RESEARCH ARTICLE

Relationship between obesity and clinical outcome in adults with acute myeloid leukemia: A pooled analysis from four CALGB (alliance) clinical trials

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Obesity has been previously suggested as an adverse prognostic marker in patients with acute leukemia. To evaluate the relationship between obesity and clinical outcome, disease-free survival (DFS) and overall survival (OS), in patients with acute myelogenous leukemia (AML), including acute promyelocytic leukemia (APL), we performed a pooled analysis of four CALGB (Alliance) clinical trials. Our study included 446 patients with APL from CALGB 9710, and 1,648 patients between 18 and 60 years of age with non-APL AML from CALGB 9621, 10503, and 19808. Obesity was defined as BMI $\geq$30 kg/m^2. Multivariate Cox proportional-hazard regression models were fitted for DFS and OS. Obesity was seen in 50% and 38% of APL and non-APL AML patients, respectively. In APL patients, obesity was associated with worse DFS (HR 1.53, 95% CI 1.03–2.27; $P = 0.04$) and OS (HR 1.72, 95% CI 1.15–2.58; $P = 0.01$) after adjusting for age, sex, performance status, race, ethnicity, treatment arm and baseline white blood cell count. Obesity was not significantly associated with DFS or OS in the non-APL AML patients. In conclusion, our study indicates that obesity has significant prognostic value for DFS and OS in APL patients, but not for non-APL AML patients.

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Introduction

Acute myeloid leukemia (AML) represents 80% of the cases of acute leukemia in adults. According to the Surveillance, Epidemiology and End Results (SEER) database, the median age at diagnosis is 67 years, and the age-adjusted incidence rate is 4.0 per 100,000 individuals per year, with approximately 20,000 new cases diagnosed each year in the United States (US) alone [1]. AML is a relatively chemotherapy-resistant disease, especially in older patients who are rarely cured. The current standard of care includes intensive chemotherapy followed by consolidation therapy or allogeneic stem cell transplantation [2]. Acute promyelocytic leukemia (APL) is a subtype of AML, which accounts for 5 to 20% of the cases. While once considered a deadly disease, the use of all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO) alone or in combination with standard intensive chemotherapy has led to a cure rate of approximately 85% [3–5].

There is increasing evidence that obesity is associated with an increased risk of developing acute myeloid leukemia (AML), and specifically acute promyelocytic leukemia (APL). In a recent meta-analysis of prospective cohort studies, obesity increased the risk of developing AML by 53% when compared with individuals of normal weight [6]. One study identified an association between obesity and APL independent of age, sex and race [7]. However, the role of obesity in relation to clinical outcomes in patients with AML and specifically APL is unclear. A previous meta-analysis suggested an increased mortality in male obese patients with AML when compared with normal weight individuals [6]; however, prior studies have provided inconsistent results in this area [8,9]. One recent study showed increased disease relapse rates and higher incidence of differentiation syndrome in obese APL patients [10].

Our primary objective in this study was to assess the effect of obesity on survival rates in AML and APL based on data from four Cancer and Leukemia Group B (CALGB) prospective clinical trials. CALGB is now part of the Alliance for Clinical Trials in Oncology.

Methods

Patient selection. Individual data on 2,173 patients 18 years or older with a diagnosis of AML (APL or non-APL) were collected through four prospective clinical trials led by the CALGB/Alliance. Seventy-nine patients were excluded: 72 patients were cancelled before receiving treatment or were deemed ineligible, and 7 patients did not have available height or weight data. Three studies were in de novo AML: CALGB 9621 ($n = 393$; age range: 18–59 years), 10503 ($n = 541$; age range: 18–60 years) and 19808 ($n = 714$; age range: 18–59

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years), and one study was specifically in de novo APL: 9710 ($n = 446$; age range: 18–80 years) [11–14]. Given the underlying differences in prognosis between APL and non-APL patients, we evaluated these as two separate cohorts, where the non-APL cohort is referred to hereafter simply as AML. Patients in the three AML studies (9621, 19808, and 10503) were pooled for those analyses, as each study had similar eligibilities and were all conducted through the CALGB member network. For the trials 9710, 9621, and 19808, longer patient follow-up was available for this analysis than previously published and therefore the number of deaths may be greater and the survival estimates may differ slightly from that presented in the primary manuscripts. All studies used actual body weight for body surface area calculation to eliminate the risk of error and the introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages was considered a major protocol deviation. All analyses were based on the study database frozen May 18, 2015.

Definition of variables. Body mass index (BMI) was calculated as [BMI = weight/(height^2)] using the Quetelet formula [15]. BMI was evaluated as a continuous variable and also using current WHO criteria to categorize patients as underweight/normal (BMI <25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2) [16]. In addition, morbid obesity was defined as BMI ≥40 kg/m^2. Baseline BMI was evaluated in relation to clinical characteristics at time of study entry, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), race, ethnicity, and year of enrollment. White blood cell (WBC) count was evaluated and adjusted for in APL patients, where WBC ≤10 × 10^9/L and >10 × 10^9/L were considered low/intermediate and high-risk categories, respectively [17]. Overall survival (OS) was defined as the time elapsed from study registration until death from any cause. For patients achieving a complete response (CR), disease-free survival (DFS) was defined as the time elapsed between documentation of CR and either evidence of disease progression or death from any cause. Patients not experiencing an event of interest were censored as of their last follow-up date.

Statistical analysis. Univariable and multivariable logistic regression models were used to assess the relations of clinical factors with obesity. The impact of BMI and other clinical factors were evaluated in relation to OS in all patients, and in relation to DFS in those who achieved a CR. OS and DFS were evaluated using the Kaplan-Meier method [18], and differences in survival distributions between groups were assessed using log-rank tests [19]. Multivariable Cox proportional-hazard regression models were fit to assess the prognostic impact of obesity on OS and DFS while adjusting for age, sex, performance status, race, ethnicity, treatment arm, year of enrollment and baseline WBC [20]. P values <0.05 were considered statistically significant. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center.

Results

Patients' characteristics

Our study included a total of 2,094 patients, 446 with APL and 1,648 with AML. APL patients were followed for a median of 102 months (95% CI 95–106) and AML patients for 120 months (95% CI 116–122). The median age of AML patients was 46 years (range 18–60 years), and 43 years (range 18–80 years) for APL patients. BMI was somewhat higher in APL patients: 50% of APL patients were obese; 38% of AML patients were obese. The median BMI in APL patients was 30 kg/m^2 (range 17–61 kg/m^2) and 28 kg/m^2 (range 14–60 kg/m^2) in AML patients. In addition, 10% of APL patients and 9% of AML patients were classified as morbidly obese (BMI ≥40 kg/m^2). In AML patients, the rate of obesity increased from 36% in 1997 to 42% in 2004 to 49% in 2010 ($P < 0.001$ for association). Detailed characteristics of the study population are found in Table I.

TABLE I. Clinical Characteristics of the Study Population According to Type of Leukemia

Category	APL N (%)	AML N (%)
Age (yr)		
<40	191 (43)	534 (32)
40–60	180 (40)	1114 (68)
>60	75 (17)	0 (0)
Sex		
Female	214 (48)	777 (47)
Male	232 (52)	871 (53)
Race		
Caucasian	367 (82)	1366 (83)
African American	28 (6)	132 (8)
Other	51 (11)	150 (9)
Ethnicity		
Hispanic	49 (11)	117 (7)
Non-Hispanic	383 (86)	1432 (87)
Not reported	14 (3)	99 (6)
Body mass index		
Normal/underweight	103 (23)	521 (32)
Overweight	121 (27)	506 (31)
Obese	222 (50)	621 (38)
Performance status		
Good (ECOG 0-1)	361 (81)	1402 (85)
Poor (ECOG 2)	81 (18)	212 (13)
Missing	4 (1)	34 (2)
Region		
Midwest	137 (31)	515 (31)
Northeast	147 (33)	600 (36)
Puerto Rico	11 (2)	43 (3)
South	96 (22)	435 (26)
West	36 (8)	50 (3)
Missing	19 (4)	5 (0)
Year of enrollment		
1997–2003[a]	288 (65)	755 (46)
2004–2010	158 (35)	893 (54)

AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group.
[a] APL patients were enrolled between 1999 and 2005.

Relationship between obesity and clinical factors

Associations between obesity and baseline clinical factors were fit in both univariable and multivariable logistic regression models separately for APL and AML patients. In the univariable analysis for APL patients, the age group 40 to 60 years had higher rates of obesity than those <40 years. Caucasians were at greater risk for obesity than non-Caucasian/non-African Americans (OR 0.40, 95% CI 0.21–0.75; $P < 0.01$). In the multivariable analysis, the age group 40 to 60 years retained its significance, and was independently associated with a higher rate of obesity (OR 1.64, 95% CI 1.07–2.51; $P = 0.02$). Those in other races group (non-Caucasian/non-African American) maintained a lower risk of obesity than Caucasians (OR 0.44, 95% CI 0.22–0.89; $P = 0.02$). For AML patients, the univariable and multivariable analyses showed that both the age group 40 to 60 years (vs. <40 years) and women (vs. men) had higher rates of obesity. Patients in other races group were associated with lower odds of being obese than Caucasians. Detailed results of the logistic regression models are shown in Table II. Cytogenetic data were available in 820 patients (50%) with AML. Among obese patients, 16% had favorable risk, while 84% had unfavorable. In non-obese, 15% had favorable and 85% unfavorable cytogenetic abnormalities ($P = 0.79$).

Relationship between BMI and clinical outcome: DFS and OS

The rate of CR did not differ between obese and non-obese patients (76% in each group). In the univariable analysis, obese patients with APL had significantly worse DFS than non-obese patients (Fig. 1A). The 5-year DFS rate for obese, overweight, and normal/underweight patients with APL were 74% (95% CI 67–79%), 82% (95% CI 73–88%), and 83% (95% CI 74–89%). Those classified as overweight performed equivalently to normal/underweight patients, further supporting evaluation of obese versus non-obese patients. When we further stratified to incorporate disease risk (based on WBC at study entry), there was a trend for obese patients to have worse DFS independent of the APL risk status (Fig. 1B). On the contrary, there was no significant difference in DFS between obese and non-obese patients with AML (Fig. 1A). The 5-year DFS rates

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TABLE II. Logistic Regression Models Evaluating Associations Between Clinical Variables and Obesity in Adult APL and AML Patients

	Univariable analysis		Multivariable analysis	
APL	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (yr)				
40–60 vs. <40 yr	1.70 (1.13–2.56)	0.01	1.64 (1.07–2.51)	0.02
>60 vs. <40 yr	1.64 (0.96–2.80)	0.07	1.49 (0.85–2.59)	0.16
Sex				
Male vs. female	1.14 (0.78–1.65)	0.50	1.20 (0.81–1.78)	0.35
Race				
AA vs. Caucasian	2.01 (0.89–4.56)	0.10	2.12 (0.87–5.13)	0.10
Other vs. Caucasian	0.40 (0.21–0.75)	0.01	0.44 (0.22–0.89)	0.02
Ethnicity				
Hispanic vs. non-Hispanic	0.55 (0.30–1.01)	0.06	0.81 (0.41–1.62)	0.56
NR vs. non-Hispanic	0.94 (0.33–2.74)	0.92	1.05 (0.35–3.17)	0.93
Performance status				
Poor vs. good	1.16 (0.72–1.89)	0.54	1.06 (0.64–1.75)	0.83
Baseline WBC (risk)				
High vs. low/intermediate	1.24 (0.80–1.92)	0.34	1.29 (0.81–2.07)	0.29
	Univariable analysis		Multivariable analysis	
AML	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (yr)				
40–60 vs. <40 yr	1.49 (1.20–1.86)	<0.001	1.46 (1.16–1.82)	0.001
Sex				
Male vs. female	0.78 (0.64–0.95)	0.01	0.79 (0.65–0.97)	0.03
Race				
AA vs. Caucasians	1.40 (0.98–2.01)	0.07	1.44 (0.99–2.08)	0.05
Other vs. Caucasians	0.61 (0.42–0.89)	0.01	0.66 (0.43–1.03)	0.07
Ethnicity				
Hispanic vs. non-Hispanic	0.72 (0.48–1.08)	0.11	1.03 (0.64–1.66)	0.90
NR vs. non-Hispanic	1.01 (0.66–1.53)	0.97	0.86 (0.55–1.33)	0.49
Performance status				
Poor vs. good	1.03 (0.77–1.39)	0.85	1.13 (0.83–1.53)	0.43
Year of enrollment				
Year enrolled (1997–2010)	1.06 (1.03–1.09)	<0.001	1.06 (1.03–1.09)	<0.001

AA: African American; APL: acute promyelocytic leukemia; AML: acute myeloid leukemia; OR: odds ratio; CI: confidence interval; NR: not reported.

for obese, overweight and normal/underweight patients with AML were 36% (95% CI 32–40%), 37% (95% CI 32–41%), and 36% (95% CI 31–41%), respectively. Given that the APL patients were all from the same trial, we also evaluated BMI and obesity when controlling for differential induction therapies. For APL patients, multivariable analyses showed that treatment with ATRA alone (vs. ATRA and ATO) and high-risk APL were each associated with worse DFS. Adjusting for these other risk factors, there remained a significantly worse DFS for obese patients. For AML patients, factors significantly associated with worse DFS were older age and African American race (vs. Caucasian). Obesity was not significantly associated with DFS in AML patients. Detailed information on the multivariable Cox models for DFS is presented in Table III.

In the univariable analysis, obese patients with APL had worse OS than non-obese patients (Fig. 1C). However, there was no difference in OS between overweight and normal/underweight patients with APL. The 5-year OS rates for obese, overweight and normal/underweight patients with APL were 76% (95% CI 69–81%), 85% (95% CI 77–90%), and 86% (78–92%). There was a trend toward worse OS in obese patients independent of WBC at study entry (Fig. 1D). There was no significant difference in survival between obese and non-obese patients with AML (Fig. 1C). The 5-year OS rates for obese, overweight and normal/underweight patients with AML were 35% (95% CI 31–39%), 38% (95% CI 34–43%), and 39% (95% CI 34–43%), respectively. As expected, patients with higher cytogenetic risk had worse OS ($P < 0.001$). However, among those with unfavorable cytogenetic risk, OS did not significantly differ with obesity ($P = 0.83$). For APL patients, the multivariable analysis showed that obese patients had worse OS than non-obese patients. Other factors associated with worse survival in the multivariable model included older age, poor performance status, Hispanic ethnicity, induction treatment with ATRA alone, and high-risk APL. For AML patients, significant prognostic factors associated with worse OS were older age, poor performance status and African American race. Contrary to APL, obesity was not significantly associated with OS in AML patients. Detailed information on the multivariable Cox models for OS is shown in Table III.

Discussion

Based on the results of this pooled analysis, obesity is associated with worse survival outcomes in patients with APL but not in patients with AML. There are points worth discussing: (1) A higher percentage of APL patients were obese than AML patients (50% vs. 38%, respectively; $P < 0.01$), (2) obesity was associated with a worse DFS and OS in APL patients but not in AML patients.

The increased proportion of obese individuals (50%) seen among APL patients in this pooled analysis is consistent with previous reports [7,10,21,22]. In that study, APL patients had median BMI of 28, while the median BMI for non-APL patients was 25. In our study, the median BMI in APL patients was 30, and in AML patients was 28 although the BMI range between APL and AML patients did not differ. Our study, however, shows that while the height of patients with AML and APL did not differ greatly, APL patients were 'heavier' than AML patients (medians: 87 kg and 82 kg, respectively). There are mounting data supporting an increased rate of AML in obese individuals compared with individuals with normal weight in two separate meta-analyses [6,23]. A recent laboratory study has shown that weight gain through increased

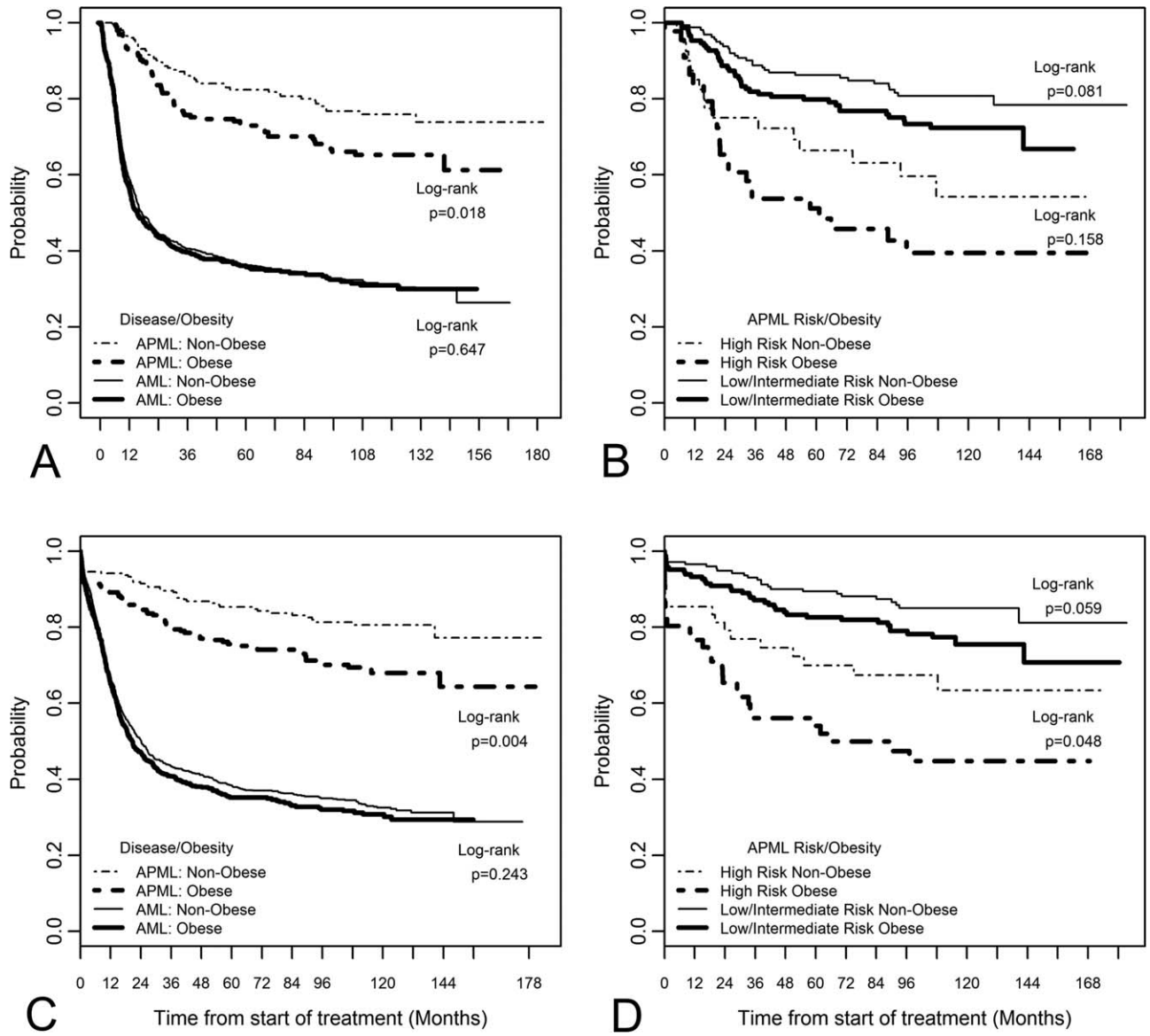

Figure 1. Disease-free survival in obese and non-obese adult patients with AML and APL: (A) AML vs. APL (B) low-intermediate vs. high risk in APL patients only. Overall survival in obese and non-obese adult patients with AML and APL: (C) AML vs. APL (D) low-intermediate vs. high risk in APL patients only.

fat intake is a promoter of leukemogenesis in mice, likely mediated by Insulin Growth Factor 1 (IGF-1) [24], providing the rationale of dietary intervention and/or IGF-1 targeting as potential therapeutic approaches for APL.

We found there is a direct relation between age and BMI in APL patients. The NHANES III study showed a proportion of obesity (BMI $\geq$30 kg/m^2) of 33%, 37%, and 37% in individuals 20 to 39, 40 to 59, and $\geq$60 years, respectively [25]. In our study, APL patients older than 60 had increased odds of obesity than patients 40 to 60 years of age, which differs from NHANES III. Also, we found that Caucasians had higher odds of obesity in comparison with African Americans and individuals of other races. This is in contrast with the findings from NHANES III, where the proportion of obesity was 34%, 50%, and 39% for non-Hispanic Caucasians, non-Hispanic African Americans and Hispanics, respectively. For AML, however, the findings of our study of higher odds of obesity in women and African Americans are consistent with NHANES III. The differences seen between APL and AML potentially stem from the smaller sample size of APL patients. However, it is possible there is a distinct biological relation between obesity in APL, which is not apparent in AML.

Obese APL patients had lower rates of 5-year DFS than non-obese patients. Obesity, however, was not associated with worse DFS outcomes among AML patients. In order to enter the DFS analysis, patients needed to achieve CR status after induction chemotherapy. Hence, obesity was associated with a higher risk of relapse and/or death from any cause after obtaining a CR, regardless of APL risk. Deaths can therefore occur after relapse or in remission.

Obesity was associated with worse OS in APL but not in AML, independent of well-known prognostic factors such as age, performance status, APL risk and use of ATO. There are several potential explanations for this finding. Obese patients might have been underdosed increasing the risk of not achieving a CR and/or dying from relapsed disease. Our data argue against this hypothesis, as there were no discernible differences in the rate of relapse between obese and non-obese APL patients. Additionally, no capping based on BSA was allowed in the therapeutic protocol for APL patients. Obese APL patients might have an inherent increased risk of developing life-threatening complications. There is mounting evidence that obese APL patients might have higher risk of differentiation syndrome, a

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TABLE III. Multivariable Cox Proportional-Hazard Regression Models for Overall and Disease-Free Survival in Adult Patients with APL and AML

	Overall survival		Disease-free survival	
APL	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (yr)				
40–60 vs. <40 yr	1.37 (0.87–2.16)	0.17	1.06 (0.69–1.62)	0.80
>60 vs. <40 yr	2.42 (1.47–3.99)	<0.001	1.21 (0.71–2.07)	0.48
BMI				
Obese vs. non-obese	1.72 (1.15–2.58)	0.01	1.53 (1.03–2.27)	0.04
Sex				
Male vs. female	1.23 (0.83–1.82)	0.31	1.34 (0.91–1.98)	0.14
ECOG				
Poor vs. good	1.70 (1.10–2.63)	0.02	1.55 (0.98–2.47)	0.06
Race				
AA vs. Caucasian	1.09 (0.49–2.41)	0.84	0.85 (0.38–1.88)	0.68
Other vs. Caucasian	1. 30 (0.70–2.41)	0.40	0.95 (0.50–1.79)	0.86
Ethnicity				
Hispanic vs. non-Hispanic	2.17 (1.23–3.86)	0.01	1.67 (0.94–2.99)	0.08
NR vs. non-Hispanic	0.67 (0.16–2.74)	0.57	0.87 (0.27–2.78)	0.81
Treatment arm				
ATRA vs. ATRA + ATO	1.55 (1.05–2.29)	0.03	3.50 (2.29–5.36)	<0.0001
Baseline WBC (risk)				
High vs. low/intermediate	2.97 (1.99–4.43)	<0.0001	2.91 (1.94–4.36)	<0.0001
	Overall survival		Disease-free survival	
AML	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (yr)				
40–60 vs. <40	1.46 (1.28–1.68)	<.0001	1.21 (1.04–1.41)	0.01
BMI				
Obese vs. non-obese	1.06 (0.94–1.21)	0.33	1.03 (0.89–1.19)	0.69
Sex				
Male vs. female	1.07 (0.95–1.21)	0.27	1.05 (0.91–1.21)	0.48
ECOG				
Poor vs. good	1.31 (1.09–1.56)	<0.01	1.14 (0.92–1.42)	0.23
Race				
AA vs. Caucasian	1.44 (1.18–1.77)	<0.001	1.36 (1.05–1.75)	0.02
Other vs. Caucasian	0.88 (0.67–1.15)	0.34	0.79 (0.58–1.08)	0.14
Ethnicity				
Hispanic vs. non-Hispanic	1.09 (0.81–1.46)	0.58	1.25 (0.91–1.72)	0.17
NR vs. non-Hispanic	0.92 (0.70–1.21)	0.56	0.93 (0.69–1.25)	0.63
Treatment				
9621 vs. 19808	1.16 (0.86–1.55)	0.34	1.08 (0.76–1.52)	0.68
10503 vs. 19808	0.77 (0.57–1.04)	0.09	0.78 (0.56–1.10)	0.16
Year of enrollment				
Year enrolled (1997–2010)	1.01 (0.96–1.06)	0.69	1.02 (0.96–1.08)	0.53

APL: acute promyelocytic leukemia; AML: acute myeloid leukemia; HR: hazard ratio; CI: confidence interval; BMI: body mass index; AA: African American; ECOG: Eastern Cooperative Oncology Group; NR: not reported.

systemic inflammatory response seen in patients with APL treated with ATRA or ATO characterized by the development of pulmonary infiltrates and hypoxia [26–29]. A recent Italian study has shown that obese APL patients have seven times higher odds of differentiation syndrome than normal weight patients after adjusting for age, sex, white blood cell count, hemoglobin level, platelet counts, PML-RAR subtype, and FAB variant [10]. At least two other smaller studies have reached similar results [21,22].

Another explanation is that obese patients might have been appropriately dosed based on BSA, but finally reached subtherapeutic or supratherapeutic serum levels making them functionally underdosed or overdosed, respectively. A number of studies specifically evaluating the pharmacokinetic (PK) and pharmacodynamics (PD) of chemotherapy in obese patients have shown recurrent problems [30]. A key component of the PK modeling is the volume of distribution, which in obese individuals can be uncertain. Additionally, when using higher doses of chemotherapy, the elimination rate might not follow a linear pattern and the properties of the drug may lead to a preferential adipose distribution. Also, obese individuals might have problems with plasma protein volume with erratic drug binding, altered blood flow to kidneys, and decreased drug clearance due to liver dysfunction. One could argue that similar problems should affect obese AML patients and no worse outcome was identified in our study. However, the outcome of AML patients is markedly worse than APL and as such the efficacy of chemotherapy is limited regardless of how obese patients metabolize chemotherapy. Factors associated with a worse OS in AML patients in our study were older age and African American race. The poor outcome seen in African Americans is consistent with findings from previous studies [31].

Our study has several limitations. Our pooled analyses are limited to patients with AML (APL and non-APL) who participated in CALGB (Alliance) prospective clinical trials; hence, our study might not be representative of the general population. Characteristically, clinical trial participants are younger and have a better performance status than patients in the community. Additionally, other races and ethnicities besides Caucasians are frequently underrepresented in these studies. The sample size of APL patients could be considered small giving way to findings of spurious (non-)significance. Despite these limitations, we have been able to show that obese APL patients have worse DFS and OS rates than non-obese patients, even accounting for the use of ATO, now

considered standard therapy especially in those with non-high-risk APL [4]. The biological or PK/PD reasons for these findings should be subject of further investigation in order to improve the outcomes of obese patients with APL.

In conclusion, our study supports worse outcomes in obese patients with APL. Further research is needed to confirm these findings and understand the biological reasons behind them. In addition, novel therapeutic approaches might need to be studied in obese patients with APL in order to improve outcomes.

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