ORIGINAL ARTICLE

Mortality predictors after percutaneous coronary intervention – a prospective single-center registry study

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Abstract: **Objectives –** To evaluate the predictors of three-year cardiovascular mortality after percutaneous coronary intervention (PCI) in a Romanian tertiary cardiovascular center. **Methods –** Consecutive patients treated by PCI in the Emergency Institute for Cardiovascular Diseases and Transplantation of Targu Mures were included prospectively in a local PCI Registry. Demographic, clinical, and procedural parameters of the patients enrolled in the year 2016 were statistically analyzed as possible predictors of three-year cardiovascular mortality post-PCI. **Results –** 1079 patients were included: 254 (23.5%) with ST-segment elevation acute myocardial infarction (STEMI), 278 (25.8%) with non-ST segment elevation acute coronary syndrome (NSTEACS) and 547 (50.7%) with chronic coronary syndrome (CCS). Three-year cardiovascular mortality was 20.1%, 10.8% and 5.7% after PCI for STEMI, NSTEACS and CCS, respectively. Cox proportional hazards regression evidenced as independent predictors of long-term mortality after PCI: low left ventricular ejection fraction (LVEF), renal dysfunction, presentation with cardiogenic shock or with cardiac arrest in the case of acute coronary syndromes, and the history of significant valvular heart disease and low LVEF in the case of CCS (all p ≤0.01). **Conclusions –** Simple clinical variables but no procedural factors were the main predictors of 3-year cardiovascular mortality after PCI in this all-comers population.
Keywords: coronary artery disease, percutaneous coronary intervention, mortality.

Rezumat: **Obiective –** Evaluarea predictorilor mortalității cardiovasculare pe termen lung după intervențiile coronariene percutane (PCI) efectuate într-un centru cardiovascular terțiar român. **Metode –** Pacienți consecutivi tratați prin PCI au fost incluși prospectiv în Registrul PCI al Institutului de Urgență pentru Boli Cardiovasculare și Transplant din Târgu Mureș. Datele demografice, clinice și procedurale ale pacienților din 2016 au fost analizate statistic ca predictori posibili ai mortalității cardiovasculare la trei ani post-PCI. **Rezultate –** Au fost incluși 1079 pacienți: 254 (23,5%) cu infarct miocardic acut cu supradenivelare de segment-ST (STEMI), 278 (25,8%) cu sindrom coronarian acut fără supradenivelare de segment-ST (NSTEACS) si 547 (50,7%) cu sindrom coronarian cronic (CCS). Mortalitatea de cauză cardiovasculară la 3 ani post-PCI s-a ridicat la: 20,1% după STEMI, 10,8% după NSTEACS și 5,7% după CCS. Analiza de regresie multivariabilă Cox a evidențiat ca predictori independenți ai mortalității pe termen lung: fracția de ejecție a ventriculului stâng (LVEF) deprimată, disfuncția renală, prezentarea cu șoc cardiogen sau post-resuscitare în cazul sindroamelor coronariene acute; LVEF scăzută și prezența bolii valvulare semnificative în cazul CCS (toate valorile p ≤0,01). **Concluzii –** Variabile clinice simple, dar nu și cele procedurale au fost asociate în mod independent cu mortalitatea pe termen lung în populația analizată.
Cuvinte cheie: boală coronariană, intervenție coronariană percutană, mortalitate.

BACKGROUND

The diseases of the circulatory system are the leading cause of death in the European Union, accounting for 37% of the total mortality in this territory[1]. Cardiovascular mortality is even higher in Romania: according to the European health statistics, 58.2% of all deaths had a cardiovascular cause in 2016 in our country[2]. The main pathology responsible for this high mortality rate is coronary artery disease (CAD), with standardized death rates rising to 368.4 and 247.5 per 100000 males and females respectively[2]. Percutaneous coronary intervention (PCI) is the most frequently performed

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cardiovascular procedure in Europe[2]. Although in Romania there was a 146% increase in the number of PCIs between 2012 and 2017, from 82.7 to 120.7 procedures per 100000 residents, the country remained in the upper quartile of the European Union regarding CAD mortality in 2016[2].

The short-term clinical evolution of patients treated by PCI in Romania is well documented, most of the studies reporting in-hospital- or 30-day mortality as a clinical outcome[3-11]. However, contemporary data regarding long term mortality of CAD treated by PCI is mainly lacking in Romania: a few studies evaluated this subject, and only for special PCI indications, such as acute ST-elevation myocardial infarction (STEMI; 1-year follow-up)[12,13] or STEMI complicating left main CAD (1- and 3-year follow-up)[14,15].

The present study analyzes the predictors of 3-year cardiovascular mortality in an all-comers patient population treated by PCI in a Romanian tertiary cardiovascular center.

MATERIAL AND METHODS

Study population

All patients older than 18 years and treated by PCI in the Emergency Institute for Cardiovascular Diseases and Transplantation of Târgu Mureș have been included prospectively after hospital discharge in the local PCI Registry of the Institute since January 01. 2016. The Registry is accessible on-line at the website http://pci.cardio.ro/, and is based on the criteria of *Cardiology Audit and Registration Data Standards* (CARDS) developed by the *Department of Health and Children, European Society of Cardiology, Irish Cardiac Society,* and the *European Commission*[16]. All the information available regarding all the variables proposed in that document were collected in case of each included patient, at every PCI. Briefly, the CARDS recommendations address data regarding demographics, relevant medical history and comorbid conditions, clinical status at hospital admission, PCI indication, affected and instrumented coronary artery segments, different invasive diagnostic and therapeutic devices, procedural complications, medical treatment and in-hospital evolution[16]. In the current analysis were included consecutive patients treated by PCI for an acute- or chronic coronary syndrome during the year 2016, as 3-year mortality data was available for this population. Acute coronary syndromes (ACSs) included STEMI (according to the universal definition of acute myocardial infarction[17]) and non-ST segment elevation acute coronary syndrome (NSTEACS: unstable angina pectoris and acute myocardial infarction without persistent ST segment elevation, according to the definitions stated in the 2015 Guidelines of the *European Society of Cardiology* – ESC[18]). All the other PCI procedures were performed electively in patients with stable angina pectoris and/or documented myocardial ischemia. This latter group was recently redefined as chronic coronary syndromes (CCS)[19]. Patients with missing data regarding any of the studied clinical/angiographic/follow-up parameters were excluded. However, very high-risk patients often excluded from clinical trials, such as those with cardiogenic shock or resuscitated cardiac arrest, were all included in the present analysis. Subjects with multiple interventions during 2016 were included only once, considering for analysis only the first PCI procedure. All patients (or their legal representatives) signed a written informed consent regarding their participation in the study. The study protocol complied with the *Declaration of Helsinki* and was approved by the Local Ethical Committee.

Percutaneous coronary intervention

All the PCI procedures were indicated and performed according to the clinical practice guidelines of the ESC considered current in 2016[18,20]. All patients received unfractionated heparin as periprocedural anticoagulation. The decision regarding the type of the implanted stent was left at the discretion of the operator in case of STEMI. In complex cases a heart-team based approach was used for decision-making regarding the best revascularization strategy. Like in case of other similar analyses, the procedure was considered successful when a final Thrombolysis in Myocardial Infarction (TIMI) flow ≥2 was achieved with a residual stenosis of <20% after stent implantation or <50% after balloon angioplasty[21].

Assessed demographic, clinical, and procedural variables

The following demographic and baseline clinical parameters were evaluated as possible predictors of mortality after PCI: patients' age and sex, the presence of cardiovascular risk factors (hypertension, diabetes mellitus, active smoking, hypercholesterolemia and obesity, i.e. body mass index ≥30kg/m^2), medical history of: previous myocardial infarction, congestive heart failure, stroke, hemodynamically significant valvular heart disease or prior valvular heart surgery/replacement/intervention, peripheral vascular disease, previous PCI or coronary artery by-pass grafting. Additional clinical parameters assessed were: the left ventricular

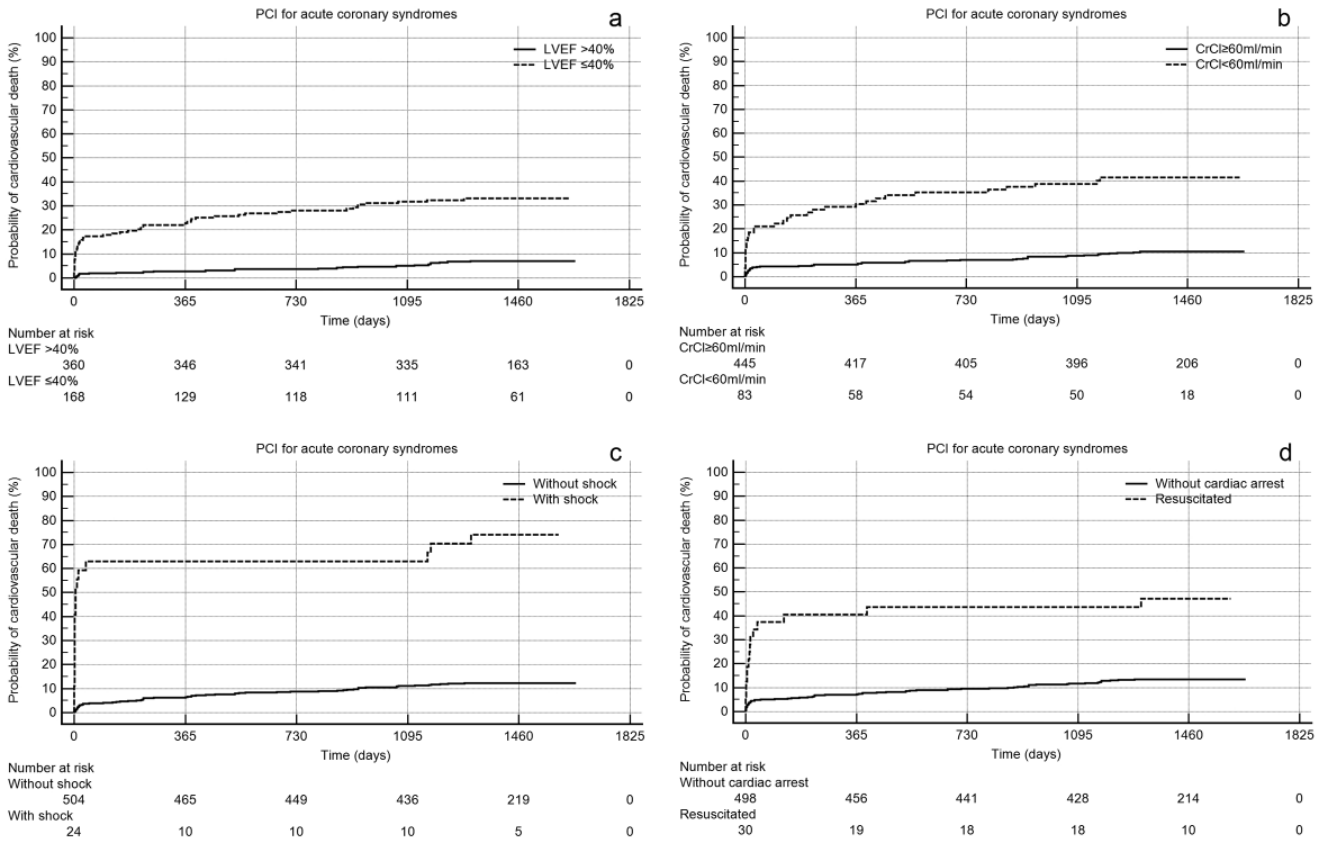

Figure 1. Kaplan-Meier survival curves of acute coronary syndrome patients treated interventionally, according to different independent predictors of 3-year mortality: in case of depressed left ventricular systolic function (a), in the presence of renal dysfunction (b), in case of presentation with cardiogenic shock (c), or resuscitated cardiac arrest (d). All log-rank p values were <0.001. CrCl – creatinine clearance, LVEF – left ventricular ejection fraction, PCI – percutaneous coronary intervention.

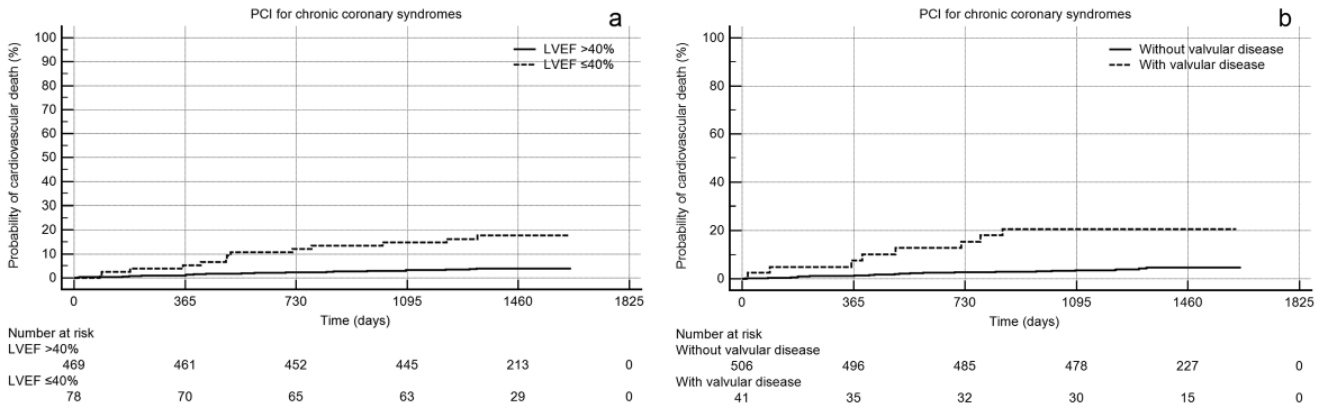

Figure 2. Kaplan-Meier survival curves of patients treated electively by PCI, according to different independent predictors of 3-year mortality: in case of depressed left ventricular systolic function (a), and in the presence of hemodynamically significant valvular heart disease or prior valvular heart surgery/replacement/intervention (b). All log-rank p values were <0.001. LVEF – left ventricular ejection fraction, PCI – percutaneous coronary intervention.

ejection fraction as determined by transthoracic echocardiography (the lowest value in percentage, during hospitalization), the presence of renal dysfunction (creatinine clearance<60 ml/min[21] as calculated according to the Cockroft-Gault formula[22]), presentation with cardiogenic shock or resuscitated cardiac arrest.

Regarding the PCI procedure, the subsequent variables were analyzed: the arterial access site (radial vs. other), the presence of triple-vessel disease (defined by the presence of at least one ≥50% diameter stenosis of a coronary branch with a diameter of ≥1.5 mm in the territory of the left anterior descending-, the left circumflex- and the right coronary artery or the presence of a stent in these vessels), left main stem disease (diameter stenosis ≥50% or the presence of a stent), TIMI flow after the PCI, and the number and type (drug eluting vs. bare metal or a combination of these two) of the implanted stents. The occurrence of the following PCI-related complications was evaluated: acute vessel closure, coronary perforation, angiographic no-reflow phenomenon (TIMI flow ≤2 observed during or at the end of PCI, in the absence of dissection, residual stenosis, spasm or thrombus[23]), heart block requiring emergent pacing, resuscitation during PCI, shock induced by the procedure, stroke, and post-procedural in-hospital major bleeding: overt clinical bleeding associated with a drop in Hgb of >5 g/dl (0.5g/l) or in Htc of 15%[15]. Data regarding the antiplatelet medication (aspirin, clopidogrel, ticagrelor and eptifibatide – the only glycoprotein IIB/IIIA blocker used) administered in the peri-procedural period was also analyzed.

Clinical endpoint and follow-up

The clinical endpoint of the present study was the incidence of cardiovascular death in the first 3 years of evolution after the index PCI. In-hospital mortality data was available from the PCI Registry. While 1-, 2- and 3-year mortality rates were achieved from the database of the Romanian National Health Insurance System, the information regarding the exact date and cause (cardiovascular vs. other) of death were obtained from the *Regional Statistics Office* of the *Romanian National Institute of Statistics*.

Statistical analysis

To reduce the possibility of bias, the in-hospital, 1-, 2- and 3-year death rates were statistically compared between the groups of included and excluded patients. Patients were categorized in three groups, according to PCI indication: those with STEMI, NSTEACS and CCS, respectively. The univariate predictors of 3-year cardiovascular mortality were separately assessed in these groups. Normal data distribution was tested with the help of the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies (%) and were analyzed using the chi-squared test. Continuous variables were summarized as medians (range) and were compared using the Mann-Whitney test or the Kruskal-Wallis test with Conover post-hoc analysis, as appropriate. Kaplan-Meier analysis with log-rank test was used to compare the survival curves of different patient groups. Two Cox multivariate proportional hazard models were built to identify the independent predictors of long-term cardiovascular mortality after PCI performed in patients with acute- and chronic coronary syndromes, respectively. In the first model were included all the variables presenting a statistically significant association with 3-year cardiovascular mortality at univariate analyses in patients with STEMI or NSTEACS. The second model contained the univariate mortality predictors after PCI performed for CCS. The following cut-off values were used for the continuous variables included in the Cox proportional hazard model: a CrCl of <60 ml/min (a widely accepted threshold for the definition of chronic kidney disease[21]), a LVEF ≤40% (corresponding to an at least moderately depressed left ventricular systolic function[24]) and an age of >62 years; this latter was established by receiver operating characteristic (ROC) curve analysis. All tests were two-tailed, and a probability value of <0.05 was considered statistically significant. The statistical analysis was performed using the MedCalc Statistical Software version 19.4.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

RESULTS

Study population

In the PCI Registry of our institution were included 1168 patients in 2016. Eighty-nine of them were excluded because of missing clinical (52 patients), angiographic (33 patients) or follow-up (4 patients) data. In consequence, 1079 patients were included in the final statistical analysis. Their demographic, clinical and invasive procedural characteristics are presented according to the PCI indication in Table 1. PCI was performed for a STEMI indication in 254 patients (23.5% of the whole population) and for NSTEACS in 278 subjects (25.8% of the whole population). Procedural success was achieved in 96.8% of the included patients. More than 93% of the implanted stents were drug-elu-

Table 1. Demographic and baseline clinical and PCI-related characteristics of the included patients according to the procedural indication

Variable	Total patients (N=1079)	PCI indication			
		STEMI (N=254)	NSTEACS (N=278)	CCS (N=547)	p
Age (years)	63.9 (29-89)	63.0 (31-89)	64.8 (29-87)	63.8 (37-88)	0.08
Female gender	329 (30.5)	86 (33.9)	103 (37.1)	140 (25.6)	0.001
BMI (kg/m^2)	28.4 (15.8-62.0)	27.8 (15.8-62.0)	28.4 (19.0-54.2)	28.5 (19.0-50.8)	0.18
Arterial hypertension	868 (80.4)	171 (67.3)	226 (81.3)	471 (86.1)	<0.001
Diabetes mellitus	335 (31)	65 (25.6)	95 (34.2)	175 (32.0)	0.08
Hypercholesterolemia	640 (59.3)	110 (43.3)	165 (59.4)	365 (66.7)	<0.001
Active smoking	236 (21.9)	109 (42.9)	57 (20.5)	70 (12.8)	<0.001
History of congestive heart failure	151 (14)	27 (10.6)	45 (16.2)	79 (14.4)	0.16
History of valvular heart disease	86 (8.0)	17 (6.7)	28 (10.1)	41 (7.5)	0.30
History of peripheral arterial disease	146 (13.5)	13 (5.1)	35 (12.6)	98 (17.9)	<0.001
History of stroke	68 (6.3)	17 (6.7)	24 (8.6)	27 (4.9)	0.11
Previous myocardial infarction	308 (28.5)	35 (13.8)	74 (26.6)	199 (36.4)	<0.001
Previous PCI	292 (27.1)	20 (7.9)	67 (24.1)	205 (37.5)	<0.001
Previous CABG	45 (4.2)	2 (0.8)	11 (4.0)	32 (5.9)	<0.01
CrCl (ml/min)	103.9 (7.0-711.8)	100.1 (8.2-263.6)	101.0 (26.0-285.4)	107.4 (7.0-711.6)#	0.01
Left ventricular ejection fraction (%)	50 (10-80)	45 (10-60)#	50 (20-65)#	55 (20-80)#	<0.001
Presentation with cardiogenic shock	27 (2.5%)	25 (9.8)	2 (0.7)	0 (0.0)	<0.001
Cardiac arrest before PCI	32 (3.0)	28 (11.0)	4 (1.4)	0 (0.0)	<0.001
Radial arterial access site	708 (65.6)	136 (53.5)	182 (65.5)	390 (71.3)	<0.001
Three-vessel disease	387 (35.9)	77 (30.3)	106 (38.1)	204 (37.3)	0.10
Left main stem disease	88 (8.2)	16 (6.3)	29 (10.4)	43 (7.9)	0.20
TIMI flow<2 post-PCI	35 (3.2)	6 (2.4)	11 (4.0)	18 (3.3)	<0.58
PCI without stent implantation	81 (7.5)	19 (7.5)	26 (9.4)	36 (6.6)	0.36
Number of implanted stents >1	328 (30.4)	58 (22.8)	97 (34.9)	173 (31.6)	<0.01
Only drug-eluting stents implanted*	934 (93.6)	209 (88.9)	241 (95.6)	484 (94.7)	<0.01
Dual antiplatelet therapy	1031 (95.6)	248 (97.6)	267 (96.0)	516 (94.3)	0.09
Clopidogrel as second antiplatelet (vs. ticagrelor)**	817 (76.3)	143 (56.5)	217 (78.3)	457 (84.5)	<0.001
GPIIbIIIa inhibitor administered	143 (13.3)	110 (43.3)	20 (7.2)	13 (2.4)	<0.001

Categorical data are presented as frequencies (N) and percentages (%) and were compared using the Chi-squared test. Continuous data are expressed as median (range) and were compared with the help of Kruskal-Wallis test. BMI – body mass index; CABG – coronary artery by-pass graft operation; CCS – chronic coronary syndrome; CrCl – creatinine clearance; NSTEACS – non-ST segment elevation acute coronary syndrome; PCI – percutaneous coronary intervention; STEMI – ST segment elevation acute myocardial infarction. *N=998 patients received at least 1 stent; **N=1071 patients received and ADP receptor agonist. #Significantly different from the other median values (Conover post-hoc analysis).

ting. Complications of PCI occurred significantly more frequent in case of STEMI (Table 2). A remarkably high incidence of presentation with cardiogenic shock and/or cardiac arrest was noted: 39 patients (7.3% of the ACS population) suffered from at least one of these conditions.

Mortality after PCI

The incidence of in-hospital death, and 1-, 2- or 3-year cardiovascular mortality was not different between the excluded and included patient groups (Table 3).

Ten of the 536 ACS patients (5.6%) and none of the 547 CCS patients died in the in-hospital period. As expected, in-hospital mortality was high in patients presenting with cardiogenic shock (16 of the 27 patients, 59.3%) and resuscitated cardiac arrest (11 of the 32 patients, 34.4%). Conversely, only 10 of the 483 ACS patients presenting without these two conditions (2.1%) died during the in-hospital period: 6 of the 210 STEMI- and 4 of the 273 NSTEACS patients (2.9% and 1.5%, respectively, p = 0.28). The in-hospital mortality in the ACS population was 2.8% in the absence of cardiogenic shock.

After a median follow-up of 1433 days, 112 patients (10.4% of the whole study population) died of cardiovascular causes. The clinical and procedural variables associated with 3-year cardiovascular mortality are summarized in Table 4. Long-term mortality was also significantly higher in patients who suffered an ACS (Table 3), especially in the case of high-risk presentation. Accordingly, 3-year cardiovascular mortality was as high as 74.1% and 46.9% after an ACS complicated by cardiogenic shock or resuscitated cardiac arrest, respectively. If these high-risk cases were excluded, a 3-year post-ACS cardiovascular mortality of 11.8%

Table 2. The incidence of PCI-related complications in the studied population

Variable	Total patients (N=1079)	PCI indication			
		STEMI (N=254)	NSTEACS (N=278)	CCS (N=547)	p
Any PCI-related complication	89 (8.2)	50 (19.7)	14 (5.0)	25 (4.6)	<0.001
Acute vessel closure	22 (2.0)	4 (1.6)	6 (2.2)	12 (2.2)	0.83
Coronary perforation	10 (0.9)	2 (0.8)	3 (1.1)	5 (0.9)	0.93
Angiographic no-reflow phenomenon	35 (3.2)	28 (11.0)	2 (0.7)	5 (0.9)	<0.001
Heart block requiring emergent pacing	9 (0.8)	7 (2.8)	1 (0.4)	1 (0.2)	<0.001
Resuscitation during PCI	13 (1.2)	9 (3.5)	2 (0.7)	2 (0.4)	<0.001
Shock induced by the procedure	4 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)	0.99
Stroke	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	0.37
Major bleeding post-PCI until discharge	5 (0.5)	2 (0.8)	1 (0.4)	2 (0.4)	0.68

Data are presented as frequencies (N) and percentages (%) and were compared using the Chi-squared test. CCS – chronic coronary syndrome; NSTEACS – non-ST segment elevation acute coronary syndrome; PCI – percutaneous coronary intervention; STEMI – ST segment elevation acute myocardial infarction.

Table 3. Post-PCI mortality rates of the patients included in the PCI Registry

Mortality	Included vs. excluded patients			PCI Indication (included patients)			
	Included patients (N=1079)	Excluded patients (N=89)	p	STEMI (N=254)	NSTEACS (N=278)	CCS (N=547)	p
In-hospital mortality	30 (2.8)	3 (3.4)	0.74	23 (9.1)	7 (2.5)	0 (0.0)	<0.001
1-year cardiovascular mortality	58 (5.4)	5 (5.9)*	0.84	34 (13.4)	15 (5.4)	9 (1.6)	<0.001
2-year cardiovascular mortality	81 (7.5)	6 (7.1)*	0.87	41 (16.1)	20 (7.2)	20 (3.7)	<0.001
3-year cardiovascular mortality	112 (10.4)	6 (7.1)*	0.32	51 (20.1)	30 (10.8)	31 (5.7)	<0.001

Data are presented as frequencies (N) and percentages (%) and were compared using the Chi-squared test. CCS – chronic coronary syndrome; NSTEACS – non-ST segment elevation acute coronary syndrome; PCI – percutaneous coronary intervention; STEMI – ST segment elevation acute myocardial infarction. *As 4 patients were excluded due to missing follow-up data, this result refers to the N=85 patients excluded because of missing clinical or angiographic data.

was found. However, this was still significantly higher than the 3-year cardiovascular death rate of 5.7% observed after elective interventions (p <0.001).

Receiver-operator characteristic curve analysis confirmed the significant association between advanced age and increased mortality after PCI for an ACS, with a cut-off value of 62 years (area under the curve (AUC): 0.65, 95% CI: 0.60-0.69, p<0.001). The two Cox proportional hazards regression models predicted 3-year cardiovascular mortality with the following characteristics described by ROC-curve analysis: AUC: 0.86, 95%CI: 0.83-0.89, p<0.0001 (ACS model), and AUC: 0.71, 95%CI: 0.67-0.75, p<0.0001 (CCS model). The independent predictors of long-term cardiovascular mortality after PCI identified by Cox proportional hazards regression analysis in ACS patients were: the presence of renal dysfunction (HR = 2.12, 95% CI: 1.22-3.68, p <0.01), a depressed left ventricular systolic function (LVEF ≤40%, HR = 3.30, 95% CI: 1.95-5.59, p <0.001), the presentation with cardiogenic shock (HR = 3.85, 95% CI 1.91-7.72, p <0.001) or with resuscitated cardiac arrest (HR=3.4, 95% CI: 1.83-6.43, p <0.001). In case of CCS, only two independent predictors of long-term cardiovascular mortality were evidenced: low LVEF (a value of ≤40% was associated with a HR of 3.05, 95% CI: 1.29-7.24, p = 0.01) and the history of hemodynamically significant valvular heart disease/prior valvular heart surgery/replacement/intervention (HR = 2.89, 95% CI: 1.20-6.95, p = 0.01). Survival curves according to these independent predictors of long-term mortality are presented in Figure 1 and Figure 2. In the case of ACS all the independent predictors had an initial significant impact, corresponding to the in-hospital deaths (Figure 1); the divergence of the curves is especially striking in case of high-risk clinical presentation, such as cardiogenic shock (Figure 1c) or after resuscitation (Figure 1d). Conversely, a more gradual effect of the two independent predictors is observed after elective PCI (Figure 2).

In conclusion, the main predictors of long-term mortality remained clinical variables: comorbidities and high-risk clinical presentation. None of the angiographic and invasive procedural characteristics or complications had significant, independent impact on the 3-year cardiovascular mortality in this patient population.

Table 4. Demographic, clinical, and procedural parameters according to 3-year cardiovascular mortality after PCI

Variable	Total patients (N=1079)			STEMI (N=254)			NSTEACS (N=278)			CCS (N=547)		
	Deceased (N=112)	Alive (N=967)	p	Deceased (N=51)	Alive (N=203)	p	Deceased (N=30)	Alive (N=248)	p	Deceased (N=31)	Alive (N=516)	p
Age (years)	67.7 (42-89)	63.1 (29-89)	<0.001	66.1 (42-89)	62.0 (31-85)	0.001	70.2 (48-83)	64.4 (29-87)	0.001	66.1 (49-81)	63.1 (37-89)	0.07
Female gender	47 (42.0)	282 (29.2)	<0.01	25 (49.0)	61 (30.0)	0.01	15 (50.0)	88 (35.5)	0.12	7 (22.6)	133 (25.8)	0.69
BMI (kg/m^2)	27.8 (15.8-45.3)	28.4 (18.6-62.0)	0.67	27.7 (15.8-38.1)	28.1 (18.6-62.0)	0.42	27.5 (19.6-44.4)	28.4 (19.0-54.2)	0.36	29.5 (23.1-45.3)	28.4 (19.0-50.8)	0.10
Arterial hypertension	20 (80.2)	92 (82.1)	0.63	39 (76.5)	132 (65.0)	0.12	6 (81.5)	24 (80.0)	0.84	29 (93.5)	442 (85.7)	0.21
Diabetes mellitus	41 (36.6)	294 (30.4)	0.17	12 (23.5)	53 (26.1)	0.70	16 (53.3)	79 (31.9)	0.01	13 (41.9)	162 (31.4)	0.22
Hypercholesterolemia	56 (50.0)	584 (60.4)	0.03	21 (41.2)	89 (43.8)	0.73	13 (43.3)	152 (61.3)	0.05	22 (66.5)	343 (71)	0.60
Active smoking	27 (24.1)	209 (21.6)	0.54	18 (35.3)	91 (44.8)	0.21	3 (10.0)	54 (21.8)	0.13	6 (19.4)	64 (12.4)	0.26
History of congestive heart failure	33 (29.5)	118 (12.2)	<0.001	11 (21.6)	16 (7.9)	<0.01	11 (36.7)	34 (13.7)	0.001	11 (35.5)	68 (13.2)	<0.001
History of valvular heart disease	23 (20.5)	63 (6.5)	<0.001	7 (13.7)	10 (4.9)	0.02	8 (26.7)	20 (8.1)	0.001	8 (28.5)	33 (6.4)	<0.001
History of peripheral arterial disease	19 (17.0)	127 (13.1)	0.26	5 (9.8)	8 (3.9)	0.09	7 (23.3)	28 (11.3)	0.06	7 (22.6)	91 (17.6)	0.48
History of stroke	59 (6.1)	9 (8.0)	0.42	2 (3.9)	15 (7.4)	0.37	6 (20.0)	18 (7.3)	0.01	1 (3.2)	26 (5.0)	0.65
Previous myocardial infarction	35 (31.2)	273 (28.2)	0.50	9 (17.6)	26 (12.8)	0.37	10 (33.3)	64 (25.8)	0.37	16 (51.6)	183 (35.5)	0.06
Previous PCI	24 (21.4)	268 (27.7)	0.15	6 (11.8)	14 (6.9)	0.24	7 (23.3)	60 (24.2)	0.91	11 (35.5)	194 (37.6)	0.81
Previous CABG	2 (1.8)	43 (4.4)	0.18	0 (0.0)	2 (1.0)	0.47	0 (0.0)	11 (4.4)	0.24	2 (6.5)	30 (5.8)	0.88
CrCl (ml/min)	79.2 (7.0-175.6)	107.4 (7.6-711.8)	<0.001	59.0 (8.2-154.3)	111.4 (15.5-263.6)	<0.001	71.1 (34.8-124.6)	103.6 (26.0-285.4)	<0.001	112.5 (7.0-175.6)	106.8 (7.6-711.8)	0.71
Left ventricular ejection fraction (%)	40 (10-65)	50 (20-80)	<0.001	35 (10-60)	45 (25-60)	<0.001	45 (20-60)	53 (20-65)	<0.001	45 (25-65)	55 (20-80)	<0.01
Presentation with cardiogenic shock	20 (17.9)	7 (0.7)	<0.001	18 (35.3)	7 (3.4)	<0.001	2 (6.7)	0 (0.0)	<0.001	0	0	-
Cardiac arrest before PCI	15 (13.4)	17 (1.8)	<0.001	12 (23.5)	16 (7.9)	0.001	3 (10.0)	1 (0.4)	<0.001	0	0	-
Radial arterial access site	55 (49.1)	653 (67.5)	0.001	16 (31.4)	120 (59.1)	<0.001	17 (56.7)	165 (66.5)	0.28	22 (71.0)	368 (71.3)	0.96
Three-vessel disease	49 (43.7)	340 (35.2)	0.07	20 (39.2)	57 (28.1)	0.12	13 (43.3)	93 (37.5)	0.53	16 (51.6)	190 (36.8)	0.09
Left main stem disease	19 (17.0)	77 (8.0)	0.001	8 (15.7)	9 (4.4)	<0.01	8 (2.7)	23 (9.3)	<0.01	3 (9.7)	45 (8.7)	0.85
TIMI flow <2 post-PCI	8 (7.1)	27 (2.8)	0.01	4 (7.8)	2 (1.0)	<0.01	3 (10.0)	8 (3.2)	0.07	1 (3.2)	17 (3.3)	0.98
PCI without stent implantation	17 (15.2)	64 (6.6)	0.001	9 (17.6)	10 (4.9)	<0.01	7 (23.3)	19 (7.7)	<0.01	1 (3.2)	35 (6.8)	0.43
Number of implanted stents >1	35 (31.2)	293 (30.3)	0.83	10 (19.6)	48 (23.6)	0.54	12 (40.0)	85 (34.3)	0.53	13 (41.9)	160 (31.0)	0.20
Only drug-eluting stents implanted*	83 (87.4)	851 (94.2)	<0.01	33 (78.6)	176 (91.2)	0.01	20 (87.0)	221 (96.5)	0.03	30 (100.0)	454 (94.4)	0.18
Dual antiplatelet therapy	104 (92.9)	927 (95.9)	0.14	49 (96.1)	199 (98.0)	0.41	28 (93.3)	239 (96.4)	0.42	27 (87.1)	489 (94.8)	0.07
Clopidogrel as second antiplatelet (vs. ticagrelor)**	85 (77.3)	732 (76.2)	0.79	31 (62.0)	112 (55.2)	0.38	26 (89.7)	191 (77.0)	0.11	28 (90.3)	429 (84.1)	0.35
GPIIbIIIa inhibitor administered	25 (22.3)	118 (12.2)	<0.01	22 (43.1)	88 (43.3)	0.97	3 (10.0)	17 (6.9)	0.52	0 (0.0)	13 (2.5)	0.37
Any PCI-related complication	23 (20.5)	66 (6.8)	<0.001	19 (37.3)	31 (15.3)	<0.001	3 (10.0)	11 (4.4)	0.18	1 (3.2)	24 (4.7)	0.71

Categorical data are presented as frequencies (N) and percentages (%) and were compared using the Chi-squared test. Continuous data are expressed as median (range) and were compared with the help of Mann-Whitney test. BMI – body mass index; CABG – coronary artery by-pass graft operation; CCS – chronic coronary syndrome; CrCl – creatinine clearance; NSTEACS – non-ST segment elevation acute coronary syndrome; PCI – percutaneous coronary intervention; STEMI – ST segment elevation acute myocardial infarction. *N=998 patients received at least 1 stent; **N=1071 patients received and ADP receptor agonist.

DISCUSSION

To the best of our knowledge, the present work is the first one evaluating the long-term post-PCI mortality and its predictors in an all-comers population in Romania. Patients were prospectively included in the institutional PCI Registry, and a complete 3-year follow-up was accomplished regarding cardiovascular mortality in the selected population. Nevertheless, the results reflect the remarkable technical advancement emerged worldwide in the field of percutaneous coronary revascularization in the past few decades (high procedural success rate, the more frequent use of radial arterial approach and drug-eluting stents).

Cardiovascular death rate

The average in-hospital and 3-year mortality after PCI in different recent large registry studies ranges between 0.65-2.60%[25-27] and 5.6-9.8%[28-30], respectively. However, very high risk patients (e.g. with cardiogenic shock) were excluded[25] or represented substantially less[26-30] in these works, partially explaining the higher mortality rates observed in our cohort. The presentation with cardiogenic shock in the analyzed ACS population (i.e. 5.1%, Table 1) was higher than the incidence of this complication in the ACS population of the Coronary Angiography and PCI registry of the German Cardiac Society (3.8%)[27]. The in-hospital mortality rates of these two populations are quite similar in the absence of cardiogenic shock: 2.8% in our cohort and 2.9% in the German ACS population[27]. However, the presentation with cardiogenic shock was associated with an undoubtedly higher in-hospital mortality rate in our ACS population (59.3% vs. 42.2% in the German ACS registry). These observations might contribute to the explanation of the higher CAD mortality rates observed in Romania[2], and emphasizes the necessity of patient information and education, as well as the need for the continuous development of the existing intensive care facilities in our country.

Predictors of long-term mortality

While in the case of ACS both clinical and procedural factors were identified as univariate predictors of long-term post-PCI mortality, this outcome was associated with only clinical variables after elective procedures (Table 4). However, multivariate analysis evidenced as independent predictors of long-term cardiovascular mortality only some of the clinical characteristics even in ACS patients.

Not surprisingly, the history of significant valvular heart disease was associated with 3-year cardiovascular mortality in ACS and CCS patients. However, this association was an independent one only in the case of elective interventions in our patient population. Both conditions: CAD and valvular heart disease could lead to cardiovascular death. Moreover, aortic stenosis[31] and mitral regurgitation[32] were both identified previously as independent predictors of mortality in different subsets of CAD patients.

Renal dysfunction, a well-known predictor of mortality in CAD patients[33-35] was also an independent predictor of long term mortality after PCI for ACS . In addition to the possible acute kidney injury related to the PCI procedure itself[36], renal dysfunction is associated with the higher occurrence of other procedure- or disease-related complications, such as the no-reflow phenomenon[37] or atrial fibrillation[38] in case of percutaneous coronary revascularization for STEMI.

The depressed systolic function of the left ventricle was the single independent predictor of long-term cardiovascular mortality after both urgent and elective PCI. This negative effect of left ventricular dysfunction on post-PCI mortality is well-known[26,39]; left ventricular ejection fraction is incorporated in many prognostic scores currently used for risk stratification in CAD patients[40-42].

Renal dysfunction and poor left ventricular function had a similar effect on the followed clinical outcome: both conditions were associated with an abrupt increase in mortality during hospital admission, followed by a more gradual, but continuous divergence of the Kaplan-Meier curves in case of ACS (Figure 1a and b). Contrary to this, other independent predictors of long-term mortality after an ACS, such as presentation with cardiogenic shock or resuscitated cardiac arrest had mainly an acute initial impact, remarkably increasing in-hospital mortality (Figure 1c and d).

The mortality of resuscitated patients and those with cardiogenic shock is disappointingly high, even in the current era of emergent revascularization in PCI centers with 24/7 availability[7,27,43]. Although there is a continuous effort to reduce this high mortality, including the development of dedicated "regionalized cardiogenic shock systems"[44], and "fourth level centers"[44] equipped with extracorporeal life support and ventricular assist devices, these measures are mainly unavailable in our country[7]. However, as cardiogenic shock complicating acute coronary syndromes is one of the main determinants of post-PCI long-term mortality[7,27] and given its early major impact on survival, these measures applied as early as possible in cardiogenic shock patients might represent a possible way to lower further the long-term mortality rate of CAD in Romania.

Study limitations

The major limitation of our study is the reduced number of the included patients, all of them recruited from a single center. In consequence, our results should be interpreted with some caution regarding the possibility of insufficient statistical power. However, we tried to reduce this limitation by extensive data collection and excluding as few patients as possible. The reader cannot consider these results as representative for the whole country; however, results from large multicenter registries are still waited for this purpose. The

current research represents preliminary findings from an on-going PCI registry. The future results of this project probably will add further details regarding the evolution of the disease causing most of the deaths in Romania.

CONCLUSIONS

Clinical variables (poor left ventricular function, renal dysfunction, presentation with cardiogenic shock or cardiac arrest in the case of ACS; low LVEF and the history of valvular heart disease in the case of CCS), but no procedural factors were the main predictors of 3-year cardiovascular mortality after PCI in this all-comers population.

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