# The nutritional risk and short, medium and long-term mortality of hospitalized patients with atrial fibrillation

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## ABSTRACT

**Objective**: To determine the association between the level of nutritional risk and the mortality of hospitalized patients with atrial fibrillation.

**Methods**: In a prospective cohort study, we included patients hospitalized with atrial fibrillation in an internal medicine department in 2007. We calculated the nutritional risk with the Controlling Nutritional Status (CONUT) score and conducted a 10-year follow-up. To determine the variables associated with mortality in the short (3 months), medium (1 year) and long term (10 years), we constructed a Cox proportional hazards regression model and calculated the Kaplan-Meier survival curves.

**Results**: The study included 282 patients with a mean (SD) age of 81.2 (7.9) years. The mean CONUT score was 4.7 (2.8) points. Thirty-six patients had zero nutritional risk, 110 had a low risk, 106 had a moderate risk, and 30 had a high risk. The median survival of the patients with zero, low, moderate and high risk was 33 months, 21 months, 10 months and 60 days, respectively. The CONUT score was independently associated with mortality at 3 months (HR, 1.144; 95% CI 1.062-1.233), 12 months (HR, 1.102; 95% CI 1.030-1.179) and 10 years (HR, 1.051; 95% CI 1.000-1.103).

**Conclusions**: Nutritional risk is associated with the short, medium and long-term mortality of hospitalized patients with atrial fibrillation.



**KEYWORDS**

Atrial fibrillation; Nutrition; Mortality; Cohort study.

## BACKGROUND

Atrial fibrillation (AF) is an increasingly prevalent condition that is mainly diagnosed in the elderly. The prevalence of AF increases with age from 0.12-0.16% in those younger than 50 years to 10-17% in those older than 80 years [1]. In Spain, AF affects 4.4% of the population [2] and is present in up to 31% of patients older than 70 years hospitalized in internal medicine and geriatric medicine departments [3].

Frailty is a common condition in the elderly with AF and is associated with increased mortality and longer mean hospital stays [4-6], and a deficient nutritional state is one of the risk factors for frailty [7]. Nutritional disorders are also common in the patients with AF, with a recent systematic review suggesting a U-shaped relationship between nutrition and AF, such that both obesity and malnutrition are associated with poorer clinical results [8]. Detecting malnutrition could therefore help in managing AF.

In this context, simple-to-use tools that enable clinicians to differentiate patients with a greater risk of malnutrition and who are therefore susceptible to presenting greater short-term mortality are of considerable use in daily clinical practice [9]. Screening tools enable an initial assessment designed for the early detection of malnourished patients or those at risk for developing malnutrition, to thereby refer them to a more specific nutritional assessment and, if necessary, start them on nutritional therapy. The Controlling Nutritional Status (CONUT) is a simple index that establishes a nutritional risk alert level [10].

The aim of this study was to assess the association between the level of nutritional risk and mortality in patients with AF.

## MATERIAL AND METHODS

We performed a prospective cohort study that included all patients with a primary or secondary diagnosis of AF hospitalized in an internal medicine department during 2007. The AF could be paroxysmal, persistent or permanent and valvular or nonvalvular, according to the criteria of the European Society of Cardiology [11].

### Procedures

The following data were collected for each patient: age, sex, history of AF prior to admission, congestive heart failure, arterial hypertension, diabetes mellitus, ischemic stroke or transient ischemic attack (TIA), presence of mitral valve disease or carrier of prosthetic valve, reason for hospital admission, albumin and cholesterol levels, total lymphocyte count, presence of anemia, embolic risk, nutritional risk and prescription of oral anticoagulants. We calculated the embolic risk with the $CHADS_2$ scale [12] and the nutritional risk with the CONUT index [10], the latter of which was constructed based on cholesterol and albumin levels and total lymphocyte counts and was scored from 0 to 12 points. The CONUT index establishes 4 nutritional risk alert levels: null, for scores 0-1; low, for scores 2-4; moderate, for 5-8 points; and high or severe, for 9-12 points. We excluded those patients for whom the CONUT index could not be calculated. Anemia was defined according to World Health Organization criteria (hemoglobin level <13 g/dL in men and <12 g/dL in women). Renal failure was considered when the estimated creatinine clearance was <60 mL/min.

We subsequently conducted a 10-year follow-up, assessing short (1 month), medium (90 days) and long-term (10 years) survival from the hospital discharge. This follow-up was conducted by consulting the electronic medical records, by telephone calls and by consulting the Spanish National Death Index [13].

The study was approved by the Clinical Research Ethics Committee of Aragon (PI 12/006) and was conducted according to the research principles of the Declaration of Helsinki and the Organic Law on Data Protection.

**Statistical analysis**

The qualitative variables are expressed as absolute frequencies (n) and percentages (%), and the quantitative variables are shown as mean and standard deviation (SD). The qualitative variables were compared between the groups with different nutritional risks using the chi-squared test, and the quantitative variables were compared using the analysis of variance (ANOVA) test.

To study the variables associated with mortality, we constructed a Cox proportional regression model. The multivariate analysis included CHADS2 score and those variables with a p-value <0.1 in the univariate analysis. We analyzed the survival of the various groups with Kaplan-Meier survival curves and the log-rank test.

For all analyses, we set the level of statistical significance at $p<0.05$.

For the statistical analysis, we employed the Statistical Package for the Social Sciences (SPSS) 21.0 program for Windows.

## RESULTS

Figure 1 shows the flow diagram for patient inclusion. The study included 282 patients, 155 (55.0%) of whom were women, with a mean age of 81.2 (7.9) years. AF was previously known in 181 (64.2%) patients. The most common causes of hospitalization were infection (66 patients, 23.4%), heart failure (53, 18.8%), ischemic stroke/TIA (32, 11.3%), acute respiratory failure or exacerbation of chronic obstructive pulmonary disease (24, 8.5%) and hemorrhage (16, 5.7%). The patients' baseline characteristics are listed in Table 1.

### Nutritional risk

The mean CONUT score was 4.7 (2.8) points, and the nutritional risk was zero for 36 (12.8%) patients, low for 110 (39.0%), moderate for 106 (37.6%) and high for 30 (10.6%). The high-risk patients were older and more frequently presented anemia but less frequently had heart failure, hypertension, mitral valve disease and valvular prosthesis. The high-risk patients were more frequently hospitalized for infection and less frequently for stroke/TIA.

In the patients who were discharged alive, the prescription of oral anticoagulation was lower the greater the nutritional risk (52.9%, 57.0%, 46.7% and 17.6% for the patients with zero, slight, moderate and high risk, respectively; p=0.024).

**Survival**

Thirty-eight (13.5%) patients died during hospitalization, 91 (32.4%) died at 3 months, 133 (47.2%) died at 1 year, and 259 (91.8%) died at 10 years, with only one loss during follow-up. The mortality was greater for the patients with highest nutritional risk (Table 2). Figure 2 shows the Kaplan-Meier survival curve. The median survival of the patients with zero, low, moderate and high risk was 33 months, 21 months, 10 months and 60 days, respectively.

The factors associated with mortality are listed in Table 3. The CONUT index was independently associated with mortality at 3 months (HR, 1.144; 95% CI 1.062-1.233, p<0.001), 12 months (HR, 1.102; 95% CI 1.030-1.179, p=0.005) and 10 years (HR, 1.051; 95% CI 1.000-1.103, p=0.049).

## DISCUSSION

Our study's main findings were that almost half of the patients with AF hospitalized in internal medicine departments had a moderate to high nutritional risk, that these patients had greater short, medium and long-term mortality and that they underwent less treatment with oral anticoagulants.

In a multinational analysis, 38.7% of hospitalized patients were malnourished [4]. A study in Spain with hospitalized patients older than 65 years found a prevalence of nutritional risk of 42% (measured with the Mini Nutritional Assessment) and 39% (measured with the CONUT index) [15]. According to the minimum basic data set, the mean age of patients discharged from internal medicine departments was 71.2 years in 2007, and each year this mean age has increased [16]. The patients included in our study had a mean age of 81 years (10 years older), which could explain the high prevalence of nutritional risk. Also, they were acutely hospitalized patients and had a high comorbidity.

Malnutrition is associated with poorer health results [17], which makes its early detection important for correcting its causes and reversing the malnutrition [18,19]. Screening within the first 24 hours of hospital admission is recommended. Among the screening tools employed is the CONUT index [10], which assesses 3 laboratory parameters: cholesterol, albumin and total lymphocytes, which are measured in practically all patients who remain hospitalized for more than a day. The index helps automate the process by establishing malnutrition risk levels. The index has been validated and is recommended by a number of scientific societies [20-22].

In a number of studies on hospitalized patients, the prevalence of malnutrition has been associated with heart disease and was higher in medicine departments [23]. However, little attention has been focused on the relationship between malnutrition and AF. In their review on the impact of the nutritional state on the prognosis of AF, Anaszewicz et al. found conflicting results [8]. On one hand, obesity and excess weight seem to increase the risk of developing AF, but on the other hand, the authors also observed the obesity paradox, with lower all-cause mortality in patients with excess weight. It appears that both malnutrition and obesity are associated with a poorer prognosis for patients with AF.

Malnutrition has been associated with poorer health results for patients with heart failure [24] and those with acute stroke [25]. However, the relationship between malnutrition and AF results has been scarcely studied. It has been observed that a low body mass index is associated with a greater rate of stroke and higher mortality [26]. In a Polish study with approximately 5000 patients hospitalized for heart disease, AF was associated with lower nutritional parameters, greater hospital mortality and higher readmission rates [27]. To our knowledge, this study is the first to assess the influence of malnutrition on medium and long-term mortality in patients with AF.

In our patients, renal failure was associated with greater short, medium and long-term mortality. Other studies have already shown the influence of renal failure on the prognosis of patients hospitalized with AF [28], and the association between malnutrition, renal failure and mortality is already widely known [29].

An interesting finding from our study is that the malnourished patients less frequently received oral anticoagulants at discharge. It has been suggested that malnutrition could be a factor that increases vulnerability to warfarin and could therefore precipitate the onset of hemorrhaging [30]. Adjusting the dosage to weight is recommended for a number of direct-acting anticoagulants [31], and it is therefore important to determine the presence of malnutrition or the risk of presenting it in patients with AF. In this case, the appropriate approach is to attempt to correct the malnutrition and not deprive patients of oral anticoagulant therapy.

In clinical trials, nutritional intervention for patients with heart failure has been shown to decrease mortality [32]. Similar results might be achieved in patients with AF, with or without heart failure, but new clinical trials will need to be established to determine this possibility.

Our study has a number of limitations. Firstly, the study was conducted at a single center, and included only patients from the wards, not from intensive care unit, which could limit the generalization of its results. Secondly, we began the study in 2007, and we took the ACC/AHA/ESC 2006 as a reference. Currently, the guidelines recommend the use of the CHA2DS2-Vasc score, but in our elderly population using this scoring system does not change the main results. Thirdly, the nutritional status was based on the condition at admission, and could have changed during the follow up. Finally, we collected results regarding only mortality; the influence of malnutrition risk on the onset of stroke and hemorrhaging would have been of interest. However, there were no restrictions in the inclusion criteria except for the inability to calculate the CONUT score.

There was also a long-term follow-up of the patients, with only a single loss in 10 years, which strengthens our results.

In conclusion, we recommend assessing the malnutrition risk of patients hospitalized with AF, for which the CONUT index can be of use. For patients with a moderate to high malnutrition risk, a nutritional intervention is essential.

**Ethical statement**

- The manuscript has not been submitted to more than one journal for simultaneous consideration.
- The manuscript has not been published previously.
- There is no. "salami-publishing".
- No data have been fabricated or manipulated to support the conclusions.
- No data, text, or theories by others are presented as if they were the author's own.
- Consent to submit has been received explicitly from all co-authors, as well as from the responsible authorities at the institute/organization where the work has been carried out, before the work is submitted.

**Contributor statement**

We assure that all authors included on a paper fulfill the criteria of authorship. J. Díez-Manglano designed the study. J. Díez-Manglano, and Carolina Clemente-Sarasa performed data collection and data analysis. The manuscript was drafted by J. Díez-Manglano, and all authors helped with its revision and gave final approval of this version.

**Compliance with ethical standards**

- The authors declare no potential conflicts of interest.
- The study was approved by the Ethical Research Committee of Aragon and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.
- All patients, or its relatives if they were cognitive impaired, gave their informed consent.
- This article does not contain any studies with animals performed by any of the authors.

**Conflicts of Interest**
On behalf of all authors, the corresponding author states that there is no conflict of interest

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Table 1 Baseline characteristics of included patients

| | Total (N=282) | Level of nutritional risk | | | | p |
|---|---|---|---|---|---|---|
| | | Null (n=36) | Low (n=110) | Moderate (n=106) | High (n=30) | |
| Age | 81.2 (7.9) | 78.5 (7.7) | 80.8 (6.5) | 81.6 (9.1) | 84.5 (6.9) | 0.019 |
| Female sex* | 155 (55.0) | 21 (58.3) | 62 (56.4) | 60 (56.6) | 12 (40.0) | 0.379 |
| Previous AF* | 181 (64.2) | 24 (66.7) | 77 (70.0) | 66 (62.3) | 14 (46.7) | 0.117 |
| Comorbidities* | | | | | | |
| Heart failure | 81 (28.7) | 9 (25.0) | 36 (32.7) | 34 (32.1) | 2 (6.7) | 0.032 |
| Arterial hypertension | 177 (62.8) | 25 (69.4) | 77 (70.0) | 61 (57.5) | 14 (46.7) | 0.052 |
| Diabetes mellitus | 88 (31.2) | 10 (27.8) | 40 (36.4) | 32 (30.2) | 6 (20.0) | 0.339 |
| Stroke / previous transient ischemic attack | 58 (20.6) | 12 (33.3) | 22 (20.0) | 19 (17.9) | 5 (16.7) | 0.227 |
| Anemia | 150 (53.2) | 9 (25.0) | 46 (41.8) | 68 (64.2) | 27 (90.0) | <0.001 |
| Mitral valve disease or valvular prosthesis | 59 (20.9) | 13 (36.1) | 25 (22.7) | 20 (18.9) | 1 (3.9) | 0.011 |
| Chronic renal failure | 117 (41.5) | 8 (22.2) | 46 (41.8) | 48 (45.3) | 15 (50.0) | 0.071 |
| Analytical parameters | | | | | | |
| Cholesterol, mg/dL | 148 (42) | 191 (28) | 160 (36) | 133 (35) | 104 (27) | <0.001 |
| Albumin, g/dL | 3.3 (0.5) | 3.8 (0.2) | 3.6 (0.3) | 3.1 (0.3) | 2.5 (0.3) | <0.001 |
| Creatinine, mg/dL | 1.2 (0.8) | 1.0 (0.6) | 1.1 (0.5) | 1.3 (0.9) | 1.5 (1.6) | 0.068 |
| Hemoglobin, g/dL | 11.8 (2.2) | 13.0 (2.1) | 12.4 (2.1) | 11.2 (2.2) | 10.6 (1.5) | <0.001 |
| Lymphocytes, n/µL | 1184 (685) | 2119 (816) | 1253 (581) | 921 (464) | 743 (382) | <0.001 |
| $CHADS_2$ score | 2.4 (1.3) | 2.6 (1.4) | 2.6 (1.3) | 2.4 (1.3) | 1.9 (1.1) | 0.089 |

Data is presented as mean (standard deviation) or *n (%).
Abbreviation: AF, atrial fibrillation.

Table 2. Mortality according to nutritional risk level

| Mortality | Total (N=282) | Level of nutritional risk | | | | p |
|---|---|---|---|---|---|---|
| | | Null (n=36) | Low (n=110) | Moderate (n=106) | High (n=30) | |
| During hospitalization | 38 (13.5) | 1 (2.8) | 14 (12.7) | 12 (11.3) | 11 (36.7) | <0.001 |
| At 3 months | 91 (32.4) | 6 (16.7) | 28 (25.5) | 37 (35.2) | 20 (66.7) | <0.001 |
| At 1 year | 133 (47.2) | 9 (25.0) | 45 (40.9) | 57 (53.8) | 22 (73.3) | <0.001 |
| At 10 years | 259 (91.8) | 31 (86.1) | 100 (90.9) | 99 (93.4) | 29 (96.7) | 0.395 |

The data are presented as n (%).

Table 3. Factors associated with short, medium and long-term mortality

| | | | | |
|---|---|---|---|---|
| Short-term (3 months) | | | | |
| | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | p | HR (95% CI) | p |
| Age | 1.054 (1.022-1.087) | 0.001 | 1.034 (1.000-1.069) | 0.051 |
| Heart failure | 0.654 (0.396-1.074) | 0.093 | 0.711 (0.422-1.200) | 0.202 |
| Mitral valve disease / valvular prosthesis | 0.410 (0.212-0.791) | 0.008 | 0.551 (0.282-1.078) | 0.082 |
| Renal impairment | 2.003 (1.323-3.031) | 0.001 | 1.855 (1.216-2.828) | 0.004 |
| CHADS2 score | 1.042 (0.717-1.516) | 0.828 | 1.011 (0.656-1.556) | 0.962 |
| CONUT | 1.197 (1.114-1.286) | <0.001 | 1.144 (1.062-1.233) | <0.001 |
| | | | | |
| In the medium term (1 year) | | | | |
| Age | 1.072 (1.044-1.100) | <0.001 | 1.058 (1.030-1.088) | <0.001 |
| Mitral valve disease / valvular prosthesis | 0.446 (0.268-0.742) | 0.002 | 0.613 (0.364-1.031) | 0.065 |
| Renal impairment | 1.770 (1.259-2.488) | 0.001 | 1.651 (1.163-2.343) | 0.005 |
| Anemia | 1.507 (1.064-2.135) | 0.021 | 1.058 (0.727-1.540) | 0.769 |
| CHADS" score | 1.124 (0.821-1.538) | 0.465 | 0.923 (0.651-1.308) | 0.651 |
| CONUT | 1.160 (1.091-1.233) | <0.001 | 1.102 (1.030-1.179) | 0.005 |
| | | | | |
| Long-term (10 years) | | | | |
| Age | 1.072 (1.051-1.093) | <0.001 | 1.061 (1.039-1.084) | <0.001 |
| Arterial hypertension | 0.752 (0.585-0.968) | 0.027 | 0.784 (0.583-1.055) | 0.109 |
| Mitral valve disease / valvular prosthesis | 0.605 (0.442-0.826) | 0.002 | 0.776 (0.564-1.067) | 0.119 |
| Renal impairment | 1.560 (1.217-1.998) | <0.001 | 1.418 (1.100-1.827) | 0.007 |
| Anemia | 1.242 (0.972-1.586) | 0.083 | 1.049 (0.800-1.377) | 0.729 |
| CHADS2 score | 1.234 (0.985-1.545) | 0.068 | 1.091 (0.822-1.448) | 0.546 |
| CONUT | 1.088 (1.041-1.138) | <0.001 | 1.051 (1.000-1.103) | 0.049 |

Abbreviations: CI, confidence interval; CONUT, Controlling Nutritional Status; HR, hazard ratio.

**Figure legends**

Figure 1. Flow diagram of patient inclusion.

Abbreviation: AF, atrial fibrillation; CONUT, Controlling Nutritional Status.

Figure 2. Kaplan-Meier survival curve

Figure 1

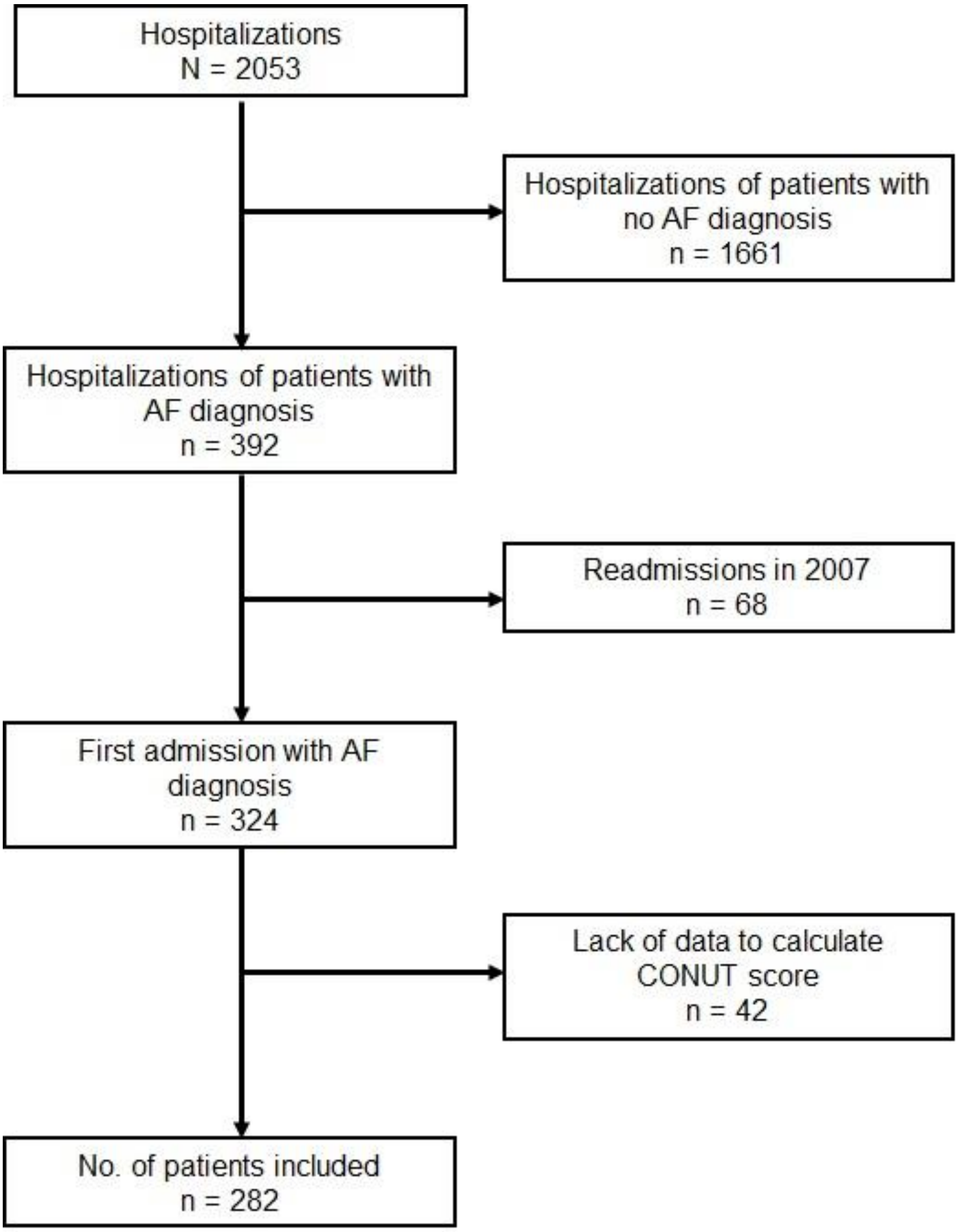
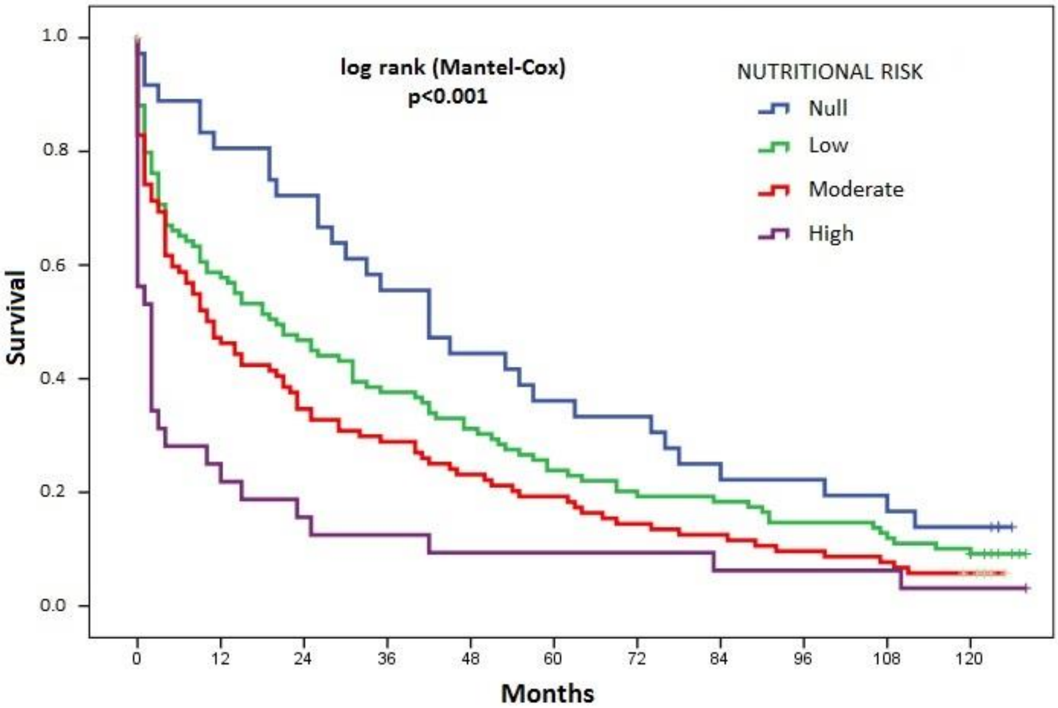

Hospitalizations
N = 2053
Hospitalizations of patients with no AF diagnosis
n = 1661
Hospitalizations of patients with AF diagnosis
n = 392
Readmissions in 2007
n = 68
First admission with AF diagnosis
n = 324
Lack of data to calculate CONUT score
n = 42
No. of patients included
n = 282

Figure 2



log rank (Mantel-Cox)
p<0.001
NUTRITIONAL RISK
Null
Low
Moderate
High
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Months