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The assessment of no-reflow phenomenon incidence in early versus delayed percutaneous coronary intervention following a primary fibrinolysis

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OriginalArticle

Abstract

BACKGROUND: Percutaneous coronary intervention (PCI) is the gold standard approach to ST-Segment Elevation Myocardial Infarction (STEMI). Fibrinolysis followed by PCI has been recommended. The current study aims to investigate the no-reflow phenomenon incidence in patients undergoing post-thrombolytic therapy PCI.

METHODS: This cross-sectional study was conducted on 250 patients with STEMI who primarily received fibrinolytic therapy followed by early (3-24 hours) (n=231) or delayed (> 24 hours) (n=19) PCI. They were also subcategorized into four intervals: <6 hours (n=98), 6-12 hours (n=93), 12-24 hours (n=38), and ≥24 hours (n=21). The demographic and medical data of the patients were retrieved. The Thrombolysis in Myocardial Infarction score (TIMI) was assessed at baseline and at the end of PCI. A TIMI score other than 3 was defined as no-reflow.

RESULTS: The incidence of the no-reflow phenomenon was not associated with any of the underlying demographic and medical characteristics of the patients (P-value>0.05). Despite the significantly higher rate of improvement in TIMI grading among those undergoing early PCI (P-value=0.04), as well as within less than 6 hours after thrombolytic therapy (P-value=0.031), the rate of the no-reflow phenomenon did not differ between the groups, neither by sorting them as early versus delayed (P-value=0.518) nor by categorizing them into four intervals (P-value=0.367).

CONCLUSION: Based on the findings of the current study, early PCI after fibrinolysis led to significantly improved TIMI flow. However, the incidence of no-reflow did not differ between the groups with early versus delayed post-fibrinolysis PCI.

Keywords: ST-Elevation Myocardial Infarction, Percutaneous Coronary Intervention, Fibrinolysis, No-Reflow Phenomenon, Myocardial Infarction

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Introduction

Acute Coronary Syndrome, including ST-segment Elevation Myocardial Infarction (STEMI), is the major leading cause of mortality and disability worldwide, affecting millions of people annually. It has been well-elucidated that prehospital care given by emergency settings can significantly reduce mortality and morbidity, as well as improve long-term outcomes[1].

To date, the primary Percutaneous Coronary Intervention (PCI) is the gold-standard strategy to restore the patency of occluded coronary arteries and salvage the injured ischemic myocardium. This leads to the preservation of the Left Ventricular Ejection Fraction (LVEF), which is a determinant of short- and long-term outcomes of a STEMI[2,3]. Nevertheless, many people might experience STEMI in hospitals where PCI is not available or do not refer to PCI centers within the time range suggested by guidelines. Given that, fibrinolytics are the alternative treatment applied for these cases. They should be initiated within the first 12 hours after the incidence of STEMI; otherwise, thrombolysis is not only unhelpful but also increases the risk of complications, with bleeding at the top of the list[4].

According to the guidelines, the optimal time for patients receiving thrombolytics to undergo PCI is within 3-24 hours. However, the data regarding this time span are controversial. On one hand, there is potential for better preclusion of the early prothrombotic phase and reduced chances of reocclusion in cases undergoing earlier PCI after fibrinolysis. On the other hand, some authors propose a decrease in bleeding complications as a reason for recommending delayed PCI[5-8]. The best time to perform PCI after thrombolysis remains a matter of debate, which is the focus of the current study.

Methods

Study population

The current cross-sectional, single-center study was conducted on 250 patients with STEMI. These patients were admitted to the Shahid Chamran Cardiology Center, affiliated with Isfahan University of Medical Sciences, for PCI from January to December 2022.

The study was designed according to the tenets of the Helsinki Declaration and was proposed to the Ethics Committee of Isfahan University of Medical Sciences. It was approved under the code number IR.MUI.MED.REC.1401.371. The protocol was then explained to the patients/legal guardians. They were reassured regarding the confidentiality of their personal information and provided their written consent.

Patients over 18 years old with a confirmed STEMI diagnosis, who were primarily treated with thrombolytics (reteplase only), and then underwent PCI, were included. A STEMI diagnosis was made in patients who met two of the following three criteria:

1- Chest pain or equivalent symptoms lasting for at least 20 minutes, occurring within 24 hours before admission to perform PCI.
2- ST-segment elevation in two leads compatible with one of the epicardial coronary arteries territory or a new onset Left Bundle Branch Block (LBBB).
3- A positive cardiac troponin.

Exclusion criteria included death before the study's completion, a previous history of myocardial ischemia, or the incidence of a new onset STEMI after admission to the hospital or after the performance of PCI.

Patients were entered into the study through convenience sampling among those who met the study criteria.

Data collection

The patients' demographic (age and sex) and medical data (hypertension, diabetes mellitus, dyslipidemia), as well as the interval between symptom initiation to receiving thrombolytic therapy and the interval between thrombolytic therapy and PCI performance, were retrieved from the medical records. The patients were categorized into two groups: early versus delayed PCI, corresponding to the interval between thrombolytic therapy and PCI performance. Accordingly, those who underwent PCI within 24 hours after thrombolytic therapy were categorized as 'early', and those who intervened after 24 hours as 'delayed' PCI.

The Thrombolysis in Myocardial Infarction score (TIMI) was evaluated at baseline and then at the end of the intervention. TIMI flow grading was assessed as follows:

0: No penetration of contrast in the infarct-related vessel.
1: Penetration of some contrast beyond the

obstruction, but no perfusion in the distal coronaries.
2: Perfusion in the whole infarct-related vessel, but with delayed flow.
3: Full perfusion of the infarct-related vessel and normal flow[9].

Moreover, the main objective of the current study was to evaluate the impact of early versus delayed PCI on the incidence of the no-reflow phenomenon in STEMI patients receiving thrombolytics. Accordingly, a targeted expert fellowship in interventional cardiology assessed the films of PCIs to detect the no-reflow phenomenon in the intervened patients, defined as a post-PCI TIMI flow of less than three[7]. In addition, we aimed to categorize the patients into four subgroups of PCI with four intervals: <6 hours, 6-12 hours, 12-24 hours, and ≥24 hours. Similar assessments were performed.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS Inc. PASW Statistics for Windows, Chicago) version 24. Categorical variables were presented as absolute numbers and percentages, while continuous variables were presented as mean ± standard deviation. Chi-square, Fisher's exact, and logistic regression tests were applied to compare the categorical data. Continuous variables were compared using the independent t-test. A P-value of less than 0.05 was considered the level of significance.

Results

In the current study, 250 STEMI patients receiving thrombolytics were compared in two groups: early versus delayed PCI. The mean age of the studied population was 59.62±10.27.

Table 1 demonstrates the demographic, medical,

Table 1. The characteristics of patients in two groups of early versus delayed PCI

Variables	Early PCI (n=231)	Delayed PCI (n=19)	P
Demographic characteristics			
Age (year), M±SD	59.53±10.32	60.68±9.86	0.63
Sex, n (%)			
Male	17 (7.6)	208 (92.4)	0.891
Female	2 (8.3)	22 (91.7)	
Total	19 (7.6)	230 (92.4)	
Addicted, n (%)			
Yes	4 (8.5)	43 (91.5)	0.794
No	15 (7.4)	188 (92.6)	
Total	19 (7.6)	231 (92.4)	
Smoking, n (%)			
Yes	2 (10)	18 (90)	0.677
No	17 (7.4)	212 (92.6)	
Total	19 (7.6)	230 (92.4)	
Body mass index, M±SD	25.05 (2.61)	26.17 (3.2)	0.17
Medical characteristics			
Diabetes mellitus, n (%)	40 (17.3)	8 (42.1)	0.015
Hypertension, n (%)	77 (33.3)	8 (42.1)	0.43
Dyslipidemia, n (%)	10 (4.3)	1 (5.3)	0.58
History of ischemic heart disease, n (%)	4 (1.7)	1 (5.3)	0.32
Clinical characteristics			
The interval between symptoms initiation and thrombolytic therapy (hours), median [IQR]	3 [2, 6]	2 [2, 4]	0.802
The interval between thrombolytic therapy and PCI (hours), median [IQR]	11 [8, 16.5]	32 [28, 54]	<0.001
The interval between symptoms initiation and PCI (hours), median [IQR]	28 [25, 48]	7 [5, 11]	<0.001

* Chi-square test
** Independent t-test

M±SD: Mean ± standard deviation, PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction score

and clinical characteristics of the patients in the two groups of early versus delayed PCI. Based on this table, the patients were similar in terms of age (P-value=0.63), hypertension (P-value=0.43), dyslipidemia (P-value=0.58), the history of ischemic heart disease (P-value=0.32), and the interval between symptom initiation and thrombolytic therapy (P-value=0.802). However, diabetes mellitus was significantly more frequent among those undergoing delayed PCI (P-value=0.015). Detailed information is demonstrated in Table 1.

The main objective of this study was to investigate the incidence of the no-reflow phenomenon and TIMI score changes among the patients undergoing early versus delayed PCI. It was revealed that despite the significantly higher rate of improvement in TIMI grading among those undergoing early PCI (P-value=0.04), the rate of the no-reflow phenomenon did not differ (P-value=0.518) (Table 2).

Further investigations revealed that the incidence of the no-reflow phenomenon was not associated with any of the underlying demographic and medical characteristics of the patients (P-value>0.05) (Table 3).

Considering the subcategorization of the patients into four groups based on the interval between thrombolytic therapy and PCI, including ≤6 hours, 6-12 hours, 12-24 hours, and ≥24 hours, the patients did not differ in any of the demographic and medical characteristics (P-value>0.05). The exception was Diabetes Mellitus (DM), which was significantly higher among those undergoing PCI within over 24 hours after the primary thrombolytic therapy (P-value=0.029). Additionally, the intervals between symptom initiation and thrombolytic infusion did not differ among the groups (P-value=0.84) (Table 4).

The incidence of the no-reflow phenomenon did not differ by further subcategorization of the intervals (P-value=0.367). However, earlier PCI within less than 6 hours after thrombolytic therapy led to a significantly higher rate of improved TIMI flow compared with other intervals (P-value=0.031) (Table 5).

Table 2. The association of the no-reflow phenomenon with the time of PCI

Variables	Early PCI (n=231)	Delayed PCI (n=19)	P-value
The incidence of no-reflow phenomenon, n (%)	36 (15.6)	4 (21.1)	0.51*
Improved TIMI score after PCI, n (%)	172 (74.5)	10 (52.6)	0.04**

*Fisher's exact test
**Chi-square test
PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction score

Table 3. The association of demographic and medical characteristics with no-reflow phenomenon incidence

Variable		No-reflow phenomenon		P
		No	Yes	
Sex, n (%)	**Male**	190 (84.4)	35 (15.6)	0.503
	Female	19 (79.2)	5 (20.8)	
Age group, n (%)	**20-40**	10 (4.8)	2 (5)	0.291*
	41-60	99 (47.1)	13 (32.5)	
	61-80	96 (45.7)	24 (60)	
	>=81	5 (2.4)	1 (2.5)	
Diabetes mellitus, n (%)		42 (20)	6 (15)	0.462**
Hypertension, n (%)		73 (34.8)	12 (30)	0.560**
Dyslipidemia, n (%)		9 (4.3)	2 (5)	0.690*
History of ischemic heart disease, n (%)		5 (2.4)	0 (0)	0.999*
Addicted, n (%)		41 (87.2)	6 (12.8)	0.50
Smoking, n (%)		14 (70.0)	6 (30.0)	0.07

Table 4. The characteristics of patients in two groups of early versus delayed PCI

Variables	<6 hours (n=98)	6-12 hours (n=93)	12-24 hours (n=38)	≥24 hours (n=21)	P-value
Demographic characteristics					
Age (year), mean±standard deviation	58.12±10.37	61.87±9.37	57.82±11.39	59.86±10.27	0.51#
Medical characteristics					
Diabetes mellitus, n (%)	19 (19.4)	15 (16.1)	5 (13.2)	9 (42.9)	0.029*
Hypertension, n (%)	32 (32.7)	29 (31.2)	15 (39.5)	9 (42.9)	0.64*
Dyslipidemia, n (%)	6 (6.1)	1 (1.1)	3 (7.9)	1 (4.8)	0.129$
History of ishemic heart disease, n (%)	1 (1)	2 (2.2)	1 (2.6)	1 (4.8)	0.46$
Clinical characteristics					
The interval between symptoms initiation and thrombolytic therapy (hours), median [IQR]	3 [2-5]	3 [2-6]	2 [2-6]	2 [2-4]	0.84**
The interval between thrombolytic therapy and PCI (hours), median [IQR]	5 [4-5]	8 [7-10]	16 [14-19]	27 [25-32]	<0.001**
The interval between symptoms initiation and PCI (hours), median [IQR]	8 [6-11]	12 [10-15]	20 [16-26]	31 [28-53]	<0.001**

ANOVA
*Chi-square test
$ Fisher's exact trst
**Kruskal-Wallis test
PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction score

Table 5. The association of no re-flow phenomenon with the time of PCI

Variables	<6 hours (n=98)	6-12 hours (n=93)	12-24 hours (n=38)	≥24 hours (n=21)	P-value
The incidence of no-reflow phenomenon, n (%)	11 (11.2)	19 (20.4)	6 (15.8)	4 (19)	0.367**
Improved TIMI score after PCI, n (%)	79 (80.6)	63 (67.7)	29 (76.3)	11 (52.4)	0.031**

**Chi-square test
PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction score

Furthermore, as shown in Table 6, PCI led to a significantly improved TIMI score regardless of the time span in which it was performed (P-value<0.05).

A logistic regression was conducted to determine the impact of time to PCI on the no-reflow phenomenon in STEMI patients receiving thrombolytic therapy. The variables in the model included age, sex, history of Hypertension (HTN) and Diabetes Mellitus (DM), addiction, smoking, Body Mass Index (BMI), and the interval between thrombolytic therapy and PCI (in hours). The full model, containing all variables, was not statistically significant. This indicates that the model was not able to predict the no-reflow phenomenon (Table 7).

Discussion

Acute Myocardial Infarction occurs due to an abrupt interruption in the oxygenated blood flow of the coronary arteries supplying the myocardium, leading to the incidence of ischemia. This event primarily happens following a rupture of an atherosclerotic plaque, causing coronary artery occlusion due to secondary thrombosis. This results in myocardial injury that depends on the area of the myocardium supplied by the culprit coronary artery, the duration of occlusion, and the presence of collaterals[10,11]. Blood supply restoration is key to preserving the myocardium, and the best strategy to achieve this goal is Percutaneous Coronary Intervention (PCI). However, it might not be available in numerous hospitals in developing countries[5].

The current study primarily aimed to investigate the effect of early versus delayed PCI on the incidence of the no-reflow phenomenon in STEMI patients receiving thrombolytic therapy. It revealed that PCI, regardless of the interval between thrombolysis and PCI, led to significantly improved blood flow through the coronary arteries, considering TIMI

Table 6. The association of TIMI flow with PCI

			TIMI flow after PCI				TIMI flow before PCI	TIMI flow after PCI	P*
			0	1	2	3	Median [IQR]		
In general	**TIMI flow before PCI**	**0**	3 (2.9)	25 (23.8)	51 (48.6)	26 (24.8)	1 [0, 2]	2 [2, 3]	<0.001
		1	1 (1.9)	8 (15.1)	35 (66)	9 (17)			
		2	0 (0)	2 (3)	28 (42.4)	36 (54.5)			
		3	0 (0)	1 (3.8)	4 (15.4)	21 (80.8)			
<6 hours (n=98)	**TIMI flow before PCI**	**0**	1 (2.3)	8 (18.2)	22 (50)	13 (29.5)	1 [0, 2]	2 [2, 3]	<0.001
		1	0 (0)	2 (10.5)	12 (63.2)	5 (26.3)			
		2	0 (0)	0 (0)	9 (32.1)	19 (67.9)			
		3	0 (0)	0 (0)	2 (28.6)	5 (71.4)			
6-12 hours (n=93)	**TIMI flow before PCI**	**0**	2 (5.1)	11 (28.2)	18 (46.2)	8 (20.5)	1 [0, 2]	2 [2, 3]	<0.001
		1	1 (4.5)	3 (13.6)	16 (72.7)	2 (9.1)			
		2	0 (0)	1 (4.8)	12 (57.1)	8 (38.1)			
		3	0 (0)	1 (9.1)	2 (18.2)	8 (72.7)			
12-24 hours (n=38)	**TIMI flow before PCI**	**0**	0 (0)	4 (26.7)	10 (66.7)	1 (6.7)	1 [0, 2]	2 [2, 3]	<0.001
		1	0 (0)	1 (14.3)	4 (57.1)	2 (28.6)			
		2	0 (0)	1 (8.3)	3 (25)	8 (66.7)			
		3	0 (0)	0 (0)	0 (0)	4 (100)			
≥24 hours (n=21)	**TIMI flow before PCI**	**0**	0 (0)	2 (28.6)	1 (14.3)	4 (57.1)	1 [0, 2]	2 [2, 3]	0.003
		1	0 (0)	2 (40)	3 (60)	0 (0)			
		2	0 (0)	0 (0)	4 (80)	1 (20)			
		3	0 (0)	0 (0)	0 (0)	4 (100)			

* Wilcoxon test

PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction score

Table 7. Logistic Regression predicting no-reflow phenomenon

Variables	B	Standard error	Odds ratio	95 % CI	Wald statistics	P
Age	0.036	0.019	1.037	[1.000, 1.076]	3.784	0.052
Sex	0.254	0.572	1.289	[0.420, 3.958]	0.197	0.657
Addiction	0.485	0.502	1.624	[0.607, 4.342]	0.934	0.334
Smoking	-0.895	0.557	0.408	[0.137, 1.217]	2.583	0.108
Body mass index (BMI)	-0.091	0.060	0.913	[0.812, 1.026]	2.342	0.126
Diabetes	-0.347	0.506	0.707	[0.262, 1.905]	0.470	0.493
Hypertension	-0.346	0.419	0.708	[0.311, 1.609]	0.680	0.410
The interval between thrombolytic therapy and PCI (hours)	-0.362	0.619	0.696	[0.207, 2.341]	0.342	0.558
Constant	-0.476	2.189	0.621	-	0.047	0.828

CI: Confidence interval, PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction score

scores. Besides, our study showed that early PCI within 24 hours after an index STEMI treated with thrombolytic resulted in a statistically remarkable improvement in TIMI score, representing better blood flow in coronary arteries. However, the incidence of the no-reflow phenomenon did not differ between those who were categorized as early PCI compared with delayed PCI. The other findings of this study

represented no role for any of the demographic and medical characteristics of the patients as a leading cause of the no-reflow phenomenon, regardless of the time of PCI performance.

The secondary aim of our investigation was to evaluate whether subcategorization of PCI intervals with thrombolytic therapy might influence the incidence of the no-reflow phenomenon. We found that there was a significantly improved TIMI score among those who underwent intervention within less than 6 hours after thrombolysis. However, the incidence of the no-reflow phenomenon did not differ.

Although we observed a higher rate of the no-reflow phenomenon in late PCI, the comparison of the two groups revealed no significant differences. However, TIMI score improvement was significantly higher in early percutaneous intervention. This finding is comparable to the study by Khalfallah et al., who investigated the impact of very early PCI (performed within 3-12 hours after fibrinolytic therapy) versus early PCI (defined as PCI performance between 12-24 hours after STEMI treatment with fibrinolytics)[7].

In agreement with our findings, Feizi and colleagues conducted a study on 90 patients with a similar context. They defined early and late PCI as less than and over 48 hours after thrombolytic therapy for an index STEMI, respectively. They reported significantly fewer instances of the no-reflow phenomenon among the studied population[6].

Even in relation to the incidence of contrast-induced nephropathy, the higher probability of this condition among those undergoing early PCI did not outweigh the time span of PCI performance. Accordingly, the authors recommended performing PCI as soon as possible after thrombolytic therapy, even if it might predispose the patient to an increased risk of renal failure[8].

Contrarily, Chotechuang and colleagues evaluated in-hospital, short- and long-term major adverse cardiac events in patients undergoing primary thrombolytic therapy followed by early (3-24 hours) versus late (>24 hours) PCI. They reported a significantly higher rate of the no-reflow phenomenon among the patients in the early PCI context[12].

The major topic in this area refers to the significance of Primary Percutaneous Coronary Intervention (PPCI) versus a pharmacoinvasive strategy, which includes primary thrombolytic therapy followed by PCI. Although there is ongoing debate regarding this issue and the outcomes are controversial, some authors present significantly improved outcomes following earlier coronary intervention compared to delayed ones. Others prefer fibrinolytic therapy as the first step followed by PCI[13-16].

However, this issue remains an open question. Another topic has been proposed: if PPCI is not available, which strategy after fibrinolytic therapy is superior, early or delayed PCI? Accordingly, most studies prefer early PCI, clinically reasoning that there is an increased risk of microthrombi disintegrating and migrating distally, which causes an occlusion in distal parts of the coronary arteries leading to the no-reflow phenomenon.

Another hypothesis favoring early intervention refers to the structural no-reflow incidence where the microvessels surrounding the necrotic myocardial region under prolonged ischemia encounter endothelial swelling and edema. This occurs due to the loss of capillary integrity and microvascular obstruction. Data in this regard insist on the significance of the irreversible nature of structural no-reflow, exhibiting the necessity of earlier PCI[7]. However, they oppose the intervention in a span of time of less than three hours after thrombolytic therapy, considering the increased risk of complications such as bleeding[5,17].

Although we have not evaluated other factors that might affect the decision for early over late PCI after thrombolytic therapy, the majority of evidence tends to favor early intervention. This preference is due to fewer in-hospital adverse events, including re-infarction and mortality, occurring among those undergoing PCI within the first 24 hours after STEMI. However, it can be proposed that both events are directly associated with the incidence of the no-reflow phenomenon, indicating an inappropriate blood supply to the myocardium[5,18].

Another assessment in the current study was aimed at identifying the factors associated with the incidence of the no-reflow phenomenon among patients treated with a fibrinolytic followed by PCI. However, we found none of the demographic and medical factors to be associated with this condition.

In contrast, Yang et al. identified advanced age as a contributing determinant for the incidence of no-reflow after PCI[19]. Similarly, Refaat and colleagues identified advanced age, higher troponin levels,

diabetes mellitus, and heavy thrombus burden as factors associated with the incidence of no-reflow[20].

Other confirmatory studies have identified factors including a higher CHA2DS2VASc score, old age, hypertension, a higher KILLIP class, a higher Body Mass Index (BMI), and diabetes mellitus as being associated with the incidence of this phenomenon[21-25]. They attributed the incidence of no-reflow following PCI to pathophysiological reasons including neuro-hormonal activation and the fact that hypertension may induce interstitial fibrosis and remodeling of the small intra-myocardial vessels. In addition, they pointed to coronary microvascular dysfunction induced by diabetes mellitus. However, none of these studies have observed this condition in patients undergoing PCI after thrombolysis[22,25].

Limitations and suggestions

Indeed, the cross-sectional design of the current study and the sole assessment of the no-reflow phenomenon are significant limitations of our investigation. A shift towards a cohort design and the inclusion of several other factors, such as in-hospital, short- and long-term adverse events, could potentially enhance the research. Therefore, further investigations in this area are strongly recommended.

Conclusion

Based on the findings of the current study, the incidence of the no-reflow phenomenon was not associated with any of the demographic and medical factors. Furthermore, regardless of whether PCI was performed early or late, it led to a significantly improved TIMI score, which is a determinant of coronary artery blood flow. The main findings of this investigation revealed that early PCI after fibrinolysis led to significantly improved TIMI flow. However, the incidence of the no-reflow phenomenon did not differ between the groups with early versus delayed post-fibrinolysis PCI.

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Conflict of interest

The authors of the current study have no conflict of interest to disclose.

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Authors' Contribution

A. A. contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work

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