Is Electrocardiogram Helpful in Predicting Positive Troponin I Due to Anthracycline Cardiotoxicity?

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Abstract

OBJECTIVE

Screening patients on anthracycline-based chemotherapy regimens for the development of cardiotoxicity can be resource intensive. We therefore studied various traditional ECG parameters to correlate and possibly predict the development of positive Troponin I as a surrogate marker of anthracycline-induced cardiotoxicity.

METHODS

This was a single centre prospective cohort study done between Januray 2014 to January 2016. Baseline ECG was compared with ECG done after chemotherapy and different parameters were compared. Patients were divided into Troponin I positve and negative groups based on the test performed at the end of chemotherapy using a cut-off of 0.06 ng/dL.

RESULTS

Of the 160 patients studied, 131 (81.9%) were Troponin I negative (TnI-) and 29 (18.1%) were positive (TnI+). Breast cancer accounted for 79% of all cancers in this study. Many ECG parameters where compared between TnI- and TnI+ groups. Of them, TP and TP/QT showed a significant decrease in the TnI+ group. The mean (95% CI) TP in TnI- group was 162.9 (145.4, 180.4) and in TnI+ groups was 117.9 (89, 146.8), p = 0.03. Corresponding values for TP/QT were 0.47 (0.42, 0.51) and 0.35 (0.27, 0.42), p = 0.02. These changes were not significant in multivariate analysis and likely reflected the different mean heart rates (HR) in both the groups as shown by Pearson's partial correlation which was run with HR as confounder.

CONCLUSIONS

ECG parameters like QTcH, TP and TP/QT are not helpful in predicting Troponin I elevations in patients on anthracycline-based chemotherapy. Further studies based on hard endpoints like clinical systolic dysfunction occuring at one year would give better information on their utility.

Key Messages

Little is known regarding the ECG correlates and their role in predicting elevations in Troponin I among patients on anthracyclines. This study was an attempt to triage this group of patients who would require closer monitoring and detailed evaluation using advanced imaging modalities. Further studies based on more robust endpoints like the development of systolic dysfunction would be needed to understand a role for ECG in this setting clearly.

Introduction

Anthracyclines have been the mainstay in the treatment of many malignancies, especially breast cancer, lymphomas, sarcomas and various childhood malignancies. Anthracycline-induced cardiotoxicity has been well documented at doses exceeding 550 mg/m^2 leading to recommendations not to exceed therapeutic doses above 400–450 mg/m^2.[17, 21] Reducing the cumulative doses brings down the incidence of cardiotoxicity, but the risk persists. The current incidence of clinical heart failure due to anthracycline cardiotoxicity is 1–5%, and asymptomatic cardiac dysfunction is 5–20%.[10, 11] The risk increases with mediastinal radiation, advanced age (> 65 years), younger age (< 4 years), female sex, hypertension, diabetes, peripheral vascular disease, emphysema, bolus dose regimen and pre-existing coronary artery disease.[10, 20] It, however, still remains impossible to predict if a patient would develop cardiotoxicity with anthracyclines or not.

The usefulness of Troponin I as a biomarker of cardiotoxicity has been extensively researched in a metanalysis.[8] This study analysed Troponin I, Troponin T, BNP and NT-pro BNP and of all, only Troponin I, measured at the end of chemotherapy, showed a significant and strong association with future development of cardiotoxicity with 85% positive predictive value and 99% negative predictive value for the development of clinical heart failure at one year. However, the use of Troponin to predict the development of cardiotoxicity merely predicts the inevitable as Troponin itself is a marker of myocardial necrosis.[9] Treatment with enalapril and carvedilol has proven to be beneficial in modifying the disease course of cardiotoxicity in high-risk patients identified on the basis of Troponin I.[6] A different predictor of cardiotoxicity based on ECG would go a long way to better triage such patients.

ECG could help in predicting cardiotoxicity even before irreversible damage to cardiac myocytes has occurred. Studies done on patients receiving myeloablative chemotherapy have shown that QTc was a predictor for cardiac dysfunction.[2] The novel concept of ischemic constellation[14] rather than cascade further supports the fact that ECG could act as a useful tool to predate irreversible myocardial injury. This concept would also hold for myocardial injury due to oxidative stress, as seen during chemotherapy.[9] Moreover, there is a paucity of data regarding the diastolic correlates of ECG like TP segment and PQ intervals among patients undergoing anthracycline-based chemotherapy, which may show changes corresponding to echocardiography derived parameters of diastolic dysfunction.[16]

Cost-effectiveness studies performed in cancer survivors[19, 24, 25] suggest that although newer imaging modalities like global longitudinal strain, speckle tracking etc. have a greater sensitivity in picking up subtle changes in cardiac function, it may not be suitable for mass implementation. This calls for a need to investigate cheaper and readily available imaging modalities to help identify patients who would require closer monitoring for the development of chemotherapy-induced cardiotoxicity. This study aims to identify ECG predictors of positive Troponin in patients undergoing anthracycline-based chemotherapy.

Methods

Study population

This was a single-centre, prospective, cohort study conducted at Government Medical College Hospital, Kozhikode, Kerala, India, between January 2014 and January 2016. The study was approved by the Institutional Ethics Committee, Government Medical College, Kozhikode, Institutional Ethics Committee, Government Medical College, Kozhikode, Reg No: ECR/395/Inst./KL/2013 having approval number GMCKKD/RP 2016/IEC/76. The trial was overseen by the head of the department of cardiology. All data generated or analysed during this study are included in this published article in a Supplementary file.

All patients > 18 years of age, with malignancy and planned to be put on a doxorubicin-based chemotherapy regimen, were screened for eligibility. Those who had an ejection fraction of < 55%, moderate to severe valvular heart disease based on AHA/ACC guidelines[15] or ST-T abnormalities that could pose difficulty in measuring various intervals on baseline ECG like bundle branch blocks and AV dissociation were excluded from the study. The presence of diabetes and hypertension was ascertained based on history. Previous myocardial infarction (MI) was defined as a documented acute coronary syndrome in past or ECG evidence of pathological Q waves.[16] Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Measurement of ECG parameters

ECG was recorded using the EdanUSA SE-1200 (EdanUSA, San Diego, CA, USA) machine and was scanned to a computer as an image file (.jpeg) at 600 dpi. The various measurements taken were QT interval, RR interval, TP segment, and PQ interval (Fig. 1). These were measured using the Cardio Calipers v3.3 software (Iconico, Inc., Philadelphia, PA, USA). Heart rate (HR) was calculated from the RR interval measured in milliseconds by the formula 60,000 ÷ RR. For QT measurement, the lead showing the longest QT was taken. Lead II was used to measure TP and PQ as p waves are best delineated in this lead.[15] QTc was calculated using the Hodges formula (QTcH).[13] Two parameters, TP/QT and PQ/QT were derived to adjust TP and PQ for heart rate. QT was arbitrarily chosen as TP, PQ, and QT all change in the same direction with changes in heart rate.

Troponin I assay

Troponin I (TnI) was measured on the Beckman Coulter machine using the Access AccuTnI 3 assay. Based on the validation studies for this assay, the manufacturer claimed 99th percentile of the upper reference level was 0.04 ng/ml. At this cut-off, the total imprecision was < 14%. A value of ≥ 0.06 ng/ml had an imprecision of < 10% and was used in this study to define a positive test[4] as was used in previous studies.[8]

Data collection

Patients or the public were not directly involved in the design of the study or the collection of data. The patients were asked to report to us at specified intervals, and the institution itself did data collection. Once the patient fulfilled the criteria for enrolment, baseline demographic data collection, and risk factors assessment was done. A baseline ECG was taken, after which the patients were instructed to begin chemotherapy. At the end of their final cycle of chemotherapy, ECG was repeated, and blood samples

were collected to test for Troponin I. The study population was then divided into two groups based on their Troponin I results. They were considered Troponin I positive (TnI+) or Troponin I negative (TnI-) based on a cut-off of 0.06 ng/ml. The ECG measurements obtained were then compared between the two groups, as were the change in parameters from baseline to post-chemotherapy.

Statistical analysis

Statistical analysis was performed using SPSS v26.0 (Chicago, IL, USA). Normality of data was assessed using histograms and Normal Q-Q plots. All variables were evaluated separately in Troponin I negative and positive groups. Categorical variables were presented as frequencies in each group, and their inter-group differences were assessed using the chi-square test or Fischer's exact test depending on the variable. The normality of data was confirmed using skewness and kurtosis, as well as histograms and Normal Q-Q plots. Continuous variables were presented as mean (95% confidence intervals). The difference in means of continuous variables between groups was compared using the independent samples t-test. For assessing the difference scores of ECG parameters from baseline to post-chemotherapy, paired t-test was used. For those variables showing statistically significant differences, multivariate analysis using binary logistic regression was done. A cut-off ≤ 0.05 was used for alpha error. Also, Pearson's correlation was done on Troponin I values with significant post-chemotherapy variables followed by Pearson's partial correlation to eliminate confounders.

Results

A total of 240 patients who were referred to the cardiology department for pre-chemotherapy fitness were screened and found to be eligible. Of them, 32 patients were excluded, and another 48 patients were lost to follow-up. Hence, a total of 160 patients completed the study and were used for this analysis. There were 29 patients (18.1%) who were TnI + and 106 patients (81.9%) were TnI- (Fig. 2). Baseline characteristics (Table 1) were comparable between the two groups. The mean age in both groups was similar, 52.8 (50.7, 54.8) in TnI- group and 51.5 (47.4, 55.5) in TnI + group, $p = 0.59$. Breast cancer accounted for more than 3/4th of all cancers in both groups, and expectedly, females predominated the study population accounting for 86.3% of TnI- group and 93.1% of TnI + group. Other malignancies encountered in the remainder included bladder cancer, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, sarcoma, and stomach cancer. The risk factors considered were hypertension, diabetes, and previous myocardial infarction, and none of them showed a difference between groups. Baseline ECG parameters were also comparable between groups (Table 2).

Table 1
Comparison of baseline categorical variables between Troponin I negative and positive groups

Variable	Subgroups	% in Troponin Negative	% in Troponin Positive	*p* value
Gender	Male	13.7	6.9	0.53
	Female	86.3	93.1	
Malignancy	Bladder	0.8	0	0.7
	Breast	78.6	82.8	
	Hodgkin's lymphoma	2.3	0	
	Non-Hodgkin's lymphoma	5.3	10.3	
	Sarcoma	4.6	6.9	
	Stomach	6.9	0	
	Others	0.8	0	
Hypertension	Yes	30.5	27.7	0.75
	No	69.5	72.4	
Diabetes	Yes	16	17.2	0.53
	No	84	82.8	
Myocardial infarction	Yes	2.3	3.4	0.55
	No	97.7	96.6	

Table 2
Comparison of baseline characteristics between Troponin I negative and positive groups

	Troponin Negative		Troponin Positive		
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**	**p value**
Age	52.8	50.7, 54.8	51.5	47.4, 55.5	0.59
QT	352.8	347, 358.6	340.7	329.5, 351.9	0.08
HR	88	85.3, 90.6	93.6	88.2, 98.9	0.07
QTcH	401.7	398, 405.4	399.4	393, 405.8	0.60
TP	204.2	185.7, 223.2	170.3	137.4, 203.3	0.12
TP/QT	0.56	0.52, 0.61	0.49	0.40, 0.58	0.16
PQ	152.5	147.3, 157.7	143.5	133, 153.9	0.14
PQ/QT	0.44	0.42, 0.45	0.43	0.39, 0.46	0.59

Post-chemotherapy ECG showed a statistically significant difference in three variables between groups (Table 3). Heart rate, TP, and TP/QT had a significant difference in means. Other parameters (QT, QTcH, PQ, and PQ/QT) were not different between groups. Mean HR in TnI- groups was 97.2 (94.3, 100) and in TnI + group was 106.4 (99.8, 113.1), $p < 0.01$. Mean TP segment in TnI- group was 162.9 (145.4, 180.4) and in TnI + group was 117.9 (89, 146.8), $p = 0.03$ and TP/QT in the respective groups were 0.47 (0.42, 0.51) and 0.35 (0.27, 0.42), $p = 0.02$.

Table 3. Comparison of post-chemotherapy ECG characteristics between Troponin I negative and positive groups

	Troponin Negative		Troponin Positive		*p* value
Parameter	**Mean**	**95% CI**	**Mean**	**95% CI**	
QT	341.4	336.2, 346.6	332.4	322, 342.9	0.15
HR	97.2	94.3, 100	106.4	99.8, 113.1	**<0.01**
QTcH	405.9	401.9, 409.9	413.7	404.9, 422.4	0.11
TP	162.9	145.4, 180.4	117.9	89, 146.8	**0.03**
TP/QT	0.47	0.42, 0.51	0.35	0.27, 0.42	**0.02**
PQ	146	140.7, 151.2	144.1	134.7, 153.5	0.85
PQ/QT	0.44	0.41, 0.46	0.44	0.40, 0.47	0.72

Change in the baseline values of ECG parameters after chemotherapy were assessed using paired samples t-test. All parameters except HR and PQ/QT showed a statistically significant change from baseline (Table 4). Mean difference of QT in TnI- group was 11.5 (5.7, 17.2; $p < 0.01$), HR was − 9.2 (-11.8,

-6.7, $p < 0.01$), TP was 41.5 (26.4, 56.7, $p < 0.01$), TP/QT was 0.1 (0.06, 0.14, $p < 0.01$) and PQ was 6.6 (0.9, 12.2, $p = 0.02$). In the TnI + group, mean HR difference was − 12.9 (-18.9, -6.8, $p < 0.01$), QTcH was − 14.2 (-25.3, -3.1, $p < 0.01$), TP was 52.4 (19.5, 85.4, $p < 0.01$) and TP/QT was 0.14 (0.05, 0.23, $p < 0.01$). QT, PQ, and PQ/QT did not show a significant change in mean. Difference scores of all the ECG parameters were also calculated and compared between groups to see if this change in parameters was significant. To calculate the difference-scores, post-chemotherapy scores were subtracted from the baseline scores, and independent samples t-test was performed. It did not show a statistically significant difference in any of the measured variables (Table 4). Multivariate analysis was performed on ECG variables QTcH, TP, TP/QT, and PQ, and none of the variables showed a significant association with positive Troponin test.

Table 4. Change in ECG parameters from baseline to post-chemo in Troponin negative and positive groups

	Troponin Negative			Troponin Positive			*p* value for diff between groups
Parameter	**Mean diff**	**95% CI**	***p* value**	**Mean diff**	**95% CI**	***p* value**	
QT	11.5	5.7, 17.2	**<0.01**	8.3	-3.1, 19.6	0.15	0.64
HR	-9.2	-11.8, -6.7	**<0.01**	-12.9	-18.9, -6.8	**<0.01**	0.24
QTcH	-4.2	-9.1, 0.7	0.09	-14.2	-25.3, -3.1	**<0.01**	0.09
TP	41.5	26.4, 56.7	**<0.01**	52.4	19.5, 85.4	**<0.01**	0.55
TP/QT	0.1	0.06, 0.14	**<0.01**	0.14	0.05, 0.23	**<0.01**	0.34
PQ	6.6	0.9, 12.2	**0.02**	-0.7	-13, 11.6	0.91	0.28
PQ/QT	-0.01	-0.02, 0.02	0.98	-0.1	-0.05, 0.03	0.57	0.46

There was a linear correlation between HR, TP, TP/QT, and Troponin I values. However, when Pearson's partial correlation was run for controlling HR as a confounder, the relationship of both TP and TP/QT with Troponin I ceased to be statistically significant ($p = 0.35$).

Discussion

This is the largest single centre data available on ECG and Troponin I elevations in patients on anthracyclines. Breast cancer was the predominant malignancy for which doxorubicin was used. Our study demonstrates that HR, TP, and TP/QT showed a significant difference in Troponin positive group on univariate analysis, but this did not hold in multivariate analysis. Besides, the changes in TP and TP/QT were likely related to the changes in mean HR between groups. Other ECG parameters did not show any difference between groups, nor was a change from baseline significant in any of the parameters assessed.

Ever since animal models demonstrated a prolongation of QT interval with the use of anthracyclines,[1] QTc assessment had attracted a lot of research in its role in predicting not only arrhythmias but also heart failure. Association with heart failure was suggested by a study done in 2003 in patients

undergoing myeloablative chemotherapy.[2] Since then, numerous small studies[7, 12, 23] in patients on anthracyclines have documented a prolongation of QTc, but their clinical significance or their association with cardiotoxicity has not been ascertained. Our study too, did show a significant change in QTcH (δQTcH) from baseline in the TnI + group compared to the TnI- group. This difference was not statistically different between groups. Also, the mean δQTcH in the TnI + group was − 14.2 (-25.3, -3.1) msec, which is too small a change to have any practical application. This makes δQTcH a weak parameter to identify TnI + patients.

The diastolic ECG parameters measured in this study (PQ, PQ/QT, TP and TP/QT) have never been previously studied in the context of anthracycline cardiotoxicity to the best of our knowledge. PQ and PQ/QT did not show any difference between groups, but both TP and TP/QT showed a significant difference. There was an average drop of approximately 50 ms in the TnI + group, which was statistically significant ($p = 0.03$). With the development of diastolic dysfunction, the TP segment was expected to prolong. But in the present study, a reduction in TP and TP/QT was observed among those with positive Troponin I. This might probably be because diastolic dysfunction might not have been present and direct subclinical oxidative damage could have released Troponin I into the blood. This was indeed confirmed in studies that evaluated diastolic function on echocardiography. In a study that evaluated changes in E/A ratio, IVRT, and deceleration time in patients undergoing chemotherapy with anthracyclines, it was not found to be associated with future development of cardiotoxicity.[22] Another small study of 51 patients showed that diastolic dysfunction on echocardiography developed during chemotherapy with a significant reduction in e' and E/e'. This change was not correlated with Troponin I or ejection fraction, and thus it had limited ability to identify patients at risk of developing cardiotoxicity.[3] These studies prove that diastolic dysfunction may not necessarily be part of the spectrum of chemotherapy-induced cardiotoxicity.

TP interval is known to change with heart rate and have an inverse relationship. It is likely, in our study, that the change in the TP segment duration and TP/QT observed is merely a function of different mean HR in both groups. Both groups showed a significant decrease in mean heart rate from baseline with a reduction of 9.2 (11.8, 6.7, $p < 0.01$) bpm in the TnI- group and 12.9 (18.9, 6.8, $p < 0.01$). Although there was a numerically greater reduction in HR in those with positive Troponin I, this difference was not statistically significant, $p = 0.24$. This association was conclusively proven by Pearson's partial correlation run on the said variables controlling for HR. This further demonstrates that TP/QT is not a reliable way to control the TP segment duration for HR.

Limitations

Although Troponin I test done at the end of chemotherapy has a high negative predictive value, it is only a marker of high-risk patients. Its elevation does not always predict the development of clinically significant LV dysfunction with only 85% positive predictive value.[8] Our study was conducted to find ways to predict the development of elevated Troponin I. Testing ECG against hard endpoints, like systolic dysfunction, over a year's follow up would have provided more conclusive evidence regarding a

correlation. An interim analysis of ECG would have helped in understanding the temporal changes occurring in these parameters. It would have identified subtle changes that predate the occurrence of positive Troponin I itself.

Conclusion

None of the studied ECG parameters used in this study are useful to identify patients at risk of developing anthracycline-induced cardiotoxicity. HR, TP, and TP/QT showed a significant reduction in Troponin I positive patients on univariate analysis, but it did not prove significant in multivariate analysis. Also, the differences observed in TP and TP/QT between groups was merely a reflection of different mean heart rates in the two Troponin I groups.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee, Government Medical College, Kozhikode, Institutional Ethics Committee, Government Medical College, Kozhikode, Reg No: ECR/395/Inst./KL/2013 having approval number GMCKKD/RP 2016/IEC/76. The trial was overseen by the head of the department of cardiology.

Consent for publication

Consent was obtained from the study participants prior to inclusion.

Availability of data and materials

All data generated or analysed during this study are included in this published article in a Supplementary file.

Competing interests

None of the authors have any competing interests to declare.

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No funding was obtained for this study.

Authors’ contributions

Dr. Kader Muneer and Dr. Ajayakumar T were my guides and were instrumental in designing and planning my study. Dr. Gajendra Dubey and Dr. Kamal Sharma guided me in the analysis of my study and performing relevant statistics. Dr. Sajeev C. G and Dr. M. N. Krishnan are the current and former heads of the department of cardiology and provided the final approval for publication of the study.

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Figures

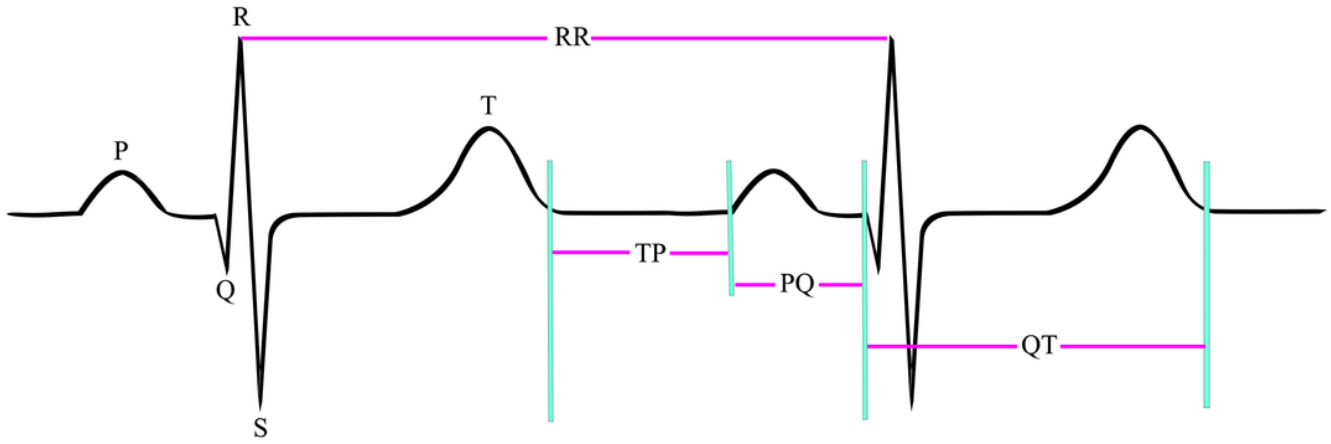

Figure 1

Various measurements of ECG segments and intervals taken for this study

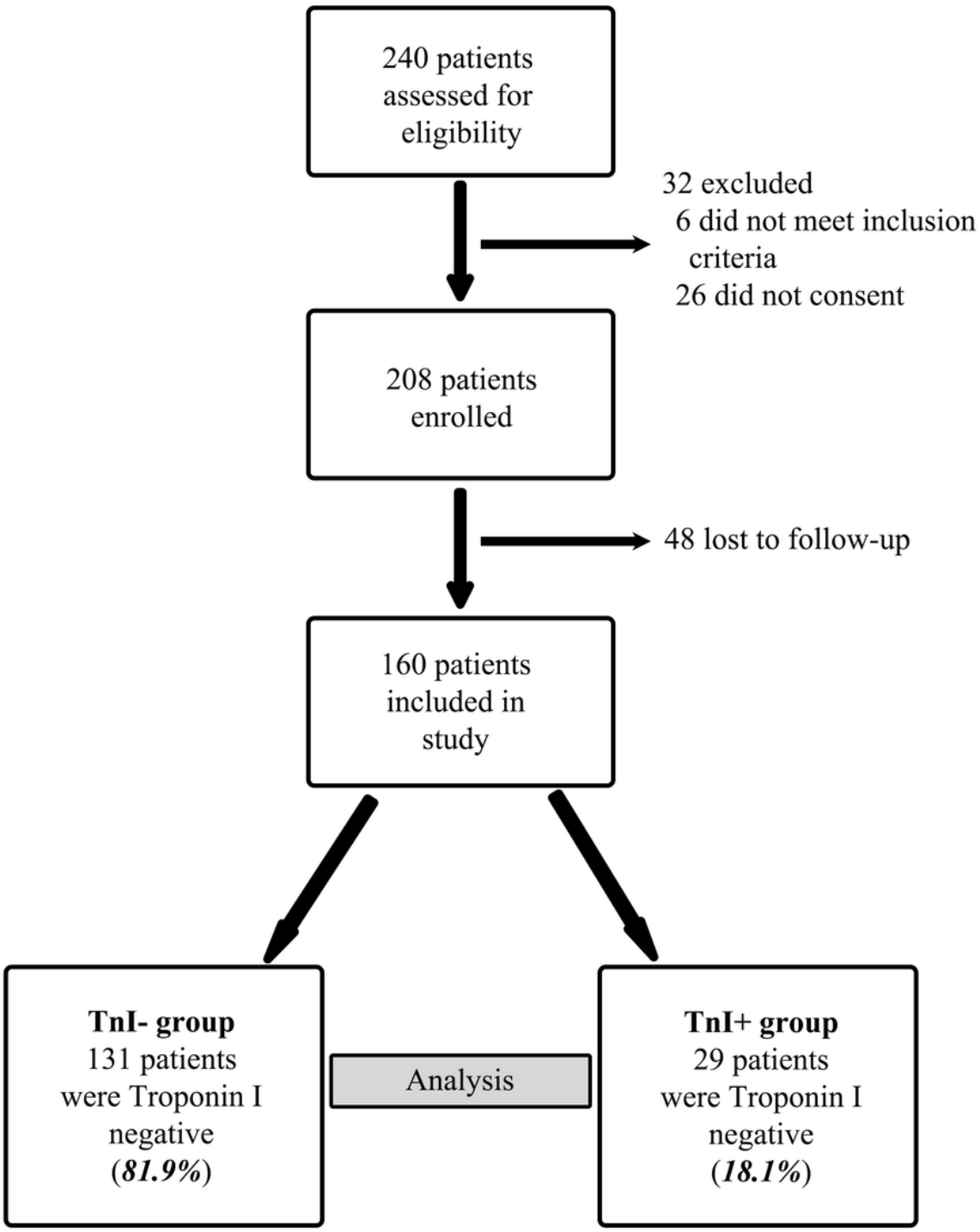

Figure 2

CONSORT diagram

Supplementary Files

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- Chemotherapystudyoutliersremoved.xlsx