**Cardiotoxicity Associated with Breast Cancer Treatment - Annotation Guidelines**

Contents

1 Background 3

1.1 Definition of cardiotoxicity 3

1.2 Definition of cancer-related cardiotoxicity 3

1.3 Known cardiotoxicity caused by breast cancer treatments 3

2 Annotation Tool 5

3 Classify cardiotoxicity 5

3.1 Y 5

3.2 Y-C 6

3.3 Y-P 6

3.4 Y-R 6

3.5 Y-O 7

3.6 N 7

# Background

## Definition of cardiotoxicity

Cardiotoxicity is considered a continuous spectrum starting from myocardial injury leading to a decline in left ventricular ejection fraction (LVEF) and development of heart failure (HF) symptoms.1,2

## Definition of cancer-related cardiotoxicity

There is no single standardized definition of cancer-related cardiotoxicity, and it has been variously defined in the literature as HF symptoms, a decrease in LVEF from baseline to an LVEF less than 55%, a 5% reduction of LVEF in symptomatic patients, or a 10% reduction of LVEF in asymptomatic patients.3,4 , or was defined as an incident case of HF following a breast cancer diagnosis5 (MD Anderson5.

Anthracycline-induced cardiotoxicity can be divided into acute, early-onset chronic progressive cardiotoxicity, and late-onset chronic progressive cardiotoxicity.[23](https://onlinelibrary.wiley.com/doi/full/10.1002/ehf2.13365#ehf213365-bib-0023)-[26](https://onlinelibrary.wiley.com/doi/full/10.1002/ehf2.13365#ehf213365-bib-0026) Acute toxicity is quite rare (<1%), and it does not depend on the dose. It occurs during the infusion of cytostatics or up to 2 weeks after its completion. The most common clinical image of acute anthracycline-induced cardiotoxicity are the supraventricular arrhythmias, symptoms suggestive of myocarditis and pericarditis, left ventricular systolic dysfunction, and changes in the electrocardiogram (non-specific ST-T segment changes and QTc interval prolongation).

## Known cardiotoxicity caused by breast cancer treatments

The following table and the signs and symptoms list contain the breast cancer treatments of interest as well as known cardiotoxicity. Please note, this provides a reference for cardiotoxicity, but may not be complete.

| **Adjuvant agents** | **Cardiovascular adverse effects** | **Prevention** |
| --- | --- | --- |
| Anthracycline (e.g. doxorubicin and epirubicin) | Left ventricular dysfunction, heart failure, myocarditis, pericarditis, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and QTc prolongation (doxorubicin) | • Identification and treatment of cardiovascular risk factors  • Limiting of cumulative dose  • Alternative delivery systems (liposomal doxorubicin)  • Continuous infusions  • The use of cardioprotective drugs: Dexrazoxane, ACE-Is or ARBs, beta-blockers, statins  • Avoiding of QT prolonging drugs and the management of electrolyte abnormalities  • Aerobic exercise |
| HER-2-directed therapies (e.g. trastuzumab and pertuzumab) | Left ventricular dysfunction and heart failure | • Identification and treatment of cardiovascular risk factors  • The use of ACE-Is, beta-blockers |
| Radiation therapy | Coronary artery disease, cardiomyopathy, valvular disease, pericardial disease, and arrhythmias | • Minimizing of cardiac radiation: lowering the dose of radiation and reducing cardiac volume exposed  • Use of modern techniques based on 3D treatment planning with a dose–volume histogram and virtual simulation programme |

HF symptoms <https://www.mayoclinic.org/diseases-conditions/heart-failure/symptoms-causes/syc-20373142>

Heart failure can be ongoing (chronic), or it may start suddenly (acute).

Heart failure signs and symptoms may include:

1. Shortness of breath with activity or when lying down
2. Fatigue and weakness
3. Swelling in the legs, ankles and feet
4. Rapid or irregular heartbeat
5. Reduced ability to exercise
6. Persistent cough or wheezing with white or pink blood-tinged mucus
7. Swelling of the belly area (abdomen)
8. Very rapid weight gain from fluid buildup
9. Nausea and lack of appetite
10. Difficulty concentrating or decreased alertness
11. Chest pain if heart failure is caused by a heart attack

**References:**

1. Cardinale D, Caruso V, Cipolla CM. The breast cancer patient in the cardioncology unit. J Thorac Dis. 2018;10(suppl 35):S4306–S4322.

2. Totzeck M, Schuler M, Stuschke M, Heusch G, Rassaf T. Cardio-oncology—strategies for management of cancer-therapy related cardiovascular disease. Int J Cardiol. 2019;280:163–175.

3. Harrison JM, Pressler SJ, Friese CR. Cardiotoxic heart failure in breast cancer survivors: a concept analysis. *J Adv Nurs*. 2016;72(7):1518–1528.

4. Levis BE, Binkley PF, Shapiro CL. Cardiotoxic effects of anthracycline-based therapy: what is the evidence and what are the potential harms?*Lancet Oncol*. 2017;18(8):e445–e456.

5. Henry, Mariana L., Jiangong Niu, Ning Zhang, Sharon H. Giordano, and Mariana Chavez-MacGregor. "Cardiotoxicity and cardiac monitoring among chemotherapy-treated breast cancer patients." *JACC: Cardiovascular Imaging* 11, no. 8 (2018): 1084-1093.

# Annotation Tool

We used Excel table in this annotation task.

# Classify cardiotoxicity

The Aim of this annotation task is to classify sentences into classes indicating various levels of association between breast cancer treatment and adverse event of toxicity.

There are 6 classes regarding cardiotoxicity: Y (yes), Y-C(yes-clinician), Y-P(yes-patient), Y-R(yes-recurrent), Y-O (yes-other), N (no)

## Y

This class refers to a certain causal relation between breast cancer treatments and adverse events of cardiotoxicity. There are 2 conditions falling into this category.

* The first condition is based on the pattern of “Treatment induced (developed, due to, in the setting of, related) cardiac problems” without prior heart problems mentioned, such as:
  + “chemo-induced cardiotoxicity (e.g., heart failure)”
  + “heart failure developed secondary to (due to, after) chemotherapy”
  + “Patient developed cardiac problems (e.g., LEF decrease) after chemotherapy treatment.”
* The second condition is based on the pattern of “Treatment discontinued (on hold, paused, stopped) due to newly developed cardiac problem”, some examples are as follows:
  + “Aromasin plus Herceptin but Herceptin discontinued Feb 2019 due to a decrease in ejection fraction”.
  + “Chemotherapy is currently on hold due to cardiac toxicity and decreased ejection fraction”

## Y-C

This class refers to clinicians’ speculations, with uncertainty keywords. Examples are:

* Cardiomyopathy, possibly chemotherapy – induced.
* Cardiomyopathy, possibly secondary to chemotherapy.
* Developed CHF, likely due to chemotherapy.

## Y-P

This class refers to patients’ complaints/reports or sentences from “patient complaints” section, here are some examples of cardiotoxicity we will need to annotate:

* Patient reported that chest pain after a full cycle of chemotherapy.
* She reports that she developed a cardiac side effect which she thought might be secondary to chemotherapy.
* Patient experience substantial chest pain after chemotherapy.

## Y-R

This class refers to recurrence of cardiac disorders caused by treatments. We intentionally separate this class for convenient post processing.

Here are some examples we will need to annotate:

* She may have had some sort of myocarditis back then, and was left with a residual left bundle branch block, and now with the chemotherapy, has taken a second hit.

## Y-O

This class refers to any possible yes of causal relation that does not belong to any previous class. Here are some examples we will need to annotate:

* Need to rule out cardiac dysfunction since Trastuzumab and pertuzumab can cause a decline in ejection fraction.
* Her treatment was complicated by decrease in ejection fraction.
* A visit for evaluation of possible cardiac toxicity from chemotherapy (Herceptin).

## N

This refers to the condition that no association between treatment and cardiotoxicity can be ascertained. For example, a list of patient’s problems with no obvious time lines, risk of cardiotoxicity after treatment, or discussions on the relation between treatment and cardiotoxicity, guideline instruction, heart function monitoring, procedures for heart protection.

* Treatment should be discontinued if there is evidence of clinical heart failure, more than 10% decline in ejection fraction, or an absolute EF of 45% or below.
* Cardiac function monitoring for cardiotoxicity with ongoing treatment/chemotherapy.