Cardiac troponin I predicts clinical outcome of patients with cancer at emergency department

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Abstract

Background Cardiac troponin I has been shown its prognostic ability in general population or cardiovascular disease but not yet in cancer patients. This study aimed to investigate the prognostic implication of cardiac troponin in cancer patients visiting emergency department.

Methods In this retrospective cohort study, cancer patients visiting emergency department were enrolled. Patients with previously known coronary artery disease or clinically indicated coronary angiography were not included. The maximal value of Siemens ADVIA Centaur troponin I Ultra assay (TnI) within 24 hour were assessed. Primary endpoint was 180-day all-cause death that included cardiovascular and non-cardiovascular death.

Results A total of 9,135 patients (mean age 63 year, male gender 60%) were enrolled. The lowest (0.006 ng/ml), assay-specific <99 percentile (0.007-0.039 ng/ml), below median of ≥ 99 percentile (0.040-0.129 ng/ml), and above median of ≥ 99 percentile (≥ 0.130 ng/ml) TnI were found in 4,487 (49.1%), 3,158 (34.6%), 852 (9.3%), and 638 (7.0%) patients. There was 3,192 (34.9%) all-cause death including 137 (1.5%) cardiovascular and 3,047 (33.4%) non-cardiovascular death in the 180-day follow-up period. The risks of all-cause, cardiovascular, and non-cardiovascular death increased across higher TnI strata (hazard ratio (HR)=1.3 to 2.9; 2.1 to 9.3; 1.3 to 1.8; $p < 0.001$, all). These findings were consistent in clinical subgroups including solid and hematologic cancer.

Conclusions Cancer patients visiting emergency department with elevated troponin I were at increased risk of 180-day death. Cancer patients with elevated TnI may need additional evaluation or careful follow-up even without diagnosis of cardiovascular disease.

Background

Patients visiting emergency department with cancer is increasing.¹ Emergency department is often the first place in which patients turn to when they have a complication or unexpected worsening of their condition. Emergency physicians frequently need to quickly evaluate the clinical needs of the patients, stratify individual risk, determine optimal treatment, and decide admission or outpatient care setting with limited time and resource. This complexity sometimes is increased when patients present to the emergency department with few or no medical records. A simple affordable risk predicting biomarker test may be helpful in such situation.

Cardiac troponin is highly sensitive and specific biomarker for myocardial infarction, and may elevate in patients without clinically overt myocardial infarction.² Cardiac troponin frequently elevates in non-ischemic cardiac conditions such as arrhythmias, heart failure, pericarditis, and also in non-cardiac conditions such as pulmonary embolism, stroke, chronic kidney disease, sepsis or systemic inflammatory response syndrome, critical illness, and drugs causing cardiotoxicity.³ Although the pathophysiology of cardiac troponin elevation in non-ischemic cardiac or non-cardiac conditions are not fully elucidated, elevated cardiac troponin showed prognostic implication not only in acute coronary syndrome but also in

various clinical settings such as patients with non-diagnosed chest pain and even primary prevention study using statin.^{4–8}

Therefore, we reasoned that troponin may predict clinical outcome of patients with cancer. We investigated the predictive ability of cardiac troponin for 180-day death risk of patients who visited emergency department.

Methods

Patients

In this retrospective single-center cohort study, we included patients who were over 18 years old and visited emergency department at Samsung Medical Center, a tertiary hospital located in Seoul, and underwent cardiac troponin I test within 24 hour between January 2007 and May 2016. Patients without current or past cancer were excluded. Patient with specific conditions that may accompany elevated cardiac troponin were also excluded; mechanical circulatory support device, underwent resuscitation. Patients with documented coronary artery disease, history of revascularization, history of heart transplantation, and patients who performed coronary angiography within 48 hours were not included.

The Samsung Medical Center Institutional Review Board approved this study based on the facts that this study did not require informed consent given the use of anonymized database and the reporting of aggregated results. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary document).

Data sources and definitions

All data were retrieved from clinical data warehouse center in Samsung Medical Center (Darwin-C). The study index date was the time of patients visiting emergency department. The time of laboratory test and death were defined using the timestamp of electrical medical record. In case of mortality outside hospital, the specific cause of death was retrieved from the data of government operating Statistics of Korea. No patient was lost to follow-up with respect to death.

Siemens ADVIA Centaur XP analyzer (Munich, Germany) was used for cardiac troponin I measurement. It has the lowest cardiac troponin I (TnI) analytic sensitivity of 0.006 ng/ml, upper reference limit with 99th percentile level of 0.040 ng/ml, and coefficient of variation < 10% at 0.030 ng/ml. The level of maximum level of TnI within 24 hours after emergency department visit was categorized into 4 categories using the lowest (0.006 ng/ml), < 99 percentile (0.007–0.039 ng/ml), less than median of ≥ 99 percentile (0.040–0.129 ng/ml), and median of ≥ 99 percentile or higher (≥ 0.130 ng/ml). In case of multiple measurements of TnI, the highest value measured within 24 hour was selected. The first measured value was used for the other laboratory tests and vital sign measurements. All electrocardiography ST-T changes were independently read and confirmed by experienced physicians (M.S. and J.C.).

Primary endpoint was 180-day all-cause death. The major cause of death was determined by the death codes in 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and used for classification of cardiac or non-cardiac death (Supplementary document).

Statistical analysis

Clinical characteristics stratified by the TnI levels were shown. Continuous data were described as mean with standard deviation. Categorical data were presented as frequency. Differences were assessed by Kruskal-Wallis or chi-square test. The changing trend across strata with TnI levels were assessed by Jonckheere-Terpstra test.

The association of TnI strata with death was assessed using Cox regression models. For sensitivity analysis, three multivariate Cox regression models adjusted for the following clinical parameters were used. Model 1 included basic demographics and visiting year. Model 2 included parameters in model 1 and additionally clinical comorbidities and dyspnea, which was the mostly associated symptom with TnI strata and had prognostic value in cancer patients visiting emergency department.⁹ Model 3 included electrocardiographic change, vital signs, and laboratory tests in addition to the parameters in model 1 and 2.

R version 3.6 (R Foundation for Statistical Computing) was used. Hazard ratios (HR) for compared outcomes are reported with a 95% confidence interval (CI). Statistical significance was defined by 2-tailed $p < 0.05$.

Results

Study population

A total of 37,747 patients who visited emergency department and underwent TnI test within 24 hours were identified. Most TnI tests were available within 2 hours at emergency department (median 1.1, interquartile range 0.8–1.9 hour). After exclusion of 28,344 patients without cancer, 268 patients who underwent cardiopulmonary resuscitation, mechanical circulatory support, with prior history of diagnosis or revascularization of coronary artery disease, heart transplantation, or urgent coronary angiography performed within 48 hours after visiting emergency department, a total of 9,135 patients were enrolled into study (Fig. 1).

Clinical presentation

The number of patients with TnI = 0.006 ng/ml, 0.007–0.039 ng/ml, 0.040–0.129 ng/ml, and ≥ 0.130 ng/ml were 4,487 (49.1%), 3,158 (34.6%), 852 (9.3%), and 638 (7.0%), respectively. Age, frequency of male gender, and frequency of most clinical risk comorbidities increased across strata with higher TnI levels. The frequency of typical angina-like chest pain did not increased but dyspnea or respiratory symptom increased across strata with higher TnI levels ($p < 0.001$) (Table 1) (Supplementary figure I).

Table 1
Clinical characteristics

	Tnl = 0.006 ng/ml (n = 4,487)	Tnl = 0.007– 0.039 ng/ml (n = 3,158)	Tnl = 0.040– 0.129 ng/ml (n = 852)	Tnl ≥ 0.130 ng/ml (n = 638)	p- value
Age	59.6 ± 12.6	65.4 ± 12.4	65.6 ± 13.3	66.5 ± 12.5	< 0.001
Age ≥ 65 years	1654 (36.9)	1862 (59.0)	493 (57.9)	386 (60.5)	< 0.001
Male gender	2585 (57.6)	1995 (63.2)	518 (60.8)	375 (58.8)	< 0.001
Diabetes	446 (9.9)	440 (13.9)	135 (15.8)	98 (15.4)	< 0.001
Hypertension	1157 (25.8)	1202 (38.1)	348 (40.8)	255 (40.0)	< 0.001
Respiratory disease	431 (9.6)	394 (12.5)	106 (12.4)	75 (11.8)	< 0.001
Hepatic disease	521 (11.6)	367 (11.6)	111 (13.0)	85 (13.3)	0.42
Solid cancer	4273 (95.2)	2922 (92.5)	773 (90.7)	578 (90.6)	< 0.001
Hematologic cancer	574 (12.8)	515 (16.3)	156 (18.3)	134 (21.0)	< 0.001
Systolic blood pressure (mmHg)	124 ± 25	124 ± 29	121 ± 31	118 ± 32	< 0.001
Diastolic blood pressure (mmHg)	77 ± 15	76 ± 16	74 ± 17	72 ± 18	< 0.001
Heart rate (/min)	92 ± 22	97 ± 24	104 ± 27)	104 ± 27	< 0.001
Body mass index (kg/m ²)	22.43 ± 3.52	22.54 ± 3.65	22.12 ± 3.81	22.16 ± 3.55	0.009
Electrocardiography available	3063 (68.3)	2444 (77.4)	671 (78.8)	500 (78.4)	< 0.001
Electrocardiography ST-T change	235 (7.7)	373 (15.3)	151 (22.5)	156 (31.2)	< 0.001
Symptom					< 0.001
Angina-like chest pain	106 (2.4)	48 (1.5)	6 (0.7)	9 (1.4)	
Atypical chest pain	227 (5.1)	154 (4.9)	24 (2.8)	43 (6.7)	

	Tnl = 0.006 ng/ml (n = 4,487)	Tnl = 0.007– 0.039 ng/ml (n = 3,158)	Tnl = 0.040– 0.129 ng/ml (n = 852)	Tnl ≥ 0.130 ng/ml (n = 638)	p- value
Body pain other than chest	54 (1.2)	31 (1.0)	5 (0.6)	3 (0.5)	
Syncope or palpitation	296 (6.6)	187 (5.9)	44 (5.2)	23 (3.6)	
Neurologic symptom	258 (5.7)	188 (6.0)	81 (9.5)	73 (11.4)	
Dyspnea or respiratory symptom	972 (21.7)	797 (25.2)	272 (31.9)	216 (33.9)	
Gastrointestinal symptom	853 (19.0)	465 (14.7)	113 (13.3)	49 (7.7)	
Fever	490 (10.9)	433 (13.7)	131 (15.4)	95 (14.9)	
Dysuria or urologic symptom	23 (0.5)	27 (0.9)	5 (0.6)	3 (0.5)	
Trauma or superficial bleeding	24 (0.5)	17 (0.5)	7 (0.8)	2 (0.3)	
General weakness	127 (2.8)	117 (3.7)	39 (4.6)	24 (3.8)	
Miscellaneous	6 (0.1)	1 (0.0)	0 (0.0)	1 (0.2)	
Not described	1051 (23.4)	693 (21.9)	125 (14.7)	97 (15.2)	
Laboratory results					
White blood cell (/mm ³)	8,490 ± 7,390	8,970 ± 9,100	10,000 ± 10,210	10520 ± 7680	< 0.001
Hemoglobin (g/dl)	11.8 ± 2.3	11.6 ± 2.4	11.2 ± 2.5	11.4 ± 2.2	< 0.001
Platelet (10 ³ /mm ³)	215.0 ± 105.7	203.1 ± 106.2	179.5 ± 104.4	183.7 ± 104.9	< 0.001
Blood urea nitrogen (mg/dl)	16.9 ± 11.5	22.6 ± 17.3	29.7 ± 24.3	30.8 ± 25.4	< 0.001
Creatinine (mg/dl)	0.88 ± 0.74	1.22 ± 1.33	1.61 ± 1.84	1.78 ± 2.01	< 0.001
eGFR (ml/1.73 m ² /min)	96.6 ± 35.7	80.4 ± 40.1	68.2 ± 37.9	64.2 ± 40.8	< 0.001

Clinical outcomes

There was a total of 3,192 (34.9%) all-cause death including 281 (3.1%) cardiac death and 2,911 (31.9%) non-cardiac death during the 180-day follow-up period. The proportion of cardiac death in the all-cause death increased across strata with higher TnI (5.4–17.2%, $p < 0.001$) (Fig. 2).

The risks of all-cause death and non-cardiovascular death increased in higher TnI levels (HR = 1.34 to 1.99; 1.32 to 1.82; $p < 0.001$, all), but there was no further increase of risk when TnI was higher than median of ≥ 99 percentile (≥ 0.130 ng/ml). The risk of cardiovascular death increased consistently across strata with higher TnI levels (HR = 2.08 to 9.30, $p < \text{Fig. 01}$) (Table 2) (Fig. 3).

Table 2
Clinical outcome

	TnI = 0.006 ng/ml (n = 4487)	TnI = 0.007– 0.039 ng/ml (n = 3158)	TnI = 0.040– 0.129 ng/ml (n = 852)	TnI ≥ 0.130 ng/ml (n = 638)	p- value
Death within 180 days					
All-cause death	1325 (29.5)	1161 (36.8)	403 (47.3)	303 (47.5)	< 0.001
Cardiovascular death	71 (1.6)	104 (3.3)	54 (6.3)	52 (8.2)	< 0.001
Non-cardiac death	1254 (27.9)	1057 (33.5)	349 (41.0)	251 (39.3)	< 0.001
Cause of death					< 0.001
Cardiovascular disease	71 (5.4)	104 (9.0)	54 (13.4)	52 (17.2)	
Gastrointestinal disease	7 (0.5)	14 (1.2)	4 (1.0)	2 (0.7)	
Infection	5 (0.4)	10 (0.9)	5 (1.2)	6 (2.0)	
Respiratory disease	9 (0.7)	29 (2.5)	12 (3.0)	14 (4.6)	
Cancer	1230 (92.8)	998 (86.0)	326 (80.9)	227 (74.9)	
Neurological disease	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.3)	
Miscellaneous	0 (0.0)	4 (0.3)	1 (0.2)	1 (0.3)	
Trauma	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	
Supplementary data					
Supplementary Fig. 1. Frequency of chief complaining symptom or electrocardiographic changes according to the cardiac troponin I (TnI) level					

In multivariate Cox regression analysis using various models, elevated TnI levels were independently associated with cardiac or non-cardiac death as well as all-cause death not only in basic simple model but also models including clinical comorbidities, electrocardiographic change, and laboratory test (HR = 1.19 to 5.63; $p < 0.05$, all, except TnI = 0.007–0.039 ng/ml in cardiac death) (Fig. 4).

Discussion

In this retrospective cohort study, elevated TnI was independently associated with higher risks of both cardiac and non-cardiac death in patients visiting emergency department with cancer but without diagnosis of specific cardiovascular disease. Higher TnI levels were associated with increasing death risk. These results were consistent in sensitivity analyses using multivariate Cox regression analysis with various models. As far as we are aware, our result is the first study that enrolled a large number of patients and showed prognostic ability of cardiac troponin in patients with cancer visiting emergency department.

Patients with cancer are frequently older individuals who are likely to have multiple chronic disease or comorbidities.¹⁰ These chronic disease or comorbidities may be preexisting or exacerbated by cancer progression or cancer treatment, which complicating the clinical picture in emergency department and prognostication. Our study subjects consisted of high mid-term risk patients with average 180-day death risk of 34.9%. In such high risk population, decision of cancer patient referral to palliative care or to hospice program is required but frequently difficult. Prior studies have reported disease progression, dyspneic symptom, performance score, functional status evaluated by hand grip strength, various biomarkers including lactate dehydrogenase and albumin.^{9 11} Use of cardiac troponin I in prognostication may help weighting assessment and medical management of patients with cancer-related complications or comorbidities.¹²

Our study showed the association but not the causal relationship among elevated cardiac troponin I and clinical outcome. Interestingly, the risk of cardiovascular death risk was proportional to the category of TnI, but the risk of non-cardiovascular death risk did not increase when the category of TnI was ≥ 0.040 ng/ml. These results suggests that high and moderate elevations of cardiac troponin may have different pathophysiology, and were caused by underlying cardiovascular disease itself and systematic toxic effect on cardiomyocytes or decreased nitric oxide bioavailability or myocardial perfusion.¹³ The underlying pathophysiology of cardiac troponin elevation in patient with cancer warrants further investigation.

The level of cardiac troponin has predictive value, but was not compared with the other parameters or predicting algorithms because of lack of standardized guideline assessing patients visiting emergency department. Patients with cancer visiting emergency department have highly heterogenous clinical picture and potentially need individualized treatment and care. In such case with limited resource or time for prognostication, cardiac troponin may be included in risk predicting algorithm and may reduce the knowledge gaps in clinical guidelines and operational challenges.

Limitation

Our study is not free from inherent limitations of retrospective single center study. We enrolled all comers visiting emergency department to minimize selection bias. The highest TnI value within 24 hours after visiting emergency department were used for analysis, which limited distinguishing acute from chronic TnI elevation. The source data was administrative claims which lack of codes for specific conditions. We

did not include patients underwent coronary angiography during hospital stay and the cause of TnI elevation was not investigated. The type, biology, and treatment setting of individual cancer were not investigated. The status of treatment including ongoing chemotherapy or surgery, cancer staging, or presence of metastasis, were not investigated. The severity of chemotherapy- or radiation-induced cardiotoxicity were not assessed.

Abbreviations

TnI

Cardiac troponin I

STROBE

Strengthening the Reporting of Observational Studies in Epidemiology

ICD-10

10th revision of the International Statistical Classification of Diseases and Related Health Problems

HR

Hazard ratios

CI

confidence interval

Key Messages

What is already known on this subject

- Cardiac troponin may elevate in patients without clinically overt myocardial infarction
- Cardiac troponin I has been shown its prognostic ability in general population.

What this study adds

- Cancer patients visiting emergency department with elevated cardiac troponin I (TnI) had increasing risk of 180-day cardiovascular and non-cardiovascular death.
- Emergency physician, cardiologists and oncologists should be informed that cancer patients with increased TnI level have increased risk of death.
- TnI may help to decide collaboratively healthcare strategy of aggressive, palliative, or hospice care in terms of medical resources in crowded emergency department.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

Nothing to disclosure

Authors' contribution

Conceptualization: JHC, SHP. Data analysis :JHC. Writing - original draft: SHP, JHC. Writing - review & editing: SHP, JHC, EJK, MS, TK, WCC, HY, SYH, TGS, MS S, IJ, SHL, HDP. Study supervision and approval of final manuscript: JHC

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Figures

Figure 1

Flowchart shows inclusion and exclusion criteria for selecting patients to enroll into the study.

Figure 2

The increase of all-cause death risk across cardiac troponin I (TnI) strata is mostly driven by the increase of cardiovascular death.

Figure 3

Panel A, B, and C shows that all the unadjusted 180-day risks of all-cause death, cardiovascular death, and non-cardiovascular death increased across strata with higher TnI levels. See supplementary table I for numerical data.

Figure 4

Panels A – C show Cox regression models using demographics and visiting years. Panels D – F show Cox regression models using clinical parameters in addition to parameters used in Panels A – C. Panels G – I show Cox regression models using laboratory results, vital signs, and ECG in addition to parameters used in Panels D – F. TnI levels and associated data are shown in blue color. TnI, cardiac troponin I; ECG, electrocardiography; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BMI, body mass index; WBC, white blood cell.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [STROBEchecklist20190131.docx](#)
- [Supplementary.docx](#)