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Evaluating high-sensitivity cardiac troponin I for early detection of treatment-related cardiotoxicity in HER2-positive breast cancer patients

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Background: Trastuzumab-related cardiotoxicity is a common adverse effect of HER2-positive breast cancer treatment, especially when combined with anthracyclines. However, to date, no definitive prognostic markers have been found to predict trastuzumab-related cardiotoxicity.

Methods: Patients diagnosed with HER2-positive breast cancer, scheduled to receive anthracyclines followed by 12 months of trastuzumab or with pertuzumab, were prospectively followed up for 27 months. Measurements of left ventricular ejection fraction LVEF, high-sesitivity troponin I hs-Tn I, and a full cardiac examination were performed at baseline, after anthracycline treatment, and after four cycles of anti-HER2 agents. Subsequently, LVEF measurement and full cardiac examination were conducted every 3 months until the end of the follow-up. Cardiotoxicity was defined as an absolute decrease in LVEF of ≥15%, or a drop in LVEF of ≥10% from the baseline to <50%.

Results: Among 78 patients, cardiotoxicity occurred in 13 (16.7%). A higher risk of cardiotoxicity was linked to hs-Tn I measured after four cycles of anti-HER2 agents ($P < 0.001$), with a significant cutoff of >84 ng/L. No short-term effects of the anthracycline agents (doxorubicin or epirubicin), were found. However, there was a slightly higher tendency to develop cardiotoxicity ($P = 0.046$) in patients treated with trastuzumab plus pertuzumab.

Conclusion: Hs-Tn I measured after four cycles of trastuzumab in HER2-positive breast cancer patients could be an important predictor of cardiotoxicity induced by chemotherapy followed by anti-HER2 agents, particularly in the first year post-treatment, with a different cutoff value than that used in other cardiac conditions.

Keywords: anthracycline, cardiotoxicity, HER2+ breast cancer, trastuzumab, troponin I

Introduction

Approximately, 15% to 30% of breast cancer (BC) patients exhibit overexpression of human epidermal growth factor receptor 2 (HER2), which is associated with a poor prognosis and a high tendency for early metastasis[1]. However, an unexpected adverse effect of cardiotoxicity has followed the treatment regimen, which was asymptomatic in most cases[2]. The reported incidence of trastuzumab-related cardiotoxicity (TRC) is about 3% to 7% in monotherapy, increasing to 27% in combination therapy with anthracycline[3]. To date, there is no reliable biomarker that can predict TRC. This study aims to evaluate whether the high-sensitivity cardiac troponin I (hs-Tn I), measured at early phase of HER2-positive (HER2+) BC therapy, can reliably predict the occurrence of TRC over 1 year after completing the full treatment regimen.

Patients and methods

Study population and study design

In this prospective cohort study, both echocardiographic and laboratories investigators were blinded. We considered all consecutive HER2+ BC patients from 01/01/2021 to 01/06/2021. We excluded the patients with a history of cardiovascular diseases, diabetes mellitus, hyperlipidemia, kidney diseases, and stage IV breast cancer.

Study protocol

All eligible patients underwent a full echocardiographic assessment and a cardiac hs-Tn I measurement at baseline when BC diagnosis was made, after four anthracyclines cycles, and then after four cycles of anti-HER2 agents. Patients were followed up clinically and via echocardiography until they completed the full treatment regimen, and then for an additional 12 months after completing the course, to monitor for the development of any cardiovascular complication during this period.

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Cardiotoxicity definition

There are various definitions according to different cardio-oncology studies, committees or societies, which are based on LVEF measurements. Therefore, we defined cardiotoxicity as a drop in LVEF ≥10% from the baseline measurement, with a decrease of LVEF to a value less than 50%, which is simple and compatible with the normal/borderline normal range recommendations, or an absolute decrease of LVEF of ≥15%.

Primary endpoint

The primary endpoint of the study was the occurrence of systolic heart failure, diagnosed by an absolute decrease in left ventricular ejection fraction (LVEF) of ≥15%, or a drop in LVEF of ≥10% with a resultant LVEF of <50%. Treatment was temporarily halted when any of the above criteria were met, or when the patients developed acute cardiac symptoms regardless to LVEF, and reassessment was conducted 1–3 months later to determine the feasibility of continuing treatment.

Secondary endpoint

The secondary endpoint of the study was the occurrence of any other cardiac event.

Imaging study

The LVEF was calculated from the apical four- and two-chamber views using a modified Simpson's biplane method. The transthoracic echocardiography study was conducted using (SIEMENS ACUSON X300), and all patients were imaged by the same machine, but by different echocardiographers who were blinded to other measurements and to the purpose of the imaging study.

Laboratory methods

Blood samples were collected and centrifuged for at least 20 minutes, and the plasma was then separated. hs-Tn I concentrations were determined by ELISA method. All positive samples were tested twice by two different blinded examiners for confirmation.

Statistical analysis

IBM SPSS Statistics 25.0 software was utilized for statistical analysis of data. A logistic regression model was utilized to analyze both univariate and multivariate cardiotoxicity associated with anti-HER2 targeted therapy in BC, as well as the prognostic significance of hs-Tn I. The receiver operating characteristic (ROC) curve was applied to predict the diagnostic value of hs-Tn I for cardiotoxicity associated with anti-HER2 targeted therapy in BC. All statistical results were considered significant at P <0.05.

Exposure to chemotherapy and anti-HER2 agents

All patients received an anthracycline agent, either doxorubicin at a dosage of 60 mg/m^2 or epirubicin at 100 mg/m^2, alongside cyclophosphamide at 600 mg/m^2, every 21 days, for a total of four cycles. This regimen was followed by taxane and anti-HER2 agents.

Patients were either given trastuzumab at an initial loading dose of 8 mg/kg, followed by a dose of 6 mg/kg every 21 days for 1 year, with or without pertuzumab at a loading dose of 840 mg, followed a dose of 420 mg every 21 days.

Study points definitions

We delineated five main phases for the study, from phase 0, at baseline, to phase 4 at the end of the follow-up or the occurrence of cardiotoxicity (Fig. 1).

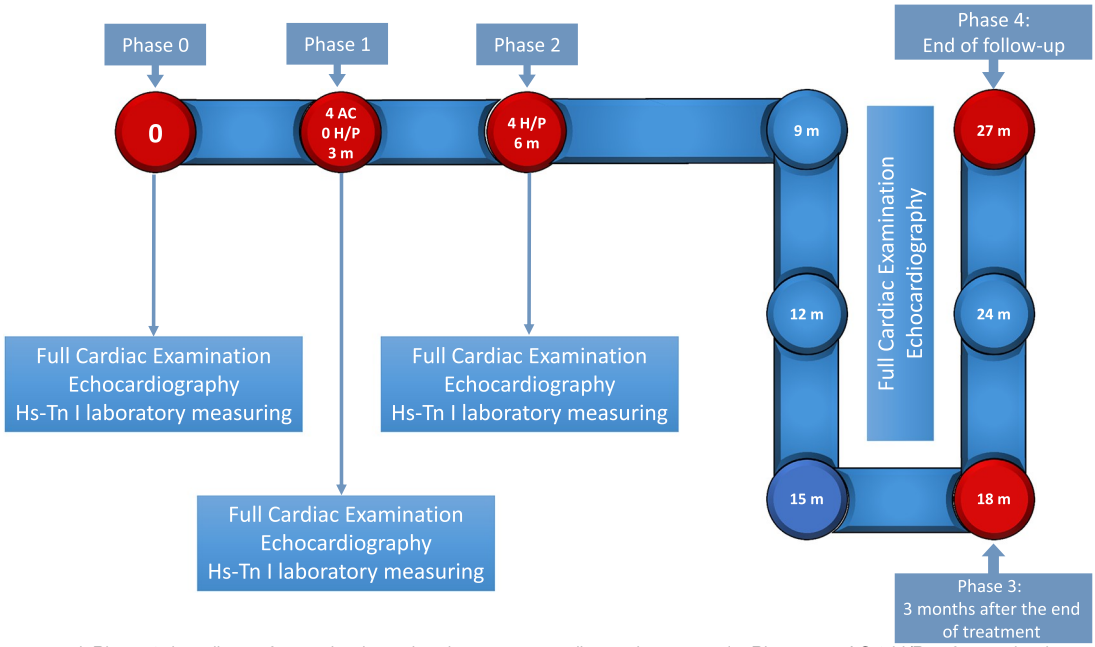

Figure 1. Study protocol. Phase 0: baseline; refers to the time when breast cancer diagnosis was made. Phase 1: 4 AC 0 H/P: refers to the time when the patient ended the four cycles of anthracyclines before starting the anti-HER2 regimen (AC: anthracyclines; H: trastuzumab; P: pertuzumab). Phase 2: after four cycles of anti-HER2 agents. Phase 3: 3 months after the end of the treatment: after 18 months of starting the full regimen. Phase 4: End of follow-up: after 27 months; the time point after ending the full treatment course.

Ethics committee approval

The authors declare that the study adhered to the principles outlined in the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects." Moreover, all participants in the study provided written informed consent.

Results

A total of 97 patients diagnosed with HER2+ BC were enrolled, 78 patients were completed the study (Fig. 2, Table 1).

EF changing during all study points

The average decline of LVEF has significantly changed during the study phases (Fig. 3). The overall change of LVEF over all the study phases among the two patients' groups (cardiotoxicity, no cardiotoxicity) is declared in Figure 4.

Cardiotoxicity and other cardiovascular events

Twenty-eight patients (35.9%) developed a cardiac event; 13 patients (16.7%) developed a cardiotoxicity, as it is described in (Table 2), and 15 patients developed a cardiac event other than the cardiotoxicity (Table 3).

Cardiac high-sensitivity troponin I (hs-Tn I) values measuring

The concentrations of hs-Tn I obviously increased during the first three phases (Table 4). Hs-Tn I could be an important prognostic marker for the HER2+ BC treatment-related cardiac complications. We found a significant predictive value of hs-Tn I after four cycles of trastuzumab, for the development of cardiotoxicity ($P < 0.001$), and a statistical importance for the development of other cardiac events ($P = 0.002$) (Table 5).

Roc curve, cutoff points, and risk values

We found that the hs-Tn I values of >84 ng/L after four cycles of anti-HER2 agents could be an important cutoff point for the high risk of cardiotoxicity development (Table 6A, Fig. 5A). Furthermore, hs-Tn I values >47 ng/L after four cycles of anthracyclines could be itself an important cutoff point for the high risk of cardiotoxicity development (Table 6B, Fig. 5B), however, it is uncertain whether this statistical significance pertains solely to the effect of anthracycline or the combined effect of anthracycline and anti-HER2 treatment.

Type of anthracycline and of anti-HER2 agent on developing the cardiotoxicity

In our study, neither the anthracycline agent, doxorubicin nor epirubicin, had an effect on the development of cardiotoxicity. Nevertheless, patients who treated with dual anti-HER2 agents, trastuzumab plus pertuzumab, exhibited a slightly higher tendency to develop cardiotoxicity ($P = 0.046$, OR = 4.37).

Discussion

The use of anti-HER2 agents, especially trastuzumab, which is the first anti-HER2 approved by FDA, has a vital role against cancer progress and recurrence, and significantly improved survival in patients either with early-stage BC or with metastatic setting[1,4]. However, increased concerns have begun when an unexpected incidence of the cardiac injury had started, particularly when using trastuzumab in combination with anthracyclines.

In this prospective study, no patient developed a cardiotoxicity during the treatment. Even though, we cannot consider that the cardiac toxicity has occurred primarily because of trastuzumab.

A meta-analysis of 9117 patients declared that the treatment with trastuzumab increased the cardiotoxicity by 2.45-fold in comparison with the treatment without it (95% CI: 1.89–3.16)[5].

TRC is not dosage-dependent, and it is reversible by discontinuing the agent and treating the cardiac dysfunction[6]. However, it is still difficult to differentiate the main cause of cardiotoxicity in patients receiving both anthracycline and trastuzumab[6]. Increased levels of troponin at the end of anthracycline cycles and before trastuzumab starts may refer to a high risk of cardiac dysfunction[7]. In this study, we have observed that the cardiotoxicity associated with elevated hs-Tn I was more statistically significant in patients with elevated troponin

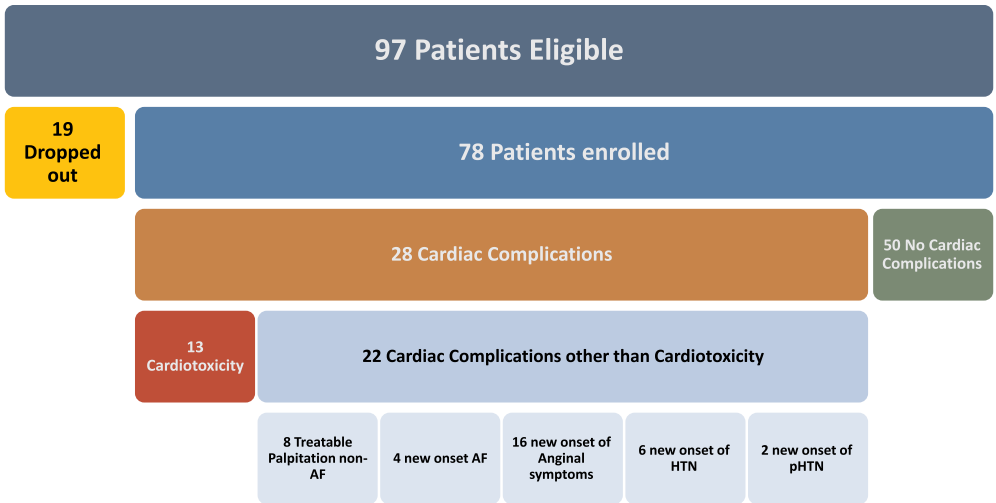

Figure 2. Study population. AF, atiral fibrillation, HTN, hypertension, pHTN, pulmonary hypertension.

Table 1

All characteristics of patients enrolled in the study

	Num	%	% of cardiotoxicity	*P* value
Type of therapy				
Adjuvant	64	82.1	15.6	>0.05
Neoadjuvant	14	17.9	21.4	
Position of tumor				
Right	37	47.4	10.8	>0.05
Left	39	50	23.1	
Bilateral	2	2.6	0	
Stage				
IA	4	5.1	0	>0.05
IB	2	2.6	0	
IC	2	2.6	0	
IIA	28	35.9	14.3	
IIB	14	17.9	14.3	
IIC	2	2.6	0	
IIIA	18	23.1	27.8	
IIIB	4	5.1	0	
IIIC	4	5.1	50	
Intraductal carcinoma	64	82	20.6	>0.05
Intraluminal carcinoma	14	18	0	
Hormonal receptors				
ER+/PR–	9	12	0	>0.05
ER–/PR+	4	5	75	0.014
All ER+	28	35.9	14.3	>0.05
All PR+	23	29.4	30.4	0.042
ER–/PR–	46	58.9	13	>0.05
ER+/PR+	19	24.3	21.1	>0.05
Ki67				
≤5%	9	11.5	0	>0.05
6%–29%	37	47.4	21.6	
≥30	32	41	15.6	
Anthracyclines				
Doxorubicin	58	74.4	22.4	>0.05
Epirubicin	20	25.6	30	
Anti-HER2 agents				
Trastuzumab monotherapy	68	83.9	21	
Dual therapy (trastuzumab + pertuzumab)	10	16.1	40	0.046
Age (mean)				
52 ± 9.3 y			13 patients (51 ± 9.7)	>0.05
BSA (mean)				
1.6 ± 0.18 m^2			13 patients (1.6 ± 0.2)	>0.05

ER, estrogen; PR, progesterone.

after anthracycline, but not in those with normal levels of troponin after anthracycline, although the cardiotoxicity was clinically important in the two groups. According to Mokuyasu *et al*, moreover, only patients treated with both anthracyclines and trastuzumab or anthracyclines alone, have shown high levels of Tn I compared to patients only treated with trastuzumab without anthracyclines[8]. Although all our patients received a treatment of both anthracycline and anti-HER2, we could agree with what Mokuyasu *et al*, concluded that the anthracycline, but not trastuzumab, might cause a direct cardiomyocytes necrosis[8]. It seems that trastuzumab exacerbates the anthracyclines effect and makes the cardiomyocytes more susceptible to anthracycline-related cardiac injury.

When investigating troponin as a biomarker for anthracycline-related cardiotoxicity, clinical studies demonstrated that the elevation of troponin is accompanied by 7-fold increased risk for LV dysfunction[9]. However, Troponin I, as a biomarker for TRC, and another non-anthracycline-related cardiotoxicity, is still being investigated.

It is known that elevation of cardiac troponin refers to myocardial necrosis. Moreover, the high-sensitivity cardiac troponin techniques allow for measuring of very low concentrations of troponin in multiple pathophysiological conditions such as heart failure[10].

Because of concomitant treatment of trastuzumab following the anthracycline cycles, biomarkers values are sometimes confused, and that depends on different factors such as the biomarkers that were being chosen to be studied, timing of measuring these biomarkers, and the follow up strategies.

However, hs-Tn is considered to be one of the most reliable biomarkers that could early detect the chemotherapy-induced cardiotoxicity[11].

Different timing of elevated hs-Tn I have been discussed in multiple studies. Investigating troponin at different time points made the results much more complicated to be interpreted in the same way. Besides that, different studies have demonstrated a relationship between increased troponin levels during trastuzumab treatment and LVEF decreased, especially when concomitant with anthracyclines[12,13]. In contrast, other studies did not demonstrate any elevation of troponin during the treatment[14-16], and others could not detect any predictive importance of early troponin measuring in detecting the cardiotoxicity[17].

However, many studies could not find any predictive importance of high troponin levels, despite of the increasing of troponin preceded LVEF changes[18-20].

In our study, 32.1% of our patients had an elevated hs-Tn I >40 ng/L after the end of the anthracycline, and 73.1% of our patients had an elevated hs-Tn I >40 ng/L after four cycles of anti-HER2 treatment.

In a study of 251 BC patients treated with trastuzumab, Cardinale *et al* considered that the troponin I is the only independent predictor for TRC (HR: 22.9; 95% CI: 11.6–45.5; $P < 0.001$). In addition, positive levels of troponin I were detected in patients received the combined treatment of anthracycline and trastuzumab suggested the anthracycline-related cardiomyocytes damage which has been exacerbated by trastuzumab effects[13].

In this cohort, we could find a predictive value of hs-Tn I for cardiotoxicity, up to 1 year after the end of the treatment, both after four cycles of anthracyclines with $P = 0.001$ and after four cycles of trastuzumab with a $P = 0.001$.

Putt *et al*, also, declared a significant correlation between hs-Tn I and cardiotoxicity development in the third month of therapy but not after 15 months of therapy[21].

	Mean ± SD	Min	Max
EF1 – EF0	-3.97 ± 3.06	-13	2
EF2 – EF1	-3.74 ± 4.65	-15	5
EF2 – EF0	-7.33 ± 3.89	-16	2
End treatment EF – EF0	-9.21 ± 3.69	-19	0
End treatment EF – EF1	-5.69 ± 4.25	-18	3
End treatment EF – EF2	-0.05 ± 4.55	-12	10
End of follow up EF – EF0	-7.78 ± 4.23	-24	2
End of follow up EF – EF1	-3.86 ± 6.26	-24	8
End of follow up EF – EF2	-0.12 ± 4.6	-12	10
End of follow up EF - End treatment EF	1.83 ± 6.14	-24	10

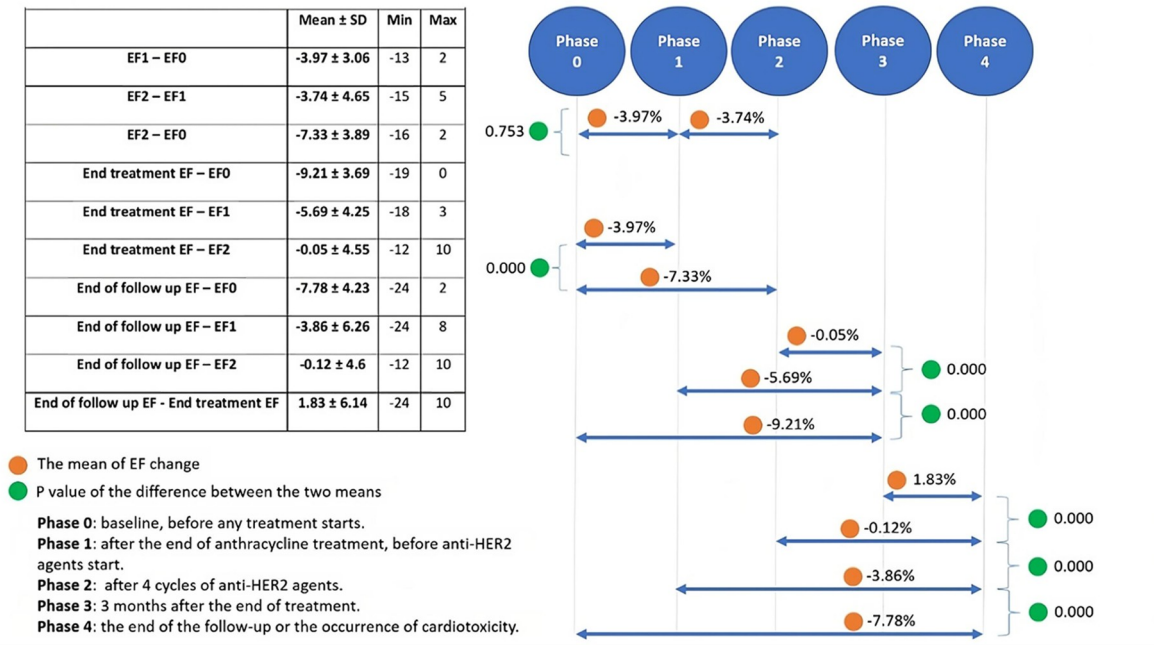

Figure 3. EF changing during all study points.

In addition, Sawaya *et al*, in two different studies, considered that the troponin I levels after 3 months of anthracyclines therapy could be a predictor of cardiotoxicity, likewise for trastuzumab where decreases of LVEF were more frequent in patients with increased troponin I. Constant elevation of troponin I at least one month after therapy was associated with a higher risk of a cardiotoxic effect than transient elevation immediately after starting of the treatment[22,23].

The reversibility of TRC is associated with troponin I levels <0.08 ng/mL[24]. In our study, moreover, we could identify a new cutoff of hs-Tn I of >47 ng/L after completion of the anthracyclines for cardiotoxicity, and another cutoff of hs-Tn I of >84 ng/L after four cycles of trastuzumab, in patients received anthracyclines followed by trastuzumab and followed up to 1 year after treatment completion.

Thus, troponin could be a good biomarker for detecting the risk of developing cancer treatment related cardiotoxicity, but it is not useful for detecting or diagnosing ongoing dysfunction post the treatment[25].

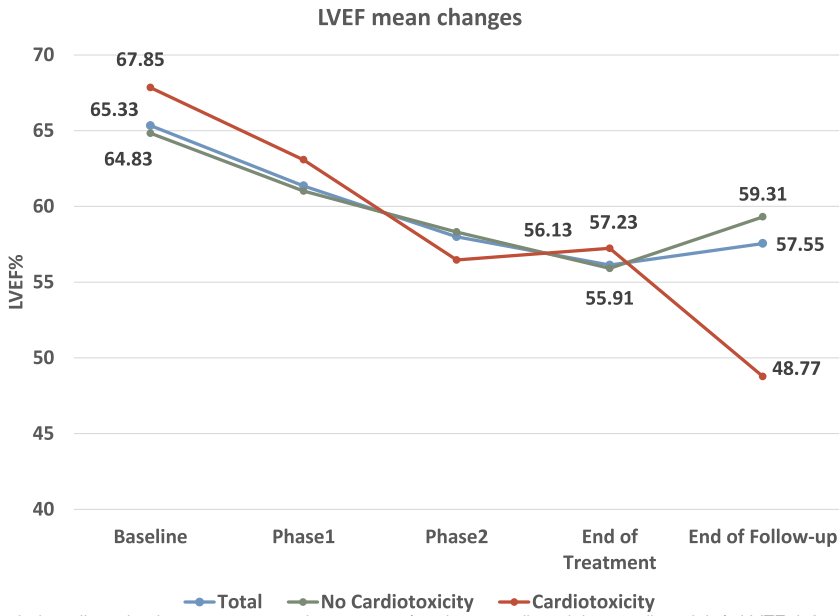

Figure 4. LVEF mean change during all study phases among patient groups (total, no cardiotoxicity, cardiotoxicity). LVEF: left ventricular ejection fraction.

Table 2

Cardiotoxicity events

In the end of treatment (after 15 months)			NYHA Class III–IV	
	Num	%	Num	%
EF decreased ≥10% below 50%	2	2.6	1	1.3
EF decreased ≥15%	1	1.3	0	0
In the end of follow-up			**NYHA Class III–IV**	
	Num	%	Num	%
EF decreased ≥10% below 50%	7	9	4	5.1
EF decreased ≥15%	3	3.8	0	0

EF, ejection fraction; NYHA, New York Heart Association

Patients who treated with dual anti-HER2 agents, trastuzumab plus pertuzumab, showed a slightly higher tendency to develop a cardiotoxicity (P = 0.046, OR = 4.37) in comparison with treatment with trastuzumab only. However, according to CLEOPATRA trial, the combined treatment of pertuzumab and trastuzumab did not rise the probability of cardiotoxicity[26], while Li Zhang *et al*, showed that patients who were treated with combined treatment of these two anti-HER2 agents have had more significant elevation in hs-Tn I in comparison with patients who received only trastuzumab, without any significant difference in the incidence of cardiotoxicity between the two groups[27].

In this study, besides cardiotoxicity, some patients developed different cardiac complications other than cardiotoxicity such as new-onset AF, non-AF palpitation requiring drug treatment for control, new-onset hypertension, new onset typical anginal symptoms, and asymptomatic increase in pulmonary hypertension measured by echocardiography. Mixed complications occurred in some patients, and some of those cardiovascular events progressed later to a cardiotoxicity in 7 patients. Further research is needed to interpret all the cardiac complications during cancer treatment and their mechanisms.

As a consequence of this study, we suggest a full clinical evaluation and a risk stratification before starting the cancer treatment (Fig. 6).

Table 3

All cardiac events occurred throughout the study

Cardiac complication and cardiotoxicity	Num	%
Need to temporary pause of anti-HER2 treatment	5	6.4
Cardiac events	28	35.9
Cardiotoxicity according to the definitions described above	13	16.7
Cardiac event other than cardiotoxicity as mentioned above	22	28.2
Cardiac events have progressed to cardiomyopathy	7	31.8 (of 22) 9 (of 78)
Treatable palpitation non-AF	8	36.4 (of 22) 10.3 (of 78)
New onset atrial fibrillation	4	18.2 (of 22) 5.1 (of 78)
New onset of anginal symptoms	16	72 (of 22) 20.5 (of 78)
New diagnosed hypertension	6	27.3 (of 22) 7.7 (of 78)
New onset pulmonary hypertension by echocardiography	2	9 (of 22) 2.6 (of 78)

AF, atrial fibrillation

Table 4

Hs-Tn I mean ± standard deviation measurements

		Hs-Tn I mean values in the first three phases		
		Phase 0	**Phase 1**	**Phase 2**
	Mean ± SD	**14.52 ± 5.79**	**38.18 ± 18.27**	**66.38 ± 22.09**
Hs-Tn I ng/L	Min	6.00	7.70	27.10
	Max	27.80	90.3	107.8

Total patients with hs-Tn I cutoff of >40 ng/L in the first three phases

	Phase 0		Phase 1		Phase 2	
	Num	**%**	**Num**	**%**	**Num**	**%**
Hs-Tn I > 40 ng/L	0	0	25	32.1	57	73.1

Hs-Tn I, high-sensitivity troponin I; SD, standard deviation

Study limitation

First, the relatively small sample number and small number of cardiac events which limit our statistical power to exclude an independent predictive role of Tn I. Second, we totally relied on simple echocardiography LVEF measurements; Modified Simpson Biplane Method, because it is the most globally usage method to detect the LV function, and the importance of finding a trusted simple method in such patients, as most of cardiotoxicity cases are subclinical.

Table 5

Logistic regression results of the prediction of hs-Tn I for developing cardiac events

	P value	Exp (B)	95% CI for Exp (B)
Hs-Tn I as a prognostic marker for any cardiac event			
Phase 0	0.468		
Phase 1	0.004	1.045	1.015–1.077
Phase 2	0.000	1.087	1.042–1.134
Hs-Tn I as a prognostic marker for cardiac events other than cardiotoxicity			
Phase 0	0.07		
Phase 1	0.641		
Phase 2	0.002	1.071	1.026–1.117
Hs-Tn I as a prognostic marker for cardiotoxicity			
Phase 0	0.872		
Phase 1	0.001	1.072	1.029–1.116
Phase 2	0.001	1.133	1.051–1.221

Hs-Tn I, high-sensitivity troponin I.

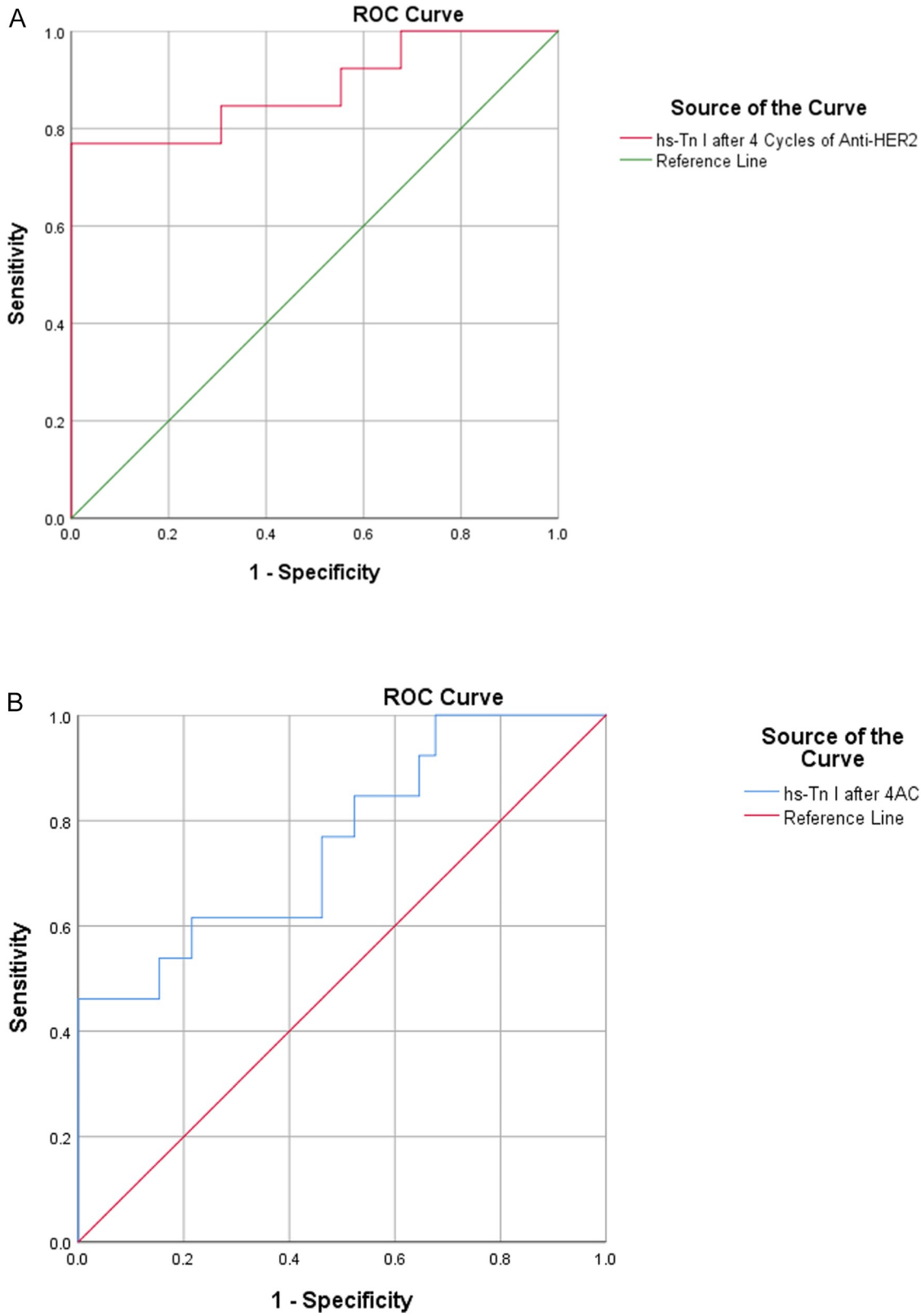

Figure 5. ROC curves of hs-Tn I for developing cardiotoxicity. (A) hs-Tn I values after four cycles of trastuzumab for developing cardiotoxicity; (B) hs-Tn I values after four cycles of anthracyclines for developing cardiotoxicity.

Table 6

Under the area of ROC curve for: A (hs-Tn I values after four cycles of trastuzumab) and B (hs-Tn I values after four cycles of anthracyclines) for developing cardiotoxicity

A: hs-Tn I values after four cycles of trastuzumab for developing cardiotoxicity								
			Asymptotic 95% CI					
Area under the curve	Std. error	Asymptotic sig.	Lower bound	Upper bound	SN	SP	PPV	NPV	RR
0.882	0.065	0.000	0.755	1.000	77%	86%	53%	95%	10.53
B: hs-Tn I values after four cycles of anthracyclines for developing cardiotoxicity									
0.759	0.077	0.003	0.607	0.910	61%	78%	36%	91%	4

Hs-Tn I, high-sensitivity troponin I; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; RR, relative risk; Sig, significance; SN, sensitivity; SP, specificity; Std, standard.

Finally, the relatively small period of follow-up; only 1 year after end of treatment.

Conclusion

Besides cardiomyopathy as the main type of cardiotoxicity that occurs with the combination of chemotherapy and trastuzumab treatment in BC patients, hs-Tn I measured after four cycles of trastuzumab treatment in BC patients treated with anthracycline plus cyclophosphamide followed by trastuzumab and taxanes could be an important predictor of the risk of cardiotoxicity occurred especially in the first year after treatment, with a different cutoff of which it is used in other cardiac conditions. Further research is needed with larger sample sizes and different measuring techniques. However, comparing findings is challenging due to different cut-off values for troponin as a marker of cardiotoxicity.

Ethical approval

Ethical approval for this study (Ethical Committee 2020-CD-ON-95) was provided by the Ethical Committee of Tishreen University Hospital, Latakia, Syria on 10 December 2020, which is adherence to the ideal Declaration of Helsinki regulating the ethics of medical research (last revised in 2013) and is conducted in accordance with the ICH Guideline for Good Clinical Practice.

Consent

Consent was obtained or waived by all participants in this study. Written informed consent was obtained from every patient for participating this study.

Sources of funding

None.

Author contribution

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work. Concept and design: N.A.A., A.S.J., F.N.R. Acquisition, analysis, or interpretation of data: N.A.A., A.S.J., F.N.R. Drafting of the manuscript: N.A.A. Critical review of the manuscript for important intellectual content: F.N.R, Z.A.A. Supervision: A.S.J., F.N.R., Z.A.A.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

Tishreen University Hospital issued approval 2020-CD-ON-95.

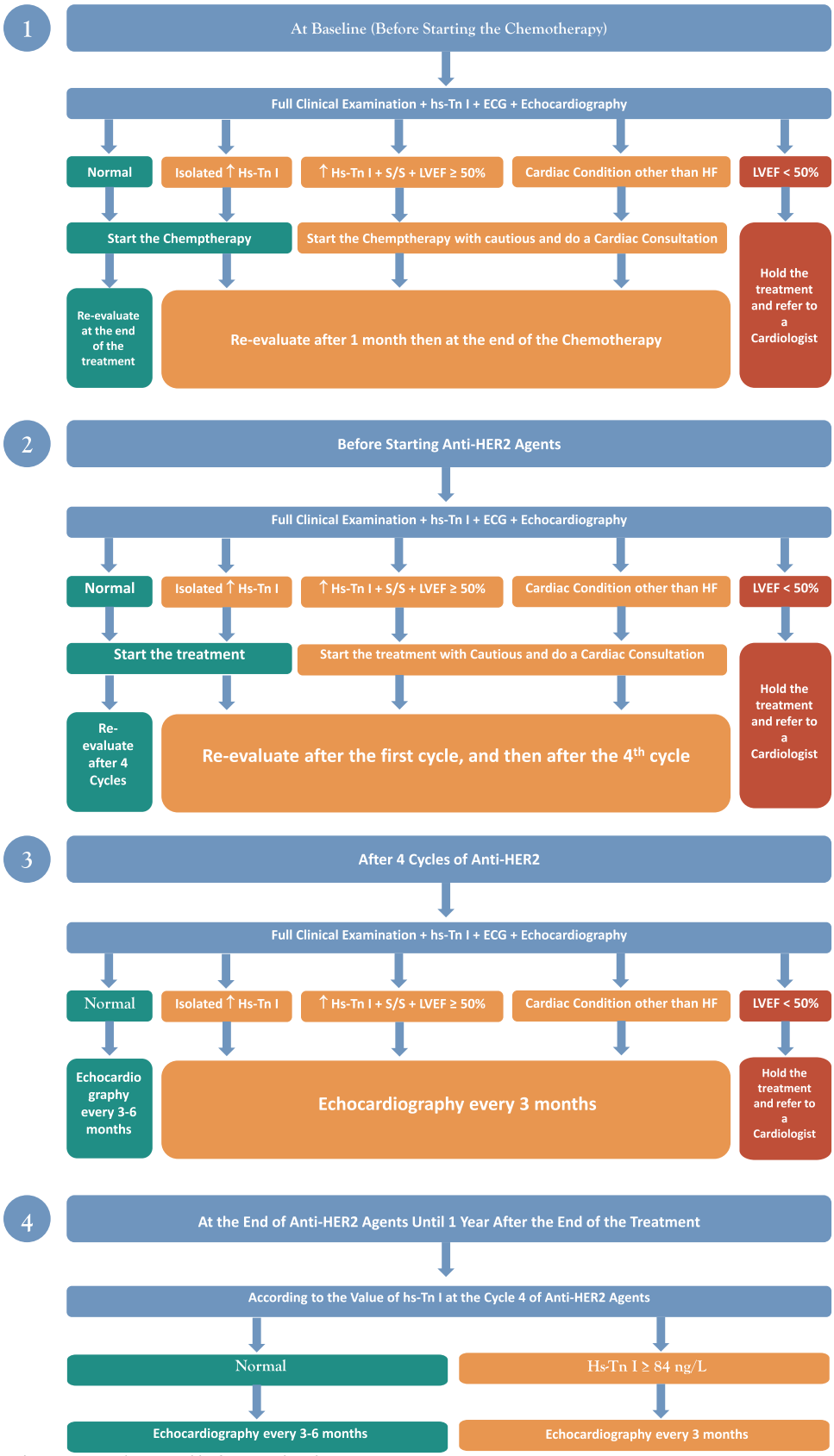

Figure 6. A risk stratification suggested protocol before starting the cancer treatment.

Guarantor

Nadeem A. Ahmed, Faisal N. Redwan, Zuheir A. Alshehabi.

Provenance and peer review

None.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Presentation

None.

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