Impact of Elevated Systolic Arterial Pulmonary Pressure on Short and Long Term All-Cause Mortality After Acute Myocardial Infarction in the Elderly

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Research Article

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Abstract

Background: Reduced left ventricular ejection fraction (LVEF) is associated with increased mortality after myocardial infarction (MI). However, the prognostic impact of elevated systolic pulmonary artery pressure (sPAP) in the elderly patients with MI is not well studied.

Purpose: We aimed to study the impact of elevated sPAP on one- and five-year all-cause mortality after acute MI in patients 80 years of age and older.

Methods: Of a total number of 353 patients(≥80 years old)that were hospitalized with acute coronary syndrome, 162 patients presenting with acute MI and with available data of sPAP on echocardiography were included and followed-up for 5 years. The survival analyses were performed using Cox-Regression models adjusted for conventional risk factors including LVEF.

Results: Altogether 65 of 162 patients (40%) had ST-segment elevation MI, and 121 (75%) of patients were treated with percutaneous coronary intervention in the acute phase. Echocardiography during the admission revealed that 78 patients (48%) had a LVEF ≤ 45% and 65 patients (40%) had a sPAP ≥40 mmHg.

After one and five years of follow-up, 23% (n=33) and 53% (n=86) of patients died, respectively. A multivariable Cox-Regression analysis showed that the elevated sPAP was an independent predictor of increased mortality in both one and five years after acute MI; HR of 3.4(95%, CI 1.4-8.2, P 0.006) and HR of 2.0(95%, CI 1.2-3.4, P 0.004) respectively, whereas LVEF did not show any statistically significant impact, neither on one- nor on five-year mortality (HR 1.4, 95% CI 0.8-2.4, p=0.158) and (HR 1.3, 95% CI 0.6-2.9, p=0.469), respectively.

Conclusion:

Elevated sPAP is an independent risk factor for one- and five-year all-cause mortality in patients with acute MI and it seems to be a better prognostic factor for death than LVEF. The risk of all-cause mortality in MI patients increased with increasing sPAP.

Introduction

The risk factor with highest association to increased mortality and morbidity after acute myocardial infarction (MI) is post-MI heart failure (HF) in all age groups, specifically in the elderly patients[1–9]. Previous studies have identified several risk factors for impaired survival rate after MI, including reduced left ventricular ejection fraction (LVEF) as a marker for structural left ventricular systolic dysfunction[10–13].Mutlak et al preformed a prospective longitudinal observational study designed to determine predictors of post myocardial infarction HF, and they demonstrated that 44% of the patients had systolic pulmonary artery pressure (sPAP) > 35 mmHg after acute MI. In addition, elevated sPAP at the index admission was a useful marker in unmasking latent subclinical HF and predicting the development of overt HF[14].

sPAP is considered to be a hemodynamic marker of left ventricular dysfunction[15].

.To the best of our knowledge, the prognostic impact of elevated systolic sPAP on mortality, specifically in the elderly is not studied. Therefore, we aimed to study the impact of elevated sPAP on short-and long-term all-cause death after acute MI in elderly patients ≥ 80 years.

Methods

Study cohort

Three hundred and fifty-three patients aged ≥80 years hospitalized due to acute coronary syndrome at the two major Cardiology departments at Sahlgrenska University Hospital (SU), (SU/Sahlgrenska and SU/Östra), affiliated with the University of Gothenburg during 2006–2007 were included consecutively. All patients presented with acute myocardial infarction and examined with echocardiography with adequate data on sPAP were included in the study and followed up regarding death for 5 years(n = 162). Treatment with percutaneous coronary intervention (PCI) or not was based on a pure clinical decision made by the cardiologist in charge. All PCIs were performed at a joint PCI center for both hospitals. Patients were retrospectively identified from the hospital patient registry. Patients from other hospitals who were referred to SU only for PCI were excluded due to incomplete follow-up data. The study protocol was approved by the Ethical Committee at the University of Gothenburg.

Echocardiography

All echocardiography examinations were performed at the department of Clinical Physiology at Sahlgrenska University Hospital by trained echo technicians or physicians according to standardized protocol. Echocardiography data were retrieved from the echocardiographic reports. LVEF was measured using Simpson biplane or when not feasible by visual estimate. Left atrial area was measured in apical 4 chamber view. LV filling pressure was qualitatively estimated by pulsed wave Doppler of mitral and pulmonary vein flow as increased or normal[16]. Mitral regurgitation was analyzed by colour and continuous wave Doppler and considered present when there more than trace regurgitation. Aortic stenosis was considered present when the peak gradient was ≥ 25 mmHg. Reference values were based on an examined local healthy population from which regression equations had been constructed based on body surface area, weight and age. The equations were incorporated in a spreadsheet, resulting in a z-score and an increased parameter-value for an individual was defined as a z-score ≥ 2.0. The reference limits where thus individually adjusted for each patient.

Estimation of systolic pulmonary artery pressure

Systolic pulmonary artery pressure (sPAP) was estimated by echocardiography from the tricuspid valve regurgitant jet velocity using the modified Bernoulli equation $4v^2$ plus right atrial pressure[17–18]. Special care was taken to align the Doppler cursor with the tricuspid regurgitation jet. Right atrial (RA) pressure was estimated from characteristics of the inferior vena cava (IVC); based on the diameter and the

respiratory variation in the diameter of the IVC: an IVC diameter ≤21 mm that collapses >50% with a sniff suggested a a normal RA pressure of 5 mmHg, whereas an IVC diameter ≤21 mm that collapses<50% or an IVC diameter >21 mm that collapses >50% with a sniff regarded as an intermediate value, 10 mmHg. AIVC diameter >21 mm that collapses <50% with a sniff or <20% on quiet inspiration regarded as a high RA pressure of 15 mmHg.

Statistics

Categorical variable were described as percentages and compared using chi-square test or Fisher exact as appropriated. Continuous variables were described as means ± standard deviation (SD) and compared using independent sample test or One-way analysis of covariance. To adjust for the underlying baseline characteristics and to analyze for probable association between different levels of the sPAP and mortality, the cohort was analyzed using multivariable Cox proportional-hazard regression models analyzing time to event. Kaplan-Meier analysis and univariable Cox proportional-hazard regression analysis were used to build multivariable models. In order to identify the lowest cut off level of the sPAP, over which increasing sPAP was associated with increased mortality multivariable models were built for a sPAP level as low as 30 mmHg and upward with 5 mmHg intervals. All collected parameters were included in the univariable models. Parameters with significant results (p <.05) from the univariable models and without crossing Kaplan-Meier curves were included in the multivariable models. Multivariable Cox regression models were built for the different levels of sPAP. The multivariable Cox models were assessed for proportional hazard assumption for covariates graphically with adjusted log minus log curves. The hazard ratios (HRs) with confidence intervals (CIs) and p-values were presented. All statistical analyses were performed using SPSS 22 statistical software.

P-value <0.05 was regarded as statistically significant.

Laboratory analysis.

All laboratory variables were analyzed, according to routine protocol, by the Clinical Chemistry Laboratory at Sahlgrenska University Hospital. Cockcroft–Gault formula was used to estimate the glomerular filtration rate (eGFR) in ml/min/1.73m^2.

Clinical outcome data

The primary endpoints were one-and five-year all-cause mortality after acute myocardial infarction. Data on time of death were obtained from the Swedish Cause of Death registry which includes all deaths of persons registered in Sweden.

Results

Clinical characteristics

The clinical characteristics of the 66 patients with a sPAP ≥40mmHg and of the 96 patients with a sPAP<40mmHg are shown in Table 1.

Table 1
Demographic and clinical characteristics of the study patients, comparing patients with systolic arterial pulmonary pressure (sPAP) ≧40 mmHg and sPAP <40 mmHg

	sPAP≧40 mmHg(n=66)	sPAP <40 mmHg (n=96)	P-value
Demographics Age, year	84.4±2.8	83.7±2.8	0.089
Gender, male	32(48.5)	58(60.4)	0.133
Weight, kg	70.7±15.4	73.2±12.0	0.265
Height, cm	167.6±22.2	169.5±8.8	0.452
BMI, kg/m^2	23.6±3.7	25.4±3.8	0.004
Smoking, yes	6(9.5)	5(5.3)	0.321
Clinical Characteristics STEMI, yes	28(42.4)	38(39.6)	0.421
Non-STEMI, yes	31(47.0)	48(50.0)	0.413
PCI, yes	44(66.7)	77(80.2)	0.051
Heart rate,bpm	81.8±16.7	80.8±29.7	0.881
Systolic BP, mmHg	145.6±28.6	150.4±26.6	0.296
Diastolic BP, mmHg	85.8±16.1	82.8±16.1	0.271
Laboratory findings Hemoglobin, g/L	129.8±15.2	131.7±17.0	0.478
eGFR, ml/min/1.73m^2	49.1±19.7	50.3±18.3	0.682
Creatinine, umol/L	110.0±104.2	110.7±77.6	0.961
Comobidities Atrial fibrillation, yes	17(27.0)	17(17.7)	0.153
History of heart failure, yes	14(23.0)	17(17.7)	0.355
Hypertension, yes	35(53.0)	40(41.7)	0.103
Diabetes, yes	13(21.0)	16(17.6)	0.374

BMI, body mass index. STEMI, ST-elevation myocardial infarction. Non-STEMI, Non-ST-elevation myocardial infarction. PCI, percutaneous coronary intervension. BP, blood pressure. eGFR, estimated glomerular filtration rate. ACEI, angiotensin converting enzyme inhibitors. ARB, angiotensin receptor blockers.

	sPAP≧40 mmHg(n=66)	sPAP <40 mmHg (n=96)	P-value
Hyperlipidaemia, yes	9(13.8)	8(8.3)	0.195
Previous stroke, yes	11(19.6)	10(11.0)	0.284
Medications β- Blockers, yes	34(51.5)	51(56.7)	0.317
ACEI/ARB, yes	20(30.3)	26(27.1)	0.517
diuretics, yes	16(24.2)	19(20.9)	0.378
Calcium channel blocker, yes	14(21.2)	36(39.1)	0.017
Statins, yes	11(16.7)	21(22.6)	0.238
Digoxin, yes	9(15.0)	10 (10.8)	0.296

BMI, body mass index. STEMI, ST-elevation myocardial infarction. Non-STEMI, Non-ST-elevation myocardial infarction. PCI, percutaneous coronary intervension. BP, blood pressure. eGFR, estimated glomerular filtration rate. ACEI, angiotensin converting enzyme inhibitors. ARB, angiotensin receptor blockers.

Patients with sPAP ≥40mmHg had lower BMI (23.6±3.7 vs. 25.4±3.8 kg/m2) and were less frequently treated with calcium channel blocker (21.2% vs.39.1%) compared to patients with a sPAP<40mmHg.There were no significant differences in gender, previous stroke or in number of patients treated with PCI, betablockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, diuretics, statins or digoxin.

Echocardiographic findings

The lowest cut-off level of sPAP over which increasing sPAP was associated with increased mortality rate was 40 mmHg. Patients with sPAP ≥40mmHgmore often had reduced LVEF (41.7% vs. 49.5%),elevated left ventricular filling pressure (43.9% vs. 21.6%), dilated left atrium (54.2% vs. 33.0%), mitral valve regurgitation (56.9% vs. 25.0%), tricuspid valve regurgitation(13.8% vs. 4.4%) and aortic valve stenosis (27.6% vs. 13.3%)compared to patients with sPAP <40 mmHg, Table 2.

Table 2
Echocardiographic characteristics of study patients, comparing patients with systolic arterial pulmonary pressure (sPAP) ≥40 mmHg and sPAP <40 mmHg

	sPAP≧40 mmHg(n=66)	sPAP <40 mmHg (n=96)	P-value
Left ventricular ejection fraction, %	41.7±10.6	49.5±10.4	<0.001
Elevated left ventricular filling pressure, yes	29(43.9)	16(21.6)	<0.001
Dilated left ventricle, yes	16(25.4)	15(16.5)	0.125
Dilated left atrium, yes	32(54.2)	29(30.2)	0.008
Mitral valve regurgitation≥ grad 1/4, yes	37(56.9)	23(25.0)	<0.001
Tricuspid valve regurgitation≥ grad 1/4, yes	9(13.8)	4(4.4)	0.036
Aortic valve stenosis, yes	16(27.6)	11 (13.3)	0.029

Outcome data

After 5-years of follow-up 86 patients died (all-cause mortality: 53.0%) while the 1-year all-cause mortality was 23.4% (38deaths). Patients with sPAP ≥40mmHg had a higher 5-year mortality rate, of 69.6% (46 events) and 1-year mortality rate, of 34.8%(23 events), compared to patients with sPAP<40 mmHg, 41.6% (40 events) (p<0.001) for 5-year mortality rate and 15.6% (15 events) (p=0.004) for 1-year mortality rate.

Association between sPAP and 1-year mortality

Table 3 illustrated the association between sPAP and 1-year all-cause mortality.

Table 3
Univariate and multivariable Cox-regression analysis of factors for association with1-year all-cause mortality.

Variables	Univariable			Multivariable		
	HR	(95%CI)	p	HR	(95%CI)	p
Age, year	1.03	0.92-1.15	0.602	0.97	0.85-1.11	0.639
Gender, male	0.79	0.42-1.49	0.471	0.97	0.31-0.90	0.518
sPAP ≥ 40mmHg	2.46	1.26-4.62	0.008	2.63	1.19-5.84	0.017
LVEF≤ 45%	1.71	0.88-3.29	0.111	1.34	0.61-2.93	0.469
Diabetes Mellitus	1.26	0.57-2.75	0.570	1.17	0.49-2.77	0.727
Treatment with percutaneous coronary intervention (PCI)	0.56	0.29-1.09	0.086	0.72	0.33-1.6	0.424
Atrial fibrillation	0.89	0.39-2.05	0.791	0.78	0.31-1.96	0.601
Estimated glomerular filtration rate ≤35 ml/min	1.94	0.96-3.95	0.067	1.99	0.88-4.48	0.097

HR, Hazard ratio. sPAP, systolic pulmonary arterial pressure. LVEF, left ventricular ejection fraction.

Multivariable analysis demonstrated an association between elevated sPAP and increased 1-year all-cause mortality rate with a cutoff level at >40 mmHg (HR 2.63, 95%CI 1.19-5.84, p=0.017), Figure 1.

As a continuous variable, every increase of 5 mmHg in sPAP was associated with 2.5% increased relative risk for all-cause mortality (HR = 1.02, 95% of CI 1.00–1.05 and p=0.05*)*.

Association between s PAP and 5-year mortality

Table 4 illustrated the association between sPAP and 5-year mortality.

Table 4
Univariate and multivariable cox-regression analysis of factors for association with 5-year all-cause mortality.

Variables	Univariable			Multivariable		
	HR	(95%CI)	p	HR	(95%CI)	p
Age, year	1.09	1.01-1.17	0.021	1.02	0.93-1.11	0.693
Gender, male	0.97	0.64-1.49	0.891	1.9	1.1-3.2	0.019
sPAP ≥ 40mmHg	2.21	1.44-3.38	<0.001	2.08	1.25-3.44	0.005
LVEF≤ 45%	1.26	0.82-1.92	0.293	1.42	0.85-2.438	0.158
Diabetes Mellitus	1.92	1.17-3.14	0.010	1.73	1.01-2.96	0.048
Treatment with percutaneous coronary intervention (PCI)	0.445	0.29-0.69	<0.001	0.48	0.29-0.82	0.004
Atrial fibrillation	2.32	1.47-43.67	<0.001	2.04	1.22-3.40	0.006
Estimated glomerular filtration rate ≤35 ml/min	2.19	1.36-3.54	0.001	2.35	1.37-4.01	0.006

HR= Hazard ratio. sPAP= systolic pulmonary arterial pressure. LVEF= left ventricle ejection fraction.

Cox proportional-hazard regression multivariable models adjusted for important clinical variables and all significant variables from univariable models demonstrated an association between elevated sPAP and increased all-cause mortality rate with a cutoff level at ≥40 mmHg (HR =2.08, 95%CI 1.25-3.44, p=0.005, Figure 2).

As a continuous variable, every increase of 5 mmHg in sPAP was associated with 3% increased relative risk for all-cause mortality (HR = 1.03, 95% of CI = 1.01–1.04 and p = 0.003*)*. Also male gender (HR 1.9, 95%CI 1.1-3.2, p=0.019), atrial fibrillation (HR 2.04, 95%CI 1.22-3.40, p=0.006) and eGFR≤35 ml/min/1.73m^2 (HR 2.35, 95%CI 1.37-4.01, p=0.006) were associated with increased 5-year mortality rate. Treatment with percutaneous coronary intervention were associated with decreased 5-year mortality, (HR 0.48, 95%CI 0.29-0.82, p=0.004).

Discussions

The results of the present study demonstrate an association between elevated sPAP levels and one as well as five-year mortality after acute MI in a cohort of elderly patients all 80 years of age or older at the baseline. After multivariable adjustment, sPAP with a cutoff level at ≥40 mmHg was a strong independent predictor witha2-fold increase risk for both one- and five-year all-cause mortality. Every increase of 5 mmHg in sPAP was associated with 2.5% and 3% increased relative risk for one- and five-year all-cause mortality, respectively.

Interestingly, sPAP was a stronger predictor for both short- and long-term mortality compared with LVEF which did not show any statistically significant impact in the Cox-regression multivariable models.

To our knowledge, the present study is the first to analyze the impact of sPAP on one- and five-year prognosis after acute MI in an elderly patient sample. A recent study has demonstrated an association between elevated sPAP and prognosis 6-months after MI[19]. However, in that study the patients were much younger compared with the patients in our study, with a mean age of years 64 years. However, the results of our study and the study published of Fan et al[19] indicate the need for further randomized studies regarding the impact of sPAP on the prognosis after acute MI. Theoretically, as secondary preventive managements, treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors might improve the prognosis.

The multivariable Cox proportional-hazards regression models found sPAP≥ 40 mmHg to be the only independent predictor for the one-year all-cause mortality after MI. Whereas, independent predictors of increased five-year all-cause mortality, beside the sPAP≥40 mmHg, were also diabetes mellitus, treatment with PCI, atrial fibrillation and eGFR≤35 ml/min. These results indicate that patients with elevated sPAP have a high risk for impaired survival already during the first year and these patients must be identified and tailored for secondary intervention managements as soon as possible. Interestingly, only 30% of patients with sPAP≥ 40 mmHg were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and only 51% with beta-blockers.

Pathophysiological mechanisms of elevated pulmonary artery pressure after acute MI.

Acute myocardial infarction may results in decreased left ventricular (LV) function and thereby increasing LV filling pressures. The increased LV filling pressures transmits backwards into the lung circulation, leading to an increase in the pulmonary artery pressure (PAP). The elevated PAP is frequently associated with a reactive increase in pulmonary vascular resistance (PVR), resulting in a further increase in PAP[20]. Thus, the pulmonary circulation after MI is characterized by elevated PAP and PVR, which increases the afterload of the right ventricle (RV) and may contribute to RV dysfunction and eventually RV failure[21].

The mechanism underlying the pulmonary vasoconstriction after MI is not completely understood, but may involve alterations in angiotensin-II[22] as well as endothelial dysfunction[20].

The pulmonary vascular endothelium is the predominant site for the angiotensin-converting enzyme which hydrolyses angiotensin-I to angiotensin-II. The pulmonary circulation is very sensitive to the

vasoconstrictive and proliferative effects of Angiotensin-II[23–24], hence, after MI develops progressive PHT and RVH with important pulmonary structural remodeling characterized by myofibroblasts proliferation and a vicious circle of cardiopulmonary dysfunction[25].

One other reason for elevated PAP level could be ischemic mitral regurgitation, which is a common complication after MI and often associated with poor prognosis[26–27].

The above mentioned evidence and mechanisms indicate that patients with elevated sPAP after acute MI might benefit from tailored and intensive treatment with angiotensin enzyme inhibitors and angiotensin receptor blockers, in order to prevent the development of post MI heart failure and thereby to improve survival.

Strengths and limitations

The data in the present study was collected from the medical records from any of the two largest cardiology centers in Gothenburg. All the echocardiography examinations were performed of echocardiography specialist at the department of clinical physiology. However, in this observational study, medical records were studied retrospectively. In addition, despite our efforts in collecting as much information as possible, some patient data were not available. Besides, despite adjustment, we cannot rule out residual confounding from unmeasured variables.

Furthermore, sPAP estimation by echocardiography includes an approximation of the right atrial pressure using inferior vena cava width and its respiratory variation. The gold standard would be right heart catheterization for measurement of pulmonary artery pressure, data which was not available in our present study.

Clinical implication

In clinical practice sPAP after acute MI can be used as a marker of poor prognosis and a target in secondary preventive managements in order to reduce the mortality and morbidity.

Conclusions

Elevated sPAP was an independent risk factor for one- and five-year all-cause mortality in patients with acute MI and seems to be a better prognostic factor for mortality than LVEF. We found that the risk of all-cause mortality in patients with MI increased with increasing sPAP.

List Of Abbreviations

LVEF, left ventricular ejection fraction. LV, Left ventricle. RA, right atrium. sPAP, Systolic pulmonary artery pressure. MI, Myocardial infarction. STEMI, ST-elevation myocardial infarction. Non-STEMI, non-ST-elevation myocardial infarction. PCI, Percutaneous coronary intervension. HF, heart failure. IVC, inferior vena cava. eGFR, estimated glomerular filtration rate. BMI, body mass index. BP, blood pressure. ACEI,

angiotensin converting enzyme inhibitors. ARB, angiotensin receptor blockers. HRs, hazard ratios. CIs, confidence intervals.

Declarations

Ethics approval and consent to participate*:* The Ethical Committee at the University of Gothenburg approved and granted permission to access and use the medical records described in the study. The ethical committee also ruled that no formal consent was necessary. The protocol was performed in accordance with the relevant guidelines and regulations according to the declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: No conflict of interest is reported by the authors.

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Authors' contributions: The corresponding author SB has built the database, performed the statistical analyses, generated tables and figures, interpreted results and was the major contributor in writing the manuscript. Also MJ, PH, ZM and SK have contributed in the interpreting of the results and writing the manuscript. All authors have read and approved the final manuscript.

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Figures

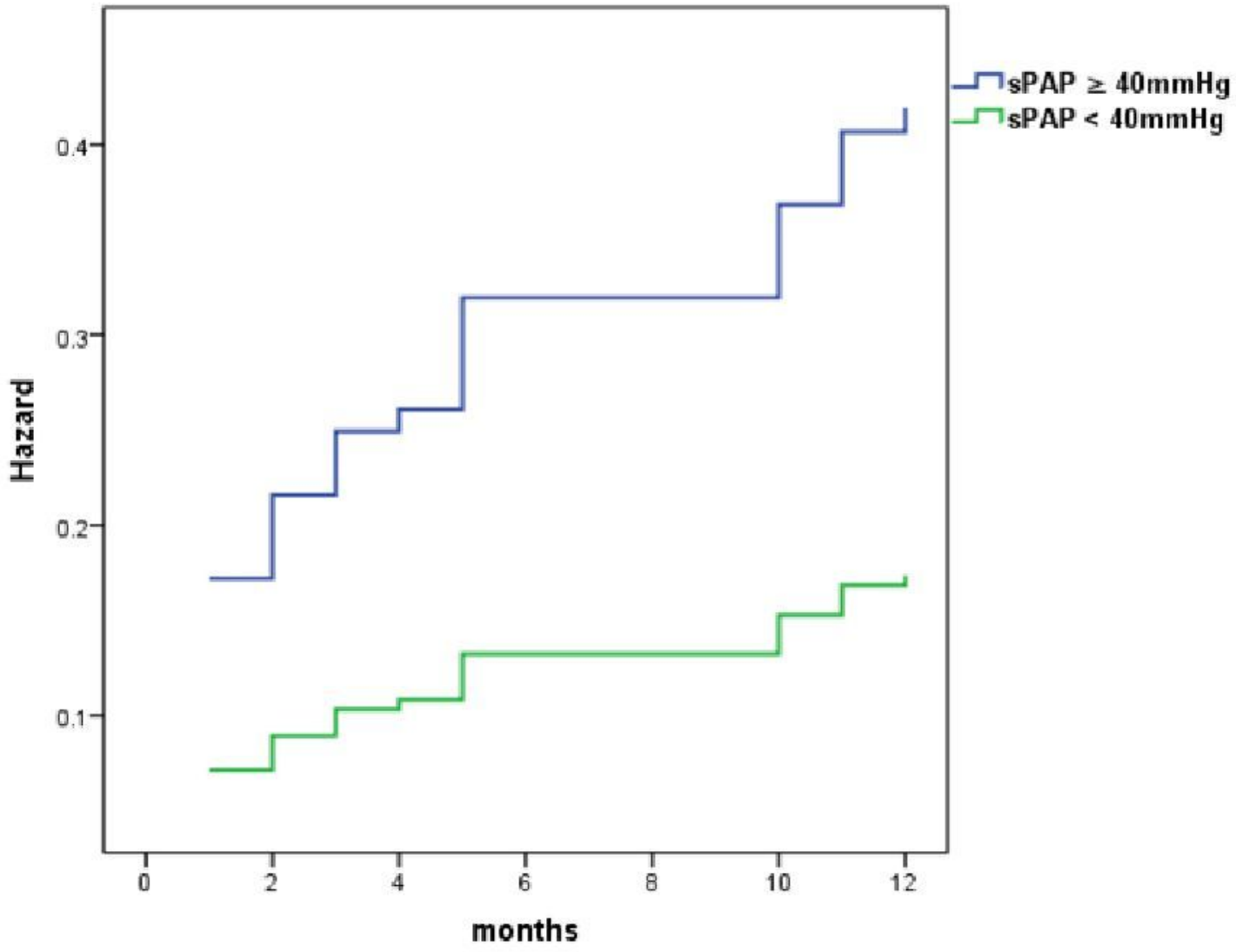

Figure 1

Comparison of 1-year risk of mortality between patients with sPAP ≥ 40 and sPAP <40mmHg.

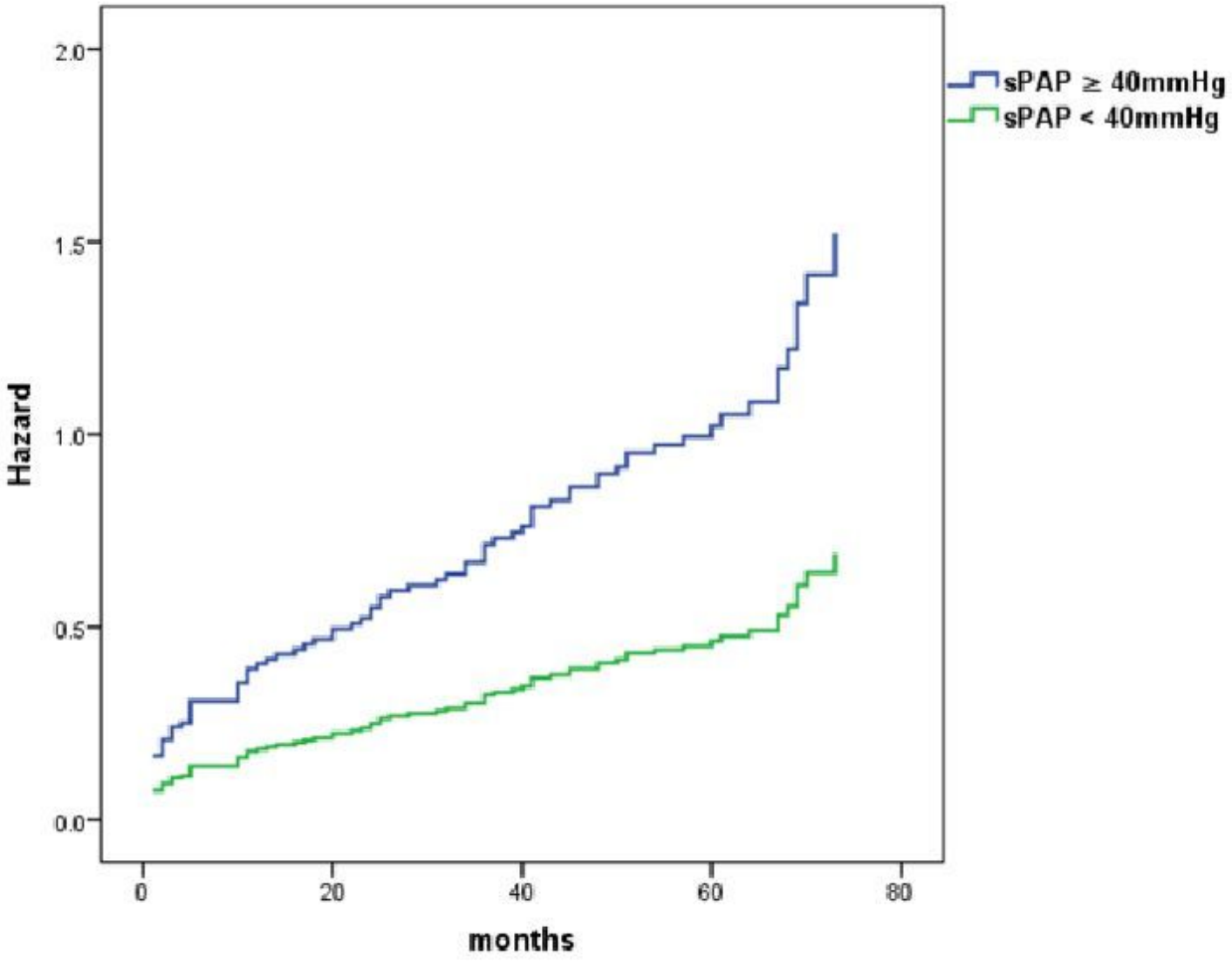

Figure 2

Comparison of 5-year risk of mortality between patients with sPAP≥ 40 and sPAP <40mmHg.