Comorbidity-adjusted relative survival in newly hospitalized heart failure patients: A population-based study

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Comorbidity-adjusted relative survival in newly hospitalized heart failure patients: a population-based study

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Abstract

Background. This study aims to identify comorbidities through various sources and to assess their short-term impact on relative survival in a cohort of Heart Failure (HF) patients.

Methods. Newly hospitalized HF patients were identified from hospital discharge abstracts (HDA) of Lombardy Region, Italy, from 2008 to 2010. Charlson comorbidities were assessed by just HDA and supplemented by drug prescriptions and disease-specific exemptions. A Cox model for one-year relative survival from HF was fitted.

Results. The cohort consisted of 51,061 HF patients (53% women; median age 80 years). After integrating information from all sources, the prevalence of diabetes, chronic pulmonary disease and renal disease raised up to 27.6%, 26.2% and 14.2%, respectively.

Survival in the HF cohort was inferior to that in the reference population and decreased with increasing number of comorbidities. Notably, the overall performance of the relative survival models was similar regardless of which strategy was used to ascertain comorbidity.

Conclusions. The effort required to implement a comprehensive search method for comorbidities is worth the potential benefit when the aim is to assess the comorbidity burden. On the contrary, a search method limited to HDA can reasonably be used to determine a comorbidity profile for mortality risk adjustment purposes.

Keywords: comorbidity; Charlson index; claims data; drug prescriptions; hospital discharges; relative survival

1. Introduction

Heart Failure (HF) is a major and growing public health issue that affects all Western countries. Around 1-2% of the population in European countries suffers from HF, with the prevalence rising to above 10% among people aged 70 years and over [1].

HF is commonly accompanied by a broad range of comorbidities, with chronic kidney disease, anaemia and diabetes being the most prevalent, which further complicate the management of care, unfavourably affecting prognosis [2, 3].

Research on the epidemiology of HF has relied on multiple data sources [4]. Of these, claims data have been increasingly used for health services utilization and outcome evaluation [5, 6].

Among methods to measure burden of comorbidity and case-mix, the Charlson comorbidity index [7] has been extensively used in claims-based investigations [8]. Nevertheless, it is recognized that administrative claims data may underestimate comorbidity burden [9, 10].

Some studies [11, 12] have explored the predictive validity of comorbidity measures when using claims data versus other clinical data sources, but few studies [9] to date have evaluated whether comorbidity-adjusted survival estimates change depending on incorporation of claims data on comorbidity from sources other than inpatient claims.

This study aims to identify comorbidities through the use of multiple administrative data sources on health care use and to assess their short-term impact on relative survival in a large Italian cohort of Heart Failure (HF) patients.

2. Methods

2.1 Study population

The Italian National Health Service (NHS) provides universal health care coverage to all Italian citizens. Essential health services are provided free of charge or at a minimal charge. Some

particular circumstances such as disability, chronic diseases, status of inability, low income or >65 years of age entitle patients to co-payment fee exemption.

The reference population for this study consists of all beneficiaries of the NHS, resident in Lombardy Region, an industrialized Italian region with 10 million inhabitants. Among these, subjects firstly hospitalized with a diagnosis of HF from January 2008 to December 2010 constitute the study population.

Data are drawn from the Lombardy Health Information System, including Hospital Discharge Abstracts (HDA) database, Drugs Prescriptions Register (DPR), Disease-specific Exemptions from co-payment (DEX) and vital status.

2.2 Algorithm to identify newly hospitalized HF cases

Our primary definition of HF was based on diagnostic codes for heart failure (428.xx) and for hypertensive heart failure (402.01, 402.11, and 402.91), according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), appearing as the primary diagnosis at the first hospitalization from HDA in the study period (referred to as index admission), as suggested by a recent study in the same setting [5]. Patients who had prior hospitalization with HF diagnosis (recorded as primary or secondary diagnoses in the previous five years) were excluded.

2.3 Ascertainment of comorbidity

Sixteen comorbid conditions were searched in the index admission for HF and in all hospital discharges in HDA that occurred within 12 months before the index date, following the Charlson algorithm [7]. We tried to maximize sensitivity in detecting comorbidities, by integrating the information from HDA with that recorded from DPR and DEX.

The mapping approach proposed by Huber et al [13] for detecting chronic conditions by using pharmacy data, was applied to ATC codes of medicaments dispensed at least twice within 12 months prior to the index admission.

All exemptions concerning any of the 16 conditions included in Charlson comorbidity index, still valid at the time of index admission or expired in the previous 12 months, were considered.

Table 1 lists codes used to identify comorbidity in each data source.

[Table 1 about here]

2.4 Statistical Analysis

We estimated 1-year relative survival from HF through the transformation approach [14]. This method consists in a transformation of all the individual survival times to a different scale, by taking into account the general population mortality. The transformed outcome variable (y) measures how long, after the HF event, and relative to the respective population, a person has lived. Population life tables of Lombardy region were provided by the Italian National Institute of Statistics.

Crude Kaplan-Meier survival probabilities, against y, were estimated both overall and stratified. Log-rank test was used to test survival differences.

Furthermore, we built two comorbidity-adjusted Cox survival models on the transformed outcome, including gender, age and the 16 selected comorbid conditions contributing to Charlson index. One model uses the comorbidity information assessed in HDA database only, whereas the other uses the enhanced information from all sources. We calculated the c-statistic for each model.

R software, version 3.3.0 and "relsurv" package were used.

3. Results

A total of 51,061 incident HF subjects were identified in the years 2008-2010. The study cohort comprised predominantly women (53.2%) and elderly patients (median age of 80 years and interquartile range from 73 to 86 years). Thirty-three thousand and twenty-one subjects (64.7%) were entitled to a co-payment exemption.

According to HDA only, at least one Charlson comorbid condition was detected for 50.9% of the study cohort. This figure raised up to 78.2% when integrating information from all sources. Integrating HDA with DEX and DPR data mainly affected prevalence of diabetes (from 19.2% to 27.6%), chronic pulmonary disease (from 15.2% to 26.2%), cancer (from 6.4% to 11.1%), rheumatic disease (from 0.9% to 17.9%) and peptic ulcer (from 0.6% to 39.3%). Details about the prevalence of each comorbid condition by data source are shown in Table 1.

After removing differences in structure for age, gender and calendar year, survival in the HF cohort is lower to that of the reference population (overall, 50% of HF patients died before their expected 37th percentile) in any of the five comorbidity categories (Figure 1).

[Figure 1 about here]

Furthermore, relative survival decreases with increasing number of comorbidities (log-rank test p-value < 0.0001).

Despite the discrepancies in the number of inferred comorbidities from HDA alone and in combination with DEX and DPR, the overall performance of the developed relative survival models was similar regardless of which data source was used. The difference among c-statistics was negligible, being 0.619 and 0.623 for the model with enhanced and original Charlson comorbidities, respectively.

As shown in Figure 1, subjects with major non-cardiac comorbidities such as diabetes, chronic pulmonary disease exhibited a moderate increase in the hazard for HF death.

4. Discussion

HF subjects typically suffer from a number of coexisting diseases that may influence the outcomes of care [2, 3, 15]. To the best of our knowledge, this is the first study (i) investigating a comprehensive search of comorbidities based on administrative data, (ii) assessing their impact on short-term survival, and (iii) trying to disentangle between mortality associated with HF from that due to all other causes through a relative survival approach.

Our findings on the major non-cardiac comorbidities in HF patients, namely diabetes, chronic pulmonary disease and renal disease, are quite in line with those reported in the literature. Our estimate of diabetes prevalence (27.6%) is consistent with that reported from a population-based study [6] on English administrative data (26.6%) and from the Cardiovascular Health Study [16] (28.5%).

Renal disease prevalence (14.2%) is slightly underestimated as compared to previous estimates [6, 16, 17], ranging from 16.1% to 32.3%, probably because DPR was not exploited to infer this comorbidity [13]. Chronic pulmonary disease burden (26.2%) was higher than published estimates [6, 16, 17], varying between 19% and 20%, since we relied on a broader definition embracing chronic obstructive pulmonary disease and asthma as well.

We observed that integrating HDA with other sources, mostly affected the detection of patients suffering from cancer, peptic ulcer and rheumatic disease. Nevertheless, these results should be interpreted with caution because the positive predictive value of the corresponding exemption code in identifying cancer is estimated to be 86% [18] and, as to peptic ulcer and rheumatic disease, we cannot rule out that the identified prescription patterns had low specificity in detecting the conditions of interest.

The present study confirms that the high mortality observed among elderly with a first hospitalization for HF is higher than that of the reference population and is in part attributable to the impact of key baseline comorbidities. Consistently with previous findings [16], major non-cardiac comorbidities exhibited a moderate increase in the hazard for HF death. Notably, the

overall performance of the developed relative survival models was similar regardless of which data source was used to ascertain comorbidity and was consistent with published findings [13].

Some study limitations must be acknowledged. The first stems from using administrative data sources and mostly concerns coding accuracy and lack of clinical information on important predictors of cardiovascular outcomes such as ejection fraction and New York Heart Association class. The lack of clinical and lifestyle predictors, most likely justifies the low discrimination ability of the developed relative survival model [19]. Secondly, with improvements in treatment and decreases in hospital resources, more patients with HF are being managed in the community [20]. As a result, patients identified in this study through hospital discharges will probably be more representative of medically complex HF population.

Despite these limitations, this study demonstrates that the effort required to implement a comprehensive search method for comorbidities is worth the potential benefit when the aim is to assess the comorbidity burden. On the contrary, a search method, limited to HDA, data can reasonably be used to determine a profile of a HF patient's comorbidity for mortality risk adjustment purposes.

Contributions: IB designed the study and wrote the manuscript; IB and DA performed the statistical analysis; LS performed data extraction; all authors contributed to results interpretation and approved the final manuscript.

References

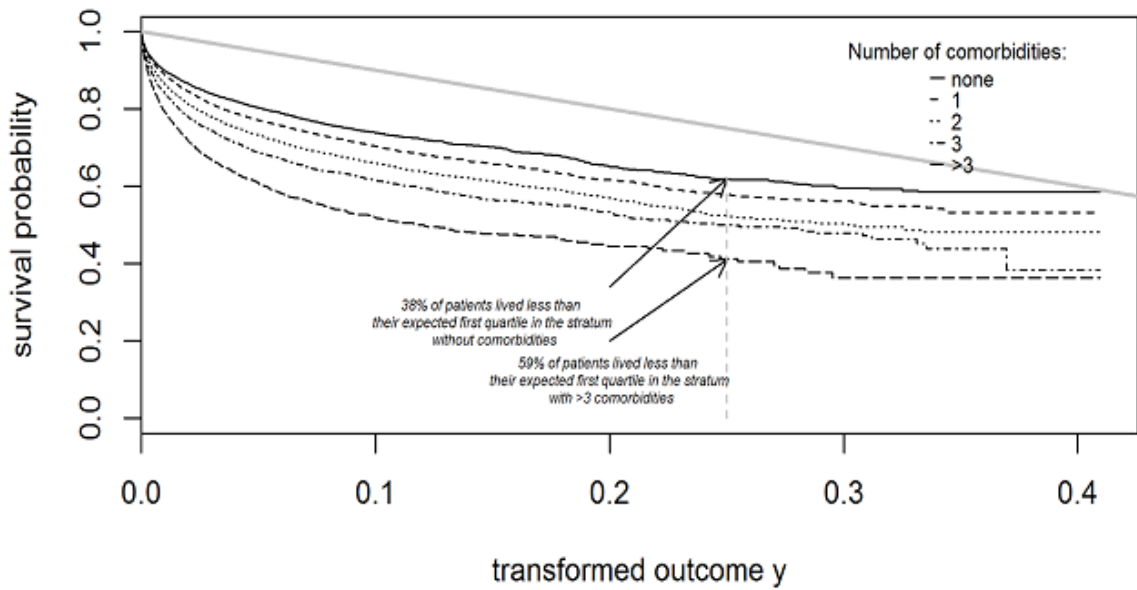[1] Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93:1137-46.

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Figure legends

Figure 1. Relative Survival analysis results. Panel A: Relative survival from HF by number of comorbidities. The estimated survival curve below/above the solid grey line indicates if the HF cohort does worse/better than the Lombardy reference population. Panel B: Forest plot of results from Cox model applied to transformed outcome *y* (which measures how long, after the HF event, and relative to the respective population, a person has lived) in the HF cohort (CPD: Chronic pulmonary disease, CVD: Cerebrovascular disease, MI: Myocardial infarction).

A

B

Variable		Hazard Ratio		p-value
Gender	female		Ref.	
	male		0.95 (0.92, 0.99)	0.0
Age_group	(0,76]		Ref.	
	(76,83]		1.02 (0.97, 1.07)	0.5
	(83,88]		1.23 (1.17, 1.29)	<0.001
	(88,100]		1.64 (1.55, 1.73)	<0.001
CPD			1.15 (1.11, 1.19)	<0.001
CVD			1.24 (1.16, 1.33)	<0.001
Dementia			1.81 (1.64, 2.00)	<0.001
Diabetes			1.07 (1.04, 1.12)	<0.001
Hemiplegia			1.80 (1.54, 2.12)	<0.001
MI			1.01 (0.96, 1.07)	0.7
Cancer			2.11 (2.02, 2.20)	<0.001
Mild_liver			1.34 (1.19, 1.52)	<0.001
Severe_liver			2.24 (1.75, 2.88)	<0.001
Renal			1.41 (1.36, 1.47)	<0.001
Rheumatic			0.91 (0.87, 0.95)	<0.001
Peptic_ulcer			1.14 (1.11, 1.18)	<0.001

Table 1. Prevalence of Charlson comorbid conditions (excluding congestive heart failure) in the HF cohort by data source along with source-specific codes.
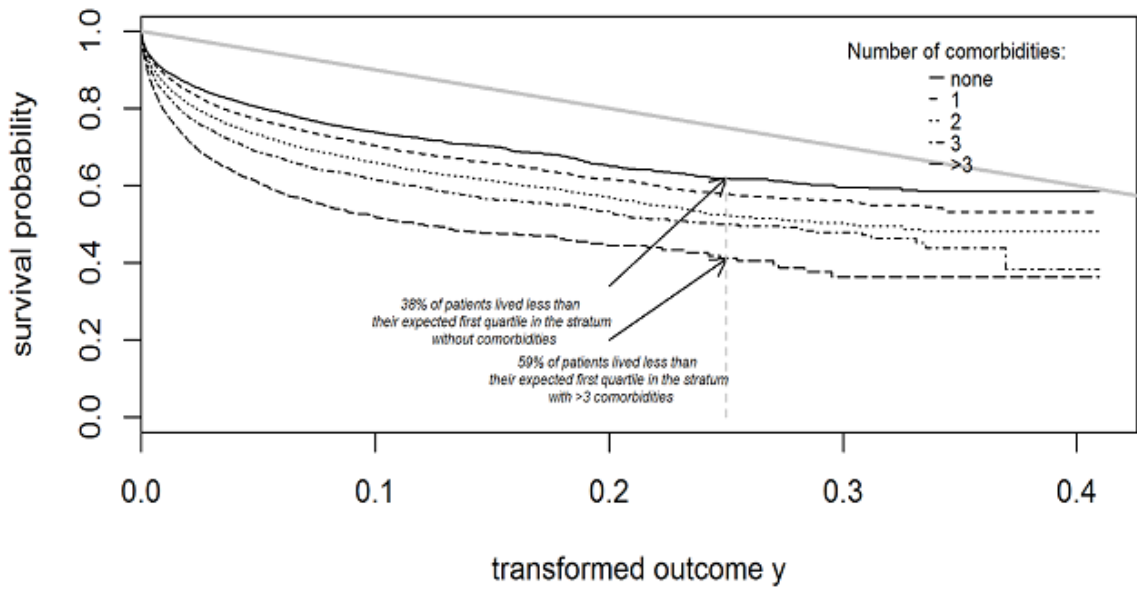
HDA		DPR		DEX		HDA+DEX*	HDA+DPR+DEX*
ICD-9-CM codes	N(%)	ATC codes	N(%)	ICD-9-CM codes	N(%)	N(%)	N(%)
Diabetes without complications 250, 250.0x–250.3x, 250.7x	7,841 (15.4)	**Diabetes mellitus** A10A, A10B, A10X	11,097 (21.7)	**Diabetes mellitus** 250	11,422 (22.4)	13,457 (26.3)	14,113 (27.6)
Diabetes with complications 250.4x–250.6x, 250.8x-250.9x	1,959 (3.8)						
Chronic pulmonary disease 490.xx-496, 500-505, 506.4	7,765 (15.2)	**Respiratory illness** R03	9,627 (18.8)	**Asthma** 493	211 (0.4)	7,867 (15.4)	13,367 (26.2)
Renal disease 582.xx, 583.xx, 585.x, 586, 588.xx	6,849 (13.4)	---	--	**Chronic kidney disease** 585	1143 (2.2)	7,241 (14.2)	7,241 (14.2)
Myocardial infarction 410.xx, 412	4,806 (9.4)	---	---	---	---	4,806 (9.4)	4,806 (9.4)
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin 140.x-171.x, 174.x.-195.x, 200.x-208.x, 273.0, 273.3,V10.46	2,582 (5.1)	**Cancer** L01	606 (1.2)	**Tumour** 048	3,966 (7.7)	5,431 (10.6)	5,743 (11.2)
Metastatic solid tumor 196.x-199.x	692 (1.3)						
Peripheral vascular disease 441.xx, 443.9, 785.4, V43.4; Procedures 38.13, 38.14, 38.16, 38.18, 38.43, 38.44, 38.46, 38.48, 38.33, 38.34, 38.36, 38.38, 39.22-39.26, 39.28, 39.29	2,487 (4.9)	---	---	**Diseases of arteries, arterioles, and capillaries** 441.2, 441.4, 441.7, 441.9, V43.4	302 (0.6)	2,694 (5.3)	2,727 (5.3)
Cerebrovascular disease 430-437.x, 438; Procedures 38.12, 38.42	2,280 (4.5)	---	---	**Cerebrovascular disease** 433, 434, 437	272 (0.5)	2,485 (4.9)	2,485 (4.9)
Mild liver disease 571.2, 571.4x–571.6	918 (1.8)	---	---	**Chronic liver disease and cirrhosis**	0 (0.0)	918 (1.8)	918 (1.8)

Comorbidity (ICD codes)							
				571.2, 571.5, 571.6 571.4			
Moderate or severe liver disease 456.0-456.21, 572.2-572.8; Procedures 39.1, 42.91	140 (0.3)	---	---	---	---	140 (0.3)	140 (0.3)
Dementia 290.xx	560 (1.1)	**Dementia** N06D	352 (0.7)	**Dementia** 290.0-290.2, 290.4	---	560 (1.1)	830 (1.6)
Rheumatic disease 710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725	437 (0.9)	**Rheumatologic conditions** M01, M02, L04AA, L04AB	8,865 (17.4)	**Rheumatoid arthritis** 714.0-714.2	---	437 (0.9)	9,131 (17.9)
Hemiplegia or paraplegia 342.xx, 344.1	350 (0.7)	---	---	---	---	350 (0.7)	350 (0.7)
Peptic ulcer disease 531.xx-534.xx	298 (0.6)	**Acid related disorders** A02	24,322 (47.6)	---	---	298 (0.6)	20,071 (39.3)
AIDS/HIV 042.x–044.x	18 (0.0)	**HIV** J05AE, J05AG, J05AR	0 (0.0)	**HIV disease** 042	0 (0.0)	18 (0.0)	18 (0.0)

*: a comorbidity appearing in more than one source is counted once per patient.

A

B

Variable		Hazard Ratio		p-value
Gender	female		Ref.	
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