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ORIGINAL ARTICLE

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Characteristics and outcome of adult patients with acute promyelocytic leukemia and increased body mass index treated with the PETHEMA Protocols

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Abstract

Objective: The obesity/overweight may have an influence on APL outcomes.

Methods: This is the biggest multicentre analysis on 1320 APL patients treated with AIDA-induction and risk-adapted consolidation between 1996 and 2012. Patients body mass index (BMI) was classified as underweight (<18.5 kg/m^2), normal

(18.5-25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2) according to the World Health Organization (WHO) criteria.

Results and conclusions: Relationship between male gender, older age, and other known laboratory abnormalities in overweight/obese patients was significant. The induction mortality rate was significantly higher in APL with BMI ≥25 vs BMI <25 (10% vs 6%; $P = .04$). APL patients with BMI ≥25 had a trend to lower OS (74% vs 80%; $P = .06$). However, in the multivariate analysis, BMI did not retain the independent predictive value ($P = .46$). There was no higher incidence of differentiation syndrome with BMI ≥25, but there was a trend in obese. There was no difference in relapse rate according to the BMI. In summary, overweight/obesity does not represent an independent risk factor for APL outcomes. The influence of obesity in APL patients treated with chemotherapy-free regimens remains to be established.

KEYWORDS

acute promyelocytic leukemia, AIDA protocol, obesity, outcome

1 | INTRODUCTION

Over the past decades, the overweight and obesity is an increasing problem in Western countries.[1,2] Following the Wold Health Organization (WHO), overweight is defined by a body mass index (BMI) of 25-29.9 kg/m^2 and obesity of ≥30 kg/m^2.[1,2] The association between overweight and obesity with an increased risk of over 20 different types of malignancies, including acute myeloid leukemia, has been described.[3-6] It was previously reported that the percentage of obese patients with acute promyelocytic leukemia (APL) is higher than that observed in patients with non-APL AML.[5,6]

Several studies[6-9] have suggested worse clinical outcome in obese/overweight patients with APL. In particular, obesity/overweight has been related to shorter overall survival (OS), higher incidence of differentiation syndrome (DS) and an increased cumulative incidence of relapse (CIR) after front-line therapy with ATRA and chemotherapy-based protocols. However, no large studies have confirmed these findings.

The aim of this study was to analyze the impact of BMI on main clinical outcomes after front-line AIDA-based therapy in a large series of patients with genetically confirmed de novo APL, homogenously treated with three consecutive multicentre PETHEMA trials.

1. What is the NEW aspect of your work?

This large series of APL patients homogeneously treated demonstrates no effect of BMI on relapse rate or in differentiation syndrome, as previously suggested in smaller studies.

2. What is the CENTRAL finding of your work?

Patients with increased BMI had more complications and mortality during induction, which was probably due to its association with older age, and other well-known laboratory abnormalities in overweight/obese patients.

3. What is (or could be) the SPECIFIC clinical relevance of your work?

APL patients with increased BMI need to be carefully managed during induction phase due to an increased mortality rate; however, the postremission strategies should not differ from normal weight patients.

2 | METHODS

2.1 | Patients and eligibility

Between November 1996 and 2012 adult patients from institutions from Spain, The Netherlands, Belgium, Argentina, Uruguay, Czech Republic, and Poland were enrolled in the PETHEMA LPA 96, 99, and 2005 consecutive protocols. In all patients, the diagnosis was genetically confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR). Eligibility criteria and protocol design have been reported elsewhere.[10-13] Informed consent was obtained from patients. According to the Declaration of Helsinki, the protocol was approved by the Research Ethics Board of each participating hospital.

2.2 | Treatment

Induction therapy consisted of oral ATRA and intravenous idarubicin (AIDA regimen). All patients in complete remission (CR) received

three anthracycline-based consolidation courses, which were risk-adapted since protocol LPA99. Consolidation was followed by 2 years of maintenance, as it was previously described.[10-13]

2.3 | BMI calculation and classification

Body mass index was calculated according to the following formula: weight [kg]/height [m^2]. According to the World Health Organization WHO criteria, patients were classified as underweight (<18.5 kg/m^2), normal (18.5-25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2).[2]

2.4 | Definitions and study end points

Hematological complete remission (HCR) and relapse were assessed according to the National Cancer Institute criteria.[14] Molecular remission was defined as the disappearance of the PML/RARA. Molecular persistence was defined as PCR positivity in two consecutive bone marrow samples collected at the end of consolidation therapy. Molecular relapse was defined as the reappearance of PCR-positivity in two consecutive bone marrow samples at any time after consolidation therapy. Risk of relapse was established at diagnosis according to a predictive model based on patient leukocyte and platelet counts at diagnosis, as reported elsewhere.[10-14]

Differentiation syndrome was defined according to previous reports[15,16]: dyspnea, unexplained fever, weight gain greater than 5 kg, unexplained hypotension, acute renal failure, and particularly by a chest radiograph demonstrating pulmonary infiltrates or pleuropericardial effusion.

The patient performance status at diagnosis was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale.[17]

2.5 | Data collection

Data were collected and registered prospectively; last patient follow-up was updated on September 15, 2017. In case of 1320 (93%) of patients height and weight data were available and were included in this analysis. Following data were collected at diagnosis: age, gender, ECOG score, thrombosis and bleeding, hemoglobin level, platelet count, WBC count, creatinine, uric acid, urea, lactate dehydrogenase (LDH), alkaline phosphatases, total bilirubin, and albumin, triglycerides, cholesterol, bilirubin levels, BCR isoforms and FLT3-internal tandem duplication (FLT3-ITD) mutations.

2.6 | Statistical analysis

To analyze differences in the distribution of variables among patient subsets chi-square with Yates' correction, Mann-Whitney U, and Student's *t* tests were used. *P* values were calculated using the two-tailed test.

Overall and event-free survival (OS and EFS) were calculated from the date of starting induction therapy, while cumulative incidence of relapse (CIR) was calculated from the date of CR. Failure to achieve HCR (defined above), relapse, and death in HCR were considered the "events," whichever occurred first, to analyze, when applicable, as censored data in EFS.

Multivariate analysis was performed using a logistic regression model.[18] For univariate comparison, unadjusted time-to-event analyses (relapse-free survival [RFS]) were performed using the Kaplan-Meier estimate,[19] as well as log-rank tests and their generalizations.[18] Patient follow-up was updated on September 15, 2017 and the median follow-up of patients alive at the time of the analysis was 82 months (range, 2-236 months) from diagnosis. Computations were performed using R.2.12 statistical software.

3 | RESULTS

3.1 | Patients characteristics

Between November 1996 and December 2012, 1419 patients with de novo APL were included in three subsequent PETHEMA trials. The information about height and weight was available in 1320 (93%) patients, and from these, 775 (59%) were overweight and obese (BMI ≥25) and 545 (41%) were underweight or normal (<25). BMI distribution was as follows: 7% with BMI <20, 37% with BMI 20-24.9, 33% with BMI 25-29.9, 16% with BMI 30-34.9, 4% with BMI 35-39.9, and 3% with BMI ≥40 (Figure 1).

The main clinical and biologic characteristics of all patients included in the study are shown in Table 1. The age, level of creatinine, urea, uric acid, bilirubin, cholesterol, and triglycerides were significantly higher in patients with BMI ≥25 vs BMI <25. In addition, male gender was related with higher frequency of overweight at diagnosis. A lower incidence of coagulopathy was observed among BMI ≥25 patients. There were no differences in PETHEMA protocol distribution, relapse-risk score, leukocytes, hemoglobin, platelet level, FLT3, BCR3, and other biological markers distribution (Table 1).

3.2 | Patient's outcome according to BMI

As it is shown in the Table 2, we found a significant higher induction mortality rate between APL with BMI <25 vs. BMI ≥ (6% vs. 10%; *P* = .04). There were no significant differences in the frequency of bleeding episodes (78% vs. 80%; *P* = .5) and only a trend in higher rate of thromboischemic events during induction among APL patients with BMI ≥25 (8% vs 5%; *P* = .06). We did not observe higher frequency of DS among patients with BMI ≥25 (29% vs 26%; *P* = .4), but a trend was found when BMI was ≥30 (32% vs 26%; *P* = .06).

TABLE 1 Clinical and biological baseline patient and leukemia characteristics according to BMI

	APL with BMI <25 n = 545		APL with BMI ≥25 n = 775		
	Mean (range)	n (%)	Mean (range)	n (%)	*P* value
Age (years)	38 (18-83)		48 (18-84)		<.0001
Gender					
Male		227 (42)		455 (58)	<.0001
Female		317 (58)		321 (42)	
ECOG (score)	0.93 (0-3)		0.96 (0-3)		.51
PETHEMA protocol					
LPA96		71 (13)		80 (10)	.25
LPA99		201 (37)		282 (37)	
LPA2005		274 (50)		412 (53)	
Leukocytes ($x10^9$/L)	12.3 (0.1-460)		11.6 (0.1-210)		.21
Platelets ($x10^9$/L)	34 (1-222)		36 (1-235)		.22
Relapse-risk category					
Low		108 (20)		176 (23)	.43
Intermediate		295 (54)		404 (53)	
High		142 (26)		195 (25)	
Creatinine (mg/dL)	0.8 (0.3-1.2)		0.9 (0.2-1.3)		<.0001
Urea (mg/dL)	29 (8-154)		35 (8-299)		<.0001
Uric acid (mg/dL)	3.8 (0.8-11.7)		4.5 (1.1-11.6)		<.0001
Bilirubin (mg/dL)	0.7 (0.1-3.3)		0.8 (0.1-4.3)		.002
Cholesterol (mg/dL)	175 (52-305)		189 (76-1276)		<.0001
Triglycerides (mg/dL)	160 (39-850)		191 (22-700)		<.0001
Presence of coagulopathy (n = 995)		324 (78)		396 (68)	.0008
Presence of FLT3-ITD (n = 360)		39 (27)		60 (28)	.82

Abbreviations: APL, acute promyelocytic leukemia; BMI, body mass index.

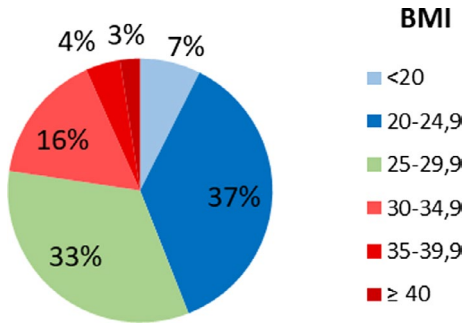

FIGURE 1 Frequency of overweight and obesity in APL patients: distribution of BMI in all APL patients [Colour figure can be viewed at wileyonlinelibrary.com]

The univariate analysis showed that APL patients with BMI ≥25 had lower 5-years OS (74%) as compared to those with BMI <25 (80%); *P* = .006 (Figure 2, Panel A). The multivariate analysis showed that older age, high relapse-risk Sanz score, and PETHEMA LPA96/99 trials were independently associated with worse OS (Table 3).

The 5-year CIR of APL with BMI ≥25 was 13% compared with 12% in APL with BMI <25 (*P* = .69) (Figure 2, Panel B). When we performed analysis between APL patient with BMI ≥30 vs BMI <30, we did not find any significant differences neither (13% vs 12%; *P* = .58). We did observe significant difference in EFS between APL with BMI ≥25 vs APL with BMI <25 (78% vs 84%, *P* = .02) (Figure 2, Panel C).

4 | DISCUSSION

This study shows a relationship between BMI ≥25 and male gender, older age, and other known laboratory abnormalities in APL, as it is seen in overweight/obese non-APL population. We could not confirm a higher incidence of DS in patients with BMI ≥25, but there was trend in obese patients. In this large series of patients treated with AIDA-based regimen, there was no difference in the relapse rate according to BMI, and as well, the BMI was not an independent adverse factor for OS in APL.

Overweight/obesity is a frequent problem in a modern world. According to the literature, overweight and obesity may increase the risk of different kind of cancers, including acute myeloid leukemia.[3-6]

TABLE 2 Clinical outcome during induction treatment according to BMI

	APL with BMI < 25 n = 545 N (%)	APL with BMI ≥ 25, n = 775 N (%)	*P* value
Thrombosis	29 (5)	63 (8)	.06
Bleeding	436 (80)	608 (78)	.5
Induction death	35 (6)	74 (10)	.04
Differentiation syndrome	143 (26)	221 (29)	.4

Abbreviations: APL, acute promyelocytic leukemia; BMI, body mass index.

Moreover, within AML overweight and obesity seems to be more frequent in a group of APL patients.[5-8,20] In this study, we can confirm, that the majority of APL patients are overweight or obese (59%). According to WHO data,[21] prevalence of overweight in general population in some European countries was similar, for example, in Spain it was 60.9% (55.7% in woman and 66.2% in man), in France 60.7% (54.7% in woman and 67.1% in man), in Italy 58.8% (53.7% in woman and 64.3% in man) and in Germany 54.8% (47.2% in woman and 62.7% in man). We did not compare the frequency of overweight and obesity with a matched cohort in general population, but it seems that the APL population had similarities in BMI distribution as the general population.

To our knowledge, this is the largest study analysing the prognostic impact of overweight/obesity, as we studied 1320 APL patients, as compared with previous studies, Castillo et al[6] (n = 446), Breccia et al[7] (n = 144), Estey et al[8] (n = 120 patients), and by Jeddi et al[22] (n = 39). In addition, Li et al, [9]performed a metanalysis including 866 APL patients.

In the present study, we show in APL patients a relationship between BMI ≥25 and male gender, older age, and other known laboratory abnormalities, such as increased creatinine, urea, uric acid, bilirubin, cholesterol, and triglycerides. This is in line with the previously reported relationship of this variable in overweight/obese non-APL population.[4-6] In a study by Breccia et al, the proportion of male gender among overweight/obese and underweight/normal APL patients was 53% and 33%, respectively ($P = .02$) whereas in ours it was of 67% and 33%, respectively ($P < .0001$). In line with our findings, Castillo et al reported that APL patients older than 60 years had increased odds of obesity than patients 40-60 years of age.[6] Interestingly, we analyzed the potential relationship between BMI and biological markers, including FLT3-ITD mutations, and we found no significant correlation.

Regarding the clinical outcomes, we found that, in line with the previous study by Breccia et al, Li et al, and Castillo et al, overweight/obese APL patients had lower OS.[6,7,9] However, we were not able to reproduce the higher relapse risk reported in the Italian study of adult APL patients homogeneously treated with ATRA and chemotherapy (5-year CIR 32% in APL with BMI ≥25% vs 11%). Thus, lower OS among APL patients with BMI ≥25 was probably due to patient´s features related with higher toxicity/early death. For example, risk modification of PETHEMA trial provokes independent improvement of OS in patients treated with protocol 2005/2012 vs 1996/1999 as it is seen in a Table 3. In fact, obese APL patients died more frequently during induction, probably because an increased susceptibility for developing life-threatening complications in view of their older age and more frequent baseline laboratory abnormalities. In particular, we observed a trend to develop more frequently thromboischemic events in APL patients with BMI ≥25, which is also a known risk factor in general population. We were not able to confirm a higher incidence of DS in patients with BMI ≥25, but we observed a trend in obese (BMI ≥30) patients. In a study of Breccia et al, performed on 144 APL patients, a BMI ≥25 was a strong predictive factor for DS. As well, Jeddi et al performed multivariate analysis on 36 APL patients showing that BMI ≥30 and WBC >20 × 10 G/L were independent factors for DS. According to Tabe et al, leptin receptor, absent on normal promyelocytes, were present on APL blasts.[23] The high risk for DS could be related to the leptin secretion by bone marrow adipocytes localized next to the leukemic cells and in that way stimulate proliferation and survival of APL cells. However, a more plausible explanation to the herein unconfirmed higher risk for developing DS in obese patients could be (a) its association with higher creatinine values and (b) a potential susceptibility to develop respiratory or other symptoms related to some degree of DS. The probable association between BMI and DS might have practical clinical implications: obese APL patients could be closely monitored to start dexamethasone therapy at the first sign or symptom of DS.

As far as we know, there is only one report analysing the influence of overweight/obesity in some APL patients treated with the combination of arsenic trioxide (ATO) and ATRA.[6] The potential role of the BMI in main outcomes, and toxicities (ie, thromboischemic events, DS, early death), remains to be established in APL patients receiving ATO + ATRA-based regimens.

In PETHEMA protocols, there are no recommendations concerning which body weight (according to measured, lean or ideal body weight) should be used to calculate the dose of ATRA, ATO or chemotherapy. As a result, each center dosed according to the local protocols. We can speculate that underdosing of obese patients might impair dose intensity and outcomes in this setting. However, we did not observe increased relapse rate in ≥25 BMI patients. In obese patients, we observed increased mortality during induction. We can speculate that this could be related to overdosing in some cases, but we consider that increased mortality was more probably related to more frequent comorbidities (renal, hepatic, metabolic), and because obesity is considered a comorbidity itself. However, prospective studies need to be performed to establish the correct dosing schedule according to BMI in order to spare toxicities.

Our study has several limitations: (a) this is a retrospective study, thus assessment of some outcomes, in particular toxicities such as DS or thromboischemic events, could be inaccurate. However, the forms included specifically field asking in detail for DS criterion and other toxicities in a systematic way; (b) not all patients had available data on

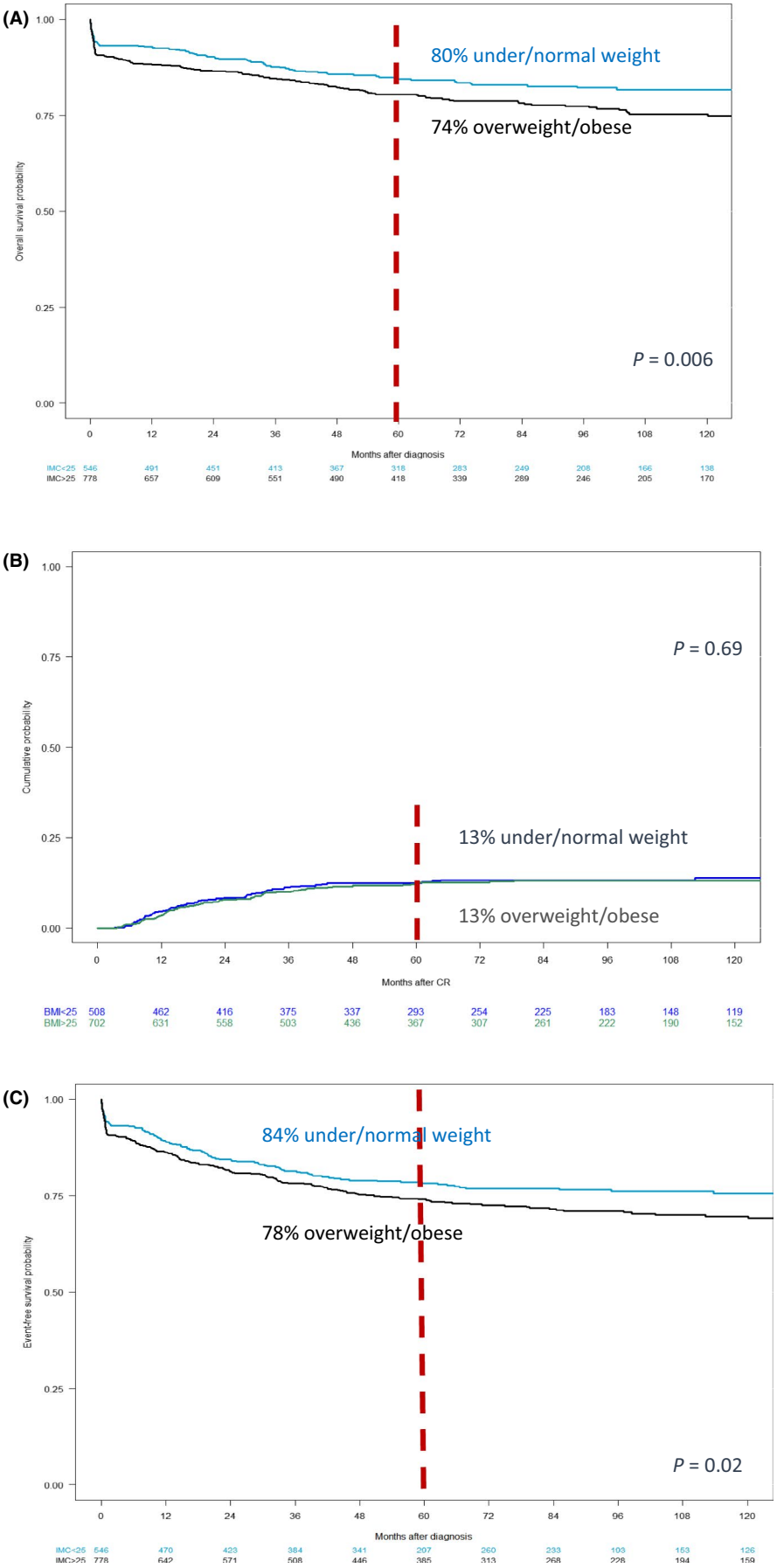

FIGURE 2 relapse (CIR) according to BMI in APL patients (at 5 years, 13% under/normal weight vs. 13% overweight/obese, p=0.69). Panel C, Event-free survival (EFS) according to BMI in APL patients (at 5 years, 84% under/normal weight vs. 78% verweight/obese, p=0.02) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Overall survival, multivariate analysis

Adverse risk factor	Hazard ratio (95% confidence interval)	*P* value
Overweight/obese (BMI ≥25)	1.11 (0.69-1.18)	.46
Older age*	1.05 (1.04-1.06)	<.0001
Higher relapse risk	2.14 (1.77-2.60)	<.0001
PETHEMA trials LPA 96/99	1.57 (1.21-2.03)	.001

Abbreviations: BMI, body mass index.

*Means augmented risk per additional year of age.

weight and height, leading to a potential selection bias. However, only 7% of our unselected registered population lacked of this information; and (c) the study was performed only in APL patients eligible for the PETHEMA protocols, so they are not fully representative of a "real-life" cohort. So our conclusions are applicable mainly to patients with de novo APL and fit enough to undergo AIDA induction.

In conclusion, in this large series of adult APL patients homogeneously treated with ATRA and chemotherapy, overweight/obesity was very frequent. Patients with increased BMI had more complications and mortality during induction, which was probably due to its association with older age, and other well-known laboratory abnormalities in overweight/obese patients. However, we could not confirm an independent adverse prognostic impact of overweight or obesity.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

M.S, P.M, and M.S conceived the study. M.S and P.M analyzed and interpreted the data; M.S, P.M wrote the paper; P.M performed the statistical analyses; R-V.R, V.E, P.M, S.J, B.T, G.C, B.S, B.J, G-C.J, R.JM, T.M, G.M, F.I, B.B included data of patients treated in their institutions. All authors reviewed the manuscript and contributed to the final draft.

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