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Data mining: Biological and temporal factors associated with blood cardiac troponin I concentration in a Chinese population

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ABSTRACT

Background: Cardiac troponin is the cornerstone biomarker for the diagnosis of acute myocardial infarction. The aims of this study were to evaluate the association of biological and temporal factors with plasma cardiac troponin I (cTnI) concentration in a large group of Chinese outpatients and to explore which factor (sex, age, time of blood sampling, and season of the year) had the largest influence on plasma cTnI levels.

Methods: Analytical data with outpatient cTnI results were downloaded from the laboratory information system from January 1, 2012 to September 20, 2018. All cTnI measurements were performed with a Siemens Dimension EXL automatic chemiluminescence immunoassay analyzer. A statistical method was used to strictly exclude outliers. A total of 86,381 outpatients were enrolled in the study.

Results: In individuals over 60 years old, cTnI levels gradually increased with age in both males and females. cTnI reached its highest levels in individuals over 80 years old (0.030 μg/L in males and 0.027 μg/L in females). In individuals over 70 years old, cTnI levels were significantly higher in males than in females ($P < .05$). cTnI concentration varied between individuals with different times of blood sampling. In both men and women, cTnI concentrations reached a maximum at 05:00 (0.030 μg/L and 0.026 μg/L, respectively) and peaked again at 20:00 (0.029 μg/L and 0.023 μg/L, respectively). Additionally, there were significant differences in cTnI levels between the four seasons of the year ($P < .05$). In winter, cTnI levels were usually higher than in spring. Linear regression analysis showed that the factor "age ≥ 80" had the greatest impact on cTnI levels.

Conclusion: Plasma cTnI levels were significantly influenced by sex, age, time of blood sampling, and season of the year. Thus, in order to avoid incorrect identification of cTnI values as abnormal, a cTnI reference interval should be established, taking into consideration the sex and age of the individual, the time of day of blood sampling, and the season of the year.

1. Introduction

Cardiac troponin is the cornerstone biomarker for the diagnosis of acute myocardial infarction (AMI) [1], a disease with increasing clinical morbidity and mortality. Cardiac troponin consists of three subunits (C, I, and T). The cardiac-specific isoforms of troponin-I (cTnI) and troponin-T (cTnT) show comparable sensitivity and specificity for the detection of myocardial injury in the general population [2]. In this study, we focused on cTnI. cTnI is a definitive marker for the assessment of myocardial injury. However, when plasma cTnI levels are measured, they are often inconsistent with the patient's clinical manifestations and electrocardiogram (ECG) results. There are three main reasons for this. First, interfering factors can cause a false increase or decrease in cTnI during the detection process. Second, biological factors, including sex, age, circadian rhythm, and kidney function and temporal factors, such as the season of the year, can influence the results. Third, an increase in cTnI may be due to non-acute coronary syndrome (non-ACS). Numerous studies have explored the factors that interfere with cTnI measurements [3–6]. These studies have shown that autoantibodies, matrix, bilirubin, heterophilic antibodies, and rheumatoid factors can cause false positive or false negative results. However, variations in repeated measurements also depend on biological

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factors. Research on this topic is rare and such studies usually take age and/or sex into consideration when exploring the effect of biological factors on cTnI concentration [7–9]. There are a few reported studies [10,11] simultaneously analyzing the effects of four factors on cTnI levels. Our laboratory has previously used clinical big data to analyze the effects of temperature, sex, age, sampling time, and seasons of the year on thyroid-stimulating hormone (TSH) concentration [12,13]. To our knowledge, there are no reported studies using clinical big data to study biological and temporal factors associated with cTnI concentration in Chinese populations.

Therefore, before each cTnI assay, quality control protocols were employed to ensure the precision of the test. Quality control measures help to avoid errors occurring during the detection process. At the same time, individuals with kidney or heart disease were excluded in order to specifically analyze the biological factors associated with plasma cTnI concentration. This study aimed to assess the influence of biological and temporal factors on plasma cTnI levels, in order to develop clinical guidelines for the use of this biomarker.

2. Materials and methods

2.1. Data collection

Data were collected from outpatients visiting Peking Union Medical College Hospital between January 1, 2012 and September 20, 2018. Information on the individuals who underwent cTnI measurement was downloaded from the laboratory information system. Medical information collected included basic information, such as patient identification number, name, sex, age, and department visited and disease-related information, such as blood collection time, cTnI test results, and the diagnosis provided by the clinician. The following exclusion criteria were applied: (1) age < 18 years old; (2) myocardial injury caused by myocardial ischemia, due to imbalance of supply and demand, tachycardia or bradycardia, aortic dissection or severe aortic valve disease, hypertrophic cardiomyopathy, cardiogenic volumetric or septic shock, severe respiratory failure, severe anemia or hypertension with or without left ventricular hypertrophy; (3) myocardial injury unrelated to myocardial ischemia, including heart contusion, surgery, radiofrequency ablation, pacing or defibrillation, rhabdomyolysis and cardiac intervention, myocarditis, or cardiotoxic drugs such as anthracyclines; (4) myocardial injury with multiple factors or uncertainties, such as heart failure, stress-induced cardiomyopathy (Takotsubo), severe pulmonary embolism or pulmonary hypertension, sepsis and critical illness, renal failure, or severe acute neurological diseases such as stroke and subarachnoid hemorrhage. These criteria were investigated during an interview when the presence of these conditions and any other cardiovascular symptoms were assessed. At enrollment, a basic transthoracic echocardiogram was performed for every volunteer to exclude the presence of any structural disease. In addition, outlying values were identified using Tukey's method, which involves the computation of the 25th (Q1) and 75th (Q3) percentiles and the interquartile range (IQR = Q3 − Q1). Outliers were excluded based on the following formula: Q1 − 3IQR and Q3 + 3IQR.

A total of 86,381 outpatients were enrolled in this study. Data were analyzed after removal of all personal identification information. This study was approved by the Ethics Committee of Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences.

2.2. Quality assurance and laboratory analysis

All blood was drawn by venipuncture and samples were transported and processed according to the Guidelines for the Collection and Transportation of Samples for Testing. Samples were centrifuged at 3000 rpm for 10 min before testing. Samples were excluded if hemolysis or lipemia were present. cTnI levels were assayed using a Siemens Dimension EXL automatic chemiluminescence immunoassay analyzer, with corresponding reagents and calibrators (Siemens, Munich, Germany). In order to monitor the precision of the instrument, quality controls (Lyphochek® Immunoassay Plus Control) were used before the analyses. Internal quality control (IQC) data were obtained during the study period to ensure the reliability of the results. The instrument was calibrated and preventively maintained every year. We also cleared external quality assessments (EQAs) by the National Center for Clinical Laboratories every year and the College of American Pathologists once every two years to guarantee the accuracy and reliability of our results [12]. The limit of blank was found to be 0.010 μg/L, the limit of detection was 0.017 μg/L, and the limit of quantity was 0.050 μg/L. According to the recommendations of the International Federation of Clinical Chemistry Committee (2007), the 99th percentile of troponin in the normal population should be used as a threshold [14]. According to the reagent manufacturer's documentation, the normal 99th percentile value is 0.00–0.056 μg/L and the 10% Coefficient of Variation limit is 0.050 μg/L.

2.3. Statistical analysis

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Before data analysis, the Tukey's test was used to exclude outliers. The Kolmogorov-Smirnov (K−S) test was used to estimate data distribution. Non-normally distributed data are presented as medians (Q1, Q3). The Mann-Whitney *U* test was used to compare cTnI levels between males and females and the Kruskal-Wallis test was used to compare cTnI levels between groups for each sex. Linear regression analysis was used to evaluate the associations between sex, age, season of the year, and time of blood sampling and cTnI levels. $P < .05$ was considered statistically significant.

3. Results

3.1. Effect of sex and age on cTnI concentrations

The distribution of cTnI concentration by sex and age is shown in

Table 1
cTnI concentrations in male and female individuals of various age groups.

Age (years)	Males		Females		*P* value
	N	cTnI (Q1, Q3) μg/L	N	cTnI (Q1, Q3) μg/L	
Overall	42,692	0.019 (0.011, 0.059)	43,689	0.017 (0.010, 0.049)	< 0.001*
18–29	2743	0.017 (0.010, 0.040)	3772	0.017 (0.009, 0.030)	< 0.001**
30–39	3573	0.017 (0.010, 0.030)	3872	0.017 (0.009, 0.027)	< 0.001**
40–49	4487	0.017 (0.010, 0.040)	4071	0.017 (0.010, 0.036)	0.019**
50–59	7251	0.017 (0.010, 0.051)	6746	0.017 (0.009, 0.040)	< 0.001**
60–69	9241	0.017 (0.011, 0.063)	9183	0.017 (0.010, 0.050)	< 0.0013**
70–79	8327	0.023 (0.012, 0.067)	8620	0.020 (0.010, 0.060)	< 0.001**
≥ 80	7070	0.030 (0.015, 0.080)	7425	0.027 (0.014, 0.074)	0.003**

* *P* values were significant (< 0.05) among groups for each sex.
** *P* values were significant (< 0.05) between male and female individuals.

Table 2
cTnI concentrations by sex and time of blood sampling.

Time of sampling	Males		Females		*P* value
	N	cTnI (Q1, Q3) μg/L	N	cTnI (Q1, Q3) μg/L	
Overall	42,692	0.019 (0.011, 0.059)	43,689	0.017 (0.010, 0.049)	< 0.001*
01:00	1167	0.018 (0.010, 0.059)	1083	0.017 (0.010, 0.050)	0.034**
02:00	970	0.020 (0.011, 0.063)	967	0.017 (0.010, 0.053)	0.065**
03:00	924	0.020 (0.013, 0.061)	857	0.019 (0.011, 0.068)	0.741**
04:00	970	0.025 (0.014, 0.080)	881	0.019 (0.012, 0.067)	0.026**
05:00	1157	0.030 (0.016, 0.083)	1079	0.026 (0.014, 0.084)	0.483**
06:00	1034	0.021 (0.014, 0.068)	973	0.020 (0.012, 0.050)	0.085**
07:00	1584	0.020 (0.013, 0.066)	1497	0.017 (0.010, 0.048)	< 0.001**
08:00	1703	0.017 (0.011, 0.044)	1649	0.017 (0.009, 0.035)	< 0.001**
09:00	2303	0.017 (0.010, 0.042)	2239	0.017 (0.010, 0.036)	0.004**
10:00	2348	0.017 (0.010, 0.050)	2544	0.017 (0.010, 0.040)	0.001**
11:00	2126	0.017 (0.010, 0.046)	2251	0.017 (0.009, 0.037)	< 0.001**
12:00	1863	0.017 (0.011, 0.050)	2149	0.017 (0.010, 0.036)	0.010**
13:00	1817	0.017 (0.010, 0.060)	1943	0.017 (0.010, 0.045)	0.029**
14:00	1895	0.017 (0.010, 0.050)	1956	0.017 (0.010, 0.042)	0.176**
15:00	2012	0.017 (0.010, 0.050)	1984	0.017 (0.009, 0.041)	0.012**
16:00	1846	0.018 (0.011, 0.053)	2111	0.017 (0.010, 0.049)	0.010**
17:00	1798	0.019 (0.011, 0.054)	1817	0.017 (0.010, 0.047)	0.059**
18:00	1566	0.017 (0.010, 0.046)	1652	0.017 (0.009, 0.044)	0.083**
19:00	1792	0.017 (0.011, 0.047)	1968	0.017 (0.009, 0.036)	< 0.001**
20:00	3387	0.029 (0.015, 0.091)	3547	0.023 (0.012, 0.079)	< 0.001**
21:00	3032	0.023 (0.013, 0.072)	3008	0.020 (0.011, 0.066)	0.008**
22:00	2185	0.019 (0.012, 0.060)	2302	0.017 (0.010, 0.050)	< 0.001**
23:00	1766	0.018 (0.010, 0.054)	1809	0.017 (0.010, 0.045)	0.002**
00:00	1447	0.019 (0.010, 0.054)	1423	0.017 (0.010, 0.043)	0.046**

* *P* values were significant (< 0.05) among groups for each sex.
** *P* values were significant (< 0.05) between male and female individuals.

Table 1. There were significant differences according to sex ($P < .05$). In men and women from 19 to 60 years old, cTnI values did not change substantially. However, after the age of 60, cTnI values gradually increased with age. cTnI levels reached their highest value in individuals ≥80 years old (0.030 μg/L in men and 0.027 μg/L in women). After the age of 70, cTnI values were significantly higher in men than in women ($P < .05$).

3.2. Effect of blood sampling time and season of the year on cTnI concentration

cTnI concentrations varied depending on the time of blood sampling and men usually showed higher values than women (Table 2, Fig. 1). In both men and women, cTnI concentration reached a maximum at 05:00 (0.030 μg/L and 0.026 μg/L, respectively) and then peaked again at 20:00 (0.029 μg/L and 0.023 μg/L, respectively). cTnI concentrations were significantly higher in men than in women at these collection times ($P < .001$).

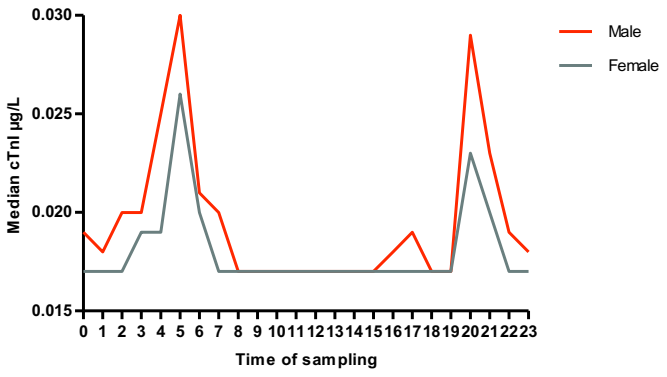

Fig. 1. Plasma cTnI concentrations in outpatients at various blood sampling times.

Differences were also detected according to the season of the year ($P < .05$). Median plasma cTnI levels in spring, summer, autumn, and winter were 0.017 μg/L, 0.017 μg/L, 0.020 μg/L, and 0.020 μg/L, respectively in men and 0.017 μg/L, 0.017 μg/L, 0.017 μg/L, and 0.019 μg/L, respectively in women. While cTnI levels did not differ between autumn and winter in men, they were higher in winter compared to all other seasons in women. cTnI levels were usually higher in winter than in spring (Fig. 2, Fig. 3).

3.3. Evaluation of the major factors associated with cTnI levels

Results of linear regression analysis are shown in Supplemental Table 1. Sex, age, season of the year, and time of blood sampling significantly influenced cTnI levels. The factor of age ≥ 80 had the greatest impact on cTnI levels (standard beta coefficient = 0.106, $P < .001$ $P < .05$). Plasma cTnI levels in men were 0.004 μg/L higher than in women. cTnI levels in summer, autumn, and winter gradually increased compared to spring. Winter cTnI levels were 0.005 μg/L higher than spring cTnI levels.

A statistically significant circadian variation in cTnI concentration was found. cTnI levels increased by 0.015 μg/L from 00:00 to 05:00 and then gradually decreased. cTnI levels at 07:00 were approximately equal to cTnI levels at 00:00 h, but from 08:00 to 19:00 they were lower than at 00:00. A second peak value was reached at 20:00, at which time, the concentration of cTnI was 0.017 μg/L higher than that at 00:00. Because sex significantly influenced plasma cTnI levels, a linear regression analysis was performed to analyze the effects of age, season of the year, and time of blood sampling. Results of linear regression analyses in male and female individuals are shown in Supplemental Table 2. In men and women, age ≥ 80 significantly influenced cTnI levels, but the impact was greater in women than in men (standard beta coefficient = 0.113, $P < .001$). The effects of season of the year, age, and time of blood sampling on cTnI levels in different sex groups were similar to those in the general population.

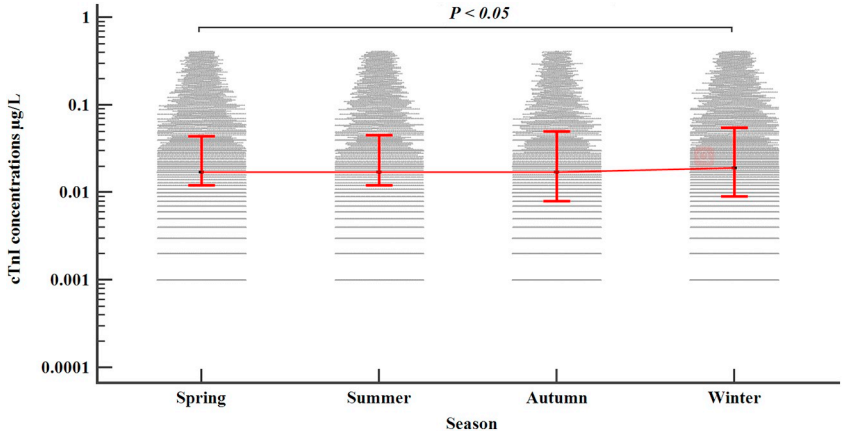

Fig. 2. Seasonal changes in plasma cTnI concentration in male outpatients.

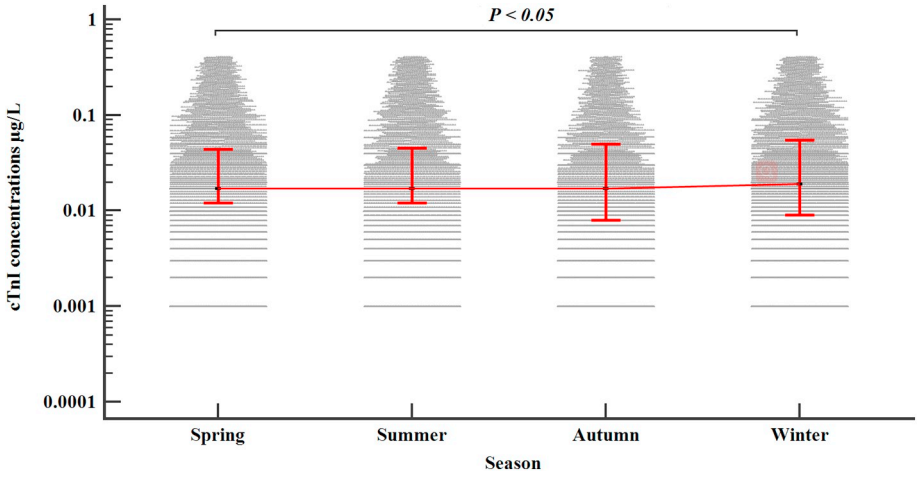

Fig. 3. Seasonal changes in plasma cTnI concentration in female outpatients.

4. Discussion

To the best of our knowledge, this is the first study to analyze the biological factors associated with plasma cTnI concentration in a large representative population covering all adult age groups. In this study, we focused our analysis on four factors (sex, age, season of the year, and time of sampling) that potentially influence the levels of cTnI.

A previous study with 599 individuals showed that the levels of cTnI are influenced by sex but are not affected by age. The 99th percentile value in that study was 0.0181 μg/L in males and 0.0086 μg/L in females [15]. However, in our study, among the four factors that potentially influence cTnI levels, age ≥ 80 had the greatest impact. Our study also reports that plasma cTnI levels were lower in women than in men, which is consistent with a previous study [10]. A study from Gore et al. [16], which determined the age- and sex-related upper limit of reference values for the high-sensitivity cardiac troponin T assay (hs-cTnT), showed that men < 50 years old and women < 65 years old had a cut-off value of 0.014 μg/L. The hs-cTnT cut-off value for males 50–64 years old and females ≥65 years old was 0.017 μg/L, whereas the cut-off value for men ≥65 years old was 0.031 μg/L. Various studies have shown that the levels of hs-cTnT increase with age and that the levels are higher in men than in women. To avoid the incorrect identification of cTnI values as abnormal and to establish a reference interval for diagnostic screening and monitoring of cTnI, the impact of age and sex should be considered.

cTnI is a diagnostic biomarker that can be measured any time during the day. This study explored the effect of time of blood sampling on plasma cTnI levels. Circadian rhythm significantly influenced plasma cTnI levels, with two peak times during the day. Plasma cTnI concentration increased from 00:00 to 05:00 and then decreased until another peak at 20:00.

In a study by Klinkenberg et al., cTnI concentration was monitored for 11 h (08:30 to 19:30), and daytime cTnI concentrations were found to gradually decrease [17]. Similarly, in a fitted diurnal model, 17 healthy young volunteers had a peak hs-TnT concentration at 06:00, while the lowest value was observed at 18:00. The absolute magnitude change of hs-TnT was 0.9 ng/L and the average concentration was 4.39 ng/L in this study. The magnitude of this change challenges the immediate inclusion/exclusion threshold published in the European Acute Coronary Syndrome Management Guide [18]. Apart from necrosis, various mechanisms, such as normal myocyte cell turnover or cellular release of proteolytic troponin degradation products, may contribute to the release of cardiac troponin in the systemic circulation [19]. Circadian clock is known to influence protein degradation [20] and it has been suggested that myocardial growth and renewal processes in animal models are more pronounced during the night. The levels of cTnI may peak during the night because the process of myocardial growth and renewal usually peaks at night.

The circadian rhythm of cTnI has been described in a previous study. In our study, we found that the ranges of cTnI levels were 0.025 μg/L and 0.029 μg/L for different sampling times in men and women, respectively. The cTnI reference interval for the Siemens ADVIA Centaur XP automatic chemiluminescence immunoassay analyzer is 0.050 μg/L. Plasma cTnI values of 0.062 μg/L in the blood samples collected from the patients at 05:00 would generally be considered an indicator of myocardial injury. However, if the sample is

drawn from the same patient at 09:00, plasma cTnI may be lower than 0.050 μg/L, which would be considered a normal level. Plasma cTnI concentration is a diagnostic indicator that can be measured any time during the day. Therefore, when the cTnI index is applied in a clinic, attention should be paid to the circadian rhythm.

The present study is a retrospective study based on big clinical data and has several advantages. First, this study not only revealed intraday rhythms but also interday rhythms, with cross-year and cross-season variations. Second, this study is the first to explore the influence of multiple factors, including sex, age, season of the year, and time of sampling, on cTnI levels.

However, this study also has several limitations. First, we did not have data on the medical history of the outpatients and any therapies they were undergoing may have had unknown effects on cTnI concentration. Second, due to a lack of instrumentation and reagents, we did not analyze the effects of biological factors on cTnT levels. Additionally, it is hard to avoid selective bias in big data analysis, and we only evaluated the effect of biological and temporal factors on cTnI in a Chinese population; therefore, in future studies, we will collaborate with foreign researchers to analyze the effect of biological and temporal factors on cTnI concentration using big data in other populations and explore whether our results may be extrapolated to other populations worldwide. However, the relationship between biological factors and plasma cTnI concentration found in this study is clear, and these limitations do not affect our conclusions.

5. Conclusions

This study demonstrated that plasma cTnI values are significantly influenced by sex, age, season of the year, and time of blood sampling. In particular, sex- and age-related variations in plasma cTnI concentrations were observed. Age ≥ 80 was the major factor influencing plasma cTnI levels. Thus, to avoid the incorrect identification of cTnI levels as abnormal, a cTnI reference interval should take into consideration sex, age, and time of blood sampling of the individuals. Further studies should be performed in populations at risk of myocardial infarction to evaluate any potential variations that may be relevant for clinical decision making.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.03.1628.

Authors' contributions

Dandan Li, Danchen Wang, and Ling Qiu designed the study; Dandan Li and Danying Wang analyzed the data; Jie Wu, Chaochao Ma, Pengchang Li, and Xiuzhi Guo contributed reagents, materials, and analysis tools. All authors reviewed the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available, but data may be available from the corresponding author upon reasonable request.

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