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Risk prediction model for long-term heart failure incidence after epirubicin chemotherapy for breast cancer – A real-world data-based, nationwide classification analysis

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ABSTRACT

Background: Dilated cardiomyopathy (DCM) incidence during and after anthracycline therapy is highly dependent on anthracycline cumulative dose (CD), but its detailed risk factors remained unexplored. Our aim was to assess heart failure (HF) incidence after epirubicin therapy and construct a HF risk-prediction score.

Methods and results: A retrospective study was conducted by anonymized integration of nationwide healthcare databases. All the analysed patients were diagnosed with breast carcinoma confirmed by histology from 2007 to 2016. Participants did not undergo chemo- or radiotherapy or suffer HF/DCM during the preceding 3 years. The HF endpoint was established by assignment of I50 International Classification of Diseases (ICD) codes upon discharge from hospital or issuance of an autopsy report. 8068 patients treated with epirubicin were analysed. The 3–10-year HF cumulative incidence was 6.9%. Using binomial logistic regression the independent predictors were identified. A CD-dependent and significant effect on HF was revealed for epirubicin (threshold dose: 709 mg/m^2, odds ratio (OR): 1.76) and docetaxel (CD: >510 mg/m^2, OR: 1.59; CD ≤510 mg/m^2, OR: 1.28, respectively). HF risk increased with age, even over 40. A risk-prediction score derived from regression coefficients consisting of age, diabetes mellitus, hypertension, coronary artery disease, stroke, epirubicin CD, docetaxel CD, capecitabine, gemcitabine, bevacizumab and cancer stage was able to classify HF risk over a wide range (2–30%).

Conclusion: Long-term HF risk for patients treated with epirubicin was stratified by our risk-prediction score with a nearly 15-fold difference between the lowest and highest groups.

1. Introduction

By means of systematic screening, earlier detection, improved surgical interventions and more potent chemo- and radiotherapy treatments, cancer mortality has decreased over recent decades [1,2]. However, without careful surveillance and treatment, cancer therapy-related cardiovascular diseases may have a detrimental effect on this benefit.

Anthracyclines possess quite a diverse mechanism of action that includes producing reactive oxygen species (ROS), intercalation to DNA and type 2 topoisomerase inhibition. Myocyte injury and the subsequent dilated cardiomyopathy (DCM) is one of the most important limiting factors during this therapy. The principal initiating mechanism of cardiotoxicity is now thought to be through the formation of topoisomerase 2β-anthracycline complexes resulting in apoptosis and inhibition of mitochondrial biogenesis. The process is partly mediated by iron-dependent ROS generation and intramitochondrial iron accumulation [3–8]. Several transporter and metabolic protein gene polymorphisms were found to be associated with higher risk of cardiotoxicity, e.g. heterozygosity for haemochromatosis gene C282Y mutation, which occurs in 10% of the general population [9–13].

Dexrazoxane, which diminishes ROS production and decreases mitochondrial iron level during anthracycline treatment, is supposed to

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decrease HF occurrence. Meanwhile, its use was associated with side effects and a nonsignificant trend to reduce anticancer efficacy [8,14].

Incidence of cardiotoxicity increases as anthracycline cumulative dose (CD) rises [15,16]. Ryberg et al. published a relatively low 4% incidence of heart failure (HF) after epirubicin therapy with a CD of 900 mg/m^2, but a rapid increase to 15% was observed with a CD of 1000 mg/m^2 [17].

There are other risk factors associated with anthracycline-related HF identified in meta-analyses of clinical trials and registries: age > 65 and <4 years, female sex (in children), black race and pre-existing cardiovascular disorders [18–20]. Albeit these datasets were insufficient for a comprehensive risk analysis, their simple, CD and age-based HF risk-prediction scores could even be used for risk assessment [20]. However, in these early studies much higher cumulative anthracycline doses were applied, than in practice nowadays. At present, anthracyclines are usually administered at CDs below the HF-causing threshold. Besides, new anticancer protocols have come into practice, therefore, previous, simple risk-prediction models are no longer effective. Pinder et al. published a large analysis of the Medicare database for elderly (>65) breast cancer patients, and identified additional predictors for HF, e.g. trastuzumab treatment, hypertension, diabetes, coronary artery disease and a more advanced cancer stage. However, in this analysis patients treated with and without anthracycline were examined together. Moreover, the doses of chemotherapeutic agents were not included in the examination [21].

Despite the considerable amount of accumulated data, a comprehensive HF risk-prediction score, which reflects the contemporary protocols, remains unavailable for patients treated with anthracyclines. The aim of this paper is to introduce an up-to-date HF risk-prediction score model, which is applicable during epirubicin-based chemotherapy. By means of the large size of the cohort in our study and the wide range of therapeutic information retrieved from the analysed databases, it was possible to perform more detailed HF risk prediction than previously published [18–21]. After having taken the applied chemotherapy CDs into account, the interaction between currently used chemotherapeutic agents in terms of HF development could be evaluated.

2. Methods

2.1. Data source

A retrospective study by integrating nationwide anonymized databases was conducted. The merged dataset consisted of the administrative in- and outpatient healthcare databases of the National Health Insurance Fund of Hungary, the database of medicine dispensation records and the prospective Hungarian National Cancer Registry. These databases represent nationwide morbidity and mortality.

This investigation conforms with the principles outlined in the *Declaration of Helsinki* (*Br. Med. J.* 1964; **ii:**177). Our analysis of medical data was approved by the institutional review board at the University of Szeged. With regard to the retrospective, anonymized method, no informed consent was required.

2.2. Study population

The study population was defined by International Classification of Diseases codes (World Health Organization (1992). International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Geneva). In the studied database, which covered the period between 1st January 2004 and 31st December 2016, all the patients diagnosed with primary breast carcinoma confirmed by histology were identified. By this means, 25,029 subjects were found.

As our aim was to explore HF risk factors and interactions precisely, the members of the anthracycline group were analysed separately. The results of patients treated with epirubicin but no other anthracyclines are covered in this paper. To ensure a sufficient follow-up period, the analysis was performed exclusively on patients with at least 3 years of follow-up data after the commencement of epirubicin therapy or reaching the endpoint of HF earlier.

To obtain a preceding observational period of at least 3 years, only patients diagnosed with breast cancer after 1st January 2007 were enrolled. Consequently, the results of HF analysis represent a cumulative incidence with a duration of 3–10 years.

Our exclusion criteria were: other primary malignancies; previous treatment with any chemo- or radiotherapy before breast cancer diagnosis; assignment of I50 (heart failure), or I420 (dilated cardiomyopathy) ICD-10 codes during either in- or outpatient care before the index chemotherapy; diagnoses of pulmonary embolism, acute myocardial infarction (MI) and aortic valve disease in any hospital-discharge or autopsy report after the index chemotherapy.

As a result, 8068 breast cancer patients treated with epirubicin were enrolled in the HF incidence analysis.

2.3. Definition of primary endpoint and composition of independent variables

The primary endpoint of our study was the occurrence of HF following the commencement of chemotherapy as defined by a multilevel algorithm. Since the analysed databases do not contain the echocardiogram results, to define HF the I50 ICD-10 code was used. For enhanced specificity, a HF event was defined by diagnoses assigned during in-patient care or an autopsy, namely in three different ways: (1) hospital discharge from departments of internal medicine, cardiology or intensive care following the diagnosis of the ICD code I50, (2) hospitalization that ended in death and an I50 code issued as a primary or secondary diagnosis or as the underlying (not immediate) cause of death, (3) autopsy report with the I50 code (except for the immediate cause of death). To further clarify the HF event, the primary endpoints with criteria fulfilled without administration of loop diuretics or potassium-sparing diuretics were disregarded.

The wide spectrum of the clinical data that was analysed provided several assessable independent variables as follows. Chemotherapeutical treatment is reimbursed in an itemized fashion in Hungary. These claims must be made in accordance with a national administrative classification based on the structure of World Health Organization's International Classification of Procedures in Medicine. Thanks to this financial scheme, the doses of drugs applied during chemotherapy were captured in the analysed database. Chemotherapy exposures and their CDs were taken into account exclusively during the period before the earliest HF endpoint. Radiotherapy was categorized with regard to the tumour localisation (left/right-sided, or both).

As cancer stage is strongly influential in terms of the choice of chemotherapy in addition to its possible impact on HF progression, 3 categories for statistical analysis were defined to take this confounding effect into account: (1) low oncological risk in the absence of any feature suggesting a higher risk; (2) medium oncological risk with spread to regional lymph nodes, or with direct tumour extension to the chest wall or skin; (3) high oncological risk with more distant lymph node metastasis, or another form of distant spread. The highest risk category registered before or 180 days after the commencement of index chemotherapy was used for statistical analysis. Tumour grade and receptor state were not captured in the databases.

Pre-existing diseases and other conditions were considered as potential predictors in the analysis. The presence of these conditions was collected from the entire database of in- and outpatient care. Age was divided into 5 categories (<40, 40–49, 50–59, 60–69, ≥70).

Since HF occurrence was supposed to be influenced by treatment with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), this relation was also taken into account. Therapy commenced previously and was ongoing with regular (at least once every three months) dispensation by pharmacies was considered an independent variable. The reference non-ACEi/ARB group for regression was selected by propensity score matching.

2.4. Statistical methods

In statistical analysis, binomial stepwise logistic regression was used to calculate odds ratios for HF associated with chemotherapy exposure or other risk factors. At each step, independent variables were incorporated into the model if the probability of its score statistic was less than 0.11 ($p < 0.11$) and removed if $p > 0.2$. Significance assessments were performed where $p < 0.05$. Statistical analyses were done using IBM SPSS Statistics Version 23.

The effect of epirubicin was analysed by taking its CD into account. Pearson's chi-square p-values were calculated for different CDs to assess its association with the HF outcome. The CD versus the corresponding p-values were plotted in a probability function. The smallest dose where $p < 0.05$ was considered a preliminary threshold dose. Based on the probability function, the epirubicin CD was then classified into 4 categories such that the above-mentioned preliminary threshold dose was used as the lowest cutoff value, and higher cutoff values were set at decreasing breakpoints of the function. Breakpoints were defined as local minima of the first derivative of the function.

The effects of concomitant chemotherapeutic agents were assessed separately. In the preliminary analysis, the CDs of concomitant chemotherapeutic agents were divided into categories to estimate dose dependency in terms of HF incidence. For agents suspected of possessing a dose-dependent effect, Pearson's chi-square p-values were calculated for different CDs to estimate the threshold dose, like that described above. Different cutoff values for CDs were then tested in the multivariate analysis to identify dose-dependency.

To calculate and validate the results, the database was randomly split in a 70/30 ratio, the majority became the derivation cohort used to calculate score points, and the minority the validation cohort. Independent variables in the multivariate model where $p < 0.1$ were considered in terms of composing the risk score, in a similar fashion to the Framingham risk score [22]. Score points were calculated by dividing each regression coefficient (B) by the smallest beta coefficient in the model, then the quotient was rounded to the nearest integer (Supplementary material A). This score can be determined by simply totalling the risk points of a subject. Natural breakpoints of the score-HF incidence diagram were chosen to create 5 risk-score groups. Statistical differences between the risk groups were determined by Pearson's chi-square test.

After having calculated the HF risk scores for each subject in the validation cohort, these patients were also grouped into the 5 above-mentioned risk groups, the observed

Table 1
Baseline characteristics of the entire cohort in the epirubicin study.

Characteristics	N	Rate	Characteristics	N	Rate
Age range (years)			Stage of cancer[a]		
<40	578	7.2%	No spread or invasion	3378	41.9%
40–49	1468	18.2%	Regional lymph node or nearby structure invasion	1927	23.9%
50–59	2439	30.2%			
60–69	2448	30.3%	Distant lymph node or other distant metastasis	837	10.3%
70+	1135	14.1%			
			Missing data	1926	23.9%
Gender			Pre-existing cardiovascular conditions and risk factors		
Male	64	0.8%	Diabetes mellitus	1160	14.4%
Female	8454	99.2%	Hypertension	5121	63.5%
Laterality of cancer			Hyperlipidaemia	1336	16.6%
Left	3774	46.8%	Previous stroke	150	1.9%
Right	3799	47.1%	Previous MI[b] or coronary revascularization	258	3.2%
Both sides	288	3.6%			
Unknown	205	2.5%			

[a] Upon initiation of chemotherapy.
[b] Myocardial Infarction.

HF event rates were then calculated for the groups. HF incidences observed in the groups of the derivation and validation cohorts were compared. The suitability of fitting the regression model in terms of the occurrence of HF was examined using the Hosmer-Lemeshow test, which was also applied to assess fitting of the derived risk-score model. The discriminative ability of the score was evaluated by analysis of the receiver operating characteristic (ROC) curve.

3. Results

3.1. Heart failure risk estimation

With the analysis of a nationwide, integrated database over 13 years, HF incidence in 8068 epirubicin-treated breast cancer patients was assessed. The baseline characteristics of patients are shown in Table 1. The cumulative, overall incidence of HF was 6.90% during the studied period (median follow-up: 5.89 years). Our crude data showed an apparent HF dependence on age and epirubicin CD (Supplementary material B).

Occurrence of oncological therapies is shown in Table 2. As presented, nowadays higher epirubicin doses are rarely administered. In our cohort, a CD over 709 mg/m^2 was only administered to 1.4% of patients (median dose: 420 mg/m^2). The results of univariate statistical analysis showed that an epirubicin CD of <450 mg/m^2 was not associated with HF risk, but in excess of this, an increasingly strong association could be observed. The epirubicin CD was divided into 4 categories for analysing dose-dependency (Table 2).

A detailed analysis of HF risk was performed on the derivation cohort. All reasonable candidate predictors were included in the logistic regression. Variables included hypertension, diabetes mellitus, coronary artery disease, previous stroke, previous and ongoing treatment with ACEi/ARB, renal failure, hypothyroidism, hyperthyroidism, hyperlipidaemia, age, gender, cancer stage, epirubicin CD, presence of dexrazoxane and use of other non-anthracycline chemotherapies, namely pyrimidine analogues (capecitabine, gemcitabine, 5-fluorouracil), taxanes (paclitaxel, docetaxel), antifolates (methotrexate), cyclophosphamide, platinum-containing drugs (carboplatin) and targeted therapies (trastuzumab, bevacizumab).

The results are summarized in Fig. 1. Epirubicin cumulative doses >709 mg/m^2 were an independent variable significantly associated with HF (odds ratio (OR): 1.76). The only other form of chemotherapy that exhibited significant CD-dependency in terms of HF, besides epirubicin, was docetaxel; above the threshold dose of 510 mg/m^2 it was more strongly (OR: 1.59) associated with HF outcome, than under this dose (OR: 1.28). HF risk significantly increased for those over 40 years of age. Furthermore, the older the patient, the more robust the impact on HF: OR for HF for those >70 years of age was 9.83 (compared to those <40). The following factors were also confirmed as significant predictors in association with HF: diabetes mellitus, hypertension, coronary artery disease (CAD) (with previous MI or revascularization OR: 1.89, without OR: 1.30), previous stroke, capecitabine, gemcitabine, bevacizumab and advanced cancer with distant metastasis (for more details see Fig. 1).

Of the analysable factors, an epirubicin CD of 541–709 mg/m^2 and intermediate cancer stage without distant metastasis were shown to be associated with higher HF risk of borderline ($0.05 < p < 0.10$) significance, whilst the regular and ongoing use of ACEi/ARB commenced before chemotherapy (present in 25.9% of the cohort) similarly reduced the HF risk (Fig. 1). In the analysed cohort, antifolates (methotrexate), cyclophosphamide, platinum-containing drugs (carboplatin) and trastuzumab (targeted therapy) were not proven to be associated with a higher long-term HF risk. A protective effect could not be confirmed with dexrazoxane. In our study, an elevated HF risk as a result of chest irradiation was not identified, not even for left-sided tumour localisation.

3.2. Heart failure risk score model

Independent variables in the multivariate model were considered whilst composing a risk score model. The HF risk score points assigned

Table 2
Frequencies of cancer therapy in the entire cohort of epirubicin.

Cancer therapy	N	Rate
Radiation	6597	81.8%
Cumulative dose of epirubicin[a] (mg/m^2)		
≤450	7271	90.1%
451–540	456	5.7%
541–709	203	2.9%
>709	111	1.4%
Non-anthracycline chemotherapies		
Cyclophosphamide	6487	80.4%
Pyrimidine analogues	4408	54.6%
Capecitabine	436	5.4%
Gemcitabine	80	1.0%
5-fluorouracil	4161	51.6%
Taxanes	3424	42.4%
Paclitaxel	1244	15.4%
Docetaxel	2658	31.8%
Carboplatin	282	3.5%
Methotrexate	105	1.3%
Vinca alkaloid	67	0.8%
Targeted therapies (antibodies)		
Trastuzumab	1506	18.7%
Bevacizumab	107	1.3%
Lapatinib	46	0.6%
Protective agents		
Dexrazoxane	267	3.3%

[a] Standard 3-week schedule, with the exception of 16 patients.

can be seen in Fig. 1. The score points were calculated for each patient in the derivation cohort. The median number of points was 7. HF event rate increased as the number of score points rose. Using natural breakpoints of the score-HF incidence diagram, score points were divided into 5 categories from very low (2.1%) to very high (31.7%) HF incidence. Detailed statistical data about the categories can be found in Supplementary materials C and D. In Fig. 2 the point categories with corresponding HF rates observed in the derivation cohort can be seen. Differences in HF incidences between the neighbouring score categories were significant ($p = 2.88 * 10^{-10}$, $6.84 * 10^{-7}$, $1.04 * 10^{-14}$, 0.0219, respectively).

3.3. Risk score validation

Hosmer-Lemeshow test was applied to assess the regression and derived score models. The tests indicated that fitting of both models was good when $p > 0.05$, 0.29 for the regression model and 0.78 for the score model, which means that the hypothesis of sufficient fitting cannot be rejected.

Cumulative HF incidence was almost identical in the derivation and validation cohorts (6.84% vs. 7.04%). The median of the score points was also 7 in the validation cohort. After having classified the subjects into the previously mentioned risk score categories, a similar HF distribution pattern was observed in the two cohorts (Fig. 2). A 15-fold increase occurred in the observed incidence of HF between the outermost risk categories. The incidences observed in the derivation and validation cohorts do not differ to a clinically significant extent. The area under the ROC curve for the score-points model was 0.79 and the optimal cut-off value of the score points was ≥9 (sensitivity: 0.79; specificity: 0.65) to effectively identify patients exposed to an elevated HF risk.

4. Discussion

Our study is the first multivariate analysis that defines the effect of common comorbid conditions, medication, cancer stage and chemotherapy CDs together comprehensively with regard to the likelihood of HF in a large epirubicin-treated population. The analysed, nationwide, real-world database represents 10 years of current therapeutical practice, therefore, the derived score model is suitable to assess the long-term HF risk of a patient.

The overall cumulative incidence of HF was 6.9%. This data is in good agreement with the previously published results [7,17]. Since CD of chemotherapeutic agents was incorporated, the dose-dependency in terms of HF has become assessable. The cumulative dose threshold of epirubicin was 709 mg/m^2, for higher doses a significant increase in HF incidence was observed.

The potential effect on left ventricular systolic function deterioration with regard to taxanes is known, especially after administration of anthracyclines [4,23,24]. Our results supported the relevance of these previous findings for docetaxel, but not for paclitaxel. Moreover, a CD-dependent effect of docetaxel for initiating HF was observed. In our analysis, no other chemotherapeutic drugs exhibited a CD-dependent effect on HF.

Fluoropyrimidine analogues (capecitabine, gemcitabine, 5-fluorouracil) are well known for their adverse cardiac effects, but these are mainly caused by coronary vasospasm or thrombosis [25–27]. Concerning 5-fluorouracil, some case reports revealed direct myocardial damage [26], the clinical impact of this effect remained unclear. Although case reports concerning capecitabine-related cardiomyopathy have been published [28], its incidence has not yet been clarified. However, our results suggest that capecitabine and gemcitabine are associated with a higher HF risk, but no elevation in risk was found for 5-fluorouracil.

Trastuzumab, the well-known ErbB2 receptor antagonist antibody, exhibits a well-understood cardiotoxic effect. In adjuvant clinical trials involving patients without a cardiovascular history, it was associated with a symptomatic HF rate of 2–5% [4,29,30]. However, thanks to the obligatory echocardiographic monitoring prescribed during this therapy and the dominantly rapidly reversible characteristic of trastuzumab-related systolic dysfunction, the long-term HF risk was only slightly elevated following this medication [31]. Accordingly, this drug was not associated with an elevated HF risk in our long-term analysis based on data from hospitalizations and autopsies. Contrarily, for bevacizumab,

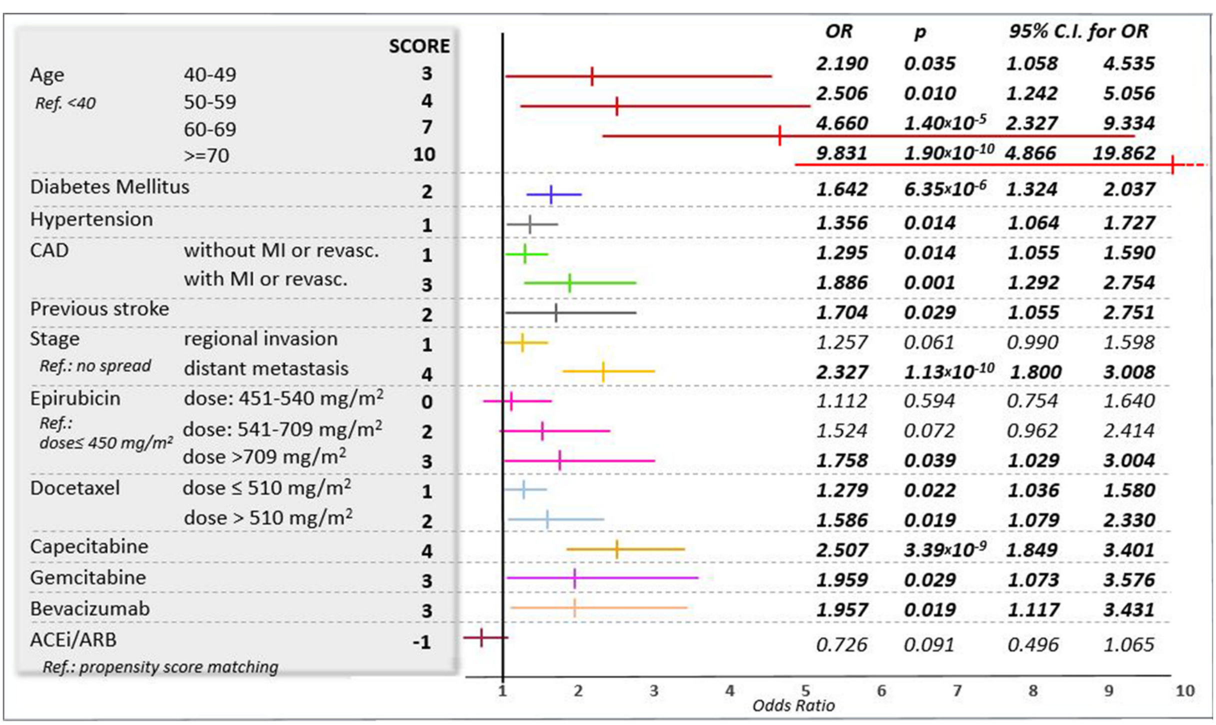

Fig. 1. Independent predictors for heart failure in the multivariate regression analysis and the corresponding odds ratios (OR) with confidence intervals (CI) and heart failure score points. DM: diabetes mellitus. CAD: coronary artery disease. MI: myocardial infarction.

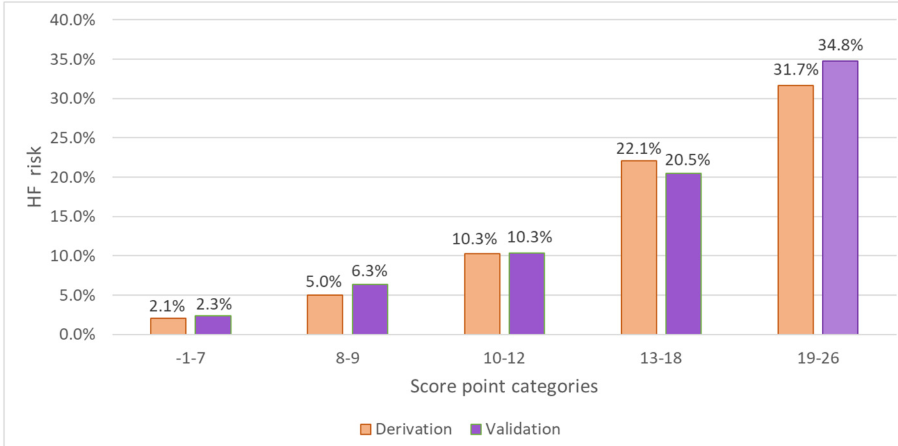

Fig. 2. Observed heart failure incidence in the derivation and validation cohorts.

an anti-vascular endothelial growth factor monoclonal antibody, administered for metastatic breast cancer, an elevated HF risk was observed. A common side effect of this drug is hypertension. Its influence on HF has yet to be thoroughly explored, but may be partly mediated by its hypertensive effect [4,32].

As a protective agent, the ability of dexrazoxane to reduce HF risk was not confirmed. Nevertheless, in spite of our screening process to filter out previous HF patients from the analysis, selection bias cannot be excluded from such a retrospective analysis. Therefore, these data should be interpreted with care.

Previous papers showed that patients over 65 were at a greater risk of HF after anthracycline chemotherapy [4,18–21]. Our data indicate that age affects HF incidence even for patients over 40, and the risk of HF increases rapidly with age. As expected, diabetes mellitus, hypertension and coronary artery disease were also proven HF risk factors. Moreover, a previous stroke was also found to be an independent HF predictor.

Since a protective effect had been supposed, modifications to HF risk associated with ACEi/ARB treatment were assessed. Compared to a propensity score-matched reference group, a reduction in the risk of HF of borderline significance was observed for regular, previously initiated and ongoing ACEi/ARB therapy.

Similarly to the previously published data [21,33], radiotherapy treatment did not cause an elevated HF risk. Presumably, modern radiation therapies, which are carried out in respect of heart protection, do not have an impact on HF development.

The suggested risk-score-points model (Fig. 1) is able to differentiate HF risk between 2 and 30%. By means of our score, an elevated long-term HF risk can be identified with good sensitivity (0.79) and acceptable specificity (0.65). A tailored assessment of HF risk can help clinicians determine the appropriate treatment. For high-risk patients, preventive strategies such as initiation of ACEi/ARB, beta-blockers, aldosterone antagonists or dexrazoxane may be considered [34–36]. Moreover, by this score, echocardiography follow-up intensity can be optimized during and after chemotherapy to ensure cardiomyopathy is diagnosed early. Combined HF therapy initiated at the early stage of anthracycline-related DCM can, at least partially, reverse the deterioration of left ventricular function [7].

4.1. Study limitations

As our analysis was performed partly on an administrative database, the method may have potential limitations. To minimize the effect of selection bias, patients with previous diagnoses of HF or DCM were ruled out. However, in this way, special populations at higher risk of developing HF (e.g. those with significant valve disease or reduced ejection fraction) may not have been enrolled. In addition, echocardiographic results were not available, hence the assessment of HF severity and differentiation between systolic and diastolic HF were not achievable. Due to low representation, the effect of very high epirubicin cumulative doses (>1000 mg/m^2) could not be evaluated.

5. Conclusion

For routinely applied epirubicin doses, the prediction of long-term HF risk became accurate with the suggested score, which is based on clinical data. By virtue of this, surveillance and preventive strategies can be individualized to reach the optimal outcome.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.013.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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