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CLINICAL INVESTIGATION

Evaluation of the effect of hospitalization on mortality in patients with heart failure followed in primary care

Evaluación del efecto de las hospitalizaciones sobre mortalidad en pacientes con Insuficiencia cardíaca seguidos en atención primaria

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Abstract

Background: *Heart failure (HF) is a serious health-care problem. The aim of this study is to evaluate the effect of the first acute episode of decompensated HF that requires a hospitalization on the survival of newly diagnosed cases of HF with follow-up for 5 years in primary care (PC).* **Methods:** *This was a longitudinal observational study of a retrospective cohort of patients with information extracted from electronic medical records of PC. Incident cases of HF from 2006 to 2010 or until death were studied through a survival analysis with Kaplan–Meier and Cox proportional hazards multivariate regression, after applying the propensity score matching technique (PSM).* **Results:** *A total of 3061 new cases of HF were identified. The PSM analysis was performed with 529 couples, with a total of 1058 patients. 5-year survival was 65% in no hospitalized and 53% in hospitalized patients. Factors with an increased risk of mortality were having prescribed nitrates (heart rate [HR] = 1.56; 1.08-2.24). Factors with protective effect were having received the annual influenza vaccine (HR = 0.04; 0.01-0.15) and having been indicated X-rays by PC physician (HR = 0.76; 0.67-0.88).* **Conclusions:** *The findings indicate that hospitalizations are associated with a significant increase in mortality in patients recently diagnosed with HF. It is important to reinforce the need for the prevention of acute decompensated HF and for strategies to improve post-discharge outcomes.*

Key words: *Heart failure. Primary care. Hospitalization. Mortality. Propensity score. Spain.*

Resumen

Antecedentes: *La insuficiencia cardiaca (IC) es un serio problema de asistencia médica. El objetivo de este estudio es evaluar el efecto del primer episodio de IC aguda descompensada que requiere una hospitalización en la supervivencia de*

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los casos de IC recientemente diagnosticados con un seguimiento de 5 años en Atención Primaria (AP). **Métodos:** *Estudio observacional longitudinal de una cohorte retrospectiva de pacientes con información extraída de la historia clínica electrónica de AP. Se estudiaron los casos incidentes de IC desde 2006 a 2010 o hasta su fallecimiento con un análisis de supervivencia de Kaplan-Meier y un modelo de regresión de Cox, después de aplicar la técnica del Propensity Score Matching (PSM).* **Resultados:** *Se identificaron 3.061 casos nuevos de IC. El análisis PSM se realizó con 529 pareja, con un total de 1.058 pacientes. La supervivencia a los cinco años fue del 65% en pacientes no hospitalizados y del 53% en pacientes hospitalizados. Los factores con mayor riesgo de mortalidad fueron tener prescritos nitratos (HR = 1,56; 1,08-2,24). Los factores con efecto protector fueron haber recibido la vacuna anual de la gripe (HR = 0,04; 0,01-0,15) y haber sido indicadas radiografías por el médico de AP (HR = 0,76; 0,67-0,88).* **Conclusiones:** *Los hallazgos indican que las hospitalizaciones se asocian con un aumento significativo de la mortalidad en pacientes diagnosticados recientemente con IC. Es importante reforzar la necesidad de prevenir la IC descompensada aguda y las estrategias para mejorar los resultados posteriores al alta.*

Palabras clave: *Insuficiencia cardiaca. Atención primaria. Hospitalización. Mortalidad. Propensity score. España.*

Introduction

Heart failure (HF) represents a serious public health problem due to the morbidity-mortality and use of health-care services associated with this disease. The diagnosis of HF is usually associated with aging, loss of quality of life, reduction of physical and mental activity, and high demand for health services[1,2]. HF is still a major cause of death with a prognosis that has been reported to be worse than some of the common cancers[3]. In fact, and despite recent advances in pharmacological therapy, survival rates have not improved over time.

HF is a complex clinical syndrome with a diverse etiology, involving multiple pathophysiological mechanisms and characterized by different clinical presentations and possible evolution. Acute decompensated HF that requires hospitalization continues to be an important marker of disease progression and poor prognosis. Nevertheless, significant variability in mortality rates after the onset of symptomatic HF has been reported which likely reflect differences either in the characteristics of HF patients or in appropriate medical therapy[4,5].

The aim of this study is to evaluate the effect of the first acute episode of decompensated HF that requires hospitalization on the survival of newly diagnosed cases of HF with 5 years of follow-up in primary care (PC).

Materials and methods

Data source

We made a multicenter longitudinal observational study of a retrospective cohort of patients with information extracted from electronic medical records. The follow-up period was from January 1, 2006, to December 31, 2010. The study setting was the San Carlos Clinical Hospital of Madrid, which is a reference hospital for 22 basic PC areas located in the city of Madrid.

The study population was composed of subjects 24 years of age or older, with a single health insurance card, an open clinical record, and at least 1 medical visit to a PC center during 2006. Information was extracted from the PC health information system (OMI-AP). A case of HF was defined through the registration of a diagnosis of HF in the electronic medical record (codes K77 and K82 of the International Classification of PC 1).

The research protocol was conducted according to the Declaration of Helsinki guidelines, and the need to obtain written informed consent was waived due to the retrospective nature of the study. Patients' records were anonymized and no identifiable personal data were available for the analysis. Research Ethics Committee at the San Carlos Clinical Hospital revised and approved the study protocol.

Variables

The primary outcome was mortality after the 5th year of follow-up. Sociodemographic variables used in this study included age, sex, economic activity (active/pensioner), and the level of income (assigning each patient the income per capita of their health center). As clinical variables, the presence of cardiovascular risk factors and associated comorbidities (valvular heart disease, hypertension, ischemic heart disease, stroke, arrhythmias, diabetes, obesity or overweight, lipid metabolism disorder, smoking, and alcoholism), influenza vaccine administration in each of the years 2006-2010 (never

Table 1. Patient's characteristics by heart failure hospitalization before and after propensity score matching

Variables	Before PSM (n = 3061), n (%)			After PSM (n = 1058), n (%)		
	Not hospitalized (n = 2526)	Hospitalized (n = 535)	p	Not hospitalized (n = 529)	Hospitalized (n = 529)	p
Age (years): mean (SD)	76.38 (10.86)	76.90 (9.26)	0.665*	77.16 (8.81)	76.94 (9.30)	0.895*
Men	945 (82.4)	202 (17.6)	0.891**	203 (50.2)	201 (49.8)	0.899**
Women	1579 (82.6)	333 (17.4)		326 (49.8)	328 (50.2)	
Low medium income	354 (85.7)	59 (14.3)	0.012†,**	79 (57.2)	59 (42.8)	0.189**
High income	1514 (80.9)	357 (19.1)		336 (48.9)	351 (51.1)	
Very high income	658 (84.7)	119 (15.3)		114 (48.9)	119 (51.1)	
Pensioner	2364 (82.1)	516 (17.9)	0.009†,**	511 (50.0)	510 (50.0)	0.867**
Active	162 (89.5)	19 (10.5)		18 (48.6)	19 (51.4)	
Referrals to cardiology: mean (SD)	0.53 (0.82)	0.66 (0.98)	0.023†,*	0.68 (0.92)	0.66 (0.98)	0.414*
Blood tests: mean (SD)	4.15 (3.87)	5.18 (4.49)	<0.001*,†	5.19 (4.48)	5.18 (4.49)	0.877*
X-rays: mean (SD)	1.21 (1.59)	1.19 (1.54)	0.858*	1.33 (1.59)	1.19 (1.54)	0.101*
Electrocardiogram: mean (SD)	0.81 (1.17)	0.78 (1.24)	0.250*	1.01 (1.39)	0.78 (1.24)	0.001†,*
Influenza vaccine: Never	496 (83.9)	95 (16.1)	0.275**	77 (44.8)	95 (55.2)	0.131**
Influenza vaccine: Some year	1444 (81.6)	326 (18.4)		317 (49.6)	322 (50.4)	
Influenza vaccine: Every year	586 (83.7)	114 (16.3)		135 (54.7)	112 (45.3)	
Diabetes	761 (30.1)	227 (42.4)	<0.001†,**	229 (43.3)	224 (42.3)	0.756**
Arterial hypertension	1882 (74.5)	416 (77.8)	0.114**	418 (79.0)	410 (77.5)	0.551**
Dyslipidemia	1136 (45.0)	237 (44.3)	0.076**	259 (49.0)	236 (44.6)	0.156**
Obesity and overweight	712 (28.2)	163 (30.5)	0.289*	176 (33.3)	160 (30.2)	0.291**
Valvulopathies	288 (11.4)	117 (21.9)	<0.001†,**	126 (23.8)	117 (22.1)	0.511**
Arrhythmias	1181 (46.8)	330 (61.7)	<0.001†,**	339 (64.1)	327 (61.8)	0.445**
Ischemic heart disease	475 (18.8)	154 (28.8)	<0.001†,**	149 (28.2)	152 (28.7)	0.838**
Stroke	304 (12.0)	73 (13.6)	0.303**	76 (14.4)	73 (13.8)	0.791**
Deaths	400 (15.8)	119 (22.2)	<0.001†,**	84 (15.9)	116 (21.9)	0.012†,**

Mean (SD) of the continuous variables, or absolute values (%) of the categorical variables. *Mann–Whitney U-test, **Chi-square test, †Significant at the 0.05 level.
SD: standard deviation

vaccinated, partially vaccinated in some but not all years of the follow-up and fully vaccinated), and the prescribed pharmacological treatment (insulin, oral hypoglycaemic agents, antithrombotic agents, beta-blockers, calcium channel blockers, ACE inhibitors, angiotensin-receptor blockers (ARBs), nitrates, lipid reducers, and diuretics). As variables for the use of services, the complementary tests requested in PC have been incorporated, such as the number of blood tests (complete blood count and serum biochemistry), X-rays, electrocardiograms, as well as the number of referrals requested to cardiology (these tests were requested but there is no information on whether the patient went to perform them).

Statistical analysis

To evaluate the effect of hospitalizations an analysis based on propensity score matching (PSM) was conducted. PSM can be used to adjust for selection bias

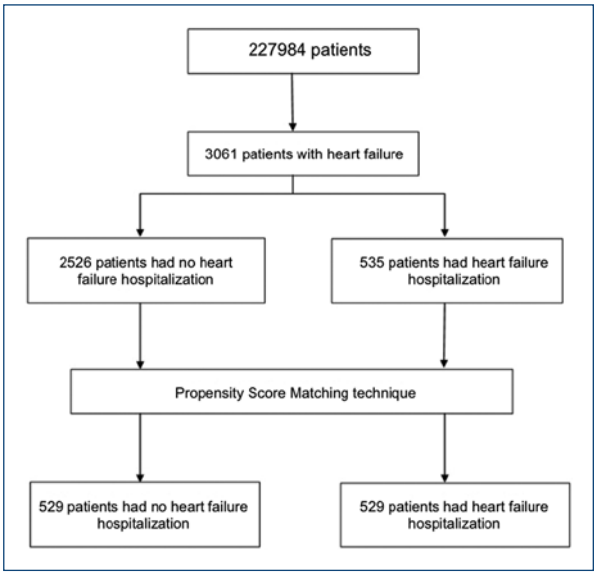

Figure 1. Flow chart for the assembly of a matched cohort.

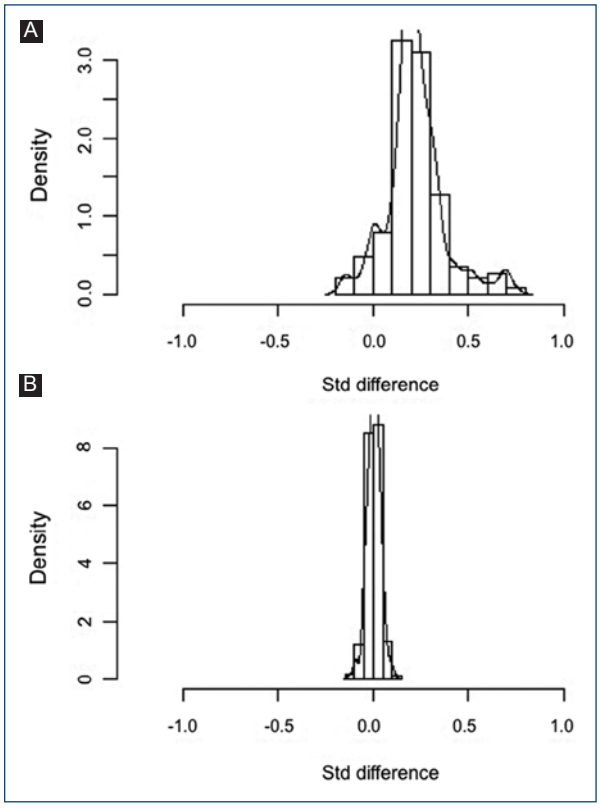

Figure 2. (**A** and **B**) Histograms with overlaid kernel density estimates of standardized differences before and after matching.

when assessing causal effects in observational studies as it permits to achieve balance between two groups, based on the conditional probability of receiving an event of interest (in this case, hospitalization due to worsening HF) given a series of measured covariates. The PSM was calculated through a binary logistic regression model based on confounding factors at baseline (Table 1), using the nearest neighbor algorithm without replacement, which consists of making 1: 1 pairings and the covariates selected as predictors. For the selection of covariates, a bivariate analysis was performed, including in the model that presents a statistically significant relationship with the dependent variable (presence or absence of hospitalization) or others that were of interest for the study objectives (according to the 2016 European Society of Cardiology [ESC] guidelines[6]).

A global imbalance χ^2 test was performed, which simultaneously evaluated whether any variable or any linear combination of the variables is unbalanced means after the pairing.

We also introduced a simple multivariate imbalance measure (Iacus, King and Porro, 2011)[7,8]. This measure presents a perfect global balance if L1 = 0, and the larger values represent a greater imbalance between the groups, with a maximum of L1 = 1. Therefore, we had a good method if $L1^{matching} \leq L1$.

The standardized mean differences were plotted, which quantify the bias in the means (or proportions) of covariates between the groups and should be close to zero after matching.

A Kaplan–Meier curve analysis was applied to determine survival at 5 years for variable hospitalizations. Differences between survival curves were assessed using the log-rank test.

Survival was estimated by taking the starting date as the date of registration of the disease in the medical history and the end date as the end of follow-up (censorship) or the date of the death of the patient. To study the mortality, death by any recorded cause in the medical record was included, and the date of death was considered as the date when the patient was removed from the health insurance card system.

The Cox proportional hazards model was used to estimate the relationship between the presence or absence of hospitalizations and mortality, adjusted for PSM and potential confounding variables. Hazard ratio and its 95% confidence interval were calculated for predictive variables. The validation of the model was carried out through the basic assumptions to verify the validation of the model: proportionality and log-linear.

Table 2: Pharmacotherapy before and after propensity score matching

Variables	Before PSM (n = 3061), n (%)			After PSM (n = 1058), n (%)		
	Not hospitalized (n = 2526)	Hospitalized (n = 535)	p	Not hospitalized (n = 529)	Hospitalized (n = 529)	p
Insulin	275 (10.9)	96 (17.9)	<0.001†,**	93 (17.6)	96 (17.6)	1.000**
Oral hypoglycemic agents	509 (20.2)	153 (28.6)	<0.001†,**	156 (29.5)	151 (28.5)	0.735**
Antithrombotic agents	1757 (69.6)	467 (87.3)	<0.001†,**	455 (86.0)	461 (87.1)	0.588**
Diuretics	1794 (71.0)	486 (90.8)	<0.001†,**	477 (90.2)	480 (90.7)	0.754**
Beta-blockers	788 (31.2)	258 (48.2)	<0.001†,**	251 (47.4)	255 (48.2)	0.806**
Calcium antagonists	842 (33.3)	205 (38.3)	0.027†,**	211 (39.9)	203 (38.4)	0.614**
ACE inhibitors	1141 (45.2)	325 (60.7)	<0.001†,**	310 (58.6)	321 (60.7)	0.491**
ARBs	746 (29.5)	202 (37.8)	<0.001†,**	196 (37.1)	197 (37.2)	0.949**
Lipid-lowering	1249 (49.4)	286 (53.5)	0.092**	312 (59.0)	283 (53.5)	0.072**
Cardiac glycosides	1458 (57.7)	390 (72.9)	<0.001†,**	394 (74.5)	386 (73.0)	0.576**
Nitrates	338 (13.4)	117 (21.9)	<0.001†,**	111 (21.0)	115 (21.7)	0.764**
Centrally acting antiadrenergic	1 (0.04)	1 (0.2)	0.319**	0 (0.0)	1 (0.2)	1**
Antiarrhythmic	206 (8.2)	49 (9.2)	0.445**	59 (11.2)	49 (9.3)	0.310**

Mean (SD) of the continuous variables, or absolute values (percentages) of the categorical variables. *Mann–Whitney U-test; **Chi-square test,
†Significant at the 0.05 level. SD: standard deviation; ACE: angiotensin-converting enzyme, ARBs: angiotensin-receptor blockers

For the statistical treatment and graphic representation of the data, the statistical package SPSS, v. 22.0 and Stata, v. 14.0 were used.

Results

PSM

The analysis is focused on a cohort of 529 couples, with a total of 1058 patients between hospitalized and non-hospitalized (Fig. 1). After matching, patients with and without HF hospitalization were balanced in all covariates (Tables 1 and 2). Table 1 shows sociodemographic characteristics, cardiovascular risk factors and associated comorbidity and use of services before and after PSM. After matching, 84 (15.9%) patients died who were not hospitalized while 116 (21.9) hospitalized patients died. Table 2 displays pharmacological treatment.

The p-value of the χ^2 balance test of Hansen and Bowers was 0.998, showing good covariate balance after matching. The results of measure L1, before matching (0.999) and after matching (0.994), confirmed the balance achieved. The histograms in figure 2a and b represent the standardized mean differences of all covariates, quadratic terms, and interactions together with the estimated (overlapping) kernel density function, before and after the PSM, where it was observed that these differences were centered at zero after matching.

Survival analysis

The survival of patients in the subpopulation after PSM was reduced from the 2nd year of follow-up compared to the cohort before PSM, with survival of 95, 84, 76, 67, and 59%, respectively, at 1, 2, 3, 4, and 5 years, with an average survival of 47.6 months (46.2-48.9), which decreased 1.4 points after applying the PSM technique[1]. Mean survival was 49.7 months (47.9-51.4) for the non-hospitalized and 45.6 months (43.5-47.6) for hospitalized patients. Figure 3 shows statistically significant differences between the curves (Log-rank test, p = 0.002). Therefore, the hospitalized group showed less survival rates.

Prognostic factors for mortality

The crude effect of being hospitalized was heart rate (HR) = 1.56 (1.17-2.06). After adjustment for PSM and confounding factors, the effect of being hospitalized decreased (HR = 1.49, 1.12-1.98) (Table 3).

Table 3: Multivariable Cox proportional hazards models after PS

HR (CI 95%)	Before PSM (n = 3061)		After PSM (n = 1058)	
	Hospitalization (crude)	Hospitalization (adjusted†)	Hospitalization (crude)	Hospitalization (adjusted for PS)
Dyslipidemia		1.091 (0.879-1.355)		1.205 (0.866-1.678)
Arterial hypertension		1.165 (0.939-1.446)		1.068 (0.763-1.496)
Obesity		1.051 (0.848-1.304)		0.927 (0.675-1.273)
Stroke		1.22 (0.955-1.559)		1.015 (0.687-1.499)
Influenza vaccine some year		0.987 (0.801-1.216)		0.982 (0.695-1.388)
Influenza vaccine every year		0.015 (0.004-0.06)*		0.036 (0.009-0.15)*
Total requested X-rays		0.815 (0.747-0.89)*		0.763 (0.665-0.875)*
Total requested ECG		0.913 (0.827-1.007)		0.961 (0.832-1.111)
Lipid-lowering		0.775 (0.61-0.985)*		0.725 (0.508-1.035)
Nitrates		1.162 (0.898-1.503)		1.557 (1.083-2.238)*
Hospitalization	1.575 (1.283-1.934)*	1.654 (1.326-2.063)*	1.555 (1.173-2.061)*	1.485 (1.116-1.977)*
-2LL	7605.53	7014.46	2480.85	2339.87
CHI2 global	19.12*	416.44*	9.56*	107.78*

†Age, sex, type of user, total referrals to cardiology, total requested blood tests, valvulopathies, arrhythmias, ischemic heart disease, diabetes mellitus, antithrombotic agents, beta-blockers, calcium antagonists, ACE inhibitors and ARA-II. *Significant at the 0.05 level. ACE: angiotensin-converting enzyme; PSM: propensity score matching; ECG: electrocardiogram; CI: confidence interval; HR: hazard ratio

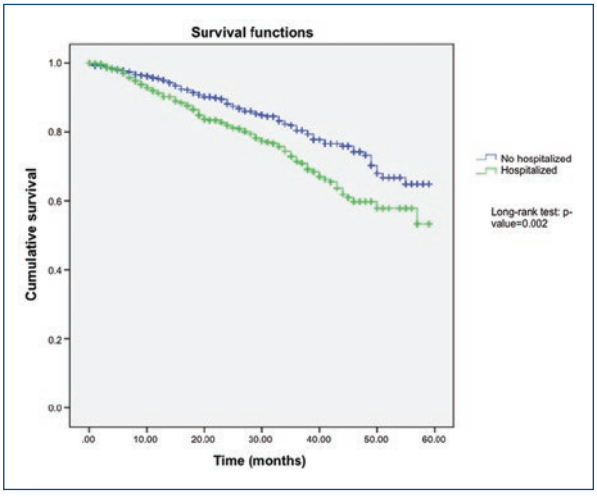

Figure 3. Kaplan–Meier estimated survival curves.

Having prescribed nitrates were associated with a higher risk of mortality after PSM (HR = 1.56, 1.08-2.24) (Table 3). Factors with a protective effect were having received influenza vaccination every year (HR = 0.04, 0.01-0.15) and X-rays having been requested by PC physicians (HR = 0.76, 0.67- 0.88) (Table 3).

Discussion

The main finding of this study is that a first acute episode of decompensated HF requiring a hospitalization increases the risk of mortality in patients with a recent diagnosis of HF followed in PC. A second relevant finding of this study is the existence of variables with both protective and risk effect in HF survival, regardless of hospitalization. These results confirm those obtained using PSM as well to identify the risk of mortality after an initial hospitalization in novel patients with HF selected from a different source of information and settings[9].

The results obtained with the Cox model after PSM indicate that having been hospitalized increased the risk of death by 59%. Consequently, the risk in this model has been reduced by 6% compared to the model applied before PSM[1].

These data also showed that nitrates have an association with mortality after PSM. Several studies have

reported an increased risk of mortality in patients with chronic HF on nitrate treatment[10-13]. According to the ESC Guide[6], treatment with nitrates should be used with great caution in patients diagnosed with mitral or aortic stenosis.

It is noteworthy to mention that the annual uptake of the influenza vaccine continues to have a strong protective effect. In fact, the influenza vaccine is often recommended to patients with HF due to their reducing effect on mortality and hospitalizations, although there are different views on the effectiveness of influenza vaccination[14-16].

X-ray indication by PC could be considered an estimate of a more intense follow-up by PC physicians, reflecting an orientation to early assessing of (and appropriate intervention in response to) an unexplained increase in signs and symptoms related with acute decompensation of the clinical status of HF patients. Although X-ray provides little information about the cardiac function, it could be still useful to rule out other explanations, particularly diseases of the respiratory system and is more easily accessible in the Spanish PC doctors than biomarkers or echocardiography.

An inherent disadvantage of the observational studies is that, by definition, treatment assignment is not the result of any randomization process. In clinical trials, randomization determines that the covariates are distributed homogeneously among the compared groups (treated/untreated) being the differences in outcomes found only due to treatment. However, observational studies are constituted by populations that are much more diverse in their characteristics. Rosenbaum and Rubin[17] implemented the PSM technique with the aim of reducing confounding and selection bias of cohort studies.

Another interesting aspect is the selection criterion used: in administrative data sources the study coding criteria and data quality control (selection bias) are not clarified. Therefore, it is necessary to have very clear the inclusion criteria: symptoms and signs of HF, elevated peptic and evaluation of the left ventricular ejection fraction. Nor is there any reference to electrocardiographic findings, which implies that having a normal electrocardiogram virtually excludes HF[6,18,19].

A limitation of the PSM is that it only takes into account the variables observed in the logistic regression model used for the PSM calculation. The existence of possible variables that have not been observed in the model can influence the PSM estimation, leading to an unbalanced model[20]. In this work, a good balance of the measured covariates between the two groups was obtained, but it is possible the presence of hidden bias after contrast due to non-measured latent variables. Therefore, in observational studies, PSM can reduce open bias (observed variables), but it cannot do the same with hidden bias (latent variables). Another issue is that large samples are required, since the larger the sample size, the lower the likelihood of unbalanced covariates[21].

Despite the limitations of this methodology, its application has been increasing. In a review published by Stürmer et al.,[22] in 2006, 192 publications from 1998 to 2003 in the field of health were considered where PSM was applied, 40% were from 2003. PSM tends to produce a lower estimation of effects than traditional methods with multivariable adjustments[23]. In this case, it can be seen that the estimates obtained after PSM show weaker associations than those before the PSM[1].

These results highlight the importance of HF hospitalization as a marker of disease progression and poor outcomes in chronic HF, reinforcing the need for prevention of HF hospitalizations and strategies to improve post-discharge outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical responsibilities disclosure

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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