1. **Background**

Non-ST segment elevation myocardial infarction (NSTEMI) is one form of acute coronary syndrome (ACS(, accompanied by severe coronary obstruction, but not total occlusion of a coronary artery. The condition is characterized by episodes of plaque rupture in the coronary arteries, resulting in the release of biochemical markers of necrosis, but without extensive patterns of cardiac muscle necrosis. Thus, no ST elevations are evident on an electrocardiogram (ECG). Typical presentation includes acute angina (or its equivalent) at rest, with a crescendo pattern. Changes in the ECG (excluding ST elevations) may be evident, as well as elevated levels of various biomarkers, such as CK-MB, troponin T, and troponin I (1).

The Global Registry of Acute Coronary Syndrome (GRACE) score estimates the risk factors and management of patients with NSTEMI. It is specifically designed for risk stratification in patients with ACS, and is more treatment-oriented, compared with other ACS risk scores. The GRACE score can also predict mortality, 1–3 years after hospitalization (2). The score considers several variables, including age, cardiac arrest, ST segment deviation, ST segment elevation on the ECG, cardiac enzymes, systolic blood pressure and heart rate at the time of hospitalization, and the use of a loop diuretic (substituted for Killip classification) and creatinine. The final score is based on the following categories: < 109, low risk (1% mortality); 109–140, intermediate risk (1%–3% mortality); > 140, high risk (above 3% mortality) (3).

The European Society of Cardiology 2015 guidelines on the management of NSTEMI separate the timing of interventional therapy, while considering clinical presentation, ECG results, and the hemodynamic and ischemic status as follows: immediate invasive strategy < 2 h; early invasive strategy < 24 h; and late invasive strategy < 72 h. An immediate invasive strategy is indicated in patients with at least one very high-risk NSTEMI criterion, such as hemodynamic instability, life-threatening arrythmia or cardiac arrest, complications of myocardial infarction (MI), persistent chest pain after medical therapy, acute heart failure, or ST-T segment changes on the ECG. The required treatment in such cases is immediate angiography and percutaneous coronary intervention (PCI).

Patients with high-risk factors, such as elevated cardiac enzyme levels, ST segment changes, or GRACE scores > 140, should be treated with an early invasive strategy. In contrast, a late invasive strategy should be used for patients with any of the following: diabetes mellitus, renal insufficiency (estimated glomerular filtration rate [EGFR] < 60), evidence of congestive heart failure, early post-infarction angina, recent PCI, prior coronary artery bypass grafting (CABG), or a GRACE score between 109 and 140. In patients with none of the above and no recurrent symptoms, non-invasive testing (such as imaging) is recommended before selecting an invasive strategy (4).

Arora et al. analyzed patients with NSTEMI undergoing coronary revascularization from 1987 to 2012. They reported improved survival in high-risk patients undergoing early PCI vs. high-risk patients who underwent late PCI at the one-year follow-up. In addition, mortality was higher in patients who underwent late PCI, probably due to prolonged ischemia prior to revascularization.

Another study conducted in Detroit, USA compared streptokinase treatment with a placebo in patients with acute ischemic symptoms. Streptokinase effectively achieved reperfusion, but induced minimal improvement in left ventricular function (6).  
Another study showed that invasive treatment decreased hospital mortality and 12-month mortality in women (from 30% to 22%) and men (from 32% to 22%); however, these results worsened every decade thereafter (7). Before PCI treatment was administered in patients with thrombolysis in myocardial infraction (TIMI) grade 2/3 and NSTEMI, no changes were observed in survival, 30-day mortality, or 12-month mortality (8,9).

Patients with NSTEMI fall into two categories; some receive immediate intervention if they are unstable, and others wait about 62 h regardless of risk categorization (4). One study conducted at the Rabin Health Center from 2000–2013 compared early intervention (up to 24 h) with late intervention (> 24 h), and showed that delayed angiography was dependently associated with increased five-year mortality (10).

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), presented at the American Heart Association Annual Conference in 2019, compared different treatment options for patients with stable ischemic heart disease and moderate-severe ischemic disease. Patients were either treated conservatively or invasively (PCI or CABG). The results showed no significant benefit of interventional therapy in mortality rate after 4 years, hospitalization rates, or other complications. The conclusions were the same for patients with chronic kidney disease and those without angina. Furthermore, the probability of any benefit in all-cause mortality among the invasive group was <10 percent (11,12).

Although previous studies have compared PCI intervention, invasive treatment (up to 3 days after), and conservative treatment in patients with NSTEMI, those studies have not considered the time factor. However, our study aims to determine a critical cut-off, after which PCI intervention will no longer be effective. Our study also aims to evaluate the outcomes of PCI treatment 3 days after the NSTEMI event, compared with PCI treatment administered later than 3 days after the event, while considering mortality and myocardial injury (ejection fraction).