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# TROPONIN I AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN ACUTE CORONARY SYNDROME: ARE THEY RELATED?

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**ABSTRACT**

**Background:** Coronary Artery Disease (CAD) is one of the leading causes of death globally. ACS patients tend to have complications, that are usually defined as Major Adverse Cardiovascular Events (MACE) which consist of heart failure, arrhythmia, stroke, and in-hospital mortality. Some factors have been researched to predict MACE in ACS, such as cardiac troponin I (cTnI) level, which has been one of the modalities to diagnose ACS. This study aims to determine the association between cTnI level and MACE in ACS patients at Adam Malik Hospital.
**Method:** This study used an observational analytic method with a cross-sectional design and a retrospective approach. The data used is secondary data that meets the inclusion and exclusion criteria.
**Result:** Among 200 patients, 175 patients (87,5%) were >45 years old and 149 patients (74,5%) were male. The most common type of ACS was NSTEMI, with 75 patients (37,5%). cTnI level was increased in 133 patients (66,5%). There were 117 patients (58,5%) who experienced MACE and were dominated by heart failure, with 80 patients (40%). There was an association found between cTnI level and MACE (p=0.001; r=0,413).
**Conclusion:** There was an association between cTnI level and MACE in ACS patients.

**Keywords:** *cTnI*, MACE, ACS, CHD

***ABSTRAK***

**Latar Belakang**: Penyakit Arteri Koroner (PAK) adalah salah satu penyebab utama kematian secara global. Pasien sindroma koroner akut (SKA) cenderung mengalami komplikasi, yang biasanya didefinisikan sebagai *Major Adverse Cardiovascular Events (MACE)* yang terdiri dari gagal jantung, aritmia, stroke, dan kematian di rumah sakit. Beberapa faktor telah diteliti untuk memprediksi MACE pada SKA, seperti *cardiac troponin I (cTnI)* jantung, yang telah menjadi salah satu modalitas untuk mendiagnosis SKA. Penelitian ini bertujuan untuk mengetahui hubungan antara tingkat cTnI dengan MACE pada pasien SKA di RS Adam Malik.
**Metode**: Penelitian ini menggunakan metode analitik observasional dengan desain *cross-sectional* dan pendekatan retrospektif. Data yang digunakan adalah data sekunder yang memenuhi kriteria inklusi dan pengecualian.
**Hasil**: Di antara 200 pasien, 175 pasien (87,5%) berusia >45 tahun dan 149 pasien (74,5%) adalah laki-laki. Jenis SKA yang paling umum adalah NSTEMI sebanyak 75 pasien (37,5%). Nilai cTnI meningkat pada 133 pasien (66,5%). Ada 117 pasien (58,5%) yang mengalami MACE dan didominasi gagal jantung sebanyak 80 pasien

(40%). Ada hubungan yang signifikan antara kadar cTnI dan MACE (p=0,001; r=0,413).
**Kesimpulan:** Terdapat hubungan yang signifikan antara kadar cTnI dan MACE pada pasien SKA.

**Kata kunci**: cTnI, MACE, SKA, PJK

## 1. Introduction

Coronary Artery Disease (CAD) has been and still is one of the leading causes of death globally with ACS as its most threatening manifestation [1]. This statement is amplified by WHO data in 2015 that cardiovascular disease accounted for 17,5 million mortality cases and 7,4 million among them were Acute Coronary Syndrome (ACS) cases. According to Kemenkes in 2016, ACS caused 51.160 hospitalizations nationally [2]. Riskesdas 2018 stated that the prevalence of CAD was 1,5% nationally and 1,3%, particularly in North Sumatra [3]. A study in Adam Malik General Hospital found that there were 661 CAD cases in 2022 [4]. ACS is a part of CAD that is caused by disruption of oxygen supply to the heart which is classified as Unstable Angina Pectoris (UAP), Non ST segment Elevation Myocardial Infarction (NSTEMI), and ST segment Elevation Myocardial Infarction (STEMI). ACS cases are predominantly manifestations of intracoronary thrombus that are caused by the rupture of atherosclerosis plaque in tunica intima [5]. The thrombus will obstruct the coronary vessel partially or totally and lead to ischemia condition. Subsequently, oxygen cessation of>20 minutes leads to myocardial necrosis that causes mechanical, electrical, and biochemistry dysfunction of the heart [6]. ACS patients tend to have Major Adverse Cardiovascular Events (MACE) which refers to a group of clinical outcomes that are commonly regarded as the main mechanism of morbidity and mortality in ACS patients [7]. MACE components were described as Acute Myocardial Infarction (AMI), stroke, heart failure, cardiogenic shock, and revascularization procedure [8] Other studies stated that MACE consists of mortality, AMI, angina, arrhythmia, and revascularization [9]. In this study, the researcher included heart failure, arrhythmia, stroke, and in-hospital mortality to be explored as MACE.

Cardiac biomarker examination is fundamental to determining myocardial infarction in ACS. cTnI is a contractile component in skeletal and cardiac muscle that consists of cTnI [10]. Troponin levels, especially cTnI have high sensitivity and specificity in diagnosing myocardial infarction and are used as a gold standard and indicator for myocardial injury [11] The main mechanism to explain the elevating cTnI level in ACS patients is cardiac necrosis [12]. Myocardial ischemia and hypoxia in ACS will cause shifting cardiac metabolism from aerobic to anaerobic and lead to myocardial injury. Prolonged cardiomyocyte injury increases the cell permeability and cytosolic protein leakage to the circulation [13]

Elevating cTnI has been used to predict the infarct size expansion and mortality risk in ACS [14]. Research in Jambi and Surabaya also found an association between cTnI and MACE in ACS patients [15] [16]. A study at Adam Malik Hospital showed that 62.5% of ACS patients were experiencing MACE [17] The high incidence of MACE and confidence of cTnI examination in ACS cases become the ground in this research to take cTnI as one of the considerations for predicting MACE in ACS patients.

## 2. Method

This research was an observational analytical study with a cross-sectional design and retrospective approach. Samples were collected using consecutive sampling. The data is secondary data from medical records where 200 patients diagnosed with ACS during 2022-2023 were included in this study. ACS diagnosis was determined in the medical resume by assessing the anamnesis, physical findings, ECG, and cardiac biomarkers. cTnI level was evaluated in the patient's clinical pathology examination with chroma II immunoassay. MACE was found in the medical resume by analyzing the patient's clinical signs, abnormal heart rate and rhythm, also neurological diagnostic tests during hospitalization. History of pulmonary embolism, chronic kidney disease, sepsis, and incomplete medical records were used to exclude the samples. This research was authorized by the ethical committee in the Faculty of Medicine, Universitas Sumatera Utara.

The data was analyzed using SPSS statistic 23 to assess the association between cTnI level and MACE through the bivariate chi-square method. The 95% confidence interval and $\alpha$=0.05 were used in this study. The result stated a significant association if the $p<0.05$.

## 3. Result

Based on Table 1, among 200 patients, 175 patients (87,5%) were >45 years old and 144 patients were male. The mean age in this study was 59 years old with the youngest patient being 24 years old and the oldest patient being 85 years old. The diagnosis was dominated by NSTEMI cases, with 75 patients (37.5%), then followed by UAP (33.5%) and STEMI (29.9%).

**Table 1** Characteristics of ACS patients

| Characteristic | Frequency | % |
|---|---|---|
| Age (years) | | |
| ≤45 | 25 | 12.5 |
| >45 | 175 | 87.5 |
| Gender | | |
| Male | 149 | 74.5 |
| Female | 51 | 25.5 |
| ACS types | | |
| UAP | 67 | 33.5 |
| NSTEMI | 75 | 37.5 |
| STEMI | 58 | 29.0 |

Based on Table 2, there were 117 patients (58.5%) experiencing MACE 80 of them were heart failure, 39 patients were having arrhythmia, 4 patients were having stroke, and 24 patients died during hospitalization.

**Table 2** Distribution of MACE

| Experiencing MACE | Frequency | % |
|---|---|---|
| Yes | 117 | 58.5 |
| Heart failure | 80 | 40 |
| Arrhythmia | 39 | 19.5 |
| Stroke | 4 | 2 |
| In hospital mortality | 24 | 12 |
| No | 83 | 41.5 |

Based on Table 3, among the total patients, there were 133 patients with elevated cTnI levels. The cTnI cut-off value used in Adam Malik General Hospital was 0.03 ng/ml. The mean cTnI level was 6.23 ng/ml. The greatest cTnI level was 77 ng/ml and the lowest cTnI level was 0 ng/ml.

**Table 3** Distribution of cTnI Level

| cTnI level (ng/ml) | Frequency | % |
|---|---|---|
| ≤ 0,03 | 67 | 33.5 |
| > 0,03 | 133 | 66.5 |

Based on Table 4, The analysis result shows that there was a significant association between cTnI level and MACE, and the p was 0.001. The R in this study was 0.413 interpreted as a moderate level of correlation.

**Table 4** Association between cTnI Level and MACE

| cTnI level (ng/ml) | MACE | | | | Total | | *p* | *r* |
|---|---|---|---|---|---|---|---|---|
| | Yes | | No | | | | | |
| | n | % | n | % | n | % | | |
| ≤ 0.03 | 20 | 29.9 | 47 | 70.1 | 67 | 100 | 0.001 | 0.413 |
| > 0.03 | 97 | 74 | 36 | 26 | 133 | 100 | 0.001 | 0.413 |

## 4. Discussion

A similar result is also shown in research in Palestine, which described that the majority of ACS patients were >45 years old [18]. Moreover, research in Aceh also discovered that 86% of ACS patients were ≥ 45 years old, and 69% of patients were male [19]. Based on an epidemiological study, the onset of cardiovascular disease in males was found 10-15 years earlier than in females. This statement might relate to the cardioprotective mechanism of estrogen such as antioxidant, vasodilator, and anti-atherosclerotic by inhibiting LDL-C oxidation [20] [21]. Age is also considered one of the independent risk factors of ACS. Oxidative stress in aging leads to inflammation and mitochondrial dysfunction and later causes cardiac metabolism and contraction dysfunction [20]. Based on the diagnosis, NSTEMI was found as the most dominant ACS type, which was discovered in 75 patients (37,5%). The research described that 70% of ACS cases in the United States were NSTEMI [22]. In some developing countries, 54% of ACS cases were NSTEMI/UAP [23].

Among the total patients, 117 of them (58.5%) had MACE in hospitalization. A synchronized result was found in Surabaya which described that 69% of ACS patients were experiencing MACE [16]. Meanwhile, research in RSCM Jakarta explained that the incidence rate of MACE in ACS was 85.7% [24]. A study in China also found that 85.96% of CAD patients were suffering from MACE in hospitalization [25].

This study revealed that heart failure accounted for 40% of the MACE cases. In the United States, 38% of ACS patients were at risk of heart failure. Cardiomyocyte stress in ACS will disrupt heart contractility while the inflammation and immune response will aggravate cardiac dysfunction [26]. Heart failure following myocardial infarction was said as the consequence of adverse ventricular remodeling, which refers to the alteration of ventricular size, shape, and function due to mechanical, neurohormonal, and inflammatory immune environments [27].

Arrhythmia cases were found in 19.5% of ACS patients. A similar result was also found in Surabaya, which showed that 17.6% of ACS patients had arrhythmia [16]. Arrhythmia induced by ACS may explained by electrolyte imbalance due to ischemia condition. ATP deficiency, acidosis, potassium, and lysophosphatidylcholine imbalance may impair the conducting and contractility of the heart [28]. Atrial remodeling in ACS will cause electrical and calcium channel dysfunction that leads to atrial fibrillation [29][30]. Tachycardia in ACS may be caused by sympathetic response whilst bradycardia may occur due to contractile dysfunction [31]. RBBB may caused by left descending artery occlusion and LBBB may represent an extent of injury in the distal conducting system [32] [33].

Cardiomyocyte dysfunction, ventricle hypokinesis, and atrial dysfunction in ACS can stimulate thrombogenesis and embolism that may lead to stroke, which is shown in 2% of ACS patients in this study [34]. The exact number was also obtained through research in Finland which described that 2.1% of ACS patients were suffering stroke during hospitalization [35]. Among the total patients, 24 patients died during hospitalization. A similar result was also found in research in Kediri that described the incidence of in-hospital mortality in ACS as 15.4% [36]. Mortality in ACS is usually caused by lethal ventricular arrhythmia. Mechanical complications such as ventricle rupture, cardiac tamponade, and valvular dysfunction also may resemble lethal arrhythmia [37].

Based on the data shown above, cTnI level was elevated in 133 patients (66.5%). The cut-off value used in Adam Malik Hospital was 0.03 ng/ml. The instrument used to assess cTnI in Adam Malik was i-Chroma II Immunoassay. The same value was also used in research that described cTnI level >0.03 ng/ml may indicate cardiomyocyte injury [38]. Heart ischemia will cause cardiac necrosis and proteolytic enzyme activation that will increase cardiomyocyte permeability and lead to the release of the cTnI in circulation [39] [40].

This study discovered a significant association between cTnI and MACE in ACS patients (p=0.001). A similar result was found through research in Jambi (p=0.006) and Surabaya (p=0.002) [15] [16]. A moderate level of correlation was figured by the r (0.413). These findings are supported by ESC recommendation to assess serial cTnI levels to determine ACS prognosis [41]. High cardiac metabolic demand and microinjury secondary to dislodgment of thrombi in small coronary vessels may explain the increased cTnI level and severe outcomes in ACS [42]. Elevating cTnI level has been researched as associated with infarct size, triple vessel disease, and stenosis severity [43]. AHA stated that ACS patients with elevated cTnI levels tend to have complex corona lesions, intracoronary thrombus, and severe blood supply disruption [44]. cTnI is also associated with atherosclerosis progressivity, angina duration, worse ECG findings, and more severe lesions such as ulcerated, bifurcated, eccentric, and irregular [45]. Patients with elevated cTnI levels were studied and had a three-fold acceleration in deteriorating atherosclerosis plaque as well [42].

cTnI has been studied as a predictor of heart failure risk in ACS. High cTnI level was analyzed as associated with heart failure due to heart contractility impairment, which leads to hemodynamic instability [46][47]. In acute heart failure, cTnI elevation has been discovered related to decreasing systolic pressure, ejection fraction, and severe cardiac dysfunction [48]. Elevating cTnI level has been linked with the severe Killip class, worse clinical presentation, and in-hospital mortality incidence [49]. Stroke co-occurring in ACS also has been perceived as linked with cTnI elevation [50].

The limitation of this study was retrospective design and performed by a single healthcare system, so the results may not be generalizable and the bias of the information was quite large.

## 5. Conclusion

ACS cases in this study were dominated by male and > 45-year-old patients. NSTEMI was discovered as the most prevailing ACS type. The majority of ACS patients have MACE with heart failure as the most frequent type. A significant association with a moderate level of correlation between cTnI level and MACE was found with p=0.001 and r=0.413. Therefore, through this research, cTnI may be considered for predicting MACE in ACS patients to prevent and anticipate ACS complications. However, the cross-sectional and retrospective

approach used in this study couldn't ensure the causal relationship because the variables were measured simultaneously. For this reason, other research with a higher level of evidence is needed to complement this research.

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**Conflict of interest**
I declare there's no conflict of interest in this research

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