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Comparison of Mayo And HFA-ICOS Cardiotoxicity Risk Score Validity for Predicting Cardiotoxicity in Anthracycline Chemotherapy Patients

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ABSTRACT

Background: Anthracycline can cause cardiotoxicity. In estimating the risk of cardiotoxicity, various risk prediction scores have been developed. Mayo cardiotoxicity risk score has long been used. The newest protocol is the HFA-ICOS cardiotoxicity risk score. There have been no studies that directly compare the validity of these scores. ***Objective:*** This study aims to compare the validity of the Mayo and HFA-ICOS cardiotoxicity risk scores for predicting cardiotoxicity in anthracycline chemotherapy patients. ***Method:*** This research was a retrospective cohort. It began by searching for patients who underwent baseline evaluation before anthracycline chemotherapy in a tertiary hospital. Seventy patients who met the criteria were included. Baseline data was used for cardiotoxicity risk score assessment. Cardiotoxicity follow-up was carried out with echocardiography. Statistical analysis was carried out using STATA Se 17.0 statistical software. ***Result:*** Twenty of 70 patients (28.6%) experienced cardiotoxicity. The average total dose of doxorubicin used was 433.8 mg/m2. The majority of patients were women. The most common cardiovascular risk factor was hypertension. The AUC for the Mayo cardiotoxicity risk score was 0.695 (sensitivity 65%, specificity 74 %). The HFA-ICOS cardiotoxicity risk score was 0.59 (sensitivity 30 %, specificity 88 %). The Mayo cardiotoxicity risk score is better to role-out cardiotoxicity (NPV 84.1%) compared to the HFA-ICOS cardiotoxicity risk score (NPV 75.9%). ***Conclusion:*** There is a difference between Mayo and HFA-ICOS validity for predicting cardiotoxicity. Overall, the Mayo cardiotoxicity risk score is better compared to the HFA-ICOS cardiotoxicity risk score.

Keywords: cardiotoxicity; Mayo; HFA-ICOS; cardiotoxicity risk score; validity; AUC; chemotherapy; anthracycline

INTRODUCTION

Cancer is the main cause of death worldwide.[1] According to the WHO Report on Cancer 2020, 1 in 6 deaths is caused by cancer. In 2018, there were 18.1 million new cancer cases with 9.6 million cancer deaths worldwide and it is estimated that this number will continue to increase [1]. In Indonesia, the number of new cancer cases according to Globocan (Global Cancer Observatory) 2020 was 396.914 people [2]. Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cells in the body. There are various mechanisms of action of chemotherapy, including alkylating agents, anti-metabolites, platinum compounds, anti-tumor antibiotics, topoisomerase inhibitors, mitotic inhibitors, and corticosteroids [3]. Anthracycline is a type of anti-tumor antibiotic chemotherapy that has a working mechanism by inhibiting enzymes in the DNA replication process. Anthracyclines work on all phases of the cell cycle, so these drugs are widely used in various types of cancer. Seeing the mechanism of action of anthracyclines which can work in all phases of the cell cycle, high doses of anthracyclines can cause cardiotoxicity [3].

In type 1 cardiotoxicity, where the most common abnormality is left ventricular dysfunction, cell death occurs (necrosis or apoptosis) which causes permanent damage which is very dependent on the cumulative dose of anthracycline given [4]. In estimating the risk of cardiotoxicity, various risk prediction scores were developed, including the Mayo cardiotoxicity risk score and the ESC 2022 risk prediction score. In general, this risk prediction model includes the criteria for chemotherapy to be given and the presence of risk factors that cause cardiotoxicity [5-8]. This risk prediction model makes clinicians estimate the size of the risk of cardiotoxicity so cardioprotectors can be administered. In current protocols in Indonesia, the Mayo cardiotoxicity risk score is used to estimate the risk of cardiotoxicity in patients undergoing chemotherapy [9]. Meanwhile, ESC also published the latest protocol HFA-ICOS cardiotoxicity risk score in 2022 to predict cardiotoxicity [5].

It is necessary to check the validity of the risk prediction model for cardiotoxicity.

There has been no research that directly compares the validity of the Mayo and HFA-ICOS cardiotoxicity risk scores to estimate the occurrence of cardiotoxicity and see which of the two scoring systems is better used in clinical practice. This study aims to compare the validity of the Mayo and HFA-ICOS cardiotoxicity risk scores for predicting cardiotoxicity in anthracycline chemotherapy patients.

METHODS

This study is an analytical observational study with a retrospective cohort research design. This study began with an anthracycline pre-chemotherapy baseline evaluation and assessed predictors of both scores using these data. Baseline data collection is carried out through medical records. The follow-up is carried out for at least 1 year after the first anthracycline chemotherapy. The sampling technique was consecutive sampling. This research was carried out for 6 months at Prof. Dr. IGNG Ngoerah Central General Hospital, Denpasar, Indonesia, a tertiary hospital.

Post-chemotherapy follow-up, subjects were re-contacted for assessment and transthoracic echocardiography examination. Assessment is carried out by history and physical examination which suggests cardiotoxicity, especially symptoms of heart failure.

Cardiotoxicity was defined as one of three following: decreased EF >10% from baseline until EF <50%, diastolic dysfunction, signs and symptoms of heart failure. Mayo and HFA-ICOS cardiotoxicity risk scores were assessed using a form. The scoring indicators were obtained using baseline characteristics. Due to a lack of baseline data, the cardiac biomarker was not added to the score. Parameters of the two scoring systems obtained are then added together to obtain the result of cardiotoxicity risk. Validity tests were carried out to assess the sensitivity and specificity of each score and to test differences in sensitivity and specificity between scores. A validity test is also used to assess the predictive value of the score by making a 2x2 cross-tabulation. STATA Se 17.0 was used for data analysis.

RESULTS

The research involved 70 subjects who met the research criteria. The study was conducted with the mean duration between the last anthracycline chemotherapy and follow-up is 8.8±2.83 months with an average total doxorubicin dose of 373.5±130.6 mg/m^2. The most common disease that uses anthracycline chemotherapy is breast cancer (91.43%). The majority of subjects were female (94.3%) and the average age was 49.06±9.29 years. Six subjects were found to have a BMI >30 kg/m^2. The most common cardiovascular risk factor found was hypertension (32.9%).

TABLE 1: Subject Characteristic.

Characteristic	Total (N=70)
Cancer type	
Breast cancer, n (%)	64 (91.43)
NHL, n (%)	4 (5.71)
Thyroid cancer, n (%)	1 (1.43)
Fibrosarcoma, n (%)	1 (1.43)
Duration of chemotherapy follow-up	
First follow-up, month, mean±SD	12.86±2.37
Last follow-up, month, mean±SD	8.8±2.83
Total dose doxorubicin, mg/m^2, mean±SD	373.5±130.6
Sex	
Male, n (%)	4 (5.7)
Female, n (%)	66 (94.3)
Age, years old, mean±SD	***49.06±9,29***
Age <65 years old, n (%)	66 (94.3)
Age 65-79 years old, n (%)	4 (5.7)
BMI, kg/m^2, mean±SD	***24.51±3.72***
BMI ≤30 kg/m^2, n (%)	64 (91.4)
BMI >30 kg/m^2, n (%)	6 (8.6)
Risk Factors and Comorbid	
Cardiomyopathy/HF/CTRCD, n (%)	2 (2.9)
Hypertension, n (%)	23 (32.9)
Diabetes melitus, n (%)	4 (5.7)
CAD/equivalent, n (%)	1 (1.4)
MI/PCI/CABG, n (%)	1 (1.4)
GFR <60 mL/min/1.73 m^2, n (%)	3 (4.3)
Chest radiation, n (%)	4 (5.7)
Smoking, n (%)	1 (1.4)

- Numerical data that is normally distributed is displayed in the mean ± standard deviation (SD), and data that is not normally distributed is displayed in the median (interquartile range (IQR)).
- Categorical data is displayed in frequency (n) and percentage (%).
- NHL: non-Hodgkin's lymphoma; BMI: body mass index; HF: heart failure; CTRCD: chemotherapy-related cardiac dysfunction; CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary. artery. bypass graft; GFR: glomerulus filtration rate.

In the study, 18 subjects (28.7%) had symptoms of heart failure. The mean baseline EF of subjects was 63.30±4.69% and follow-up EF 57.69±7.40% with 6 subjects having follow-up EF <50%. Changes in follow-up EF >10% of baseline were present in 31 patients. In addition, there were 13 patients with diastolic dysfunction and 21 patients with new regional wall motion abnormality (RWMA). Of the 70 subjects, there were 20 subjects (28.6%) who met the definition of cardiotoxicity in the study.

TABLE 2: Clinical Characteristics and Echocardiography.

Characteristic	Total (N=70)
Complaint	
NYHA class II, n (%)	18 (25.7)
Baseline EF, %, mean±SD	63.30±4.69
Follow-up EF, %, mean±SD	57.69±7.40
Follow-up EF < 50%, n (%)	8 (11.43)
EF change, %, mean±S	-5.53±8.63
Diastolic dysfunction, n (%)	13 (18.6)
New RWMA, n (%)	21 (30)
Delta EF > 10%, n (%)	31 (44.3)
Cardiotoxicity, n (%)	20 (28.6)
Mayo score	
Intermediate, n (%)	2 (2.86)
High, n (%)	62 (88.57)
Very high, n (%)	6 (8.57)
HFA-ICOS score	
Low, n (%)	58 (82.86)
Moderate, n (%)	10 (14.28)
High, n (%)	0 (0)
Very high, n (%)	2 (2.86)

- Numerical data that is normally distributed is displayed in the mean ± standard deviation (SD), and data that is not normally distributed is displayed in the median (interquartile range (IQR)).
- Categorical data is displayed in frequency (n) and percentage (%).
- NYHA: New York Heart Association; EF: ejection fraction, RWMA: regional wall motion abnormalities.

The Mayo score in the study varied from moderate to very high risk, while the HFA-ICOS score varied from low to very high risk. Most subjects were at high risk (88.57%) if calculated using the Mayo score and low risk (82.86%) if calculated using the HFA-ICOS score. There were no subjects with a high risk of cardiotoxicity calculated using the HFA-ICOS score.

TABLE 3: Subjects Characteristic with Cardiotoxicity.

Characteristic	Total (N=20)
Total dose doxorubicin, mg/m^2, mean±SD	433.8±130.39
Age, year, mean±SD	49.15±10.89
Female, n (%)	17 (85)
Complaint, n (%)	18 (90)
Baseline EF, %, mean±SD	63.11±5.4
Follow-up EF, %, mean±SD	51.17±9.6
EF change, %, mean±SD	-11.93±10.09
Diastolic dysfunction, n (%)	13 (65)

Characteristic	Total (N=20)
New RWMA, n (%)	17 (85)
Cardiomyopathy/HF, n (%)	2 (10)
CAD/equivalent, n (%)	1 (5)
Hypertension, n (%)	11 (55)
Diabetes Mellitus, n (%)	1 (5)
Chest Radiation, n (%)	3 (15)
Baseline EF 50-54%, n (%)	1 (5)
Age 65-79 years old, n (%)	2 (10)
GFR <60 ml/min/1.73m^2, n (%)	1 (5)
Smoking, n (%)	1 (5)
BMI >30 kg/m^2, n (%)	2 (10)

- Numerical data that is normally distributed is displayed in the mean ± standard deviation (SD), and data that is not normally distributed is displayed in the median (interquartile range (IQR)).
- Categorical data is displayed in frequency (n) and percentage (%).
- EF: ejection fraction; RWMA: regional wall motion abnormalities; HF: heart failure; CAD: coronary. artery disease; GFR: glomerulus filtration rate; BMI: body mass index.

It was found that the Mayo cardiotoxicity risk score cut-off was at a sensitivity between 0.05-0.75 and a specificity approaching 0.75. Thus, it was found that patients at risk of experiencing cardiotoxicity had a Mayo cardiotoxicity risk score >6 (sensitivity 65%, specificity 74%). It was found that 13 out of 20 subjects were at risk and experienced cardiotoxicity (sensitivity 65%). There were 37 of 50 subjects who were at least risk based on the Mayo score and did not experience cardiotoxicity (specificity 74%). If the Mayo score is >6, then the possibility of the subject experiencing cardiotoxicity is 50%. If the Mayo score is <6, then the probability that the subject will not experience cardiotoxicity is 84.1%.

TABLE 4: Validity of Mayo Cardiotoxicity Risk Score.

Variable	Cardiotoxicity		Sensitivity	Specificity	PPV	NPV
	Yes	No				
Score						
≥ 6[a]	13	13	65% (40.8-84.6%)	74% (59.7-89.4%)	50% (29.9-70.1%)	84.1% (69.9-93.4%)
< 6[b]	7	37				

• PPV: positive predictive value, NPV: negative predictive value
a. high to very high-risk
b. intermediate to high risk

It was found that subjects with the HFA-ICOS risk type were at moderate to very high risk of experiencing cardiotoxicity events in the future. It was found that 6 out of 20 subjects were at risk and experienced cardiotoxicity (sensitivity 30%). There were 44 of 50 subjects who were less at risk based on the HFA-ICOS score and did not experience cardiotoxicity (specificity 88%). If the HFA-ICOS score is obtained as a moderate risk (score >2), then the probability that the subject will experience cardiotoxicity is 50%. If the HFA-ICOS score is low risk (score >1), then the probability that the subject will not experience cardiotoxicity is 75.9%.

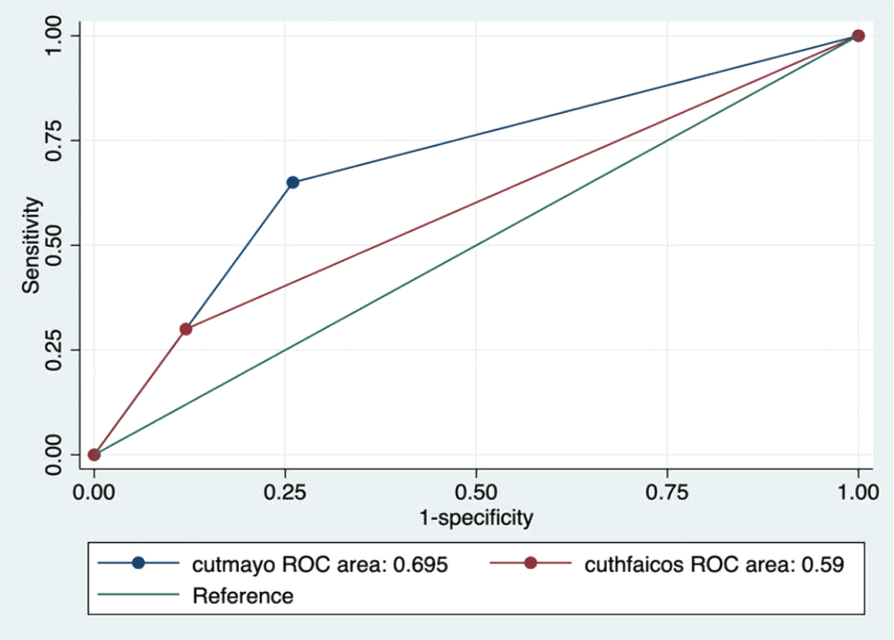
TABLE 5: Validity of HFA-ICOS Cardiotoxicity Risk Score.

Variable	Cardiotoxicity		Sensitivity	Specificity	NPP	NPN
	Yes	No				
Score						
≥ 2[a]	6	6	30% (11.9-54.3%)	88% (75.7-95.5%)	50% (21.1-78.9%)	75.9% (62.8-86.1%)
< 2[b]	14	44				

• PPV: positive predictive value, NPV: negative predictive value
a. moderate to very high-risk
b. low risk

The AUC Mayo cardiotoxicity risk score was 0.695 (95% CI: 0.571-0.819). The AUC of the HFA-ICOS cardiotoxicity risk score was 0.59 (95% CI: 0.477-0.703).

Based on the graph above, the Mayo cardiotoxicity risk score has better sensitivity, while the HFA-ICOS cardiotoxicity risk score has better specificity.



GRAPHIC 1: AUC Mayo dan HFA-ICOS Cardiotoxicity Risk Score.

DISCUSSION

In this study, the total subjects were 70 patients. The subjects in this study were predominantly female (94.3%) and only a few male subjects (5.7%). This result is different from several existing studies. According to Sararat et. al. (2023) [10], cancer mostly occurs among men than women, which is generally caused by lifestyle. In another research by Sarah Jackson et. al. (2022) [11], the incidence of cancer is higher in men than women related to behavior (smoking and alcohol use), anthropometry (body mass index and height), and lifestyle (physical activity, diet, medication). Apart from gender, the general characteristics of the subjects in this study were predominantly aged <65 years (94.3%), with a follow-up duration of the last chemotherapy of 8.8 months and a total mean dose of doxorubicin of 373.5 mg. This is in line with research conducted by Jacobs et. al. in 2021 [12] which carried out patient follow-up for an average of 443±245 days (14.77±8.17 months). The most common risk factors and comorbidities in the subjects of this study were hypertension (32.9%), followed by diabetes mellitus (5.7%), chest radiation (5.7%) and heart failure (2.9%). The relationship between hypertension and cancer has been described in several previous studies. Cancer and hypertension are closely related, so the relationship between the two is often referred to as on-hypertension. Overlapping pathophysiological mechanisms, including inflammation and oxidative stress, are associated with common risk factors such as diabetes, smoking, obesity, physical inactivity, and obstructive sleep apnea [13].

For clinical characteristics, only around 25.7% of research subjects came with complaints of mild shortness of breath during activity or were categorized as NYHA class II.

From previous studies, around 40% of patients with cancer came with complaints of pain, while other complaints such as gastrointestinal complaints (11%), dyspnea (8.5%), and fever (7%) [14]. However, another research by Dugdeon et. al. said that around 46% of cancer patients come with complaints of shortness of breath [15]. The differences in results in several existing studies are related to the type of cancer included in the research sample and shortness of breath is a symptom that is felt very subjectively and varies for each individual, therefore there is a wide range of complaints of this shortness of breath. The average ejection fraction obtained in this study was 63.30%. Ejection fractions in the normal range are often found in patients with cancer. A study by Somaira et. al. (2018) [16], researching breast cancer that underwent echocardiography, found that 95% of patients had normal ejection fraction results, with a mean of around 63%. Even other research from Erwin Macaraeg et. al. (2024) [17], who examined patients with breast cancer in their research, around 97.7% of patients had an EF >50%. Other echocardiographic characteristics at follow-up included a decrease in the mean ejection fraction to 57.69% due to several patients experiencing cardiotoxicity. These include new RWMA and diastolic dysfunction. Most subclinical dysfunction and diastolic dysfunction that occur immediately after chemotherapy are strong predictors of anthracycline-induced cardiotoxicity, where 49 out of 100 patients experience diastolic dysfunction within the first year of chemotherapy [18].

In this study, the Mayo score obtained was predominantly high risk (88.57%). The Mayo score is predominantly high risk (score 5) caused by using anthracyclines as an indicator (score 4) and the predominance of female subjects (score 1).

The HFA-ICOS score obtained was predominantly low (82.86%), followed by moderate (14.28%) and very high (2.86%). This is in accordance with research by Glen et. al. (2023) [19]. This study is also similar to other studies which state that patients with anthracyclines whose risk of cardiotoxicity was assessed using the HFA-ICOS score were most likely to have a low risk (51%) [20].

The validity test of the Mayo cardiotoxicity risk score shows a sensitivity of 65% and a specificity of 74%. With a cardiotoxicity prevalence of 29%, the PPV Mayo cardiotoxicity risk score is 50%, and NPV is 84.1%. These results indicate that the Mayo cardiotoxicity risk score has a better ability compared to the HFA-ICOS cardiotoxicity risk score to role-out cardiotoxicity in patients receiving anthracycline therapy. Based on the results of this validity test, the Mayo cardiotoxicity risk score also can be used as a screening tool/method for early detection of cardiotoxicity. These findings corroborate the results of a retrospective cohort study conducted by Jacobs et al, in 2021 [12]. In this study, Jacobs et al compared the ASCO risk score with the Mayo cardiotoxicity risk score. It was found that the ASCO risk score had low sensitivity and specificity in predicting cardiotoxicity (sensitivity 64%, specificity 52%). On the other hand, the Mayo cardiotoxicity risk score shows a better ability to predict cardiotoxicity with an AUC value of 0.685 (CI 95%, 0.625-0.743).

The results of the validity test of the HFA-ICOS cardiotoxicity risk score showed a sensitivity of 30% and a specificity of 88%. With a cardiotoxicity prevalence of 29%, the PPV HFA-ICOS cardiotoxicity risk score is 50%, and the NPV is 75.9%. The high specificity in this study is also in line with research on this score by Cronin et. al. In this study, a sensitivity value of 26.1% and specificity of 97.9% were obtained with an AUC of 0.643 [21]. Cronin et. al. also found that the risk of cardiotoxicity in the next 5 years was in the very high-risk group (38%). These findings are also in line with the findings in this study, where all subjects in the very high-risk group experienced cardiotoxicity.

Due to a lack of baseline data, the cardiac biomarker was not included in this study. A cardiac biomarker has moderate risk factors with a score of 1 in the HFA-ICOS cardiotoxicity score assessment [5]. But, if it is not available, it can be absent in the scoring. There were also studies in which cardiac biomarkers was not included [22-23].

The analysis of differences between the two scoring systems in detecting cardiotoxicity in anthracycline chemotherapy patients showed that the AUC for the Mayo cardiotoxicity risk score was 0.695 (95% CI: 0.71-0.819). The AUC of the HFA-ICOS cardiotoxicity risk score was 0.59 (95% CI: 0.477-0.703). This difference is likely caused by the different cut-offs for each score in determining cardiotoxicity. These cut-off differences are also likely due to variations in subject characteristics and cardiotoxicity events found. Compared to the HFA-ICOS cardiotoxicity risk score, the Mayo cardiotoxicity risk score has a better ability to detect cardiotoxicity in anthracycline chemotherapy patients with echocardiography findings as the gold standard.

In estimating the risk of cardiotoxicity, risk prediction models, such as Mayo and HFA-ICOS cardiotoxicity risk score were developed to make it easier for clinicians to predict the risk of cardiotoxicity. Cardioprotectors are given as an effort to prevent and protect the heart from the risk of cardiotoxicity through its effect on changes in systolic function due to the use of chemotherapy. In patients with high-risk and very high-risk cardiotoxicity criteria according to Mayo, it is recommended to give cardioprotectors as initial prevention.7 In the case of cardioprotectors to prevent or reduce cardiotoxicity in anthracycline chemotherapy patients by looking at the sensitivity and specificity of the Mayo and HFA-ICOS cardiotoxicity risk score, a screening program will be selected that is as effective as possible. For the program to be effective, it is hoped that patients will receive cardioprotectors as early as possible, even before cardiotoxicity occurs. In other words, try to minimize false negatives so that the test chosen so that the false negative rate is low is a test with high sensitivity but medium specificity [24]. In this case, the test chosen is the Mayo cardiotoxicity risk score.

The findings in this study are in line with studies in tertiary hospitals in Belgium. It found that Mayo cardiotoxicity risk score is the best scoring instrument for predicting cardiotoxicity [24]. Mayo cardiotoxicity risk score still requires further refinement to improve adequate cardiovascular risk prediction [12]. Although there have been a number of recommendations for the use of scoring in predicting chemotherapy-related cardiotoxicity in cancer patients, there is no validated scoring system so that a number of researchers are still comparing various scoring systems recommended in various research centers around the world, including in Italy, Belgium, and Germany [12,26-27].

The ability of the Mayo cardiotoxicity risk score to predict cardiotoxicity cannot be separated from the components assessed in this scoring system, which combines aspects of cardiovascular risk factors and cancer therapy received by the patient. However, this scoring system has never been validated in prospective studies and its clinical significance has not been established [28].

STUDY LIMITATION

This research only compares validity testing on 2 cardiotoxicity risk score systems so further research needs to be developed for other scoring systems. The authors did not include data regarding cardiac biomarkers which are part of the HFA-ICOS cardiotoxicity risk score scoring system. Cardiac biomarkers have a score of 1 as a moderate risk factor for cardiotoxicity. Research was only carried out at a single center, which is a tertiary hospital, so that the characteristics of patients who are research subjects become less diverse and less representative of the population.

CONCLUSION

The validity of the Mayo cardiotoxicity risk score for predicting cardiotoxicity in anthracycline chemotherapy patients is sensitivity of 65% and specificity of 74%. The validity of the HFA-ICOS cardiotoxicity risk score for predicting cardiotoxicity in anthracycline chemotherapy patients is a sensitivity of 30% and specificity of 88%. There is a difference in the validity of the Mayo and HFA-ICOS cardiotoxicity risk scores for predicting cardiotoxicity in anthracycline chemotherapy patients. Mayo cardiotoxicity risk score has higher sensitivity while the HFA-ICOS cardiotoxicity risk score has higher specificity.

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Declarations

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