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# The Role of Troponin Measured on Admission to the Emergency Department in Patients with Acute Ischemic Stroke to Predict Stroke Severity and Neurological Outcome

# Akut İskemik İnme Hastalarında Acil Servise Başvuru Sırasında Ölçülen Troponinin İnme Şiddetini ve Nörolojik Sonuçları Öngörmedeki Rolü

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**ABSTRACT**

**Objective:** This study aims to investigate the prognostic value of cardiac troponin levels measured at admission to the emergency department (ED) for stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS) and neurological outcomes determined by Modified Rankin Scale (mRS) scores in patients diagnosed with acute ischemic stroke (AIS).

**Materials and Methods:** Patients presenting to ED with a diagnosis of AIS confirmed by neuroimaging findings were included. Patients were divided into 2 groups based on troponin-I levels: elevated and normal. NIHSS during admission, 30-day all-cause mortality data, and 30-day mRS were examined. In comparisons between groups, categorical variables were evaluated with Chi-square and continuous variables were evaluated with the Mann-Whitney-U test. To determine the prognostic value of troponin with poor outcomes in stroke patients, diagnostic 2x2 tables were made.

**Results:** The study was conducted with 200 patients. Troponin elevation was detected in 37, and mortality was significantly higher in this group. The sensitivity of troponin to predict mortality was 88.89%, and PLR (positive likelihood ratio) was 5.85 (3.89–8.79). The 30-day mRS scores were significantly higher in the elevated troponin group. NIHSS scores didn't show a significant difference between groups.

**Conclusions:** Troponin levels assessed at admission in AIS patients may be a prognostic marker for mortality and adverse neurological outcomes.

**Keywords:** Ischemic stroke, mortality, troponin

**ÖZ**

**Amaç:** Bu çalışmanın amacı, akut iskemik inme (Aİİ) tanısı alan hastalarda acil servise (AS) başvuru sırasında ölçülen kardiyak troponin düzeylerinin, Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) ile değerlendirilen inme şiddeti ve Modifiye Rankin Ölçeği (mRS) ile belirlenen nörolojik sonlanımı belirlemedeki prognostik değerini araştırmaktır.

**Materyal ve Metot:** Acil servise Aİİ tanısı ile başvuran ve tanısı nörogörüntüleme bulguları ile doğrulanan hastalar dahil edildi. Hastalar troponin I düzeylerine göre yüksek ve normal olmak üzere iki gruba ayrıldı. Başvuru sırasındaki NIHSS, 30 günlük tüm nedenlere bağlı mortalite verileri ve 30 günlük mRS incelendi. Gruplar arası karşılaştırmalarda kategorik değişkenler Ki-kare ile sürekli değişkenler ise Mann Whitney U testi ile değerlendirildi. Troponinin inme hastalarında kötü sonlanımla prognostik değerini belirlemek için, tanısal 2x2 tablolar yapıldı.

**Bulgular:** Çalışma 200 hasta ile gerçekleştirildi. Troponin yüksekliği 37 hastada tespit edildi ve bu grupta mortalite anlamlı olarak daha yüksekti. Troponin'in mortaliteyi öngörmedeki duyarlılığı %89, PLR (pozitif olabilirilik testi) 5,85 (3,89–8,79) idi. Troponin yüksekliği olan grupta 30 günlük mRS skorları anlamlı derecede yüksekti. NIHSS skorları gruplar arasında anlamlı bir fark göstermedi.

**Sonuç:** Aİİ hastalarında başvuru sırasında ölçülen troponin düzeyleri mortalite ve olumsuz nörolojik sonuçlar açısından prognostik bir belirteç olabilir.

**Anahtar Kelimeler:** İskemik inme, mortalite, troponin

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## INTRODUCTION

Because of the increased availability of reliable biomarkers, the role of the laboratory in the decision-making process has become undeniable in modern clinical practice. Cardiac troponins are one of the most valuable biomarkers, especially the "high-sensitive" ones, widely used for early detection of myocardial infarction.[1] It is a known fact that cardiac troponin levels predict mortality in clinical conditions due to cardiac causes. However, in recent years, it has been shown that troponin levels help to predict mortality in many non-cardiac medical conditions, such as strokes, pulmonary diseases, and sepsis.[2]

Ischemic stroke (IS) remains one of the most common causes of death and the leading cause of disability worldwide; thus, prediction of prognosis is still an important need for IS patients.[3] Recent studies have demonstrated that troponin positivity on admission is an independent predictor of mortality in acute ischemic stroke (AIS).[3,4] Even moderately elevated troponin levels in AIS are associated with in-hospital deaths and unfavourable neurologic outcomes at hospital discharge.[5] The elevation of troponin in IS is believed to be caused by comorbid conditions and cardiac complications; however, in a TRELAS study, it was demonstrated that despite similar baseline troponin levels, coronary culprit lesions were significantly less frequent in IS patients compared with age and sex and matched non-ST elevated acute coronary syndrome patients.[6] Therefore, the exact mechanism of myocardial injury after IS is still unclear, and ongoing studies elucidating hypotheses related to etiology, such as demand ischemia and the overshooting systemic response, are currently being conducted.[7]

Although many studies exist about the relationship between mortality and troponin in IS, there are limited publications on the predictive role of troponin in stroke severity and neurological outcome. This study aims to evaluate the interaction between the neurologic severity of IS patients and troponin levels at emergency department (ED) admission and determine the prognostic role of troponin at admission on mortality and neurological outcome.

## MATERIALS AND METHODS

***Ethical Committee Approval:*** Our study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 08.03.2022, decision no: 2012-KAEK-15/2489). The study was conducted following the Helsinki Declaration throughout the research process. The written informed consent form for all participants was obtained.

***Study Design and Population:*** Patients admitted to the Keçiören Training and Research Hospital ED between April 2022 and December 2022 and diagnosed with AIS were consecutively included in the study. The patients were diagnosed with AIS based on their history, neurological examination, radiological findings, and neurology consultation. All the patients with a suspicion of stroke first had cranial CT (computerized tomography), and then, in case of ongoing suspicion, they had diffusion-weighted magnetic resonance imaging (DWMRI). The most common radiologic finding in cranial CT was hypodense lesions and acute diffusion restriction in DWMRI. (A summary of the radiologic findings is given in Table 1). Being older than 40 years of age (since the etiological causes of IS in patients under 40 years of age need to be elucidated) and being neurologically intact before an AIS attack were determined as inclusion criteria. Pregnant patients, patients with kidney failure, those with atrial fibrillation, atrial flutter, and ventricular arrhythmia detected on ECG at the time of admission, patients diagnosed with acute coronary syndrome according to ECG, clinical and laboratory findings on admission, those who had cardiac intervention (angiography, by -pass) in the last 4 weeks, patients who had stroke in last 4 weeks, and those who could not be followed up for 30 days were excluded.

***Study Process:*** The patients' demographic variables, medical history, medications, vital signs, ECG findings, radiological findings, and ED outcomes (discharge, inward admission, intensive care unit admission) were recorded in the study forms. The troponin I levels of the patients were examined from blood samples taken at ED admission with an Abbott Alinity high-sensitive device. Normal levels were defined as <15.6 ng/L for males and <34 ng/L for females, according to the standard reference values.

To understand the clinical severity of the stroke, for all patients diagnosed with AIS in the ED, National Institutes of Health Stroke Scale (NIHSS) scores were calculated. NIHSS is a widely used scale that evaluates different brain functions, such as consciousness, sight, sensation, movement, speech and language, whose score ranges from 0 to 42. NIHSS scores above 16 highly predict mortality and poor neurologic outcomes, and scores lower than 6 predict good outcomes.[8] Since our hospital does not have a stroke center, most of our stroke patients' conditions are mild in severity. Therefore, we determined our group as patients suffering from a mild stroke (NIHSS score ≤4) and others (NIHSS score >4) for diagnostic tests (≤4 is the determined limit for mild stroke according to NIHSS).[9]

We used the Modified Rankin Scale (mRS) to evaluate the patients' neurological outcomes. This scale

contains 7 levels, ranging from 0 (no neurologic symptom) to 6 (dead); scores of 0-1-2 define functional independence, and 3-4-5 categorize patients as functionally dependent.[10] Patients were evaluated on the 30th day after the first admission; this control was done with phone calls to patients or their first-degree relatives. Modified Rankin Scales were calculated, and mRS scores ≥3 were accepted as a poor neurologic outcome.

***Outcomes:*** The study's first aim is to examine the relationship between troponin levels at admission to the ED and the clinical severity of the AIS patients, which the NIHSS determined. The second aim is to examine the relationship between troponin and the patients' 30th-day neurological outcome, which is defined according to the mRS. The study's third aim is to examine the relationship between troponin levels and mortality of AIS patients.

***Sample Size and Power Analysis:*** All consecutive AIS patients who applied to the ED between April 2022 and December 2022 and met the study criteria were included. Out of 280 patients, 80 were excluded due to the exclusion criteria, and statistical analyses were performed on the data of the 200 remaining patients (Figure 1).

Post-hoc power analyses were conducted with the G Power 3.1.9.7 program. For the neurological outcome endpoint, a significant difference was detected between the troponin positive and negative groups (p=0.002) with a 5% type-1 error; the power of the study was calculated as 0.99.

***Statistical Analysis:*** Data analysis was effectuated using SPSS for Windows 22 (IBM, Chicago, USA). After determining whether the data showed a normal distribution using the Kolmogorov–Smirnov test, all data were presented as mean±standard deviation or median value and interquartile difference (IQR: 25–75%). For comparisons between groups, categorical variables were evaluated with the chi-square test, and continuous variables were evaluated with the Mann–Whitney U test. To determine the predictive value of troponin in terms of poor outcome and the severity of the stroke, diagnostic 2 × 2 tables were used. The Spearman correlation test was used to analyze the correlation between troponin levels and NIHSS and mRS. The statistical significance level was accepted as $p<0.05$.

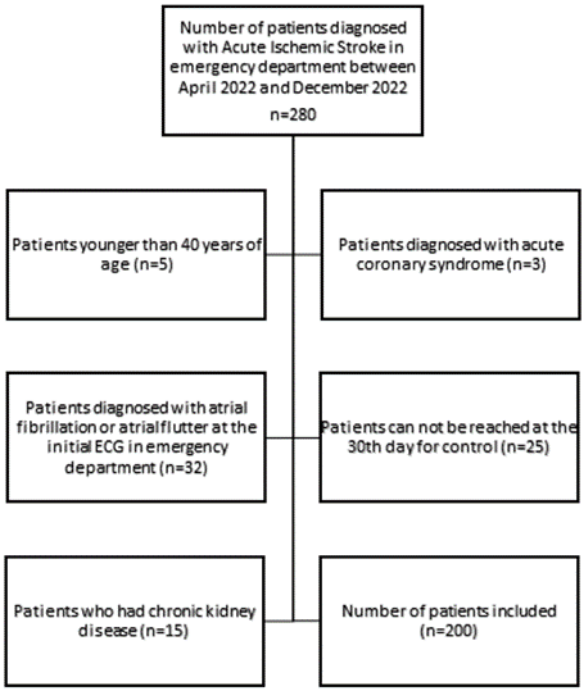


**Figure 1.** Flow chart.

## RESULTS

A total of 200 patients were included in the study with a median age of 68 (IQR: 25–75; 61–76), and 98 of them were female. The most common comorbid conditions were hypertension (66.5%), diabetes mellitus (45%), and coronary artery disease (27%). The median NIHSS score was 2 (IQR: 25–75; 1–4), and the median mRS score was 1 (IQR: 25–75; 0–2). Nine of the patients passed away within 30 days. The median troponin level of all patients was 5.45 ng/mL (IQR: 2.3–18.9); troponin levels were higher than the reference limits in 37 patients. General characteristics, laboratory findings, and the NIHSS and mRS scores of the patients are summarized in Table 1.

Patients were divided into 2 groups: normal troponin (n=163) and high troponin (n=37). Age and sex distributions were similar between the two groups. There was no difference in comorbid conditions, except in heart deficiency, which was higher in the troponin-positive group (p = 0.012). Urea and creatinine levels were higher in the troponin-positive group. NIHSS scores were similar between the groups, but the mRS score was significantly higher in the troponin-positive group (p=0.002). In addition, mortality was significantly higher in the troponin-positive group (p<0.001) (8 vs. 1 patient). Data that shows comparisons between the two groups are given in Table 2.

**Table 1.** Characteristics and general findings of the study population. (n=200).

| Parameters | | | Data |
|---|---|---|---|
| **Demographics** | | Age, median IQR(25-75) | 68 (61–76) years |
| | | Sex Female, n (%) | 98 (49) |
| | | Male, n (%) | 102 (51) |
| **Comorbidities** | | Hypertension, n (%) | 133 (66.5) |
| | | Diabetes mellitus, n (%) | 90 (45) |
| | | Coroner artery disease, n (%) | 54 (27) |
| | | Medical history of stroke, n (%) | 28 (14) |
| | | Heart failure, n (%) | 9 (4.5) |
| | | Other*, n (%) | 68 (34) |
| **Radiologic Findings** | Cranial CT | No acute pathology | 117 (58.5) |
| | | Hypodense lesion | 30 (15) |
| | | Other** | 53 (26.5) |
| | Diffusion weighted MRI | Acute diffusion restriction | 167 (83.9) |
| | | Hypointense region | 2(1) |
| | | Hyperintense region | 30 (15.1) |
| **Laboratory findings** | | Urea, mg/dL, median IQR(25-75) | 38 (29–49) |
| | | Creatinine, mg/dL, median IQR(25-75) | 0.99 (0.88–1.19) |
| | | Troponin, ng/L, median IQR(25-75) | 5.45 (2.3–18.9) |
| **Number of patients with high troponin levels, n (%)** | | | 37 (18.5) |
| **30-day mortality, n (%)** | | | 9 (4.5) |
| **NIHSS, median IQR(25-75)** | | | 2 (1–4) |
| **mRS, median IQR(25-75)** | | | 1 (0–2) |

*: Chronic obstructive pulmonary disease, asthma, epilepsy, hyperlipidemia, and rheumatism; NIHSS: National Institutes of Health Stroke; Scale; mRS: Modified Rankin Scale; **: Other findings in cranial CT were encephalomalacia, atrophy, meningioma; Abbreviations: CT; computerized tomography, MRI; Magnetic Resonance Imaging.

**Table 2.** Comparison of demographic and clinical findings between the normal troponin and high troponin groups (variables are given as n (%) or median IQR (25–75)).

| Parameters | | Normal Troponin n=163 | High Troponin n=37 | p-value |
|---|---|---|---|---|
| **Demographics** | Age, median IQR(25-75) | 68 (61–76) | 70 (62–77) | 0.502 |
| | Sex Female, n (%) | 81 (49.7) | 17 (45.9) | 0.681 |
| | Male, n (%) | 82 (50.3) | 20 (54.1) | |
| **Comorbidities** | Hypertension, n (%) | 106 (65) | 27 (73) | 0.355 |
| | Diabetes mellitus, n (%) | 76 (46.6) | 14 (37.8) | 0.332 |
| | Coroner artery disease, n (%) | 41 (25.2) | 13 (35.1) | 0.217 |
| | Medical history of stroke, n (%) | 21 (12.9) | 7 (18.9) | 0.339 |
| | Heart failure, n (%) | 4 (2.5) | 5 (13.5) | **0.012** |
| | Other*, n (%) | 56 (34.4) | 12 (32.4) | 0.824 |
| **Laboratory findings** | Urea, mg/dL, median IQR(25-75) | 37 (28–48) | 49 (38–60) | **0.001** |
| | Creatinine, mg/dL, median IQR(25-75) | 0.97 (0.86–1.14) | 1.24 (0.99–1.72) | **0.001** |
| | Troponin, ng/L, median IQR(25-75) | 3.8 (1.8–8,6) | 69.8 (38–137) | **0.001** |
| **NIHSS,** median IQR(25-75) | | 2 (1–3) | 2 (1–4) | 0.969 |
| **30-day mortality,** n (%) | | 1 (0.6) | 8 (21.6) | **0.001** |
| **mRS,** median IQR(25-75) | | 1 (0–2) | 1 (1–5) | **0.002** |

*: Chronic obstructive pulmonary disease, asthma, epilepsy, hyperlipidemia, and rheumatism; F: Female; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale.

The diagnostic value of troponin in determining stroke severity, defined according to NIHSS, poor outcome according to the mRS, and mortality were investigated. Although a NIHSS value of ≥16 includes moderate and severe stroke groups, since the highest NIHSS value in our current data is 14, the groups were determined as the mild stroke group with a NIHSS value of ≤4 and others. According to this data, the sensitivity of troponin in predicting moderate and more severe strokes was calculated as 19.35%. For the prediction of poor outcomes, troponin sensitivity was 39.47%. In terms of mortality prediction, the sensitivity of troponin was 88.89%, and the specificity was 84.82%. Data about troponin's prognostic value is presented in Table 3. We also analyzed the correlation between troponin and NIHSS, mRS and mortality. There was no correlation between NIHSS and troponin (p=0.053), but between troponin and mRS and troponin and mortality, there was a significant weak positive correlation (p<0.001 for both and r=0.304 and r=0.300, respectively).

**Table 3.** Prognostic value of troponin.

| | **Prognostic value of troponin for predicting moderate and more severe stroke based on NIHSS** | **Prognostic value of troponin for predicting poor outcome based on mRS** | **Prognostic value of troponin for predicting mortality** |
|---|---|---|---|
| **Sensitivity**, % (95% CI) | 19.35 (7.45–37.47) | 39.47 (24.04–56.61) | 88.89 (51.75–99.72) |
| **Specificity**,% (95% CI) | 81.66 (74.99–87.18) | 86.42 (80.16–91.29) | 84.82 (78.93–89.59) |
| **PLR**,% (95% CI) | 1.06 (0.48–2.33) | 2.91 (1.67–5.06) | 5.85 (3.89–8.79) |
| **NLR**,% (95% CI) | 0.99 (0.82–1.19) | 0.7 (0.54–0.91) | 0.13 (0.02–0.83) |
| **Accuracy**,% (95% CI) | 72 (65.23–78.1) | 77.5 (71.08–83.09) | 85 (79.28–89.64) |

## DISCUSSION AND CONCLUSION

In this study, we evaluate the relationship between cardiac troponin levels at the admission of IS patients, mortality, and stroke severity determined according to the NIHSS and stroke outcome was determined according to the mRS. We found that troponin has a predictive role in mortality at high sensitivity (89%) and specificity (85%). However, despite a significant troponin increase in the poor outcome group, sensitivity was only 39% in this group. Troponin levels did not differ between the groups in terms of severity.

Cardiac involvement and troponin elevation in IS is a much-needed research initiative, and recent studies supporting the fact that the cardiac consequences of stroke are associated with higher mortality and poor neurological outcomes have been conducted.[11-13] This condition, called stroke-heart syndrome, points to an integrated pathogenesis involving post-stroke neurocardiogenic mechanisms.[14] Autonomic dysfunction, increased inflammation, the effect of local and systemic mediators, and, consequently, changes in cardiomyocyte metabolism are thought to be the primarily responsible mechanisms.[15] However, the underlying causes and clinical significance are still debated.

In recent meta-analyses, elevated troponin rates among all adult AIS patients vary between 9.7% and 54.4%.[16] This rate was 18.5% in our study. The literature has conflicting results for the correlation of NIHSS and troponin. In a prospective observational study conducted by Ahn et al., 1,092 IS patients were observed, and the NIHSS median score was 8 (IQR: 25–75; 3–14) in patients with increased troponin levels; the median score was 4 (IQR: 25–75; 2–8) in patients with minimally increased troponin levels, and the median score was 3 (IQR: 25–75; 1–6) in patients with undetectable troponin levels.[17] However, in Abdi et al.'s study, no significant difference was found between the troponin levels of patients with NIHSS scores of 0–9 and patients with scores between 10–42 (p=0.140).[12] We believe that the lack of a significant correlation between NIHSS and troponin in our study may be related to the fact that the center where we conducted the research was not a stroke center; therefore, most of our cases consisted of patients with mild symptoms who could be admitted as outpatients.

In addition to predicting the severity of AIS, studies evaluating the predictive power of troponin on long-term neurological outcomes exist. In one of these, 81 (79.4%) of 103 patients with troponin elevation were found to have mRS >2 at the time of hospital discharge.[18] In the same study, a major neurological improvement, defined as an improvement in an NIHSS score of ≥8 points or regression of NIHSS between 0–1, was detected in 26.4% of patients with elevated troponin levels and 51.5% of patients with normal troponin levels.[18] Similar to the literature, mRS levels showed a significant difference between the troponin-positive and negative groups in our study (p=0.002). Mild stroke patients made up the majority of all patients. Despite this, this observed difference can be interpreted as troponin being a good marker for an IS outcome.

In studies examining the predictive role of troponin in terms of mortality in IS, the relative risk of increased troponin in all-cause deaths was found to be

2.53 (95% CI; 2.09–5.98).[3] In Esteak et al.'s study, patients with high troponin levels had a higher 90-day mortality (p=0.022).[4] In our study, although patients were categorized only according to the reference range and no classification such as normal-mild elevation-severe elevation was made, the findings were consistent with the literature.

Elevated troponin in AIS may be due to 2 different reasons. These are primary changes resulting from pre-existing cardiac problems and secondary findings superimposed on primary changes before and after the stroke.[17-20] In our study, heart failure was more common in the troponin-positive group. These results may be from a two-way relationship between the heart and brain, and the pathologies of both organs may be predisposing for the other.

In the present study, urea and creatinine levels were significantly higher in the group with high troponin. In the beginning, we excluded patients with chronic renal failure and excluded troponin elevations that may have been due to this condition. However, acute deterioration in renal functions may be the result of the pathophysiological process of stroke and could be an indicator of a poor prognosis. Abdi et al. found that IS patients with increased troponin levels also had higher creatinine levels and showed that higher creatinine levels were correlated with stroke severity.[12] Our study demonstrated that troponin plays a crucial prognostic role in AIS. However, clarifying the underlying pathogenesis with future studies is necessary.

The study's most important limitation is that it was conducted in a hospital that does not serve as a stroke center. For this reason, many patients were referred to an external center, and the treatments given could not be examined in detail. Therefore, the treatments applied may have played a role in prognosis. Additionally, most of our patients were in the mild stroke group. Another limitation is that patients with atrial fibrillation were excluded. At the beginning of the study, it was decided to exclude patients with atrial fibrillation so that patients with arrhythmia would not have a distracting effect regarding troponin positivity. However, because we excluded a critical risk factor for stroke, this may have caused us to exclude a significant group of patients. Another limitation is we included the patients with heart failure. Despite there was a significant difference between in group comparison of HF frequency in troponin positive and negative groups, nine HF patients had distributed to groups, nearly equal (4 patient in the troponin negative group and 5 in the positive group). We think that troponin positivity might be related to stroke-heart syndrome; but we couldn't exclude the heart failure itself as a reason for this positivity.

In conclusion, troponin may be an important prognostic factor for mortality and poor neurological outcomes, even in patients experiencing mild strokes. In our study, no significant correlation was found between NIHSS and troponin on admission, and this might be due to the mild stroke severity of most of our patients. As a result, troponin levels measured during ED admission can be used as a biomarker to determine the prognosis in patients presenting with AIS.

***Ethics Committee Approval:*** Our study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 08.03.2022, decision no: 2012-KAEK-15/2489).

***Conflict of Interest:*** No conflict of interest was declared by the authors.

***Author Contributions:*** Concept – GCI, OK, YC; Supervision – GCI, SKC, YC; Materials – SY, OK; Data Collection and/or Processing – SY, GCI, FK, OK; Analysis and/or Interpretation – SY, GCI, FK, SKC, OK, YC; Writing – SY, GCI, FK

***Peer-review:*** Externally peer-reviewed.

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