Impact of frailty and disability on 30-day mortality in older patients with acute heart failure

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FJMS 1-9; ERA 1-5; MTV 1, 5; GLG 2; JGC 2,5; MAR 2,5; AA 2,5; PP 2,5; PLA 2,5; PL 5; PH 5; JJ 5; CF 3,5,6; HB 5; OM 5,7,9. 1. Study concept and design ; 2. Acquisition of the data ; 3. Analysis and interpretation of the data; 4. Drafting of the manuscript ; 5. Critical revision of the manuscript for important intellectual content; 6. Statistical expertise ; 7. Obtained funding ; 8. Administrative, technical, or material support ; 9. Study supervision

ABSTRACT

Objectives: To determine the impact of frailty and disability on 30-day mortality and whether the addition of these variables to HFRSS EFFECT risk score improves the short-term mortality predictive capacity of both HFRSS EFFECT and BI-EFFECT models among older patients with acute decompensated heart failure(ADHF) attended in the Emergency Department(ED).

Methodology: We performed a retrospective analysis of OAK Registry including all consecutive patients ≥65 years attended with ADHF in 3 Spanish EDs over 4 months. Frailty and disability were categorized into 6 groups: G1:Non-frail,no/mildly dependent; G2:Frail,no/mildly dependent; G3:Non-frail,moderately dependent; G4:Frail,moderately dependent; G5:Severely dependent; G6:Very severely dependent. FBI-EFFECT model was developed by adjusting probabilities of HFRSS EFFECT risk categories according to the 6 groups. We calculated the ROC area under curve (AUC) for HFRSS EFFECT, BI-EFFECT, and FBI-EFFECT.

Results: We included 596 patients (mean age: 83(SD7); 61.2% females). The 30-day mortality was 11.6% with statistically significant differences among the six groups(p<0.001). After adjusting for HFRSS EFFECT risk categories, we observed a progressive increase in hazard ratios from groups 2 to 6 compared to G1 (reference): G2=1.3 (95%CI0.4-4.9;p=0.647); G3=1.6 (95%CI0.6-4.4;p=0.380); G4=2.6 (95%CI1.1-5.9;p=0.022); G5=4.3 (95%CI1.9-10.0;p=0.001); and G6=7.7 (95%CI3.5-17.0;p<0.001). The AUCs of HFRSS EFFECT, BI-EFFECT, FBI-EFFECT were 0.64(95%CI0.59-0.70), 0.72(95%CI0.66-0,79), 0.76(95%CI0.70-0.82), respectively. FBI-EFFECT and BI-EFFECT had a better prognostic accuracy than HFRSS EFFECT(p<0.001 and p<0.001,respectively), and FBI-EFFECT had a trend to a better prediction than BI-EFFECT(p=0.067).

Conclusion: Severe disability and frailty in patients with moderate disability are associated with 30-day mortality in ADHF providing additional value to HFRSS EFFECT model in predicting short-term prognosis and establishing a care plan.

INTRODUCTION

Heart failure (HF) is a chronic disease, the prevalence and incidence of which increase with age[1,2]. HF is associated with Emergency Department (ED) visits, hospitalisations, and frequent readmissions, which are usually related to non-cardiovascular causes[1-3]. Moreover, the short-term mortality after hospitalisation for acute decompensated HF (ADHF) is very high, with a 30-day mortality of 10%[1-3].

Most patients with ADHF attend EDs, and thus, emergency physicians (EPs) play a crucial role in providing effective immediate treatment and in the decision-making regarding the most appropriate allocation for these patients[4-6]. Approximately 16% to 36% of patients with ADHF are discharged directly home after being attended in EDs[4-6]. Although this decision-making is still mainly empirical, experts widely recommend that it should be based on risk score models[4-6].

Several risk score models have described risk stratification in ADHF[7]. The Heart Failure Risk Scoring System (HFRSS) of the EFFECT study (HFRSS EFFECT) is one of the most commonly used risk stratification scores in clinical practice. This scoring system includes demographic, comorbidity, and clinical and laboratory data, and it predicts 30-day and 1-year mortality[8]. The Bi-EFFECT model is a modification of the HFRSS EFFECT risk score model. This modified model adjusts the predicted probabilities of the HFRSS EFFECT risk categories by the presence of severe functional baseline dependence (cut-off of 60 points in the Barthel index)[9]. This approach has shown a better short-term prognostic capacity in older patients with ADHF attended in EDs[9].

Frailty is a state of vulnerability in older populations, which increases the risk of adverse health outcomes[10]. Previous studies have shown that frailty is very frequent in non-severely disabled older patients with ADHF[11,12], and it is associated with a poor short-term prognosis[13]. Some authors have suggested that frailty should be included in risk stratification instruments[14] and should be taken into account in the development of care plans[15,16]. In fact, it is currently recommended to assess both the frailty phenotype and disability in older patients with ADHF attended in EDs[16].

Despite these findings, no studies have yet been performed to evaluate the impact of adding frailty and disability to HF risk score models. Thus, the aims of the present study were to (1) know the impact of frailty and disability on 30-day mortality; (2) to categorize the predicted probabilities of short-term mortality of the HFRSS EFFECT risk score model

according to frailty and disability; and (3) to determine whether this adjustment of the HFRSS EFFECT risk categories by frailty and disability provides any additional value to HFRSS EFFECT and Bi-EFFECT risk score models in predicting 30-day mortality among older patients with ADHF attended in EDs.

METHODOLOGY

Design

We performed a retrospective analysis of the Older Acute Heart Failure Key Data (OAK) Registry, a prospective observational multicenter cohort study[13]. The present study was approved by the Clinical Ethical Committees of all the participating hospitals.

Patients and Setting

The OAK Registry prospectively included all patients ≥ 65 years attended with AHF in 3 Spanish EDs (HCSC, Madrid; HRS, Murcia, and HSCSP, Barcelona) over a 4-month period, in 2-monthly periods (November-December 2011 and January-February 2014). Patients were initially selected by attending EPs considering clinical, electrocardiographic and radiological findings and, if available, natriuretic peptide levels and bedside ultrasound features. The principal investigator of each centre reviewed all the cases and finally included those fulfilling the diagnostic criteria of the HF guidelines of the European Society of Cardiology (ESC)[17]. The exclusion criteria were: a diagnosis of ST segment elevation acute myocardial infarction concomitant with AHF and non-consent to participate in the study.

For the present study, we selected older patients included in the OAK Registry with frailty and disability assessment and data related to vital status during the first 30 days after the index visit (Fig. 1). A brief geriatric assessment including frailty (Fried phenotype) and disability (Barthel index) was performed by a trained physician in each centre who was not responsible for the care of the patient during the first 12 hours of care in the ED on week days (Monday to Friday) from 8 am to 10 pm. Patients were asked about the presence or not of frailty criteria and disability one month before the ED visit.

Variables.

EPs collected demographic data (age and gender), medical history (arterial hypertension, diabetes mellitus, dyslipidemia, ischaemic heart disease, chronic renal failure, cerebrovascular disease, atrial fibrillation, peripheral artery disease, heart valve disease, chronic obstructive pulmonary disease, hepatic cirrhosis, cancer, previous diagnosis of HF and left ventricular ejection fraction), grade of comorbidity (Charlson index), baseline cardio-respiratory performance (New York Heart Association [NYHA] class), acute episode data (cardiac and respiratory rates, systolic blood pressure, oxygen

saturation measured by pulse oximetry, NYHA class for the episode, haemoglobin, sodium, blood urea nitrogen, renal clearance by MDRD-4, and NT-proBNP) and treatment requirements (oxygen, non-invasive ventilation, intravenous diuretics, nitroglycerin, angiotensin-converting enzyme inhibitors [ACE-I], angiotensin receptor blocker [ARB], beta-blockers [BB] and digoxin) and final allocation.

Frailty was defined according to Fried modified criteria as the presence of 3 or more positive answers to the following self-reported questions: 1) Exhaustion: Do you usually feel that everything you do is an effort and you cannot get going?; 2) Muscle strength: Do you have difficulty standing up from a chair?; 3) Walking time equivalent: Do you have significant difficulty in walking outside of the dwelling?; 4) Physical activity: Do you rarely ever engage in physical activity?; 5) Weight loss: Have you unintentionally lost weight in the last year?[13,16,18]. Disability was assessed by asking questions about the ability to independently perform basic activities of daily living and mobility (Barthel index)[19].

Considering that frailty should only be assessed in older patients with non-established severe disability and different degrees of disability, we categorized frailty and disability in 6 groups: 1) Non-frail, no/mildly dependent (< 3 Fried criteria and Barthel index ≥ 90 points); 2) Frail, no/mildly dependent (≥ 3 Fried criteria and Barthel index ≥ 90 points); 3) Non-frail, moderately dependent (< 3 Fried criteria and Barthel index 85-60 points); 4) Frail, moderately dependent (≥ 3 Fried criteria and Barthel index 85-60 points); 5) Severely dependent (Barthel index 55-40 points); 6) Very severely dependent (Barthel index < 40 points)[16].

For the present study, a new modified HFRSS EFFECT risk score model (FBI-EFFECT score, Frailty and Barthel Index in addition to HFRSS EFFECT) was developed by adjusting the HFRSS EFFECT risk categories according to the previously defined 6 groups of frailty and disability. The HFRSS EFFECT Risk Model was calculated to stratify the risk of 30-day mortality (http://www.ccort.ca/Research/CHFRiskModel.aspx), and older patients were categorized as very low or low risk (≤ 90 points), intermediate risk (91-120 points) or high or very high risk (> 120 points)[8]. The Bi-EFFECT was calculated considering the severe disability variable (cut-off of 60 points in the Barthel index) in conjunction with the HFRSS risk categories[9].

The main outcome was all-cause mortality within 30 days after attending the ED which was obtained through a review of the clinical history of each patient or by a telephone call to either a patient or a relative 31 to 60 days after discharge.

Statistical analysis.

Quantitative variables were expressed as means and standard deviation (SD) or median and interquartile ranges (IQR) and qualitative variables as absolute numbers and percentages. For univariate comparisons the Student's t or ANOVA test was used for the quantitative variables with a normal distribution (determined using the Kolmogorov-Smirnov test) or with the non-parametric test of the median in cases without a normal distribution. The Chi-square or the Fisher exact test was used for qualitative variables. The P for linear trend was also estimated. The sample was divided into 6 groups according to the presence of frailty and different levels of disability. Cox regression analysis was performed to determine whether the frailty and disability groups were independent prognostic factors of 30-day mortality. Survival curves were constructed using the Kaplan-Meier model. Differences among the different survival curves were determined using log-rank statistics and each group was compared with reference group. The effect of the different groups of frailty and disability on 30-day mortality was expressed as crude hazard ratios (HR), with 95% confidence intervals (95% CI), and then adjusted HR by HFRSS risk categories (very low or low risk (≤ 90 points), intermediate (91-120 points) or high or very high (>120 points) using a direct Cox regression analysis. A direct Cox regression was used to estimate predictive probabilities of 30-day mortality of the HFRSS EFFECT, BI-EFFECT (adding severe functional dependence) and FBI-EFFECT (adding frailty and disability groups) risk score models. Dynamic ROC curves were used to determine the discriminatory capacities of the HFRSS EFFECT, BI-EFFECT and FBI-EFFECT risk score models. The areas under the curve (AUC) of the risk models were compared using a non-parametric test. We considered differences to be statistically significant if the p value was less than 0.05, and the 95% CI of the HR excluded 1 or 95% CI of AUC ROC excluded 0.5. All the analyses were performed with SPSS 18.0 and STATA 12.0 statistical package.

RESULTS

Of the 952 older patients consecutively included in the OAK Registry, 318 had not undergone a brief geriatric assessment, and 38 had not had a 30-day follow-up. Therefore, 596 out of 952 (62.6%) patients were ultimately selected for the present study (Fig. 1). Comparison between included and non-included patients showed significant differences in age, ischaemic heart disease, dementia, cardio-respiratory and functional baseline status, and NT-proBNP levels (Supplementary Table 1).

The patients had a mean age of 83.2 (SD7.1) years, 363 (61.2%) were female, 318 (56.2%) patients had severe comorbidity (Charlson index≥3), and 378 (63.4%) had a previous diagnosis of HF. Table 1 shows the characteristics of the patients included in the study.

Two hundred and eighty-one (47.1%) patients were independent or mildly dependent, 192 (32.2%) moderately dependent, 60 (10.1%) severely dependent, and 63 (10.6%) very severely dependent. Out of 473 patients without severe and very severe functional dependence, 314 (66.4%) met the frailty criteria. Supplementary tables 2-5 show the univariate analysis according to the presence of frailty in patients with non-severe dependence and the degree of disability. Regarding the 6 groups of frailty and disability, 235 (39.4%) patients were non-frail, no/mildly dependent; 46 (7.7%) frail, no/mildly dependent, 79 (13.3%) non-frail, moderately dependent; 113 (19.0%) frail, moderately dependent; 60 (10.1%) severely dependent; and 63 (10.6%) very severely dependent.

Sixty-nine (11.6%) older patients died in the first 30 days after being attended in EDs. According to the HFRSS EFFECT risk model, 73 (12.2%) cases had very low and low risk, 246 (41.3%) intermediate risk, and 277 (46.5%) had high or very high risk, with the percentage of 30-day mortality in each category being 2.7%, 7.7%, and 17.3%, respectively. Concerning the frailty and disability groups, the rate of 30-day mortality was statistically different among the six groups: 4.3%, 6.5%, 7.6%, 12.4%, 21.7%, and 36.5%, respectively ($p<0.001$). After adjusting for the HFRSS EFFECT risk categories, the presence of frailty in moderately dependent (adjusted HR=2.6; 95%CI 1.1-5.9;p=0.022), severe disability (adjusted HR=4.3; 95%CI 1.9-10.0;p=0.001) and very severe disability (adjusted HR=7.7; 95%CI 3.5-17.0;$p<0.001$) was independently associated with 30-day mortality compared to non-frail, no/mildly dependent patients (Fig. 2). Figure 3 shows predictive probabilities of

30-day mortality of the FBI-EFFECT risk model after adjusting the estimated risk of each HFRSS EFFECT category for the six predefined groups.

The AUC of the FBI-EFFECT risk model was 0.76 (95%CI 0.70-0.82). The AUC was 0.64 (95%CI 0.59-0.70) for the HFRSS EFFECT risk model and 0.72 (95% 0.66-0.79) for the Bi-EFFECT risk model. Statistically significant differences were observed between the FBI-EFFECT and HFRSS EFFECT ($p<0.001$) and BI-EFFECT and HFRSS EFFECT ($p<0.001$) models, with the FBI-EFFECT and BI-EFFECT models showing a trend to a better prediction of 30-day mortality ($p=0.067$) (Fig. 4).

DISCUSSION.

The present study shows that frailty and disability have an impact on 30-day mortality among older patients with ADHF attended in EDs. The presence of the frailty phenotype (≥3 Fried criteria) in patients with moderate baseline functional dependence (Barthel index 60-85 points) and the presence of severe disability (Barthel index < 60 points) are factors independently associated with a poor short-term prognosis. These results suggest that the baseline functional status (basic activities of daily living and mobility) should be assessed in all older patients with ADHF attended in EDs. Moreover, frailty (frailty phenotype) should be included in patient assessment, particularly in those with moderate baseline functional dependence (Barthel index 60-85 points).

Previous studies have reported that frailty[13,20,21] and severe baseline functional dependence[9,22] are prognostic factors in older patients with ADHF. Our findings provide additional evidence to demonstrate that frailty and severe baseline functional dependence are poor short-term prognostic factors in older patients with ADHF attended in EDs[9,13,22]. Severe and very severe disabilities present the highest level of vulnerability and frailty has a significant impact on non-severely disabled older patients. In addition, concurrency of these two factors, particularly in patients with moderate functional dependence, could have a synergistic effect on short-term mortality. This is in agreement with previous studies, which have described progression of chronic HF when both frailty and disability were present[18].

Secondly, the adjustment of three HFRSS EFFECT risk categories according to 6 different frailty and disability groups has derived a new modified HFRSS EFFECT (FBI-EFFECT) score with 18 predictive probabilities of 30-day mortality. Previous HF risk models have only considered demographic, clinical and analytical variables[7]. It is well known that biological age is a stronger correlate of mortality than chronological age[23]. Moreover, frailty and disability are markers of biological age and therefore may help to assess the heterogeneity of health status among older patients[23]. In this context, the present study shows that adjustment of a classical risk model by the presence of frailty and disability may improve prognostic accuracy in older patients with a decompensated chronic condition.

Thirdly, the FBI-EFFECT risk model has a good prognostic capacity. We found it to have a higher prognostic accuracy compared to the HFRSS EFFECT Risk Model and a trend towards better prediction compared to the BI-EFFECT risk model. Moreover, in addition to improvement in risk stratification, this new approach could suggest a different plan of care

guided by the presence or not of both severe disability and frailty in patients with moderate disability[16,24]. Frailty is a potentially reversible syndrome and should, therefore, be addressed early[16,24]. A broader intervention beyond HF management is necessary in frail patients, including treatment of concurrent decompensated chronic conditions, minimizing polypharmacy and inappropriate medication prescription, monitoring patient capacities during and after hospitalisation in order to minimize disability, and prescribing physical exercise and nutritional supplementation[25,26]. The presence of severe disability in ADHF patients represents the highest risk scenario and, according to the poor short-term outcome of these patients, suggests a conservative attitude regarding invasive procedures and the aim to improve the quality of life[16]. Distinction between severe and very severe disability improved the accuracy of the short-term prognosis and identified a group of older patients with ADHF in EDs in whom the treatment should address symptom relief and palliative care[16]. Therefore, unlike the previous models, the FBI-EFFECT risk model could have both prognostic and therapeutic utility.

Fourthly, the presence of the frailty syndrome in the context of ADHF is difficult to interpret and could be considered a sign of disease severity. Even though frailty may overlap with comorbidity and disability[27], it is considered as a specific entity mainly showing a physical function[18]. In our study, frailty was associated with older age and female gender but not with a higher comorbidity index or clinical and analytical data of HF acuteness such as tachycardia, tachypnoea, hypoxemia, anaemia, hyponatraemia or hypotension. However frail patients had higher levels of B-type natriuretic peptide than non-frail patients, similar to findings described by other authors[28]. Although these higher B-type natriuretic peptide levels are not clearly understood, they suggest the presence of different pathological mechanisms or common pathological pathways between HF and frailty involving inflammatory processes, and metabolic or autonomic disturbances, as other authors have previously indicated[29].

On the contrary, in our cohort the degree of disability, which is usually multifactorial and is considered as dependency for activities of daily living, was associated with age, gender, severe comorbidity, chronic cardio-pulmonary and renal diseases, dementia and cerebrovascular disorders and cancer. Patients with higher disability also showed more clinical and analytical data of severity (tachycardia, tachypnoea, hypoxemia, anaemia, hyponatraemia, and elevated B-type natriuretic peptide levels) in agreement with a recent

study including patients hospitalized with ADHF from 12 different countries describing a higher frequency of these variables, except for B-type natriuretic peptide levels in older disabled patients[30].

The present study has several limitations. This was an exploratory analysis in a large multipurpose cohort which may have limited the statistical power of the analysis. Although significant clinical differences were not found between older included and non-included patients, a selection bias cannot be ruled out because the results were derived from a voluntary multicentre registry, and the frailty assessment was performed between 8 am and 10 pm on weekdays. The assessment of frailty was based on self-reported questions, and not on performance measures, since the measurement of some components requires specific instruments, is time consuming and not very feasible in the ED. Treatments prescribed at discharge were not controlled but left to the attending physician's criteria with no specific guidance, and this may have had influenced outpatient outcomes. Lastly, information related to echocardiographic or other plasma biomarker data were not available, primarily because they are not routinely performed in all patients with AHF attended in Spanish EDs. However, this may make our results more realistic and ultimately easier to apply in real ED practice.

Despite these limitations, we conclude that frailty and disability, particularly severe disability and the presence frailty in patients with moderate baseline disability, are associated with 30-day mortality in older patients with ADHF attended in the ED. Our results also provide additional value to the HFRSS EFFECT and BI-EFFECT risk scores in predicting short-term prognosis and helping in the decision making related to care planning in these patients. Nonetheless, these findings should be validated in a larger cohort.

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TABLES Y FIGURES

Figure 1.-Flowchart of the patients included in the study.

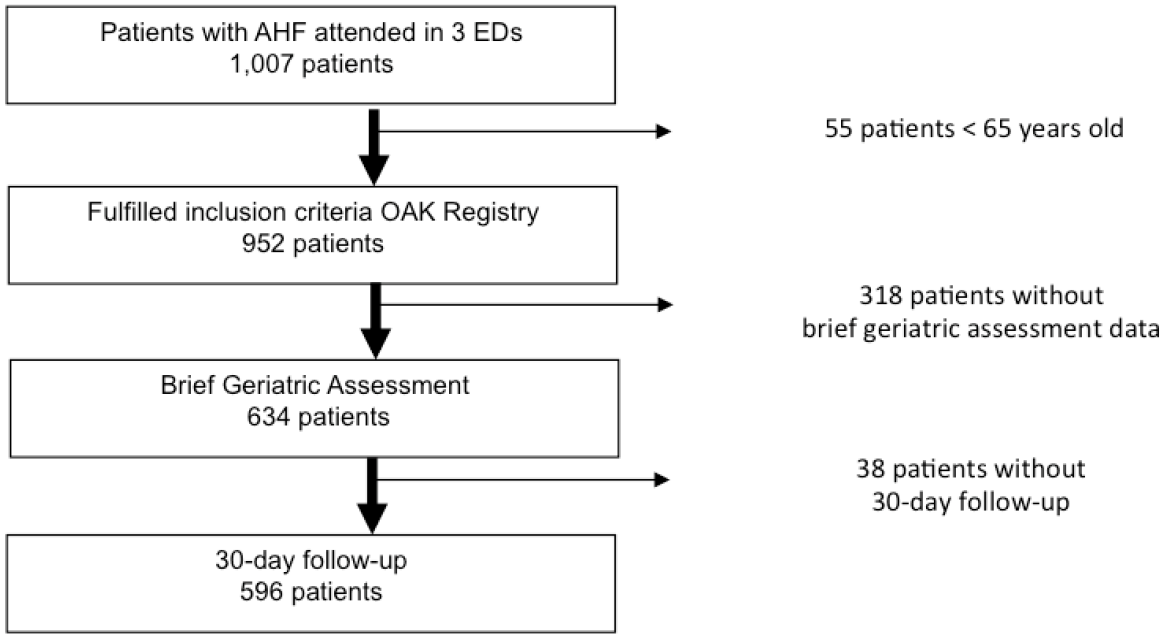
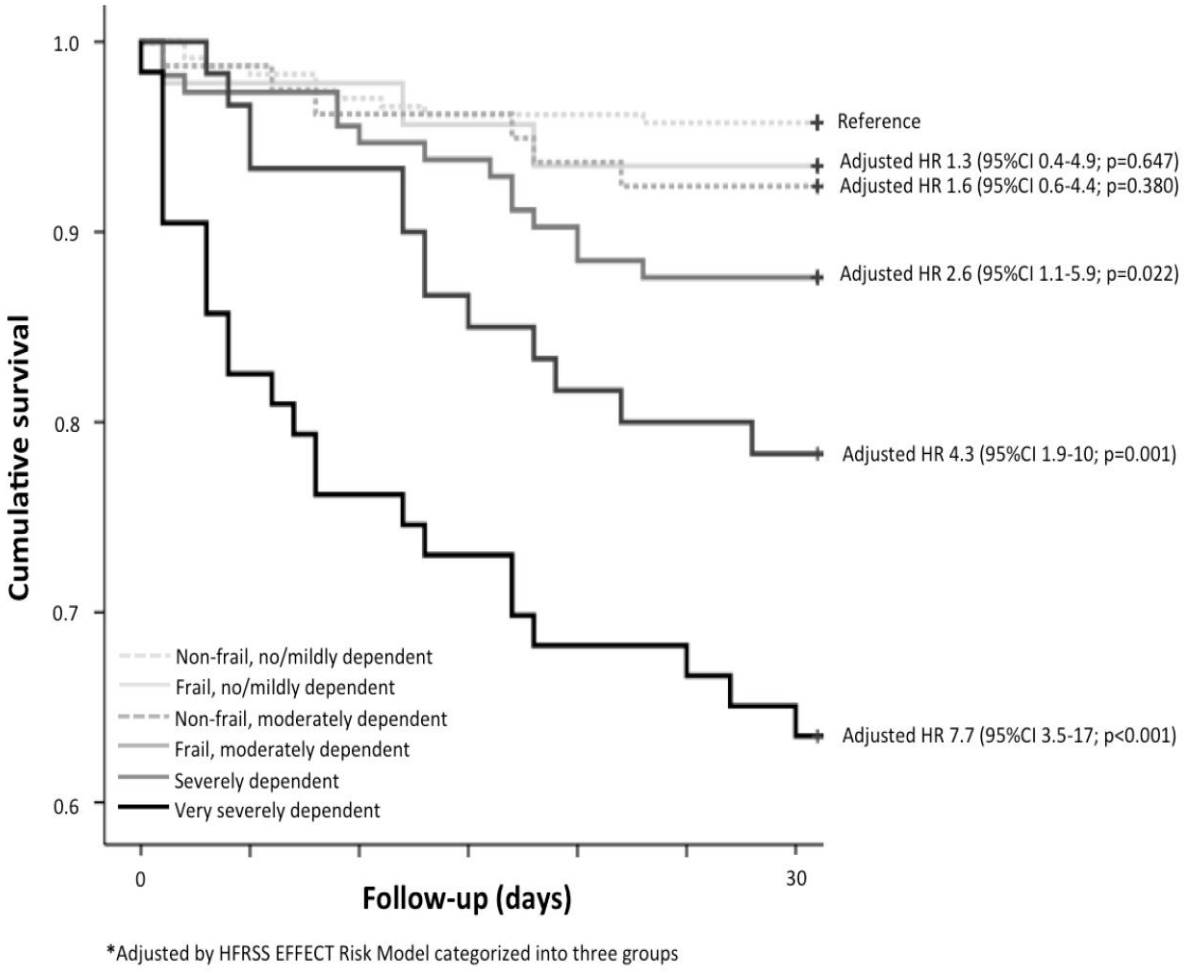


Table 1.-Characteristics of the patients included in the study.

	Total (N=596)
Demographic data	
Age (years) [mean (SD)]	83.2 (7.1)
Female sex [N(%)]	363 (61.2)
Medical history	
Arterial hypertension [N(%)]	528 (88.6)
Diabetes mellitus [N(%)]	221 (37.1)
Dyslipidaemia [N(%)]	305 (51.3)
Ischaemic heart disease [N(%)]	179 (30.0)
Chronic kidney failure [N(%)]	181 (30.4)
Cerebrovascular disease [N(%)]	105 (17.6)
Atrial fibrillation [N(%)]	360 (60.4)
Peripheral arterial disease [N(%)]	88 (14.8)
Heart valve disease [N(%)]	178 (29.9)
Chronic obstructive pulmonary disease [N(%)]	135 (22.7)
Previous diagnosis of heart failure [N(%)]	378 (63.4)
Dementia [N(%)]	106 (17.8)
Cirrhosis [N(%)]	17 (2.9)
Cancer [N(%)]	98 (16.4)
Severe comorbidity (Charlson index ≥ 3) [N(%)]	318 (56.2)
Baseline status	
Cardio-respiratory (NYHA III-IV class) [N(%)]	143 (24.3)
Left ventricular ejection fraction ≤ 45% [N(%)]	107 (57.8)
Acute episode clinical and biochemical data	
SBP <100 mmHg [N(%)]	29 (5.0)
Tachycardia (≥100 bpm) [N(%)]	141 (24.1)
Tachypnoea (>20 rpm) [N(%)]	227 (38.1)
Basal oxygen saturation < 90% [N(%)]	150 (26.7)
Hyponatraemia (natraemia< 135mEq/L) [N(%)]	93 (15.9)
Kidney failure (Acl<60 ml/min/m2) [N(%)]	339 (58.8)
Anaemia (Hb<10 g/L) [N(%)]	86(14.6)
NT-proBNP> 5,180 pg/ml [N(%)]	173 (41.9)
Acute episode treatment and final destination	
Oxygen [N(%)]	418 (70.3)
Non-invasive ventilation [N(%)]	27 (4.5)
Intravenous diuretics [N(%)]	535 (89.9)
Intravenous nitroglycerine [N(%)]	30 (5.0)
ACE-I /ARB [N(%)]	191 (32.1)
BB [N(%)]	105 (17.6)
Digoxin [N(%)]	99 (16.6)
Hospital admission[N(%)]	526 (88.3)

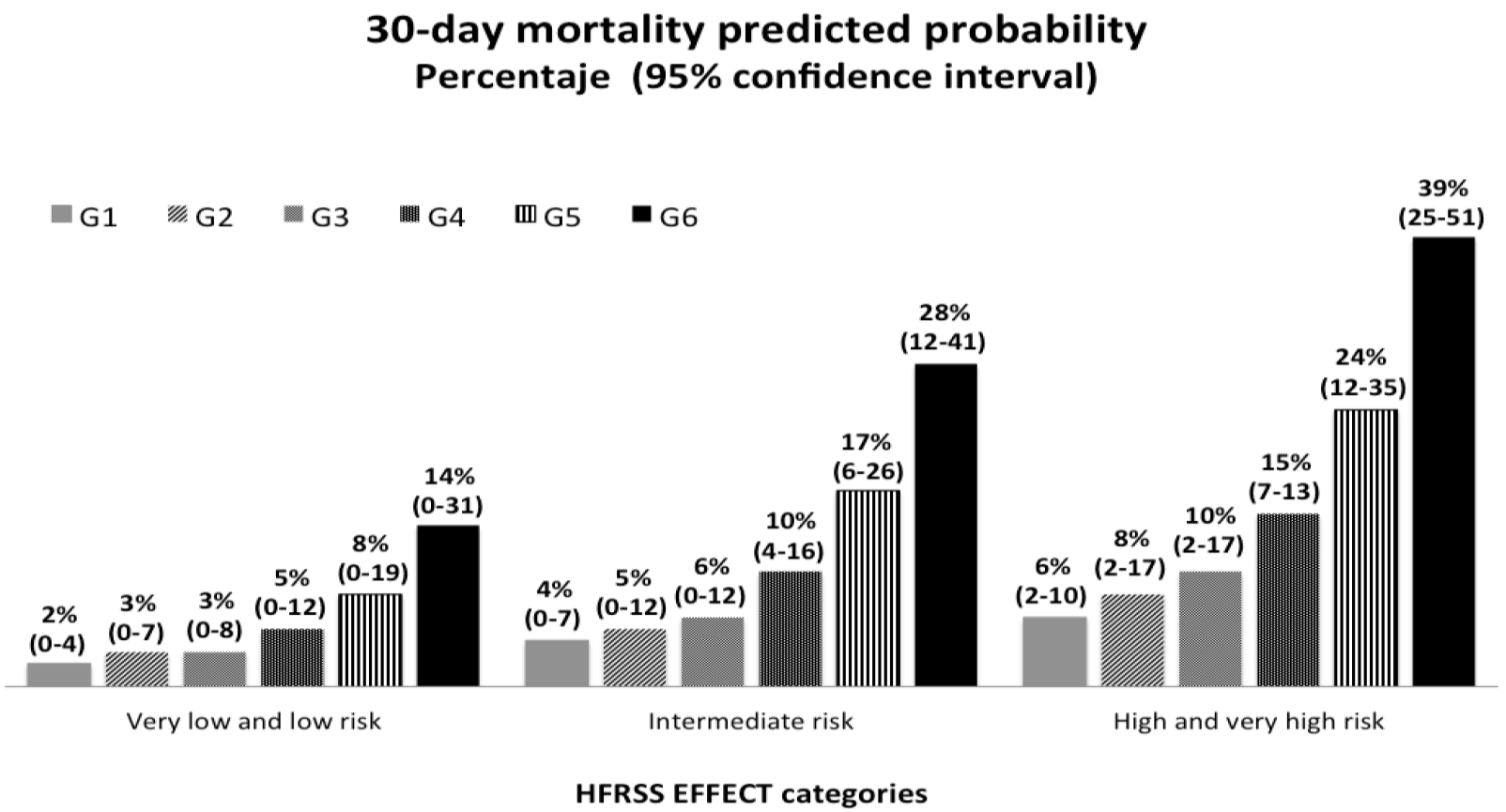
*SD: standard deviation; NYHA: new york heart association; SBP: systolic blood pressure; bpm: beat per minute; rpm: respiration per minute; Erc: estimated renal clearance; Hb: haemoglobin; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blocker

Figure2.-Impact of frailty and disability grouped after adjustment for the HFRSS EFFECT risk categories for predicting 30-day mortality in older patients with ADHF attended in the ED.



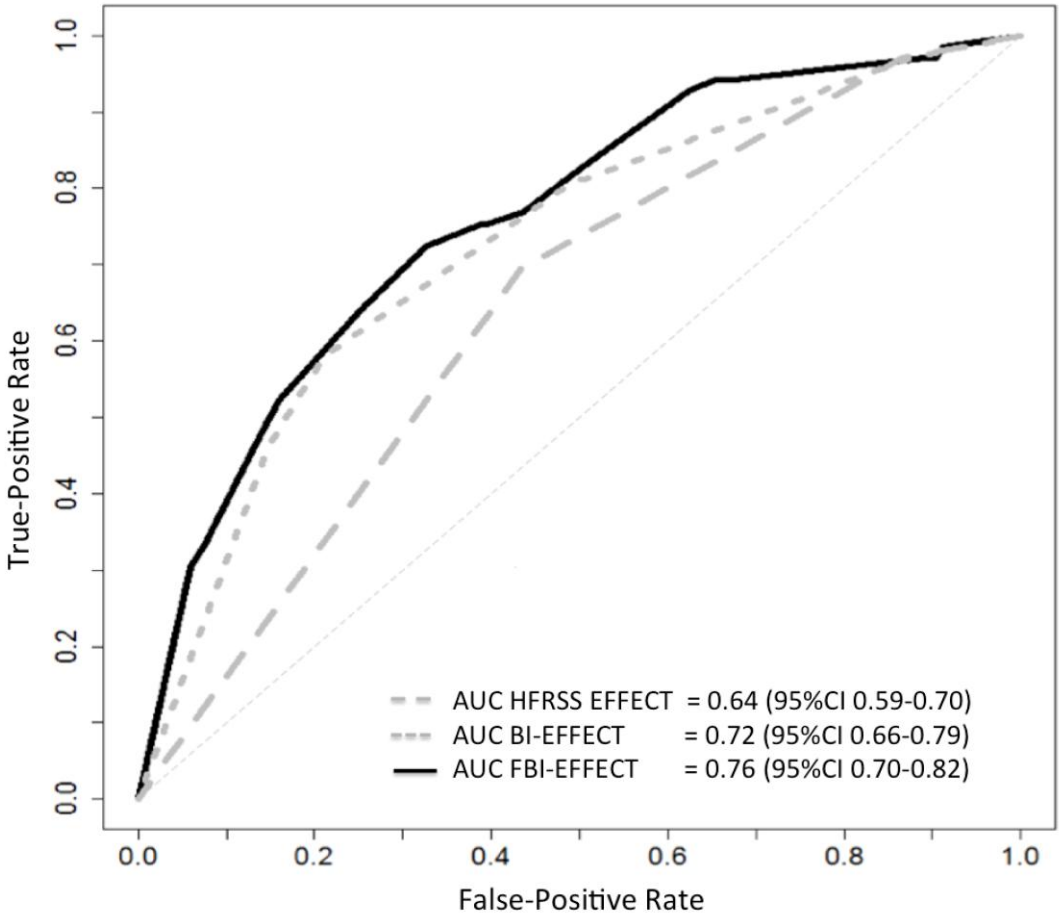
*HZ: hazard ratio; CI: confidence interval; ADHF: acute decompensated heart failure; ED: emergency department.

Figure 3.-Short-term mortality predicted probabilities of the FBI-EFFECT risk model.



G1: Non-frail, no/mildly dependent; G2: Frail, no/mildly dependent; G3: Non-frail, moderately dependent; G4: Frail, moderately dependent; G5: Severely dependent; G6: Very severely dependent

Figure 4.- ROC curves of the HFRSFF EFFECT, Bi-EFFECT and FBI-EFFECT risk models for predicting 30-day mortality in older patients with ADHF attended in the ED.



*AUC: area under curve; CI: confidence interval; ADHF: acute decompensated heart failure; ED: emergency department.

**p value <0.001 AUC of FBI-EFFECT vs. AUC of HFRSS EFFECT; p value = 0.067 AUC of FBI-EFFECT vs. AUC of BI-EFFECT; p value <0.001 AUC of BI-EFFECT vs. AUC of HFRSS EFFECT.

Supplementary material.

Table 1.-Comparison between patients included and not-included in the study.

	Patients Included (N=596)	**Patients Not Included** (N=356)	p
Demographic data			
Age (years) [mean (SD)]	83.19 (7.1)	82.76 (7.0)	**0.038**
Female sex [N(%)]	363 (61.2)	218 (61.1)	0.979
Medical history			
Arterial hypertension [N(%)]	528 (88.6)	301 (84.3)	0.059
Diabetes mellitus [N(%)]	221 (37.1)	149 (41.7)	0.144
Dyslipidaemia [N(%)]	305 (51.3)	171 (47.9)	0.303
Ischaemic heart disease [N(%)]	179 (30.0)	86 (24.1)	**0.044**
Chronic kidney failure [N(%)]	181 (30.4)	91 (25.5)	0.103
Cerebrovascular disease [N(%)]	105 (17.6)	52 (14.6)	0.192
Atrial fibrillation [N(%)]	360 (60.4)	190 (53.2)	0.152
Peripheral arterial disease [N(%)]	88 (14.8)	44 (12.4)	0.294
Valve disease [N(%)]	178 (29.9)	103 (28.9)	0.769
Chronic obstructive pulmonary disease [N(%)]	135 (22.7)	100 (28.0)	0.057
Previous diagnosis of heart failure [N(%)]	378 (63.4)	217 (63.8)	0.966
Dementia [N(%)]	106 (17.8)	39 (10.9)	**0.004**
Cirrhosis [N(%)]	17 (2.9)	2 (0.6)	0.625
Cancer [N(%)]	98 (16.4)	54 (15.1)	0.730
Baseline status			
Functional dependence (Barthel index) [Mean (SD)]	76 (24.8)	82 (20.5)	**<0.001**
Cardio-respiratory (NYHA III-IV class) [N(%)]	143 (24.3)	62 (18.0)	**0.024**
Left ventricular ejection fraction ≤ 45% [N(%)]	107 (57.8)	59 (59.0)	0.820
Acute episode clinical data			
Cardio-respiratory (NYHA III-IV class) [N(%)]	526 (89.8)	312 (90.7)	0.638
SBP <100 mmHg [N(%)]	29 (5.0)	14 (3.9)	0.529
Tachycardia (≥100 bpm) [N(%)]	141 (24.1)	100 (28.2)	0.166
Tachypnoea (>20 rpm) [N(%)]	227 (38.1)	132 (48.0)	0.486
Basal oxygen saturation < 90% [N(%)]	150 (26.7)	76 (22.1)	0.117
Acute episode biochemical data			
Hyponatraemia (natraemia< 135mEq/L) [N(%)]	93 (15.9)	67 (18.9)	0.214
Kidney failure (Acl<60 ml/min/m2) [N(%)]	339 (58.8)	228 (64.8)	0.083
Anaemia (Hb<13 g/L male / <12 g/L female) [N(%)]	326 (55.5)	179 (50.9)	0.170
NT-proBNP[median (IQR)]	3,795 (2,046-7,847)	4,930 (2,076-11,200)	**0.029**
All causes 30-day mortality [N(%)]	69 (11.6)	31 (9.7)	0.311

*SD: standard deviation; IQR: interquartile range; NYHA: new york heart association; SBP: systolic blood pressure; bpm: beats per minute; rpm: respiration per minute; Erc: estimated renal clearance; Hb: haemoglobin.

Table 2.-Baseline data of patients included in the study and comparison according to four categories of disability.

	Total (N=596)	Independent or mild functional dependence(N=281)	Moderate functional dependence(N=192)	Severe functional dependence (N=60)	Very severe functional dependence (N=63)	p value linear trend
Demographic data						
Age (years) [mean (SD)]	83.2 (7.1)	80.7 (7.0)	84.6 (6.6)	86.5 (6.3)	86.9 (5.8)	<0.001
Female sex [N(%)]	363 (61.2)	149 (53.0)	129 (67.9)	43 (71.7)	42 (67.7)	0.001
Medical history						
Arterial hypertension [N(%)]	528 (88.6)	243 (86.5)	176 (91.7)	56 (93.3)	53 (84.1)	0.679
Diabetes mellitus [N(%)]	221 (37.1)	97 (34.5)	70 (36.5)	30 (50.0)	24 (38.1)	0.163
Dyslipidaemia [N(%)]	305 (51.3)	146 (52.1)	107 (55.7)	27 (45.0)	25 (39.7)	0.083
Ischaemic heart disease [N(%)]	179 (30.0)	88 (31.3)	57 (29.7)	19 (31.7)	15 (23.8)	0.343
Chronic kidney failure [N(%)]	181 (30.4)	73 (26.0)	58 (30.2)	25 (41.7)	25 (39.7)	0.005
Cerebrovascular disease [N(%)]	105 (17.6)	40 (14.2)	35 (18.2)	14 (23.3)	16 (25.4)	0.013
Atrial fibrillation [N(%)]	360 (60.4)	163 (58.0)	117 (60.9)	44 (73.3)	36 (57.1)	0.378
Peripheral arterial disease [N(%)]	88 (14.8)	48 (17.1)	30 (15.6)	5 (8.3)	5 (7.9)	0.026
Heart valve disease [N(%)]	178 (29.9)	94 (33.5)	53 (27.6)	15 (25.0)	16 (25.4)	0.091
Chronic obstructive pulmonary disease [N(%)]	135 (22.7)	59 (21.0)	41 (21.4)	14 (23.3)	21 (33.3)	0.066
Previous diagnosis of heart failure [N(%)]	378 (63.4)	165 (58.7)	124 (64.6)	47 (78.3)	42 (66.7)	0.023
Dementia[N(%)]	106 (17.8)	17 (6.0)	33 (17.2)	18 (30.0)	38 (60.3)	<0.001
Cirrhosis [N(%)]	17 (2.9)	7 (2.5)	6 (3.1)	2 (3.3)	2 (3.2)	0.669
Cancer [N(%)]	98 (16.4)	41 (14.6)	27 (14.1)	9 (15.0)	21 (33.3)	0.004
Comorbidity						
Severe comorbidity (Charlson index ≥ 3) [N(%)]	318 (56.2)	125 (46.3)	106(58.9)	38 (70.4)	49 (79.0)	<0.001
Baseline status						
Cardio-respiratory (NYHA III-IV class) [N(%)]	143 (24.3)	42(15.1)	57 (30.3)	22 (36.7)	22 (35.5)	<0.001
Left ventricular ejection fraction ≤ 45% [N(%)]	107 (57.8)	50 (56.8)	36 (59.0)	14 (66.7)	7 (46.7)	0.924

* NYHA: new york heart association.

Table 3.-Follow-up and acute episode data of patients included in the study and comparison according to four categories of disability.

	Total (N=596)	Independent or mild functional dependence (N=281)	Moderate functional dependence (N=192)	Severe functional dependence (N=60)	Very severe functional dependence (N=63)	p value linear trend
Acute episode clinical data						
SBP <100 mmHg [N(%)]	29 (5.0)	8 (2.9)	12 (6.3)	3 (5.1)	6 (10.0)	0.021
Tachycardia (≥100 bpm) [N(%)]	141 (24.1)	80 (28.8)	37 (19.8)	12 (20.0)	12 (19.7)	0.040
Tachypnoea (>20 rpm) [N(%)]	227 (38.1)	94 (33.5)	68 (35.4)	32 (53.3)	33 (52.4)	0.001
Basal oxygen saturation < 90% [N(%)]	150 (26.7)	61 (22.9)	44 (24.9)	21 (35.6)	24 (40.0)	0.003
Acute episode biochemical data						
Hyponatraemia (natraemia< 135mEq/L) [N(%)]	93 (15.9)	37 (13.4)	29 (15.3)	9 (15.3)	18 (29.5)	0.008
Kidney failure (Acl<60 ml/min/m2) [N(%)]	339 (58.8)	147 (53.3)	117 (62.9)	41 (69.5)	34 (60.7)	0.039
Anaemia (Hb<10 g/L) [N(%)]	86(14.6)	33 (11.8)	24 (12.6)	10 (17.2)	19 (31.1)	<0.001
NT-proBNP> 5,180 pg/ml[N(%)]	173 (41.9)	67 (32.8)	59 (43.4)	20 (64.5)	27 (64.3)	<0.001
Acute episode treatment						
Oxygen [N(%)]	418 (70.3)	177 (63.2)	146 (76.0)	46 (76.7)	49 (77.8)	0.003
Non-invasive ventilation [N(%)]	27 (4.5)	9 (3.2)	8 (4.2)	7 (11.7)	3 (4.8)	0.099
Intravenous diuretics [N(%)]	535 (89.9)	249 (88.9)	172 (89.6)	54 (90.0)	60 (95.2)	0.188
Intravenous nitroglycerine [N(%)]	30 (5.0)	9 (3.2)	11 (5.7)	3 (5.0)	7 (11.1)	0.015
ACE-I /ARB [N(%)]	191 (32.1)	102 (36.4)	60 (31.2)	10 (16.7)	19 (30.2)	0.034
BB [N(%)]	105 (17.6)	56 (20.0)	34 (17.7)	8 (13.3)	7 (11.1)	0.057
Digoxin [N(%)]	99 (16.6)	48 (17.1)	34 (17.7)	6 (10.0)	11 (17.5)	0.626
Final destination						
Hospital admission[N(%)]	526 (88.3)	244 (86.8)	168 (87.5)	53 (88.3)	61 (96.8)	0.055
Follow-up						
All-cause 30-day mortality [N(%)]	69 (11.6)	13 (4.6)	20 (10.4)	13 (21.7)	23 (36.5)	<0.001

*IQR: interquartile range; NYHA: new york heart association; SBP: systolic blood pressure; bpm: beats per minute; rpm: respiration per minute; Erc: estimated renal clearance; Hb: haemoglobin; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blocker.

Table 4.-Baseline data of patients without severe and very severe dependence and comparison according to the frailty.

	Total (N=473)	Non-Frailty (N=314)	Frailty (N=159)	p value
Demographic data				
Age (years) [mean (SD)]	83.1 (7.1)	81.3 (7.1)	85.4 (6.4)	0.007
Female sex [N(%)]	278 (59.0)	165 (52.5)	113 (72.0)	<0.001
Medical history				
Arterial hypertension [N(%)]	419 (88.6)	272 (86.6)	147 (92.5)	0.060
Diabetes mellitus [N(%)]	167 (35.3)	111 (35.4)	56 (35.2)	0.978
Dyslipidaemia [N(%)]	253 (53.6)	166 (53.0)	87 (54.7)	0.729
Ischaemic heart disease [N(%)]	145 (30.7)	99 (31.5)	46 (28.9)	0.563
Chronic kidney failure [N(%)]	131 (27.7)	93 (29.6)	38 (23.9)	0.190
Cerebrovascular disease [N(%)]	75 (15.9)	48 (15.3)	27 (17.0)	0.634
Atrial fibrillation [N(%)]	280 (59.2)	184 (58.6)	96 (60.4)	0.710
Peripheral arterial disease [N(%)]	78 (16.5)	56 (17.8)	22 (13.8)	0.269
Heart valve disease [N(%)]	147 (31.1)	94 (29.9)	53 (33.3)	0.451
Chronic obstructive pulmonary disease [N(%)]	100 (21.1)	71 (22.6)	29 (18.2)	0.271
Previous diagnosis of heart failure [N(%)]	289 (61.1)	185 (58.9)	104 (65.4)	0.171
Dementia [N(%)]	50 (10.6)	24 (7.6)	26 (16.4)	0.004
Cirrhosis [N(%)]	13 (2.7)	8 (2.5)	5 (3.1)	0.708
Cancer [N(%)]	68 (14.4)	41 (13.1)	27 (17.0)	0.251
Comorbidity				
Severe comorbidity (Charlson index ≥ 3) [N(%)]	231 (51.3)	147 (49.5)	84 (54.9)	0.277
Baseline status				
Cardio-respiratory (NYHA III-IV class) [N(%)]	99 (21.2)	47 (15.2)	52 (33.1)	<0.001
Left ventricular ejection fraction ≤ 45% [N(%)]	86 (57.7)	55 (57.3)	31 (58.5)	0.887

* NYHA: new york heart association.

Table 5.-Follow-up and acute episode data of patients without severe and very severe dependence and comparison according to the presence of frailty.

	Total (N=473)	Non-Frailty (N=314)	Frailty (N=159)	p value
Acute episode clinical data				
SBP <100 mmHg [N(%)]	20 (4.3)	13 (4.2)	7 (4.5)	0.899
Tachycardia (≥100 bpm) [N(%)]	117 (25.2)	87 (28.1)	30 (19.4)	0.041
Tachypnoea (>20 rpm) [N(%)]	162 (34.2)	97 (30.9)	65 (40.9)	0.031
Basal oxygen saturation < 90% [N(%)]	105 (23.7)	64 (21.6)	41 (27.9)	0.144
Acute episode biochemical data				
Hyponatraemia (natraemia< 135mEq/L) [N(%)]	66 (14.2)	41 (13.3)	25 (15.9)	0.445
Kidney failure (Acl<60 ml/min/m2) [N(%)]	264 (57.1)	169 (55.0)	95 (61.3)	0.201
Anaemia (Hb<10 g/L) [N(%)]	57 (12.1)	33 (10.5)	24 (15.3)	0.134
NT-proBNP> 5,180 pg/ml [N(%)]	126 (37.1)	74 (33.2)	52 (44.4)	0.041
Acute episode treatment				
Oxygen [N(%)]	323 (68.4)	216 (69.0)	107 (67.3)	0.705
Non-invasive ventilation [N(%)]	17 (3.6)	12 (3.8)	5 (3.1)	0.704
Intravenous diuretics [N(%)]	421 (89.2)	272 (86.9)	149 (93.7)	0.024
Intravenous nitroglycerine [N(%)]	20 (4.2)	12 (3.8)	8 (5.0)	0.542
ACE-I /ARB [N(%)]	162 (34.3)	105 (33.5)	57 (35.8)	0.618
BB [N(%)]	90 (19.1)	60 (19.2)	30 (18.9)	0.937
Digoxin [N(%)]	82 (17.4)	53 (16.9)	29 (18.2)	0.723
Final destination				
Hospital admission[N(%)]	412 (87.1)	272 (86.6)	140 (88.1)	0.662
Follow-up				
All-cause 30-day mortality [N(%)]	33 (7.0)	16 (5.1)	17 (10.7)	0.024

*IQR: interquartile range; NYHA: new york heart association; SBP: systolic blood pressure; bpm: beats per minute; rpm: respiration per minute; Erc: estimated renal clearance; Hb: haemoglobin; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blocker.