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Stepwise relationship between delay to percutaneous coronary intervention and long-term mortality in patients with non-ST-segment elevation myocardial infarction

Short title: Delay to PCI and mortality in NSTEMI patients

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WHAT'S NEW?

According to the most recent guidelines on the management of acute coronary syndromes without ST-segment elevation, in non-very-high-risk patients with non-ST-segment elevation myocardial infarction (NSTEMI) coronary angiography with the intent to perform revascularization should be performed within 24 hours of hospital admission. However, since the previous studies used different, somehow arbitrary definitions of very early invasive strategies, there was little data on whether there is a stepwise relationship between the time to percutaneous coronary intervention (PCI) and long-term mortality rate in patients with NSTEMI undergoing coronary revascularization within 24 hours of admission. Therefore, we aimed to evaluate the relationship between the door-to-PCI time and long-term mortality in 37 589 patients with NSTEMI, included in the nationwide registry of acute coronary syndromes. After adjusting for 33 clinically relevant variables, we found that the longer the door-to-PCI time, the higher were 12-month and 36-month all-cause mortality rates.

ABSTRACT

Background: Current guidelines recommend coronary catheterization in patients with non-ST-segment elevation myocardial infarction (NSTEMI) within 24 hours of hospital admission. However, whether there is a stepwise relationship between the time to percutaneous coronary intervention (PCI) and long-term mortality in patients with NSTEMI treated invasively within 24 hours of admission has not been established yet.

Aims: The study aimed to evaluate the association between the door-to-PCI time and all-cause mortality at 12 and 36 months in patients with NSTEMI, presenting directly to the PCI-capable center, who underwent PCI within the first 24 hours of hospitalization.

Methods: We analyzed data of patients hospitalized for NSTEMI between 2007–2019, included in the nationwide registry of acute coronary syndromes. Patients were stratified into twelve groups based on 2-hour intervals of door-to-PCI time. The mortality rates of patients within those groups were adjusted for 33 confounding variables by propensity score weighting method using overlap weights.

Results: A total of 37 589 patients were included in the study. The median age of included patients was 66.7 (interquartile range [IQR], 59.0–75.8) years, 66.7% were male, and the median GRACE Score was 115 (98–133). There were increasing 12-month and 36-month

mortality rates in consecutive groups of patients stratified by 2-hour door-to-PCI time intervals. After adjustment for patient characteristics, there was a significant positive correlation between the time to PCI and mortality rates ($r_s = 0.61$; $P = 0.04$ and $r_s = 0.65$; $P = 0.02$ for 12-month and 36-month mortality, respectively).

Conclusions: The longer the door-to-PCI time, the higher were 12-month and 36-month all-cause mortality rates in NSTEMI patients.

Key words: coronary revascularization; early invasive strategy; non-ST-elevation myocardial infarction; percutaneous coronary intervention

INTRODUCTION

The routine invasive strategy has been shown to be superior to optimal medical management strategy in patients with non-ST-segment elevation myocardial infarction (NSTEMI). However, the optimal timing of coronary revascularization has not been established yet. Current guidelines on non-ST elevation acute coronary syndromes (NSTE-ACS) recommend coronary angiography with the intent to perform revascularization within 24 hours from hospital admission in patients with NSTEMI, except for very-high risk patients who should undergo coronary catheterization within 2 hours [1].

Currently, no evidence supports the routine immediate invasive strategy in all patients with NSTE-ACS. Unlike the NSTEMI, unstable angina does not lead directly to myocardial injury; therefore, the benefits of very early revascularization might be less pronounced in those patients [2]. Although pathophysiologically plausible that more rapid (within 24 hours) revascularization in patients with NSTEMI is associated with a mortality rate reduction, it has not been proven in randomized clinical trials [3]. However, in the largest randomized clinical trials comparing different timing strategies in NSTE-ACS patients, the calculation of the time to coronary angiography was based on the randomization time, complicating the interpretation of the results [1]. Moreover, the proportion of patients who underwent coronary revascularization was lower than 70% in most of these studies [4, 5].

The aim of the study was to evaluate whether there is a stepwise association between door-to-PCI time and long-term mortality in a cohort of NSTEMI patients who were admitted directly to a PCI-capable center and underwent PCI within 24 hours of admission.

METHODS

Patients

We analyzed the data of patients admitted to the hospital for NSTEMI between July 2007 and July 2019, included in a nationwide, prospective registry of acute coronary syndromes (Polish Registry of Acute Coronary Syndromes; PL-ACS). More details regarding PL-ACS have been described previously [6–10]. Briefly, PL-ACS is a clinical registry established in 2003, which was a joint effort of the Silesian Center for Heart Diseases in Zabrze and the Polish Ministry of Health. The goal of the PL-ACS registry is to collect data regarding clinical characteristics, treatment modalities, and outcomes of patients with acute myocardial infarction or unstable angina in Poland. Data are entered into the database by the attending physician via web form.
In the current analysis, patients with NSTEMI, who presented directly to the PCI-capable center via self-transport or arrived by ambulance, and underwent PCI during the index hospitalization, were considered. The exclusion criteria were the following: out-of-hospital cardiac arrest before admission, pulmonary edema or cardiogenic shock on admission, or missing data on these variables, as well as pain-to-admission time longer than 72 hours and admission-to-PCI time longer than 24 hours. Included patients were stratified into twelve groups based on 2-hour intervals of door-to-PCI time. Definitions used in our study are presented in the Supplementary Materials, *Definitions*.

The outcome of interest and follow-up

The outcome of interest of our study was all-cause mortality analyzed at 12 and 36 months. Vital statuses and exact death dates were obtained from the National Health Fund, the only payer for health care services financed from public funds in Poland. Follow-up data were available for 37 585 (99.99%) patients.

Statistical analysis

Continuous variables were presented as median and interquartile range. Categorical variables were presented as percentages. Door-to-PCI time in patients stratified by year of admission was compared using Jonckheere's trend test. Mortality rates in the 12 groups of patients who underwent PCI within 24 hours of hospital admission, stratified by 2-hour intervals, were presented as crude mortality rates and adjusted by propensity score weighting method using overlap weights to reduce indication bias. Overlap weighting is a novel statistical method based on propensity score to adjust for differences in characteristics between analyzed groups by assigning weights to each patient that are proportional to the probability of that patient

belonging to the opposite treatment group [11, 12]. The propensity scores were obtained using logistic regression model which included 33 clinically relevant baseline characteristic variables, which might have influenced the decision of catheterization timing. The complete list of these variables is presented in *Supplementary material, Table S1*. Before developing the propensity score model, missing data were imputed using the k-nearest neighbor algorithm. The correlations between the 12-month and 36-month unadjusted and adjusted (by propensity score weighting method using overlap weights) mortality rates and consecutive 2-hour interval groups (as ordinal variable) were analyzed using Spearman's rank correlation coefficient, and presented graphically using LOESS smoothing function. The level of statistical significance was P <0.05 (two-tailed). R version 3.6.1 (R foundation for Statistical Computing, Vienna, Austria) and PSweight: An R Package for Propensity Score Weighting Analysis, as well as Statistica version 13.3 (TIBCO Software, CA, US), were applied for computational analyses.

RESULTS

A total of 37 589 patients with NSTEMI, who underwent PCI within the first 24h of admission, were included. The frequencies and percentages of patients in the groups stratified by 2-hour-intervals of door-to-PCI time are shown in Figure 1. The median door-to-PCI time was 2.7 (1.0–7.3) hours and was increasing during the study period in patients stratified by year of admission ($P_{\text{for trend}}$ <0.001) (Figure 2). The median age of patients was 66.7 (IQR, 59.0–75.8), and two-thirds were male (66.7%). The median GRACE score was 115 (98–133). Fifty-one percent of patients had multivessel disease on coronary angiography, and in 2% of patients left main was an infarct-related artery. CABG was performed in 1.0% of patients, and 2.5% were referred for CABG after discharge. The baseline clinical, angiographic, and procedural characteristics and treatment at hospital discharge are shown in Table 1. The in-hospital mortality rate in the whole study group was 1.7%. The unadjusted 12-month mortality rate varied between 7.1% to 9.2% in groups of patients who underwent PCI between 2–4 hours and 16–18 hours after admission, respectively (Figure 3A). The minimal unadjusted 36-month mortality rate was observed in the group who underwent PCI between 2–4 hours after admission, and the maximal mortality rate was in patients who received revascularization within 20–22 hours from admission (13.6% and 18.7%, respectively; Figure 4A). After adjustment for clinical and angiographic characteristics, there was a significant positive correlation between consecutive 2-hour-intervals of door-to-PCI time and the 12-month (r_s = 0.61; P = 0.04) as well as 36-month (r_s = 0.65; P = 0.02) mortality rates (Figures 3B and 4B).

DISCUSSION

Our study showed that longer door-to-PCI time in patients with NSTEMI who underwent PCI within the first 24 hours from admission was associated with increased adjusted 12-month and 36-month mortality rates. Contrary to previous studies, which used different, mostly somehow arbitrarily selected cut-offs of very early invasive strategies [13], which limits the clinical applicability of these findings, we showed that door-to-PCI was proportionally associated with increased mortality, i.e., the longer the in-hospital delay to PCI, the higher the mortality rate.

To date, only a few large randomized controlled trials aimed to compare the strategy of immediate or very early invasive coronary angiography with standard treatment in non-high-risk patients with NSTE-ACS. VERDICT trial (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) showed that very early invasive coronary evaluation (within 12 hours) does not improve primary outcome compared with deferred strategy (within 48 to 72 hours), except for patients with the highest risk according to the GRACE risk score (>140) [5]. On the other hand, the randomized RIDDLE-NSTEMI Study ("Randomized Study of ImmeDiate Versus DeLayEd Invasive Intervention in Patients With Non ST-segment Elevation Myocardial Infarction") demonstrated that immediate invasive intervention (<2 hours after randomization), as compared with the delayed intervention (2 to 72 hours, median 61 hours), was associated with a lower rate of death or new myocardial infarction at 30 days. It was mainly attributable to a decrease in the new myocardial infarction rate before catheterization in the immediate-intervention group [14]. The aim of the recent clinical trial (Early or Delayed Revascularization for Intermediate and High-Risk Non ST-Elevation Acute Coronary Syndromes; EARLY) was to compare very early (<2 hours) and delayed (12–72 hours) invasive strategies. In this study, the reduction of the primary endpoint (composite of cardiovascular death and recurrent ischemic events at one month) was observed in the very early invasive strategy group. However, it was driven only by a reduction in recurrent ischemic events [15]. While another study (The Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI; LIPSIA-NSTEMI Trial), showed no difference in terms of peak CK-MB level in NSTEMI patients who underwent immediate invasive strategy [16].

Considering that “real-world” patients usually do not experience such long delays as patients in deferred strategy groups in clinical trials, Mahendiran et al. [17] aimed to compare outcomes of propensity-score matched patients with door-to-catheter times <12 hours and 12–24 hours hours. They found no difference in one-year major adverse cardiovascular events between these groups. Contrary to this study, our analysis encompassed a significantly larger cohort.

Moreover, we have used overlap weighting, a novel statistical method that, compared to classic propensity score matching, allows for the adjusted comparison of many groups. The advantages of this method are greatest when analyzed groups are initially very different in terms of baseline characteristics, as in the case of patients undergoing very early vs. delayed PCI [11, 12]. Although statistically significant, the association between the longer door-to-PCI time and increased mortality rates presented in our study was moderate so it might be hardly detectable in the case of a small sample size.

Immediate or very early invasive strategies for NSTE-ACS were also compared to delayed strategy in several other small randomized trials and observational studies, providing inconclusive results [18–20]. Inconsistent findings of those studies might result from non-negligible differences in timing strategies, definitions, study designs, sample sizes, or endpoints [21]. Moreover, the recent advances in the pharmacological management of NSTE-ACS might reduce the potential benefit of early PCI. Considering that our study encompassed 2007–2019, utilization of modern guideline-recommended therapies, especially potent P2Y12 inhibitors in the study population, was low [22]. However, we adjusted the propensity score model for the admission year to adjust our results for advances in pharmacological therapy over the study period.

Considering the present study's results and other studies, it seems that in patients with NSTEMI admitted directly to a PCI-capable center, avoiding unnecessary delays to PCI might be beneficial. It is of special importance in the context of increasing in-hospital delays to PCI in recent years, observed in our study. However, further randomized clinical trials are necessary to establish whether there is a benefit from this management.

Study limitations

The main limitation of our study was the observational study design. Therefore our study could not confirm the causal relationship between time to PCI and mortality. Moreover, information on the cause of death (cardiovascular or non-cardiovascular) or incidence of other adverse events in the follow-up and values of myocardial injury markers were unavailable for the study cohort, so the mechanism of increased all-cause mortality in patients with longer door-to-PCI time remains unclear. In addition, previous studies showed that the outcomes of emergency PCI might be associated with operator volume [23]. However, we could not adjust our analysis results for this potential confounder due to the lack of operator-level data in the PL-ACS. Finally, the majority of patients underwent PCI within the first hours following admission, and the median door-to-PCI time was shorter than reported for other countries [17, 24]. The

possible explanation might be the inclusion of only patients transported directly to the PCI-capable center because we could not establish the other patients' exact admission times. Moreover, the obligatory on-site standby rather than on-call duties of catheterization laboratory staff and local clinical practice in Poland may be associated with reduced delay to PCI. Therefore the results may not fully apply to other healthcare systems.

CONCLUSIONS

After adjustment for clinically relevant confounders, in patients with NSTEMI, who were admitted directly to the PCI-capable center and underwent PCI within 24 hours from admission, there were higher 12-month and 36-month mortality rates associated with longer door-to-PCI time.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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Table 1. Clinical characteristics, angiographic findings, treatment, and short- as well as long-term mortality of patients with NSTEMI who underwent PCI within 24 hours of admission.

Variables	**All patients** (n = 37 589)
Baseline characteristics	
Male sex, n (%)	25 086 (66.7)
Age, years, median (IQR)	66.7 (59.0–75.8)
Hypertension, n (%)	29 228 (77.8)
Hypercholesterolemia, n (%)	17 250 (45.9)
Obesity, n (%)	8 242 (22.4)
Previous stroke, n (%)	1 384 (3.7)
Current smokers, n (%)	10 058 (26.8)
Type 2 diabetes mellitus, n (%)	9 960 (26.5)
Chronic kidney disease, n (%)	2 257 (6.0)
Atrial fibrillation on admission, n (%)	2 009 (5.3)
Previous MI, n (%)	8 912 (23.7)
Previous PCI, n (%)	7 983 (21.2)
Previous CABG, n (%)	2 185 (5.8)
PAD, n (%)	1 795 (4.8)
LVEF <40%, n (%)	4 128 (11.0)
Pain-to-admission time, hours, median (IQR)	5.7 (2.8–12.4)
Killip class II, n (%)	3 980 (10.6)
GRACE Risk Score, median (IQR)	115 (98–133)
Door-to-PCI time, median (IQR)	2.7 (1.0–7.3)
LM – IRA, n (%)	766 (2.0)
MVD, n (%)	6 938 (51.4)
CABG during the index hospitalization, n (%)	380 (1.0)
CABG planned after discharge, n (%)	956 (2.5)
Medical therapy at discharge	

Aspirin, n (%)	34 890 (94.5)
Clopidogrel, n (%)	30 605 (82.9)
Ticagrelor, n (%)	2 462 (6.7)
Prasugrel, n (%)	401 (1.1)
Beta-blocker, n (%)	31 552 (85.5)
ACE-I/ARB, n (%)	30 093 (81.4)
Statin, n (%)	32 784 (88.7)
Outcomes	
In-hospital mortality rate, n (%)	638 (1.7)
12-month mortality rate, n (%)	2 935 (7.8)
36-month mortality rate, n (%)	5 550 (14.8)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; IRA, infarct-related artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; MVD, multivessel disease; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention

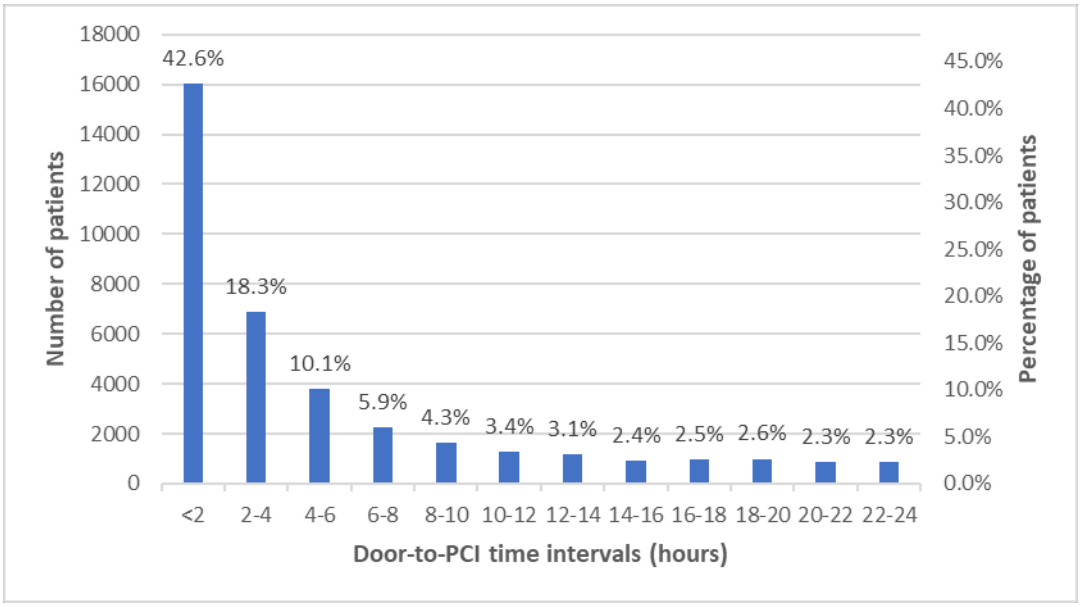

Figure 1. Frequencies and percentages of patients stratified by the door-to-PCI time (hours)

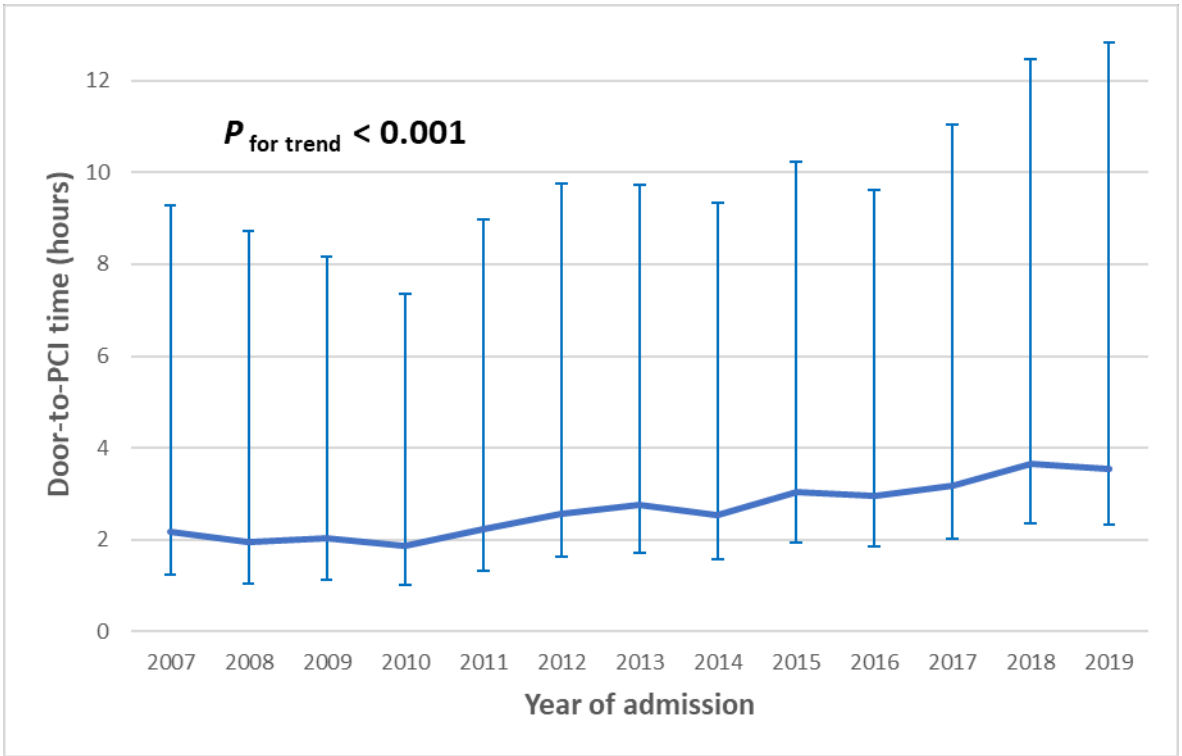

Figure 2. Median (interquartile range) door-to-PCI time (hours) according to a year of admission

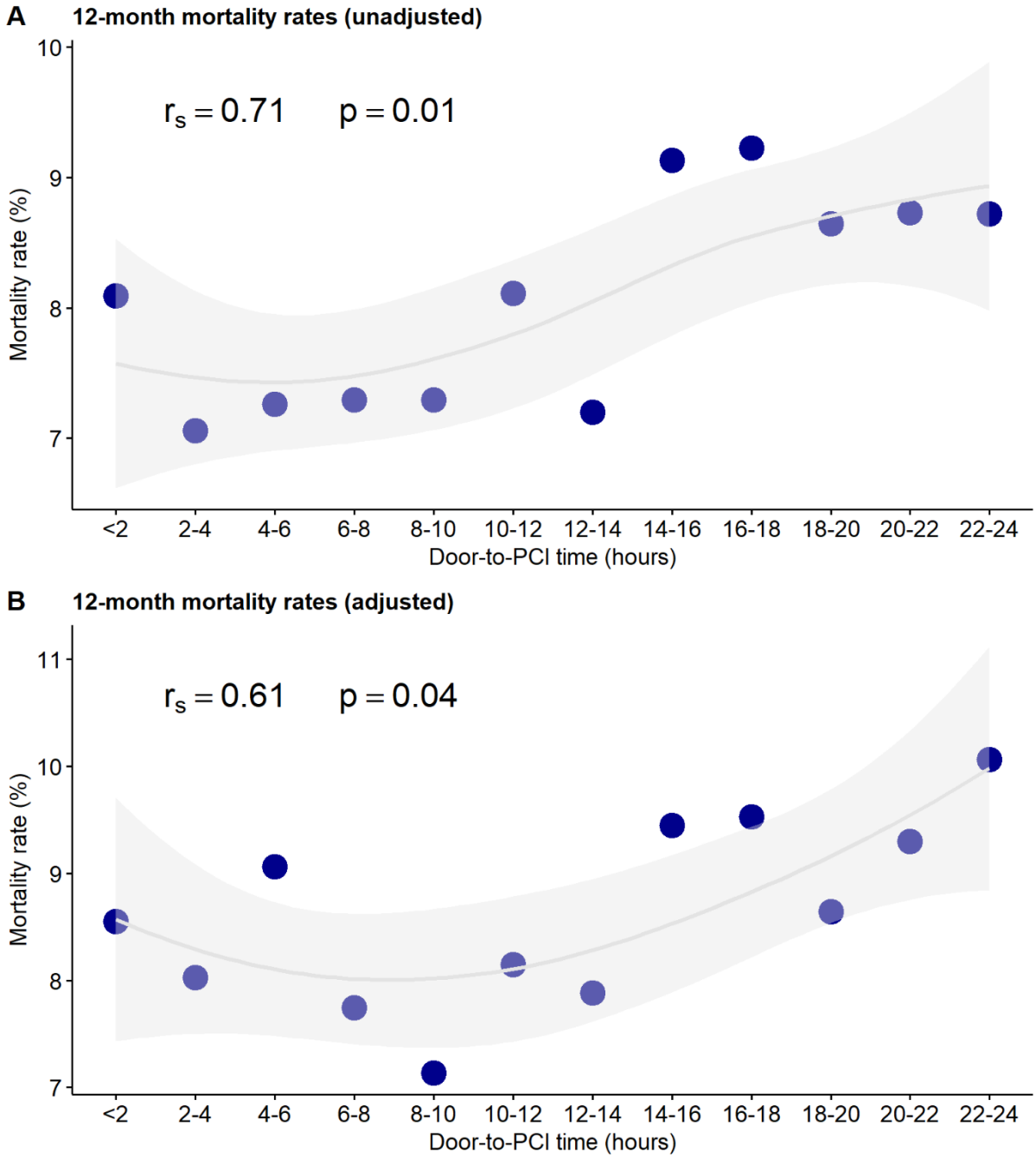

Figure 3. Unadjusted (**A**) and adjusted (**B**) 12-month mortality rates in patients stratified by the door-to-PCI time

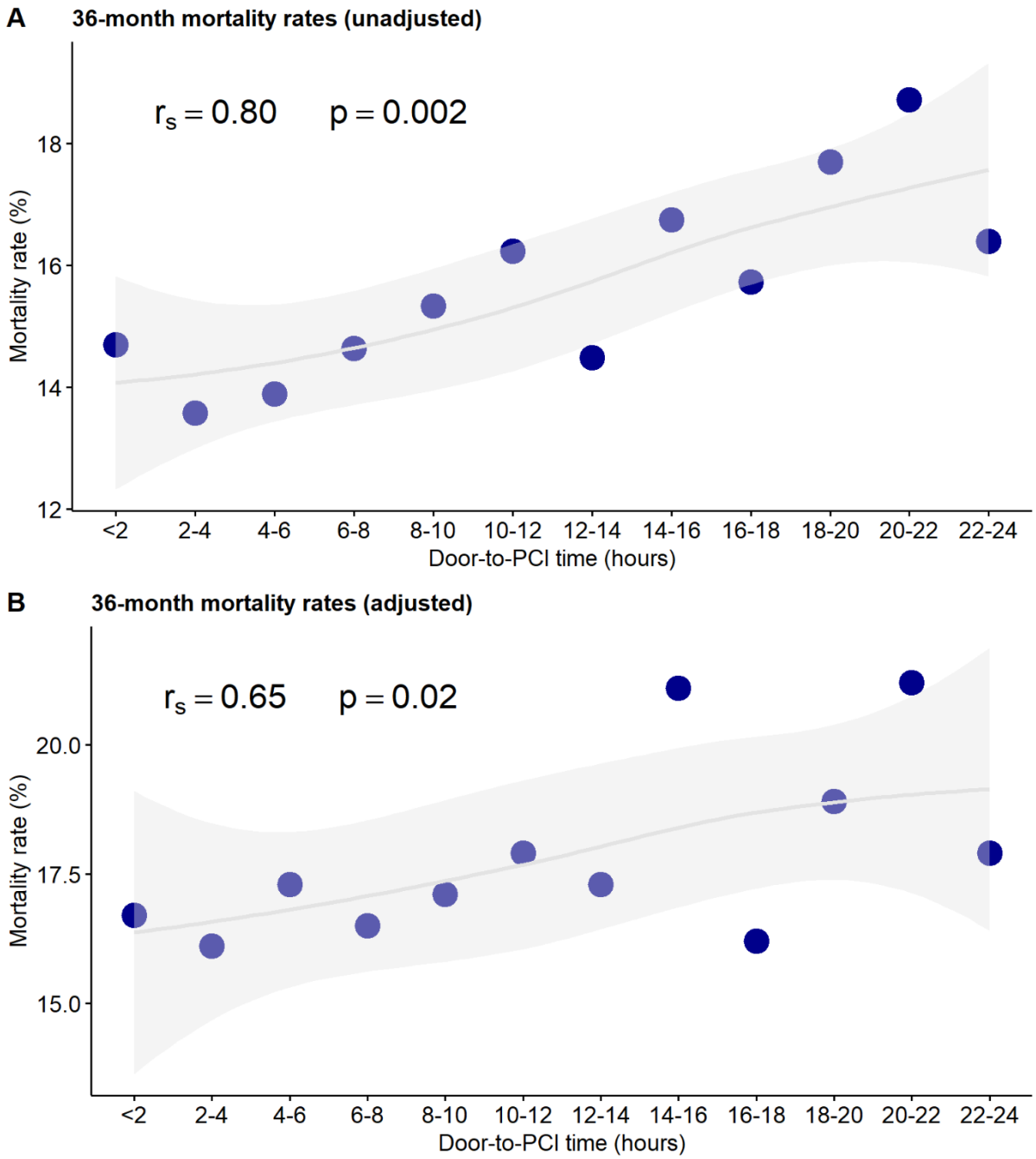

Figure 4. Unadjusted (**A**) and adjusted (**B**) 36-month mortality rates adjusted for confounders in patients stratified by the door-to-PCI time