

Asymptomatic Troponin Elevation and Early Mortality Following Immune Checkpoint Inhibitor Therapy in Patients Without Cardiac Adverse Events

YUMA SHIBUTANI¹, TAKURO IMAOKA², ATSUKO SUZUKI³ and KAZUKO TAJIRI^{2,4}

¹Department of Pharmacy, National Cancer Center Hospital East, Kashiwa, Japan;

²Department of Cardiology, National Cancer Center Hospital East, Kashiwa, Japan;

³Department of Clinical Laboratory, National Cancer Center Hospital East, Kashiwa, Japan;

⁴Tsukuba Life Science Innovation Program (T-LSI), School of Integrative and Global Majors (SIGMA), University of Tsukuba, Tsukuba, Japan

Abstract

Background/Aim: Although immune checkpoint inhibitors (ICIs) have demonstrated high therapeutic efficacy against malignant tumors, immune-related cardiovascular adverse events remain a significant concern. While myocarditis is a well-recognized complication, mild troponin elevations without clinical symptoms have been increasingly observed. The prognostic significance of such subclinical elevations remains unclear. This study aimed to evaluate the relationship between asymptomatic troponin elevation and early mortality in patients receiving ICIs without cardiac adverse events. **Patients and Methods:** This retrospective, single-center study included 108 patients who received ICIs and had high-sensitivity troponin T (hs-TnT) levels measured at baseline and after treatment initiation. Patients diagnosed with myocarditis or other overt cardiac events were excluded. The patients were categorized into two groups based on hs-TnT elevation after ICI therapy. **Results:** Among the 108 patients, 26 (24.1%) exhibited hs-TnT elevation post-ICI without developing myocarditis or other cardiac diseases. The peak hs-TnT levels were significantly higher in these patients compared to those without elevation [28 (IQR=18-38) ng/l vs. 11 (8-13) ng/l, $p<0.001$], though still mildly elevated. Over a median follow-up of 174 days, 24 patients died, all due to cancer progression. Notably, those who died within one month of peak hs-TnT had higher levels than those who died after 1-3 or >3 months.

Conclusion: Subclinical troponin elevation is common in patients treated with ICIs. Higher troponin levels may be associated with earlier death; however, the underlying mechanisms remain unclear. Careful interpretation is needed and further research is required to clarify its prognostic value.

Keywords: Immune checkpoint inhibitors, troponin elevation, cardiotoxicity, subclinical myocarditis, cancer immunotherapy.



Kazuko Tajiri, Department of Cardiology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. Tel: +81 471331111, Fax: +81 471346879, e-mail: ktajiri@east.ncc.go.jp

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Introduction

Immune checkpoint inhibitors (ICIs) are a novel class of immunotherapeutic drugs that improve survival rates in a broad range of cancers. ICIs are increasingly used in the early stages of several solid and hematological malignancies (1-5). However, ICIs can cause immune-related toxicities that may affect any organ and can be severe, necessitating prompt diagnosis and treatment (6-9). ICI-associated myocarditis is recognized as a life-threatening complication with a mortality rate of 36%-67% (10-14). Therefore, early diagnosis and management of myocarditis have become important and are receiving increasing attention.

Cardiac troponins (troponin T/I) are useful biomarkers for the screening and diagnosis of ICI-induced myocarditis (15, 16) and were demonstrated to serve as surrogates for assessing myocarditis severity in previous studies (14, 17, 18). However, screening for troponin in patients receiving ICI treatment frequently reveals mild but noticeable elevations in troponin levels despite not meeting the diagnostic criteria for myocarditis and no other apparent cardiac diseases. Tomsitz *et al.* (19) reported that 112 patients (40% of the 280 studied patients) did not develop myocarditis, but experienced high-sensitivity troponin T (hs-TnT) elevation following ICI treatment. This phenomenon of elevated troponin levels after ICI treatment despite the absence of myocarditis or other cardiac diseases was also reported by Tamura *et al.* (20). In a retrospective cohort study, they found that among 18 patients (14% of 129 cohort patients) with elevated hs-TnI levels following ICI treatment, 12 did not develop myocarditis. Asymptomatic troponin elevation has been observed in clinical practice; however, its implications on patient outcomes and prognosis in such cases remains unclear.

This study aimed to investigate the relationship between cardiac troponin levels and prognosis in patients who received ICIs but did not develop overt cardiac events.

Patients and Methods

This was a single-center retrospective study, and all data were extracted from the medical records. We used an institutional database to identify all patients treated with ICIs between October 2021 and July 2023. This trial complied with the Declaration of Helsinki and was approved by the Ethics Committee of the National Cancer Center (Research number: 2022-384). Due to the retrospective nature of the study, the requirement for informed consent was waived by the Clinical Trials Ethics Committee of the National Cancer Center. No potentially identifying information or images of human participants are included in this article. All methods were carried out in accordance with relevant guidelines and regulations.

The hs-TnT levels were determined using electrochemiluminescence immunoassay using ECLusys® (Roche Diagnostics, Tokyo, Japan), and the normal hs-TnT value at our hospital is ≤ 14 ng/l (99th percentile concentration for the general population). Detailed protocols for the frequency and timing of hs-TnT measurements were absent and testing was conducted at the oncologist's discretion. In our institutional registry, hs-TnT levels were measured in a total of 424 patients treated with ICIs. Among them, we excluded 19 patients who developed myocarditis ($n=13$), met Bonaca's diagnostic criteria for ICI-associated myocarditis (21), or had other overt cardiac events, such as myocardial infarction ($n=2$) and heart failure ($n=4$). To examine the trend of troponin levels following ICI therapy, we excluded 295 patients whose troponin levels were not measured before and after ICI initiation and two patients who received ICIs in a clinical trial setting. The remaining 108 patients were included in the final analyses.

The patients were divided into the following two groups: the hs-TnT elevation group, where hs-TnT levels exceeded 14 ng/l (the upper limit of normal) after ICI administration, or baseline hs-TnT was >14 ng/ml and increased by more than 20% after ICI administration; and the no hs-TnT elevation group, where hs-TnT values remained within the normal range (≤ 14 ng/l) after ICI

administration, or baseline hs-TnT was >14 ng/ml, it did not increase by more than 20% after ICI administration.

Regarding patient characteristics, patients were evaluated for a history of hypertension, diabetes, dyslipidemia, and cardiovascular disease. The cardiovascular diseases included in this study were arrhythmias such as atrial fibrillation, supraventricular tachycardia, heart failure, valvular disease, and coronary artery disease. Performance status was assessed using the Eastern Cooperative Oncology Group Scale. The estimated glomerular filtration rate (eGFR) was calculated using the following formula for Japanese patients: $\text{eGFR} = 194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094} \times [0.739 \text{ for women}]$ (22).

Statistical analysis. Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as numbers and percentages. The Wilcoxon signed-rank sum test was used to assess the changes in troponin levels. The Shapiro-Wilk test was used to test for normality. Continuous variables were compared using the unpaired Student's *t*-test or Mann-Whitney *U*-test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Statistical significance was set at *p*-value <0.05. Statistical analyses were performed using SPSS Statistics ver. 28.0 (IBM, Armonk, NY, USA).

Results

The characteristics of the 108 patients included in the analysis are shown in Table I. Among them, 26 patients (24.1%) experienced hs-TnT elevation after ICI initiation without overt cardiac events, including myocarditis. Patients with elevated troponin levels had higher body mass index (BMI) and lower eGFR. Regarding primary cancer types, the proportion of renal cell carcinoma was higher in the hs-TnT elevation group than in the no hs-TnT elevation group.

The baseline hs-TnT levels were significantly higher in the hs-TnT elevation group than in the no hs-TnT elevation group (13 ng/l vs. 8 ng/l, *p*<0.001). Peak hs-TnT levels were also significantly higher in the hs-TnT elevation group than in the

no hs-TnT elevation group (28 ng/l vs. 11 ng/l, *p*<0.001). Even in patients without elevated hs-TnT levels, the hs-TnT levels increased significantly after ICI treatment (Figure 1). However, hs-TnT elevation remained mild, ranging from 3 to 208 ng/ml (15-208 ng/l in the hs-TnT elevation group and 3-49 ng/l in the no hs-TnT elevation group).

In the study cohort, 24 patients died during the median follow-up period of 174 days (interquartile range=97-350 days). The cause of death was cancer progression in all cases. As shown in Figure 2, patients who died earlier had higher peak hs-TnT levels: 5.55 ng/l, 1.90 ng/l, and 1.05 ng/l than patients who died within 1, 1-3, and >3 months after the peak hs-TnT measurement, respectively.

Discussion

One of the important observations of our study was that asymptomatic increases in hs-TnT are common in patients treated with ICI. In our institutional registry, 24% of the patients treated with ICIs experienced elevated hs-TnT levels following treatment without developing myocarditis or other overt cardiac events. This finding is consistent with previous reports by Tomsitz *et al.* (19), Tamura *et al.* (20), and van den Berg *et al.* (23), in which 10%-40% of patients experienced troponin elevation after ICI initiation without overt cardiac adverse events. As van den Berg *et al.* (23) mentioned, hypertroponinemia, characterized solely by elevated hs-TnT levels, may represent a distinct clinical entity that warrants differentiation from low-grade aggressive forms of ICI myocarditis, necessitating tailored therapeutic approaches. However, further research is required to better understand the relevance and impact of these elevations for guiding clinical decisions regarding ICI therapy.

Interestingly, our study revealed that patients who died earlier had higher peak hs-TnT levels (Figure 2); however, their cause of death was cancer progression and not cardiovascular disease. These results suggest that patients with elevated troponin levels after ICI administration may have a poor prognosis even if they do not develop myocarditis or other cardiac conditions, and thus warrant close monitoring.

Table I. Baseline patient characteristics according to high-sensitivity troponin T (hs-TnT) elevation after immune checkpoint inhibitor (ICI) initiation.

	Total (N=108)	No hs-TnT elevation (N=82)	hs-TnT elevation (N=26)	p-Value
Sex: Female	53 (49)	42 (51)	11 (42)	0.50
Age (years)	67 (55-73)	66 (54-73)	70 (59-73)	0.23
BMI (kg/m ²)	21 (18-24)	21 (19-23)	23 (21-25)	0.04
ECOG performance status				
0	72 (67)	54 (66)	18 (69)	0.82
1	35 (32)	27 (33)	8 (31)	
2	1 (1)	1 (1)	0 (0)	
Medical history				
Hypertension	37 (34)	26 (32)	11 (42)	0.34
Diabetes	14 (13)	11 (13)	3 (12)	0.99
Dyslipidemia	9 (8)	7 (9)	2 (8)	0.99
Baseline eGFR (ml/min/1.73m ²)	64 (52-81)	69 (54-84)	53 (48-72)	0.02
ICI				
Atezolizumab	4 (4)	3 (4)	1 (4)	0.99
Avelumab	5 (5)	3 (4)	2 (8)	0.59
Pembrolizumab	55 (51)	45 (55)	10 (38)	0.14
Nivolumab	35 (32)	26 (32)	9 (35)	0.78
Durvalumab	1 (1)	0	1 (4)	0.24
Nivolumab + Ipilimumab	9 (8)	5 (6)	4 (15)	0.21
Primary cancer type				
Head and neck	22 (20)	16 (20)	6 (23)	0.69
Breast	19 (18)	15 (18)	4 (15)	0.96
Lung	4 (4)	3 (4)	1 (4)	0.99
Hepatocellular carcinoma	1 (1)	1 (1)	0 (0)	0.99
Esophageal/stomach	13 (12)/3 (3)	12 (15)/1 (1)	1 (4)/2 (8)	0.75
Renal cell carcinoma	13 (12)	6 (7)	7 (27)	0.01
Malignant melanoma	5 (5)	5 (6)	0 (0)	0.33
Uterus	17 (16)	14 (17)	3 (12)	0.75
Bladder	8 (7)	8 (10)	0 (0)	0.19
Other	3 (3)	1 (1)	2 (8)	0.14
Follow-up				
Treatment period (days)	98 (42-189)	98 (52-187)	90 (37-192)	0.58
Observation period (days)	174 (97-350)	168 (101-332)	188 (93-356)	0.95
hs-TnT levels				
Baseline hs-TnT (ng/l)	9 (6-13)	8 (6-11)	13 (11-18)	<0.001
Peak hs-TnT (ng/l)	12 (8-18)	11 (8-13)	28 (18-38)	<0.001
Time to peak hs-TnT from ICI initiation (days)	60 (26-112)	52 (21-106)	70 (40-170)	0.18

Data are expressed as n (%) or median (interquartile range). BMI: Body mass index; eGFR: estimated glomerular filtration rate; ECOG: Eastern Cooperative Oncology Group; hs-TnT: high-sensitivity troponin T; ICI: immune checkpoint inhibitor.

The mechanism underlying the elevation of cardiac troponin levels after ICI administration in the absence of overt cardiac disease remains unclear; however, several factors may be involved. Cardiac troponins, which are typically associated with heart muscle damage, are abnormally expressed in certain cancers, including lung and colorectal cancers (24-26), and may play a role in cancer progression and carcinogenesis. Therefore,

because of the cancer cell damage caused by ICI administration, troponin present within cancer cells may leak into the bloodstream, leading to increased circulating troponin levels. Additionally, troponin levels can be influenced by various factors such as renal impairment, advanced age, sepsis, and thyroid dysfunction (27-29). Considering our finding that patients who died earlier had higher troponin levels, elevated troponin levels may also

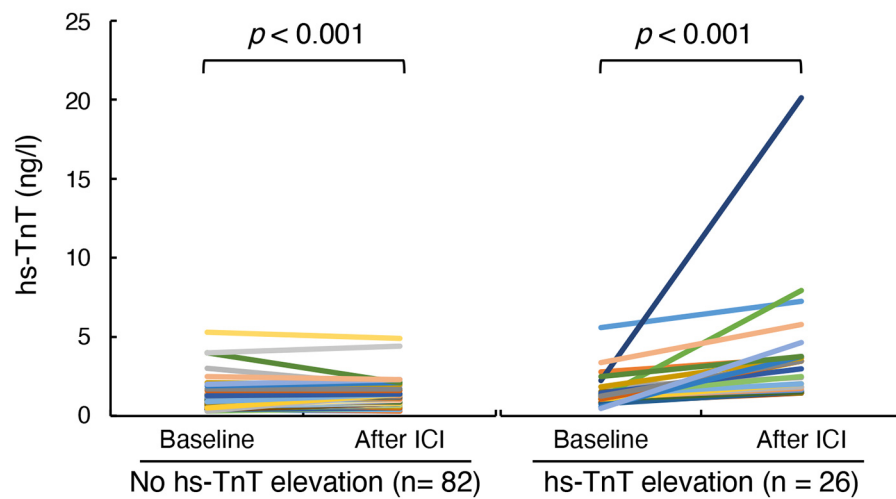


Figure 1. Changes in cardiac troponin levels after immune checkpoint inhibitor (ICI) administration. Comparison of baseline and peak high-sensitivity troponin (hs-TnT) levels between patients with and without elevated troponin levels following ICI therapy.

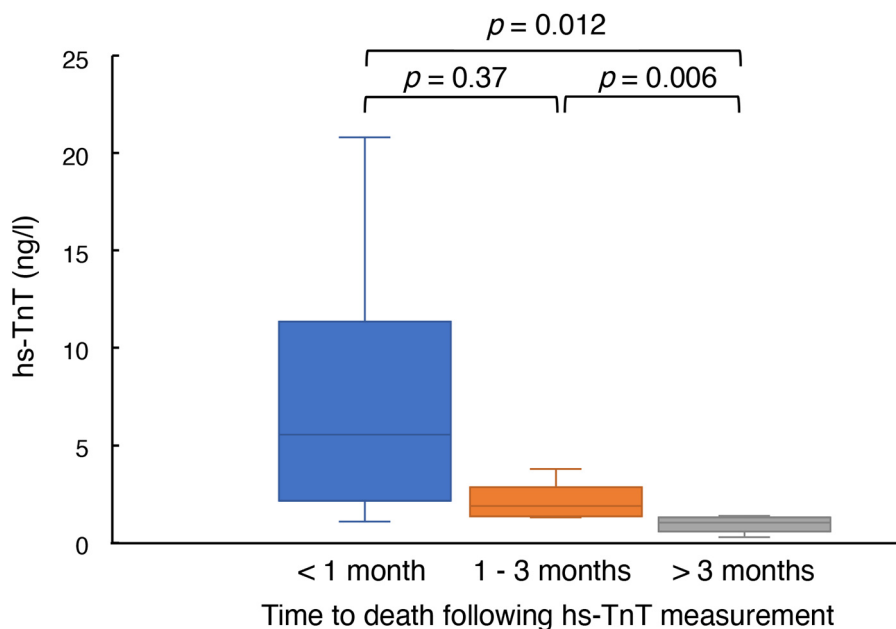


Figure 2. Association between troponin levels and mortality. Peak high-sensitivity troponin (hs-TnT) values and time from peak hs-TnT measurement to death. ICI: Immune checkpoint inhibitor.

reflect an overall deterioration in the patient's condition. It is also possible that ICI administration induces mild myocardial inflammation, resulting in asymptomatic myocardial injury that does not meet the diagnostic

criteria for ICI myocarditis, but causes a mild elevation in troponin levels. Therefore, careful interpretation of troponin elevation is required, and further investigation is warranted.

Study limitations. First, because this study was retrospective, no specific protocol was followed for measuring troponin levels in ICI treatment. Therefore, the timing of testing was left to the discretion of the individual physicians, which may have affected the study results. Second, we measured troponin T levels instead of troponin I levels to evaluate the risk of cardiac injury. Troponin I has been reported to be more cardiac-specific than troponin T, and troponin T may be falsely elevated in patients with diseased skeletal muscle (30-32). Considering these limitations, larger prospective studies considering both troponin T and troponin I levels are needed to validate the external validity of this study.

Conclusion

Subclinical troponin elevation is common in patients treated with ICI, with 24% of patients in our cohort exhibiting elevated troponin levels after ICI initiation. Furthermore, patients who died earlier had higher troponin levels. However, the mechanism underlying the subclinical troponin elevation remains unclear. Therefore, careful interpretation of elevated troponin levels is required and further studies are needed to elucidate their relationship with prognosis.

Conflicts of Interest

Kazuko Tajiri has received honoraria from Bristol Myers Squibb, Pfizer, Ono Pharmaceuticals, MSD, Chugai, and AstraZeneca. The funders had no role in the study design, data collection, analyses, interpretation, manuscript writing, or decision to publish the results. The other Authors declare no conflicts of interest.

Authors' Contributions

YS and KT designed the study. YS performed experiments and formal analysis. YS was the major contributor to writing – original draft and KT revised the manuscript. TI and AS critically read and approved the final manuscript.

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Artificial intelligence (AI) Disclosure

No AI tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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