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Frailty And Preoperative Anemia Are Predictors of Worst In-Hospital Outcomes After Coronary Artery Bypass Graftin

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Abstract

Background: CABG is the most performed cardiovascular surgery in the world, being the standard treatment for complex coronary artery disease. However, the surgical risk prediction still has important gaps. In this context, frailty and preoperative anemia may have an important role in a better risk prediction. Our main objective was evaluated the impact of frailty and preoperative anemia on post-CABG in-hospital outcomes.

Methods: a cohort of consecutive patients undergoing isolated CABG was assembled from 2013 to 2017. Frailty was defined as any impairment in Katz Index. Of 1508 patients, 126 (8.4%) were frail. Baseline characteristics and outcomes were compared by univariate analysis. Multivariate regression models were applied for adjusted analysis of outcomes. The predictive accuracy of the regression models was accessed by ROC curves. The additional predictive accuracy of frailty and anemia, when associated with surgical risk scores, was analyzed by ROC curves comparison with DeLong test.

Results: Frail patients were older, were more likely to be female, and had more associated comorbidities. Frailty was an independent predictor of in-hospital mortality (OR 5.55, 95%CI 1.92-16.06, p = 0.002) and MACCE (OR 5.60, 95%CI 1.93-16.2, p = 0.001). Additionally, frailty was associated with longer hospital stay after CABG (B 4.61, 95%CI 2.12 - 7.10, p <0.001). Preoperative anemia was also an independent predictor of mortality (OR 2.23, 95%CI 1.08-4.61, p = 0.029) and MACCE (OR 2.43, 95%CI 1.20-4.95, p = 0.014). When associated with surgical risk scores, frailty and anemia improved the accuracy of the scores for mortality (EuroScore1 AUC = 0.70 x EuroScore1 Associated AUC = 0.77, p = 0.035 - EuroScore2 AUC = 0.71 x EuroScore2 Associated = AUC 0.77, p = 0.049).

Conclusions: Frailty and preoperative anemia are independent predictors of in-hospital mortality and MACCE post-CABG. Frailty was also a strong predictor of longer hospital stay. The association of frailty and anemia with surgical risk scores showed better predictive accuracy than isolated scores. The frailty screening by the Katz Index improves risk assessment for isolated CABG, and if associated with anemia, it may identify a subgroup of patients who may benefit from preoperative optimization.

Keywords: Frailty; anemia; CABG; euro score; mortality; MACCE; hospital discharge

Introduction

Every year there are 16 million deaths associated with cardiovascular diseases worldwide. Coronary artery disease has the highest prevalence and is directly associated with high risk of death and worst quality of life (1). Since the 1960s, the standard treatment for complex ischemic coronary diseases is the Coronary Artery Bypass Grafting (CABG), the most commonly performed cardiovascular surgical procedure in the world (2).

The increase in the life expectancy of the population also expanded the indication of surgical interventions in patients of advanced age groups and with associated comorbidities. To know the risk profile of these patients is mandatory, in order to obtain good surgical results. For this reason, surgical risk scores were developed to estimate the risk of death associated with cardiovascular surgery. Now these prognostic models are used in large scale and, in specific cases, are even applied to support the indication or contraindication of surgical procedures (3-7). However, the scores have important limitations and poor predictive power in some subgroups of cardiac patients. Because this, making continuous improvement of cardiovascular prognostic models is critical (8, 9).

The emergence of transcatheter valve implantations in elderly patients with prohibitive surgical risk demonstrated the need to complement the prognostic studies with some kind of frailty assessment. This condition is defined as a geriatric syndrome characterized by the decrease of resilience to stressors caused by the deterioration of multiple physiological systems, being related to greater risk of cardiovascular death (10, 11). Despite it is great predictive potential, frailty assessments are not standardized and some are too complex to be introduced into the health care routine (12, 13).

In this context, the search for risk factors that may indicate if a patient is frail and has a high surgical risk gained prominence more recently. Studies have demonstrated promising results in assessing the degree of mobility through the Katz Index of Independence in Activities of Daily Living (ADL) as marker of frailty and, consequently, a predictor of post-cardiac surgery risk of death (11, 14-17).

The preoperative anemia also is associated with worst outcomes. Anemia is a debilitating condition and influences the patients' physical ability, mobility, and ability to perform their daily living activities (18). The degree of mobility and preoperative anemia are considered as emerging surgical risk factors and require new studies that may establish their importance as determinants in prognostic studies (18, 19). The goal of this study was to evaluate the impact of frailty – classified by the Katz Index - and the preoperative anemia on in-hospital outcomes of a cohort of 1508 patients submitted to isolated CABG.

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METHODS

Patient Population

We identified and included consecutively all patients undergoing isolated CABG at the São Francisco Hospital of Santa Casa de Misericórdia, Porto Alegre, Rio Grande do Sul, Brazil, between January 2013 and December 2017. In this period were performed 2834 cardiovascular surgeries, including isolated CABG, CABG associated with valve replacements, isolated valve replacements, surgery of aorta and other associations of major surgeries. Only the patients undergoing isolated CABG were included, totalizing 1508 patients.

Ethical Aspects

The study protocol was approved by the Research Ethics Committees of the Santa Casa de Misericórdia of Porto Alegre and the Universidade Federal de Ciências da Saúde de Porto Alegre.

Data collection and variable selection

The data used in this study were obtained through the Cardiovascular Surgical Registry of the Hospital São Francisco. Created in 2010, the registry stores pre, trans, and postoperative variables. In all, there are 96 variables prospectively assessed. The data are collected and tabulated by trained cardiovascular scientists who follow a pre-established standard of definitions and classifications of Society of Thoracic Surgery (STS). From 2013 to 2017, the percentage of missing data did not exceed 1% in any of the variables.

The preoperative variables considered for the study were: gender, age, weight, hypertension, diabetes *mellitus*, myocardial infarction, renal impairment, creatinine, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral artery disease, documented episode or current atrial fibrillation, pulmonary artery pressure, left ventricular ejection fraction, heart failure NYHA Class III - IV, hemoglobin, unstable angina, previous cardiovascular surgery, previous percutaneous coronary intervention, EuroScore 1, EuroScore 2, frailty and anemia.

Frailty markers were the Katz Index of Independence in ADL (20, 21) (stratification variable) and preoperative anemia (secondary marker). The Katz Index was the only variable collected retrospectively, and for this, three trained researchers accessed the electronic records of each patient, collect and tabulate the data. The Katz Index was easily obtained through the preoperative evaluations notes of the physical therapy, nursing and medical teams. It was possible to collect the Katz Index from all patients in the study.

In addition to the value attributed to the Katz Index, each of the six items that compose the index was collected and tabulated individually: bathing (bathes self completely or needs help only a single part of the body), dressing (gets clothes from closets and puts on clothes complete), toileting (goes to toilet, gets on and off, clean genital area without help), transferring (moves in or out bed or chair unassisted), continence (exercise complete self-control over urination or defecation) and feeding (gets food from plate into mouth without help). Based on these activities of daily living, patients receive scores from 0 (fully dependent) to 6 (fully independent). For this study, the patients were classified into two groups according to the Katz Index: scores from 0 to 5 (Frail Group) and score equal to 6 (Non-Frail Group).

The anemia was defined based on the preoperative hemoglobin value, being considered the one closest to the surgery. Following the recommendations of International Federation of Clinical Chemistry (22), we adopted the local reference values based on a population study for the State of Rio Grande do Sul. Men with hemoglobin values below 12.8 g / dL and women with values below 11.6 g / dL were considered anemic (23).

The trans-operative characteristics evaluated included emergency or urgency surgery, use of cardiopulmonary bypass, cardiopulmonary bypass time, aortic clamping time, use of internal thoracic artery graft, number of coronary vessels with significant obstructions (stenosis > 70%), stenosis > 50% in the left main coronary artery, number of distal anastomoses performed in the intervention, complete revascularization according to the preoperative plan and need for conversion the off-pump to on-pump technique.

Surgical Technique

Most patients underwent on-pump CABG (76.1%). The option to operate with or without extracorporeal support was performed by the surgeon according to the anatomical characteristics of the coronary stenosis, the left ventricular function and the approval of the health insurance. The cardioplegia developed by del Nido (24) was used to preserve the heart during on-pump surgeries. The solution was cooled to 4 ° C and delivered anterograde to the heart. All the surgeries were performed in the Hospital São Francisco, in the same operation rooms and by the same team of surgeons and perfusionists.

Outcomes

The primary outcomes of this study were in-hospital mortality, major cardiovascular and cerebrovascular events (MACCE – association of death, acute myocardial infarctation, stroke and or new revascularization), and length of hospital stay after the surgery. The need for new revascularization, stroke, acute myocardial infarctation, bleeding, pleural effusion, respiratory infection and sepsis were the secondary outcomes.

Statistical analysis

The categorical variables were described by absolute numbers and frequencies. The continuous variables were described by mean and standard deviation. The normality evaluation was performed by analysis of asymmetry, kurtosis and Shapiro-Wilk test. The preoperative, transoperative and postoperative in-hospital outcomes were compared by univariate analysis with Pearson's Chi-square test, for categorical variables, and the T-Test for Independent Samples, for continuous variables.

Variables identified as statically associated and clinically relevant with outcomes ($p \leq 0.10$) in the univariate statistical tests were included in the adjusted multivariate models. The collinearity analysis was performed using the correlation matrix ($r \geq 0.3$). The association between frailty, anemia and in-hospital outcomes were examined using binary logistic regression (mortality and MACCE) and Cox regression (length of hospital stay). The predictive accuracy of each model was evaluated using ROC curves based on predicted probabilities obtained through the regression models.

The DeLong Test for comparison of ROC curves was used to evaluate the predictive accuracy of the surgical risk scores (EuroScore 1 and EuroScore 2), isolates and associates with frailty and anemia. Area under the curve and exact binomial confidence interval were used to describe the prediction curves.

Multivariate analyzes, as well as univariate analyzes and ROC curves comparison, were interpreted based on a significance level of 5% ($p \leq 0.05$). Statistical analysis was performed with SPSS software version 21 (IBM). The authors of the study had access to all data and take full responsibility for the integrity of the analyzes and information obtained. In the same way, they assume knowledge and agreement with the final writing.

Results

Baseline Characteristics

Between January 2013 and December 2017, a total of 1,508 patients underwent isolated CABG in our institution. The Katz Index of Independence in ADL was used as the primary marker of frailty and as a parameter for stratification the patients in two groups: "Non-Frail" (patients with a Katz Index equal 6, n = 1,382, 91.7%) and "Frail "(Patients with Katz Index between 0 and 5, n = 126, 8.3%). Among the frail patients, the activity of daily living compromised with greater prevalence was transferring (96, 76.2%), followed by the bathing (85, 67.5%) and the toileting (73, 57.9%). In addition, the secondary marker of frailty of this study, preoperative anemia, was identified in 519 (34.4%) patients.

In-Hospital Mortality

Unadjusted analysis: In the univariate analysis, the frailty was associated with higher in-hospital mortality (non-frail 2.5%, frail 15.9%, p <0.001).Additionally, when the analysis of mortality was stratified in four groups according to the frailty and anemic status, the mortality rate for frail and anemic patients was 19.2%, while frail patients without anemia had 11.3%, non-frail patients with anemia had 4.7% and non-frail and non-anemic patients had 1.5% of mortality ($p < 0.001$).

Adjusted analysis: the variables considered to build the mortality logistic regression model were significantly associated with the outcome by univariate analysis and included: female sex, age, diabetes, atrial fibrillation, cerebrovascular disease, hypertension, heart failure with NYHA Class III - IV, chronic obstructive pulmonary disease, pulmonary

artery pressure, myocardial infarctation, hemodialysis, anemia, on-pump technique, no use of internal thoracic artery graft, anemia and frailty.

The results obtained by logistic regression, adjusted for comorbidities, showed that frailty was an independent predictor of risk for in-hospital mortality (OR 5.55, 95%CI 1.92-16.06, p = 0.002). The preoperative anemia was also classified as an independent predictor of death (OR 2.23, 95%CI 1.08-4.61, p = 0.029). Additionally, when associates, frailty and anemia showed better predictive ability with an even greater odds ratio for the occurrence of hospital mortality (OR 7.92, 95%CI 3.26-19.20, p <0.001). Hemodialysis, chronic obstructive pulmonary disease and on-pump technique were also predictors of mortality.

In-Hospital MACCE

Unadjusted analysis: frailty was associated with higher MACCE (non-frail 8.0%, frail 30.2%, p < 0.001) - Table 3. Additionally, in the same way of mortality, when the analysis of MACCE was stratified in four groups according to the frailty and anemic status, the MACCE rate for frail and anemic patients was 32.9%, while frail patients without anemia had 26.4%, non-frail patients with anemia had 10.1% and non-frail and non-anemic patients had 6.9% of MACCE (p < 0.001).

Adjusted analysis: the variables considered to build the MACCE logistic regression model were significantly associated with the outcome by univariate analysis and included: female sex, age, diabetes, atrial fibrillation, cerebrovascular disease, heart failure NYHA Class III - IV, chronic obstructive pulmonary disease, pulmonary artery pressure, peripheral artery disease, myocardial infarctation, creatinine clearance, on-pump technique, no use of internal thoracic artery as graft, anemia and frailty.

The logistic regression, adjusted for comorbidities, showed the frailty as an independent risk predictor for in-hospital MACCE (OR 5.60, 95% CI 1.93 - 16.2, p = 0.001). Preoperative anemia was also classified as an independent predictor (OR 2.43, 95% CI 1.20 - 4.95, P = 0.014). And when associated, frailty and anemia were a risk predictor with an even greater OR for MACCE (OR 8.23, 95% CI 3.42 - 19.8, P <0.001). Chronic obstructive pulmonary disease and the on-pump technique were also characterized as predictors of MACCE. The regression model showed predictive accuracy of 80.4%.

Hospital Stay After CABG

Unadjusted analysis: frailty was also associated with longer post-CABG hospital stay in the unadjusted analysis. While the mean time of hospitalization after the surgery of non-frail patients was 10 days, the mean time of hospitalization of fragile patients was 16 days (p = 0.009).

Adjusted analysis: the longer hospital stays associated, by univariate analysis, with the frail patients was confirmed by multiple linear regression adjusted for comorbidities. The adjusted analysis showed that frail patients tend to remain hospitalized four days longer than non-frail patients (B 4.61, 95%CI +2.12 to +7.10, p <0.001). On the other hand, anemia did not have a significant impact on the length of hospital stay post-CABG (B -0.93, 95%IC -0.244 to -0.58, p = 0.228). Female sex, diabetes, hemodialysis and time of cardiopulmonary bypass also showed a significant impact on the length of hospital stay.

Predictive accuracy of Surgical Risk Scores, Frailty and Anemia

The analysis of the predictive accuracy of the surgical risk scores showed that EuroScore 1 and EuroScore 2 isolated showed significantly lower accuracy than when associated with frailty and anemia. While EuroScore 1 presented an area under the curve of 0.70, the association of EuroScore 1, frailty and anemia presented an area under the curve of 0.77 (p = 0.035). The EuroScore 2 had similar results and presented an area under the curve of 0.71, but when associated with frailty and anemia also presented a higher area under the curve of 0.77 (p = 0.049). These results showed that the association of surgical risk scores with the frailty and anemia improved significantly the predictive accuracy of the EuroScore 1 and the EuroScore 2.

DISCUSSION

Our study showed the preoperative anemia and frailty, as measured by the Katz Index, are both independent predictors for in-hospital mortality and MACCE after isolated CABG. Frailty was also associated with longer hospital stay. When utilized together with commonly used surgical risk scores, anemia and frailty improved the predictive ability of the scores, added predictive accuracy.

The frailty still represents an emerging concept and therefore its classification is heterogeneous and still does not have standardization, being a characteristic that can be verified by several different tools (12, 13, 25). The main concepts of frailty usually include a number of clinical features - loss of muscle mass, low levels of activity and endurance are examples of frequent characteristics. Given that the association between dependence to perform one or more activities of daily living and frailty has already been well demonstrated previously (11-13), we chose to use the Katz Index of Independence in ADL to identify and classify frail patients. The index is widely accepted and used since the 1970s to measure the degree of dependence, especially in patients with more advanced age (20, 21, 26).

At the same time, studies evaluating the impact of frailty on patients undergoing transcatheter aortic valve implantation (TAVI) played an important role in stimulating the observation of the condition in patients undergoing conventional heart surgery (27, 28). In 2014, Sündermann *et al.*, evaluating 450 patients undergoing cardiac surgery, concluded that frailty is an independent predictor of risk for short- and medium-term mortality after the surgical procedure. To identify frail patients, the researchers used the Comprehensive Assesment of Frailty and the Frailty Predicts Death One Year After Elective Cardiac Surgery Test (28). Sapehri *et al.*, also in 2014, concluded that frail patients, identified by several different tools, are at higher risk of death, as well as functional decline and increased risk of MACCE after cardiac surgery (8). More recently, in 2018, Reichart *et al.* evaluated, through the Clinical Frailty Scale, the impact of frailty on the occurrence of death after CABG. The researchers analyzed the data of 6,156 patients submitted to surgical revascularization and concluded that the frailty predicts mortality in the short and medium term in patients submitted to isolated CABG (25).

The present study also found similar results to the studies cited so far. However, our investigation had the additional analysis of the impact of preoperative anemia on post-CABG outcomes. The results showed that anemia is also a predictor risk of in-hospital mortality and MACCE. Because it is a debilitating condition and affects the functional capacity of patients, anemia is a factor that enhances frailty. The adjusted mortality analysis showed that frail and anemic patients had a higher *Odds Ratio* for death and MACCE than non-anemic frail patients and only anemic patients. We also identified that anemia and frailty improved the predictive ability of risk surgical scores for in-hospital mortality.

Previous results have been showed that surgical risks scores have poor accuracy for specifically groups of patients undergoing to CABG, including the elderly population (29-31). Because this, the better predictive accuracy associated with the EuroScore 1 and EuroScore 2 when the scores were linked with frailty and anemia it was a very important finding. The future perspectives certainly should include new studies for improve the prognostic models of cardiovascular surgery with the addition of emergent risk factors as frailty and anemia.

We were able to confirm that frail patients have a more severe risk profile. It was possible to verify that they were older and had a higher prevalence of comorbidities such as diabetes, chronic obstructive pulmonary disease, heart failure NYHA Class III - IV, previous myocardial infarctation, cerebrovascular disease and anemia. The prevalence of previous cardiovascular surgery in the group of frail patients was also higher. In addition, the two surgical risk scores assessed in this study were higher in frail patients. However, these differences between the groups did not impact the results obtained, since they were corrected and mitigated by performing specific and adjusted multivariate analysis models for the outcomes of interest (in-hospital mortality and MACCE and length of hospital stay).

With the perform of this work, we can demonstrate the impact that a simple classification of frailty, performed only with the Katz Index, can have on the prediction of post-CABG in-hospital outcomes. Unlike other tools used to measure and classify frailty, the index only assesses patients' ability to perform six basic daily living activities - bathing, dressing, toileting, transferring, continence, and feeding. Independent patients had a Katz Index of 6 and were considered non-frail. Dependent patients had a Katz Index between 0 and 5 and were considered frail. In the same way, as previous studies (11, 12, 32), we also found a strong association between frailty classified by the Katz Index and the occurrence of worse post-procedure outcomes.

The results obtained with this study lead us to question whether revascularization surgery is always justified in frail patients, especially for the patients with associated preoperative anemia and high surgical risk. The results presented by our group and by other researchers in previous studies indicate that patients with this risk profile are operated regularly within the routines of cardiovascular surgery services, even though the surgical results are significantly worse. In addition, these patients are likely to receive inaccurate information about their real risk when only the surgical risk score is considered. It is important that the

teams involved in surgical care to mitigate the risks associated with frail patients through the adequacy of healthcare protocols. Our study suggests the use of programs to improve the mobility of frail patients safely and supervised by a multidisciplinary team. In addition, for elective patients, measures may be taken to correct anemia prior to cardiovascular surgery. However, these preoperative measures should be tested in randomized clinical trials prior to wide implementation.

The main limitation of the study was the retrospective collection of the Katz Index. However, the collection of the index was possible for all patients with safety and precision because the data was produced prospectively and described in the electronic hospital register. In this way, only the collection of the Katz Index was retrospective. All other variables were prospectively collected from a standardized institutional register and fed by a single team of researchers. Although the study involved a single center, which may limit the number of patients analyzed, this delimitation allowed all patients to be operated on the same operation rooms, with the same technological support and by the same surgical team. All patients received exactly the same care and were submitted to the same protocols of medical care, nursing, physical therapy and nutrition. In addition, rigorous statistical methods were adopted and the data were extensively audited and reviewed. The rate of missing of data did not exceed 1% in any of the study variables, guaranteeing the performance of the statistical processes through tests with great statistical power of determination.

Conclusions

In conclusion, we were able to demonstrate that the preoperative classification of frailty through the Katz Index for Independence in ADL showed an association with in-hospital mortality, MACCE and longer hospitalization stay after the surgery. We have identified the risk-enhancing role that preoperative anemia exerts specially on frail patients. In addition, we have found that the association between frailty and anemia improves the predictive accuracy of EuroScore 1 and EuroScore 2 for in-hospital mortality. To identify the most severe patients enables them to be better informed about the procedure for which they were referred and also allows the health multidisciplinary team apply the best care protocols and lead the patient to surgery at the most favorable time, considering the risk scores, the evaluation of the frailty and the preoperative anemia.

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