

Risk Prediction Model for Heart Failure and Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer

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Background—Adjuvant trastuzumab improves survival for women with human epidermal growth factor receptor 2-positive breast cancer, but increases risk for heart failure (HF) and cardiomyopathy (CM). However, clinical trials may underestimate HF/CM risk because they enroll younger subjects with fewer cardiac risk factors. We sought to develop a clinical risk score that identifies older women with breast cancer who are at higher risk of HF or CM after trastuzumab.

Methods and Results—Using the Surveillance, Epidemiology and End Results (SEER)-Medicare database, we identified women with breast cancer who received adjuvant trastuzumab. Using a split-sample design, we used a proportional hazards model to identify candidate predictors of HF/CM in a derivation cohort. A risk score was constructed using regression coefficients, and HF/CM rates were calculated in the validation cohort. The sample consisted of 1664 older women (mean age 73.6 years) with 3-year HF/CM rate of 19.1%. A risk score consisting of age, adjuvant chemotherapy, coronary artery disease, atrial fibrillation or flutter, diabetes mellitus, hypertension, and renal failure was able to classify HF/CM risk into low (0 to 3 points), medium (4 to 5 points), and high (≥ 6 points) risk strata with 3-year rates of 16.2%, 26.0%, and 39.5%, respectively.

Conclusions—A 7-factor risk score was able to stratify 3-year risk of HF/CM after trastuzumab between the lowest and highest risk groups by more than 2-fold in a Medicare population. These findings will inform future research aimed at further developing a clinical risk score for HF/CM for breast cancer patients of all ages. (*J Am Heart Assoc.* 2014;3:e000472 doi: 10.1161/JAHA.113.000472)

Key Words: breast cancer • cardiomyopathy • heart failure • trastuzumab

Randomized clinical trials have demonstrated that adding trastuzumab to adjuvant chemotherapy for women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer improves overall and disease-free survival.^{1–3} A serious complication of trastuzumab therapy is left ventricular systolic dysfunction (LVSD) which can lead to cardiomyopathy (CM) and overt heart failure (HF).⁴ Clinical trials of trastuzumab have reported HF in 1.7% to 4.1% of subjects, and

reduced left ventricular ejection fraction (LVEF) in 7.1% to 18.6% of subjects treated with adjuvant chemotherapy and trastuzumab.^{1–3}

However, HF and CM rates after adjuvant trastuzumab therapy were considerably higher for patients in registry cohorts outside of clinical trials.^{5–7} For example, data from the Cancer Research Network found 5-year combined HF/CM rates of 12.1% for patients treated with trastuzumab alone, and 20.1% for patients treated with trastuzumab and anthracyclines.⁵ The likely explanation for this difference is that clinical trials typically enrolled younger and healthier subjects, while excluding older patients or those with existing heart disease or cardiac risk factors such as uncontrolled hypertension.¹ Because women older than 65 years comprise nearly 40% of all breast cancer patients,⁸ estimates of cardiac risk from clinical trials may not necessarily be appropriate for many patients in the general population.

Personalized risk assessment for cardiac complications following adjuvant trastuzumab therapy could offer several potential benefits to patients. Identifying individuals at high risk for LVSD may inform decisions about the duration of adjuvant treatments.^{9,10} More precise risk stratification may also identify patients who may benefit from more frequent

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Accompanying Appendix S1 is available at <http://jaha.ahajournals.org/content/3/1/e000472/suppl/DC1>

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screening of LVEF for earlier detection of LVSD, or more accurately identify clinical scenarios where emerging strategies such as use of biomarkers or novel imaging technologies aimed at identifying subjects at high risk may be employed more effectively.¹¹

Accordingly, we used the Surveillance, Epidemiology and End Results (SEER)-Medicare dataset to develop and validate a risk score for predicting HF and CM in women with nonmetastatic breast cancer treated with adjuvant trastuzumab.

Methods

Data Source

SEER-Medicare is a database of tumor registries linked to Medicare claims data created by a collaboration between the National Cancer Institute, SEER, and the Centers for Medicare and Medicaid Services. SEER-Medicare contains data on patient demographics and cancer characteristics as well as chemotherapy, biologic therapy, and procedures ascertained from billing claims by hospitals, outpatient facilities, and physicians.^{12,13}

Study Cohort

The study cohort consisted of women 67 to 94 years old from the SEER-Medicare database diagnosed with early-stage breast cancer (stages I to III) from January 1, 2000 to December 31, 2009. We included women who underwent surgery and adjuvant trastuzumab treatment (diagnosis through 9 months post surgery). Breast cancer stage was collected in the SEER registries. Type of breast surgery and adjuvant chemotherapy was determined from Medicare claims (see Appendix for relevant claims codes).

Subjects were excluded if they had any of the following: (1) pre-existing HF or CM, defined as International Classification of Disease, 9th Edition, Clinical Modification (ICD-9-CM) diagnosis of HF or CM (see Appendix) in the 2 years prior breast cancer diagnosis; (2) pre-existing cancer diagnosis (ie, breast cancer was not the initial tumor diagnosis reported to SEER or Medicare claims include any cancer diagnosis 2 years before the initial diagnosis of breast cancer); (3) chemotherapy or trastuzumab initiated more than 9 months after surgery; (4) failure to have continuous fee-for-service Medicare Part A or Part B coverage and at least one approved Medicare claim from 2 years before breast cancer diagnosis through death or end of follow-up; (5) breast cancer diagnosis from autopsy or death certificate; (6) the month of breast cancer diagnosis was missing or the patient died during the month of diagnosis (because we were unable to ascertain the specific date of diagnosis to establish order of events); or (7) tumor stage recorded as missing or histology was reported to be not of epithelial origin.

Construction of Variables

The outcome of interest was incident HF or CM within 3 years after diagnosis. As recommended by current algorithms, incident HF or CM was defined as ICD-9-CM codes that appeared in at least one inpatient claim or 2 outpatient claims at least 30 days apart, in order to increase specificity.^{6,14}

Candidate predictors of HF or CM included age and race (classified into white and nonwhite) as well as the following cardiovascular conditions and risk factors: coronary artery disease, stroke/transient ischemic attack (TIA), atrial fibrillation or flutter, hyperlipidemia, hypertension, diabetes mellitus, and renal failure (see Appendix for diagnosis codes). Cardiovascular conditions and risk factors were ascertained from ICD-9-CM codes from clinical encounters that occurred any time within the 2 years prior to breast cancer diagnosis. Noncardiovascular comorbidities were similarly ascertained from ICD-9-CM codes using the Elixhauser method¹⁵ which is commonly used in studies requiring risk-adjustment based on administrative claims. The number of noncardiovascular comorbidities was also evaluated as a potential predictor.

A number of breast cancer characteristics were also evaluated, including: stage at diagnosis (I to III), grade, tumor size, number of positive lymph nodes, type of surgery (breast conservation or mastectomy), and site of radiation (left, right, none). Adjuvant chemotherapy was classified into 3 categories: anthracycline-based, nonanthracycline-based, or no chemotherapy. Anthracycline-based regimens were defined as those which included doxorubicin or epirubicin.

We also examined the impact of including proxies of the intensity of healthcare interaction in the multivariate analysis, since the study outcomes were ascertained by claims data and may have been influenced to some extent by access to healthcare. These proxy variables included influenza vaccination, the presence of at least one physician visit, and number of days hospitalized during the 2 years prior to breast cancer diagnosis.

Statistical Analysis

Risk score derivation

The overall sample was randomly split into equal-sized derivation and validation cohorts. In the derivation sample, chi-square tests were used to identify bivariate relationships between the candidate predictors and the HF/CM outcome. Age was classified into 3 categories (67 to 74, 75 to 79, and ≥ 80 years). We did not find age to be an effect measure modifier with any variable included in the preliminary model. Variables with bivariate *P* values < 0.20 were entered into a multivariate Cox proportional hazard model examining time

until first HF/CM claim in the derivation sample. Independent variables in the multivariate model with P values <0.10 were then used to construct a risk score, in a similar manner to the Framingham Risk Score.¹⁶ Briefly, the number of points assigned to each covariate predictor equaled its regression coefficient divided by the coefficient in the model with the smallest absolute value, and then rounded to the nearest integer. The overall risk score for a given individual was the total sum of points.

Risk score validation

The risk score was then calculated for each subject in the validation cohort, and the 3-year HF/CM event rate was calculated for each point score value. SEER-Medicare policy precludes publication of tables with cell sizes less than 11 subjects. Accordingly, risk score groups were combined in the tables to comply with a minimum cell size. Natural breakpoints of risk scores were evaluated to identify high- and low-risk groups. Statistical differences in risk groups were assessed using the chi-squared test. We tested the lack of fit using the Hosmer-Lemeshow statistic in a logistic regression for occurrence of HF/CM within 3 years according to risk score. The test indicated that the model fit sufficiently well with a P value=0.76, which indicated that we were not able to reject the hypothesis that the model fit was good.

Statistical analyses were performed using SAS software version 9.2 (SAS Inc). Statistical significance testing was assessed at the $P=0.05$ level. The Yale Human Investigation Committee and the Kaiser Permanente Mid-Atlantic States Institutional Review Board deemed that this study did not directly involve human subjects.

Results

Study Population

The overall study cohort consisted of 1664 older women who had mean age of 73.6 years (standard deviation 5.3) and were predominately of white race (88.5%). A total of 597 (35.9%) women were treated with anthracycline chemotherapy, 794 (47.7%) with nonanthracycline chemotherapy, and 273 (16.4%) received no adjuvant chemotherapy. The majority of women had stage II cancer (45.6%) and poorly-differentiated grade (63.3%) (Table 1). The mean 3-year HF/CM rate in the overall cohort was 19.1%.

Pre-existing cardiovascular conditions and risk factors were common, such as hypertension (60.2%), hyperlipidemia (59.0%), and diabetes mellitus (19.5%). Coronary artery disease and prior stroke/TIA were present in 3.6% and 4.9% of the cohort, respectively. At least one noncardiovascular comorbidity was present in 35.5% of patients.

Risk Score Derivation

Of the candidate predictors we selected age, chemotherapy type, coronary artery disease, atrial fibrillation/flutter, diabetes mellitus, hypertension, and renal failure as components for the risk score (Table 2). Adjuvant chemotherapy increased the risk of HF/CM for both anthracyclines (hazard ratio [HR]=1.93) and nonanthracyclines (HR=1.64) compared with no chemotherapy. Risk of HF/CM was higher with increasing age: age 75 to 79 years (HR=1.36) and age 80 to 94 years (HR=2.04) compared with age 67 to 74 years. Risk of HF/CM was doubled for patients with prior coronary artery disease (HR=2.16) and renal failure (HR=1.99). Diabetes mellitus (HR=1.50), hypertension (HR=1.44), and atrial fibrillation / flutter (HR=1.69) were also associated with higher risk HF/CM.

We considered a woman 67 to 74 years old who did not receive identified chemotherapy and had none of the pre-existing cardiovascular conditions and risk factors as the reference; she would have a risk score of 0. Individual risk factors contributed 1 or 2 points to the risk score. Age showed a dose response with individuals 75 to 79 being assigned 1 point and women 80 to 94 being assigned 2 points. Receipt of either anthracycline containing or nonanthracycline chemotherapy conferred 2 points. Prior coronary artery disease was associated with more than 2-fold increased risk of HF/CM, and was strongly statistically significant ($P=0.009$). Additionally prior diagnosis of diabetes mellitus was associated with 50% increased risk of HF/CM ($P=0.034$).

In the derivation cohort, the risk score for subjects ranged from 0 to 9. The median risk score was 3, with a 3-year HF/CM event rate of 16.2%. The risk of HF/CM increased with higher risk score, ranging from 13.0% for a risk score of 0 to 2 to 42.9% for a risk score of 6 to 9. Natural breakpoints of 0 to 3, 4 to 5, and ≥ 6 points were selected to stratify the cohort into 3-year HF/CM event rates of $<20\%$, 20 to 39%, and $\geq 40\%$ for evaluation in the validation cohort (Table 3).

Risk Score Validation

In the validation cohort, the 3-year HF/CM event rates increased as risk score increased: 16.2% for subjects with a risk score of 0 to 3; 26.0% for a risk score of 4 or 5; and 39.5% for the highest risk group with a risk score of 6 or more ($P<0.001$) (Table 3). When the risk score was classified using natural breakpoints of 3-year HF/CM rates at $<20\%$ (low), 20% to 39% (medium) and $>40\%$ (high) in the derivation cohort, a similar pattern was observed in HF/CM outcomes in the validation cohort (Figure). Patients with a risk score of 6 or more points had more than 2-fold risk of HF/CM compared with patients with a risk score of 0 to 3 ($P<0.001$).

Table 1. Baseline Characteristics of Full Study Sample

Characteristics	N	%
Overall	1664	100.0
Adjuvant therapy		
Anthracycline chemotherapy	597	35.9
Non-anthracycline chemotherapy	794	47.7
No identified chemotherapy	273	16.4
Age category, y		
67 to 69	437	26.3
70 to 74	608	36.5
75 to 79	366	22.0
80 to 94	253	15.2
Race		
White	1473	88.5
Nonwhite	191	11.5
Pre-existing cardiovascular conditions and risk factors		
Coronary artery disease	60	3.6
Stroke/Transient ischemic attack	81	4.9
Atrial fibrillation/flutter	90	5.4
Diabetes mellitus	325	19.5
Hypertension	1002	60.2
Renal failure	39	2.3
Hyperlipidemia	981	59.0
Number of noncardiovascular comorbidities		
None	1074	64.5
1 to 2	524	31.5
3 or more	66	4.0
Breast cancer characteristics		
Stage		
I	446	26.8
II	758	45.6
III	460	27.6
Grade		
Well differentiated	52	3.1
Moderately differentiated	443	26.6
Poorly differentiated	1053	63.3
Undifferentiated; anaplastic	37	2.2
Unknown	74	4.4
Tumor size, cm		
<2.0	606	36.4
2.0 to ≤5.0	835	50.2
>5.0	165	9.9
Missing	58	3.5

Continued

Table 1. Continued

Characteristics	N	%
Number of positive lymph nodes		
No positive nodes	750	45.1
1 to 3 positive nodes	455	27.3
4+ positive nodes	372	22.4
No nodes examined	57	3.4
Unknown no. positive nodes	30	1.8
Surgery		
Breast conserving	708	42.5
Mastectomy	956	57.5
Radiation therapy		
Right side	445	26.7
Left side	504	30.3
None	715	43.0
Healthcare system interaction in past year		
Influenza vaccination		
Yes	1008	60.6
No	656	39.4
Physician visit		
Yes	1567	94.2
No	97	5.8
Hospitalization		
Yes	512	30.8
No	1152	69.2
Days hospitalized		
0 days	1152	69.2
1 to 2 days	246	14.8
3 to 4 days	79	4.7
5+ days	187	11.2

Discussion

This study demonstrates that a risk score derived from SEER-Medicare was able to identify a high-risk group for HF/CM among older women who received adjuvant trastuzumab for breast cancer. Our score incorporated risk factors readily obtainable by practitioners, and was able to successfully stratify patients into low, moderate and high-risk groups for developing HF/CM, with the high-risk group had more than double the 3-year HF/CM rate compared with the low risk group. Although risk factors and outcomes from SEER-Medicare were based on administrative claims, our findings demonstrate feasibility of identifying a high-risk subgroup for LVSD, serving as proof-of-concept for future clinically-derived risk models.

Table 2. Cox Regression Coefficients and Point Assignment for Each Risk Factor

Risk Factor	Hazard Ratio (95% Confidence Interval)	Regression Coefficient	P Value	Points Assigned
Adjuvant therapy				
Anthracycline chemotherapy	1.93 (1.11 to 3.36)	0.66	0.020	2
Non-anthracycline chemotherapy	1.64 (0.99 to 2.73)	0.50	0.055	2
No identified chemotherapy	Reference	Reference		
Age category, y				
67 to 74	Reference	Reference		
75 to 79	1.36 (0.92 to 2.01)	0.31	0.125	1
80 to 94	2.04 (1.29 to 3.24)	0.71	0.003	2
Cardiovascular conditions and risk factors				
Coronary artery disease	2.16 (1.21 to 3.86)	0.77	0.009	2
Atrial fibrillation/flutter	1.69 (0.98 to 2.91)	0.53	0.058	2
Diabetes mellitus	1.50 (1.03 to 2.18)	0.41	0.034	1
Hypertension	1.44 (0.99 to 2.08)	0.36	0.054	1
Renal failure	1.99 (0.96 to 4.14)	0.69	0.065	2

Table 3. 3-Year Risk of HF/CM by Risk Score

Risk Score	Derivation			Validation		
	Total	HF/CM 3 Years		Total	HF/CM 3 Years	
	N	N	%	N	N	%
0, 1, 2, or 3	595	86	14.5	594	96	16.2
4 or 5	195	51	26.2	200	52	26.0
6, 7, 8, or 9	42	18	42.9	38	15	39.5

CM indicates cardiomyopathy; HF, heart failure.

Identifying women at high risk for HF/CM after adjuvant breast cancer therapy has several potentially important applications. First, clinicians may decide to assess LVEF more frequently for patients at highest risk for HF/CM associated with adjuvant therapy in order to detect LVSD earlier. While guidelines exist for frequency of LVEF assessment for trastuzumab therapy,^{17,18} the evidence base for timing is sparse, and our findings suggest more frequent assessment of LVEF in the highest-risk patients may be potentially warranted. A strategy of selective LVEF assessment is also consistent with a previous study of early-stage breast cancer that found that routine LVEF screening did not influence treatment decisions for women less than 65 years of age without cardiac risk factors.¹⁹ The study’s implication that LVEF screening is unlikely to alter treatment decisions for low-risk patients, suggests that the converse may also be the case where more frequent LVEF screening would have clinical utility for individuals at increased risk. While suggestive, the

question of which patients should be screened more often (or less often) during trastuzumab therapy and its downstream effects will require prospective evaluation.

Several biomarkers, such as troponin and B-natriuretic peptide (BNP), have been proposed as potential alternatives or supplements to routine LVEF assessment for predicting LVSD after adjuvant therapy.^{11,20–22} Advanced techniques such as echocardiographic strain or cardiac magnetic resonance imaging have also been offered as ways to improve LVEF prediction.^{11,22–25} A strategy of using biomarker with clinical assessment may have a more favorable cost-effectiveness profile compared with advanced cardiac imaging, but in the absence of a clinical risk prediction model, the extent to which any of these strategies improve upon clinical assessment alone is unknown. While novel biomarker or imaging strategies may individually predict future HF/CM events independently, this does not imply there is significant incremental predictive ability above clinical assessment. The value of using a clinical risk model framework as a baseline can be seen in the example of the Framingham Risk Score, where the additional predictive ability of novel imaging (such as coronary calcium scoring) or novel biochemical assays (such as C-reactive protein) have to be proven against a clinical risk score.^{26,27} In an era of constrained resources, demonstrating incremental utility is crucial, and a clinical risk score can be a valuable tool for parsing out which novel strategies would be both clinically effective and cost-effective to adopt in the future.

Third, identifying high-risk patients may play a role for identifying which individuals would derive the most benefit from prophylaxis medications currently under investigation for

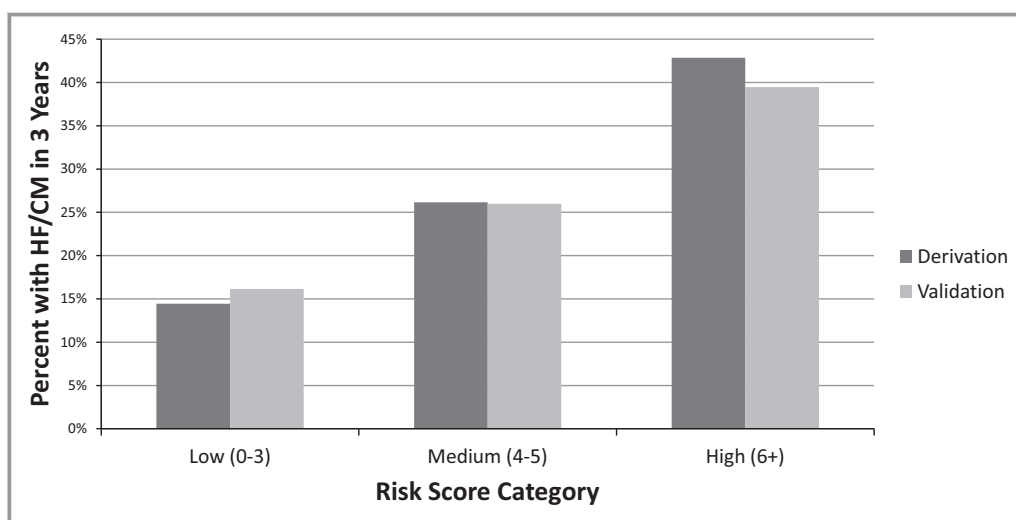


Figure. 3-year cumulative HF/CM rate by risk score category. CM indicates cardiomyopathy; HF, heart failure.

preventing trastuzumab-associated LVSD. Small studies have suggested that angiotensin-converting enzyme (ACE)-inhibitors and β -blockers may reduce risk of HF/CM after adjuvant chemotherapy or trastuzumab therapy,^{28–30} with clinical trials currently underway.^{31,32} A clinical risk score can potentially identify patients at highest absolute risk where preventative therapy would be most effective. While the side-effect profile of many of the medications under investigation is typically tolerable, it still may not be clinically appropriate for patients at very low risk to commit to these medications if the number-needed-to-treat to prevent one HF/CM case is high. Such an approach is analogous to current guidelines not recommending statins for individuals at low cardiovascular risk as determined by the Framingham Risk Score.³³

Finally, in an era of patient-centered care it is important that clinicians provide tailored assessments of risk and benefit. Real-life trastuzumab-associated HF/CM event rates from clinical registries are substantially higher than those from clinical trials of younger and more selective population, and as such patients may be inaccurately informed. For example, women at high risk for HF/CM with trastuzumab therapy may elect to undergo alternative adjuvant treatment regimens, such as the protocol of the FinHer trial.¹⁰ Even if the choice of cancer therapy remains unaltered, patients deserve to have as accurate knowledge of the risks of complications as possible—a risk score can provide a simple and effective method for providing such information.

A prior study based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial derived a risk score for predicting symptomatic HF with corresponding LVEF decline and definite or probable cardiac death.³⁴ In contrast to our study, only age and baseline LVEF were predictive of HF or cardiac death over 5 years. Risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking status, and family

history were not found to be statistically significant in the NSABP B-31 study. A possible explanation for this difference is that the trial population was considerably younger with fewer or less severe comorbidity—median age was 49 years compared with 73.6 years in our study, with lower rates of hypertension (20.4% versus 60.2%) and diabetes mellitus (3.8% versus 19.5%). The NSABP B-31 cohort consisted of low-risk patients with few cardiovascular risk factors, and this low variability may have limited the ability for a clinical risk score to be developed in a cohort of younger women. Overall, future studies should examine the combined role of cardiovascular risk factors and baseline LVEF for predicting cardiac events in cancer patients drawn from the general population.

Limitations

Our study's use of administrative data has a number of potential limitations. While we acknowledge that a risk score in clinical practice would ideally be derived from clinical data rather than administrative data, our aim was to demonstrate proof-of-concept that a high-risk group could be identified from clinical risk factors alone. HF and CM events and comorbidities were ascertained through administrative codes and not confirmed clinically. However, administrative codes for HF and cardiovascular comorbidities have high specificity ($\approx 95\%$) and positive predictive value (95%).^{35–38} In addition, measures of left ventricular systolic function were not available, and neither the severity of CM nor differentiation of systolic from diastolic HF could be established. Lastly, information on medication use in SEER-Medicare was limited, which may introduce residual confounding if cardiovascular therapies such as β -blockers and ACE-inhibitors reduce risk of trastuzumab-associated LVSD and the use of these therapies varied significantly across risk strata.

Conclusion

In a cohort of older women with breast cancer we demonstrate proof-of-concept that a 7-factor clinical risk score is able to stratify risk of developing HF or CM after trastuzumab adjuvant therapy for breast cancer by more than 2-fold.

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Disclosures

None.

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