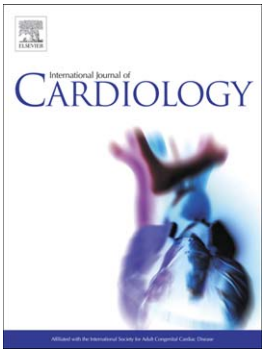

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Combining heart rate and systolic blood pressure to improve risk stratification in older patients with heart failure: Findings from the RICA Registry.

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Abstract

Objectives: Heart rate (HR) and systolic blood pressure (SBP) are independent prognostic variables in patients with heart failure (HF). We evaluated if combining HR and SBP could improve prognostic assessment in older patients.

Methods: Variables associated with all-cause mortality and readmission for HF during 9 months of follow-up were analyzed from the Spanish Heart Failure Registry (RICA). HR and SBP values were stratified in three combined groups.

Results: We evaluated 1551 patients, 82 years and 56% women. Using HR strata of <70 and >= 70 bpm we found mortality rates of 9.8 and 13.6%, respectively (hazard ratio 1.0 and 1.35). For SBP >=140, 120-140 and <120 mmHg, mortality rates were 8.2, 10.4 and 20.3%. respectively (hazard ratio 1.0, 1.34 and 2.76). Using combined strata of HR < 70 bpm and SBP >= 140 mmHg (n=176; low-risk), HR <70 and SBP <140 + HR >= 70 and SBP < 120 (n=1089; moderate-risk) and HR >= 70 and SBP < 120 (n=286; high-risk) we found mortality rates of 4.5%, 11.0% and 24.0%, respectively. Multivariate Cox regression for all-cause mortality shows for low-, middle- and high-risk groups was 1 (reference), 1.93 (95% CI: 0.93 – 3.99, p = 0.077) and 4.32 (95% CI: 2.04 - 9.14, p < 0.001). BMI, NYHA, MDRD, hypertension and sodium were also independent prognostic factors.

Conclusions

The combination provides better risk discrimination than use of HR and SBP alone and may provide a simple and reliable tool for risk assessment for older HF patients in clinical practice.

Keywords: Heart failure. Mortality. Systolic blood pressure. Heart rate. RICA registry. Prognosis.

Introduction

Heart failure (HF) is a growing public health problem with high prevalence, morbidity and mortality especially in older patients [1]. A major challenge in the management of HF is the availability of reliable and simple tools that enable patients and physicians to have a realistic expectation of prognosis, and to guide treatment options. A number of risk models have been proposed obtained mostly through observational studies or clinical trials in patients with systolic HF less than 70 years[2-8]. We previously developed a risk model from the SENIORS dataset, based on widely available clinical and laboratory variables to predict prognosis in ambulant HF more than 70 years [9], and have recently validated its usefulness in the RICA register of elderly patients with acute HF and mostly preserved ejection fraction [10].

Heart rate (HR) and systolic blood pressure (SBP) are powerful prognostic factors. Increased HR or lower SBP are independently associated with higher risk of morbidity and mortality [11, 12]. As HR and SBP are established as important prognostic variables, combining these factors could improve risk assessment compared to using them individually. We assessed the value of the combination of SBP and HR in the prognostic stratification of elderly patients with heart failure in a “real world|” clinical setting.

Methods

Patients were included from the multicentre prospective RICA registry, coordinated by the Working Group of Heart Failure of the Spanish Society of Internal Medicine [12, 13]. This registry includes data from public and private hospitals in Spain, and was approved by the Ethics Committee of the Hospital University Reina Sofia in Córdoba. From March 2008 to September 2013, a total of 3054 patients, consecutively admitted to Internal Medicine units with acute decompensated HF from 52 centres, were enrolled. In addition to giving their informed consent, patients were recruited if they were ≥ 50 years old with HF diagnosed according to the criteria of the European Society of Cardiology [14]. Data were collected through a secure website (www.registrorica.org). The registry recorded demographic data, blood pressure, heart rate (HR), body weight and height, atrial fibrillation (AF), ejection fraction, co-morbidities, functional status, routine laboratory data, complications during admission and prescriptions at discharge. Follow-up consisted of two mandatory visits scheduled at 3 months and at 1 year, where new hospitalizations or deaths were recorded.

In this analysis we collected baseline information 3 months after discharge for acute HF to avoid clinical instability, and outcomes were evaluated in those patients ≥ 70 years old with at least a follow-up of 12 months from discharge (average of 9 months follow up). Main outcome was all-cause (AC) mortality. Secondary end-points were HF readmission or the composite of AC mortality or HF readmission.

Statistical analysis.

For SBP the cutoffs point were based on the tertiles of the sample (120 and 140 bpm) and in the case of HR the cutoff point resulted to be the same that in the BEAUTIFUL study (70 bpm) [15] to analyse the risk pattern using hazard ratios and 95% confidence

intervals (CI). We then combined HR and SBP in three clinically relevant groups: "low-risk" (HR < 70 bpm & SBP >= 140 mmHg), "moderate-risk" (HR < 70 bpm & SBP < 140 mmHg + HR >= 70 bmp & SBP >= 120 mmHg), and "high-risk" (HR >= 70 bpm & SBP < 120 mmHg). We developed Kaplan-Meier curves and Cox proportional hazard models to compare risk for each group, both in all patients and those with sinus rhythm. We constructed the following 2 Cox proportional hazard models; a) unadjusted, b) fully adjusted for age, sex, clinical status, comorbidity and medications. We included the following covariates which potentially influence the outcomes: age, sex, SBP, diastolic blood pressure (DBP), HR, NT-proBNP, sodium, beta-blocker, body mass index (BMI), New York Heart Association (NYHA) class, glomerular filtration rate measured by the modification of diet in renal disease (MDRD) formula, diabetes, digoxin, AF, left ventricular ejection fraction (LVEF), acenocumarol and haemoglobin. The multivariate analysis was performed using the stepwise model, selecting those variables with a statistical p significance < 0.10 in the univariate analysis

Statistical analysis was performed using SPSS Statistics 21.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was defined P-value less than 0.05.

Results

Patients

A total of 1551 patients were included with mean age was 82 years and 56 % were women. Patients were divided into three groups according to their risk based on the combined HR and SBP groups; low-risk (n: 176) moderate risk (n: 1089) and high-risk (n:286). At final follow-up 191 patients had died (12.3%), 191 were readmitted (12.0%), and 360 (23%) were readmitted or dead.

Baseline clinical characteristics 3 months after discharge, overall and in the combined HR & SBP strata risk subgroups are shown in Table 1. NYHA III class, AF, NT-proBNP and use of spironolactone were associated with high-risk group, while diabetes, BMI and serum sodium with low-risk group. There were no apparent differences in comorbidities, LVEF and other clinical and biological data.

Mortality using HR and SBP alone.

Using HR strata of <70 and >= 70 bpm we found mortality rates of 9.8 and 13.6%, respectively (hazard ratio 1.0 and 1.35). For SBP >=140, 120-140 and <120 mmHg, mortality rates were 8.2, 10.4 and 20.3%. respectively (hazard ratio 1.0, 1.34 and 2.76).

Mortality in the three risk groups combining HR and SBP

Using combined strata of HR < 70 bpm and SBP >= 140 mmHg (n=176; low risk), HR <70 and SBP <140 + HR >= 70 and SBP < 120 (n=1089; moderate risk) and HR >= 70 and SBP < 120 (n=286; high risk) we found mortality rates of 4.5%, 11.0% and 24.0%, respectively from 3 months to 12 months after discharge (P<0.001) (Figure 1, Table 2).

Multivariate Cox regression for all-cause mortality shows for low-, middle- and high-risk groups was 1 (reference), 1.93 (95% CI: 0.93 – 3.99, p = 0.077) and 4.32 (95% CI:

2.04 - 9.14, p < 0.001). BMI, NYHA, MDRD, hypertension and sodium were also independent prognostic factors.

There were no significant differences in readmission rates in the three groups. For the composite outcome of HF readmission or AC mortality, rates were 16%, 22% and 34% in the low-, moderate- and high-risk groups, respectively (p < 0.001), driven by differences in AC mortality (data not shown).

Mortality in the risk groups combining HR and SBP in patients with sinus rhythm.

Sinus rhythm was observed in 540 patients (35 % of total) with an overall mortality of 12%. In the low-, moderate- and high-risk groups mortality rates were 2.6%, 10% and 29% (hazard ratio 1.0, 4.0 and 15.9, respectively (p <0.001; Figure 2). The sinus rhythm group had similar results to the overall group for readmission and composite of readmission or AC mortality (data not shown).

Discussion

This is the first analysis combining information about HR and SBP in elderly patients with HF and a great percentage with preserved systolic function and atrial fibrillation, showing an improved ability to distinguish low-, moderate- and high-risk groups for all-cause mortality, compared to each one alone. Our cohort included elderly HF patients with high rates of AF and preserved ejection fraction, receiving treatments similar to other "real world" registries [16, 17]. The simplicity of this risk model could make it easier to translate into clinical practice than more complex models.

Our findings are consistent with another publication combining HR and SBP to predict mortality in HF but this was in a younger cohort (mean age 68) and sinus rhythm [17]. We provide further evidence showing that the prognostic value of combining HR and SBP is also applicable to older patients with mixed sinus rhythm and AF.

Previous studies have demonstrated the relationship of increased HR with adverse outcomes in HF [11]. The mechanisms are not entirely clear but it is possible that tachycardia with reduced myocardial contractility leads to deteriorating cardiac output. It is possible that the adverse effects of faster HR is different in sinus rhythm vs AF. In line with this, a meta-analysis of individual patients data of beta-blockers in HF has shown a lack of benefit of beta blockers in patients with AF [18]. Our study supports this finding, since the gradation of mortality risk was higher in patients with sinus rhythm.

Lower blood pressure has been also established as an adverse prognostic factor in HF [12, 19]. A plausible explanation could be poor tissue perfusion associated with impaired heart function and a worse prognosis.

In general established risk factors tracked the risk stratification gradient for HR and SBP except for diabetes and high BMI which were more frequent in the lower risk group which is different to previous observations [20-22]. High BMI is associated with a better prognosis in HF, and is also associated with diabetes and this may partially explain this observation [23].

Several risk models in HF have been developed and validated, using data from observational studies and clinical trials, but these have mostly included patients younger than 70 years with systolic dysfunction [24 - 27]. Since HF is a disease predominantly affecting the elderly, it would be of importance to have a risk stratification tool specific for this patient population. Using the SENIORS cohort, we generate a risk model with a number of clinical and laboratory variables in stable HF patients older than 70 years, that was validate in another RICA registry study [9, 10, 29]. Our study using combining only two variables, HR and SBP, might add value because it is simpler to use in clinical practice.

Limitations

The aim was to include HF patients admitted to general internal medicine wards but some of the sicker patients were unable to give consent which could have introduced a selection bias. The moderate-risk group is much larger than the lower and high risk groups, but we did not think that it could have significantly influence the results. The HR and SBP thresholds for each group were selected, arbitrarily, based on previous studies, however they work well in our analysis. Finally we have not performed an internal validation exercise e.g. partitioning the cohort into derivation and validation sample. Previous experience shows that this approach overestimates the validity of a

risk prediction model and the only reliable way to test the usefulness of the model is to apply it to a separate cohort ideally prospectively [9].

Conclusions:

These results suggest that an approach of combining HR and SBP may provide a simple and reliable clinical tool for mortality risk assessment in HF that could be used in clinical practice in elderly patients. This approach could also be tested in other cohorts and against existing risk models.

Appendix:

RICA Registry members:

Aramburu O, Arévalo-Lorido JC, Arias JL, Casado J, Cerqueiro JM, Conde A, Díez-Manglano J, Formiga F, González-Franco A, Guisado E, Llácer P, López-Castellanos G, Manzano L, Martín-Ezquerro A, Montero-Pérez-Barquero M, Muela A, Quirós R, Ruiz-Ortega R, Salamanca MP, Sánchez-Moruno M, Serrado A, Trullàs JC.

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Tables and figures.

Table 1. Baseline characteristics at 3 months after Hospital discharge in the overall and in the subgroups according strata risk

Variables	***Total*** (N = 1551)	Low-risk (HR < 70 & SBP >= 140) (N=176)	Moderate-risk (HR < 70 & SBP < 140) + (HR >=70 & SBP>=120) (N=1089)	High-risk (HR >= 70 & SBP < 120) (N=286)	***p-value***
Age, years (M±SD)	81.5±5.5	81.8±5.6	81.4±5.4	81.8±5.9	0.398
Sex, Women, n (%)	861 (56%)	93 (53%)	632 (58%)	136 (48%)	0.005
BMI (M±SD)	28.4±6.5	29.0±5.8	28.6±6.9	27.2±5.0	0.002
SBP, mmHg (M±SD)	130.8±21.1	153.3±13.3	133.9±17.9	105.2±9.2	<0.001
DBP, mmHg (M±SD)	71.5±12.7	74.9±11.6	73.1±12.7	63.1±9.4	<0.001
HR, bpm/min (M±SD)	75.2±13.7	61.6±5.9	75.3±13.3	83.1±11.9	<0.001
NYHA I, n (%)	206 (13%)	22 (13%)	151 (14%)	33 (12%)	0.545
HYHA II, n (%)	905 (59%)	112 (64%)	647 (60%)	146 (51%)	0.012
NYHA III, n (%)	408 (26%)	36 (20%)	274 (25%)	98 (34%)	0.001
NYHA IV, n (%)	25 (1.6%)	6 (3.4%)	11 (1.0%)	8 (2.8%)	0.014
Etiology					
Ischemic, n (%)	410 (26%)	58 (33%)	272 (25%)	80 (28%)	0.069
Hypertensive, n (%)	630 (41%)	72 (41%)	467 (43%)	91 (32%)	0.003
Valvulopathy, n (%)	285 (18%)	29 (16%)	193 (18%)	63 (22%)	0.196
Others, n (%)	225 (14.5%)	17 (9.7%)	156 (14%)	52 (18%)	0.039
Charlson index (M±SD)	2.8±2.4	2.9±2.4	2.7±2.3	2.9±2.5	0.322
Barthel index (M±SD)	83.9±19.9	84.7±21.2	84.2±19.6	82.5±20.3	0.424
Diabetes, n (%)	663 (43%)	86 (49%)	475 (44%)	102 (36%)	0.012
Hypertension, *n (%)*	1.343 (87%)	158 (90%)	959 (88%)	226 (79%)	<0.001
Prior MI, n (%)	333 (21%)	43 (24%)	220 (20%)	70 (24%)	0.181
COPD, n (%)	395 (26%)	44 (25%)	256 (24%)	95 (33%)	0.004
AF, n (%)	866 (56%)	82 (47%)	605 (56%)	179 (63%)	0.004

LVEF,% (M±SD)	51.9±14.9	52.5±14.3	52.5±14.7	49.3±15.7	0.005
LVEF < 40%, n (%)	322 (21%)	31 (18%)	219 (20%)	72 (26%)	0.093
LVH, n (%)	400 (26%)	50 (30%)	286 (27%)	64 (23%)	0.224
RBBB, *n (%)*	190 (12%)	23 (13%)	136 (13%)	31 (11%)	0.690
LBBB*, n (%)*	307 (20%)	33 (19%)	199 (18%)	75 (26%)	0.012
Laboratory (M±SD)					
Hemoglobin (mg/dL)	12.4±3.2	13.0±8.2	12.3±1.7	12.5±1.7	0.057
Creatinine (mg/dL)	1.3±0.6	1.3±0.6	1.3±0.6	1.4±0.7	0.064
Sodium (mEq/L)	140.0±4.0	140.8±3.9	139.9±3.9	139.6±4.1	0.006
GFR(mL/min/1.73 m2)	57.4±24.0	55.9±21.5	57.2±24.1	58.8±24.9	0.424
GFR <30, n (%)	83 (5.4%)	11 (6.3%)	56 (5.2%)	16 (5.6%)	0.819
GFR 30-59, n (%)	386 (25%)	51 (29%)	266 (24%)	69 (24%)	0.414
GFR >=60, n (%)	112 (7.2%)	12 (6.8%)	79 (7.3%)	21 (7.3%)	0.974
BNP (pg/mL). n = 101	655±935	587±922	563±893	974±1.040	0.196
NT-proBNP. n = 350	3.672±5.822	2.786±2.863	3.452±5.233	5.001±8.458	0.092
Treatment:					
Digoxin, n (%)	370 (24%)	36 (20%)	256 (24%)	78 (27%)	0.220
Loop diuretic, n (%)	1.366 (88%)	160 (91%)	949 (87%)	257 (90%)	0.211
Beta-blockers, n (%)	859 (55%)	89 (51%)	610 (56%)	160 (56%)	0.394
ACEI, n (%)	698 (45%)	80 (45%)	481 (44%)	137 (48%)	0.524
ARBs, n (%)	459 (30%)	53 (30%)	331 (30%)	75 (26%)	0.383
Anticoagulants directs, n (%)	63 (4.1%)	7 (4.0%)	39 (3.6%)	17 (5.9%)	0.197
Acenocumarol, n (%)	750 (48%)	76 (43%)	526 (48%)	148 (52%)	0.201
Spironolactone, n (%)	420 (27%)	36 (20%)	278 (26%)	106 (37%)	<0.001
CCB, n (%)	294 (19%)	44 (25%)	204 (19%)	46 (16%)	0.056
Readmission after 9-months, n (%)	191 (12%)	21 (12%)	129 (12%)	41 (14%)	0.515
Readmission or mortality at 9-months	360 (23%)	29 (16%)	235 (22%)	96 (34%)	<0.001

Mortality at 9-months	191 (12.3%)	8 (4.5%)	115 (11%)	68 (24%)	<0.001

SD: standard deviation; BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; NYHA: New York Heart Association; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LBBB: left branch bundle block; RBBB: right branch bundle block; GFR: glomerular filtration by MDRD: modification of diet in renal disease; ACEI: angiotensin converting enzyme inhibitor; ARBs: angiotensin receptor blockers; CCB: calcium cannel-blockers.

Table 2. All-cause mortality for different combinations of SBP and HR during nine months of follow-up

	SBP (<120 mmHg)	SBP (120-140 mmHg)	SBP (>=140 mmHg)
HR (<70 bpm)	12.9% Moderate-risk group (n =132)	12.3% Moderate-risk group (n = 204)	4.5% Low-risk group (n = 176)
HR (>=70 bpm)	23.8% High-risk group (n = 286)	9.5% Moderate-risk group (n = 380)	9.9% Moderate-risk group (n = 373)

SBP: systolic blood pressure; HR: heart rate. BPM: beats per minute

Tabla 3. Univariate and multivariate analysis. Proportional hazards model: all-cause mortality at 9-months.

	Univariate		Multivariate	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
Low-risk group*	1 (ref.)		1 (ref.)	
Moderate-risk group**	2.29 (1.12-4.69)	0.023	1.93 (0.93-3.99)	0.077
High-risk group***	5.76 (2.77-11.99)	<0.001	4.32 (2.04-9.14)	<0.001
Age	1.05 (1.02-1.08)	<0.001		
Beta blocker	0.71 (0.54-0.95)	0.019		
BMI	0.93 (0.91-0.96)	<0.001	0.92 (0.89-0.95)	<0.001
NYHA II	0.43 (0.32-0.58)	<0.001		
NYHA III	2.56 (1.93-3.40)	<0.001	2.67 (1.94-3.68)	<0.001
NYHA IV	7.72 (4.39-13.58)	<0.001	16.78 (9.03-31.17)	<0.001
DBP	0.98 (0.97-0.99)	<0.001		
MDRD	0.98 (0.98-0.99)	<0.001	0.99 (0.98-1.00)	<0.001
Diabetes	1.07 (0.80-1.42)	0.648		
Digoxin	1.27 (0.93-1.74)	0.131		
AF	0.91 (0.68-1.21)	0.500		
Sex (Man)	1.28 (0.97-1.70)	0.086		
LVEF < 40%	1.43 (1.04-1.96)	0.029		
Anticoagulation	0.72 (0.27-1.94)	0.518		
Hemoglobin	0.81 (0.74-0.88)	<0.001		
Hypertension	1.51 (0.92-2.49)	0.104		
Sodium	0.91 (0.88-0.94)	<0.001	0.92 (0.90-0.95)	<0.001
CCB	0.95 (0.66-1.38)	0.804		

HR: hazard ratio; CI: confidence interval; * heart rate < 70 bpm and systolic blood pressure >= 140 mmHg; **heart rate < 70 bpm & systolic blood pressure < 140 mmHg and heart rate >=70 bpm & systolic blood pressure >=120 mmHg; ***heart rate >=70 bpm and systolic blood pressure < 120 mmHg; BMI: Body mass index; DBP: diastolic blood pressure; NYHA: New York

Heart Association; MDRD: modification of diet in renal disease; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; CCB: calcium cannel-blockers.

Legend of the Figures:

Figure 1: Kaplan-Meier curve for all cause mortality in the whole low-risk (HR <70 bpm & SBP> 140 mmHg), moderate-risk (HR 70 - 80 bpm & SBP 140 – 120 mmHg), and high-risk groups (HR > 80 bpm and SBP < 120 mmHg); HR: heart rate; SBP: systolic blood pressure;

Figure 2: Kaplan-Meier curve for all cause mortality **in patients with sinus rhythm;** low-risk group (HR <70 bpm & SBP> 140 mmHg), moderate-risk group (HR 70 - 80 bpm & SBP 140 – 120 mmHg), and high-risk group (HR > 80 bpm and SBP < 120 mmHg) HR: heart rate; SBP: systolic blood pressure.

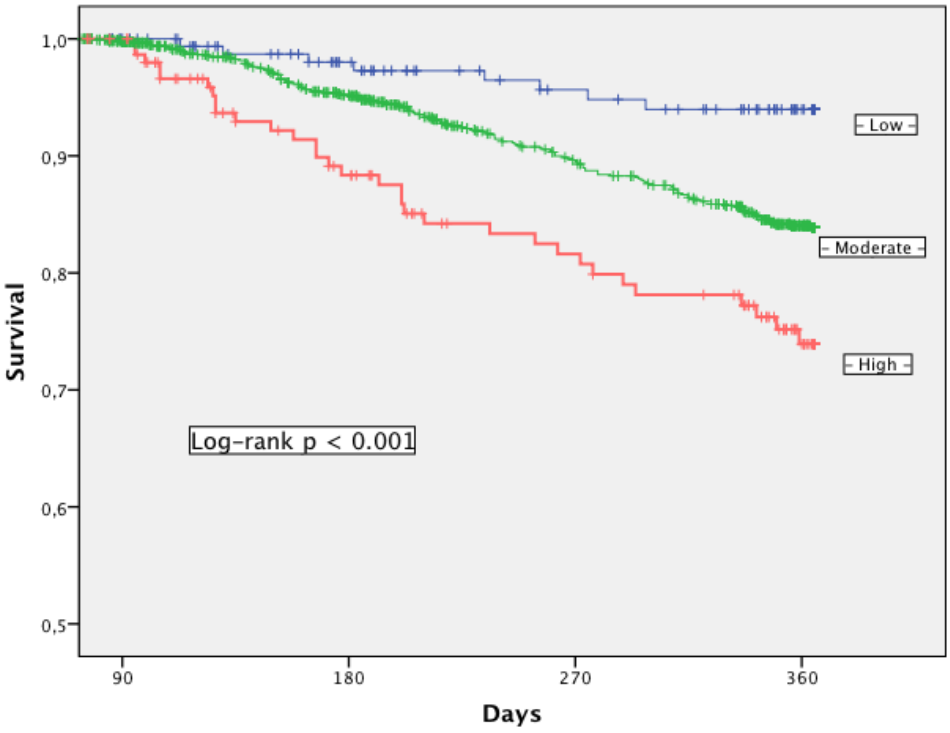

Figure 1

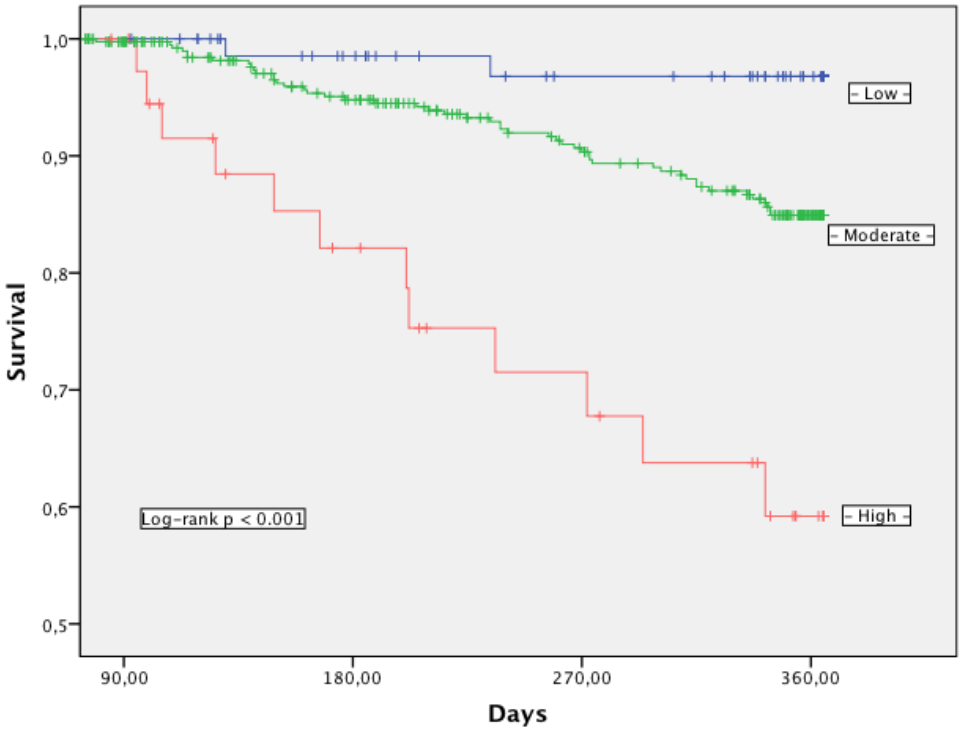

Figure 2