

## ORIGINAL RESEARCH

# Symptomatic Heart Failure in Acute Leukemia Patients Treated With Anthracyclines



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## ABSTRACT

**OBJECTIVES** The purpose of this study was to investigate the occurrence and develop a risk score for heart failure (HF) in acute leukemia.

**BACKGROUND** Knowledge is scarce regarding the incidence and risk factors of symptomatic HF in patients with acute leukemia.

**METHODS** Baseline clinical and echocardiographic parameters, including indices of cardiac function (left ventricular ejection fraction and myocardial strain [global longitudinal strain; GLS]), were obtained in 450 patients with acute leukemia treated with anthracyclines, before chemotherapy initiation. Potential risk factors for HF were evaluated using Fine and Gray's regression analysis, and from this, a 21-point risk score was generated.

**RESULTS** Forty patients (8.9%) developed HF. The HF risk score included a baseline GLS  $>-15\%$  (indicative of greater impairment) (6 points), baseline left ventricular ejection fraction  $<50\%$ , pre-existing cardiovascular disease, acute myeloid leukemia (4 points each), cumulative anthracycline dose  $\geq 250$  mg/m<sup>2</sup> (2 points), and age  $>60$  years (1 point). Patients were stratified into low (score 0 to 6), moderate (score 7 to 13), and high risk (score 14 to 21). The estimated 1-year cumulative incidence of HF for low-, moderate-, and high-risk groups was 1.0%, 13.6%, and 35.0%, respectively ( $p < 0.001$ ). The HF risk score was also predictive of all-cause mortality ( $p < 0.001$ ). After adjustment for age and leukemia type, however, only GLS was significantly associated with all-cause mortality (hazard ratio: 1.73; 95% confidence interval: 1.30 to 2.31;  $p < 0.001$ ).

**CONCLUSIONS** We developed a baseline risk score to determine risk of HF in patients with acute leukemia. Additional studies are needed to determine the external validity of these findings. (J Am Coll Cardiol CardioOnc 2019;1:208-17) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Over the past decade, the incidence of acute leukemia has been increasing, approximately 0.5% per year from 2004 and 2007 for both sexes, and by 1.6% per year in men and 0.6% per year in women from 2007 to 2011. An estimated 25,480 new cases of acute leukemia will be diagnosed in the United States in 2018 (1,2). In parallel, leukemia-directed therapy has improved, leading to a significant increase in the overall survival of patients with leukemia. The incidence of death has declined by 0.8% in male and 1.4% in female patients from 2004 to 2007, and approximately 1.0% per year in both sexes from 2006 to 2015 (1,2). Improved survival, however, un-masks the impact of comorbidities. Heart failure (HF), compounded by the use of cardiotoxic cancer therapy, is now a leading cause of death and disability among cancer survivors (3,4). For example, HF as a result of anthracycline therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy.

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Standard induction regimens used for most patients with acute leukemia are based on a backbone of anthracyclines plus cytarabine (acute myeloid leukemia [AML]) or vincristine, corticosteroid (acute lymphoblastic leukemia [ALL]). For patients who cannot tolerate anthracyclines, a less intensive anthracycline-free therapy may be selected (5,6). In an analysis of 2,285 patients treated with anthracyclines, the highest rate of symptomatic HF and cardiac death was detected in patients with hematologic malignancies, as compared with other cancers (7). However, studies pertaining to comorbidities in adult patients with acute leukemia have been limited, and little is known about the incidence and risk stratification of symptomatic HF in this population.

Myocardial strain, a measure of myocardial deformation, can be quantified by echocardiography. Peak global longitudinal systolic strain has been used for the early detection of myocardial injury in various cardiac diseases, in particular in patients exposed to anthracyclines (8-12). An early worsening in peak longitudinal strain predicts subsequent decreases in left ventricular ejection fraction (LVEF) (13,14). Therefore, the objective of the present study was to detail the occurrence of symptomatic HF in a large contemporaneous population of patients with acute leukemia. Furthermore, we aimed to develop a risk score, derived from the combination of clinical risk factors, as well as myocardial strain.

## METHODS

This study was conducted at the Hospital of the University of Pennsylvania (HUP). HUP maintains an integrated medical record system of all encounters that identifies each patient with a unique number, which served as the basis for our analysis. This unique number was also used in other hospitals or outpatient clinics within the University of Pennsylvania Health System. The institutional review board of the University of Pennsylvania approved the study.

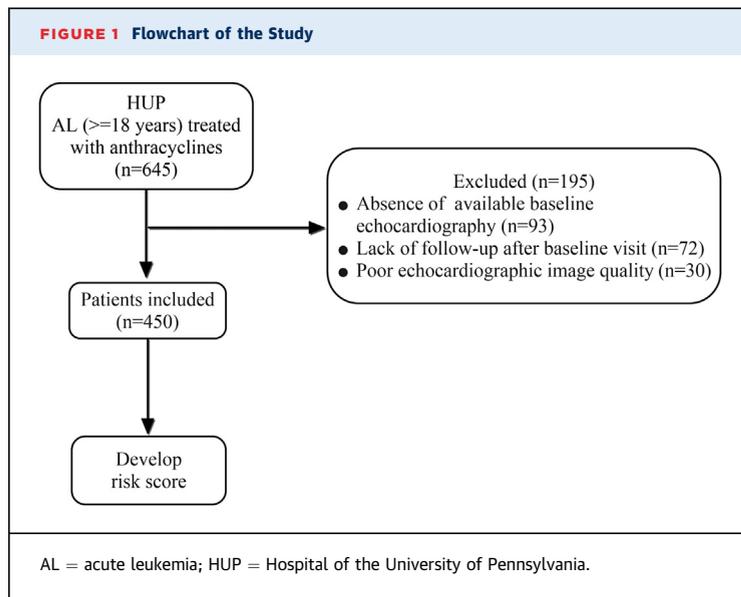
**IDENTIFICATION OF PATIENTS AND ENDPOINTS.** All consecutive adult patients ( $\geq 18$  years of age) with newly diagnosed AML or ALL treated with anthracyclines at HUP between January 2004 and April 2018 were identified. Patients without available baseline echocardiographic images or with poor echocardiographic image quality (defined as  $>2$  nonvisualized segments) or lack of follow-

up record after the first hospital admission were excluded. We accessed each individual's medical record from HUP and other hospitals or outpatient clinics within the entire University of Pennsylvania Health System. Patients were monitored based on a recommended protocol (15), that included quarterly visits throughout the first to third year and biannual visits; thereafter, ensuring that events of interest could be successfully captured. If patients had no encounters over the preceding 12 months before the end of the study (June 30, 2018), there was a search for published obituaries. Incomplete follow-up was defined as no encounters within 12 months of the end of the study (June 30, 2018) and no notice of death.

We defined symptomatic HF based on the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials (15). Symptomatic HF was confirmed if the patients had at least 1 of the new-onset or worsening HF symptoms (dyspnea, decreased exercise tolerance, fatigue, other symptoms of worsened end-organ perfusion or volume overload) as well as 1 of the following criteria: 1) at least 2 physical examination findings (peripheral edema, increasing abdominal distension or ascites in the absence of primary hepatic disease, pulmonary rales/crackles/crepitations, increased jugular venous pressure and/or hepatojugular reflux, S3 gallop, significant/rapid weight gain related to fluid retention) or 1 physical examination finding and at least 1 piece of laboratory evidence supporting the diagnosis (increased B-type natriuretic peptide/N-terminal

## ABBREVIATIONS AND ACRONYMS

<b>ALL</b>	= acute lymphoblastic leukemia
<b>AML</b>	= acute myeloid leukemia
<b>AUC</b>	= area under the curve
<b>BIC</b>	= Bayesian information criteria
<b>CI</b>	= confidence interval
<b>CV</b>	= cardiovascular
<b>GLS</b>	= global longitudinal strain
<b>HF</b>	= heart failure
<b>HR</b>	= hazard ratio
<b>HUP</b>	= Hospital of the University of Pennsylvania
<b>ICC</b>	= intraclass correlation coefficient
<b>ICD</b>	= International Classification of Diseases
<b>LS</b>	= longitudinal strain
<b>LVEF</b>	= left ventricular ejection fraction



pro-B-type natriuretic peptide; radiological evidence of pulmonary congestion; noninvasive evidence of elevated left- or right-sided ventricular filling pressure or low cardiac output; invasive diagnostic evidence of elevated pulmonary capillary wedge pressure, central venous pressure, or low cardiac index); and 2) at least 1 relevant HF therapy, whether pharmacological, mechanical, or both. Symptomatic HF was adjudicated by 2 independent cardiologists (YK and BL). A decrease in LVEF secondary to sepsis was not adjudicated as HF. Disagreement between the 2 readers was adjudicated by a third cardiologist (MSC).

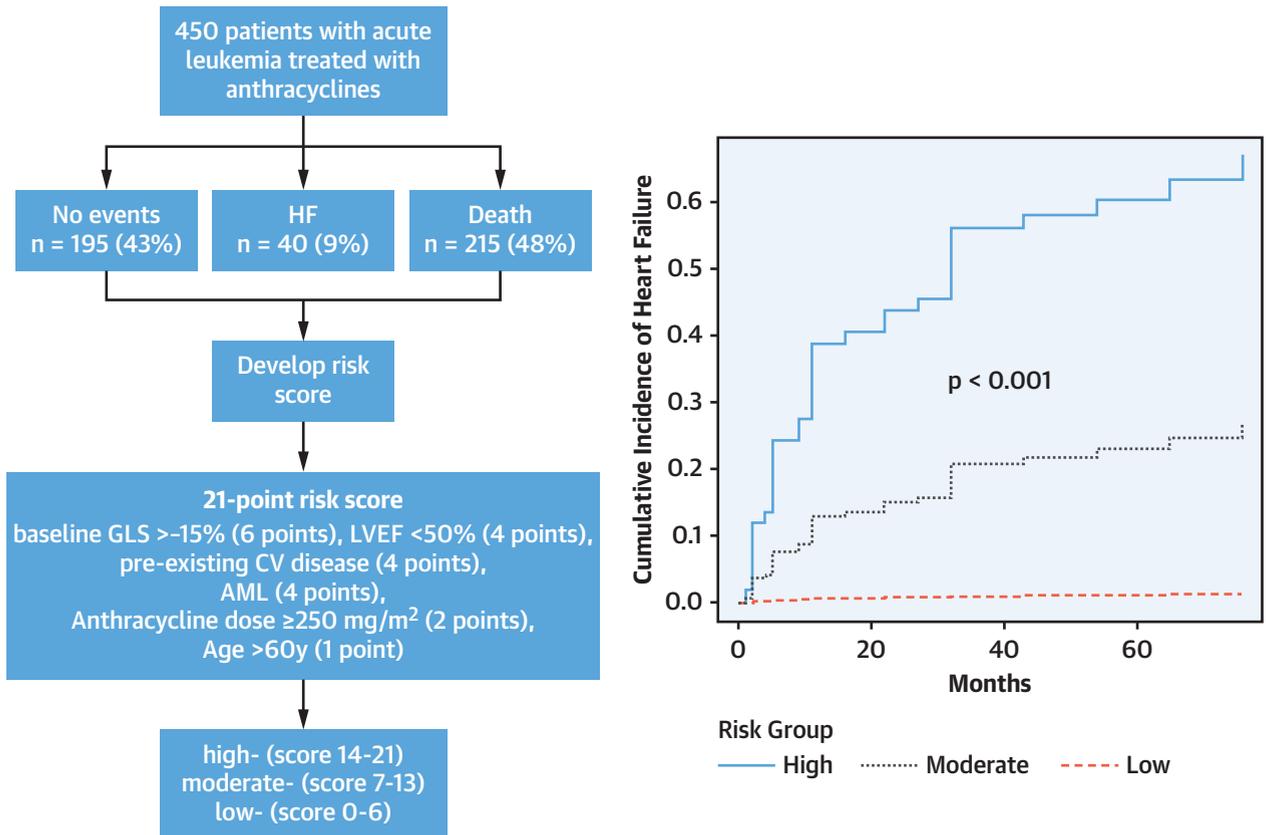
Pre-existing cardiovascular (CV) risk factors and CV diseases were extracted electronically from the chart using the relevant International Classification of Diseases-9th and/or 10th Revision-Clinical Modification (ICD-9 and/or ICD-10) codes. Pre-existing CV diseases were defined as coronary artery disease, chronic HF, atrial fibrillation, and stroke/transient ischemic attack. Cardiovascular risk factors included obesity, hypertension, hypercholesterolemia, and diabetes. The confirmation of all the pre-existing diseases or risk factors required the presence of diagnostic codes (ICD-9 and/or ICD-10) as well as either relevant pharmacological therapies or objective findings or signs, including laboratory evidence supporting the diagnosis. Each chart was reviewed individually to determine HF occurrence, pre-existing CV disease, or CV risk factors. Anthracycline dose was calculated based on the following doxorubicin hematologic toxicity equivalence: daunorubicin, 1.0; idarubicin, 5.0; epirubicin, 0.67; and

mitoxantrone, 4.0 (16). Noncardiac death was also noted. Death due to septic shock, multiple organ failure, or death after being transferred to hospice was counted as a noncardiac death.

**ECHOCARDIOGRAPHY AND STRAIN ANALYSIS.** Pre-chemotherapy echocardiographic images (within 3 months preceding the diagnosis of acute leukemia) were extracted from a hospital-wide echocardiographic database. LVEF was calculated using the modified Simpson's biplane method. Other echocardiographic parameters of cardiac size and function were measured according to the recommendations of the American Society of Echocardiography (17). Endocardial longitudinal strain was quantified by an offline vendor-independent analysis program (2D Cardiac Performance Analysis; TomTec Imaging Systems, Munich, Germany) at a frame rate of 30 frames per second. The endocardial borders were traced from the 3 apical views by an observer blinded to the clinical characteristics. Global longitudinal strain (GLS) was calculated by measuring the entire endocardial line length at the end-diastole and end-systole in each view and averaging the results from the 3 views (18). Each measurement was taken from the average of 3 consecutive cardiac cycles. Intra- and interobserver variability of LVEF and GLS were assessed by calculating the difference between the values of 10 randomly selected patients measured by 1 observer twice (intra) and by a second observer (inter).

**STATISTICAL ANALYSIS, RISK SCORE MODEL DEVELOPMENT, AND VALIDATION.** Values are expressed as mean  $\pm$  SD or counts (percentages). Follow-up time is presented as median (25th and 75th percentile). Differences between patients with AML or ALL or between patients included or excluded in the study were determined using one-way analysis of variance or Kruskal-Wallis test. Categorical variables were compared using the chi-square test. Intra-observer and interobserver reproducibility of LVEF and GLS was assessed using intraclass correlation coefficients (ICCs). Time-on-study was used as time scale in all survival analyses. Follow-up began at the start of anthracyclines and ended in case of death, event of interest, or the date of last encounter (before June 30, 2018), whichever came first. The cumulative incidence function was used to estimate the incidence of HF, with noncardiac death as a competing event. Univariable Cox proportional hazard regression models were used to analyze the association between baseline variables and HF. Time-dependent covariates were used to assess the presence of nonproportional

**CENTRAL ILLUSTRATION** Cumulative Incidence of Heart Failure Was Significantly Different in 3 Risk Score Groups

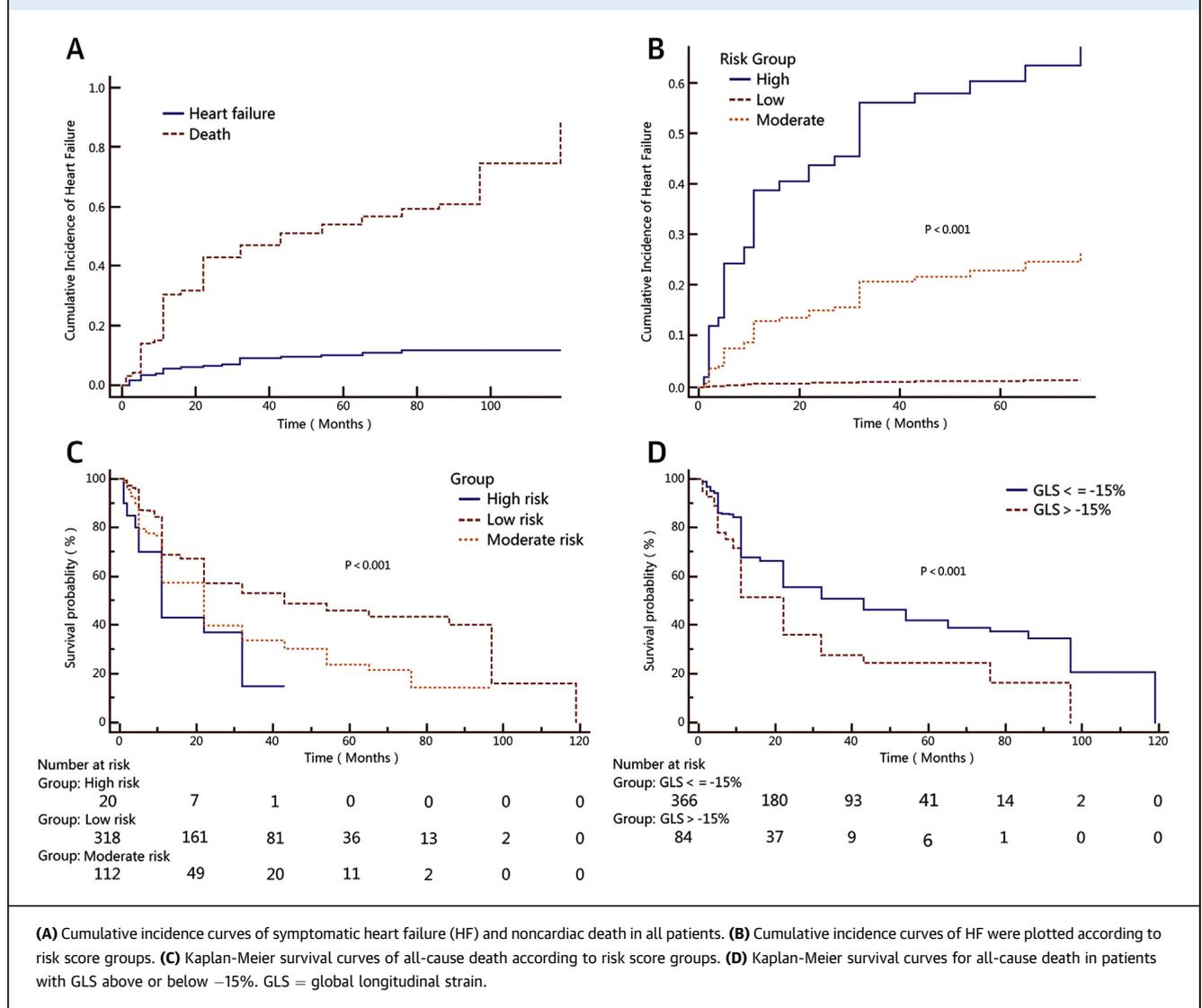


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(Left) Flowchart of the study. (Right) Cumulative incidence curves of HF plotted according to different risk score groups. AML = acute myeloid leukemia; CV = cardiovascular; GLS = global longitudinal strain; HF = heart failure; LVEF = left ventricular ejection fraction.

hazards by including interactions of each covariates with a function of time (19). Because of competing risks, univariable Fine and Gray's subdistribution hazard regression models were also used to determine the association between clinical parameters and HF. The results of Cox proportional hazard models and Fine-Gray subdistribution hazard models were presented as hazard ratios (HRs) with 95% confidence interval (CI). We developed a multivariable Fine and Gray's subdistribution hazard regression model through the inclusion of variables with a  $p < 0.10$  in univariable analysis, and according to their hypothesized clinical relevance to avoid colinearity. For continuous variables, the variables were categorized using recognized clinical meaningful categories, as follows: age: <40 years of age, 40 to 60 years of age, and >60 years of age; cumulative dose of anthracyclines: <250 mg/m<sup>2</sup>,  $\geq 250$  mg/m<sup>2</sup>; LVEF: <50% and  $\geq 50\%$ ; and GLS: >-15% (more impaired) and  $\leq -15\%$  (20,21).

To develop the risk score, we used a stepwise forward approach to establish the multivariable regression model and selected the best model by calculating the time-dependent area under the receiver operating characteristics curve (AUC) and Bayesian information criteria (BIC) for each regression model (22,23). Model performance was further evaluated using Brier scores by 10-fold cross-validation method (23). Risk points were assigned to the variable proportional to their regression coefficient (24). The sum of all points was calculated for each patient. The patients were then divided into subgroups on the basis of the score. The cumulative incidence of HF for the subgroups were used to define 3 groups: high, moderate, and low risk for HF (24). Cumulative incidence function curves for patients in the 3 risk groups were generated to illustrate the partitioning of the risk of symptomatic HF, and Fine and Gray's method was used to determine if there were significant differences between groups.

**FIGURE 2** Cumulative Incidence Curves and Kaplan-Meier Survival Curves

In exploratory analyses, we also evaluated the relationship between the risk model and the outcome of all-cause death. Here, the association of each variable in the risk score with mortality was also tested using the Cox proportional hazard model. Kaplan-Meier survival curves for different GLS values were also generated for this outcome.

Data were analyzed by SPSS version 16.0 (SPSS, Chicago, Illinois) and R version ii386 3.5.0 (Vienna, Austria). A  $p < 0.05$  was considered statistically significant.

## RESULTS

**PATIENT ENROLLMENT.** A total of 645 patients with AML or ALL were treated with anthracyclines at HUP

from January 2004 to April 2018. After excluding patients without an echocardiogram before the initiation of anthracycline treatment, lack of follow-up after baseline visit (as defined by lack of follow-up record after the first hospital admission), and poor echocardiographic image quality, a total of 450 patients (218 men, ranging in age from 18 to 83 years) were included in the study cohort (median follow-up period: 16 months; range: 1 to 132 months; first to third quartiles: 10 to 32 months) (Figure 1). Baseline clinical characteristics were similar between the included and excluded patients, with the exception of sex (Supplemental Table 1). Nine patients (2.0%) had incomplete follow-up (age:  $38 \pm 13$  years, ranging from 22 to 55 years; median follow-up time: 70 months, ranging from 60 to 96 months; mean

cumulative dose of anthracyclines: 263 ± 98 mg/m<sup>2</sup>, ranging from 140 to 450 mg/m<sup>2</sup>).

Forty patients (8.9%) developed symptomatic HF, including 1 patient with decompensated HF who subsequently died (Central Illustration). The median time to develop HF was 10 months (range, 1 to 76 months; interquartile range: 5 to 32 months); 215 patients (47.8%) died of a noncardiac cause. The cumulative incidence of HF and noncardiac death are shown in Figure 2A.

**CLINICAL CHARACTERISTICS OF ENROLLED PATIENTS.** The baseline clinical characteristics of the enrolled patients are presented in Table 1. Patients who developed HF were older, with a higher prevalence of previous HF, atrial fibrillation, and pre-existing CV diseases.

**BASILINE ECHOCARDIOGRAPHIC CHARACTERISTICS OF PATIENTS.** Baseline echocardiographic findings are listed in Table 2. The overall baseline LVEF was 63 ± 8%. Patients with HF had larger indexed left ventricular end-diastolic volume and left ventricular end-systolic volumes with lower LVEF, compared with patients with noncardiac death and patients with no events. Baseline GLS values were worse (more impaired) in patients who developed HF, compared with patients with noncardiac death and patients with no events (−13.0 ± −3.6%, −17.2 ± −3.2%, and −18.4 ± −2.6%, respectively).

**RELIABILITY OF GLS AND LVEF ANALYSIS.** The ICC was 0.92 for LVEF and 0.91 for GLS for the intra-observer variability. The ICC was 0.88 for LVEF and 0.89 for GLS for interobserver variability.

**DEVELOPMENT OF A RISK SCORE.** Baseline clinical and echocardiographic parameters associated with HF by univariable Cox proportional hazard analysis and by Fine and Gray’s subdistribution hazard analysis are presented in Supplemental Table 2.

Covariates with a p < 0.10 in univariable analyses were older than 60 years, previous HF, atrial fibrillation, pre-existing CV diseases, prescribed angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, presence of AML, cumulative dosage of anthracyclines ≥250 mg/m<sup>2</sup>, baseline left ventricular end-systolic dimension, left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular mass index, LVEF <50%, and GLS >−15% (indicative of greater impairment) in both Cox proportional hazard analysis and Fine and Gray’s subdistribution proportional hazard analysis. To avoid collinearity, we chose pre-existing CV disease rather than previous HF or atrial fibrillation, and baseline LVEF <50% and baseline

**TABLE 1 Baseline Clinical Characteristics of the Study Cohort**

	Cohort (N = 450)	No Events (n = 195)	Noncardiac Death (n = 215)	HF (n = 40)
<b>Demographics</b>				
Age, yrs	51 ± 15	46 ± 15	55 ± 15	55 ± 14
Male	218 (48)	89 (46)	107 (50)	22 (55)
BMI, kg/m <sup>2</sup>	27.5 ± 5.7	27.6 ± 5.7	27.6 ± 5.8	26.5 ± 4.7
<b>Cardiovascular disease history</b>				
Hypercholesterolemia	97 (22)	47 (24)	42 (20)	8 (20)
Hypertension	163 (36)	69 (35)	80 (37)	14 (35)
Diabetes	36 (8)	17 (9)	17 (8)	2 (5)
Current/previous smoker	182 (40)	61 (31)	103 (48)	18 (45)
≥2 CV risk factors*	117 (39)	54 (28)	54 (25)	9 (25)
Congestive HF	11 (2)	0 (0)	2 (1)	9 (23)
Coronary heart disease	27 (6)	8 (4)	15 (7)	4 (10)
Atrial fibrillation	34 (8)	6 (3)	18 (8)	10 (25)
Peripheral artery disease	8 (2)	2 (1)	5 (2)	1 (3)
Chronic kidney disease	12 (3)	6 (3)	4 (2)	2 (5)
Pre-existing CV diseases†	67 (15)	13 (7)	33 (15)	21 (53)
<b>Cardiovascular medication</b>				
Beta-blockers	85 (19)	37 (19)	38 (18)	10 (25)
ACEI/ARBs	83 (18)	25 (13)	46 (21)	12 (30)
Statins	84 (19)	42 (22)	33 (15)	9 (23)
<b>Leukemia type</b>				
ALL	149 (33)	90 (60)	54 (36)	5 (3)
AML	301 (67)	105 (35)	161 (53)	35 (12)
<b>Oncological history</b>				
Previous anthracycline exposure	31 (7)	15 (8)	12 (6)	4 (10)
Cumulative anthracycline dose, mg/m <sup>2</sup>	183 ± 86	189 ± 94	174 ± 78	296 ± 88
BMT/PBSCT	204 (45)	96 (49)	89 (41)	19 (48)

Values are mean ± SD or n (%). \*CV risk factors include obesity, hypertension, hypercholesterolemia and diabetes. †CV diseases include coronary artery disease, chronic heart failure, atrial fibrillation, and stroke/transient ischemic attack.  
ACEI = angiotensin-converting enzyme inhibitor; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ARB = angiotensin II receptor blocker; BMI = body mass index; BMT = bone marrow transplantation; CV = cardiovascular; HF = heart failure; PBSCT = peripheral blood stem cell transplantation.

GLS rather than other echocardiographic parameters. We included age and cumulative anthracycline dose as clinically relevant variables. Thus, 6 variables (age >60 years, cumulative anthracycline dose ≥250 mg/m<sup>2</sup>, presence of AML, pre-existing CV disease, baseline LVEF <50%, and baseline GLS >−15%) were selected based on their statistical significance and clinical relevance. We tested combinations of these variables. Adding GLS in the model with clinical characteristics and LVEF reduced the BIC (from 436.19 to 416.01) and increased AUC, providing incremental value (Supplemental Figure 1A). The best discriminative HF model (smallest BIC, highest AUC) was achieved by including age >60 years, cumulative dose of anthracyclines ≥250 mg/m<sup>2</sup>, the presence of pre-existing CV disease, presence of AML, baseline LVEF <50%, and baseline GLS >−15%. Therefore, we chose these parameters to establish the risk score. The Brier scores were calculated to test the predictive accuracy of the model (Supplemental Figure 1B). We

**TABLE 2** Baseline Echocardiographic Parameters of the Study Cohort

	Cohort (N = 450)	No Events (n = 195)	Noncardiac Death (n = 215)	HF (n = 40)
LVEDD, mm	46 ± 6	46 ± 7	46 ± 5	48 ± 9
LVEDS, mm	31 ± 6	30 ± 5	31 ± 5	35 ± 7
LVEDVi, ml/m <sup>2</sup>	53.0 ± 15.0	53.0 ± 14.4	51.8 ± 13.3	59.7 ± 23.1
LVESVi, ml/m <sup>2</sup>	19.7 ± 8.1	18.8 ± 6.5	18.9 ± 6.4	28.1 ± 15.3
RWT	0.44 ± 0.21	0.44 ± 0.28	0.44 ± 0.10	0.41 ± 0.10
LV mass index, g/m <sup>2</sup>	83.5 ± 23.2	79.1 ± 21.8	85.3 ± 22.5	95.4 ± 27.9
LVEF, %	63 ± 8	65 ± 6	64 ± 7	55 ± 11
LVEF <53%	30 (7)	4 (2)	8 (4)	18 (45)
DT, ms	181 ± 55	181 ± 51	184 ± 58	173 ± 62
E/E'	7.8 ± 3.5	7.3 ± 2.5	8.2 ± 4.2	8.6 ± 3.2
GLS, %	-17.3 ± 3.3	-18.4 ± 2.6	-17.2 ± 3.2	-13.0 ± 3.6
GLS >-15%	84 (19)	13 (7)	44 (20)	27 (68)

Values are mean ± SD or n (%).

DT = deceleration time; E/E' = ratio between early mitral inflow velocity (E) measured by pulsed-wave Doppler and mitral annular early diastolic velocity (E') estimated by tissue Doppler; GLS = global longitudinal strain; HF = heart failure; LVEDD = left ventricular end-diastolic dimension; LVEDVi = indexed left ventricular diastolic volume; LVEF = left ventricular ejection fraction; LVEDS = left ventricular end-systolic dimension; LVESVi = indexed left ventricular systolic volume; RWT = relative wall thickness.

assigned points to each of the variables that were related proportionally to the  $\beta$  regression coefficient values (24) (Table 3), with the total risk score ranging from 0 to 21. The sum of all points was calculated for each patient (median score: 5; range 0 to 21; first to third quartiles: 4 to 7). The patients were then divided into 16 subgroups on the basis of the score. The cumulative incidence of HF for the 16 subgroups was used to define 3 risk groups: low (score 0 to 6), moderate (score 7 to 13), and high risk (score 14 to 21) (24).

A total of 318 (70.7%) patients were in the low-risk group, 112 (24.9%) in the moderate-risk, and 20 (4.4%) in the high-risk group. In the low-, moderate-, and high-risk groups, there were 3 (0.9%) of 318, 24 (18.8%) of 112, and 13 (65.0%) of 20 patients with HF, respectively ( $p < 0.001$ ). The 1-year estimated cumulative incidence of HF for the low-, moderate-, and high-risk groups was 1.0%, 13.6%, and 35.0%, respectively (Central Illustration, Figure 2B). For male and female patients, the 1-year estimated cumulative

incidence of HF for the low-, moderate-, and high-risk groups was 0.8%, 15.8%, and 33.7%, and 1.3%, 11.6%, and 38.8%, respectively.

**RISK SCORE IN PATIENTS WITH AML OR ALL.** Patients with AML had a higher incidence of HF and noncardiac mortality than patients with ALL (11.6% vs. 3.4%, 52.8% vs. 34.9%, respectively;  $p < 0.001$  for both). The baseline characteristics of patients with either AML or ALL are shown in Supplemental Table 3. Patients with AML were older and received higher doses of anthracyclines; however, after adjustment for age and cumulative anthracycline dose, the presence of AML was still associated with symptomatic HF (HR: 2.77; 95% CI: 1.01 to 7.63;  $p = 0.048$ ).

We further tested a modified risk score in patients with ALL separately. After excluding presence of AML, the modified risk score, that is, a 17-point score including a baseline GLS >-15% (6 points), pre-existing CV disease (4 points), baseline LVEF <50% (4 points), a cumulative dose of anthracycline  $\geq 250$  mg/m<sup>2</sup> (2 points), and age >60 years (1 point) stratified patients with ALL (n = 149) into low (score 0 to 1, n = 103), moderate (score 2 to 10, n = 40), and high risk (score 11 and above, n = 4). The 1-year estimated cumulative incidence of symptomatic HF of low-, moderate-, and high-risk groups in patients with ALL was <0.1%, 3.6%, and 17.0%, respectively ( $p < 0.001$ ).

**RELATIONSHIP OF THE RISK SCORE, GLS, AND OVERALL MORTALITY.** In exploratory analyses, the risk score was also associated with all-cause death (HR: 1.36; 95% CI: 1.23 to 1.50;  $p < 0.001$ ). The overall survival time was significantly greater in patients in low-risk score group than those in moderate- and high-risk groups ( $p < 0.001$ ) (Figure 2C). After adjustment for age and leukemia type, only GLS >-15% remained independently related to all-cause death (HR: 1.73; 95% CI: 1.30 to 2.31;  $p < 0.001$ ) (Figure 2D). The presence of pre-existing CV disease and baseline LVEF <50% were not independently associated with overall mortality.

## DISCUSSION

The present study demonstrates that patients with AML and ALL treated with anthracyclines are at risk of HF, most of which occurs within 1 year after the exposure of anthracyclines. We determined that a risk score based on baseline clinical and echocardiographic variables can stratify patients at low or high risk for HF after treatment for acute leukemia.

The population studied consisted of patients with acute leukemia treated with anthracyclines, whose clinical characteristics were similar to those encountered in everyday clinical practice, in terms of the

**TABLE 3** Variables Included in Multivariable Fine and Gray's Subdistribution Hazard Regression Model

	HR (95% CI)	$\beta$ Coefficient Value	p Value	Score Points
GLS >-15%	6.91 (3.27-14.59)	1.93	<0.001	6
Pre-existing CV disease	3.74 (1.82-7.67)	1.32	<0.001	4
Leukemia type (AML)	4.10 (1.90-8.85)	1.41	<0.001	4
EF <50%	3.50 (1.64-7.51)	1.25	<0.001	4
Age >60 yrs	1.36 (0.76-2.44)	0.31	0.300	1
Anthracycline dose $\geq 250$ mg/m <sup>2</sup>	1.96 (1.06-3.61)	0.67	0.030	2

CI = confidence interval; CV = cardiovascular; EF = ejection fraction; GLS = global longitudinal strain; HR = hazard ratio.

age, distribution of gender, and leukemia type (25,26). The prevalence of CV risk factors was similar to that of the general population (27). Of note, the prevalence of symptomatic HF in patients with acute leukemia treated with anthracyclines (9%) was higher than what has been reported previously in the general population of patients with cancer treated with anthracyclines (2% to 5%) (7,28,29). Anthracyclines remain a standard therapy for acute leukemia and are delivered as high doses over a very short period, a treatment schedule that increases their toxicity. In addition, leukemia is a systemic disease that may be accompanied by high cytokine release (30,31), as well as possible cardiac infiltration or ischemic cardiac disease due to vessel infiltration with malignant cells. These factors may contribute to the high incidence of symptomatic HF in this specific population.

Patients with AML had a higher incidence of death and of HF compared with patients with ALL. The underlying mechanisms may be multifactorial. Patients with AML were older and had higher doses of anthracyclines. However, even after adjustment for age and dose of anthracyclines, AML was still associated with HF. In addition, the presence of several somatic mutations frequently found in myeloid malignancies has been associated with incident coronary heart disease, early-onset myocardial infarction, and ischemic stroke (32,33). Furthermore, mutations in isocitrate dehydrogenase 1 and 2, with an overall frequency of approximately 9% to 16% in patients with AML (34-36), have been implicated in cardiac dysfunction (37,38).

In concordance with some previous studies (14,39), the present study illustrated that baseline reduction of GLS is associated with cardiac events after anthracycline exposure. Although LVEF had prognostic value, GLS provided additional information to a model including clinical variable and LVEF. It is conceivable that patients with lower prechemotherapy GLS are more susceptible to the cardiac effects of the leukemia treatment or the leukemia itself.

Based on the Fine and Gray's regression model, a risk score derived by combining points for 6 baseline features (i.e., age, higher accumulative dose of anthracycline, pre-existing CV disease, AML, low LVEF, and low GLS) accurately classified patients into subgroups at low, medium, and high risk for symptomatic HF. In addition, in patients with ALL, the modified risk score system also could distinguish patients at high risk of HF. With further study, this risk score system may be able differentiate patients at high risk or low risk of HF and may allow cardiologists and oncologists to tailor therapies and balance the risks of oncologic efficacy and cardiovascular toxicity for individual patients.

In exploratory analyses, the risk score also was associated with overall mortality (1,2); however, when adjusted for age and leukemia type, only reduced GLS in baseline echocardiography was independently associated with all-cause death. A high production of proinflammatory cytokines, in particular tumor necrosis factor- $\alpha$  and interleukin-6 (30,31), is associated with a poor prognosis in patients with cancer (40). High levels of proinflammatory cytokines also exert cardio-depressant effects that lead to decreased myocardial contractility and left ventricular performance (41). Thus, GLS may be an indicator of disease burden in patients with cancer. In addition, patients with reduced left ventricular function might not receive as aggressive a cancer treatment as patients with normal cardiac function.

**STUDY LIMITATIONS.** This risk score was developed in a single, tertiary care center. Although the cohort was representative of patients with acute leukemia, the risk score has not been validated prospectively or validated externally in a separate cohort. Second, selection bias might have occurred, because we excluded patients with a lack of follow-up. However, the baseline characteristics between patients who were included and excluded showed no substantial differences. A large-scale prospective validation across multiple distinct medical centers would substantially strengthen this risk score. Without a comparator group, we could not further investigate whether the use of anthracyclines, or various anthracycline treatment schedules, had an effect on the occurrence of HF. We did, however, find that a cumulative dose of anthracyclines  $\geq 250$  mg/m<sup>2</sup> was a risk factor for HF.

## CONCLUSIONS

We developed a risk score based on 4 readily acquired baseline clinical and echocardiographic variables to stratify patients according to a low or high risk of symptomatic HF. With further study, a scoring system may be useful to clinicians to balance the benefits of cancer treatment and potential cardiac damage.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE AND IN PATIENT CARE:**

Patients with acute myeloid leukemia and acute lymphocytic leukemia treated with anthracyclines are at risk of symptomatic heart failure, most of which occurs within 1 year after exposure to anthracyclines. A risk score based on baseline clinical and echocardiographic variables can be used to classify patients as low or high risk for heart failure after anthracyclines.

**TRANSLATIONAL OUTLOOK:**

Baseline clinical and echocardiographic parameters are associated with symptomatic heart failure in patients with acute leukemia. Additional studies are needed to further validate the score, and determine both the efficacy and effectiveness of such a risk score in clinical practice.

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**KEY WORDS** acute leukemia, anthracycline, cardiotoxicity, global longitudinal strain, heart failure, risk score

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**APPENDIX** For supplemental tables and a figure, please see the online version of this paper.