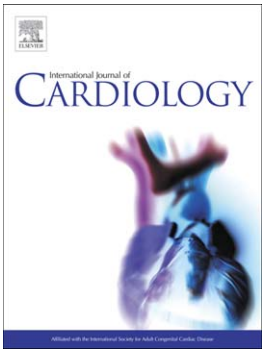

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Comorbidity-adjusted relative survival in newly hospitalized heart failure patients: a population-based study

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Abstract

Background. This study aims to identify comorbidities through various sources and 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 using the HDA and supplemented with drug prescriptions and disease-specific exemptions. A Cox model was fit for the one-year relative survival from HF.

Results. The cohort consisted of 51,061 HF patients (53% women; median age 80 years). After integrating information from all sources, the prevalence rates of diabetes, chronic pulmonary disease and renal disease were 27.6%, 26.2% and 14.2%, respectively. The prevalence of comorbidity increased to 78%. Survival in the HF cohort was worse with increasing number of comorbidities and was inferior to that in the reference population. Notably, the overall performance of the relative survival models was similar regardless of the strategy used to ascertain comorbidity.

Conclusions. Comorbidities cluster in hospitalized HF patients, and increasing comorbidity burden is associated with worse survival. Integration of a comprehensive search of electronic records to supplement HDA improves the prevalence estimates of comorbidities, although it does not improve discrimination of the risk prediction models.

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

1. Introduction

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

HF is commonly accompanied by a broad range of comorbidities, complicating the management and unfavourably affecting the prognosis [2, 3].

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

Among the methods used to measure the 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 claims data may underestimate the comorbidity burden [9, 10].

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

This study aims to identify comorbidities using multiple administrative data sources on healthcare use and to assess their short-term impact on the 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 healthcare coverage to all Italian citizens. Essential health services are provided free of charge or at a minimal charge, and some circumstances entitle patients to a co-payment fee exemption.

The reference population for this study consists of beneficiaries of the NHS residing in Lombardy, an Italian region with 10 million inhabitants. Among them, subjects first 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 the Hospital Discharge Abstracts (HDA), Drugs Prescriptions Register (DPR), Disease-specific Exemptions from co-payment (DEX) and vital status.

2.2 Algorithm to identify newly hospitalized HF cases

Our definition of HF was based on diagnostic codes for heart failure (428.xx) and 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 study in the same setting [5]. Patients who had a prior hospitalization for HF (recorded as a primary or secondary diagnosis in the previous five years based on data availability) were excluded.

2.3 Ascertainment of comorbidity

Sixteen comorbid conditions were searched in the index admission for HF. All hospital discharges in HDA occurred within 12 months before the index date based on the Charlson algorithm [7]. We tried to maximize the 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 using pharmacy data was applied to ATC codes of medications dispensed at least twice within the 12 months prior to index admission.

All exemptions for any of the 16 conditions included in the Charlson index at the time of index admission or expired in the previous 12 months were considered.

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

[Table 1 about here]

2.4 Statistical Analysis

We estimated the 1-year relative survival from HF through the transformation approach [14]. This method consists of transformation of individual survival times to a different scale by considering 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 the Lombardy region were provided by the Italian National Institute of Statistics.

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

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

R software version 3.3.0 was used.

3. Results

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

According to HDA alone, at least one Charlson comorbid condition was detected for 50.9% of the study cohort. This figure increased to 78.2% when integrating information from all sources. Integrating HDA with DEX and DPR data mainly affected the prevalence of diabetes (+8.4%), chronic pulmonary disease (+11%), cancer (+4.7%), rheumatic disease (+17%) and peptic ulcer (+38.7%). Details about the prevalence of each comorbid condition by data source are shown in Table 1.

After removing differences by the 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 the 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 relative survival models was similar for all data sources (c-statistics 0.619 vs. 0.623 for the model with enhanced and original Charlson comorbidities, respectively).

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

4. Discussion

HF subjects typically suffer from several 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 differentiate between mortality associated with HF versus due to all other causes through a relative survival approach.

Our findings on the major non-cardiac comorbidities in HF patients are in agreement with those reported in the literature. Our estimate of the 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 compared to previous estimates [6, 16, 17], ranging from 16.1% to 32.3%, which is probably because the DPR was not exploited to infer this comorbidity [13]. The chronic pulmonary disease burden (26.2%) was higher than published estimates [6, 16, 17], varying between 19% and 20%, because we relied on a broader definition that included asthma.

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 predictive value of the corresponding exemption code in identifying cancer is estimated as 86% [18] and, as for 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 the reference population and is somewhat attributable to the impact of key baseline comorbidities. Consistent with previous findings [16], major non-cardiac comorbidities exhibited a moderate increase in the hazard for HF death. Notably, the overall performance of the relative survival models was similar regardless of the data source used to ascertain comorbidity and was consistent with published findings [13].

Some study limitations must be acknowledged. The first is the use of administrative data sources, which relies on the coding accuracy, and there may be lack of clinical information on important predictors of cardiovascular outcomes, such as the 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]. Second, with improvements

in treatment and decreases in hospital resources, more patients with HF are being managed in the community [20].Therefore, patients identified in this study through hospital discharges are likely more representative of the medically complex HF population.

Finally, any attempt to use claims data to identify patients with a specific disease is limited by both the algorithm and database. This may raise concerns about generalizability of the findings to other health systems.

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. By contrast, a search method limited to HDA can be reasonably used to determine a profile of an HF patient's comorbidity for mortality risk adjustment.

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

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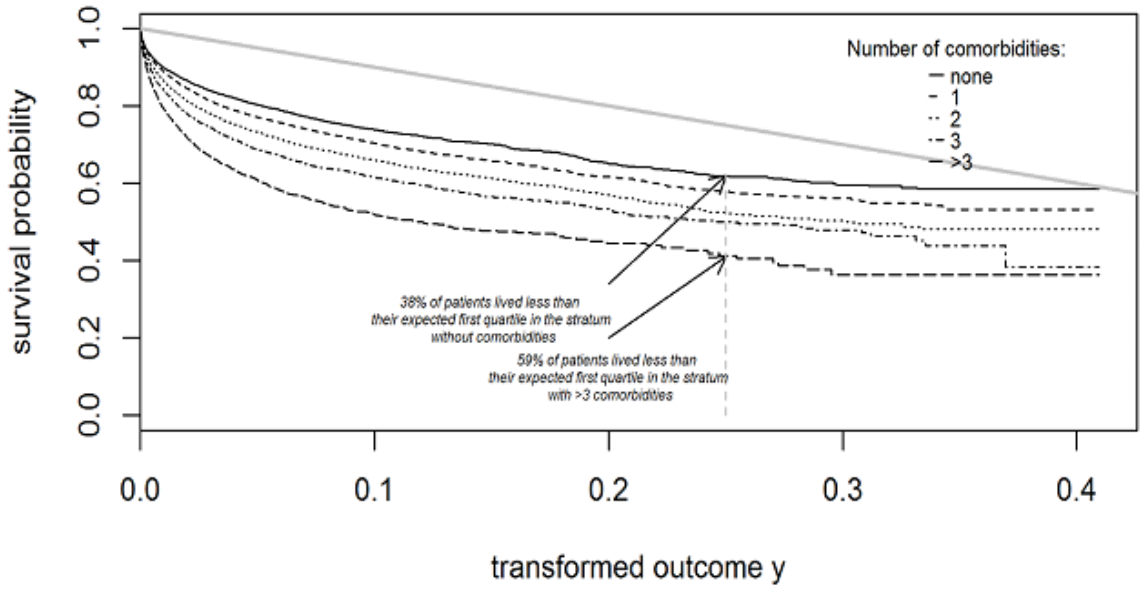
Figure legend

Figure 1. Relative survival analysis results. Panel A: Relative survival for HF by number of comorbidities. The estimated survival curve below/above the solid grey line indicates whether the HF cohort does worse/better than the Lombardy reference population. Panel B: Forest plot of results from the Cox model applied to transformed outcome *y* (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, and 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

1 1.5 2 2.5

Figure 1

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)

				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.