# Cardiac Markers: A Clear Cause for Point of Care Testing in Newly Diagnosed Acute Coronary Syndrome Patients

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**Abstract**

**Background:** Acute Coronary Syndromes (ACS) includes unstable angina and Myocardial Infarction (MI) with or without ST-segment elevation. The rate of short term and intermediate term cardiac events are strongly related to a number of positive biomarkers at admission.

**Methods:** A prognostic cohort study carried out to evaluation of serum cTroponin-I (cTrop-I), Creatine Kinase Myocardial Band (CK-MB) and High Sensitivity C-Reactive Protein (hsCRP) as prognostic tools among the 100 patients with newly diagnosed ACS selected purposively from the Bangabandhu Sheikh Mujib Medical University (BSMMU) and National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh. Serum cTrop-I, CK-MB, hsCRP concentrations were measured and for each marker the study populations were divided into two groups on the basis of their empirical cut off value. All the patients were treated and managed identically by conventional standard management protocol.

**Results:** The mean age of the study populations were 49.61±10.28 years with the age range 30-70 years. ACS patients in group II having high baseline serum Troponin-I, CK-MB and hsCRP concentration had significantly high morbidity and mortality in comparison to group I patients. Empirical cut off value of Trop-I group II ≥4ng/ml bad prognosis almost double to good prognosis, RR=1.85 in 95% CI. CK-MB (group II ≥10ng/ml) RR=1.88 in 95% CI. The empirical cut off value of hsCRP (group II ≥5mg/l) RR=2.05 in 95% CI. According to the spearman rank correlation test, the relation between good recoveries, morbidity, mortality with cTroponin, CK-MB, hsCRP concentration is statistically significant. Among the raised group the concentration of markers invades the prognosis. The study compares the prognosis between single or no marker raised with multiple markers and results revealed significantly particularly when all three markers raised group compare with none, single and more than one marker raised groups.

**Conclusion:** Higher serum cTrop-I, CK-MB and hsCRP concentrations are associated with more adverse clinical outcomes in newly diagnosed ACS patients.

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## Introduction

Coronary heart disease (CHD) is the most common form of heart disease and most important cause of death in Europe, North and South America, Australia and New Zealand. By 2020 coronary heart disease will be the major cause of death in all regions of the world. Disease of the coronary arteries is almost always due to atheroma and its complications, particularly thrombosis. Occasionally, the coronary arteries are involved in other disorders such as aortitis, polyarteritis and other connective tissue disorders.[1] Acute Coronary Syndromes (ACS), which include unstable angina and myocardial infarction (MI) with or without ST-segment elevation. ACS is life-threatening disorders which is a source of high morbidity and mortality despite advances of treatment.[2]

Each year in the United States, approximately 1.36 million people are hospitalized due to ACS. Among them 0.81 million are for myocardial infarction (MI) and the remainder are for unstable angina. Roughly two-thirds of patients with MI have non ST segment elevation myocardial infarction; the rest have ST elevation myocardial infarction.[3] According to statistics from the American Heart Association (AHA), approximately 18% of men and 23% of women over the age of 40 will die within 1 year of having an initial recognized MI.[2]

Acute coronary syndrome is a common presentation of ischemic heart disease (IHD). WHO estimated that about 12.4 percent of deaths worldwide were for ischemic heart disease (IHD) in 2002. IHD is the leading cause of death in developed countries. The South Asian countries like India, Pakistan, Bangladesh, Srilanka and Nepal accounts for about a quarter of the world's population and contribute to the highest proportion of cardiovascular disease burden compared with any other region globally.[4] The prevalence of coronary heart diseases in Bangladesh was found to be 33 per 10000 in 1976, which is increase more than fivefold to be 172 per 10000 in 1998. Gradually the incidence is increasing day by day.[5] The overall heart disease rates among South Asian people the incidence is more in man than women.[6]

Patients who develop symptoms consistent with acute coronary syndrome require timely evaluation to determine the cause. Following recovery from an acute episode of ACS, patients continue to be at heightened risk of heart attack and stroke for which a range of secondary preventive treatment are available.[7]

The risk of cardiovascular death, recurrent myocardial infarction (MI) or progression to MI in patients initially presenting with unstable angina (UA) is greatest during the first two months after the acute event.[8] Because atherosclerotic plaque is often present throughout the arterial tree, patients who survive after an episode of ACS live with an ongoing risk of recurrent acute cardiovascular event, AMI sudden cardiac death or stroke.[9]

Female, old age, diabetes mellitus, hypertension, dyslipidemia, and obesity were more prevalent in non ST elevation ACS patients. ST elevation myocardial infarction patients were more likely to be smokers and less likely to be taking aspirin prior to the admission. Chronic renal failure (CRF) and diabetes mellitus were independent predictors of in-hospital heart failure in non ST elevation ACS, while CRF and hypertension were predictors of ST elevation myocardial infarction. Female sex and CRF were independent predictors of mortality in ST elevation myocardial infarction. Assessment of the prevalence of cardiovascular risk factor in the acute coronary presentation is of important prognostic value for in-hospital morbidity and mortality. Cardiovascular risk

factor and its impact may differ according to ACS type, age and sex.[10]

It is estimated that 2% to 4% of patients with an acute coronary syndrome are mistakenly sent home from the emergency department, and this misdiagnosis results in significantly increased morbidity and mortality. Moreover, previous research suggests that more than 50% of patients admitted with the diagnosis of an acute coronary syndrome are subsequently discharged with a diagnosis of noncardiac chest pain, which may contribute unnecessary economic strain to the health care system.[11] Cardiac biomarkers have had a major impact on the management of this disease and are now the cornerstone in its diagnosis and prognosis.[12]

Cardiac Troponin-I (cTnI) and Troponin T (cTnT) are expressed only in cardiac muscle, which allows these biomarkers to achieve extremely high specificity for myocardial damage.[13] cTn subunits are detectable in the peripheral circulation when damage to the cardiac myocyte first leads to the release of cytoplasmic cTn, which accounts of 3% to 5% of cTnI and 7% of cTnT levels.[14] The release of bound cTn subunits contributes to the continued rise in peripheral levels. After infarction, cTn remains detectable for days (4–7 days for cTnI and 10–14 days for cTnT), cleared from the circulation primarily by the reticuloendothelial system, and fragmented into molecules that are cleared by renal system. Although cTn elevation persists for days, initial detection is delayed after myocardial injury, as necrosis typically requires 2–4 h to occur in the setting of ischemia.[15]

Cardiac Troponin-I is a well-established biomarker for diagnosis and prognosis of ACS. With current high quality analytic methods, cardiac Troponin measurement is highly sensitive and specific for myocardial injury. Minor elevations of Troponin identify high risk underlying coronary morphology like patients with plaque rupture, large thrombus burden and distal embolization.[16] Elevations in troponin T and I are associated with abnormal tissue level perfusion. These patients clearly benefit from aggressive anti-platelet, anti-thrombotic and revascularization therapy.[17] The cTnI begins to elevate 3 h from the onset of chest pain in MI. Because of the continuous release, cTnI elevation persists for days (cTnI: 7-10 days). cTnI typically increases more than 20 times above the upper limit of the reference range in myocardial infarction as compared to creatinine kinase-myocardial band (CK-MB) which usually increases 10 times above the reference range. This prolonged course of release with Troponin I is advantageous for the late diagnosis of MI, however, it limits the diagnosis of early reinfarction.[12]

hsC-reactive protein (CRP) is the inflammatory marker receiving the most attention as a prognostic indicator of coronary artery disease. It is an acute phase reactant normally present in plasma at low levels, and increases >100- fold in response to inflammatory stimuli. It is produced by hepatocytes in response to stimulation by interleukin-6. It is also produced by human coronary artery smooth muscle cells.[18] These levels increased at around 6 hours and reached their peak values at between 36 hours and 48 hours. Peak levels are much higher in infarction with ST-segment elevation, intermediate in non-ST-elevation infarction, and low unstable angina. The increase in CRP levels followed that of cTnI.[19]

hsCRP in addition to BNP and cTnI does appear to provide some additional value in the prognostication of ACS.[20] In the absence of infarction hsCRP levels correlate to the extent of atherosclerosis and some studies have shown that it predicts coronary events in

patients of unstable angina independent of cTnI level.[20] The biggest contribution of hsCRP to prognosis is in the prediction of medium to long-term mortality. High sensitive CRP levels above 10 mg/L between 24 hours to 48 hours after onset of non-ST-elevation ACS are associated with a greater probability of events, particularly death, in the following months.[18]

CK-MB is an enzyme that is abundantly present in myocardial tissue. After the onset of symptoms of acute myocardial infarction (AMI), circulating levels of CK-MB begin to increase within a few hours (4-6 hours), peak at 12 to 24 hours and after reaching a peak fall to normal ranges within 48-72 hours.[21] Therefore, it is a sensitive marker of myocardial infarction (MI) but has relatively low specificity because of presence of CK-MB in skeletal muscles. If CK-MB in an AMI patient is at a low level in serum at the time of admission, it indicates minimal amount of myocardial damage, and the possibility of successful treatment exists as a result of which mortality and morbidity could be decreased.[22] Although now more new sensitive and more specific markers are available, CK–MB is still widely used in developing countries like Pakistan, Bangladesh for confirming the diagnosis of AMI. Recent clinical data have suggested that CK-MB concentration in serum at the time of presentation (admission CK-MB) is an independent predictor for the short and long term cardiac outcomes.[23]

Importance of biomarkers, both in diagnosis and prognosis of ACS is now well established. Troponin-I, CK-MB and hsCRP are in wide clinical use and have important therapeutic and prognostic implication of ACS patients. Moreover, these biomarkers would be mutually complementary to each other and thus multi-marker testing would help in better characterizing each case of ACS and may be the future norm.[12] Troponin-I, CK-MB and hsCRP provide independent and complementary information about pathophysiology, diagnosis and prognosis. Multiple marker strategies or biochemical profiling may be used in the future to characterize individuals.

**Methods**

This Prognostic cohort study was carried out in the department of Biochemistry, BSMMU in cooperation with the department of Cardiology, BSMMU and NICVD, Dhaka, Bangladesh. A total 100 newly diagnosed acute coronary syndrome patients, age range 30 to 70 years irrespective of sex, were included according to purposive sampling technique.

Serum cTropI, CK-MB, hsCRP concentrations were measured and then grouping of the study subjects was done on the basis of their empirical cut off value. For each marker, study populations were divided into two groups. In the case of Group I cTropI <4 ngm/ml, CK-MB <10 ngm/ml and hsCRP <5mg/l. In Group II patients having cTrop I ≥4 ngm/ml, CK-MB ≥10ng/ml and hsCRP ≥5mg/l. All the patients were treated and managed identically by conventional standard management protocol. The serum cTnI and CK-MB estimated by MicroParticle Enzyme Immunoassay (MEIA) method and hsCRP estimated by Immunonephelometric method.

All patients were followed from their admission up to discharge from the hospital. After discharge all patients were followed up periodically in every month up to three months. Patients were evaluated on the basis of clinical assessment, ECG, Echocardiogram, CAG, cardiac markers according to the merit of the individual case. ACS patients with good outcomes who those had no complaints of further chest pain, were feeling better with medication and change in lifestyle can carry

out day to day activities and follow up ECG change came back to normal and no further ECG change. ACS patients with bad outcomes showed morbidity (recurrent ACS, heart failure, arrhythmia and revascularization) and mortality.

At the end of follow-up patient's clinical outcomes were evaluated on the perspective of their baseline serum concentration. Statistical analysis was performed by using Windows SPSS 16.0 version. To evaluate the association of serum Trop-I, CK-MB, hsCRP with clinical outcome were done by Chi-Squaretest. Finally, relation of cardiac marker concentration with prognostic outcome was done by Kruskal –Wallis H test and correlation of prognosis with biomarker done by Spearman rank correlation test.

**Result**

The clinical presentation varies from unstable angina to STEMI or NSTEMI. In this study, 100 diagnosed acute coronary syndrome (ACS) patients free from heart failure, renal failure, previous cardiac chest pain and hepatic disorder were enrolled from the cardiology emergency department of BSMMU and NICVD.

Among 100 patients, 86 were male and 14 were female with the mean age of 49.61±10.28 years and age ranges were 30-70 years, of them 30 were NSTEMI, 65 were STEMI and 5 were unstable anginas.

Table I: Association of cTroponin I concentration with clinical outcomes of study populations

| Clinical outcome | cTroponin I | | P value |
|---|---|---|---|
| | Group I (<4 ng/ml) | Group II (≥4 ng/ml) | |
| Good prognosis | 13(65.0%) | 28(35.0%) | 0.044 |
| Morbidity | 7(35.0%) | 49(61.3%) | |
| Mortality | 0(0.0%) | 3(3.7%) | |
| Total | 20 | 80 | |

Table I showed, serum cTroponin-I associated with clinical outcome of study populations. In group-I out of 20 ACS patients good prognosis, morbidity and mortality were 65.0%, 35.0% and no mortality respectively and those in group-II, out of 80 ACS patients good prognosis, morbidity and mortality were 35.0%, 61.3% and 3.7% respectively. In group-II having high serum Troponin-I concentration, significantly low good recovery but significantly high morbidity and mortality found compared to those in group I patient having low serum Trop-I concentration (p=0.044).

Table II: Association of CK-MB concentration with clinical outcome of study populations

| Clinical outcome | CK-MB | | P value |
|---|---|---|---|
| | Group I (<10 ng/ml) | Group II (≥10 ng/ml) | |
| Good prognosis | 12(66.7%) | 29(35.4%) | 0.045 |
| Morbidity | 6(33.3%) | 50(61.0%) | |
| Mortality | 0(0.0%) | 3(3.6%) | |
| Total | 18 | 82 | |

Table II showed serum CK-MB associated with clinical outcome of the study populations. In group-I out of 18 ACS patients, good prognosis, morbidity and mortality were 66.7%, 33.3% and no mortality respectively and those in group-II, out of 82 ACS patients good prognosis, morbidity and mortality were 35.4%, 61.0% & 3.6% respectively. In group-II, having high serum CK-MB concentration, significantly low good recovery but significantly high morbidity and mortality found compared to those in group-I patients having low serum CK-MB concentration (p=0.045).

Table III: Association of hsCRP concentration with clinical outcome of study populations

| Clinical outcome | hsCRP | | P value |
|---|---|---|---|
| | Group I (<5 ng/ml) | Group II (≥5 ng/ml) | |
| Good prognosis | 22(61.1%) | 19(29.7%) | 0.009 |
| Morbidity | 13(36.1%) | 43(67.2%) | |
| Mortality | 1(2.8%) | 2(3.1%) | |
| Total | 36 | 64 | |

Table III showed, serum hsCRP associated with clinical outcome of study populations. In group-I out of 36 ACS patient good prognosis, morbidity and mortality were 61.1%, 36.1% and 2.8% respectively and those in group-II, out of 64 ACS good prognosis, morbidity and mortality were 29.7%, 67.2% and 3.1% respectively. In group-II having high serum hsCRP concentration, significantly low good recovery but significantly high morbidity and mortality found compared to those in group-I patient having low serum hsCRP concentration (p=0.009).

Table IV: Risk of morbidity and mortality in patients with high (Group-II) cTroponin I

| Troponin I | Prognosis | | RR | 95% CI |
|---|---|---|---|---|
| | Good n (%) | Bad n (%) | | |
| Group-I (< 4 ng/ml) | 13 (31.7) | 7 (11.9) | 1.85 | 1.19–2.88 |
| Group-II (≥ 4 ng/ml) | 28 (68.3) | 52 (88.1) | | |
| Total | 41 (100.0) | 59 (100.0) | | |

Table IV showed that the risk of morbidity and mortality in patients with high cTroponin-I in group-II. Relative risk 1.85 in 95% CI (1.19-2.88), that indicates 1.85 times more chance of having a bad prognosis in group-II patients in 95% CI.

Table V showed the risk of morbidity and mortality in patients with high CK-MB in group-II. Relative risk ratio 1.88 in 95% CI (1.21-2.92), that indicates 1.88 times more chance of having bad a prognosis in group II patients in 95% CI.

Table V: Risk of morbidity and mortality in patients with high (Group-II) CK-MB

| CK-MB | Prognosis | | RR | 95% CI |
|---|---|---|---|---|
| | Good n (%) | Bad n (%) | | |
| Group-I (< 10 ng/ml) | 12 (29.3) | 6 (10.2) | 1.88 | 1.21–2.92 |
| Group-II (≥10 ng/ml) | 29 (70.7) | 53 (89.8) | | |
| Total | 41 (100.0) | 59 (100.0) | | |

Table VI: Risk of morbidity and mortality in patients with high (Group-II) hsCRP

| hsCRP | Prognosis | | RR | 95% CI |
|---|---|---|---|---|
| | Good n (%) | Bad n (%) | | |
| Group-I (< 5 mg/l) | 22 (53.7) | 14 (23.7) | 2.05 | 1.30–3.25 |
| Group-II (≥ 5 mg/l) | 19 (46.3) | 45 (76.3) | | |
| Total | 41 (100.0) | 59 (100.0) | | |

Table VI showed, the risk of morbidity and mortality in patients with high hsCRP in group-II. Relative risk 2.05 in 95% CI (1.30-3.25), that indicates 2.05 times more chance of having bad a prognosis in group II patients in 95% CI.

Table VII: Correlation of prognosis (good and bad outcome) with cTroponin I, CK-MB and hsCRP concentration

| Biomarkers | r value | p value |
|---|---|---|
| cTroponin-I (ng/ml | 0.316 | 0.001 |
| CK-MB (ng/ml) | 0.279 | 0.005 |
| hsCRP (mg/l | 0.197 | 0.049 |

Table VII showed, correlation of prognostic outcome (good and bad) with cTroponin-I, CK-MB, hsCRP. In case of TnI r was 0.316 & p was 0.001. In case of CK-MB r was 0.279 & p was 0.005. In the case of hsCRP r was 0.197 & p was 0.049. TnI, CK-MB and hsCRP were significantly and positively correlated with prognosis.

Table VIII: Comparison of outcome among the study subjects having three and two bio markers raised

| Biomarkers | Prognosis | | P value |
|---|---|---|---|
| | Good | Bad | |
| Three markers raised | 12(37.5%) | 39(68.4%) | 0.005 |
| Two markers raised | 20(62.5%) | 18(31.6%) | |
| Total | 32 | 57 | |

Table VIII shows the comparison of outcome among ACS patients having three and two markers raised (concentration of cTnI, CK-MB, hsCRP above cut off value, in case of cTnI it was ≥4ng/ml, in case of CK-MB it was 10 ng/ml, in case of hsCRP it was 5mg/l). In the case of three markers raised good outcome 12 (37.5%) and bad outcome 39 (68.4%). In the case of two markers raised good outcome 20 (62.5%) and bad outcome

18 (31.6%). There were statistically significant differences found between biomarkers concentration and prognosis.

Table IX: Comparison of outcome among the study subjects patients having three and one bio markers raised

| | Prognosis | | |
|---|---|---|---|
| Biomarkers | Good | Bad | P value |
| Three markers raised | 12(80.0%) | 39(100%) | 0.004 |
| One markers raised | 3(20.0%) | 0(0%) | |
| Total | 15 | 39 | |

Table IX shows the comparison of outcome among ACS patients having three and one marker raised (concentration of cTnI, CK-MB, hsCRP above cut off value). In case of three markers raised good outcome 12 (80.0%) and bad outcome 39 (100.0%).Incase of one marker raised good outcome 3 (20.0%) and no bad outcome. There were statistically significant differences found between biomarkers concentration and prognosis.

Table X: Comparison of outcome among the study subjects having three and no biomarkers raised

| | Prognosis | | |
|---|---|---|---|
| Biomarkers | Good | Bad | P value |
| Three markers raised | 12(67.7%) | 39(95.1%) | 0.003 |
| No markers raised | 3(33.3%) | 2(4.9%) | |
| Total | 18 | 41 | |

Table X shows the comparison of outcome among ACS patients having three and no markers raised(concentration of cTnI, CK-MB, hsCRP above cut off value, in case of cTnI it was ≥4ng/ml, in case of CK-MB it was 10 ng/ml, in case of hsCRP it was 5mg/l).Incase of three markers raised good outcome 12 (66.7%) and bad outcome 39 (100.0%). In case of none markers raised good outcome 6 (33.3%) and bad outcome 2 (5.1%). There were statistically significant difference found between biomarkers concentration and prognosis.

**Discussion**

Among 100 study subjects 86 patients were male and 14 patients were female with the mean age of 49.61±10.28 years and age range was 30-70 years. This study result support one previous report.[24]

In this study ACS patients in group II having high baseline serum Troponin I concentration had significantly high morbidity and mortality (p-0.044) in comparison to group I patients. These were consistent with the finding of patient with baseline cTnI ≥0.04µg/l were at higher risk of death due to myocardial infarction at 30 days than were patients with a negative cTnI.[25]

ACS patient in group II having high baseline serum CK-MB concentration; significantly low good recovery but high morbidity and mortality (p-0.045) found compared to those in group I. Another study showed that CK-MB mass emerges as an independent marker (p= 0.002) for major cardiovascular events at 6-months follow-up.[23]

ACS patient in group II having high baseline serum hsCRP concentration; group II having high serum hsCRP concentration (>5ng/dl); significantly low good recovery but high morbidity and mortality (P-0.009) found

compared to those in group I patient having low serum hsCRP concentration.

One study found that 90 days follow up mortality 12% and overall incidence of major coronary events was 87% in patient with abnormal CRP versus 13% in patients with a normal CRP.[26]
Sensitivity/specificity for AMI diagnosis was directly proportional to the time. So, considering all the cardiac markers hsCRP, Troponin I is the most sensitive and is better to predict the outcome of the patient (p-0.009, p-0.044).

In this study empirical cut off value of Troponin-I in group II ≥4ng/ml bad prognosis almost double to good prognosis, relative risk 1.85 in 95% CI (1.19-2.88), that indicate 1.85 times more chance of having bad prognosis in group II patient in 95% CI. On the other hand CK-MB (group II≥10ng/ml) RR 1.88 in 95% CI (1.21-2.92), that indicates 1.88 times more chance of having a bad prognosis in group II patients in 95% CI (p=0.002). The empirical cut off value of hsCRP (group II ≥5mg/l RR 2.05 in 95% CI (1.30-3.25), that indicates 2.05 times more chance of having a bad prognosis in group II patients in 95% CI.
This consist with previous meta-analysis where risk ratios for death or MI for Troponin I positive was 4.2 for Troponin I (95% CI, 2.7 to 6.4; $p < 0.001$).[27] CK-MB mass was not a significant independent predictor for the combined event of death or infarction (re-infarction) in 30 days (odds ratio [OR] 1.16; confidence interval [CI] 95% 0.52 to 2.58; $p = 0.71$) which not support this study.[28]

According to the spearman rank correlation test, the relation between good recovery, morbidity, mortality with cTroponin, CK-MB, hsCRP concentration is statistically significant (p-0.001, p-0.005, p-0.049). Among the raised group the concentration of markers invades the prognosis.

The mortality rate depends on concentration of Troponin I at 42 days.[29] Each increase of 1ng/ml in the cardiac Troponin I level was associated with a significant increase (p=0.03) in the risk ratio for death after adjustment for the baseline characteristics that were independently predictive of mortality. According to another study, an abnormal CRP (>5.0 mg/l) with a major cardiac event was compared to 3.0 mg/l for the 135 patients without a major cardiac event.[30]

The study compares the prognosis between single or no marker raised with multiple markers and results revealed significantly particularly when all three markers raised group compare with non, single and more than one marker raised groups (p-0.003, 0.004 and 0.005 respectively). Multivariate model include both markers showed improved performance in comparison with model with a single marker (p-0.001).[30]
We can assess the prognosis of newly diagnosed ACS patients with estimation of these biomarkers and can take precaution to prevent the complication. Thus helps the right patient to receive the right treatment at the right time. This study is for prediction of ACS patient prognosis by estimation of multiple biomarkers.

*Conclusion*

Mortality and morbidity of ACS patients are independently related to each of the biomarkers. The rate of short term and intermediate term cardiac events are strongly related to a number of positive biomarkers at admission. It can be concluded from this study that, higher serum cTroponin- I, CK-MB and hsCRP concentrations are associated with more adverse clinical outcomes in newly diagnosed ACS patients. These markers have appeared as independent predictors of major cardiac events as well as death of ACS patients. Serum cTroponin I, CK-MB and hsCRP at the onset of the disease have shown

the incremental prognostic importance. Therefore, serum cTroponin I, CK-MB and hsCRP can be used clinically as biomarkers of prognosis in newly diagnosed ACS patients.

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