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Long-term follow-up in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention

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Long-term follow-up after primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI) beyond 5 years is poorly described. There are no risk-stratification systems available for routine use. This retrospective, academic, two-centre analysis included consecutive patients who presented with acute STEMI between March 2008 and December 2019. In total, 5263 patients underwent pPCI; all patients were included in the analysis only once. Baseline characteristics were gathered from prospective local registries and based on initial hospitalization. The study enrolled 5263 patients who had been treated with pPCI; it found that cardiovascular mortality was the most frequent cause of death (65.0%) on long-term follow-up to 12 years. Myocardial infarction associated mortality was 27.2%. Cardiovascular mortality was dominant, including in the landmark analysis beyond 1 year. Multivariate analysis identified significant predictors for long-term cardiovascular mortality: age, history of diabetes mellitus, history of renal insufficiency, history of heart failure, Killip class, and successful pPCI at presentation. A predictive model was built to evaluate the risk of cardiovascular death with a high discrimination value (C-statistic = 0.84). Cardiovascular diseases remain the leading cause of long-term mortality after pPCI in the Central European population. Our novel predictive model provides risk stratification; it could identify patients who would experience the greatest benefit from aggressive secondary prevention measures.

Introduction

Primary percutaneous coronary intervention (pPCI) is a well-established minimally invasive non-surgical treatment for ST-segment elevation myocardial infarction (STEMI). To our knowledge, there have been few long-term follow-up reports beyond 5 years for STEMI patients who underwent pPCI. Previous studies have reported long-term 5-year or longer follow-ups and mortality rates after STEMI.[1–9] Despite the use of pPCI, overall long-term mortality after STEMI remains high: ~20.0% over 5 years.[10] The annual risk of mortality between 1 and 5 years after STEMI was ~2.0% per year.[5,9,10] Cardiovascular mortality over 5 years of follow-up has been reported to range from 4.7% to 16.0%.[1,2,4,5,8,9] Annual cardiac mortality in STEMI patients has been reported to range from 1.1% to 1.5%.[4,5,10] A

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Swedish trial [3] reported the complete dataset of all STEMI patients who underwent pPCI between 2006 and 2010 from the national SWEDEHEART registry. A study of cardiovascular mortality after pPCI for STEMI [5] demonstrated that cardiovascular problems were the leading cause of death in the first 6 months.

A predictive model for the cardiovascular mortality risk over long-term follow-up may help to identify patients who could benefit from intensive secondary preventive care. The aim of this study was to analyse missing information concerning long-term outcomes in STEMI patients treated with pPCI in the Czech Republic.

Methods

This retrospective, two-centre analysis included all consecutive patients who presented with acute STEMI between March 2008 and December 2019. The study was approved by the Ethics Committee of the Third Faculty of Medicine, Charles University. The study was performed in accordance with the Declaration of Helsinki. All patients were treated with pPCI and included in the study only once. Baseline characteristics were gathered from prospective local registries and based on initial-hospitalization data. Cardiovascular risk factors and comorbidities were evaluated using medical histories obtained at the time of initial presentation. Mortality data were extracted from the State Institute of Health Information and Statistics of the Czech Republic on 14 May 2021. The complete dataset contained information regarding the date of death and primary cause of death on the basis of the International Classification of Diseases-10 (ICD-10). Cardiovascular mortality was defined as ICD-10 cardiac categories I2xx, I4xx, I5xx, and I6xx. Tumour-associated mortality was defined as ICD-10 tumour categories C and D. Standard definitions of comorbidities, time intervals, and interpretations of coronary angiography were used. Successful pPCI was defined as final residual stenosis $<$20% of the diameter and thrombolysis in myocardial infarction flow 3 by the operator.

The ejection fraction of the left ventricle was evaluated based on echocardiography performed prior to discharge. The Killip class of heart failure was determined at admission in the catheterization laboratory (CathLab). Symptoms-to-CathLab was defined as the interval between patient symptom onset and patient arrival in the CathLab. The STEMI localization was evaluated on the basis of the type of myocardial infarction during discharge; only anterior and inferior myocardial infarctions were included because of clear identification on electrocardiography. Coronary angiography was used to assess the number of diseased coronary arteries, regardless of the causative lesion. Landmark analysis was performed beyond 1 year to exclude cardiovascular mortality related to the myocardial infarction at presentation.

Statistical analysis

The Kolmogorov–Smirnov test for goodness-of-fit was used to determine the normality of the data distribution. Continuous variables are presented as means and standard deviations. Continuous variables were analysed using Student's *t*-test or the Mann–Whitney U-test. Categorical variables were analysed using the χ^2 test and Fisher's exact test. Kaplan–Meier survival analysis was used to calculate the cumulative survival at different time intervals; the log-rank test was used to assess differences in survival. Landmark analysis was used to evaluate the impacts of predictors on mortality. Logistic regression was performed to evaluate the effects of selected predictors on cardiovascular mortality. Predictors of mortality in the univariate analysis with *P*-values $<$0.05 were entered into a backwards stepwise logistic regression model. The predictors that remained significant with *P*-values $<$0.05 were retained in the final model. A receiver operator characteristic curve was used for the analysis of the risk scores[11] to assess discrimination; the Hosmer–Lemeshow goodness-of-fit test was used to assess calibration.[12] Results were considered statistically significant at *P*-values $<$0.05. All statistical analyses were performed using SPSS Statistics software, version 26 (IBM Corp., Armonk, NY, USA). Graphical analyses were performed using Sigma Plot, version 14.

Results

In total, 5263 STEMI patients were treated with pPCI in two centres between March 2008 and December 2019; the mean follow-up duration was 5.1 years. The mean patient age was 63.9 years; of the patients, 29.3% were women and 70.7% were men. The majority of the patients exhibited Killip Class 1 heart failure at the time of admission. The inferior/posterior STEMIs were slightly more common than anterior STEMIs. Approximately half of the patients had single-vessel disease; two-thirds of the patients had a good left ventricular ejection fraction (LVEF) on discharge.

The baseline characteristics of the sample are shown in *Table 1*.

Mortality data

Overall mortality was 26.5% during 12 years of follow-up after pPCI. Approximately two-thirds of the patients (65%) died of cardiovascular causes, while one-third of the patients (35%) died of non-cardiovascular causes. Myocardial infarction-associated mortality was 27.2%. Cardiovascular mortality after STEMI was the main cause of death in the 1st year of follow-up. Kaplan–Meier analysis demonstrated consistently higher risk of cardiovascular mortality after pPCI, compared with tumour-related mortality and other causes of mortality.

The long-term cardiovascular mortality data are shown in *Figure 1*.

Cardiovascular mortality

Univariate predictors for long-term cardiovascular mortality

Univariate analysis revealed factors with a significant influence on cardiovascular mortality: age, sex, arterial hypertension, stroke, renal insufficiency, diabetes mellitus,

Table 1 Baseline characteristics of the study population

Baseline characteristics	
Age (years, mean ± standard deviation)	63.9 ± 12.8
Sex (female/male)	29.3%/70.7%
Medical history at presentation	
Known arterial hypertension	53.4%
Previous stroke	4.8%
Known renal insufficiency	2.5%
Known diabetes mellitus	22.0%
Previous myocardial infarction	14.8%
Previous heart failure	1.9%
Active smokers	56.7%
Clinical characteristics at presentation	
Pain to CathLab (min, mean ± standard deviation)	263.3 ± 266.6
Killip class	
Class 1	84.0%
Class 2	7.0%
Class 3	1.8%
Class 4	5.8%
STEMI localization	
Anterior STEMI	41.9%
Inferior/posterior STEMI	47.6%
Other	10.5%
Coronary angiography	
One-vessel disease	48.5%
Two-vessel disease	29.0%
Three-vessel disease	21.5%
Successful pPCI	95.9%
Clinical characteristics during discharge	
LVEF %	
LVEF >50%	62.5%
LVEF 30–49%	33.5%
LVEF <30%	4.0%

CathLab, catheterization laboratory; LVEF, left ventricle ejection fraction; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

myocardial infarction, heart failure, active smoking, Killip score, STEMI localization, single- or multi-vessel disease, successful pPCI, and LVEF. Patients who were smokers at the time of presentation demonstrated significantly better cardiovascular outcomes. Histories of stroke and renal insufficiency were the strongest predictors for cardiovascular outcomes, with an incidence approximately two-fold higher than in other patients. Patients with cardiovascular mortality were significantly older (73.7 years) at presentation, compared with the remaining patients (61.9 years). Cardiovascular mortality was higher in women (24.3%) than in men (14.3%) ($P < 0.0001$). Women (77.2 ± 11.2 years) were significantly older ($P < 0.0001$) than men (71.2 ± 11.6 years). No significant differences were found in the symptoms-to-CathLab time among survivors and deceased individuals ($P = 0.102$). Most cardiovascular deaths were caused by myocardial ischaemia and heart failures, while pulmonary embolisms and strokes were reported as the causes of death in 9 and 53 patients, respectively.

The predictors for adverse outcomes in STEMI patients after pPCI are shown in *Table 2*.

Multivariate predictors for long-term cardiovascular mortality and predictive model

Multivariate analysis revealed independent predictors for cardiovascular mortality (*Table 3*). Significant predictors based on the regression analysis were identified in the following categories: age, diabetes mellitus, renal insufficiency, heart failure, Killip class, and successful/unsuccessful pPCI. A predictive model was built to evaluate the risk of cardiovascular death with a high discrimination value (C-statistic = 0.84). The receiver operating characteristic curve for the predictive model is shown in *Figure 2*. The equation to assess the long-term risk of cardiovascular death is:

$$\begin{aligned}\text{logit } p = &-8.737 + (0.330 \text{ x known diabetes mellitus}) \\ &+ (0.731 \text{ x Killip class}) \\ &+ (0.722 \text{ x known renal insufficiency}) \\ &+ (1.246 \text{ x past heart failure}) \\ &+ (0.015 \text{ x successful/unsuccessful pPCI}) \\ &+ (0.091 \text{ x age})\end{aligned}$$

Landmark analysis

Cardiovascular mortality was assessed for 1 year and up to 12 years. Landmark analysis was performed beyond 1 year to exclude cardiovascular mortality related to myocardial infarction at presentation. The presence of renal insufficiency was the predictor with the worst outcome. Landmark analysis demonstrated the following predictors: diabetes mellitus, renal insufficiency, Killip class, and successful/unsuccessful pPCI (*Figure 3*).

Discussion

Long-term mortality after STEMI remains high. The result of this trial is unique about the possibility of identifying patients with a high risk of cardiovascular death with little or no symptoms.

Cardiovascular diseases were responsible for most deaths in our cohort, including in the landmark analysis after the 1st year.

We built a predictive model based on the multivariate predictor analysis. This predictive model could identify patients at high risk of cardiovascular death in the long-term perspective.

Geographical differences may influence cardiovascular mortality. A Scandinavian study [4] found that non-cardiovascular mortality was the major cause of death during long-term follow-up beyond 30 days after pPCI for STEMI; in our study, cardiovascular mortality was the major cause of death. These findings could reflect different lifestyles among nations. In the Czech Republic, there is a high prevalence of cardiovascular risk factors.[13] These geographical differences may have impacts on local primary and secondary preventive care.

In a previous study [5], multivariate analysis showed that independent risk factors for all-cause mortality on follow-up beyond 6 months after pPCI for STEMI included advanced age, previous heart failure, renal dysfunction, and liver cirrhosis. In our study, multivariate analysis showed that predictors for cardiovascular mortality were similar to

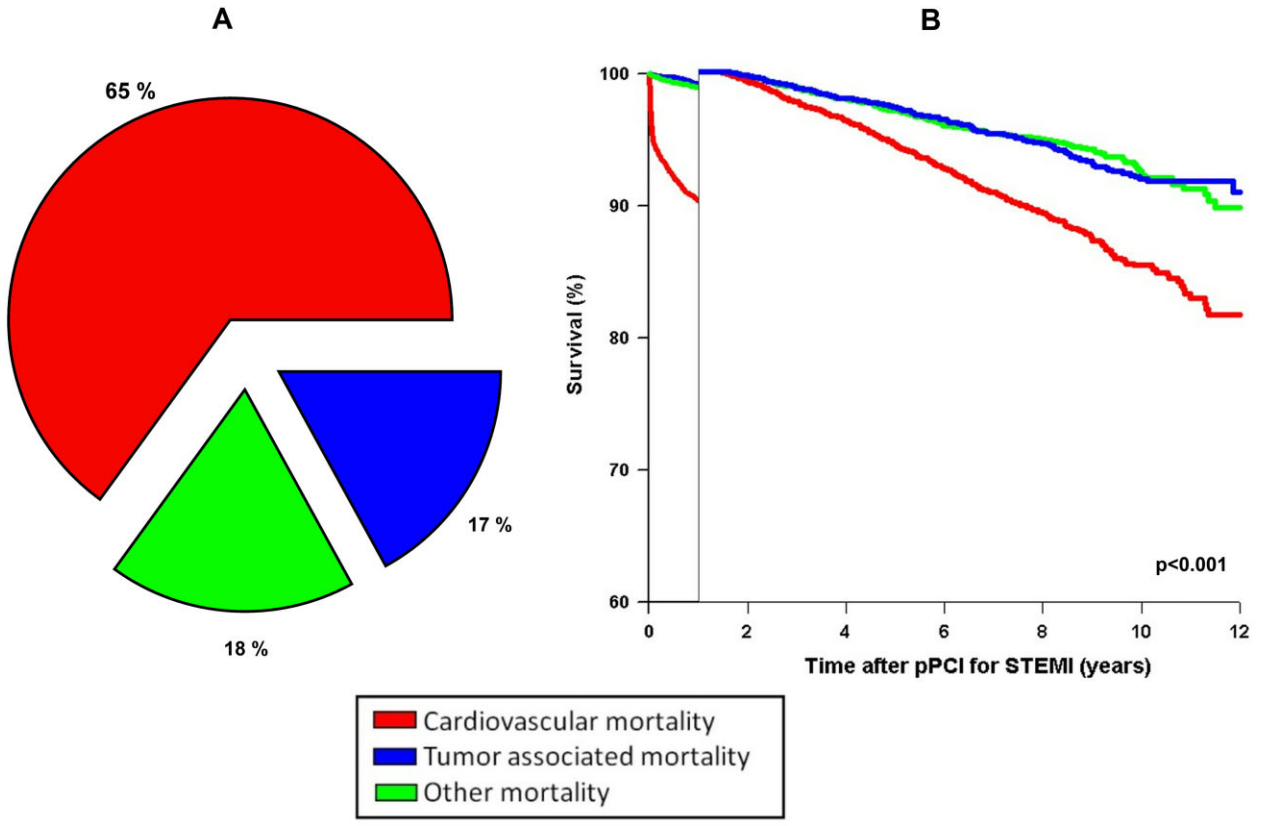

Figure 1 (*A*) Long-term mortality analysis according to the cause of death. (*B*) Landmark analysis for long-term cardiovascular mortality. pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

the predictors for all-cause mortality; they included age, renal insufficiency, and previous heart failure (*Table 3*). Predictors for 1-year cardiac mortality were identified in a previous study[14]: age, diabetes mellitus, Killip class, cardiac arrest, creatinine, haemoglobin and troponin on admission, and left ventricular ejection fraction during hospitalization. Predictors for long-term cardiovascular mortality after the 1st year were age, diabetes mellitus, renal insufficiency, previous heart failure, Killip class at presentation, and successful pPCI. Patients who were smokers at presentation had better outcomes than did non-smokers. This paradox was previously reported[4, 15] it presumably arises because many patients quit smoking for secondary prevention.

With respect to the predictive model for cardiovascular mortality presented above, patient stratification could help to provide more focused secondary preventive care for high-risk patients. Modern hypolipidaemic treatment using PCSK9 inhibitors is effective for high-risk patients. For better follow-up, computed tomography angiography, stress examinations, and other examinations may be used.

The Pain-to-CathLab time was not a significant predictor for long-term cardiovascular mortality. In the event of chest pain, early emergency calls could shorten the time from pain to diagnosis. However, the quality of the time period reported by the patients and physicians is also questionable. Mortality in women was higher because women in the sample were significantly older (6.0 years).

Recurrent angina is a significant symptom in long-term follow-up in patients after pPCI for STEMI which may have an important impact on the intensity of the follow-up. Patients with recurrent stable angina are more likely to be older, women with previous heart failure, multi-vessel disease and have a higher risk of coronary revascularization in long-term follow-up against patients without stable angina.[16] The presence of stable angina is weakly associated with cardiovascular mortality, myocardial infarction, and stroke.[16]

In the Czech Republic, patients have regular check-ups via ambulatory cardiologists in secondary prevention of cardiovascular morbidity and mortality. Patients with recurrent angina are often seen by an ambulatory cardiologist before an acute coronary syndrome occurs. The question is how to identify patients with little or no symptoms.

The matter of more intensive long-term follow-up in patients after STEMI with the presence of severe comorbidities identified via our trial is debatable. On the one hand, the specific and more expensive treatment is usually reserved for patients with better prognoses, mostly patients with less comorbidities. But on the other hand, more intensive follow-up may have an impact not only on the higher usage of expensive medication but also may focus better on compensation of blood pressure, diabetes mellitus, etc. via standard medication resulting in better compensation of comorbidities. These factors may have an impact on long-term cardiovascular outcomes. Better compensation

Table 2 Cardiovascular mortality

Cardiovascular death	No ($n = 4352$)	Yes ($n = 911$)	*P*-value
Baseline characteristics			
Age (years, mean ± standard deviation)	61.9 ± 12.0	73.7 ± 11.7	<0.001
Sex (female/male)	75.7%/85.7%	24.3%/14.3%	<0.001
Medical history at presentation			
Known arterial hypertension	14.0%	20.1%	<0.001
Previous stroke	22.2%	51.7%	<0.001
Known renal insufficiency	22.7%	56.3%	<0.001
Known diabetes mellitus	15.3%	24.3%	<0.001
Previous myocardial infarction	21.6%	35.1%	<0.001
Previous heart failure	9.9%	18.5%	<0.001
Active smokers	15.9%	8.1%	<0.001
Clinical characteristics at presentation			
Pain to CathLab (min, mean ± standard deviation)	261.6 ± 269.6	269.0 ± 256.4	0.102
Killip class			<0.001
Class 1	87.6%	12.4%	
Class 2	64.6%	35.4%	
Class 3	55.7%	44.3%	
Class 4	43.2%	56.8%	
STEMI localization			0.001
Anterior STEMI	81.2%	18.8%	
Inferior/posterior STEMI	84.9%	15.1%	
Coronary angiography			<0.001
One-vessel disease	88.7%	11.3%	
Two-vessel disease	83.0%	17.0%	
Three-vessel disease	70.1%	29.9%	
Successful pPCI	84.2%	15.8%	<0.001
Unsuccessful pPCI	49.2%	50.8%	
LVEF %			<0.001
LVEF >50%	91.2%	8.8%	
LVEF 30–49%	77.2%	22.8%	
LVEF <30%	39.7%	60.3%	

CathLab, catheterization laboratory; LVEF, left ventricle ejection fraction; pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 3 Predictive model for cardiovascular mortality

	Odds ratio	95% confidence interval	*P*-value
Medical history at presentation			
Age	1.0950	1.0839–1.1063	<0.0001
Known diabetes mellitus	1.3915	1.0873–1.7808	0.0314
Known renal insufficiency	2.0586	1.1224–3.7757	0.0202
Previous heart failure	3.4773	1.6171–7.4774	0.0025
Clinical characteristics at presentation			
Killip class	2.0780	1.8760–2.3019	<0.0001
Successful/unsuccessful pPCI	1.0153	1.0049–1.0259	0.0019

pPCI, primary percutaneous coronary intervention.

of cardiovascular morbidity may have an impact on the whole outcome of patients. We suppose that modern treatment for patients with hyperlipidaemia via PCSK9i and SGLT2i for patients with diabetes mellitus or heart failure may lead to a better cardiovascular outcome.

Age as a predictor of death should be assessed separately. Older patients more often have multi-vessel ischaemic heart disease with calcified lesions that may not be appropriate for revascularization. This may lead to a more conservative approach.

Overall, centralized secondary prevention and complex national registries could provide an opportunity and overview for better follow-up of high-risk patients; they might enable more intensive and precise treatment of the underlying risk factors.

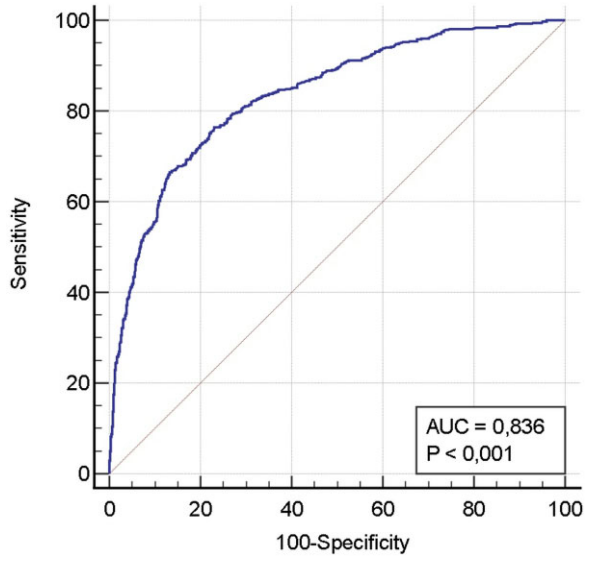

Figure 2 Receiver operating characteristic curve for the predictive model.

Limitations

This was a retrospective, academic study with a large sample from two cardiac centres. Our dataset only included parameters from two independent hospital registries; therefore, it did not include routinely collected data [e.g. the type of stent used (bare-metal or drug-eluting) and whether only balloon angioplasty was conducted]. The long-term outcomes were only evaluated from a mortality perspective; data regarding morbidity and hospitalizations were unavailable.

Conclusion

The mortality associated with myocardial infarction remains high despite intensive secondary preventive care. Cardiovascular diseases remain the leading cause of long-term mortality after pPCI in the Central European population. Our novel predictive model provides risk stratification and could identify high-risk patients who might benefit from a more aggressive approach. Benefits may include

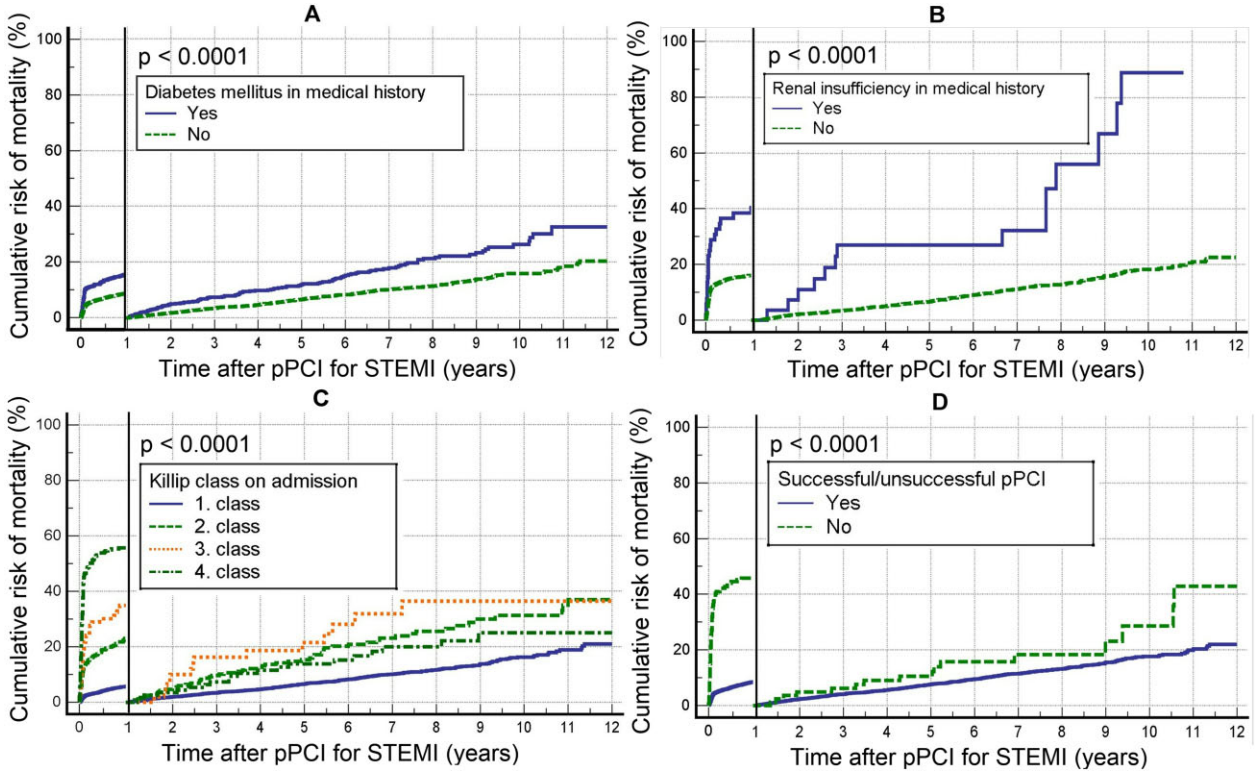

Figure 3 (*A*) Patients with a history of diabetes mellitus at presentation. (*B*) Patients with a history of renal insufficiency at presentation. (*C*) Killip classification for heart failure at presentation. (*D*) Patients with successful/unsuccessful primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. pPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

improvements in quality of life and life expectancy, as well as reduced socioeconomic consequences.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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