included in reports of observational studies.
(DOCX)

S1 Appendix. Appendix—contains the following: Appendix Table 1. ICD-codes for the diseases included in present study. Appendix Table 2. Different variables in Model A—E.
(DOCX)

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Author Contributions

Methodology: Anders Halling.

Resources: Anders Halling.

Supervision: Anders Halling.

Writing – original draft: Mia Scholten.

Writing – review & editing: Anders Halling.

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Paper IV

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RESEARCH ARTICLE

Comorbidities in heart failure patients that predict cardiovascular readmissions within 100 days—An observational study

Mia Scholten[1]*, **Jason Davidge**[1,2], **Björn Agvall**[1,3], **Anders Halling**[1]

1 Center for Primary Health Care Research, Department of Clinical Sciences, Lund University, Lund, Sweden, **2** Capio Vårdcentral Halmstad, Halmstad, Sweden, **3** Department of Research and Development, Region Halland, Halmstad, Sweden

* mia.scholten@med.lu.se

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Abstract

Background

Heart failure (HF) commonly arises as a complication to cardiovascular diseases and is closely associated with various comorbidities. The impacts of these comorbidities in patients with HF are diverse. We aimed to analyze the increased risk for cardiovascular-related readmission within 100 days after discharge in patients with HF depending on their different comorbidities.

Methods

A population-based retrospective study was conducted in Region Halland with 5029 patients admitted to hospital with a diagnosis of HF during 2017–2019. The occurrence and number of comorbidities were recorded. Competing risk regression was employed to analyze the hazard ratio (HR) of 10 comorbidities for cardiovascular-related readmission within 100 days after discharge. A composite measure of the 10 common comorbidities was constructed with the comorbidities as dichotomous indicator variables and Rasch analysis. Receiver operating characteristic (ROC) and area under curve (AUC) after logistic regression were used to estimate how well the model explained the probability of death or readmission within 100 days after discharge according to their individual comorbidity level.

Results

HF patients with atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, peripheral artery disease or diabetes mellitus as comorbidities had an increased HR for readmission within 100 days after discharge. When these comorbidities were adjusted together, only atrial fibrillation, chronic kidney disease and chronic obstructive pulmonary disease had an increased HR for readmission. ROC analysis after the most complete models using logistic regression with the comorbidities as dichotomous indicator variables or Rasch analysis had a low AUC.

Conclusions

Atrial fibrillation, chronic kidney disease or chronic obstructive pulmonary disease were significantly associated with increased risk for readmission in HF patients, but ROC analysis showed a low AUC, which indicates that other factors are more important for predicting the increased risk of readmission.

Introduction

HF is associated with multimorbidity [1], but different subgroups of HF are reported to have varying comorbidities [2]. These comorbidities could exacerbate HF and consequently increase the need for hospitalizations. Most of the comorbidities share risk factors resulting in various degrees of impairment and need for hospitalization in HF patients. However, some of the common comorbidities are attributable to HF, which appear early or after long-term exposure. Common comorbidities in HF patients such as atrial fibrillation, peripheral artery disease (PAD), cerebrovascular insults (CVI), valvular heart disease, ischemic heart disease, acute myocardial infarction, chronic kidney disease (CKD), diabetes mellitus, chronic obstructive pulmonary disease (COPD) and hypertension are usually linked with each other in the pathophysiology contributing to HF diagnosis.

HF is a prevalent comorbidity in patients with diabetes mellitus, as indicated by scientific studies [3, 4]. The heightened prevalence of HF in diabetes mellitus patients remains significant even after adjusting for coronary heart disease and its associated risk factors, including age, gender, race, smoking, physical inactivity, obesity, hypertension, and hyperlipidemia [3]. The diabetic myocardium has a typical characteristic of left ventricular concentric remodeling, promoting impaired myocardial metabolism and systolic dysfunction [4, 5]. The subsequent increase in myocardial stiffness may translate to diastolic dysfunction, atrial enlargement and valvular heart disease, which facilitates the incidence of atrial fibrillation in patients with diabetes mellitus [5–8]. Diabetes mellitus has been reported as a predictor of cardiovascular mortality or HF hospitalization, particularly among HF patients with high HbA1c [3, 9]. After adjustment for age, gender, a 1-mmol/L-rise of fasting plasma glucose was associated with a 1.10-fold-increased risk of HF hospitalization [10]. Furthermore, those patients with diabetes mellitus tend to have a poorer prognosis compared to patients without [11].

COPD patients have an elevated risk of developing HF due to shared risk factors like smoking, age, and inflammation [14, 15]. The prevalence of HF precursors, such as diabetes, atrial fibrillation, hypertension, and ischemic heart disease, is higher in COPD patients [16–19]. Those with both HF and COPD have a higher mortality rate compared to those with only one these conditions [15]. A meta-analysis reported that COPD was associated with an increased risk of all-cause hospitalization and HF specific hospitalization in the chronic HF population [12].

In a Canadian study of elderly HF patients, 5.6% were readmitted within seven days and 18% were readmitted within 30 days after hospital discharge. The readmission rates increased significantly with advancing age and were associated with comorbidities including kidney disease [13].

A previous European study examined the presence of comorbidites in 3226 outpatients diagnosed with chronic HF. The comorbidities considered included CKD, anemia, CVI, hyper- and hypothyroidism, COPD, sleep apnea and diabetes mellitus. These comorbidities were independently associated with higher age, NYHA functional class, heart rate, ischemic etiology of HF, hypertension, and atrial fibrillation [14]. The most prevalent comorbidities

observed in the study group were CKD, anemia and DM, which were all strongly associated with higher mortality rates and/or HF hospitalization [14].

It has been previously reported that the increased risk for cardiovascular-related readmission within 100 days after discharge in HF patients in southern Sweden was associated with advanced age, hospital stay > 6 days, renal impairment, elevated heart rate and higher N-terminal-pro Brain Natriuretic Peptide (NT-proBNP) levels [23]. The likelihood of readmission decreased when a combination of beta-blockers and renal-angiotensin-aldosterone-system inhibitors was administered alongside an echocardiography performed upon admission.

The present study aims to determine the extent to which 10 common comorbidities affect the risk for cardiovascular-related readmission within 100 days after discharge in HF patients.

Methods

Setting and study population

Region Halland is located in south-western Sweden and has an estimated population of 320,000 inhabitants. There are three acute care hospitals, 40 inpatient wards, two emergency departments, 30 specialized outpatient clinics and 48 healthcare providers in primary care. This is a retrospective population-based study in Region Halland, encompassing patients who were hospitalized with a diagnosis of HF between 2017 and 2019. The data extraction took place between the 1st of September 2020 and the 1st of June 2021 for research purposes. A total of 5029 individuals were admitted for HF and subsequently discharged. The clinical characteristics were recorded from the date of admission until 100 days following their post-discharge.

Data source and measurements

The data for this study were sourced from the Regional Healthcare Information Platform (RHIP) administered by Region Halland. RHIP comprises comprehensive data from both primary healthcare, including private and public healthcare providers, and secondary healthcare levels. The database incorporates comprehensive healthcare information, spanning healthcare utilization, health economics, staff utilization, pharmacotherapy and various chronic diseases including HF. Data comprising ICD-diagnoses, laboratory samples and examinations undergone by each patient within Region Halland are accessible, but no information about the severity of each condition or results of treatments. A detailed description of the database can be found in a previous publication [15]. Within this HF cohort, every echocardiography has been successfully conducted and the ejection fraction has been established in 99% of the patients, enabling determination of the HF-subgroup in these individuals [24]. The authors did not have access to data that could identify individual participants during or after data collection. The data used in this study were pseudo-anonymized, which means that the participants' identities were concealed from the researchers. However, through specific administrative processes, the identities could potentially be revealed. In this study, no participant identities were disclosed to the researchers.

The study participants were enrolled if they were hospitalized with an ICD-10 diagnosis of HF according to Table 1 in S1 Appendix, and subsequently discharged with a HF diagnosis. The registered comorbidities, which were collected during the lookback period from the 1st of January 2013 until the 31st of December 2019, included: hypertension, ischemic heart disease, acute myocardial infarction, CVI, atrial fibrillation, diabetes mellitus, valvular heart disease, COPD, PAD, CKD, until they were hospitalized (Table 1). A patient could only be included once in the study. For those patients admitted to hospital more than once during the study period, only the first hospitalization was included. Readmission due to a cardiovascular disease within 100 days after discharge was registered. Within the study period of 2017–2019 at RH, a

Table 1. Prevalence of heart failure patients and their comorbidities within different age groups, subgroups and levels of renal function.

	HF	AF	PAD	CVI	VHD	HTN	IHD	AMI	CKD	DM	COPD
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)											
<50	99 (1)	18 (1)	1(0)	1 (0)	9 (1)	22 (1)	19 (1)	16 (2)	9 (1)	16 (1)	1 (0)
50–75	1416 (28)	645 (22)	63 (25)	160 (20)	248 (24)	923 (24)	662 (29)	357 (37)	257 (22)	460 (35)	303 (33)
>75	3514 (70)	2243 (77)	184 (74)	641 (80)	787 (75)	2831 (75)	1633 (71)	587 (61)	900 (77)	855 (64)	604 (67)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HF—subgroup											
HFpEF	1147 (23)	704 (24)	56 (23)	164 (20)	369 (35)	924 (24)	474 (20)	199 (21)	290 (25)	301 (23)	238 (26)
HFmrEF	898 (18)	487 (17)	45 (18)	140 (17)	193 (18)	637 (17)	525 (23)	286 (30)	205 (18)	243 (18)	142 (16)
HFrEF	1010 (20)	540 (19)	58 (23)	132 (16)	215 (21)	662 (18)	581 (25)	273 (28)	239 (21)	291 (22)	133 (15)
HF-NDP	1974 (40)	1175 (40)	89 (36)	366 (46)	267 (26)	1553 (41)	734 (32)	202 (21)	432 (37)	496 (37)	395 (44)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Renal function (ml/min)											
eGFR ≥ 60	1826 (36)	880 (30)	69 (28)	268 (33)	339 (32)	1184 (31)	783 (34)	377 (39)	68 (6)	445 (33)	375 (41)
eGFR 30–59	2437 (49)	1542 (53)	128 (52)	408 (51)	551 (53)	1934 (51)	1160 (50)	438 (46)	542 (46)	622 (47)	422 (46)
eGFR <30	753 (15)	481 (17)	50 (20)	124 (15)	154 (15)	652 (17)	364 (16)	142 (15)	556 (48)	263 (20)	110 (12)
P-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note; HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HF—NDP = heart failure with no defined subgroup, AF = atrial fibrillation, CKD = chronic kidney disease, VHD = valvular heart disease, PAD = peripheral artery disease, IHD = ischemic heart disease, AMI = acute myocardial infarction, CVI = cerebrovascular insult, VHD = valvular heart disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HTN = hypertension, eGFR = estimated glomerular filtration rate (ml/min).

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total of 7436 patients were identified with HF. Among them, 5494 had a hospital admission for HF, and 465 patients died before discharge. Consequently, the study included 5029 patients who were hospitalized for HF and subsequently discharged with a confirmed HF diagnosis. A flowchart for the study procedure is displayed in Figure (S1 Appendix).

The HF-subgroups were divided into HF with preserved ejection fraction (HFpEF), HF with mildly reduced ejection fraction (HFmrEF), HF with reduced ejection fraction (HFrEF), and HF with no defined subgroup (HF-NDP) [16]. NT-proBNP was used as a biomarker for HF. The recorded NT-proBNP values were retrieved from the time of hospitalization and the highest values during the period seven days before the index and throughout the hospitalization. NT-proBNP levels were measured at a new onset or acute worsening of HF symptoms and further divided into three groups to determine the probability of HF in different age groups: A NT-proBNP value < 300 ng/L was considered normal and defined as HF unlikely; Elevated values were defined depending on the patient age as grey-zone or HF likely (Table 2 in S1 Appendix) [17]. Renal function was determined by eGFR (ml/min/1.73 m^2). Renal function was defined as normal when eGFR ≥ 60 ml/min, lowered when eGFR was 30–59 ml/min or impaired when eGFR < 30 ml/min.

Statistical analyses

The prevalence of 10 common comorbidities were compared among HF patients based on age, HF-subgroup and levels of renal function. Frequencies, percentages and cross-tabulations were used for descriptive analysis and Chi-square-test was used to calculate the p-values. P-value ≤ 0.05 was considered statistically significant.

Primary outcome was readmission due to cardiovascular-related events within 100 days after discharge. The 100-day follow-up after hospital discharge with HF was chosen since it is considered as the most vulnerable period. Competing risk regression was used to estimate the HR of all HF patients with and without 10 common comorbidities for cardiovascular-related readmission within 100 days after discharge, which even considered the mortality during the study period. The HR was stratified for age, gender, HF-subgroup, levels of NT-proBNP and renal function. The comorbidities in HF patients with statistically significant HR were further adjusted in the same model to compare with the HRs for these comorbidities separately.

ROC and AUC were used to estimate how well the model explained the probability of death or readmission within 100 days after discharge according to their individual comorbidity level calculated by logistic regression or Rasch analysis [18]. Linear predictions were made based on models by adding variables in steps (models xb1—xb6), e.g. comorbidities, age, gender, HF-subgroup, NT-proBNP, renal function. Comorbidities were included as a composite measure that had been constructed using logistic regression or Rasch analysis (Table 3 in S1 Appendix).

All calculations and graphs were performed with STATA version 17.0 (Stata Corporation, Texas, USA).

Ethics

The Swedish Ethical Review Authority, Stockholm Department 2 Medicine, granted approval to conduct the study under registration number 2020–00455. The requirement for informed consent was waived, which received approval from the Swedish Ethical Review Authority, Stockholm Department 2 Medicine. All the methods in this study were carried out in accordance with relevant guidelines and regulations.

Results

The total prevalence of the comorbidities in HF patients was 58% for atrial fibrillation, 5% for PAD, 16% for CVI, 21% for valvular heart disease, 75% for hypertension, 46% for ischemic heart disease, 19% for acute myocardial infarction, 23% for CKD, 26% for diabetes mellitus and 18% for COPD (Table 1). Almost all the HF patients with atrial fibrillation, ischemic heart disease, PAD, CVI, valvular heart disease, acute myocardial infarction, hypertension, CKD, diabetes mellitus or COPD as comorbidity were over 50 years old (Table 1). Most HF patients with acute myocardial infarction (61%), diabetes mellitus (64%), COPD (67%), ischemic heart disease (71%), PAD (74%), valvular heart disease (75%), hypertension (75%), atrial fibrillation (77%), CKD (77%) or CVI (80%) as comorbidity were over 75 years of age (Table 1).

HF patients with atrial fibrillation (HR 1.22, 95% CI 1.09–1.37), COPD (HR 1.17, 95% CI 1.03–1.34), CKD (HR 1.29, 95% CI 1.12–1.48), PAD (HR 1.28, 95% CI 1.03–1.61) or diabetes mellitus (HR 1.13, 95% CI 1.00–1.27) as comorbidity had an increased HR for readmission within 100 days after discharge (Table 2). When adjusting these comorbidities in the same model, diabetes mellitus and PAD lost their significance for the risk of readmission, i.e. only CKD, atrial fibrillation or COPD remained as factors associated with an increased risk of readmission within 100 days after discharge.

58% of the HF patients had atrial fibrillation as comorbidity, thus representing the most prevalent comorbidity causing an increased risk for readmissions in our study (Tables 1 and 2). Hypertension was the most prevalent (75%) comorbidity in HF patients in the current study, but these patients had no increased risk for readmissions. PAD, however, as the smallest patient group of comorbidity, constituting only 5% of HF patients, had an increased risk for readmissions within 100 days after discharge (Tables 1 and 2). Coronary artery disease is recognized as the main etiological factor in more than 50% of HF patients

Table 2. Competing risk regression for readmissions within 100 days after discharge in HF patients with different comorbidities.

	HF	AF	PAD	CKD	DM	COPD	MM	
							1.09 (0.97–1.23)	**DM**
	1	1.22 (1.09–1.37)	1.28 (1.03–1.61)	1.29 (1.12–1.48)	1.13 (1.00–1.27)	1.17 (1.03–1.34)	1.22 (0.97–1.54)	**PAD**
							1.23 (1.10–1.38)	**AF**
							1.25 (1.09–1.44)	**CKD**
							1.17 (1.02–1.33)	**COPD**
Age (years)								
< 50	1	1	1	1	1	1	1	
50–75	1.38 (0.78–2.43)	1.32 (0.74–2.34)	1.37 (0.77–2.41)	1.40 (0.79–2.48)	1.36 (0.77–2.41)	1.33 (0.75–2.36)	1.27 (0.72–2.25)	
>75	1.47 (0.84–2.60)	1.38 (0.78–2.43)	1.46 (0.83–2.57)	1.52 (0.86–2.69)	1.48 (0.84–2.61)	1.44 (0.81–2.54)	1.36 (0.77–2.42)	
Gender								
women	1	1	1	1	1	1	1	
men	1.15 (1.03–1.28)	1.13 (1.01–1.26)	1.14 (1.03–1.27)	1.13 (1.01–1.26)	1.14 (1.02–1.27)	1.15 (1.03–1.28)	1.10 (0.99–1.23)	
HF-subgroup								
HFrEF	1	1	1	1	1	1	1	
HFmrEF	0.92 (0.78–1.10)	0.91 (0.77–1.09)	0.92 (0.78–1.10)	0.92 (0.77–1.09)	0.93 (0.78–1.10)	0.92 (0.77–1.09)	0.90 (0.76–1.07)	
HFpEF	1.16 (0.99–1.35)	1.13 (0.97–1.32)	1.16 (0.99–1.35)	1.14 (0.98–1.33)	1.15 (0.99–1.35)	1.14 (0.98–1.33)	1.11 (0.95–1.29)	
HF-NDP	0.97 (0.84–1.13)	0.96 (0.83–1.11)	0.98 (0.84–1.13)	0.98 (0.84–1.13)	0.98 (0.84–1.13)	0.96 (0.83–1.12)	0.95 (0.82–1.11)	
NT-proBNP								
HF unlikely	1	1	1	1	1	1	1	
"Grey zone"	1.16 (1.01–1.33)	1.11 (0.96–1.28)	1.15 (1.01–1.33)	1.16 (1.01–1.33)	1.16 (1.01–1.33)	1.17 (1.02–1.34)	1.12 (0.97–1.29)	
HF likely	1.52 (1.33–1.75)	1.47 (1.28–1.69)	1.52 (1.32–1.74)	1.51 (1.31–1.73)	1.53 (1.33–1.75)	1.53 (1.33–1.75)	1.47 (1.27–1.68)	
Renal function (ml/min)								
eGFR ≥ 60	1	1	1	1	1	1	1	
eGFR 30–59	1.15 (1.01–1.30)	1.14 (1.00–1.29)	1.14 (1.00–1.30)	1.08 (0.95–1.24)	1.14 (1.00–1.30)	1.15 (1.01–1.31)	1.08 (0.94–1.23)	
eGFR < 30	1.29 (1.09–1.53)	1.29 (1.09–1.52)	1.29 (1.09–1.52)	1.07 (0.88–1.31)	1.27 (1.07–1.50)	1.30 (1.10–1.54)	1.08 (0.89–1.32)	

Note; Hazard ratio with 95% confidence interval. HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HF-NDP = heart failure with no defined subgroup, NT-proBNP = natriuretic terminal pro brain natriuretic peptide, AF = atrial fibrillation, CKD = chronic kidney disease, VHD = valvular heart disease, PAD = peripheral artery disease, IHD = ischemic heart disease, AMI = acute myocardial infarction, CVI = cerebrovascular insult, VHD = valvular heart disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HTN = hypertension, MM = multimorbidity, eGFR = estimated glomerular filtration rate (ml/min).

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in North America and Europe [19], but the comorbidities ischemic heart disease or acute myocardial infarction had no impact on the risk for readmission within 100 days after discharge. Neither did the HF patients with CVI or valvular heart disease as comorbidity (Tables 1 and 2). For a more extensive description of this study population, please see the Table 1 in a prior study [20].

Logistic regression was performed with models of increasing complexity using the comorbidities as dichotomous indicator variables or by constructing a comorbidity measure of the 10 comorbidities using Rasch analysis. ROC analysis after the univariate logistic regression using the comorbidities as dichotomous indicator variables or Rasch analysis to estimate individual comorbidity level was 0.57 (95% CI 0.55–0.59) (xb1, Fig 1) and 0.56 (95% CI 0.54–0.57) respectively (xb1, Fig 2). AUC was significantly improved by adding the variables NT-proBNP and renal function (xb5, xb6, Figs 1 and 2). ROC analysis after the most complete models using logistic regression with the comorbidities as dichotomous indicator variables or Rasch analysis had an AUC of 0.63 (95% CI 0.61–0.64) and 0.62 (95% CI 0.60–0.64), respectively.

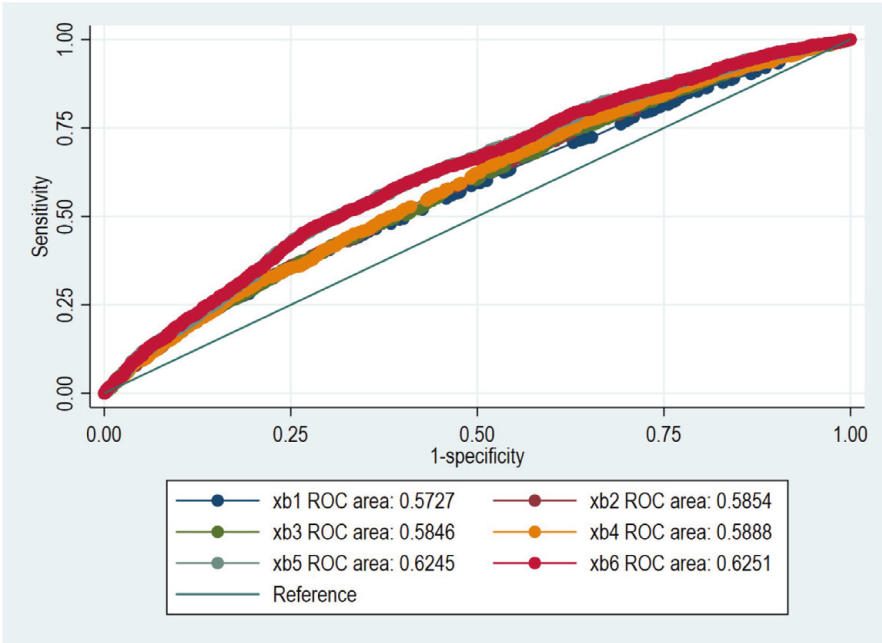

Fig 1. The receiver operating characteristic curve (ROC) and area under curve (AUC) of the probability of death or cardiovascular-related readmission within 100 days after discharge in the following models: xb1, xb2, xb3, xb4, xb5, xb6. Individual comorbidity level was calculated using logistic regression with the comorbidities as dichotomous indicator variables.

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Discussion

The present study included individuals admitted to hospital with a HF diagnosis and closely monitored these patients for 100 days post-discharge to determine whether presence of common comorbidities affected the risk of readmission. The comorbidities atrial fibrillation, CKD or COPD had an increased HR when adjusted in the same model, which explained the increased risk for readmission in HF patients with diabetes mellitus or PAD, regardless of age, gender, HF-subgroup and renal function. These results highlight the significance of the comorbidities atrial fibrillation, CKD or COPD in HF patients for the risk of cardiovascular related readmission. ROC analysis after logistic regression with comorbidities as dichotomous indicator variables and Rasch analysis to estimate individual comorbidity level was comparable, but the predictive value in the complete models was low.

Atrial fibrillation was reported to be an independent risk factor for HF readmission [21]. This is likely due to many shared pathophysiological mechanisms in both conditions and their propensity to exacerbate each other [22, 23]. Atrial fibrillation was found to be the most common comorbidity (58%) causing an increased risk for HF readmission in our study. In addition, patients with atrial fibrillation and concomitant HF have a poorer prognosis than patients with only one of these diseases [23]. Even HF patients with COPD were reported to

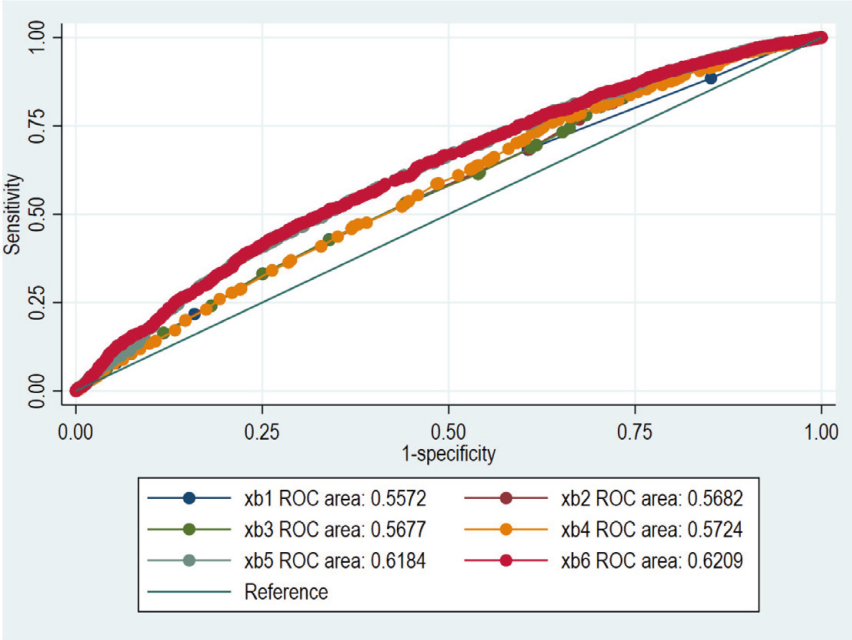

Fig 2. The receiver operating characteristic curve (ROC) and area under curve (AUC) of the probability of death or cardiovascular-related readmission within 100 days after discharge in the following models: xb1, xb2, xb3, xb4, xb5, xb6. Individual comorbidity level was calculated using Rasch analysis.

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have a higher mortality rate compared to patients with only one of these diagnoses [24, 25], which is in line with our results as only 67% of the COPD patients with HF were over 75 years old. HF treatment options could be limited among patients with CKD as a comorbidity and, thus, indirectly cause HF exacerbation and increased risk for cardiovascular-related readmission.

Ischemic heart disease is recognized as the main etiological factor in more than 50% of HF patients in North America and Europe [26], but the HF patients with acute myocardial infarction as comorbidity had a lower prevalence (61%) over 75 years than other comorbidities in our study. This patient category did not show an increased risk for readmission within 100 days after discharge, possibly due to their post-infarction follow up visits and high mortality rate as described by Solomonchuk et al. [27]. Nevertheless, the HF patients with CVI as comorbidity had the highest prevalence (80%) in the age group over 75 years, but no impact on the risk for readmission within 100 days after discharge, which suggests that this patient category is probably less related to cardiovascular events than other comorbidities in our study.

PAD had an increased risk for readmissions within 100 days after discharge although this patient group constituted only 5% of the HF patients. A retrospective cohort study was conducted from 2005 to 2016 and a total of 1481 elderly patients were hospitalized with acute

decompensation of HF and discharged [28]. In total, 207 (14%) of these patients had a diagnosis of PAD and had an increased risk of at least one HF readmission, both within 30 days and one year after discharge from the index hospitalization [28]. The pathophysiology likely involved a strong association with ischemic heart disease, which could enhance the risk for HF-related readmission significantly. These results could explain our findings of HF patients with PAD, who had an increased risk for readmissions within 100 days after discharge.

A cohort study was conducted to assess adverse outcomes attributable to non-cardiac comorbidities and to compare their impact on hospitalizations in a chronic HF population between 2009 and 2013 [29]. Approximately 2300 elderly patients were recruited including 41% HFrEF and 59% HFpEF. Totally 14 non-cardiac comorbidities were considered including PAD, cerebrovascular event, dementia, COPD, rheumatologic disorders, peptic ulcer disease, diabetes mellitus, liver disease, malignancy, CKD, psychiatric disorders, anemia, obesity and hypertension. An increasing number of non-cardiac comorbidities were associated with an elevated risk for all-cause mortality, all-cause hospitalization, HF hospitalization, and non-cardiovascular hospitalization. These findings were similar for HFrEF and HFpEF, which is consistent with our findings [29].

Strengths and limitations

We used competing risk regression in our calculations, which took into account mortality during the study period. Competing risk regression is a more accurate method than cox regression as these study participants were endangered and several of their comorbidities were associated with an increased mortality rate. People with COPD and HF, for instance, had a 7-folded mortality rate compared to COPD patients without HF [24]. Logistic regression and Rasch analysis had no statistically significant difference when estimating the individual comorbidity level, indicating that our results of these analysis were reliable. The Rasch analysis, however, offered a more pedagogical way to present the individual comorbidity level. This study was an observational study through three years, which made these findings more reliable. This specific study places its primary emphasis on comorbidities and the readmission risks related to cardiovascular issues. The data utilized in this study has been refined and offers a comprehensive coverage of these aspects.

Many of the HF patients presumably had overlaps of several comorbidities, which could affect the risk for cardiovascular-related readmission and mortality rate than HF patients with only one comorbidity. The readmission could also be conferred by decompensated HF as a consequence of deficient compliance in the patients, independent of their comorbidities. We did not consider other comorbidities associated with HF, for example ventricular tachycardia, which have the propensity to increase the risk for cardiovascular-related readmissions as well [30]. Valvular heart disease, CKD, CVI and hypertension could appear without clinical symptoms and thus remain frequently underdiagnosed or become discovered by chance. We did not consider the severity of these comorbidities, which could have different implications on the risk for readmission in HF patients. Neither did we record the success of specific treatment target goal. While such information could have provided valuable insights for this study, it was not feasible within the constraints of this data collection. In Sweden, multiple care programs are available to manage various chronic illnesses. For instance, patients with a prior myocardial infarction undergo outpatient follow-up visits after hospital discharge. The risk of hospital readmission can be influenced by the quality of follow-up care and the patients' care plan. Factors like prompt follow-up in primary health care play a crucial role.

Conclusion

The increased risk for cardiovascular-related readmission within 100 days after discharge in HF patients with diabetes mellitus or PAD had no significance after adjusting for atrial fibrillation, CKD or COPD in the same model. Using two measures of individual comorbidity level did not show any statistical difference, but the predictive value was found to be low in the current study. This means that other factors than these comorbidities we studied are of more importance for reducing the risk of cardiovascular related readmission within 100 days after discharge in HF patients. When managing individuals with HF, it is crucial to recognize that comorbidities exhibit limited predictive value. Instead, healthcare providers should prioritize attention to other influential factors to effectively prevent readmissions within the critical 100-day post-discharge period.

Supporting information

S1 Appendix.
(DOCX)

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Author Contributions

Formal analysis: Mia Scholten, Anders Halling.

Methodology: Anders Halling.

Supervision: Anders Halling.

Writing – original draft: Mia Scholten.

Writing – review & editing: Jason Davidge, Björn Agvall, Anders Halling.

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