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# Investigating the Level of Troponin I and its Association With Mortality in Patients With Sepsis, Severe Sepsis, and Septic Shock

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**Abstract**

**Objectives:** To investigate the level of troponin I and its association with mortality in patients with sepsis, severe sepsis, and septic shock.

**Materials and Methods:** In general, 148 patients with sepsis, severe sepsis, and septic shock admitted to Kowsar hospital of Semnan in 2017-2019 were recruited in this study. Serum troponin levels were measured during the first 24 hours of admission. The second measurement was done in the next 48 hours, which aimed at increasing the likelihood of positive troponin over time. However, if the troponin was positive just once, the patient would be in the category of positive troponin. In addition, the patient's prognosis was recorded within 30 days.

**Results:** Based on the results, 27.7% had troponin levels higher than normal. The mortality rate in patients with normal and abnormal levels of troponin was 5.6% and 17.1%, respectively, which was a significant difference. The age of dead patients was significantly higher than the age of the living patients and the results showed that among the variables of gender, normal or abnormal level of troponin, age, and type of underlying infection, only age had a significant relationship with patients' vital status.

**Conclusions:** High levels of troponin were not effective in determining the prognosis of patients with sepsis, and only age had a significant relationship with patients' vital status while the confirmation or rejection of this hypothesis will need further studies.

**Keywords:** Sepsis, Mortality, Troponin

## Introduction

Troponin is a muscle protein that is released into the blood after the cardiac muscle cell death due to ischemia (1). High-sensitivity cardiac troponin is frequently elevated in severe sepsis or septic shock and has a relevant prognostic value, which may be important in monitoring the clinical efficacy of supporting therapy (2). Although most studies have indicated an increase in troponin levels in cardiac patients, an increase in troponin, especially type I, has been reported in other patients with no heart disease. One of the recent issues in a number of similar studies is the determination of the serum troponin level in the prognosis of hospitalized patients with sepsis, especially in the intensive care unit (3-7).

The incidence of sepsis has been rising over the past 15 years. Sepsis is one of the most common causes of mortality. It is the most common cause of morbidity and mortality in the US and its mortality rate in hospitals has been reported 18-30% (8, 9). Sepsis-induced mortality in cases that sepsis becomes severe, sepsis and septic shock may increase by 41.1% (10). According to Kumar et al (11), a person with two out of the five criteria of systemic inflammatory response syndrome (SIRS) is known to be suffering from sepsis (SIRS criteria: fever higher than 38˚C or below 36˚C, heart rate greater than 90, a respiratory rate greater than 20, the partial pressure of carbon dioxide less than 32, white blood cell count greater than 12 or less than 4000, and band cell greater than 10%). Sepsis is considered as severe sepsis, when there is at least one organ dysfunction due to reduced blood supply to tissues including renal failure, disorders of consciousness, and hematological disorders including coagulopathy, thrombocytopenia, disseminated intravascular coagulation and hypoxemia. In severe sepsis, the patient responds to fluid therapy (11, 12). Moreover, severe sepsis with hypotension (systolic blood pressure of less than 90 mm Hg or diastolic blood pressure of less than 40 mm Hg, both lower than the patient's normal blood pressure) that lasts at least one hour despite intravenous fluid therapy and requires vasopressor agents, is considered as a septic shock (13, 14).

The main hemodynamic sign of sepsis is the hyperdynamic state with high-output heart failure associated with low systemic vascular resistance (15).

In this disease, a lack of the specific marker of infection has led to problems in the differentiation between SIRS with infectious and non-infectious origins. As a result, many previous studies have been carried out to access the markers that can be useful to detect early sepsis (16).

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Key Messages

- Age was the most prognostic factor in the prediction of death since it was more prevalent in older age groups and troponin had no role in determining the prognosis of patients with sepsis. However, confirming or rejecting this issue will require more studies while it is essential to eliminate the constraints of this study.

The findings of a meta-analytic study showed that elevated troponin in patients with sepsis was common and confirmed accordingly. However, the important thing is how troponin levels, especially type I, can be useful in predicting the prognosis of sepsis patients (17). A number of studies have found that serum troponin levels increase the mortality rate of patients with sepsis (4, 5, 18). Myocardial cell injury is common in patients with septic shock and is associated with impaired cardiac function, and troponin is one of the most important cardiac markers (18). It was also reported that heart troponin levels are higher in cows with septic metritis compared to healthy cows. (19). Conversely, many other studies have not reported any correlation between serum troponin levels and mortality in patients with sepsis (20-22). These conflicts can be due to the diversity of the infection type, the type of the investigated troponins in various studies, the measurement tools of troponin in different laboratories, the numerous normal cut-off points, the abnormal level of troponin, and the difference in the time of troponin measuring at various hospitals (23). In the present study, troponin was one of the first-line tests at the time of admission and hospitalization.

Considering the importance of the issue and the high prevalence of mortality due to sepsis, severe sepsis, or septic shock, along with contradictions about the role of cardiac troponin I in predicting sepsis mortality, the present study evaluated the prognostic value of the serum level of cardiac troponin I and its association with mortality in patients with sepsis, severe sepsis, and septic shock admitted to Kowsar Hospital of Semnan.

## Materials and Methods

### Design

According to a study by Spies et al (5), this study was conducted on 148 patients with sepsis, severe sepsis, and septic shock, who were admitted to Kowsar Hospital of Semnan in 2017-2019.

### Participants

The inclusion criteria were patients with sepsis (having two criteria out of SIRS criteria), severe sepsis (having two criteria out of SIRS criteria with at least one organ dysfunction), and septic shock (having two criteria out of SIRS criteria with hypotension) in internal wards, intensive care unit (ICU), and critical care unit (CCU) admitted to the Kowsar Hospital of Semnan.

On the other hand, the exclusion criteria are myocardial infarction, trauma or chest and heart surgery, cardiopulmonary resuscitation, endocarditis or myocarditis in the past month, immunodeficiency, leukopenia (white cell count below 1000) or neutropenia (polymorphonuclear cell count less than 500), blood malignancy, and AIDS.

### Intervention

First, patients with sepsis, severe sepsis, and septic shock, who were admitted to the internal wards, ICU, and CCU of Kowsar Hospital affiliated to Semnan University of Medical Sciences, were identified and included in this study. Then, after obtaining written consent, 148 eligible patients recruited in the cross-sectional study using the available sampling method and considering the inclusion and exclusion criteria.

### Data Gathering

In this study, data were obtained from a researcher-made questionnaire (checklist) including demographic data and medical and laboratory records. Serum troponin levels were measured by a laboratory kit (AIDE) according to Lim et al (24). The sampling method was done by the nurse at the patient's bedside to determine the serum troponin level of eligible patients within 24 hours after admission to the hospital. The positive troponin levels were defined to be more than one ng/mL while negative troponin levels were defined to be less than or equal to one ng/mL (25, 26). The second measurement was performed in the next 48 hours aiming at increasing the likelihood of positive troponin over time. However, if the troponin level was positive just once, the patient would be in the category of positive troponin. Moreover, the patient's prognosis (death or discharge) was recorded within 30 days. The mortality outside the hospital was not recorded in the case of discharge less than 30 days due to the lack of the researcher's follow up and the existence of confounding and unreliable factors.

### Statistical Methods

Data were analyzed via SPSS 16 using the Shapiro-Wilk test, the *t* test (or Mann-Whitney), chi-square, Fisher's exact test, and logistic regression.

## Results

According to the results, the mean age and standard deviation were 66.45 and 15.14, respectively. The minimum and the maximum age was 23 and 95, respectively. In this study, 74 (50%) out of 148 patients were females and 74 (50%) of them were males. Moreover, 107 (72.3%) subjects had normal troponin levels while 41 (27.7%) of them had abnormal troponin levels (higher than normal). The most common underlying diseases in the subjects were sepsis of an unknown origin (25.7%), urinary tract infection (23.2%), and pneumonia (22.3%). The results of data

analysis with the Chi-square test showed that there was no statistically significant relationship between the type of infection with motility (death/discharge, $P=0.126$), the related data are shown in Table 1 and Figure 1.

In general, 135 (91.2%) out of 148 subjects were discharged and 13 (8.8%) of them died in this study. The results (Table 2) of the present study demonstrated that 5.6% and 17.1% of patients with normal and abnormal troponin died, respectively. The relationship between troponin levels and mortality was significant ($P = 0.027$).

Based on the results of the data analysis by the chi-square test, there was no significant relationship ($P = 0.126$) between the type of the underlying infection and mortality (death/discharge).

The mean age (standard deviation) of the living and dead patients was 65.6 (±15.3) and 75.5 (±9.2) years, respectively. As shown in Figure 2, the age distribution of both groups was significantly different ($P = 0.015$).

The age of dead patients was significantly higher than that of the living ones ($P = 0.015$). The data analysis results (Table 3) of Fisher's exact test represented no significant relationship between mortality status (death/discharge) and the gender of the subjects ($P = 0.282$).

The logistic regression analysis was performed to investigate the simultaneous effect of the mentioned variables on patients' vital status. The results indicated that age had significant association with mortality ($P = 0.029$, 95% CI = 1.01-1.12, OR = 1.06). Other variables such as normal or abnormal troponin levels had no significant relationship with mortality.

## Discussion

The results of this study represented that 72.3% and 27.7% of subjects had normal and abnormal troponin levels (higher than normal), respectively. Moreover, 91.2% out of 148 subjects and 8.8% were discharged and died, respectively. Based on the results of the data analysis, age was the most substantial prognostic factor in predicting the occurrence of death since it was more prevalent in older age groups. Troponin had no role in determining the prognosis of patients with sepsis, but unlike some other studies, troponin was reported as an important factor in determining the prognosis of patients with sepsis (5,27-29). A similar study evaluated the level of troponin and its association with mortality in patients with sepsis and its results indicated that the rate of mortality in patients without and with increased troponin was 17% and 31% during 30 days, respectively, which was a significant association (28). This finding contradicts the results of the present study, demonstrating that although the mortality rate was higher in patients with abnormal troponin levels in our study, the difference was not significant compared to those with normal troponin levels.

**Table 1.** Distribution of Frequency and Frequency of the Troponin Level (Normal/Abnormal) Relative to the Type of Infection in Patients

| Type of Infection | Mortality Status | | | |
|---|---|---|---|---|
| | Death | | Discharge | |
| | No. | % | No. | % |
| Central nervous system | - | - | 7 | 5.2 |
| Septic arthritis | - | - | 3 | 2.2 |
| Sepsis of unknown origin | 8 | 61.5 | 30 | 22.2 |
| Pneumonia | 2 | 15.4 | 31 | 23.0 |
| UTI | 2 | 15.4 | 32 | 23.7 |
| Digestive system | - | - | 12 | 8.9 |
| Skin | - | - | 13 | 9.6 |
| Catheter infections | 1 | 7.7 | 7 | 5.2 |
| Total | 13 | 100 | 135 | 100 |

*Note*. UTI: Urinary tract infection.

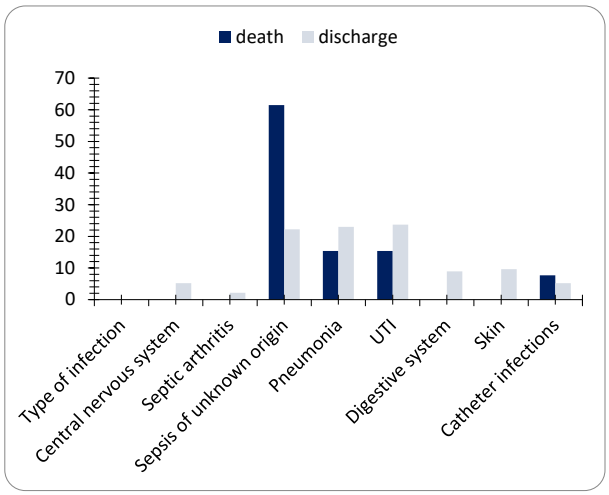


**Figure 1.** The Distribution of the Percentage of the Mental Condition in Relation to the Type of Infection in Patients. *Note*. UTI: Urinary tract infection.

**Table 2.** Death/Discharge Rate Based on Natural/Abnormal Troponin Levels in Patients

| Troponin Levels | Died | | Discharged | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Normal | 6 | 5.6 | 101 | 94.4 |
| Abnormal | 7 | 17.1 | 34 | 82.9 |
| Total | 13 | 8.8 | 135 | 91.2 |

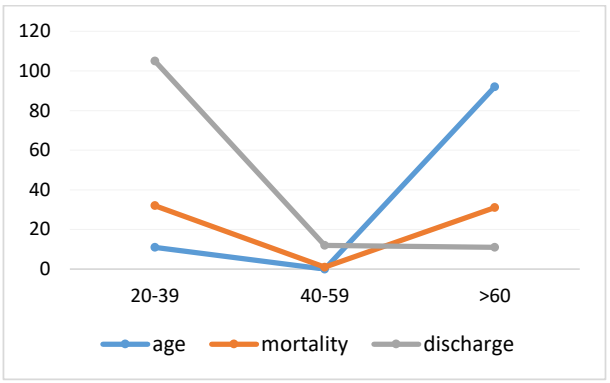


**Figure 2.** Death and Discharge Status in the Age Groups of Patients.

**Table 2.** Distribution of the Number and Percentage of Mortality Status (Death/Discharge) in Comparison With Patients' Gender

| Gender | Death | | Discharge | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Male | 8 | 10.8 | 66 | 89.2 |
| Female | 5 | 6.7 | 69 | 93.3 |

The results of a review on 23 studies including 4492 severely ill patients showed that troponin levels averagely increased by 43% in 3278 patients in 20 studies. In the conforming analysis, including 6 studies with 1706 patients, the increased troponin was associated with a higher risk of mortality. In a non-conforming analysis, containing 8 studies with 1019 patients, the increased troponin level was related to the increased length of hospitalization in the ICU for 3 days (24). In the present study, it was impossible to examine the association between troponin levels and the length of hospitalization due to the existing limitations.

Choon-ngarm et al concluded that troponin was high in 42.5% of patients with sepsis. During the study, 70% of patients with high levels of troponin died while the difference between the troponin levels of dead and discharged persons was significant. It was further found that the increased troponin could indicate the severity of the disease and increased mortality in patients with septic shock (30). This finding was also assessed and confirmed in a meta-analysis published in 2015, but due to controversy in some studies such as the present study, it was recommended to conduct further studies in this regard (17).

Although several studies concluded that the increased troponin level could be a good predictor of mortality in patients with sepsis (5,24,28-30), in other studies including the present one, this association was rejected and the patient's age was the most important factor involved in the mortality of patients with sepsis (31,32). One of the important reasons for justifying the contradiction of these results can be the type of the underlying disease in various studies. Based on the results of Abbasi et al, an increase was observed in troponin in patients with chronic renal failure due to renal clearance (31,32), and investigating the association between troponin levels with increased mortality in patients could lead to errors. In the present study, although the mortality rate, similar to the results of Abbasi et al, was only related to the age of the patients and there was no significant relationship between mortality and gender and underlying disease, it was attempted to greatly avoid the interference of confusing variables in the results by providing uniform statistical samples. It should be noted that C-reactive protein (CRP) has been another predictor of mortality in other studies and its presence, along with increased troponin significantly increased the risk of mortality in patients (33,34). Therefore, another reason for justifying contradictions between the results of various studies can be the difference in laboratory criteria, especially CRP, which has not been investigated in most of the studies similar to the present study due to the existing constraints. Hence, it is proposed to conduct more studies in this field in order to clarify the subject. Moreover, these conflicts can be due to the diversity of the types of infections, different types of evaluated troponins in various studies, the troponin measurement tools in different laboratories, the plurality of the cut-off point, the abnormality of troponin level, or the difference in the time of troponin measurements in various hospitals (17).

The pathophysiology of the increased troponin in patients with sepsis has been mostly associated with the development of myocardial disorders in sepsis patients, which mainly involved direct damage arising from microorganisms, the myotoxic effects of its endotoxins, cytokines or released oxygen free radicals, and subsequently, microorganism activity (18). In a recent study by Landesberg et al, left ventricular diastolic dysfunction and right ventricular systolic dysfunction have been shown to increase the mortality rate of patients with sepsis having increased troponin levels (35). By investigating the autopsy or *electrocardiogram* of patients, a number of studies have also suggested that increased troponin levels could indicate the severity of the disease and increased mortality in patients with septic shock (4,5,18). However, due to many other unknown causes, meta-analysis studies have recommended that more studies, especially clinical trials should be conducted to identify the cause-and-effect relationship between troponin levels and mortality in patients with sepsis.

This study had limitations. The extent of the subject and many known and unknown factors may affect the mortality of patients with sepsis. In addition, it is needed to conduct more comprehensive studies due to constraints in measuring tools, the smaller number of a statistical population, and consequently, the lower mortality rate, any definitive comment in the study of the relationship between troponin levels and the prognosis of patients with sepsis and its comparison with different parameters. Finally, it is recommended that other researchers remove all the mentioned constraints in their future studies.

## Conclusions

The results of the present study revealed that age was the most prognostic factor in the prediction of death since it was more prevalent in older age groups, and troponin had no role in determining the prognosis of patients with sepsis. However, confirming or rejecting this issue will require more investigation although it is essential to eliminate the constraints of this study. Accordingly, mortality is affected by the age of patients. In other words, the effect of age on mortality is more significant compared to the serum level of cardiac troponin I's effect.

Thus, considering the constraints of this study,

conducting more extensive studies, especially in the Iranian context, and especially the comparison of findings in case and control groups (people with sepsis and other hospitalized patients), and the quantitative measurements of troponin levels in researches are recommended. Eventually, future researchers can investigate the relationship between other factors affecting the prognosis and mortality of patients with sepsis and the way to control these factors.

### Authors' Contribution

MD wrote the manuscript and designed the study. AG developed the original idea and did a critical revision of the manuscript for important intellectual content. MB studied the concept and design. PS contributed to the development of the protocol. RG did the statistical analysis.

### Conflict of Interests

Authors have no conflict of interests.

### Ethical Issues

After explaining the objectives of the study, informed consent letters were obtained from the participants. The checklists were anonymous and included raw data and statistics. In addition, the research units were assured of data confidentiality. The approval was obtained from the Ethics Committee of Semnan University of Medical (IR.SEMUMS.REC.1395.112).

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