Article

Impact of Smoking Status on Mortality in STEMI Patients Undergoing Mechanical Reperfusion for STEMI: Insights from the ISACS–STEMI COVID-19 Registry

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Abstract: The so-called "smoking paradox", conditioning lower mortality in smokers among STEMI patients, has seldom been addressed in the settings of modern primary PCI protocols. The ISACS–STEMI COVID-19 is a large-scale retrospective multicenter registry addressing in-hospital mortality, reperfusion, and 30-day mortality among primary PCI patients in the era of the COVID-19 pandemic. Among the 16,083 STEMI patients, 6819 (42.3%) patients were active smokers, 2099 (13.1%) previous smokers, and 7165 (44.6%) non-smokers. Despite the impaired preprocedural recanalization ($p < 0.001$), active smokers had a significantly better postprocedural TIMI flow compared with non-smokers ($p < 0.001$); this was confirmed after adjustment for all baseline and procedural confounders, and the propensity score. Active smokers had a significantly lower in-hospital ($p < 0.001$) and 30-day ($p < 0.001$) mortality compared with non-smokers and previous smokers; this was confirmed after adjustment for all baseline and procedural confounders, and the propensity score. In conclusion, in our population, active smoking was significantly associated with improved epicardial recanalization and lower in-hospital and 30-day mortality compared with previous and non-smoking history.

Keywords: myocardial infarction; smoking paradox; percutaneous coronary intervention; COVID-19

1. Introduction

Coronary artery disease still represents the leading cause of mortality in developed countries. While large attention has been paid to the identification of new risk factors [1–4], traditional risk factors, especially cigarette smoking, cannot be neglected. In fact, still approximately 30% of all deaths due to coronary artery disease (CAD) in the United States annually are attributable to smoking [5].

Several studies have been conducted, especially in the setting of ST-segment elevation myocardial infarction (STEMI), suggesting the existence of a "smokers' paradox," related to the more favorable outcome of smokers compared with non-smokers [6–10]. Similar findings have been observed among patients with acute ischemic stroke, acute heart failure, and cardiac arrest [11–14].

This paradoxically lower mortality observed among smokers was mainly attributed to their younger age, fewer comorbidities, lesser extent of CAD, in addition to potential pathophysiological differences between smokers and non-smokers, including a greater thrombus burden in smokers, leading to greater efficacy of thrombolytic therapy [15–17], and greater responsiveness to antiplatelet therapies [18–21]. However, primary PCI, when applied in a timely fashion, currently represents the best indicated reperfusion therapy for the treatment of STEMI. Several reports have investigated the prognostic impact of smoking

with contrasting results. In the COVID era, the increased susceptibility of smokers to respiratory disease and the enhanced thrombotic risk associated with COVID-19 infection, could influence the existence of different outcome results according to smoking status. Moreover, recent reports have clearly shown a reduction in acute coronary cases during the pandemic, presumably due to a public fear of coronavirus contagion that impacted on patient willingness to present to a hospital [22–27]. An additional observation was the prolonged time from symptom onset to treatment [28–30] that contributed to explain the higher mortality among STEMI patients observed in 2020.

Therefore, the aim of the present study was to investigate the impact of smoking status on angiographic and clinical outcome in a large cohort of patients enrolled also during the COVID-19 pandemic.

2. Materials and Methods

Our study population is represented by patients enrolled in the International Study on Acute Coronary Syndromes—ST-segment Elevation Myocardial Infarction (ISACS–STEMI) COVID-19, a large-scale retrospective multicenter registry involving primary PCI centers from Europe, Latin America, South-East Asia, and North Africa, including patients treated from the 1st of March until the 30th of June 2019 (pre-COVID period) and from the 1st of March until the 30th of June 2020 (COVID period) who underwent SARS-Cov-2 screening [31].

We collected demographic, clinical, procedural data, data on total ischemia time, door-to-balloon time, referral to primary PCI facility, PCI procedural data, in-hospital outcomes, including death, Stent Thrombosis (according to the ARC definition, [32]), and 30-day mortality. The study was approved by the Ethical Committee of AOU Maggiore della Carità, Novara (Protocol 571/CE date of approval 20/05/2020).

Statistical data analysis was performed by the use of SPSS Statistics Software 23.0 (IBM SPSS Inc., Chicago, IL, USA). Quantitative variables were described using median and interquartile range. Absolute frequencies and percentages were used for qualitative variables. ANOVA or the Mann–Whitney and chi-square test were used for continuous and categorical variables, respectively. Normal distribution of continuous variables was tested by the Kolmogorov–Smirnov test). Primary study endpoint was in-hospital mortality. Secondary study endpoints were postprocedural TIMI 3 flow and 30-day mortality. We used the propensity score technique to account for potential confounding between groups, as previously described [33,34]. For each patient, a propensity score indicating the likelihood of being active was calculated through step-forward logistic regression analysis that identified variables independently associated with active smoking. We included baseline clinical variables associated with active smoking at univariable analysis (inclusion in the model: $p < 0.05$; exclusion from the model: $p < 0.1$). The following variables were entered into the model: age, gender, diabetes, hypertension, family history of CAD, previous STEMI, previous PCI, previous CABG, type of referral, ischemia time, door-to-balloon time, anterior STEMI, out-of-hospital cardiac arrest, cardiogenic shock, rescue PCI for failed thrombolysis, in-hospital RASI therapy, COVID positivity, year of revascularization (2019 vs. 2020), radial access, in-stent thrombosis, multivessels, disease, preprocedural TIMI flow, stenting, DES, mechanical support, DAPT, and additional PCI. The stepwise selection of the variable and estimation of significant probabilities were computed by means of maximal likelihood ratio test. The $\chi 2$ value was calculated from the log of the ratio of maximal partial likelihood functions. The additional value of each category of variables added sequentially was evaluated on the basis of the increases in the overall likelihood statistic ratio. The final score was built according to the global $\chi 2$ value of the multivariate statistical model and the $\chi 2$ value of each variable. The discriminatory performance of the propensity score was assessed by the receiver operating characteristic curve method, which indicated a good accuracy of the propensity score model (area under the curve = 0.83) [35].

The consistency of the main results for the primary outcome of the study was investigated according to propensity score values (below and over the median).

Multivariable Cox and logistic regression analyses were performed to identify the impact of smoking on primary and secondary study endpoints after adjustment for baseline con-founding factors between the two groups. All significant variables (set at a p-value < 0.1) were entered in block into the model. A $p < 0.05$ was considered statistically significant. The data coordinating center was established at the Eastern Piedmont University, Novara, Italy.

3. Results

Our population is represented by 16,083 STEMI patients. A total of 6819 (42.3%) patients were active smokers, 2099 (13.1%) previous smokers, and 7165 (44.6%) non-smokers. As shown in Table 1, active smokers were nine years younger and more often males compared with non-smokers. Smokers were less often affected by diabetes ($p < 0.001$), hypertension ($p < 0.001$), and hypercholesterolemia ($p < 0.001$), with lower prevalence of previous STEMI ($p < 0.001$), previous PCI ($p < 0.001$), or CABG ($p < 0.001$), but more often had a positive family history of CAD ($p < 0.001$). Smokers had a shorter ischemia time ($p < 0.001$), less often had anterior MI ($p < 0.001$), cardiogenic shock ($p < 0.001$), and out-of-hospital cardiac arrest ($p < 0.001$), but more often rescue PCI failed after thrombolysis ($p < 0.001$). Angiographic features are displayed in Table 2. Smokers less often had multivessel disease ($p < 0.001$), in-stent thrombosis ($p < 0.001$), received less often a mechanical support ($p < 0.001$) or underwent additional PCI ($p = 0.001$), whereas they received more often a coronary stent ($p < 0.001$), a DES ($p < 0.001$) and DAPT ($p < 0.001$). Despite the impaired preprocedural recanalization ($p < 0.001$), smokers had a significantly better postprocedural TIMI flow as compared to non-smokers ($p < 0.001$) (Figure 1). A significant association was observed with the percentage of SARS-COV 2 positive patients, and less often observed among smokers. Our main results were confirmed in both pre-COVID ($p < 0.001$) and COVID era ($p < 0.001$), and in both young ($p < 0.001$) and elderly patients ($p = 0.013$) (Figures S1 and S2). The results were additionally confirmed in the analysis based on the propensity score (Figure S3). The association between active smoking and postprocedural TIMI flow was confirmed after adjustment for all confounders (age, gender, diabetes, hypertension, hypercholesterolemia, family history of CAD, previous STEMI, previous PCI, previous CABG, access by ambulance, ischemia time, door-to-balloon time, anterior MI, out-of-hospital cardiac arrest, cardiogenic shock, rescue PCI, radial access, anterior MI, infarct-related artery, in-stent thrombosis, preprocedural TIMI flow 0, use of stent and DES, mechanical support, DAPT, multivessel disease, additional PCI, year of intervention, propensity score, and COVID positivity) (OR [95% CI] = 1.18 [1.04–1.36], $p = 0.014$).

Table 1. Baseline demographic and clinical characteristics according to smoking status.

Variable	Active Smokers	Previous Smokers	Non-Smokers	*p* Value
	(*n* = 6819)	**(*n* = 2099)**	**(*n* = 7165)**	
Age (median, IQR)	58 (51–65)	67 (59–75) (54–72)	67 (58–77) (54–72)	<0.001
Age > 75 year—*n* (%)	410 (6.0)	533 (25.4)	2104 (29.4)	<0.001
Male gender—*n* (%)	5538 (81.2)	1773 (84.5)	4853 (67.7)	<0.001
Diabetes mellitus—*n* (%)	1324 (19.4)	502 (23.9)	1986 (27.7)	<0.001
Hypertension—*n* (%)	3252 (47.7)	1280 (61.0)	4281 (59.7)	<0.001
Hypercholesterolemia—*n* (%)	2579 (37.8)	1033 (49.2)	2741 (38.3)	<0.001
Family history of CAD—*n* (%)	1667 (24.4)	495 (23.6)	1136 (15.9)	< 0.001
Previous STEMI—*n* (%)	571 (8.4)	335 (16)	637 (8.9)	<0.001
Previous PCI—*n* (%)	722 (10.6)	432 (20.6)	839 (11.7)	<0.001
Previous CABG—*n* (%)	57 (0.8)	73 (3.5)	142 (2.0)	<0.001
Referral to primary PCI hospital				

Table 1. *Cont*.

Variable	Active Smokers	Previous Smokers	Non-Smokers	*p* Value
	(*n* = 6819)	(*n* = 2099)	(*n* = 7165)	
Type				
Ambulance (from community)—*n* (%)	3328 (48.8)	1074 (51.2)	3336 (46.6)	
Direct access—*n* (%)	1820 (26.7)	512 (24.4)	2181 (30.4)	<0.001
Spoke—*n* (%)	1671 (24.5)	513 (24.4)	1648 (23.0)	
Time delays				
Ischemia time, median (25–75th)	190 (10–350)	208 (128–379)	221 (130–400)	<0.001
Total ischemia time				
<6 h—*n* (%)	5228 (76.7)	1550 (73.8)	5144 (71.8)	
6–12 h—*n* (%)	973 (14.3)	328((15.6)	1198 (16.7)	
12–24 h—*n* (%)	415 (6.1)	142 (6.8)	531 (7.4)	<0.001
>24 h—*n* (%)	2.3 (3.0)	79 (3.8)	292 (4.1)	
Total ischemia time > 12 h—*n* (%)	618 (9.1)	221 (10.5)	823 (11.5)	<0.001
Door-to-balloon time, median (25–75th)	40 (25–60)	38 (21–65)	40 (25–73)	<0.001
Door-to-balloon time				
<30 min—*n* (%)	2827 (41.5)	887 (42.3)	2719 (37.9)	
30–60 min—*n* (%)	2305 (33.8)	636 (30.3)	2318 (32.4)	<0.001
>60 min—*n* (%)	1687 (24.7)	576 (27.4)	2128 (29.7)	
Door-to-balloon time > 30 min (%)—*n* (%)	3992 (58.5)	1212 (57.7)	4446 (62.1)	<0.001
Clinical presentation				
Anterior STEMI—*n* (%)	2994 (43.9)	869 (41.4)	3583 (50.0)	<0.001
Out-of-hospital cardiac arrest—*n* (%)	374 (5.5)	91 (4.3)	491 (6.9)	<0.001
Cardiogenic shock—*n* (%)	408 (6.0)	157 (7.5)	603 (8.4)	<0.001
Rescue PCI for failed thrombolysis—*n* (%)	579 (8.5)	77 (3.7)	443 (6.2)	<0.001
In-hospital RASI therapy—*n* (%)	3864 (56.7)	1223 (58.3)	3810 (53.2)	<0.001
COVID positivity (%)	28 (0.4%)	16 (0.8%)	65 (0.9%)	<0.001

A Mann–Whitney test. CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG 0 = coronary artery bypass graft.

Table 2. Angiographic and procedural characteristics.

	Active Smokers	Previous Smokers	Non-Smokers	*p* Value
	(*n* = 6819)	(*n* = 2099)	(*n* = 7165)	
Radial Access (%)	5289 (77.6)	1698 (80.9)	5281 (73.7)	<0.001
Culprit vessel				
Left main—*n* (%)	82 (1.2)	49 (2.3)	121 (1.7)	
Left anterior descending artery—*n* (%)	2976 (43.6)	852 (40.6)	3530 (49.3)	
Circumflex—*n* (%)	1064 (15.6)	362 (17.2)	924 (12.9)	
Right coronary artery—*n* (%)	2664 (39.1)	812 (38.7)	2525 (35.2)	<0.001
Anterolateral branch—*n* (%)	12 (0.2)	7 (0.3)	22 (0.3)	
SVG *n* (%)	20 (0.3)	17 (0.8)	42 (0.6)	
In-stent thrombosis—*n* (%)	238 (3.5)	127 (6.1)	267 (3.7)	<0.001
Multivessel disease—*n* (%)	3145 (46.1)	1062 (50.6)	3679 (51.3)	<0.001
Preprocedural TIMI 0 flow—*n* (%)	4632 (67.9)	1353 (64.5)	4746 (66.2)	0.007
Thrombectomy—*n* (%)	1112 (16.3)	342 (16.3)	1109 (15.5)	0.36
Stenting—*n* (%)	6391 (93.7)	1929 (91.9)	6447 (90)	<0.001
Drug-eluting stent—*n* (%)	6150 (90.2)	1858 (88.5)	6246 (87.2)	<0.001
Postprocedural TIMI 3 flow—*n* (%)	6402 (93.9)	1958 (93.3)	6461 (90.2)	<0.001
Gp IIb-IIIa inhibitors/cangrelor—*n* (%)	1404 (20.6)	441 (21.0)	1422 (19.8)	0.38
Bivalirudin—*n* (%)	18 (0.3)	9 (0.4)	25 (0.3)	0.44
Mechanical support—*n* (%)	164 (2.4.)	68 (3.2)	265 (3.7)	<0.001
Additional PCI				
During the index procedure—*n* (%)	627 (9.2)	260 (12.4)	689 (9.6)	
Staged—*n* (%)	716 (10.5)	223 (10.6)	747 (10.4)	0.001
DAPT therapy—*n* (%)	6769 (99.3)	2071 (98.7)	7065 (98.6)	<0.001

TIMI = thrombolysis in myocardial infarction; DAPT = dual antiplatelet therapy; RASI: renin-angiotensin system inhibitors.
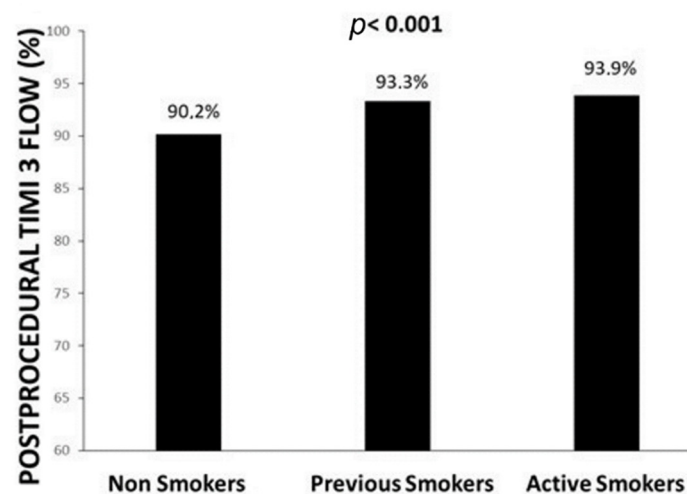
Figure 1. Bar graphs show the association between smoking status and postprocedural TIMI flow.

Smokers had a significantly lower in-hospital (Figure 2) and 30-day (Figure 3) mortality compared with non-smokers and previous smokers; this was confirmed in both pre-COVID ($p < 0.001$) and COVID era ($p < 0.001$) and in young ($p < 0.001$) and older patients ($p < 0.001$) (Figures S4, S5, S7 and S8). The results were additionally confirmed in the analysis based on the propensity score (Figures S6 and S9). The association between active smoking and better survival was confirmed at multivariate analysis after adjustment for all confounders (age, gender, diabetes, hypertension, hypercholesterolemia, family history of CAD, previous STEMI, previous PCI, previous CABG, access by ambulance, ischemia time, door-to-balloon time, anterior MI, out-of-hospital cardiac arrest, cardiogenic shock, rescue PCI, radial access, anterior MI, infarct-related artery, in-stent thrombosis, preprocedural TIMI flow 0, use of stent and DES, mechanical support, DAPT, multivessel disease, additional PCI, year of intervention, propensity score, and COVID positivity) (in-hospital death: OR [95% CI] = 0.75 [0.62–0.9], $p = 0.003$; 30-day death: HR [95% CI] = 0.74 [0.64–0.86], $p < 0.0001$).
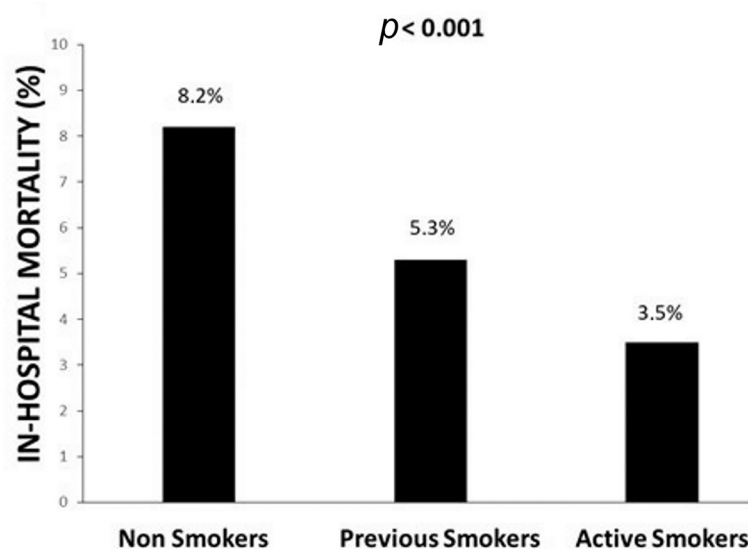

Figure 2. Bar graphs show the association between smoking status and in-hospital mortality.
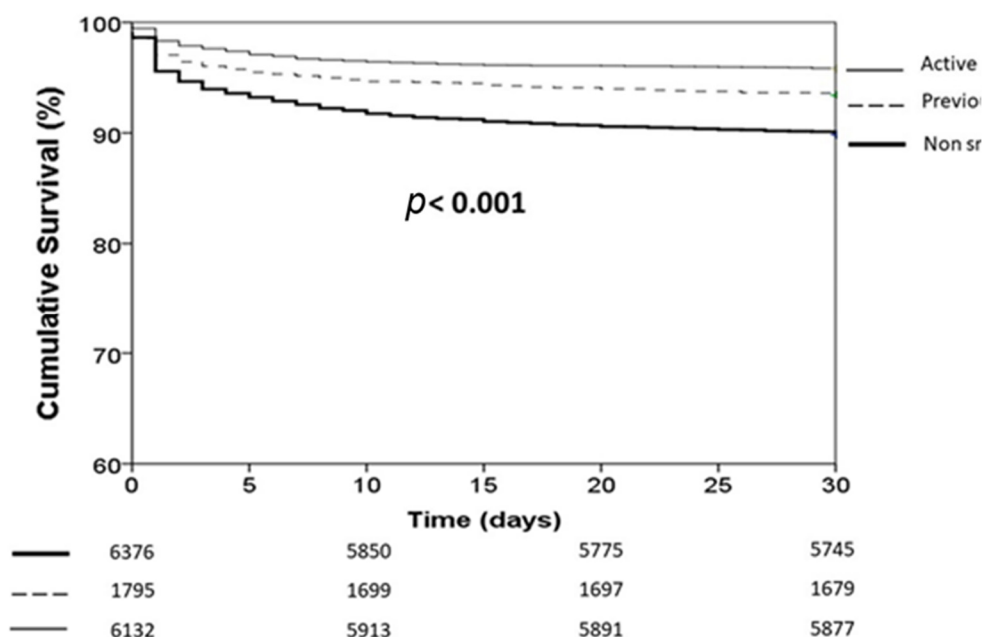
Figure 3. Kaplan–Meier survival curves of STEMI patients according to smoking status.

4. Discussion

Our study is one of the largest reports on the association between smoking status and mortality in STEMI patients undergoing primary angioplasty, especially during the COVID pandemic. We found that active smokers had significantly better epicardial reperfusion and both in-hospital and 30-day survival compared with previous smokers and non-smokers. The association persisted even after correction for all baseline confounders, including the year of intervention, COVID positivity, and the propensity score.

Cigarette smoking is a well-known risk factor for coronary artery disease [5,36]. In fact, smokers were younger than non-smokers and were less likely to have additional established risk factors than non-smokers, suggesting the deleterious effect of smoking as a cause of myocardial infarction. However, despite the adjustment for all these confounders, smoking was still associated with a reduced mortality. While we cannot certainly exclude masked unmeasured confounders, it is possible that underlying biological differences in pathophysiology and response to the treatment in smokers versus non-smokers with STEMI could also have accounted, at least in part, for this paradoxical association.

Several studies conducted with thrombolysis have shown that smoking was associated with a lower mortality at both short- and long-term follow up [37–39]. Although, in most of these studies, the association between smoking and reduced mortality disappeared after correction for multiple confounders, some other studies observed a persistently lower mortality, even after adjustment. One of the explanations is the fact the smoking does not affect atherosclerotic plaque vulnerability, whereas it induces a hypercoagulation and prothrombotic state by endothelial dysfunction, increased platelet activation and aggregation, increased circulating levels of fibrinogen, and increased thrombin generation [40,41]. It has been shown, indeed, that components of cigarette smoke impair fibrin crosslinking [42]. Therefore, smoking may be predominantly thrombogenic and less likely atherogenic, making these patients more amenable for thrombolytic therapy and able to obtain more benefits from antiplatelet therapies. In fact, among patients reperfused with thrombolysis, smoking is associated with better epicardial [38] and myocardial reperfusion [43] compared with non-smokers.

Several studies have recently investigated the smoking paradox among patients undergoing mechanical reperfusion, with conflicting results. Redfors et al. [44] reported the prognostic impact of smoking among patients enrolled in CADILLAC trial. The authors observed a significantly lower mortality at 30-day and 1-year follow up in smokers com-

pared with non-smokers. However, the difference disappeared after adjustment for all confounding factors. In another study by Steele et al. [45] including 3133 STEMI patients undergoing mechanical reperfusion, smoking was associated with a significantly increased mortality (hazard ratio 1.35 (95% CI 1.04–1.74)) compared with never smokers at 3 years after adjustment for differences in baseline variables. The risk for ex-smokers (hazard ratio 0.99 (0.76–1.28)) was similar to never smokers.

Opposite findings have been observed in the largest study so far conducted in primary PCI. Gupta et al., including more than 900.000 STEMI patients [46], found that smoking was associated with a significantly lower mortality, even after the adjustment for all baseline confounders. However, the mortality difference between smokers and non-smokers diminished substantially with increasing age and was no longer significant in nonagenarians with STEMI. These data suggest that the overall association of smoking with lower in-hospital mortality is driven mostly by younger age groups. However, given the lack of angiographic data, the authors were unable to account for the severity of CAD or to assess the procedural success of PCI. Another limitation is the very short-term follow up.

The present study is one of the largest on primary PCI, including more than 16,000 STEMI patients, and the first study conducted in the COVID era. In fact, the COVID-19 pandemic has been shown to increase mortality among STEMI patients by both direct and indirect effects, including a longer delay to presentation. We found that active smoking was associated with a significantly improved epicardial reperfusion (TIMI 3), especially as compared with non-smokers. Furthermore, active smokers had a significantly lower mortality as compared with non-smokers and previous smokers. Our results were confirmed in the sub analysis according to the year of intervention (COVID and pre-COVID era), age (older and younger than 75 years of age), and in patients with low or high propensity score values (below or upper the median value). The association between active smoking and angio-graphic and clinical outcome was confirmed after multivariate adjustment for all confounders, including the year of intervention and the propensity score.

A possible biological mechanism may explain that the paradoxically lower mortality among smokers treated by primary PCI is the potential different pathophysiology underlying the onset of infarction, mainly related among smokers to hypercoagulation and prothrombotic state by endothelial dysfunction, increased platelet activation and aggregation, increased circulating levels of fibrinogen, and increased thrombin generation [40,41], rather than atherosclerotic plaque vulnerability. This may also condition the response to several antithrombotic therapies.

In fact, a sub analysis of the HORIZONS-AMI trial also showed that, among STEMI patients undergoing pPCI for STEMI, bivalirudin monotherapy was associated with lower 30-day and 1-year mortality compared with unfractionated heparin plus glycoprotein IIb/IIIa inhibitors in smokers but not in non-smokers [47].

Furthermore, it has been suggested that smoking could affect responsiveness to antiplatelet therapies, mainly ADP antagonists. A sub analysis of the CLARITY-TIMI 28 trial, showed that clopidogrel reduced the rate of the primary end point (combined rates of occluded infarct-related artery or death and MI before angiography), especially among patients who smoked ≥10 cigarettes per day versus those who did not [48]. Similarly, in the CHARISMA trial clopidogrel reduced all-cause and cardiovascular mortality at 28 months in current smokers but not in non-smokers [19]. Similar impacts of smoking on the benefits from clopidogrel has been reported in other studies [18]. Pharmacokinetic and pharmacodynamics studies demonstrated that among patients treated with clopidogrel, smoking was associated with a greater inhibition of platelet aggregation, lower P2Y12 reaction units, and showed high platelet reactivity less often [20]. The induction of cytochrome P450 1A2 and 2B6 enzymes by cigarette smoking, both of which are involved in the hepatic biotransformation of clopidogrel to its active metabolite [49] has been identified as a possible explanation of the different response to clopidogrel between smokers versus non-smokers. Additional studies have been conducted on prasugrel, suggesting a similar effect of smoking status. A platelet-function sub study of the TRILOGY-ACS trial [21]

showed that, among medically managed ACS patients randomly assigned to prasugrel or clopidogrel, smokers had lower P2Y12 reaction unit values at 6 months in both treatment groups compared with non-smokers. It has been demonstrated that nicotine is associated with higher P2Y12 receptor expression in human platelet lysates; this, therefore, could explain the observed effect of smoking on platelet inhibition [50]. These findings can contribute to understanding the observed significant reduction of ischemic outcomes with prasugrel versus clopidogrel among smokers [21].

These data on the differential clinical efficacy of antithrombotic therapies in smokers versus non-smokers could be a possible mechanistic explanation for the association of smoking with lower in-hospital mortality in patients undergoing pPCI for STEMI.

It must be emphasized that our findings and the overall concept of the smoking paradox should not erroneously interpreted as the beneficial effects from cigarette smoking. In fact, the lower prevalence of conventional risk factors among active smokers indirectly support the promotion of atherothrombosis, by active smoking, that led to STEMI at a younger age. The harmful effects of smoking have been largely proven, and these modest differences in short-term survival would likely be offset by the long-term mortality attributable to cigarette smoking. Therefore, all efforts should be carried out to strongly promote smoking cessation as a public health measure to reduce the burden of cardiovascular disease and its related mortality.

Study Limitations

This study is limited by its retrospective design. It was conducted during a pandemic emergency, which was challenging and expected to encounter missing data. Cumulative smoking exposure in terms of number of pack years could not be quantified, and we were unable to study the association of the amount of smoking with outcomes. We were also unable to determine the time of smoking cessation for former smokers and neither did we assess infarct size. Moreover, even after statistical correction, the large differences in some strong prognostically relevant variables, particularly much younger age, do not allow for us to exclude that smoking is mostly a marker of STEMI at a younger age, where this risk factor is largely predominant as a direct prothrombotic cause of coronary occlusion. Therefore, the large differences in prognostically relevant baseline characteristics suggest prudence with regard to causal conclusions.

5. Conclusions

Our study showed that smoking is independently associated with improved epicardial re-canalization and lower in-hospital and 30-day mortality as compared with both previous smokers and non-smokers.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11226722/s1, Figure S1. Bar Graphs show the association between smoking status and postprocedural TIMI 3 flow in patients treated in 2019 (precovid era, left graph) and 2020 (covid era, right graph). Figure S2. Bar Graphs show the association between smoking status and postprocedural TIMI 3 flow in young (left graph) and older (right graph) patients. Figure S3. Bar Graphs show the association between smoking status and postprocedural TIMI 3 flow in in patients with low (left graph) and high (right graph) propensity score. Figure S4. Bar Graphs show the association between smoking status and in-hospital mortality in patients treated in 2019 (precovid era, left graph) and 2020 (covid era, right graph). Figure S5. Bar Graphs show the association between smoking status and in-hospital mortality in young (left graph) and older (right graph) patients. Figure S6. Bar Graphs show the association between smoking status and in-hospital mortality in patients with low (right graph) and high (left graph) propensity score. Figure S7. Kaplan-Meier survival curves according to smoking status in patients treated in 2019 (left graph) and 2020 (right graph). Figure S8. Kaplan-Meier survival curves according to smoking status in young (left graph) and older (right graph) patients. Figure S9. Kaplan-Meier survival curves according to smoking status in patients with low (left graph) and high (right graph) propensity score.

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