Prognostic value of formulas estimating excretory renal function in the elderly with systolic heart failure

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Abstract

Background: reduced renal excretory function (REF) is increasingly being appreciated as a potent prognostic factor in chronic heart failure (CHF). The Cockroft–Gault (CG) and the simplified Modification of Diet in Renal Disease (MDRD) equations have been recommended to estimate REF. However, limitations for both formulas have been reported in the elderly. Their prognostic performance in older CHF patients has not been investigated.

Objectives: to assess the factors independently associated with all-cause mortality and compare the prognostic value of formulas estimating REF in CHF patients aged ≥70 years.

Design: a longitudinal study with a median follow-up of 859 days. The end-point was all-cause mortality.

Setting: Division of Cardiology and Cardiac Rehabilitation.

Subjects: two hundred and sixty-six patients aged ≥70 years with systolic CHF.

Methods: REF was estimated using the CG (eCrClCG) and the MDRD (eGFRMDRD) formulas. Cox proportional hazards model was used to assess the factors independently associated with mortality and compare the prognostic value of estimating formulas. Receiver-operating characteristic (ROC) curve analysis was also performed.

Results: Kaplan–Meier estimates of the rates of death at 1 and 2 years were 85% and 73%, respectively. At multivariate analysis, eCrClCG < 50 mL/min (P = 0.005), anaemia (P = 0.012), non-prescription of beta-blockers (P = 0.006) and left ventricular ejection fraction (P = 0.03) were the only independent predictors of mortality. On ROC analysis, the eCrClCG was significantly more accurate than the eGFRMDRD.

Conclusions: among CHF patients aged ≥70 years, reduced REF is the most powerful independent predictor of survival. The excess in risk conferred by reduced REF is better appraised by means of the CG than the MDRD equation.

Keywords: elderly, heart failure, renal dysfunction

Introduction

Elderly patients are the most prevalent category in chronic heart failure (CHF) and provide the major contribution to mortality and morbidity from CHF [1–3]. Nearly 80% of HF deaths occur in patients aged 75 years or older [2] and advanced age is strongly associated with an increased risk of unplanned hospitalisation for worsening HF [3]. Notwithstanding, old CHF patients are underrepresented in prognostic studies and randomised clinical trials [4]. The lack of a representative sample of old patients in these studies poses challenges to the achievement of optimal outcomes in this growing and clinically important population of CHF patients.

Reduced renal excretory function (REF) is increasingly being appreciated as a potent prognostic factor in CHF [5]; however, its impact on survival in elderly with CHF has been scarcely investigated. Serum creatinine (Scr) is an insensitive marker of renal function [6], especially in this age group [7], and glomerular filtration rate (GFR) is considered to be the best overall measure of kidney function [6, 8]. As direct measurement of GFR is expensive and cumbersome in clinical practice, the use of the Cockroft–Gault (CG) and the Modification of Diet in Renal Disease (MDRD) study equations to estimate either creatinine clearance or GFR, respectively, has been recommended [6]. These equations have however been validated chiefly in populations consisting predominantly of
middle-aged patients with chronic renal disease and reduced REF [8]. Although the CG and MDRD formulas have a good average agreement, at the individual level, they can give estimates that differ substantially and cannot be used interchangeably to measure REF in elderly patients [9]. There is currently no single recommended measure of REF in the elderly and limitations for both formulas have been reported in this age group [8]. Their prognostic performance in elderly with CHF has not been investigated.

The aim of the present study was to assess the factors independently associated with mortality and compare the prognostic value of formulas estimating REF in patients ≥70 years with systolic HF receiving contemporary therapy.

Methods

Study population

All patients who were discharged alive from our Division of Cardiology and Cardiac Rehabilitation from January 2001 to November 2006 with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) principal discharge diagnosis code of heart failure (428, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91) were identified using a computer-generated list obtained from our administrative database. During this period, 1,180 CHF patients were identified. All medical records were reviewed by one of the authors (DS). The following prospective criteria were used to select the patients included in the present study. Patients were included if they were 70 years or older and had symptoms of HF from at least 6 months and a left ventricular ejection fraction (LVEF) ≤40%, as assessed by two-dimensional echocardiography. Exclusion criteria were recent myocardial infarction (<3 months); angina pectoris or exercise-induced myocardial ischaemia; not surgically corrected valvular or congenital heart disease; chronic cor pulmonale; obstructive, hypertrophic or restrictive cardiomyopathy. During hospitalisation, treatment with renin–angiotensin system inhibitors (RAS-Is) or beta-blockers was implemented or titrated to maximally tolerated dose, if needed, by the in-hospital referring heart failure specialist. The study was approved by the local Institutional Review Board.

Laboratory methods

Serum creatinine measurements were performed at our chemical laboratory by means of a modified kinetic Jaffe reaction (IL Test Creatinine-0018255540) with a reference range of 0.7 to 1.3 mg/dL for males and 0.6 to 1.1 mg/dL for females, using an ILab 600 analyser (Instrumentation Laboratory-Lexington, MA, USA). Serum creatinine and electrolytes levels were monitored during hospitalisation, when appropriate. REF was estimated by using the SCr measurement at discharge or the last SCr value measured during hospitalisation. Estimate of REF was obtained by the CG (eCrClCG) and the four-variable MDRD (eGFRMDRD) equations: eCrClCG (mL/min) = [(140 – age) × (weight)]/ (72 × SCr) × 0.85 (if female) [8]; eGFRMDRD (mL/min/1.73 m²) = 186.3 × SCr⁻¹.¹⁵⁴ × age⁻⁰.²⁰⁵ × 0.742 (if female) [8]. eCrClCG normalised to a body surface area (BSA) of 1.73 m² (eCrClCG–BSA) was calculated as GFRCG × (1.73/BSA). Because all our patients were white, no correction for race was introduced.

The threshold for reduced REF was set at 50 mL/min. This conservative value was chosen for two reasons. First, to represent a decreased REF that would not be attributable to normal ageing alone [7]. Second, a value of 50 was demonstrated to be the appropriate risk threshold for all-cause mortality in CHF [10]; above this cut point, no association between decreased REF and mortality was observed [10].

Statistical analysis

The primary end-point was all-cause mortality. The vital status was ascertained by interviewing patients, their relatives and/or treating physician or by direct knowledge. Continuous variables are expressed as mean ± standard deviation. Survival curves were calculated by the Kaplan–Meier method. The Cox proportional hazards model was used to assess the factors associated with mortality and compare the prognostic value of formulas estimating REF. Variables with a P-value <0.1 at univariate analysis were entered into the multivariate model by using a forward stepwise selection. In forward-variable selection, variables are considered one at a time for entry into the model. After a variable is added to the model, all variables already in the model are examined for removal. The algorithm stops when no more variables meet entry or removal criteria, or when the resulting model is identical to a previous one. By using this method, the independent risk of REF estimated by the CG or the MDRD formula on mortality could be assessed. To compare the prognostic accuracy of the CG and the MDRD formulas, the area under the receiver-operating characteristic (ROC) curve also was calculated. The areas under the curves were compared by Z statistics.

The following variables were included in the analysis: age; gender; body mass index; history of hypertension or cerebrovascular disease; diabetes mellitus; chronic obstructive pulmonary disease (COPD), diagnosed on the basis of clinical data and the need for bronchodilator therapy; previous coronary bypass surgery; aetiology of HF; New York Heart Association (NYHA) class; atrial fibrillation; left bundle branch block; LVEF; nonsustained ventricular tachycardia at Holter monitoring; SCr concentration; eCrClCG and eGFRMDRD, dichotomised at 50 mL/min; anaemia (haemoglobin concentration <13.0 g/dL for males and <12.0 g/dL for females [11]; serum sodium concentration; non-prescription of RAS-Is or beta-blockers; furosemide daily dose >80 mg. Age, SCr and sodium concentration were dichotomised at their median values. The model χ² was recorded to develop a χ²-pie chart. To determine the contributing χ² value of each risk factor for mortality, the predictive model was calculated eliminating one risk factor.
The reduced model $\chi^2$ was recorded for each factor. Each factor’s $\chi^2$ was subtracted from the full model’s $\chi^2$ to determine its percent contribution. A pie chart was plotted to denote the relative contribution of each factor to prediction mortality. Analyses were performed using the SPSS version 8.0 statistical package.

**Results**

Six of the 272 patients included in the study were lost to follow-up. The baseline characteristics of the remaining 266 patients are shown in Table 1. The prevalence of reduced REF was 51.7% using the CG formula and 34.6% using the MDRD equation. After adjustment for BSA, 15 of the 128 patients with an eCrClCG $>50$ mL/min (11.7%) and 16 of the 138 patients with an eCrClCG $<50$ mL/min (11.6%) were re-classified as having reduced REF or not, respectively. At discharge, RAS-Is were prescribed to 235 patients (88.3%), beta-blockers to 155 (58.3%), furosemide to 245 (92.1%), aldosterone antagonists to 135 (50.8%) and a combination of RAS-Is and beta-blockers to 131 (49.3%). Reasons for non-prescription of beta-blockers ($\chi^2$ = 0.006) and LVEF ($\chi^2$ = 0.012), non-prescription of beta-blockers, 20% to anaemia, and only 15% to a LVEF <30%. Survival curves according to eCrClCG <50 mL/min (11.6%) were as follows: COPD 18%, bradyarrhythmias 8.3%, other comorbid conditions 1.5%. In 17 patients (6.4%), beta-blocker treatment was not tolerated, namely because of symptomatic hypotension. No reason could be identified in 7.5% of the patients, which can be regarded as the true undertreatment rate. Fifty patients (18.8%) had an implanted cardioverter defibrillator.

During a median follow-up of 859 days, 101 patients died. Kaplan–Meier estimates of the rates of death at 1 and 2 years were 85% and 73%, respectively. The results of univariate and multivariate Cox proportional hazards survival analyses are reported in Table 2. At multivariate analysis, eCrClCG <50 mL/min ($P = 0.005$), anaemia ($P = 0.012$), non-prescription of beta-blockers ($P = 0.006$) and LVEF ($P = 0.03$) were the only independent predictors of mortality entering the final model. Forty-four percent of the risk for mortality was attributable to renal dysfunction, 21% to non-prescription of beta-blockers, 20% to anaemia, and only 15% to a LVEF <30%. Survival curves according to eCrClCG are reported in Figure 1. Kaplan–Meier estimates of the rates of death at 1 and 2 years for patients with eCrClCG <50 mL/min were 21% and 35%, respectively, compared with 9% and 16% for those with an eCrClCG $>50$ mL/min. On ROC analysis, the eCrClCG was significantly more accurate than the eGFRMDRD in predicting mortality [area under the curves: 0.64 (SE 0.02) vs. 0.60 (SE 0.002), respectively; $P < 0.05$].

One hundred and fifty two patients (57.1%) had SCr levels within the reference range; 37 of them (24.3%) were diagnosed as having reduced REF using the CG formula compared with none using the MDRD equation. Kaplan–Meier estimates of the rates of death at 1 and 2 years for patients with an eCrClCG <50 mL/min was significantly poorer than those of patients with an eCrClCG $>50$ mL/min (80% and 67% vs. 91 and 85%, respectively; $P < 0.01$). Even after adjustment for BSA, the patients with eCrClCG <50 mL/min/1.73 m² remained at a significantly higher risk for mortality ($P = 0.01$).

**Discussion**

Although elderly patients are the most prevalent category in CHF and provide the major contribution to mortality and morbidity from CHF [1–3], there is a paucity of data on clinical correlates of unfavourable outcome among elderly with
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Table 2. Results of univariate and multivariate Cox proportional hazards survival analyses

<table>
<thead>
<tr>
<th></th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>0.14</td>
<td>0.19</td>
<td>1.15 (0.78 – 1.70)</td>
<td>0.47</td>
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<tr>
<td>Male sex</td>
<td>0.54</td>
<td>0.27</td>
<td>1.72 (1.00 – 2.93)</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index &gt;25</td>
<td>-0.41</td>
<td>0.14</td>
<td>0.66 (0.49 – 0.87)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.27</td>
<td>0.22</td>
<td>1.32 (0.84 – 2.05)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.16</td>
<td>0.20</td>
<td>0.85 (0.57 – 1.27)</td>
<td>0.43</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0.15</td>
<td>0.23</td>
<td>1.16 (0.73 – 1.86)</td>
<td>0.50</td>
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<tr>
<td>Previous cerebrovascular disease</td>
<td>-0.04</td>
<td>0.42</td>
<td>0.95 (0.41 – 2.18)</td>
<td>0.91</td>
</tr>
<tr>
<td>Previous coronary artery bypass surgery</td>
<td>0.07</td>
<td>0.24</td>
<td>1.07 (0.66 – 1.72)</td>
<td>0.77</td>
</tr>
<tr>
<td>Aetiology of heart failure (ischaemic vs. nonischaemic)</td>
<td>-0.15</td>
<td>0.19</td>
<td>0.85 (0.57 – 1.26)</td>
<td>0.42</td>
</tr>
<tr>
<td>NYHA class (III/IV vs. II)</td>
<td>0.58</td>
<td>0.21</td>
<td>1.79 (1.18 – 2.71)</td>
<td>0.005</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;30%</td>
<td>0.63</td>
<td>0.20</td>
<td>1.89 (1.26 – 2.82)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.05</td>
<td>0.24</td>
<td>1.05 (0.65 – 1.71)</td>
<td>0.81</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>0.36</td>
<td>0.24</td>
<td>1.43 (0.88 – 2.33)</td>
<td>0.14</td>
</tr>
<tr>
<td>NSVT at Holter monitoring</td>
<td>0.08</td>
<td>0.21</td>
<td>1.089 (0.71 – 1.65)</td>
<td>0.68</td>
</tr>
<tr>
<td>Serum creatinine concentration &gt; 1.35 mg/dL</td>
<td>0.57</td>
<td>0.20</td>
<td>1.77 (1.19 – 2.65)</td>
<td>0.004</td>
</tr>
<tr>
<td>eCrClCG &lt;50 mL/min</td>
<td>0.76</td>
<td>0.21</td>
<td>2.15 (1.42 – 3.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>eCrClCG adjusted for BSA &lt;50 mL/min/1.73 m²</td>
<td>0.53</td>
<td>0.20</td>
<td>1.70 (1.13 – 2.54)</td>
<td>0.009</td>
</tr>
<tr>
<td>eGFR-MDRD &lt;50 mL/min/1.73 m²</td>
<td>0.25</td>
<td>0.20</td>
<td>1.69 (1.14 – 2.50)</td>
<td>0.008</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.53</td>
<td>0.20</td>
<td>1.71 (1.15 – 2.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum sodium concentration &lt;135 mmol/L</td>
<td>0.34</td>
<td>0.20</td>
<td>1.41 (0.94 – 2.11)</td>
<td>0.09</td>
</tr>
<tr>
<td>Furosemide daily dose &gt;80 mg</td>
<td>0.61</td>
<td>0.19</td>
<td>1.84 (1.24 – 2.73)</td>
<td>0.002</td>
</tr>
<tr>
<td>No RAS-Is therapy</td>
<td>0.65</td>
<td>0.27</td>
<td>1.92 (1.12 – 3.29)</td>
<td>0.017</td>
</tr>
<tr>
<td>No beta-blockers therapy</td>
<td>0.51</td>
<td>0.20</td>
<td>1.67 (1.12 – 2.1)</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
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</tr>
<tr>
<td>eCrClCG &lt;50 mL/min</td>
<td>0.61</td>
<td>0.21</td>
<td>1.84 (1.20 – 2.82)</td>
<td>0.005</td>
</tr>
<tr>
<td>No beta-blocker treatment</td>
<td>0.55</td>
<td>0.20</td>
<td>1.73 (1.16 – 2.28)</td>
<td>0.006</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.50</td>
<td>0.20</td>
<td>1.65 (1.11 – 2.47)</td>
<td>0.012</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;30%</td>
<td>0.45</td>
<td>0.21</td>
<td>1.57 (1.03 – 2.38)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1 (CI: confidence intervals).

**Figure 1.** Kaplan–Meier survival curves according to the glomerular filtration rate estimated using the Cockcroft–Gault formula.

CHF receiving contemporary therapy. In the present study, beta-blockers were prescribed to 58% of the patients, RAS-Is to nearly 90% and a combination of RAS-Is and beta-blocker to 49%. Reduced REF was the most powerful independent prognostic factor; almost half of the risk for mortality was attributable to renal impairment. Anaemia, non-prescription of beta-blockers and a severely reduced LVEF were also independently associated with an increased risk for mortality. Although anaemia and reduced REF are generally reported as being strongly related, both these factors independently influenced the likelihood of survival.

The use of the CG and MDRD prediction equations to estimate REF has been recommended by the National Kidney Foundation for diagnosing and staging renal dysfunction [6]. However, a noticeable discrepancy between the two formulas has been observed in the elderly [9, 12]. Also, the common threshold for abnormal and normal REF may not be applicable in this age group [6]. To our knowledge, the present study is unique in assessing the prognostic value of the formulas estimating REF in elderly with systolic HF. We found that among CHF patients >70 years, reduced REF, as defined by an eCrClCG of less than 50 mL/min, is independently associated with an 84% increased relative mortality risk and an absolute 2-year mortality rate as high as 35%. In the final multivariate model, the increased mortality risk of reduced eREF was evident only with the CG formula and not with the MDRD equation.

The CG and MDRD formulas can give estimates that differ substantially in elderly people [9]. In the study of Pedone et al. [9], the magnitude of the discrepancy was inversely related to SCr levels and the maximum of the difference was found in the normal range of SCr levels. This is
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an important feature as older patients are at special risk of having normal SCr despite the presence of an impaired REF [13]. Fifty seven percent of our patients had SCr within the reference range. Among such patients, an eCrClCG <50 mL/min was quite prevalent and associated with a significantly poorer survival. Since none of the patients with SCr within the reference range had a GFRMDRD <50 mL/min/1.73 m², only the eCrClCG could discriminate those at higher risk for death. This finding is in line with the nature of the MDRD equation, which was drawn from a patient population aged <70 years with advanced chronic kidney disease and SCr values ranging from 1.2 to 7.0 mg/dL (mean: 2.3 mg/dL) [14].

Adjustment for BSA did not improve the overall prognostic performance of the eCrClCG. The practice of indexing eCrClCG for BSA is however unlikely to reflect standard clinical practice [15], is not immune from criticisms [16] and may be misleading [16]. For survival analysis, we did not stage REF according to the National Kidney Foundation classification [6], but dichotomised estimates of GFR at a threshold value which was lower than the routinely used cut-off for abnormal or normal levels of REF. Further, it should be taken into account that our patients had a mean BSA of 1.75 m², not different from the reference value of 1.73 m². As a result, adjustment for BSA had only a marginal effect on categorisation of patients as having reduced REF or not.

So far, in the clinical setting of CHF, the CG and the MDRD formulas have been validated and their prognostic value compared only by Smilde et al. [17] who studied 110 patients with a mean age of 58 years, followed up for 1 year. Using the 125I-iothalamate-measured GFR as gold standard, they found the MDRD equation to have higher precision but also higher bias in predicting measured GFR than the CG formula; however, the performance of the formulas varied substantially within patient subgroups stratified by both variables included in the formulas, especially SCr, and baseline clinical characteristics [17]. At the values providing the best overall discrimination on ROC curve analysis, the eGFRMDRD resulted to be significantly more accurate than the eCrClCG in predicting death, heart transplantation, myocardial infarction or a first hospitalisation for heart failure [16]. However, at the recommended threshold value of 60 mL/min/1.73 m² [7], the eCrClCG adjusted for BSA was equally sensitive (70%) but more specific (73% vs. 66%) than the eGFRMDRD [16]. We did not directly measure GFR, so we cannot determine the extent to which either eCrClCG or eGFRMDRD reflected true REF. However, in a validation study of elderly patients, total misclassification errors with respect to a measured GFR threshold value of 50 mL/min/1.73 m² were lower for the CG than the MDRD formula [18]. As the variable performance of REF formulas within subgroups can affect their value and usefulness in clinical practice [17], differences in patient populations can be relevant to the discrepancy between our results and those of Smilde et al. In the present study, patients were 18 years older, the prevalence of obesity (BMI ≥30) was lower, advanced HF (NYHA III/IV class), reduced REF and the use of furosemide were more prevalent, the end-point was mortality instead of a composite of fatal and nonfatal events and 1-year survival was definitely poorer. Furthermore, we adjusted for confounders by performing multivariate analysis. These comparative data strengthen the concept that the selected prediction formula should be tailored to the population of interest [17].

Ultimately, the most important test of a policy of estimating REF in a specific clinical setting must relate directly to clinical outcomes [15]. We have provided evidence that an eCrClCG <50 mL/min independently and strongly relates to survival in elderly with systolic heart failure.

Limitations of the study

Although the patients were selected from a cohort of consecutive patients according to prospective criteria, this was a retrospective study in nature. This was a single-centre study, and each patient was attended to by a cardiologist experienced in the management of HF. Therefore, our patients may not be representative of the general population of elderly CHF patients. Women were poorly represented. We did not measure cystatin C concentration, an endogenous filtration marker that has been reported to be a strong predictor of cardiovascular death in elderly persons [19]. Furthermore, proteinuria, which has been recognised to be a risk factor, was not measured. Finally, data on biomarkers such as NT-proBNP were not available for all patients and were not considered in the analysis. This, however, does not detract our results as REF has been shown to predict outcome independently of NT-proBNP in systolic heart failure patients [20].

Conclusions

Among patients ≥70 years with systolic HF, reduced REF is highly prevalent and the most powerful independent predictor of survival, exceeding established prognostic indicators in CHF such as NYHA class and LVEF. The excess in risk conferred by reduced REF is better appraised by means of the CG than the MDRD equation. Anaemia, non-prescription of beta-blockers and severely reduced LVEF were also independently associated with increased mortality risk.

Key points

- Although reduced renal excretory function (REF) is increasingly being appreciated as a potent prognostic factor in CHF, its impact on survival in elderly with chronic heart failure (CHF) has been scarcely investigated. Limitations for both the Cockcroft–Gault and the Modification of Diet in Renal Disease study equations estimating REF have been reported in the elderly. Their prognostic value in older patients with CHF has not been investigated.
Prognostic value of formulas estimating excretory renal function in elderly with systolic heart failure

We followed up 266 elderly patients with systolic CHF receiving contemporary therapy. During a median follow-up of 859 days, 101 patients died.

Reduced REF emerged as the most powerful independent predictor of survival. The excess in risk conferred by REF was better appraised by means of the Cockroft–Gault than the Modification of Diet in Renal Disease equation. Anaemia, non-prescription of beta-blockers and severely reduced LVEF were also independently associated with increased mortality risk.

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We are very grateful to the nurse Giovanna Pontrandolfo for her assistance in preparing the database.

Conflicts of interest
The authors confirm that there is no conflict of interest to declare. DS (first author) devised the study, reviewed all medical records and prepared the manuscript. DS and AP designed the study protocol. Data analysis was undertaken by AP. All authors were involved in the interpretation of the results and approval of the final version of the paper.

References

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