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Original Research Article

# Correlation Between Corrected TIMI Frame Count with the Extent of Myocardial Fibrosis on ST-Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention

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**Abstract**

**Background**: Microvascular injury after primary percutaneous coronary intervention (PPCI) reperfusion contributes to necrosis propagation. Corrected TIMI Frame Count (CTFC) is a surrogate marker of microvascular dysfunction and can stratify in-hospital mortality risk in patients with final TIMI flow 3. The extent of myocardial fibrosis after STEMI is associated with a higher incidence of major cardiovascular events. This study was aimed to determine the relationship between CTFC in the infarct-related artery and myocardial fibrosis area based on cardiac magnetic resonance (CMR) in STEMI patients undergoing PPCI.

**Methods**: This retrospective cohort study included 31 STEMI patients who had undergone PPCI and CMR examination between days 60 and 75 after STEMI as the sample. CTFC was measured in the infarct-related artery from post-PPCI angiogram recordings. The myocardial fibrosis area was measured from late gadolinium enhancement CMR (LGE-CMR) imaging results.

**Results**: In this study, the mean age was 51.61±10.49 years, 90.3% were male, non-anterior infarction location was 58.1%, mean total ischemic time was 489.48±228.33 minutes, mean CTFC was 27.4±9.3 frames, and mean myocardial fibrosis was 18.33±7.87%. There was no significant correlation found between CTFC and myocardial fibrosis (p=0.530), however total ischemic time had a positive and significant correlation with myocardial fibrosis (p=0.025, r=0.403).

**Conclusion**: CTFC in the infarct-related artery is not correlated with myocardial fibrosis area in STEMI patients undergoing PCI.

**Keywords:** *CTFC; myocardial fibrosis; LGE-CMR; STEMI; PPCI*
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## INTRODUCTION

In Indonesia, death from coronary heart disease is one of two leading causes of death after stroke.[1] Reperfusion therapy, either by thrombolysis or primary percutaneous coronary intervention (PPCI) in patients with ST-elevation myocardial infarction (STEMI) is the preferred treatment recommendation[2] and is aimed to save the myocardium and reduce mortality.[3] Patency of epicardial coronary artery flow on the infarct-related artery is a successful marker of reperfusion therapy, but despite good and effective blood flow in the epicardial vessels, myocardial tissue perfusion remains ineffective in the presence of coronary microvascular dysfunction, and it contributes significantly to the final severity of infarction and is an independent predictor of morbidity and mortality.[4]

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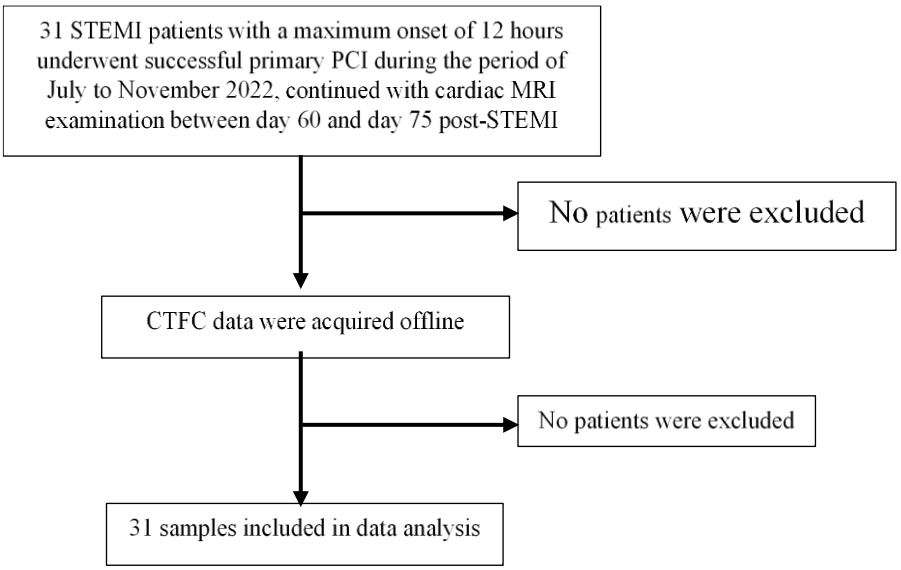


**Figure 1**. Research Flow Diagram

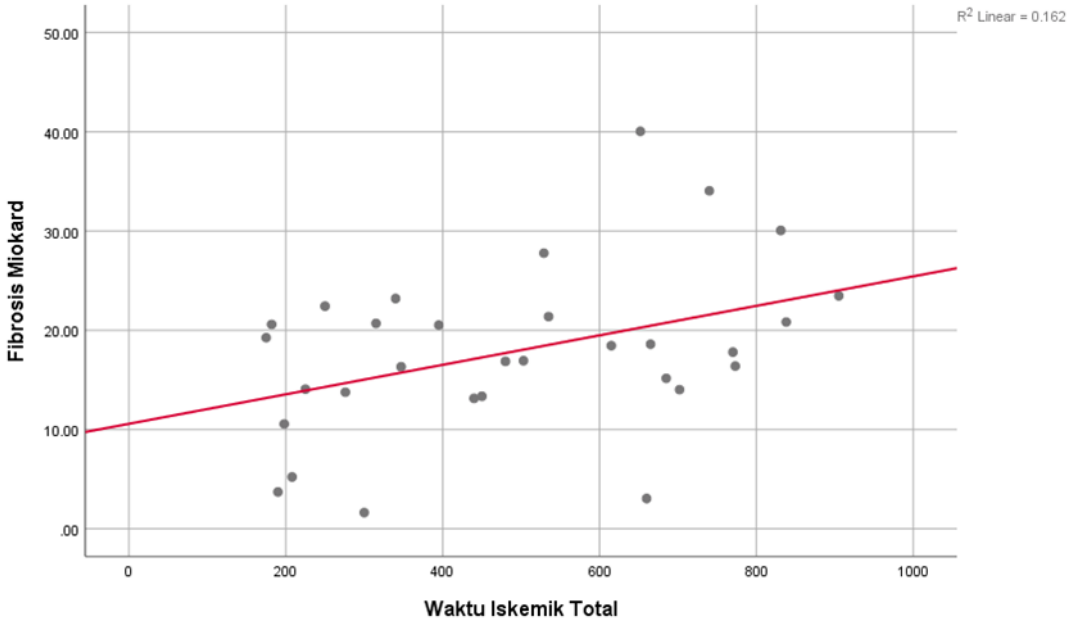


**Figure 2.** Pearson Correlation Test Between Total Ischemic Time and The Extent of Myocardial Fibrosis

Corrected TIMI frame count (CTFC) quantifies the extent of TIMI flow using the time required for contrast to fill the length of the epicardial artery and is one of the diagnostic methods for microvascular disorder in STEMI. This method is consistent with the results of SPECT and has been associated with various clinical outcomes such as improved mortality[5], better functional recovery and lower complication rates in patients undergoing PPCI.[6] Cardiac remodelling after acute myocardial infarction is characterized by the presence of fibrosis in myocardial tissue, which also has implications for long-term prognosis, causing contractile and rhythm dysfunction[7,8] Late gadolinium enhancement (LGE) imaging from cardiac magnetic resonance (CMR) is considered the gold standard for assessing infarct size and fibrosis. CMR-based infarct size is a strong independent predictor of all-cause mortality and heart failure hospitalization within 1 year.[9] 27 This study aimed to find a relationship between CTFC and myocardial fibrosis in STEMI patients undergoing PPCI.

## METHODS

### Study Design and Participants

This was a retrospective cohort study done in Kariadi Hospital, Semarang, Indonesia from July to November 2022. Infarct size was measured using cardiac magnetic resonance in patients who had undergone successful PPCI. The goal was to determine a relationship between CTFC and infarct size. Patients were enrolled at the Dr. Kariadi General Hospital, Semarang, Indonesia who met the following criteria; (1) had a first-ever ST-segment elevation myocardial infarction (STEMI) with onset within 12 hours; and (2) had successfully completed a

PPCI procedure (final TIMI flow III criteria and having residual stenosis of less than 30% in the culprit artery); (3) had underwent CMR examination in 60 – 75 days post myocardial infarction. Patients with a history of previous PCI, a history of previous coronary artery bypass graft (CABG) surgery, patients with non-ischemic heart valve disease greater than moderate degree, atrial fibrillation, pulmonary hypertension, hypertrophic cardiomyopathy, chronic kidney failure, a history of previous heart failure and patients with contraindications to MRI examination were excluded from study. The institutional Ethics Committee of Dr. Kariadi General Hospital had approved the study. (Ethical approval No. 1478/EC/KEPK-RSDK/2023) The research flow diagram can be seen in figure 1.

**CTFC Acquisition**

The assessment of CTFC was performed offline on the last angiographic image of the infarct related artery after the procedure had finished using RadiAnt DICOM software. The acquisition method of CTFC was as described by Gibson. CTFC were acquired by 2 observers blinded to subject data.

**CMR Image Acquisition**

The assessment of myocardial fibrosis was performed using LGE-CMR between day 60 and day 75 after STEMI, with an average examination time of 68±4 days. The GE Signa Voyager 1.5 Tesla MRI machine was used for the assessment of myocardial fibrosis. LGE imaging was performed 10-15 minutes after the intravenous bolus injection of 0.2 mmol/kg body weight of Gadobutrol contrast agent (Gadovist 1.0, Bayer Inc.). The MRI results were then analyzed using Philips Intellispace Portal 12 software by 2 observers blinded to subject data.

**Table 1.** Demographic Data

| Variable | Description (n=31) |
|---|---|
| Age (y.o)* | 51,61±10,49 |
| Male** | 28 (90,3%) |
| Systolic Blood Pressure (mmHg)* | 126,41±34,29 |
| Diastolic Blood Pressure (mmHg)* | 81,25±20,3 |
| Heart Rate (beats per minute)* | 74,83±15,48 |
| CAD Risk Factors** | |
| Dyslipidemia | 23 (74,2%) |
| Smoker | 21 (67,7%) |
| Hypertension | 16 (51,6%) |
| Diabetes Melitus | 12 (38,7%) |
| Medical Therapy** | |
| Aspirin | 31(100%) |
| Ticagrelor | 26 (83,9%) |
| clopidogrel | 5 (16,1%) |
| ACE-Inhibitors | 30 (96,8%) |
| Beta-blockers | 24 (77,4%) |
| Statin | 31 (100%) |
| Spironolactone | 11 (35,5%) |
| Laboratorium | |
| Hemoglobin (g/dl)* | 14,6±1,47 |
| Random Blood Glucose (mg/dl)* | 156±64 |
| creatinin (mg/dl)* | 1,17±0,24 |
| Angiographic Parameters | |
| Total Ischemic Time (minutes)* | 489,48±228,33 |
| < 360 minutes | 12 (38,7%) |
| ≥ 360 minutes | 19 (61,3%) |
| Infarct Location | |
| Anterior** | 13 (41,9%) |
| Non-anterior | 18 (58,1%) |
| Culprit Lesion** | |
| LAD | 13 (41,9%) |
| LCX | 3 (9,7%) |
| RCA | 15 (48,4%) |
| CTFC* | 27,4±9,3 frames |
| ≤ 27 frames** | 17 (54,8%) |
| > 27 frames** | 14 (45,2%) |
| Multivessel Disease** | |
| Yes | 16 (51,6%) |
| **No** | 15 (48,4%) |
| Complete Revascularization** | 17 (54,8%) |
| Echocardiographic Parameter* | |
| LVEF biplane (%) | 52,82±8,96 |
| GLS (%) | -11,49±3,15 |

**Statistical Analysis**

The mean, standard deviation, and percentage of the data were presented. The data's normality was examined using the Shapiro-Wilk test. Data CTFC and fibrosis area were examined using Pearson's correlation test. The IBM SPSS software version 23 was used to conduct all statistical analyses, and a P value of 0.05 was utilized to determine statistical significance.

## RESULTS

**Clinical and Demographic Data**

A total of 31 subjects met the inclusion criteria. The baseline characteristics of patients are shown in Table 1. The majority of patients in this study were male, with a total of 28 patients (90%). Among the risk factors for coronary heart disease, dyslipidemia was the most commonly found risk factor, accounting for 74% of the cases. The mean body mass index (BMI) was indicative of obesity, with a value of 25.17±4.45 kg/m2. The most common location of the infarction was in the non-anterior region, with 18 patients (58.1%). High-intensity statins were given to all patients along with dual antiplatelet treatment. ACE inhibitors were given to a total of 30 patients (97%) and beta-blockers to 24 individuals (77%) in total. When patients had arrived at the hospital, the average STEMI symptom onset time was 6.16±3.43 hours, and the mean total ischemic time was 489.48±228.33 minutes. 17 patients (54.8%) underwent complete revascularization, while 16 patients (51.6%) had multivessel disease. There were 15 patients (48.4%) with the culprit vessel in the right coronary artery**.**

**Correlation Between CTFC and the Extent of Fibrosis**

The mean CTFC for the entire sample in this study was 27.4±9.17 frames. The mean infarct size measure by LGE-CMR were 18.33±7.87%. The analysis using Pearson's correlation showed no significant correlation between CTFC and infarct size by LGE-CMR (p=0.530, r=0.117).

**Correlation Between Total Ischemic Time and the Extent of Fibrosis**

In this study, we found that the mean total ischemic time was 489.48±228.33 minutes. The infarct size and total ischemic time were correlated using Pearson's correlation, and the analysis produced a p-value of 0.025, showing that the correlation was significant (Figure 2). A positive correlation with a moderate strength of correlation is indicated by the r = 0.403.

## DISCUSSION

In this study, no significant correlation was found between CTFC in infarct related artery and the area of myocardial fibrosis assessed by CMR. De Luca et al[10] in their study had showed a significant linear relationship between CTFC and enzymatically assessed infarct size according to CKMB concentration. Creatine kinase (CK) is an intracellular enzyme that catalyzes the reversible conversion of creatine and ATP to creatine phosphate and ADP.[11] Disruption of cell membranes due to hypoxia or other damage results in the release of the CK enzyme through cell cytoplasm into the circulatory system[12], the CKMB isoenzyme is found specifically and predominantly in myocardial tissue and its release occurs only upon cardiomyocyte death.[13] However, due to its high molecular weight, it cannot detect small myocardial damage and its elevation may be caused by non-cardiovascular causes.[14] The study by Dai et al[15] showed a significant correlation between the incidence of perivascular fibrosis and CTFC in the LAD , describes the impairment of coronary blood flow in patients with non-ischemic heart failure. However, this study only included patients with non-ischemic heart failure.

Microvascular injury after PCI in STEMI patients is caused by a combination of external capillary compression due to interstitial edema and intramyocardial hemorrhage, as well as intraluminal obstruction processes. This microvascular injury will cause prolonged myocardial tissue hypoperfusion so that areas expected to improve after reperfusion still undergo prolonged ischemia which causes myocardial necrosis and infarcts, and ultimately will affect the final extent of myocardial fibrosis after STEMI. CTFC is a surrogate marker to detect microvascular injury. Based on the data above, the researchers assumed that microvascular injury after PCI as depicted by longer CTFC values would correlate with the final extent of myocardial fibrosis seen on CMR examination. However, the results of this study did not show a correlation between the two.

Confounding factors for CTFC had been accounted in the analysis of this study. These factors included heart rate, hemoglobin, random blood glucose, total ischemic time, and whether multivessel disease was present or not. All of these confounding factors had no correlation to CTFC. (p=0.647; p=0.203; p=0.313; p=0.774; p=0.552 respectively)

According to the study, it is believed that the duration of ischemia has a greater impact on the area of myocardial fibrosis. The increase in myocardial fibrosis area caused by continued microvascular injury after reperfusion does not seem to be as significant as compared to the damage that has already occurred before reperfusion, particularly before 360 minutes. The findings of Reimer and Jennings et al[16] who used canine models with total occlusion of the LCx artery are worth mention mentioning here. They discovered that irreversible ischemic myocyte death initially occurred in the subendocardial region and progressively spread like a wave moving towards the subepicardial region within 6 hours. Cell death was not formed immediately or simultaneously even in areas experiencing severe ischemia.[17] Occlusion of the LCx for 15 minutes was still completely reversible, in that reperfusion completely prevented necrosis, but sometimes small foci of necrosis were found after 20 minutes of occlusion. Reperfusion after 40 minutes of occlusion will always result in foci or confluences of subendocardial necrosis. Occlusion for 3 hours results in significantly more average necrosis, where usually there is confluence in the subendocardial myocardium with involvement of foci in the mid- or subepicardial myocardium. At 6 to 24 hours, the spread of necrosis is almost transmural. Viable myocardium at this point is mainly seen in subepicardial foci, which are often adjacent to blood vessels.[16]

Microvascular damage that occurs after or is caused by reperfusion will not add to the myocardial fibrosis area because a) reperfusion results in a smaller average infarct expansion within 3 hours and no difference after 6 hours compared to permanent infarcts, and b) the transmural progression of myocyte necrosis appears to precede the development of vascular damage.[16] The earliest cell death occurs in the subendocardial zone of the severely ischemic area and about half of the myocardium experiencing ischemia and becoming necrotic at 24 hours has died at 40 minutes of total occlusion. However, cell death usually occurs more slowly in the mid- and subepicardial areas, where on average about a third of the ischemic and at-risk myocardium can still be salvaged at 3 hours. By 6 hours, only a little myocardium can be salvaged.[16] Therefore, although microvascular injury is detected as indicated by prolonged CTFC after reperfusion, the myocardial fibrosis area will not increase too much if reperfusion is performed after 6 hours, because the most substantial myocardial cell necrosis occurs within 3 hours of total occlusion, and its progression will be relatively small after 6 hours of occlusion.

No correlation was found between CTFC and myocardial fibrosis area mainly affected by total ischemic time exceeding 360 minutes, where even if microvascular injury was detected by the prolonged CTFC, the progression of myocardial fibrosis was relatively slow because the damage had already been extensive and there's only a small percentage of salvageable myocardium left. If the reperfusion was completed with total ischemic time less than 360 minutes, the microvascular injury, that was indicated by prolonged CTFC, may still add to the expansion of myocardial fibrosis area because at time between 180 to 360 minutes of occlusion there's more percentage of salvageable myocardium left that may become fibrotic due to post reperfusion microvascular injury. Our study was limited by the retrospective design, small total sample number of patients, total ischemic time that exceeded 360 minutes, and the majority of non-anterior infarct location. However, this is only a pilot study, further study with prospective design may be needed to confirm our findings.

## CONCLUSION

From this study we conclude that CTFC was not correlated with the extent of fibrosis based on LGE-CMR on STEMI patients who underwent PPCI. Further prospective studies with larger total sample number may be needed to confirm our findings which including sample of anterior infarct location (LAD and LCX infarct related artery) only, and total ischemic time less than 360 minutes so that there's still bigger percentage of salvageable myocardium to see the progression of fibrosis and the sample is more homogenous.

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