Clinical frailty scale and outcome after coronary artery bypass grafting

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Order of Authors:	Daniel Reichart
	Stefano Rosato
	Wail Nammas
	Francesco Onorati
	Magnus Dalén
	Liesa Castro
	Riccardo Gherli
	Giuseppe Gatti
	Ilaria Franzese
	Giuseppe Faggian
	Marisa De Feo
	Sorosh Khodabandeh
	Giuseppe Santarpino
	Antonio Rubino
	Daniele Maselli
	Saverio Nardella
	Antonio Salsano
	Francesco Nicolini
	Marco Zanobini
	Matteo Saccocci
	Karl Bounader
	Eeva-Maija Kinnunen
	Tuomas Tauriainen
	Juhani Airaksinen
	Fulvia Seccareccia
	Giovanni Mariscalco
	Vito G Ruggieri
	Andrea Perrotti
	Fausto Biancari, M.D., Ph.D.
Corresponding Author:	Fausto Biancari, M.D., Ph.D. University of Turku Turku, FINLAND
Corresponding Author E-Mail:	faustobiancari@yahoo.it
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Author Comments:	Dear Editor, we would be grateful if you could consider the revised version of the article entitled: "Clinical Frailty Scale and Outcome after Coronary Artery Bypass Grafting", for possible publication in the European Journal of Cardiothoracic Surgery. We greatly appreciated the encouraging and constructive comments by the Reviewers, which were valuable in refining the manuscript. Again, we appreciated your interest in publishing the findings from our study, and sincerely hope that our comments to the criticisms and the revisions to the manuscript are to the satisfaction of the Reviewers and the Editors of the European Journal of Cardiothoracic Surgery. The authors state that: * The manuscript has not previously been published in print or electronic form and is not under consideration by any another publication; * All authors have contributed significantly to the content of the article; * All authors have read and approve the submission of the manuscript to EJCTS; * Subject to acceptance, authors will sign an exclusive licence to publish; * There is no ethical problem or conflict of interest. Kind regards. Prof. Fausto Biancari
Abstract:	Objectives: The aim of this study was to assess the impact of frailty on the outcome after coronary artery bypass grafting (CABG) and whether it may improve the predictive ability of EuroSCORE II. Methods: The Clinical Frailty Scale (CFS) was assessed preoperatively in patients undergoing isolated CABG from the multicenter E-CABG registry and patients were stratified in three classes: scores 1-2, scores 3-4 and scores 5-7. Results: Of 6156 patients enrolled, 39.2% had CFS scores 1-2, 57.6% scores 3-4, and 3.2% scores 5-7. Logistic regression adjusted for multiple covariates showed that the CFS was an independent predictor of hospital/30-day mortality (CFS scores 3-4, OR 3.95, 95%CI 2.19-7.14; CFS scores 5-7, OR 5.90, 95%CI 2.67-13.05) and resulted in an Integrated Improvement Index of 1.3 (p<0.001) and a Net Reclassification Index of 55.6 (p<0.001) for prediction of hospital/30-day mortality. Adding the CFS classes to EuroSCORE II resulted in an Integrated Improvement Index of 0.9 (p< p<0.001) and Net Reclassification Index of 59.6 (p< p<0.001) for prediction of hospital/30-day mortality, with a significantly larger area under the receiver operating characteristics curve (0.809 vs. 0.781, p=0.028). The CFS was an independent predictor of mid-term mortality (CFS scores 3-4, HR 2.05, 95%CI 1.43-2.85; CFS scores 5-7, HR 3.05, 95%CI 1.83-5.06). Conclusions: The CFS predicted early and mid-term mortality in patients undergoing isolated CABG. Further studies are needed to evaluate whether frailty may improve the estimation of the operative risk of patients undergoing adult cardiac surgery.
Response to Reviewers:	Please find below our itemized responses to the Reviewer 4's comments: - Reviewer 4: 1. Line 162: "Lemeshowew's" -> "Lemeshow". Response: Thank you for this advice. Change: We made the suggested change. 2. Lines 163-164: I think "de Long" should be "DeLong", as per Professor Elisabeth DeLong. Response: Thank you for this advice. Change: We made the suggested change.

3. Table 3: please add units for continuous measures. For example, age (years). This is so that it is clear that the effect size corresponds to a unit increase in the risk factor. Same for eGFR.
Response: Thank you for this advice.
Change: We made the suggested changes to Table 3.

4. Table 4: P-values >0.1 should be reported to 2 decimal places only.
Response: Thank you for this advice.
Change: We made the suggested changes to Table 4.

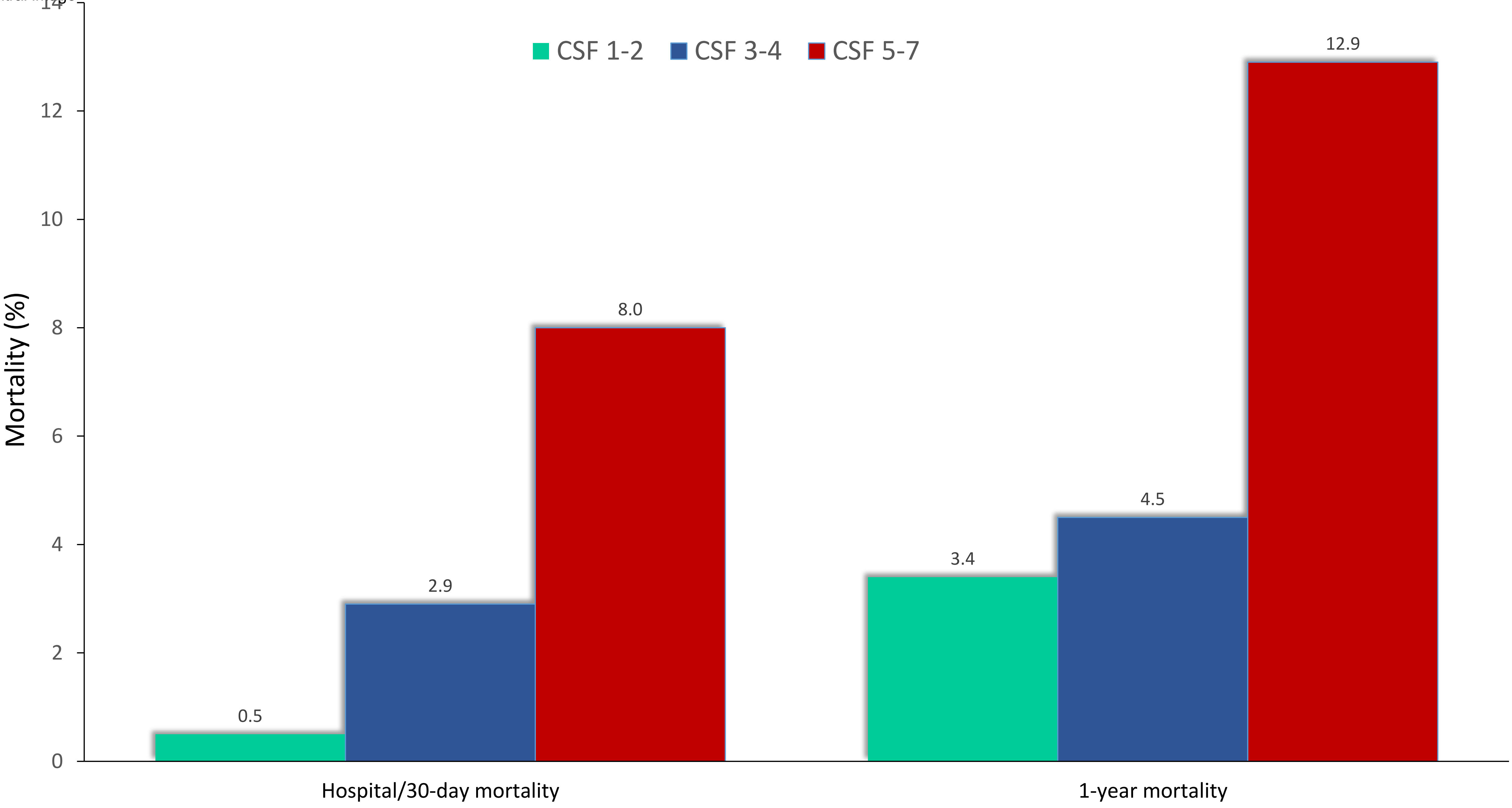
5. Table 4: if I recall correctly, the Hosmer-Lemeshow test applied externally (i.e. the first column labelled "EuroSCORE II"), i.e. without recalibration or additional calibration, should be performed on 10 degrees of freedom. Only if apply the test to a model adjusted for the data at hand should the degrees of freedom be 8. See: Hosmer DW, Lemeshow S. Applied Logistic Regression. 2nd Ed. New Jersey: John Wiley & Sons, Inc.; 2000.
Response: These analysis were done using probabilities from logistic regression in which the covariate was EuroSCORE II. Furthermore, SAS macro does not allow analysis on 10 degrees of freedom. We could provide the output of this analysis for checking.
Change: No changes made.

6. Line 154: rather than listing multiple tests in a single sentence, please give the reader an indication for their use. For example, if you had categorical data between groups, what was your criteria for using the chi square test over the Fisher exact test? Such information makes the analysis reproducible.
Response: Thank you for this advice. However, it is not usual to report all the information about each statistical test used. Therefore, we added only the information regarding the use of chi-square and Fisher exact test.
Change: We added this information to Methods section.

7. Table 1: I still remain confused how the authors managed to include albumin in a multivariable model. Did they perform a complete-cases analysis? I am still unsure about the value of the ordinal regression in Table 1. Does this add sufficient value over a comparison of groups test (i.e. Kruskal-Wallis or chi square test)? If you do choose to keep it, I suggest making it clear that you are using the proportional odds model.
Response: We do agree with this Reviewer about the value of ordinal regression and on the analysis with incomplete data on albumin.
Changes: We deleted the information regarding albumin and the results of ordinal regression.

Please feel free to contact us in case you would need further data and/or revisions.

Central image



Revised version – Revisions are in red

Clinical Frailty Scale and Outcome after Coronary Artery Bypass Grafting

Short title: Clinical Frailty Scale in CABG

Daniel Reichart,[1] Stefano Rosato,[2] Wail Nammas,[3] Francesco Onorati,[4] Magnus Dalén,[5] Liesa Castro,[1] Riccardo Gherli,[6] Giuseppe Gatti,[7] Ilaria Franzese,[4] Giuseppe Faggian,[4] Marisa De Feo,[8] Sorosh Khodabandeh,[5] Giuseppe Santarpino,[9] Antonino S. Rubino,[10] Daniele Maselli,[11] Saverio Nardella,[11] Antonio Salsano,[12] Francesco Nicolini,[13] Marco Zanobini,[14] Matteo Saccocci,[14] Karl Bounader,[15] Eeva-Maija Kinnunen,[16] Tuomas Tauriainen,[16] Juhani Airaksinen,[3] Fulvia Seccareccia,[2] Giovanni Mariscalco,[17] Vito G. Ruggieri,[18] Andrea Perrotti,[19] Fausto Biancari.[3,15,20]

[1]Hamburg University Heart Center, Hamburg, Germany;
[2]National Center of Global Health, Istituto Superiore di Sanità, Rome, Italy;
[3]Heart Center, Turku University Hospital, University of Turku, Turku, Finland;
[4]Division of Cardiovascular Surgery, Verona University Hospital, Verona, Italy;
[5]Department of Molecular Medicine and Surgery, Department of Cardiac Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden;
[6]Department of Cardiovascular Sciences, Cardiac Surgery Unit, S. Camillo-Forlanini Hospital, Rome, Italy;
[7]Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy;
[8]Department of Cardiothoracic Sciences, University of Campania, Naples, Italy;
[9]Cardiovascular Center, Paracelsus Medical University, Nuremberg, Germany; Città di Lecce Hospital GVM Care&Research, Lecce, Italy;
[10]Centro Clinico-Diagnostico "G.B. Morgagni", Centro Cuore, Pedara, Italy;
[11]Department of Cardiac Surgery, St. Anna Hospital, Catanzaro, Italy;
[12]Division of Cardiac Surgery, University of Genoa, Genoa, Italy;
[13]Division of Cardiac Surgery, University of Parma, Parma, Italy;
[14]Department of Cardiac Surgery, Centro Cardiologico – Fondazione Monzino IRCCS, University of Milan, Italy;
[15]Division of Cardiothoracic and Vascular Surgery, Pontchaillou University Hospital, Rennes, France;
[16]Department of Surgery, Oulu University Hospital and University of Oulu, Oulu, Finland;
[17]Department of Cardiovascular Sciences, Clinical Sciences Wing, University of Leicester, Glenfield Hospital, Leicester, UK;
[18]Division of Cardiothoracic and Vascular Surgery, Robert Debré University Hospital, Reims, France;
[19]Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France;
[20]Department of Surgery, University of Turku, Turku, Finland

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Corresponding Author:
Prof. Fausto Biancari,
Heart Center,
Turku University Hospital,
PO Box 52, 20521 Turku, Finland
E-mail: faustobiancari@yahoo.it

Key question: Is frailty associated with increased mortality and morbidity after coronary artery bypass grafting?

Key findings: Frailty was associated with poor outcome after coronary surgery and improved the predictive ability of EuroSCORE II.

Take-home message: Clinical Frailty Scale predicts adverse events after coronary surgery and may improve the predictive ability of current risk scores.

Abstract

Objectives: The aim of this study was to assess the impact of frailty on the outcome after coronary artery bypass grafting (CABG) and whether it may improve the predictive ability of EuroSCORE II.

Methods: The Clinical Frailty Scale (CFS) was assessed preoperatively in patients undergoing isolated CABG from the multicenter E-CABG registry and patients were stratified in three classes: scores 1-2, scores 3-4 and scores 5-7.

Results: Of 6156 patients enrolled, 39.2% had CFS scores 1-2, 57.6% scores 3-4, and 3.2% scores 5-7. Logistic regression adjusted for multiple covariates showed that the CFS was an independent predictor of hospital/30-day mortality (CFS scores 3-4, OR 3.95, 95%CI 2.19-7.14; CFS scores 5-7, OR 5.90, 95%CI 2.67-13.05) and resulted in an Integrated Improvement Index of 1.3 (p<0.001) and a Net Reclassification Index of 55.6 (p<0.001) for prediction of hospital/30-day mortality. Adding the CFS classes to EuroSCORE II resulted in an Integrated Improvement Index of 0.9 (p< p<0.001) and Net Reclassification Index of 59.6 (p< p<0.001) for prediction of hospital/30-day mortality, with a significantly larger area under the receiver operating characteristics curve (0.809 vs. 0.781, p=0.028). The CFS was an independent predictor of mid-term mortality (CFS scores 3-4, HR 2.05, 95%CI 1.43-2.85; CFS scores 5-7, HR 3.05, 95%CI 1.83-5.06).

Conclusions: The CFS predicted early and mid-term mortality in patients undergoing isolated CABG. Further studies are needed to evaluate whether frailty may improve the estimation of the operative risk of patients undergoing adult cardiac surgery.

Key words: Frailty; Clinical Frailty Scale; Coronary artery bypass grafting; Cardiac Surgery.

Introduction

Preoperative surgical risk assessment is crucial for weighing the risk and benefit of cardiac surgery [1]. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II risk prediction model is widely employed to evaluate the risk of perioperative mortality and morbidity in patients undergoing cardiac surgery [2]. Nevertheless, the EuroSCORE II tends to under- and overestimate operative risk in different subsets of patients [3]. These limitations might derive from weighing of age and other comorbidities without an assessment of the patient's functional status.

Frailty is defined as impaired physiologic response to stressors, which portends increased vulnerability to adverse outcome after medical or surgical stressful conditions [4]. A few studies showed that frailty is associated with increased morbidity and mortality after cardiac surgery [5-8]. Among the currently available frailty scales, the Clinical Frailty Scale (CFS) is a simple, semi-quantitative tool that provides a clinically valuable evaluation of frailty [9]. Herein we evaluated the prognostic impact of the CFS on early and mid-term mortality in patients undergoing isolated coronary artery bypass grafting (CABG).

Material and Methods

Study Cohort

The E-CABG registry is a prospective, multicenter study that enrolled patients undergoing isolated CABG at 16 European centers of cardiac surgery in Finland, France, Italy, Germany, Sweden and the United Kingdom. The detailed protocol and definition criteria have been previously published [10]. The study was approved by the Institutional Review Board of the participating centers, and it was not supported financially. Informed consent was obtained in institutions where it was specifically required by the internal Institutional Review Board, otherwise it was waived. The study is registered in Clinicaltrials.gov (Identifier: NCT02319083). Shortly, this registry included 7352 consecutive patients who underwent isolated CABG at the participating hospitals from January 2015 to May 2017. Patients who underwent any other concomitant procedure on the heart valves, ascending aorta and ventricular wall were not included in this registry. Data were collected prospectively and underwent robust validation and checking of its quality. Data submissions were constantly verified with regular data quality reports, with review of administrative and medical chart audits in order to correct clinical and temporal conflicts and/or discrepancies. Complete data on pre-, intra- and postoperative variables were obtained in 99.1% of patients with the exception of the CFS and baseline pulmonary artery pressure. Data on the CFS was complete in 83.7% of patients because three centers (missing rates: Catanzaro, 22.7%; Rennes, 99.4%; Hamburg, 32.4%) did not collect data on the frailty status of all patients. Otherwise, data on the frailty status was obtained in >99% of patients from other 13 centers. Data on pulmonary artery pressure was available in 56.3% of patients as a thermodilution catheter was not inserted preoperatively in all patients.

Definitions and endpoints

Data on preoperative functional status was stratified preoperatively according to the CFS criteria. This frailty scale encompasses 7 scores of increasing frailty, from 1 (very fit) to 7 (terminally ill) (7). For the sake of simplicity, the CFS scores were stratified in three classes of increasing frailty: scores 1-2, scores 3-4 and scores 5-7. This simplified stratification was based on the fact that classes 1 and 2 include patients without significant frailty, classes 3 and 4 include patients who are not active, but are independent, whereas classes 5 to 7 include patients with severe limitations in the activities.

The main outcome measure of this study was hospital/30-day death. Secondary outcomes were length of stay in the intensive care unit, stroke, prolonged inotropic support, deep sternal wound infection/mediastinitis, acute kidney injury, postoperative atrial fibrillation, severe-massive bleeding according to the E-CABG bleeding severity criteria and mid-term all-cause mortality. The definition criteria of these outcomes were reported in detail elsewhere [10]. Data on mortality was retrieved from National registries in four centers (Genoa, Leicester, Oulu, Stockholm) and by contacting the patients, their general practitioners and/or cardiologists as well as by reviewing hospital records in the other centers. Survival data after discharge was retrieved in 98.8% of patients.

Statistical Analysis

Statistical analysis was performed using SPSS statistical software v. 24.0 (IBM Corporation, New York, USA), and SAS statistical package v. 9.4 (SAS Institute Inc., Cary, NC, USA) following the Hickey et al. [11,12] guidelines. Covariates and outcomes were reported as counts and percentages, mean and standard deviation or median and interquartile range. Mann-Whitney, Kruskall-Wallis and Chi-square tests were used to compare baseline and operative covariates between the study cohorts. Fisher exact test was used when cells have expected frequencies less than 5. The Mantel-Haenszel test was used for trend analysis of ordinal data. Since the study cohorts had a significantly different distribution of baseline and operative covariates, a logistic regression with backward selection method including all baseline risk factors listed in Table 1 was performed to identify the independent predictors of hospital/30-day mortality. These covariates were then employed to adjust the effect of the CFS on the outcomes in logistic and linear regression. The effect of CFS on the outcome was also adjusted for the logit of EuroSCORE II. Goodness-of-fit of the logistic regression models was assessed by the Hosmer-Lemeshow's test. The discriminatory ability of regression models was assessed by the receiver operating characteristics (ROC) curve test. The DeLong test was used to compare the areas under the ROC curves. The improvement of predictive accuracy of the regression models before and after the addition of the CFS was estimated by calculating the net reclassification index (NRI) and integrated discrimination improvement (IDI) [13]. NRI was used with the category-free definition. Mid-term survival in the CFS classes was estimated by the Kaplan-Meier method and was adjusted for baseline covariates using the Cox proportional hazard method with a backward selection including all baseline risk factors listed in Table 1. The proportionality assumption in the Cox regression model was assessed by evaluating the log-minus-log plot. Risk estimates were reported as odds ratio (OR), hazard ratio (HR) and coefficients with 95% confidence interval (CI). Analyses of the prognostic impact of CFS were performed in the subgroups of patients undergoing elective, urgent and emergency operation as well as in octogenarians. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

Results

Baseline data

Of 7352 patients enrolled in the E-CABG registry, 6156 had valid data on the CFS: 2413 (39.2%) has scores 1-2, 3543 (57.6%) scores 3-4, and 200 (3.2%) scores 5-7. Mean follow-up was 1.2±0.7 years. Baseline characteristics and operative data of patients in the three CFS classes (scores 1-2, scores 3-4 and scores 5-7) are summarized in Table 1.

Early and Mid-Term Outcomes

Hospital/30-day mortality rate was 2.1% and 1-year mortality rate was 3.7%. The main outcomes according to increasing CFS classes are summarized in Table 2. Logistic regression showed that age (p=0.001), female gender (p<0.001), estimated glomerular filtration rate (p<0.001), pulmonary disease (p<0.001), preoperative atrial fibrillation (p=0.025), left ventricular ejection fraction ≤50% (p=0.001), presentation with ST-elevation myocardial infarction (p=0.011), urgency of the procedure (p<0.001) and critical preoperative state (p<0.001) were independent predictors of hospital/30-day mortality (Hosmer-Lemeshow's test: p=0.385; ROC AUC 0.800, 95%CI 0.757-0.843). These covariates were included in multiple covariates logistic regression models. Logistic regression model with the aforementioned covariates and CFS classes showed that these frailty classes were independent predictors of hospital/30-day mortality (p<0.001) (Tab. 3), and the AUC of this regression model (AUC 0.823, 95%CI 0.783-0.863) was significantly larger than the AUC of the previous regression model (p=0.016). The IDI was 1.3 (p=<0.0001) and NRI 55.6 (p<0.001) (Tab. 4).

Adding the CFS classes to the EuroSCORE II for prediction of hospital/30-day mortality resulted in a significantly larger AUC (0.809, 95%CI 0.771-0.848) than that of the EuroSCORE II (AUC 0.781, 95%CI 0.738-0.824) (p=0.028). The IDI was 0.9 (p<0.001) and NRI was 59.6 (p<0.001) (Tab. 3).

The CFS along with other variables listed in Table 3, was an independent predictor of mid-term mortality either as a continuous variable (per 1 score increment, HR 1.37, 95%CI 1.21-1.55) or as a three-classes variable (CFS scores 3-4, HR 2.02, 95%CI 1.43-2.85; CFS scores 5-7, HR 3.05, 95%CI 1.83-5.06) (Fig. 1).

The CFS adjusted for the aforementioned covariates and for the EuroSCORE II was an independent predictor of prolonged inotropic support, acute kidney injury, severe and massive perioperative bleeding and prolonged stay in the intensive care unit (Tab. 2).

Clinical Frailty Scale and Mortality According to Urgency of the Operation

Analysis of the outcome according to the urgency of the operation showed that hospital/30-day mortality increased along with increasing frailty in elective (p=0.002), urgent (p<0.001) and emergency procedures (p=0.026) (Fig. 2). Similarly, 1-year mortality increased along with increasing frailty elective (p=0.010), urgent (p<0.001) and emergency procedures (p=0.006) (Fig. 3).

Clinical Frailty Scale and Mortality in Octogenarians

Among 427 patients aged ≥80 years included in this study, the CFS was predictive of hospital/30-day mortality (scores 1-2, 0.9%; scores 3-4, 5.5%; scores 5-7, 14.3%; p=0.004; covariates-adjusted OR 5.83, 95%CI 0.74-45.88; and OR 18.59, 95%CI 1.79-139.10, respectively) and mid-term mortality (at 1-year: scores 1-2, 3.3%; scores 3-4, 8.1%; scores 5-7, 27.0%; p=0.001; covariates-adjusted HR, 2.27, 95%CI 0.67 -7.62; and HR 6.65, 95%CI 1.71-25.89, respectively) (Fig. 4).

Discussion

The present study showed that the CFS predicted early and mid-term all-cause mortality in patients undergoing isolated CABG, after adjustment for multiple confounding factors as well as for EuroSCORE II.

Prediction of risk of poor outcome after cardiac surgical procedures helps inform treatment decision and improve selection of patients. However, current cardiac surgery risk models might over- or underestimate the mortality risk [2,14]. Such risk models are based on demographic and clinical factors, and other measurable indices of comorbidity, but do not take into account comprehensive assessment of frailty, which may be an important determinant of outcome, particularly in the elderly. Indeed, there is a growing evidence that frailty assessment tools are valuable in predicting early and mid-term mortality, in-hospital major adverse events, and quality of life following cardiac surgery [5,6,15-19]. Similar findings were observed with frailty assessment to predict outcome after transcatheter aortic valve replacement [19-22].

There is lack of consensus on the optimal tool to assess frailty in real-life clinical practice, and whether the resources needed for implementing such methods are warranted by meaningful improvement in risk discrimination. In the current study, we adopted the CFS because it is a rather simple semi-quantitative assessment tool based on clinical judgement that weighs frailty in terms of activity level, mobility, and independence of the patient during daily physical and cognitive activity [8]. It includes no objective measurement of mobility, muscle strength, or any indices of nutritional status. Furthermore, the CFS assessment is inexpensive and easy-to-perform. Yet, there is some concern about its subjective nature, which might reduce its reproducibility and ability to estimate the operative risk. One recent study showed that more complex frailty assessment scales, which are based on objective assessment of mobility, muscle strength, and cognitive impairment, had better predictive ability of 1-year poor functional survival in patients undergoing cardiac surgery, compared with the CFS [16]. Another recent study by Afilalo and coworkers [23] confirmed that frailty is a risk factor for mortality in 374 patients undergoing surgical or transcatheter aortic valve replacement. The authors proposed the Essential Frailty Toolset (EFT) scale, a simple 4-item scale including lower-extremity weakness, cognitive impairment, anemia and hypoalbuminemia, which performed better than other frailty scales currently in use. In the study by Afilalo and coworkers [23], the CFS had a ROC AUC of 0.743 in predicting 1-year mortality, whereas the EFT scale had a ROC AUC of 0.784, a finding which confirms the validity of the CFS in this setting. However, patients were divided into two cohorts (CFS scores <4, and CFS scores ≥ 4) and this might have resulted in a suboptimal dichotomization of this frailty scale (1-year mortality in scores 1-2 was 3%, in scores 3-4 was 7% to 14%, and in scores 4-9 was 25% to 35%), which limits the validation of the CFS patients undergoing aortic valve replacement. Still, objective frailty indexes are expected to provide an even more accurate stratification of the risk of these patients as well as a measure of possible recovery from CABG.

In the present study, the CFS predicted early- and mid-term mortality and other adverse events in patients undergoing isolated CABG after adjustment for potential confounders as well as for EuroSCORE II. Furthermore, ROC curve analysis, NRI and IDI showed an improvement in predicting early mortality when the CFS was added to the present regression models and to EuroSCORE II. Indeed, patients in the more advanced categories of frailty experienced rather high early and mid-term mortality, particularly after urgent or emergency CABG procedure. Similarly, octogenarians with CFS scores 5 to 7 had a prohibitive risk of early and 1-year survival (Fig. 4). We speculate that such patients could have had a better outcome with less invasive percutaneous coronary intervention, but this needs to be confirmed in further studies.

Limitations

The present study has some limitations including unmeasured confounders and selection bias, which might have influenced the results. Since the current study is observational in nature, its results are dependent on the accurateness and completeness of data collected. Furthermore, the subjective nature of the CFS might reduce its reproducibility. These findings substantiate the validity this simple method of assessing frailty in patients undergoing coronary surgery. Finally, this dataset did not allow us to evaluate the impact of preoperative CFS on functional survival, i.e. patients who are alive with a good quality of life [12].

In conclusion, in this study the CFS independently predicted mortality and major adverse events in patients undergoing isolated CABG. The CFS classes improved the predictive ability of EuroSCORE II as shown by IDI and NRI. Additional validation studies are needed to evaluate whether frailty may improve the estimation of the operative risk of patients undergoing adult cardiac surgery.

Conflict of interest

None.

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Figure legends

Central image. Hospital/30-day and 1-year mortality according to increasing Clinical Frailty Scale classes (both $p<0.001$).

Figure 1. Multiple covariates adjusted estimates of mid-term mortality in patients according to increasing Clinical Frailty Scale classes ($p<0.001$)

Figure 2. Hospital/30-day mortality according to increasing Clinical Frailty Scale classes in elective ($p=0.002$), urgent ($p<0.001$) and emergency procedures ($p=0.0.26$). Mortality rates are Kaplan-Meier's estimates.

Figure 3. One-year mortality after in elective ($p=0.010$), urgent ($p<0.001$) and emergency procedures ($p=0.006$) in increasing Clinical Frailty Scale classes. Mortality rates are Kaplan-Meier's estimates.

Figure 4. Hospital/30-day mortality ($p=0.004$) and 1-year mortality ($p<0.001$) according to increasing Clinical Frailty Scale classes in the subgroup of patients aged ≥80 years. Mortality rates are Kaplan-Meier's estimates.

Table 1. Baseline characteristics and operative data in the different Clinical Frailty Scale classes

Covariates	Class 1-2 (N=2413)	Class 3-4 (N=3543)	Class 5-7 (N=200)	p value
Baseline risk factors				
Age (years)	65.3±9.6	68.6±9.1	69.9±9.4	<0.001
Female	353 (14.6)	648 (18.3)	39 (19.5)	0.001
Body mass index (kg/m^2)	27.6±4.1	27.5±4.2	27.7±4.2	0.79
eGFR (mL/min/1.73 m^2)	83.9±24.3	80.7±26.6	75.1±29.1	<0.001
Anemia[a]	496 (20.6)	900 (25.4)	82 (41.0)	<0.001
Dialysis	22 (0.9)	40 (1.1)	9 (4.5)	<0.001
Diabetes	740 (30.7)	1170 (33.0)	77 (38.5)	0.02
Recent ST-elevation myocardial infarction	162 (6.7)	250 (7.1)	18 (9.0)	0.46
Prior stroke/transient ischemic attack	94 (3.9)	242 (6.8)	19 (9.5)	<0.001
Atrial fibrillation	146 (6.1)	337 (9.5)	33 (16.5)	<0.001
Pulmonary disease	192 (8.0)	425 (12.0)	42 (21.0)	<0.001
Extracardiac arteriopathy	484 (20.1)	886 (25.0)	55 (27.5)	<0.001
Left ventricular ejection fraction ≤50%	619 (25.7)	1146 (32.4)	86 (43.0)	<0.001
Prior percutaneous coronary intervention	477 (19.8)	730 (20.6)	37 (18.5)	0.60
Prior cardiac surgery	11 (0.5)	24 (0.7)	2 (1.0)	0.42
Critical preoperative state	194 (8.0)	200 (5.6)	42 (21.0)	<0.001
Urgency of procedure				<0.001
Elective	1345 (55.8)	1705 (48.1)	60 (30.0)	
Urgent	995 (41.3)	1630 (46.0)	115 (57.5)	
Emergency	72 (3.0)	208 (5.9)	25 (12.5)	
P2Y12r inhibitors within 5 days	299 (12.4)	626 (17.7)	33 (16.6)	<0.001
EuroSCORE II (%)	2.3±3.1	3.2±4.5	7.4±9.3	<0.001
Operative data				
No. of aortic anastomoses	1.2±0.9	0.8±0.8	1.1±0.9	<0.001
No. of distal anastomoses	2.6±0.9	2.8±0.9	3.2±1.1	<0.001
Cardiopulmonary bypass time (min)	82.8±32.7	88.1±35.9	103.9±35.4	<0.001
Aortic clamping time (min)	53.3±23.6	59.6±26.8	70.6±34.2	<0.001
Untouched ascending aorta	234 (9.7)	540 (15.3)	28 (14.0)	<0.001
Off-pump surgery	307 (12.7)	795 (22.4)	81 (40.5)	<0.001
Bilateral internal mammary artery grafts	563 (23.3)	1337 (37.7)	65 (32.5)	<0.001

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as counts and percentages. [a], Anemia is defined as <12.0g/L in women and <13.0 g/L in men. eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation; EuroSCORE, European System for Cardiac Operative Risk Evaluation. Clinical variables are according to the EuroSCORE II definition criteria.

Table 2. Outcomes according to increasing Clinical Frailty Scale classes.

	Class 1-2 (N=2413)	Class 3-4 (N=3543)	Class 5-7 (N=200)	Univariable / multivariable analysis p value	AUC of ROC curve of regression models
Hospital/30-day death	13 (0.5)	102 (2.9)	16 (8.0)	**<0.001**	
Adjusted for multiple covariates[a]	Reference	3.95, 2.19 - 7.14	5.90, 2.67 -13.05	**<0.001**	0.823, 0.783-0.863
Adjusted for EuroSCORE II[a]	Reference	4.08, 2.27-7.32	5.56, 2.52-12.26	**<0.001**	0.809, 0.771-0.848
One-year mortality	35 (3.4)	151 (4.5)	23 (12.9)	**<0.001**	
Adjusted for multiple covariates[b]	Reference	2.02, 1.43-2.85	3.05, 1.83-5.06	**<0.001**	-
Adjusted for EuroSCORE II[b]	Reference	2.14, 1.52-3.01	3.07, 1.85-5.09	**<0.001**	-
Intensive care unit stay (days)	2.0 (2.0)	2.0 (2.00)	2.0 (3.0)	**<0.001**	
Adjusted for multiple covariates[c]	Reference	0.59, 0.35-0.82	1.00, 0.35-0.1.65	**<0.001**	-
Adjusted for EuroSCORE II[c]	Reference	0.44, 0.20-0.67	0.69, 0.04-1.34	**<0.001**	-
Stroke	22 (0.9)	41 (1.2)	3 (1.5)	0.28	
Adjusted for multiple covariates[a]	Reference	1.14, 0.66 -1.94	0.96, 0.28 -3.37	0.87	0.664, 0.595-0.732
Adjusted for EuroSCORE II[a]	Reference	1.07, 0.63-1.82	0.86, 0.24-3.02	0.91	0.654, 0.586-0.723
Prolonged inotropic support	686 (28.4)	1039 (29.3)	120 (60.0)	**<0.001**	
Adjusted for multiple covariates[a]	Reference	0.97, 0.85 - 1.09	2.66, 1.94 -3.65	**<0.001**	0.647, 0.632-0.662
Adjusted for EuroSCORE II[a]	Reference	0.92, 0.77 – 9.98	2.14, 1.56-2.94	**<0.001**	0.653, 0.638-0.668
Deep sternal wound infection	44 (1.8)	79 (2.2)	12 (6.0)	**0.008**	
Adjusted for multiple covariates[a]	Reference	1.06, 0.72 – 1.56	2.14, 1.07 -4.27	0.08	0.691, 0.641 -0.741
Adjusted for EuroSCORE II[a]	Reference	1.06, 0.73-1.55	1.96, 0.98-3.92	0.146	0.669, 0.622 -0.716
KDIGO acute kidney injury[a]	387 (16.3)	965 (27.8)	63 (33.2)	**<0.001**	
Adjusted for multiple covariates[a]	Reference	1.78, 1.55– 2.04	1.84, 1.32 -2.58	**<0.001**	0.647, 0.630 -0.664
Adjusted for EuroSCORE II[a]	Reference	1.78, 1.55– 2.03	1.64, 1.18 -2.30	**<0.001**	0.639, 0.622 -0.655
Renal replacement therapy[d]	26 (1.1)	88 (2.5)	9 (4.7)	**<0.001**	
Adjusted for multiple covariates[a]	Reference	1.87, 1.19– 2.94	2.18, 0.95 -4.99	**0.02**	0.732, 0.678 -0.786
Adjusted for EuroSCORE II[a]	Reference	1.87, 1.20-2.93	1.88, 0.83-4.25	**0.022**	0.706, 0.654-0.758
Atrial fibrillation	597 (24.7)	969 (27.3)	77 (38.5)	**<0.001**	
Adjusted for multiple covariates[a]	Reference	0.90, 0.79– 1.02	1.22, 0.88 -1.70	0.06	0.685, 0.670 -0.700
Adjusted for EuroSCORE II[a]	Reference	1.04, 0.92– 1.17	1.33, 0.98-1.82	0.19	0.595, 0.579-0.611
E-CABG bleeding grades 2-3	126 (5.2)	258 (7.3)	37 (18.5)	**<0.001**	
Adjusted for multiple covariates[a]	Reference	1.24, 0.99– 1.56	2.30, 1.49 -3.54	**0.001**	0.712, 0.684 -0.740
Adjusted for EuroSCORE II[a]	Reference	1.15, 0.91-1.44	1.92, 1.24-2.95	**0.013**	0.699, 0.671 -0.726

Continuous variables are reported as the median and interquartile range (in parentheses). Categorical variables are reported as counts and percentages (in parentheses). Estimates are a, odds ratios, [b], hazard ratios and [c], coefficients or area under the curve and 95%confidence interval (CI). EuroSCORE indicates European System for Cardiac Operative Risk Evaluation; KDIGO, Kidney Disease Improving Global Outcomes. In bold are statistical significant values. [d]: patients with CKD class 5 excluded from the analysis.

Table 3. Predictors of hospital/30-day mortality and of mid-term mortality.

Hospital/30-day mortality	*p-value*	*OR, 95%CI*
Clinical Frailty Scale		
CFS 1-2	<0.001	Reference
CFS 3-4	<0.001	3.97, 2.20-7.19
CFS 5-7	<0.001	
Age (years)	0.015	1.03, 1.01-1.05
Female	<0.001	2.05, 1.38-3.04
eGFR (mL/min/1.73 m^2)	<0.001	0.99, 0.98-0.99
Pulmonary disease	<0.001	2.79, 1.82-4.27
Atrial fibrillation	0.021	1.73, 1.09-2.77
Left ventricular ejection fraction ≤50%	0.009	1.66, 1.14-2.43
Recent ST-elevation myocardial infarction	0.006	1.99, 1.21-3.27
Urgency of the operation		
Elective	<0.001	Reference
Urgent	0.002	2.05, 1.31-3.22
Emergency	<0.001	3.49, 1.84-6.61
Critical preoperative state	<0.001	2.59, 1.59-4.24

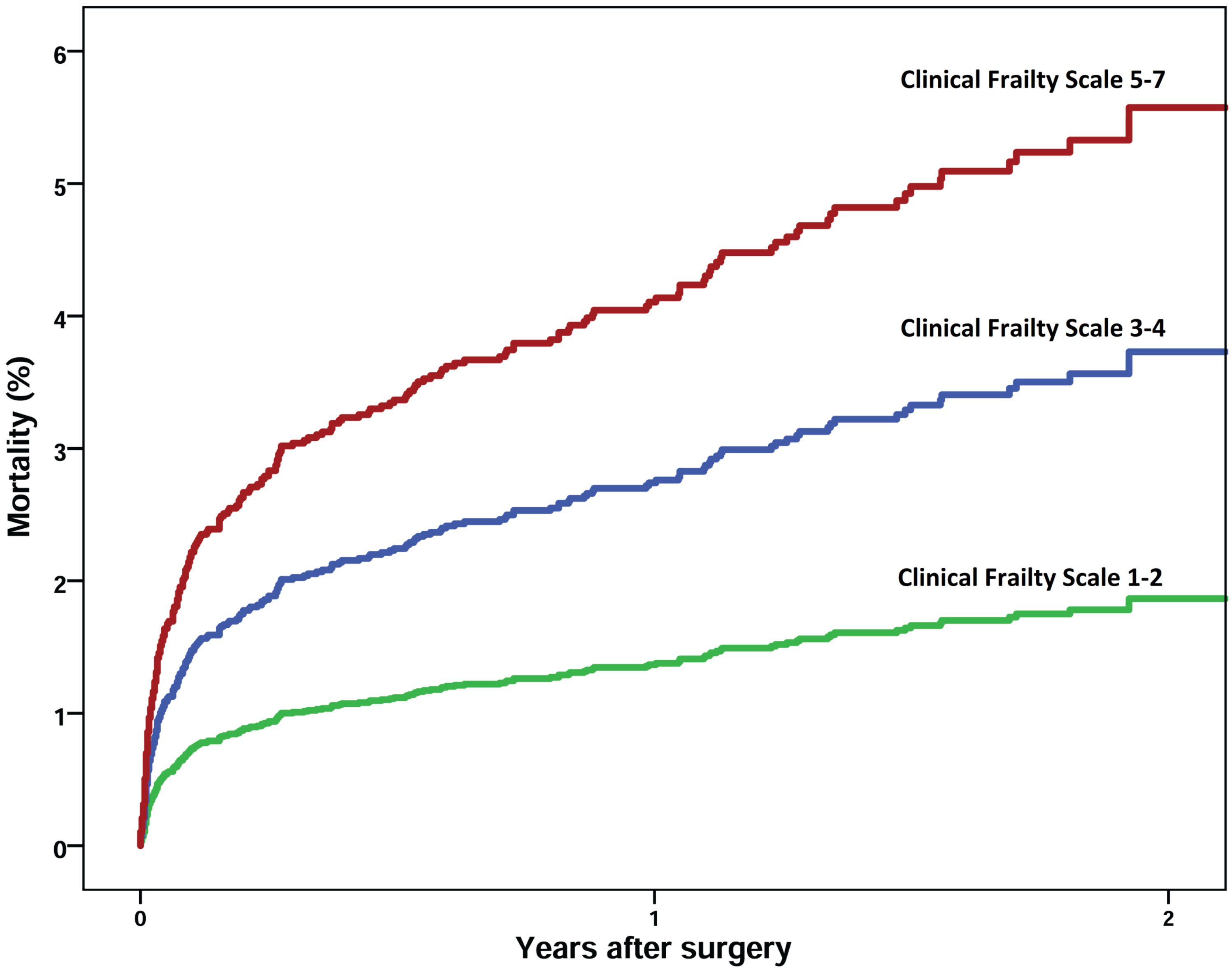
Mid-term mortality		*HR, 95%CI*
Clinical Frailty Scale		
CFS 1-2	<0.001	Reference
CFS 3-4	<0.001	2.02, 1.43-2.85
CFS 5-7	<0.001	3.05, 1.83-5.06
Age (years)	0.001	1.03, 1.01-1.04
Female	0.012	1.46, 1.09-1.96
Anemia	0.014	1.41, 1.07-1.85
eGFR (mL/min/1.73 m^2)	<0.001	0.99, 0.98-1.00
Extracardiac arteriopathy	<0.001	1.63, 1.25-2.14
Pulmonary disease	<0.001	2.07, 1.52-2.82
Atrial fibrillation	0.003	1.64, 1.18-2.28
Left ventricular ejection fraction ≤50%	<0.001	2.07, 1.59, 2.70
Urgency of the operation		
Elective	<0.001	Reference
Urgent	0.011	1.48, 1.10-1.99
Emergency	<0.001	3.08, 1.99-4.79
Critical preoperative state	<0.001	2.51, 1.45-2.93

Effect size of continuous variables corresponds to a unit increase in the risk factor. eGFR, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation. OR, odds ratio; HR: hazard ratio.

Table 4. Performance of regression models without and with Clinical Frailty Scale Classes in predicting hospital/30-day mortality.

	EuroSCORE II	EuroSCORE II *plus* CFS Classes	EuroSCORE II *versus* EuroSCORE II *plus* CFS Classes	Multiple covariates model	Multicovariates model *plus* CFS Classes	Multicovariates model *versus* Multicovariates model *plus* CFS Classes
NRI			59.6			55.60
NRI 95%CI			49.0, 70.3			44.1, 67.2
p-value			<0.0001			<0.0001
% of events correctly reclassified			80%			75%
% of nonevents correctly reclassified			20%			20%
IDI			0.9			1.3
IDI 95%CI			0.6, 1.3			0.9, 1.7
p-value			<0.0001			<0.0001
Mean probability for event	7.6%	6.7%		8.6%	9.9%	
Mean probability for nonevents	2.0%	2.0%		2.0%	1.9%	
AUC	0.781	0.809		0.800	0.823	
AUC 95%CI	0.738, 0.824	0.771, 0.848		0.757, 0.843	0.783, 0.863	
Difference in AUC (95%CI)			0.028 (0.006, 0.051)			0.023 (0.004, 0.041)
p-value for AUC difference			0.0146			0.0163
Hosmer-Lemeshow Chi-square	5.7	3.1		10.3	9.1	
Degrees of freedom	8	8		8	8	
p-value	0.68	0.93		0.25	0.33	

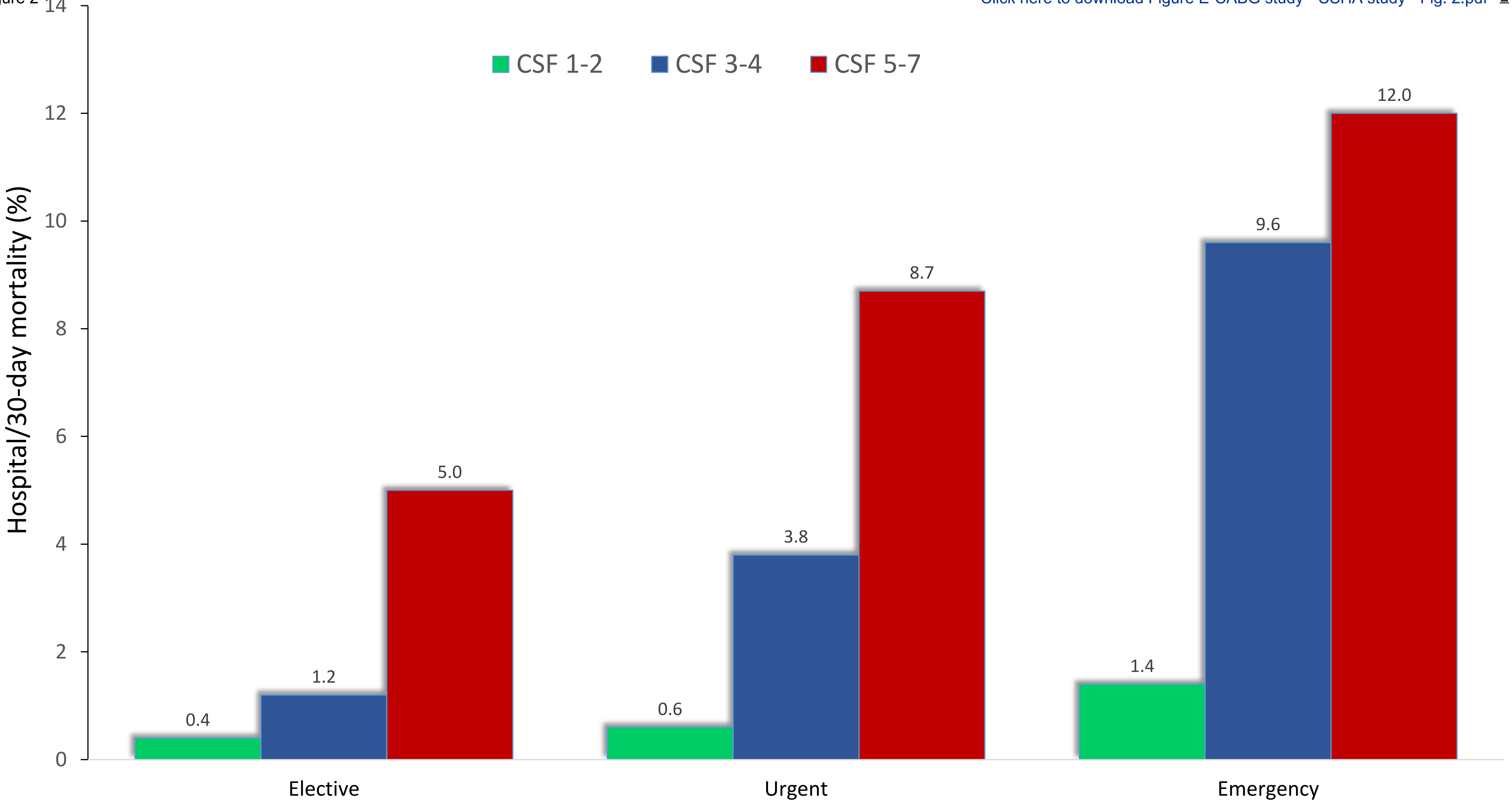
NRI, net reclassification index; IDI, Integrated Improvement Index; CI, confidence interval; AUC, area under the curve.



Patients at risk

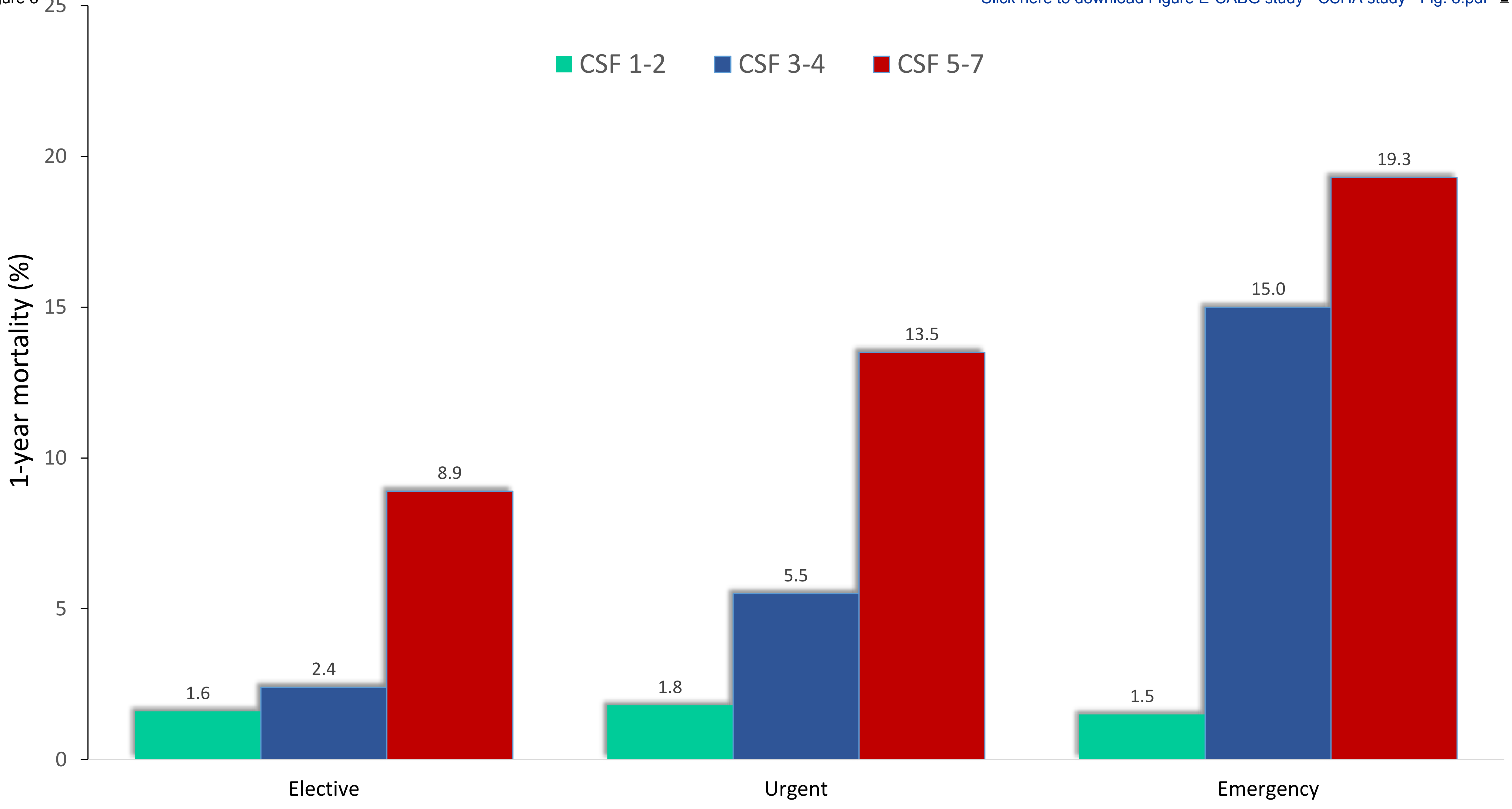
Clinical Frailty Scale 1-2	2413	1432	369
Clinical Frailty Scale 3-4	3543	2130	394
Clinical Frailty Scale 5-7	200	87	26

Figure 2



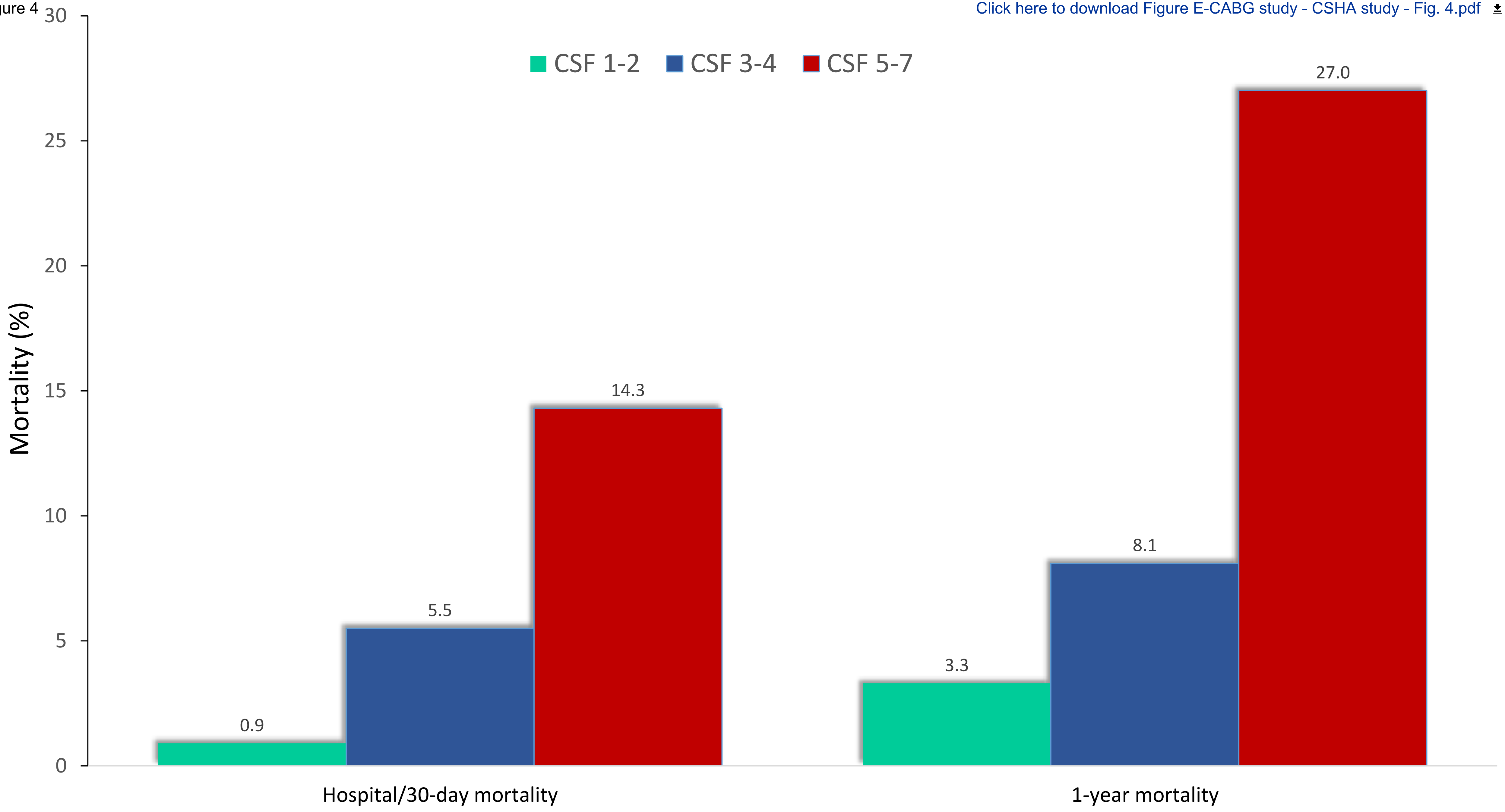
CSF 1-2
CSF 3-4
CSF 5-7
Hospital/30-day mortality (%)
0
2
4
6
8
10
12
14
0.4
1.2
5.0
0.6
3.8
8.7
1.4
9.6
12.0
Elective
Urgent
Emergency

Figure 3



CSF 1-2
CSF 3-4
CSF 5-7
1-year mortality (%)
25
20
15
10
5
0
1.6
2.4
8.9
1.8
5.5
13.5
1.5
15.0
19.3
Elective
Urgent
Emergency

Figure 4


CSF 1-2
CSF 3-4
CSF 5-7
Mortality (%)
30
25
20
15
10
5
0
0.9
5.5
14.3
3.3
8.1
27.0
Hospital/30-day mortality
1-year mortality