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Predictors of long-term outcome of percutaneous coronary intervention in octogenarians with acute coronary syndrome

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ABSTRACT

The majority of patients with acute coronary syndrome (ACS) are elderly. Limited evidence makes decision-making on the use of percutaneous coronary intervention (PCI) mainly empirical. Old age is one risk factor, but other factors than age may have an impact on mortality as well. Therefore, we investigated predictors of long-term all-cause mortality among octogenarians who have undergone PCI due to ACS. A total of 182 patients ≥ 80 years who underwent PCI during 2006–2007 at Sahlgrenska University Hospital were studied consecutively from recorded clinical data. All-cause five-year mortality of follow-up was 46.2%. Mean age was 83.7 ± 2.8, 62% were male, 76% were in sinus rhythm, and 42% had left ventricular ejection fraction < 45%. Indications for PCI were STEMI (52%), NSTEMI (36%) and unstable angina (11%). Multivariate analysis in two steps identified atrial fibrillation, moderate tricuspid valve regurgitation, moderate mitral valve regurgitation, dependency in ADL and eGFR ≤ 30 ml/min at the first step and moderate mitral valve regurgitation, atrial fibrillation and eGFR ≤ 30 ml/min at the last step, as independent predictors of all-cause mortality. Kaplan Meier analysis of positive parameters from both steps of multivariate analysis showed high significant difference in survival between patients having these parameters and those who were free from these parameters, with worst prognosis in patients with accumulation of these parameters. Accordingly, we have, in an octogenarian patient cohort who suffered from ACS, undergone PCI in daily clinical practice, identified five prognostic predictors for all-cause death after five years' follow-up.

1. Introduction

Current guidelines on the use of reperfusion therapy in acute coronary syndrome (ACS) are based on data derived from randomized clinical trials (RCTs) [1–3]. However, data regarding percutaneous coronary intervention (PCI) in octogenarians are not only very limited but also inconsistent. There are data in favor of PCI in the elderly [4–6]. However, several observational studies have demonstrated that old age is associated with both higher in-hospital mortality and frequent complications such as renal failure and bleedings after PCI [7,8]. Results from studies on mid- and long-term outcomes of PCI are more ambiguous. For example, incidence rates among elderly patients of major adverse cardiac events (MACE), defined as the combined events of death, revascularization and myocardial infarction, have been found to be both higher and similar to rates among younger patients [9–12].

The paucity and inconsistency of data on the use of PCI in the elderly have several implications. In our daily clinical practice, it is difficult for physicians to make well-grounded decisions on the use of PCI in the elderly. Elderly patients have been found to be less likely than younger patients to undergo PCI, despite adjusting for contraindications and co-morbidities that may be of relevance, partly because some of the existing data suggest that age is associated with negative outcomes [13–15]. The suggestion that elderly patients are sometimes withheld PCI solely because of their age is contrary to prevailing ethical principles. Moreover, the elderly constitute a heterogeneous group. The term 'elderly' is a broad term comprising the "young" old (65–74 years),

Abbreviations: ADL, Activities of daily living; ARBs, Angiotensin receptor blockers; ACE-I, Angiotensin converting enzyme inhibitors; AS, Aortic valve stenosis; AV-block, Atrioventricular block; CVP, Central venous pressure; CABG, Coronary artery bypass grafting; eGFR, Estimated glomerular filtration rate; MR, Mitral valve regurgitation; NSTEMI, Non-ST-segment elevation myocardial infarction; PA-P, Pulmonary atrial pressure; STEMI, ST-segment elevation myocardial infarction; TR, Tricuspid valve regurgitation.

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the "older" old (75–84 years) and the "oldest" old (≥85 years) [16] with considerable individual variation in co-morbidities and physical capabilities. In view of the heterogeneity of the elderly patient group it is likely that some of them have better prospects of gaining from PCI in the setting of ACS than others. Therefore it is essential to identify prognostic factors that indicate increased risk for death in patients with acute coronary syndrome despite PCI, which might be helpful in decision making in clinical practice.

2. Materials and methods

2.1. Study cohort

A total of 182 patients ≥ 80 years who had been treated with PCI due to acute coronary syndrome (ACS) during 2006–2007 at Sahlgrenska University Hospital, Gothenburg, were included consecutively and studied retrospectively from January 2 to May 30, 2012. All together 145 parameters covering social, functional and medical domains were entered into a database. The time-period 2006–2007 was chosen to allow a follow-up period of at least five years. PCI procedures for the specified age group and time period were identified from the hospital registry. The selection process is illustrated in Fig. 1. Three exclusion criteria for the study were applied. Firstly, since the catchment area of the Sahlgrenska University Hospital for performing PCI during emergency hours is larger than during office hours a substantial amount of the procedures were performed in individuals who are not normally patients of the hospital. These patients were excluded from the study since medical records from before and after the procedure were not accessible. Secondly, in some cases two or more PCI procedures were performed in the same patient. In these cases only the first PCI the individual patient underwent at the age of ≥80 years were studied. Thirdly, since the objective of the study was to evaluate prognosis after PCI in ACS, elective PCI procedures with the indication of stable angina pectoris were excluded (Fig. 1). This is based on the fact that current PCI-indication in the case of stable angina is to relive symptoms rather than prognostic benefit. The study protocol was approved by the Ethical Committee at the University of Gothenburg.

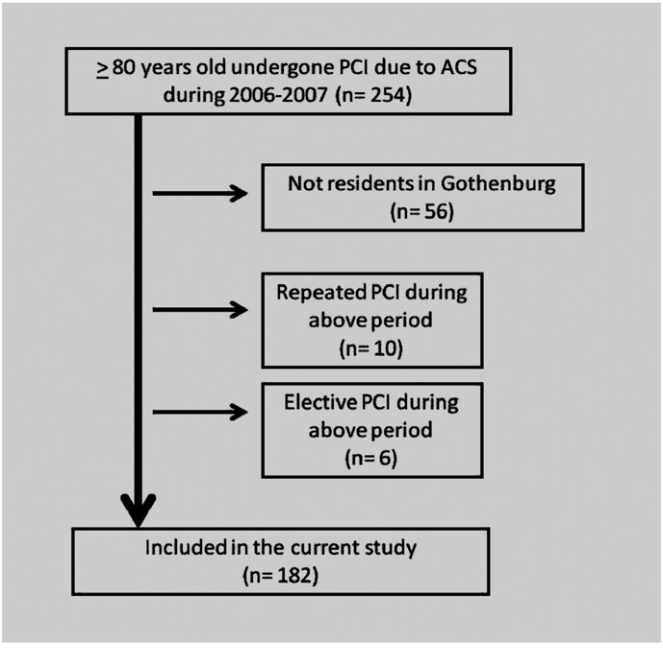

Fig. 1. Outline for patient selection process.

2.2. Laboratory analyses

All laboratory variables examined were analyzed routinely by the laboratory services provided by the Clinical Chemistry Laboratory at Sahlgrenska University Hospital. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula in ml/min.

2.3. Statistics

The results are presented as percentage and mean ± standard deviation (SD) or as median and inter-quartile range (IQR) when values were not normally distributed. In the case of continuous variables, statistical analysis was performed using Student's unpaired *t*-test or the Mann–Whitney U-test for non-normally distributed variables. For discrete variables, the chi-square test was used. One-way ANCOVA or the Mann–Whitney U-test was used to assess statistical significance for non-normally distributed variables. $P < 0.05$ was regarded as statistically significant. All parameters were analyzed with Kaplan Meier analysis. Parameters with "crossing" curves were excluded from univariate analysis. Parameters with high clinical relevance and with low percentage data missing (<17%) as well as with statistical significance from univariate analysis were further tested in multivariate models (Cox proportional hazards analysis) which were done in two steps. At the first step the parameters were divided into two models, in a way to avoid multicollinearity. Then all significant parameters from the first step were further analyzed together in one multivariate model. Factors with statistical significance from all three models were further analyzed with Kaplan–Meier analysis, both in separate and in combinations. The hazard ratios (HR) with confidence intervals (CI) and P-values were presented. The PASW Statistics 18 (USA) statistical package was used for all the data analyses.

The primary endpoint was all-cause mortality based on hospital records which were available for all studied patients during time period January 2 to May 30, 2012.

3. Results

3.1. Clinical characteristics of whole study population and clinical outcome five years after undergoing percutaneous coronary intervention (PCI)

Data were selectively presented in Table 1 and explicitly presented in the supplementary Table. The primary endpoint was all-cause mortality based on hospital records and the Death Registry at the National Board for Welfare in Sweden. All-cause mortality after five years' follow-up was 46.2%. Mean age was 83.7 ± 2.8 years, 62% were male, 18% were physically inactive, 10% had urinary or bowel incontinence and 65% had a history of hypertension. Mean heart rate was 79 ± 24 beats per minute, 76% were in sinus rhythm, and 48% had ejection fraction < 45%. Indications for PCI were STEMI (52%), NSTEMI (36%) and unstable angina (11%). At discharge patients received treatment with aspirin (80%), clopidogrel (89%), beta blockers (84%), ACE-I/ARBs (59%) and statins (71%).

3.2. Clinical characteristics of those patients who died compared with those who survived five years after undergoing percutaneous coronary intervention (PCI)

In general, those who died were older, had a higher percentage of ADL-dependency, higher heart rate, more often valve diseases, more often PCI-related complications, including bleedings, cardiogenic shock, AV-block needing temporary pacemaker, different kinds of coronary artery dissections, occurred more often in those who died. However, other PCI parameters such as the number of stents, the type of stent (bare metal or drug-eluting stents), the access site (radial artery or femoral artery), one or multi-vessel disease and the indication for PCI did

Table 1
Characteristics of the study cohort between survivors and not survivors, at least 5-years after PCI.

	Total	Dead	Alive	P
N	184	84	98	
Age (years)	83.7 ± 2.8	84.2 ± 3	83.2 ± 2.5	0.015
Male (%)	61.5	63.1	60.2	0.689
Social and functional status				
Living alone (%), n = 182	44.5	42.9	45.5	0.526
Dependency in ADL (%), n = 182	6	10.7	2	0.014
Social support dependency (%), n = 159	27.5	32.1	23.2	0.053
Physical inactivity (%), n = 132	18.7	25.0	13.3	0.008
Clinical parameters during admission				
BMI ≥ 26 kg/m^2 (%), n = 166	24.9 ± 3.7	24.7 ± 4.0	25 ± 3.4	0.448
Heart rate (beats/min) (mean ± SD), n = 170	79 ± 23	84 ± 27	75 ± 20	0.012
Systolic BP (mm Hg) (mean ± SD), n = 171	150 ± 29	147 ± 34	152 ± 24	0.192
Diastolic BP (mm Hg) (mean ± SD), n = 170	84 ± 16	84 ± 16	85 ± 16	0.407
Clinical parameters at discharge				
Heart rate (beats/min) (mean ± SD), n = 158	67 ± 14	71 ± 19	64 ± 9	0.004
Systolic BP (mm Hg) (mean ± SD), n = 147	138 ± 22	135 ± 20	139 ± 23	0.256
Diastolic BP (mm Hg) (mean ± SD), n = 147	72 ± 10	72 ± 10	72 ± 10	0.854
Echocardiography				
EF % (mean ± SD), n = 162	48 ± 10.7	46.5 ± 11.5	49.2 ± 9.9	0.117
EF ≤ 45 (%), n = 162	42.3	42.9	41.4	0.574
MR, grade ≥ 1 (scale 0.5–4) (%), n = 152	28	35.7	21.2	0.009
AS of any grade (%), n = 143	12.1	19	3.1	0.008
TR, grade > 2 (scale 0.5–4) (%), n = 152	5.5	10.7	1.0	0.005
CVP ≥ 10 mm Hg (%), n = 126	6	9.5	3.1	0.031
ECG parameters				
Atria fibrillation (%), n = 175	19.8	34.5	7.1	<0.001
AV-block, different types (%), n = 174	12.6	16.7	9.2	0.160
Cardiovascular risk factors				
Current smoker (%), n = 177	4.9	6	4.0	0.560
Prior smoker (%), n = 130	31.5	44.6	32.3	0.010
Hypertension (%), n = 181	64.8	71.4	58.6	0.065
Diabetes mellitus (%), n = 168	19.2	29.8	10.1	0.000
Cardiovascular diseases				
Prior myocardial infarction (%), n = 180	29.1	35.7	23.2	0.078
Angina pectoris (%) n = 181	40.1	45.2	35.4	0.186
Congestive heart failure (%) n = 156	18.1	21.4	15.2	0.130
Cardiovascular interventions				
Prior CABG (%), n = 181	5.5	10.7	1.0	0.004
Prior PCI (%), n = 180	6.6	7.1	6.1	0.749
Laboratory parameters at admission				
Hemoglobin (g/L) (mean ± SD) n = 169	133 ± 16	131 ± 15	134 ± 16	0.136
eGFR (ml/min) (mean ± SD) n = 164	53 ± 17	50 ± 19	55 ± 15	0.038
Total cholesterol (mmol/L) (mean ± SD)	4.5 ± 1.1	4.4 ± 1.1	4.6 ± 1	0.441
Medications at admission				
Aspirin (%)	46.7	56	38.8	0.021
Beta-blockers (%)	52.2	57.1	48.0	0.164
ACE-inhibitors (%)	17.6	23.8	12.2	0.032
Loop diuretics (%)	22.5	33.3	13.3	0.001
PCI indication				
STEMI (%)	35.7	35.4	35.90	0.95
NSTEMI (%)	51.6	51.9	51.50	0.88
Unstable angina pectoris (%)	11	11.4	10.70	0.87

Activities of daily living, ADL. Body mass index, BMI. Mitral valve regurgitation, MR. Aortic valve stenosis, AS. Tricuspid valve regurgitation, TR. Central venous pressure, CVP. Estimated glomerular filtration rate, eGFR. ST-segment elevation myocardial infarction, STEMI. Non-ST-segment elevation myocardial infarction, NSTEMI.

not differ significantly between the two groups. Moreover, those who died were more likely to be prior smokers and had a higher percentage of diabetes mellitus and prior myocardial infarction. No significant differences in cerebrovascular diseases such as prior stroke or transient ischemic attack were found between the two groups. In all patients, a total of 24 co-morbidities were registered. Among them renal insufficiency with eGFR ≤ 30 ml/min was more frequently seen in those who died. Regarding medications, during admission, those who died had more prescriptions of aspirin, warfarin, ACE-I, loop diuretics and sulfonylureas. At discharge, all patients, regardless of whether dead or alive, had significantly increased use of aspirin, beta-blockers, ACE-I, diuretics and statins compared with those during admission. However, at discharge those who died had less aspirin, beta-blockers and statins, but more warfarin, diuretics and proton pump inhibitors compared with those who were alive.

3.3. Predictors of five-year all cause mortality

As shown in Table 2, univariate analyses demonstrated 32 significant predictors of five-year mortality. Further analyses in 2 different

Table 2
Univariate analysis of all-cause mortality, at least five years after PCI. All factors in Table 1 were subject to analysis. Only significant prognostic predictors are listed in the table.

	HR	95% CI	P
Social and functional status			
Physical inactivity	2.4	1.4–4.2	0.002
Walking aid dependency	2.8	1.7–4.6	<0.001
Dependency in activities of daily living	2.9	1.4–5.8	0.003
Urinary or bowel incontinence	2.4	1.2–4.7	0.007
Clinical parameters			
Heart rate > 75 beats/min, at admission.	2.1	1.3–3.4	0.001
Heart rate > 65 beats/min, at discharge.	2.0	1.2–3.3	0.006
Poor R-wave progression	1.7	1.0–2.9	0.040
Dilated right atrium	1.9	1.1–3.4	0.023
Significant aortic valve stenosis	2.2	1.2–3.9	0.005
Mitral valve regurgitation grade ≥ 1[a]	2.2	1.3–3.6	0.001
Tricuspid valve regurgitation grade > 2[a]	5.3	2.5–11.1	<0.001
Pulmonary pressure ≥ 40 mm Hg	1.8	1.0–3.2	0.024
Central venous pressure ≥ 10 mm Hg	2.6	1.2–5.5	0.013
Complications during admission[b]	2.0	1.2–3.5	0.007
Laboratory parameters			
Estimated glomerular filtration rate ≤ 30 ml/min, at admission.	3.5	1.8–6.9	<0.001
High white blood cell count, at admission.	1.0	1.0–1.1	0.004
Hemoglobin gm/L, at discharge.	1.8	1.0–3.3	0.038
Cardiovascular risk factors			
Prior smoker	1.8	1.0–3.1	0.030
Diabetes mellitus	2.3	1.4–3.8	<0.001
Cardiovascular diseases			
Prior coronary artery bypass grafting	2.9	1.4–6.0	0.002
Atrial fibrillation	2.8	1.8–4.5	<0.001
Co-morbidities			
Dementia	2.2	1.1–4.2	0.015
Rheumatic diseases	2.0	1.1–3.6	0.022
Medications, at admission			
Aspirin	1.7	1.1–2.6	0.016
ACE-I/ARBs	1.8	1.1–3.0	0.019
Loop diuretics	2.5	1.5–3.9	<0.001
Medications, at discharge			
Beta blockers	0.3	0.1–0.7	0.004
Statins	0.5	0.3–0.8	0.013
Warfarin	2.1	1.0–4.1	0.031
Proton pump inhibitors	1.7	1.0–2.8	0.027
Corticosteroids	2.3	1.2–4.6	0.012
Sulfonylureas	2.7	1.5–5.0	0.001

[a] Scale 0.5–4.
[b] Local and systemic complications.

multivariate predictive models confirmed 5 significant prognostic predictors: atrial fibrillation, eGFR ≤ 30 ml/min, tricuspid valve regurgitation grade > 2 (scale 0.5–4), dependency in activities of daily living and mitral valve regurgitation grade ≥ 1 (scale 0.5–4) (Tables 3A–3B). Above significant predictors were finally analyzed all together in one model resulting in atrial fibrillation, eGFR ≤30 ml/min and mitral valve regurgitation grade ≥ 1 (scale 0.5–4) as independent predictors of all-cause mortality (Table 3C). Kaplan Meier analysis of predictors from both steps of multivariate analysis demonstrated significant differences in survival in whole population, not only in separate but also in combinations (Figs. 2–4).

Table 3A
Multivariate analysis of all-cause mortality, at least 5 years after PCI (step 1, model 1).

Predictors	HR	95% CI	P
Left ventricular ejection fraction ≤ 35%	1.8	0.8–3.8	0.102
Prior myocardial infarction	1.3	0.7–2.5	0.319
Tricuspid valve regurgitation grade > 2 (scale, 0.5–4)	3.9	1.6–9.6	0.002
Estimated glomerular filtration rate ≤ 30 ml/min	4.0	1.8–10.0	0.003
Hemoglobin ≤ 110 g/l, at admission	1.2	0.5–3.8	0.607

Table 3B
Multivariate analysis of all-cause mortality, at least five years after PCI (step 1 model 2).

Predictors	HR	95% CI	P
Diabetes mellitus	1.6	0.9–2.9	0.078
Dependency in activities of daily living	2.5	1.1–5.6	0.029
Mitral valve regurgitation grade ≥ 1 (scale, 0.5–4)	1.9	1.1–3.3	0.013
Atrial fibrillation	2.4	1.4–4.2	0.002
Prior coronary artery bypass grafting	2.0	0.8–4.9	0.095

4. Discussion

The present study, to our knowledge for the first time, identified prognostic predictors for death five years after undergoing percutaneous coronary intervention (PCI) due to acute coronary syndrome in an octogenarian patient cohort from daily clinical practice (Fig. 5).

In the present study, the death rate of all-cause mortality five years after PCI was 46% which is not high in a population with a mean age of 83 years. However, there were substantial differences in mortality rate between those with more than one risk predictor (16.5% of patient population with mortality rate, 80%) and those with less than one risk predictor (83.5% of patient population with mortality rate, 39%). Kaplan Meier survival analyses showed a mean Survival time at 31 months with confidence interval (22–41) and 71 months with confidence interval (64–77) in high and low risk groups, respectively.

There was no statistical significant difference in survival rate between those with STEMI and those with NSTEMI.

Up to now limited data about prognostic prediction in patients aged ≥ 80 years with acute coronary syndrome were available. Therefore decision-making about PCI has been highly empirical. The majority of our patients were male, had well-controlled blood pressure, had acceptable BMI, had normal hemoglobin level and were in sinus rhythm. Only 6.6% had chronic obstructive pulmonary disease. Such patient profile indeed reflects the reality of daily clinical practice in an elderly patient population ≥ 80 years, where evidence of favorable effects of PCI is lacking. Therefore decision-making has until now often been in favor of relatively healthier elderly individuals. This empiric decision-making has discriminated other elderly patients who might have had benefited from PCI. Nevertheless, despite this selection bias our study population is still representative for this aged group. As a matter of fact, no exclusion was applied when patients were included in this study except age < 80 years and patients not belonging to our hospital's catchment area. Despite the current clinical reality worldwide that the healthier octogenarian patients are often favored for PCI in the setting of ACS in the absence of evidence-based recommendation, our patient cohort is actually not so healthy. A substantial proportion of them have different comorbidities. For instance 65% had hypertension, 24% had AF, 42% had left ventricular ejection fraction < 45%, 27% were in need for social support and 51% and 41% were with vision and hearing disorders respectively.

In order to establish a multivariate predictive model, 145 parameters were registered and divided into 14 domains. To avoid multicollinearity multivariate analysis was done in two steps to pick up all predictors with prognostic predictive value. By Kaplan Meier analysis we were able to further evaluate predictors. For instance moderate tricuspid valve regurgitation gave significant results in Kaplan Meier analysis, but not in multivariate analysis indicating the high risk for type I statistical error.

Table 3C
Multivariate analysis of all-cause mortality, at least 5 years after PCI (step 2).

Predictors	HR	95% CI	P
Estimated glomerular filtration rate ≤ 30 ml/min	3.0	1.2–7.8	0.019
Dependency in activities of daily living	1.6	0.6–4.0	0.273
Mitral valve regurgitation grade ≥ 1 (scale, 0.5–4)	1.8	1.0–3.2	0.043
Atrial fibrillation	2.8	1.5–5.1	0.001
Tricuspid valve regurgitation grade > 2 (scale, 0.5–4)	2.1	0.9–5.1	0.085

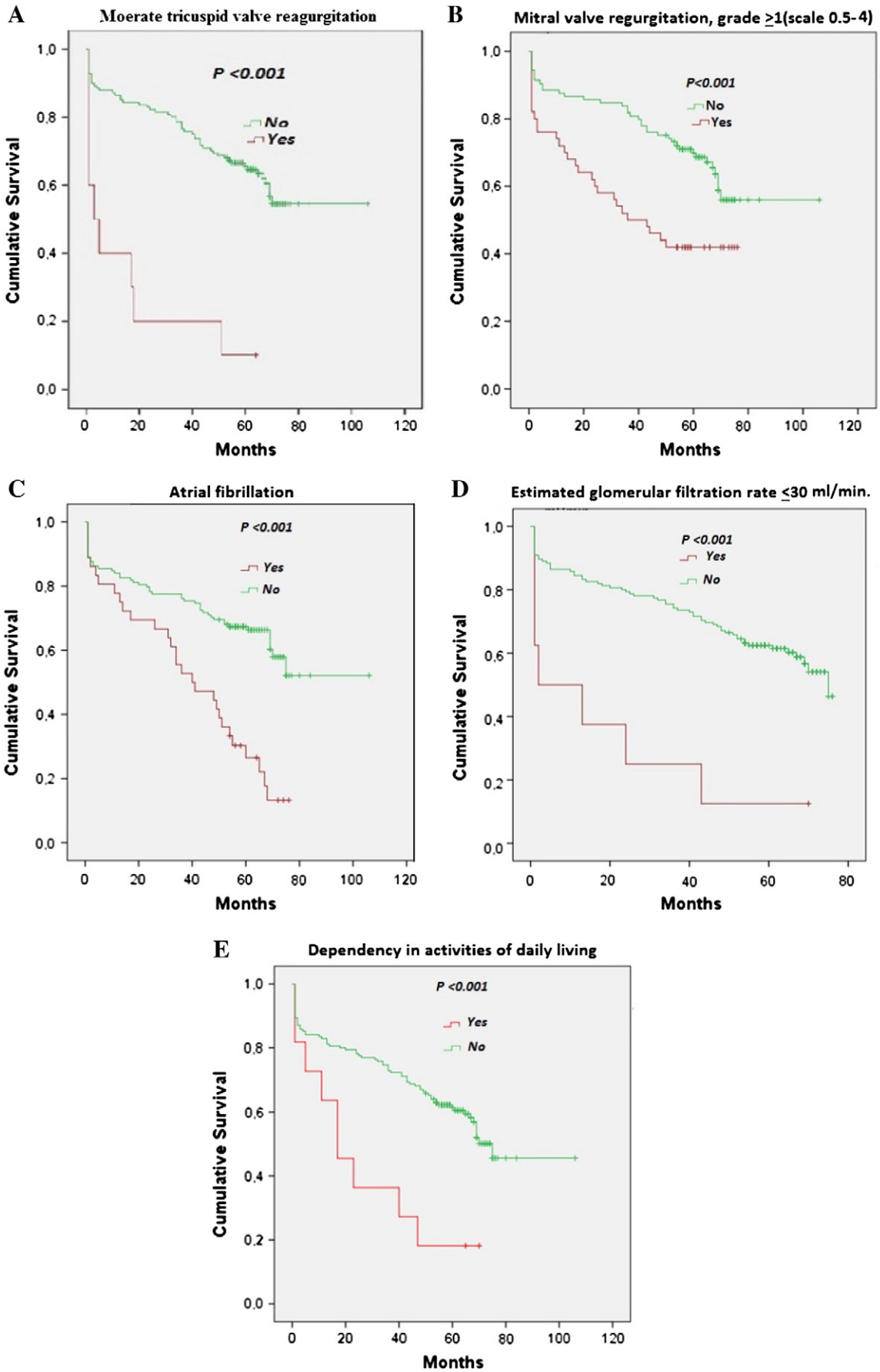

Fig. 2. Kaplan–Meier survival curve for whole study population: A: Tricuspid valve regurgitation as one of prognostic predictors. B: Mitral valve regurgitation as one of prognostic predictors. C: Atrial fibrillation as one of prognostic predictors. D: eGFR ≤ 30 ml/min as one of prognostic predictors. E: Dependency in activities of daily living as one of prognostic predictors.

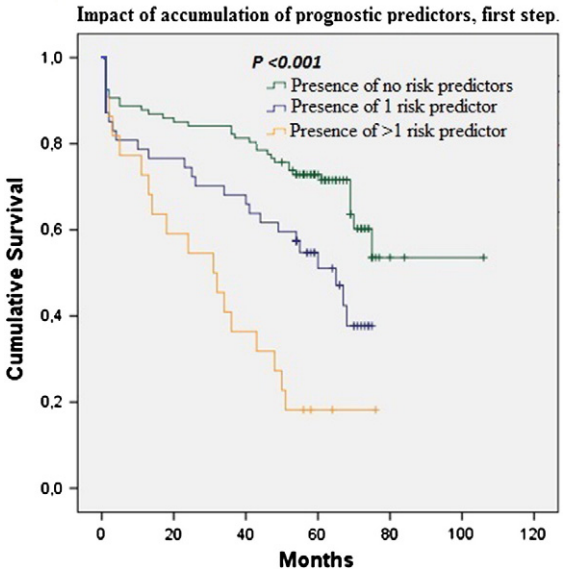

Fig. 3. Impact of accumulation of prognostic predictors from first stage of multivariate analysis on survival.

Through complete multivariate analysis 3 significant predictors were identified as independent predictors for all-cause death; atrial fibrillation, estimated glomerular filtration rate (eGFR) ≤ 30 ml/min and mitral valve regurgitation grade ≥ 1 (scale 0.5–4). Some of them are expected such as eGFR ≤ 30 ml/min and atrial fibrillation. Some of them are not unexpected but have surprisingly high impact on prognosis after PCI such as mitral valve regurgitation grade ≥ 1 (scale 0.5–4). This might indicate that mitral regurgitation is a better marker of left ventricular function than ejection fraction which did not have any impact on survival in our study. Atrial fibrillation and eGFR ≤ 30 ml/min were the strongest predictors for all-cause death. It is well known that AF is usually combined with severe cardiovascular comorbidity [17] and eGFR ≤ 30 indicates severe renal failure which has itself poor prognosis, and is also usually combined with cardiovascular comorbidity [18]. Treatment with beta blockers had a strong positive effect on the prognosis which is consistent with available randomized trials in patients with ischemic heart disease indicating that beta blockers are not only beneficial in younger patients but also in octogenarians.

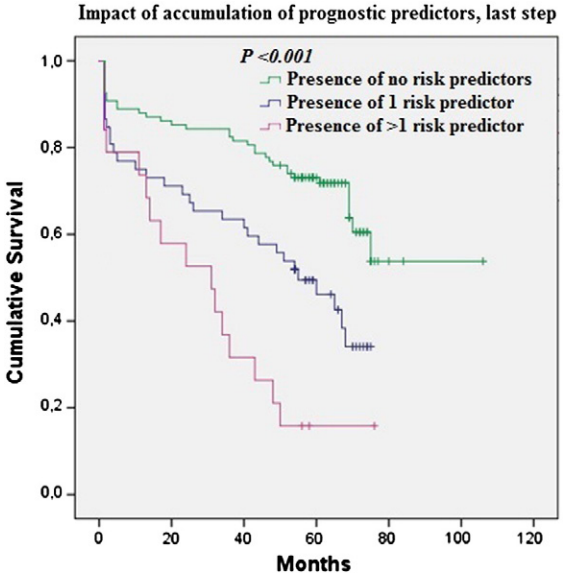

Fig. 4. Impact of accumulation of prognostic predictors from last stage of multivariate analysis on survival.

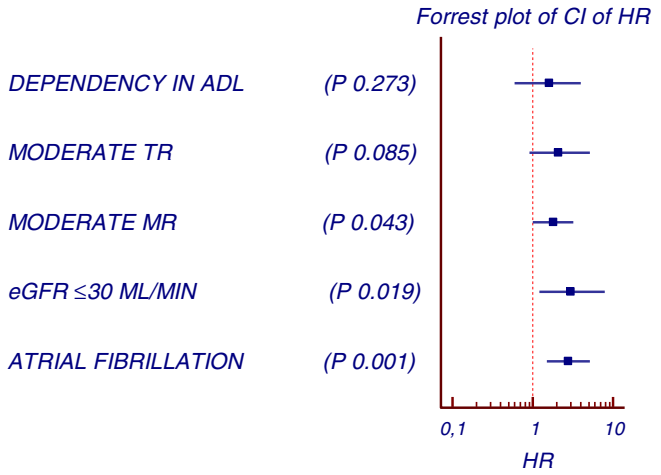

Fig. 5. Forrest plot of different prognostic factors.

Our study also implies that among patients ≥ 80 years there is indeed a big subgroup of patients who have only few risk factors for increased death, with a relative excellent survival rate five years after PCI. However further studies are needed to randomize octogenarian patients between PCI and without PCI and then comparatively study their prognostic risk factors.

5. Study limitations

This is a secondary analysis of clinical data. Despite effort in catching up information as much as possible there are still data missing. Moreover, as mentioned in the discussion, patients in this cohort were selected which however is the main stream in our daily clinical practice and is impossible to be avoided in the view of limited evidence available.

6. Conclusion

In an octogenarian patient cohort who suffered from acute coronary syndrome and undergone PCI in daily clinical practice, we were able to identify prognostic predictors for all-cause death after five years of follow-up.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijchv.2014.05.004.

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