Research Article

Impact of BMI and Gender on Outcomes in DLBCL Patients Treated with R-CHOP: A Pooled Study from the LYSA

Clémentine Sarkozy,[1] Nicolas Mounier,[2] Alain Delmer,[3] Achiel Van Hoof,[4] Jean Michel Karsenti,[2] Emmanuel Fleck,[5] Marie Maerevoet,[6] Jean Claude Eisenmann,[7] Richard Delarue,[8] Michel Fabbro,[9] and Bertrand Coiffier[1]

[1] *Service d'Hématologie Clinique, Centre Hospitalier Lyon-Sud, Hospices Civiles de Lyon, 69310 Pierre Bénite, France*
[2] *Service d'Hématologie, CHU de Nice, 06000 Nice, France*
[3] *Service d'Hématologie Clinique, CHU de Reims, 51100 Reims, France*
[4] *Service d'Hématologie, General Hospital St. Jan, B8000 Brugge, Belgium*
[5] *Service d'Onco-hématologie, Hôpital Saint Louis, 1700 La Rochelle, France*
[6] *Service d'Hématologie Clinique, Institut Jules Bordet, 1000 Bruxelles, Belgium*
[7] *Service d'Hématologie, Centre Hospitalier de Mulhouse Hasenrein, 68100 Mulhouse, France*
[8] *Service d'Hématologie, Centre Hospitalier Necker, 75015 Paris, France*
[9] *Institut Régional du Cancer, 34070 Montpellier, France*

Correspondence should be addressed to Bertrand Coiffier; bertrand.coiffier@chu-lyon.fr

In diffuse large B-cell lymphoma (DLBCL), the age-adjusted International Prognostic Index (aaIPI) score is currently used to predict patient outcomes and to choose the best therapeutic treatment. Body mass index (BMI) and gender are occasionally sited as prognostic factors; however, their value has never been studied in a large series of patients included in prospective clinical trials in the rituximab era. To assess the impact of BMI and gender on OS and PFS independently of the aaIPI score, we pooled 985 patients that were prospectively included in GELA studies and uniformly treated with R-CHOP. Univariate analysis indicated that high aaIPI and male gender were associated with a worse PFS, whereas high (>25) or low (<18.5) BMI scores were not. High aaIPI score was the only factor predictive for OS. In a multivariate analysis, including aaIPI score, gender, BMI, and interaction between BMI and gender, aaIPI remained the strongest predictive factor, and BMI < 18.5 was significantly associated with a worse OS but not PFS. In conclusion, in the rituximab era, the aaIPI score remains the major predictor of outcome in DLBCL patients; however, male gender and low BMI seem to impact outcome.

1. Introduction

DLBCL is the most frequent type of NHL. The outcome of DLBCL has been remarkably improved in younger as well as elderly patients by rituximab, a chimeric monoclonal antibody targeting the CD20 antigen. A recent update of randomised trials conducted by the GELA group and others evaluating the efficacy of rituximab in addition to CHOP or intensified CHOP (namely, ACVBP: 75 mg/m^2 doxorubicin and 1200 mg/m^2 cyclophosphamide on day 1;

2 mg/m^2 vindesine and 10 mg bleomycin on days 1 and 5; and 60 mg/m^2 prednisone on days 1–5) demonstrated that the benefit of rituximab is maintained over the years [1–7]. Currently, R-CHOP is the standard of care for patients with newly diagnosed DLBCL [8, 9]. The International Prognostic Index (IPI) is commonly used to predict patient outcome and to stratify patients into low- and high-risk groups to choose the appropriate therapeutic treatment [10]. The IPI is based on 5 characteristics, age, performance status (PS), lactic dehydrogenase (LDH) levels, Ann Arbor stage, and

extranodal sites, and identifies 4 risk categories of patients with different predicted survival. A simplified score termed the age-adjusted IPI (aaIPI), based on the LDH level, Ann Arbor stage, and PS, has been developed and is widely used to direct therapeutic decision in both the younger and elderly patients.

Recent epidemiologic data has confirmed that lymphoma is more frequent in men than in women and that this difference increases with age and body mass index (BMI) [11, 12]. Indeed in several reports, being overweight (BMI $> 25 \, \text{kg/m}^2$) or obese (BMI $> 30 \, \text{kg/m}^2$) was associated with a higher risk of NHL compared with being of normal weight (BMI $18.5–25 \, \text{kg/m}^2$) [13, 14]. Some recent reports have focused on the impact of gender or BMI on the outcomes of patients with DLBCL [15–20], but this question has never been addressed in a large cohort of patients previously included in prospective trials and uniformly treated with rituximab. Thus, to assess the prognostic value of male gender and BMI independently of the aaIPI score in DLBCL patients treated with the R-CHOP, we pooled 3 GELA prospective randomised phase III trials.

2. Patients and Methods

2.1. Patients. Among the phase III studies prospectively conducted by the GELA in the rituximab era, we pooled patients from the LNH98-5 (patients between 60 and 80 years old, included between July 1998 and March 2000), LNH03-2B (patients between 18 and 59 years old with an aaIPI score of 1, included between December 2003 and December 2008, clinicaltrials.gov: NCT00140595), and LNH03-6B (patients between 60 and 80 years old, included between December 2003 and 2008; clinicaltrials.gov: NCT00144755) trials. To present homogenous data, the current study only included patients treated with R-CHOP in these different randomised studies. Details regarding the design and data management of the LNH98-5 [2], LNH03-2B [8], and LNH03-6B [21] trials have been published. These studies complied with all provisions of the Declaration of Helsinki and its current amendments and were conducted in accordance with Good Clinical Practice guidelines. The LNH98-5 and 03-2B, respectively, included 399 and 380 patients, of whom 202 and 184 were treated with R-CHOP. The LNH03-6B trial [21] included 602 patients randomised to R-CHOP treatment every 2 or 3 weeks (Figure 1).

For this analysis, the BMI (=weight/size^2) score was classified in three groups: underweight, $<18.5 \, \text{kg/m}^2$; overweight, $>25 \, \text{kg/m}^2$; and normal weight, $18.5 \, \text{kg/m}^2$ to $25 \, \text{kg/m}^2$.

2.2. Statistical Analysis. Progression-free survival (PFS) was defined as the time from inclusion until disease progression/relapse or death from any cause; overall survival (OS) was defined as the time from inclusion to death from any cause. Survival analyses were performed using the logrank test and expressed as Kaplan-Meier plots with appropriate 95% CIs. Multivariate analyses were performed with a Cox proportional hazards regression model. The prognostic value of the following variables was assessed by multivariate analyses: BMI (overweight versus normal and underweight versus normal), gender (male versus female), age ($\geq$60 years versus $<$60 years), and aaIPI score (2-3 = high score versus 0-1 = low score). Among the different clinical correlations, we paid specific attention to the interaction between BMI and gender, as this interaction stood out among the literature data. The Cox model was performed to determine the impact of each factor on OS or PFS separately, using univariate analyses as a first step and multivariate analyses in a second step. In multivariate analyses, the following variables were included: BMI in groups, gender, age, interaction between BMI and gender, and aaIPI scores. Statistical analyses were performed using the SAS software v9.2. *The aim of the analysis was to study the impact of gender and BMI independently from the IPI score. Those factors were therefore selected on the basis of clinical relevance for multivariate analysis.*

3. Results

3.1. Initial Clinical Characteristics of the 985 Patients. The global population included 985 patients (Figure 1). The patients' initial characteristics are described in Table 1(a). Patients from the LNH03-6B and 98-05 trial exhibited similar initial characteristics. Patients from the LNH03-2B study were younger and exhibited lower aaIPI scores. These patients were also less likely to exhibit elevated LDH levels, PS > 1, stage 3-4 disease, extranodal sites, high β2-microglobulin levels, or serum albumin < 35 g/L. There were no differences in B symptoms or bulk mass rates between the 3 trials.

The ages, BMI, gender, and aaIPI scores for the patients in the pooled analysis are shown in Table 1(b). There were no differences between the 3 trials with respect to the BMI subgroups, with similar median BMI values of 24.5, 24.3 and 25 kg/m^2 for the LNH 98-5, 03-2B, and 03-6B studies, respectively. Nevertheless, there were slightly fewer patients with a BMI < 18.5 in the LNH03-6B trial (1.5%) compared with the LNH03-2B or LNH98-5 studies (7.7 and 5.9%, resp.). Interestingly, although they included patients of the same age (60–80 years), the LNH98-5 trial included more women (54.5%) compared with the LNH03-6B (44.7%). This discrepancy is most likely due to the increasing difference in the incidence of lymphoma between genders. Indeed, the LNH03-6B and LNH03-2B studies were conducted during the same period of time (2003–2008) and after the LNH98-5 study (1998–2000). The repartition of patients according to gender and BMI subgroup was comparable between the 3 trials.

Finally, the CR, Cru, and PR rate at end of treatment were similar between the three studies (shown in Table 2).

3.2. Univariate Analysis. The results of the univariate analysis for OS and PFS are presented in Table 3. High aaIPI score, age older than 60 years, and male gender were associated with a shorter PFS; the median PFS was 118 months for patients with low aaIPI scores versus 41 months for patients with high score ($P < 0.0001$, HR = 1.97, 95% CI (1.62–2.38)) and 111 months for females versus 59 months for males ($P = 0.0262$, HR =
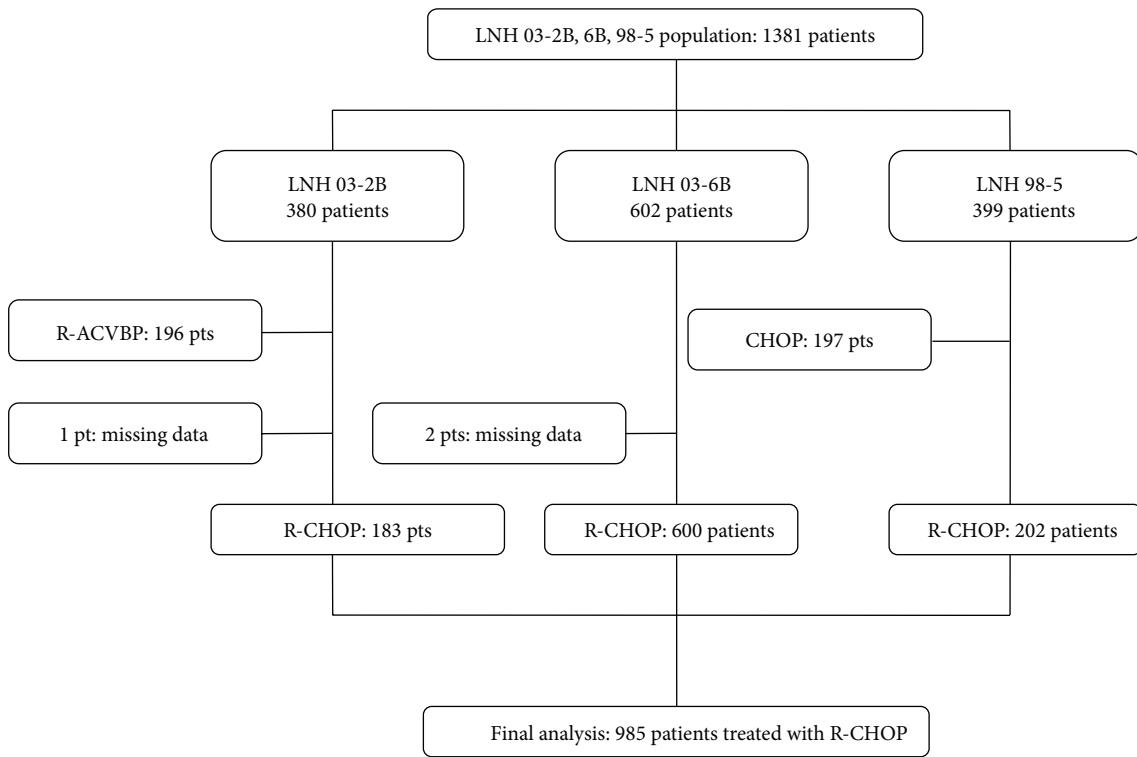
Figure 1: Consort diagram of the current study.

PFS according to gender
with number of subjects at risk and 95% confidence interval

	Number of subjects	Event	Censored	Median survival (95% CI)
Female	452	41.8% (189)	58.2% (263)	110.7 (77.6; NA)
Male	533	48.2% (257)	51.8% (276)	59.3 (49.7; 90.6)

(a)

OS according to gender
with number of subjects at risk and 95% confidence interval

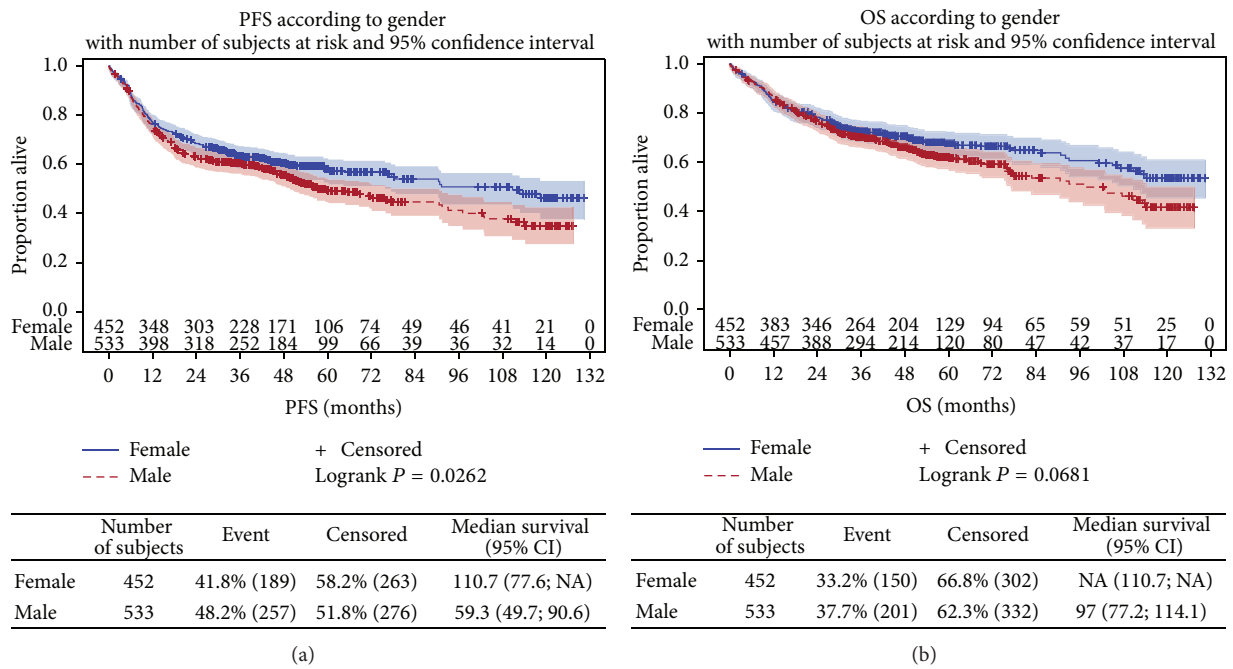|	Number of subjects	Event	Censored	Median survival (95% CI)
Female	452	33.2% (150)	66.8% (302)	NA (110.7; NA)
Male	533	37.7% (201)	62.3% (332)	97 (77.2; 114.1)

(b)

Figure 2: PFS and OS according to gender in the global population. (a) In the global population, women exhibited a better PFS than men (111 months versus 59 months): $P = 0.0262$. (b) In the global population, men exhibited a trend for worse OS, but the difference was not significant: $P = 0.068$.

Table 1: (a) Patients' initial clinical characteristics as reported by the different trials. (b) Patients' initial BMI, gender, and aaIPI scores according to the different trials.

(a)

		Protocol		R-CHOP
	LNH98-5	LNH03-2B	LNH03-6B	patients
	N = 202	N = 183	N = 600	N = 985
IPI				
0	0 (0.0%)	7 (3.8%)	1 (0.2%)	8 (0.8%)
1	29 (14.4%)	122 (66.7%)	14 (2.3%)	165 (16.8%)
2	64 (31.7%)	51 (27.9%)	133 (22.2%)	248 (25.2%)
3	78 (38.6%)	3 (1.6%)	201 (33.5%)	282 (28.6%)
4	30 (14.9%)	0 (0.0%)	173 (28.8%)	203 (20.6%)
5	1 (0.5%)	0 (0.0%)	78 (13.0%)	79 (8.0%)
Age-adjusted IPI				
0	20 (9.9%)	7 (3.8%)	10 (1.7%)	37 (3.8%)
1	61 (30.2%)	169 (92.3%)	209 (34.8%)	439 (44.6%)
2	87 (43.1%)	7 (3.8%)	276 (46.0%)	370 (37.6%)
3	34 (16.8%)	0 (0.0%)	105 (17.5%)	139 (14.1%)
aaIPI in groups				
0-1	81 (40.1%)	176 (96.2%)	219 (36.5%)	476 (48.3%)
>1	121 (59.9%)	7 (3.8%)	381 (63.5%)	509 (51.7%)
Stage				
1	0 (0.0%)	28 (15.3%)	10 (1.7%)	38 (3.9%)
2	41 (20.3%)	62 (33.9%)	60 (10.0%)	163 (16.5%)
3	33 (16.3%)	21 (11.5%)	97 (16.2%)	151 (15.3%)
4	128 (63.4%)	72 (39.3%)	433 (72.2%)	633 (64.3%)
PS				
0	67 (33.2%)	120 (65.6%)	211 (35.2%)	398 (40.4%)
1	90 (44.6%)	62 (33.9%)	254 (42.3%)	406 (41.2%)
2	45 (22.3%)	1 (0.5%)	130 (21.7%)	176 (17.9%)
3	0 (0.0%)	0 (0.0%)	5 (0.8%)	5 (0.5%)
LDH				
>ULV	131 (64.9%)	89 (48.6%)	411 (68.5%)	631 (64.1%)
Normal	71 (35.1%)	94 (51.4%)	189 (31.5%)	354 (35.9%)
Extranodal sites				
>1 extra-nodal sites	106 (52.5%)	50 (27.3%)	306 (51.0%)	462 (46.9%)
≤ 1 extra-nodal site	96 (47.5%)	133 (72.7%)	294 (49.0%)	523 (53.1%)
Bone marrow involvement				
Not involved	144 (71.3%)	155 (84.7%)	438 (73.0%)	737 (74.8%)
Involved	55 (27.2%)	27 (14.8%)	128 (21.3%)	210 (21.3%)
Not assessed	3 (1.5%)	1 (0.5%)	34 (5.7%)	38 (3.8%)
Mass > 10 cm				
Missing	1	1	0	2
No	141 (70.1%)	137 (75.3%)	496 (82.7%)	774 (78.7%)
Yes	60 (29.9%)	45 (24.7%)	104 (17.3%)	209 (21.3%)
B symptoms				
No	124 (61.4%)	136 (74.3%)	377 (62.8%)	637 (64.7%)
Yes	78 (38.6%)	47 (25.7%)	223 (37.2%)	348 (35.3%)
Beta2 microglobulin				
Missing	35	41	109	185
>ULV	97 (58.1%)	44 (31.0%)	328 (66.8%)	469 (58.6%)

(a) Continued.

| | Protocol | | | R-CHOP |
| | LNH98-5 | LNH03-2B | LNH03-6B | patients |
	$N = 202$	$N = 183$	$N = 600$	$N = 985$
Normal	70 (41.9%)	98 (69.0%)	163 (33.2%)	331 (41.4%)
Albumin				
Missing	11	27	64	102
≤35 g/L	78 (40.8%)	28 (17.9%)	183 (34.1%)	289 (32.7%)
>35 g/L	113 (59.2%)	128 (82.1%)	353 (65.9%)	594 (67.3%)

ULV: upper limit value.

(b)

| Initial characteristics | Protocol | | | R-CHOP |
| | LNH98-5 | LNH03-2B | LNH03-6B | patients |
	$N = 202$	$N = 183$	$N = 600$	$N = 985$
Gender				
Male	92 (45.5%)	109 (59.6%)	332 (55.3%)	533 (54.1%)
Female	110 (54.5%)	74 (40.4%)	268 (44.7%)	452 (45.9%)
Age at diagnosis				
Mean (SD)	69.47 (5.58)	44.73 (11.17)	70.07 (5.09)	65.24 (11.89)
Median	69.5	48.0	70.0	68.0
<60 years	1 (0.5%)	183 (100.0%)	1 (0.2%)	185 (18.8%)
≥60 years	201 (99.5%)	0 (0.0%)	599 (99.8%)	800 (81.2%)
Body mass index (kg/m^2)				
Mean (SD)	25.05 (4.36)	24.67 (4.46)	25.76 (4.50)	25.41 (4.48)
Median	24.5	24.3	25.0	24.8
Min; max	16; 41	16; 39	16; 47	16; 47
<18.5	12 (5.9%)	14 (7.7%)	9 (1.5%)	35 (3.6%)
18.5–25	96 (47.5%)	90 (49.2%)	296 (49.3%)	482 (48.9%)
>25	94 (46.5%)	79 (43.2%)	295 (49.2%)	468 (47.5%)
Gender and BMI in groups				
Male—BMI < 18.5	2 (1.0%)	5 (2.7%)	4 (0.7%)	11 (1.1%)
Male—BMI 18.5–25	43 (21.3%)	48 (26.2%)	166 (27.7%)	257 (26.1%)
Male—BMI > 25	47 (23.3%)	56 (30.6%)	162 (27.0%)	265 (26.9%)
Female—BMI < 18.5	10 (5.0%)	9 (4.9%)	5 (0.8%)	24 (2.4%)
Female—BMI 18.5–25	53 (26.2%)	42 (23.0%)	130 (21.7%)	225 (22.8%)
Female—BMI > 25	47 (23.3%)	23 (12.6%)	133 (22.2%)	203 (20.6%)
Age and BMI in groups				
Age < 60 years and BMI < 18.5	0 (0.0%)	14 (7.7%)	0 (0.0%)	14 (1.4%)
Age < 60 years and BMI 18.5–25	1 (0.5%)	90 (49.2%)	0 (0.0%)	91 (9.2%)
Age < 60 years and BMI > 25	0 (0.0%)	79 (43.2%)	1 (0.2%)	80 (8.1%)
Age ≥ 60 years and BMI < 18.5	12 (5.9%)	0 (0.0%)	9 (1.5%)	21 (2.1%)
Age ≥ 60 years and BMI 18.5–25	95 (47.0%)	0 (0.0%)	296 (49.3%)	391 (39.7%)
Age ≥ 60 years and BMI > 25	94 (46.5%)	0 (0.0%)	294 (49.0%)	388 (39.4%)
Age and gender in groups				
Male <60 years	0 (0.0%)	109 (59.6%)	0 (0.0%)	109 (11.1%)
Female <60 years	1 (0.5%)	74 (40.4%)	1 (0.2%)	76 (7.7%)
Male ≥60 years	92 (45.5%)	0 (0.0%)	332 (55.3%)	424 (43.0%)
Female ≥60 years	109 (54.0%)	0 (0.0%)	267 (44.5%)	376 (38.2%)

*When BMI classes were established using 16.5 and 30 as the cut-offs, 6 (0.6%) patients were underweight (BMI < 16.5), 838 (85.21%) exhibited a normal weight (BMI: 16.5–30), and 141 (14.3%) were overweight (BMI > 30).
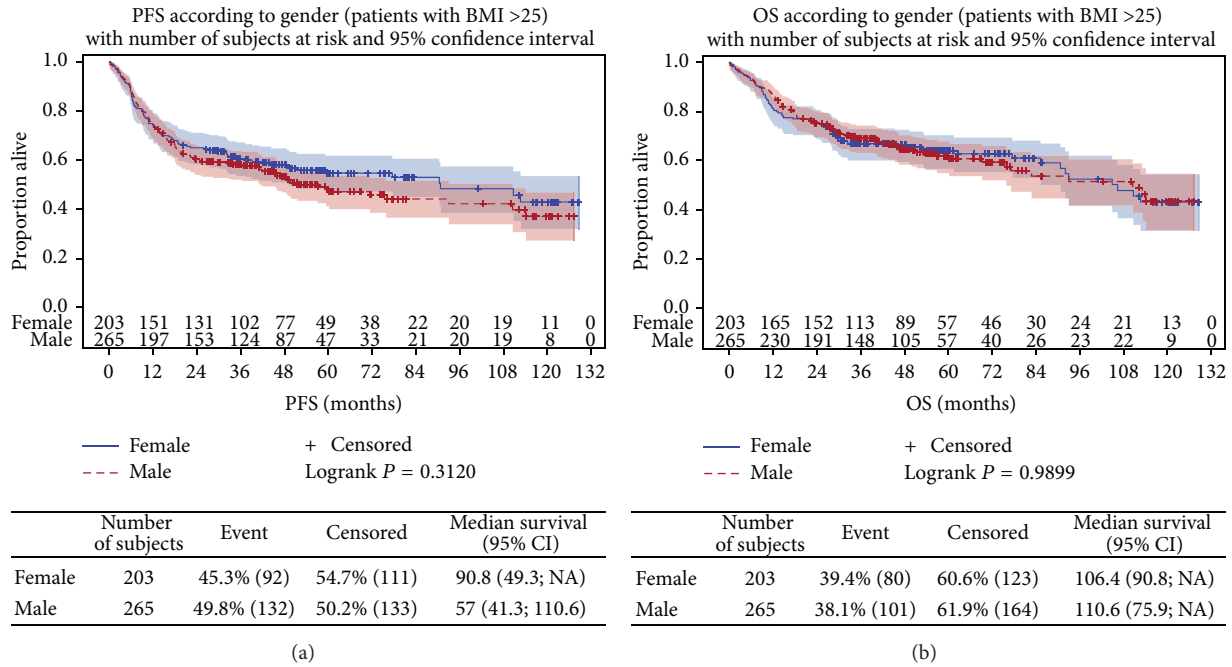
PFS according to gender (patients with BMI >25)
with number of subjects at risk and 95% confidence interval

OS according to gender (patients with BMI >25)
with number of subjects at risk and 95% confidence interval

	Number of subjects	Event	Censored	Median survival (95% CI)
Female	203	45.3% (92)	54.7% (111)	90.8 (49.3; NA)
Male	265	49.8% (132)	50.2% (133)	57 (41.3; 110.6)

(a)

	Number of subjects	Event	Censored	Median survival (95% CI)
Female	203	39.4% (80)	60.6% (123)	106.4 (90.8; NA)
Male	265	38.1% (101)	61.9% (164)	110.6 (75.9; NA)

(b)

FIGURE 3: PFS and OS according to gender in the subgroup of patients with a BMI > 25: male and female patients had a similar PFS ($P = 0.31$, median PFS 57 versus 90 for men and women, resp., HR = 1.14, 95% CI (0.87–1.49)) and OS ($P = 0.9899$, median OS 110 months and 106 months for men and women, resp.).

TABLE 2: Response rates according to the different trials.

|	Protocol			
Response rate at end of treatment	LNH98-5	LNH03-2B	LNH03-6B	R-CHOP patients
	$N = 202$	$N = 183$	$N = 600$	$N = 985$
Missing	15	0	1	16
Stable or progressive disease (including death)	20 (10.7%)	23 (12.6%)	82 (13.7%)	125 (12.9%)
CR/uCR	153 (81.8%)	146 (79.8%)	432 (72.1%)	731 (75.4%)
PR	14 (7.5%)	14 (7.6%)	85 (14.2%)	113 (11.7%)

CR: complete response; PR: partial response; uCR: unconfirmed CR.

1.24, 95% CI (1.025–1.493)) (Figures 2(a) and 2(b)). Elderly patients exhibited a median PFS of 65 months versus not reached for patients younger than 60 years ($P = 0.0011$, HR = 1.61, 95% CI (1.207–2.148)). Low (<18.5) or high BMI (>25) had no significant impact on PFS ($P = 0.74$ and $P = 0.18$, resp.).

High aaIPI score and age were the two factors significantly associated with shorter OS; the median OS was 83 months for aaIPI > 1 versus not reached for aaIPI of 0-1 ($P < 0.0001$, HR = 2.41, 95% CI (1.92–3.01)), and the median OS was 108 months versus not reached ($P < 0.0001$, HR = 2.021, 95% CI (1.409–2.898)) for patients older or younger than 60 years, respectively. Nevertheless, even if not statistically significant, female tended to have a longer OS than males ($P = 0.0681$, HR = 1.21, 95% CI (0.99–1.50): median not reached versus 97 months for females and males, resp.). Low or high BMI had no significant impact on OS ($P = 0.63$ and $P = 0.12$, resp.). Furthermore, PFS and OS were similar between obese patients (BMI > 30) and nonobese patients ($P = 0.719$ and $P = 0.069$, resp.).

We then studied the effect of gender by stratifying by BMI (Table 4). In patients with a BMI > 25 (Figures 3(a) and 3(b)), gender had no effect on PFS; the median PFS was 57 versus 90 for men and women, respectively ($P = 0.31$, HR = 1.14, 95% CI (0.87–1.49)). Gender also had no effect on OS ($P = 0.9899$, HR = 1.002, 95% CI (0.74–1.34)); the median OS was 110 months and 106 months for men and women, respectively. In the population of patients with a normal BMI (18.5–25) (Figures 4(a) and 4(b)), the effect of gender on OS and PFS was significantly different; the median OS was 97 months for men and not reached women ($P = 0.0276$, HR = 1.427, 95% CI (1.038–1.962)) and the median PFS was 64.8 months for men versus 118.3 for women ($P = 0.0455$, HR = 1.32, 95% CI (1.00–1.74)). In the population of patients with a BMI < 18.5 (Figures 5(a) and 5(b)), females tended to have a longer OS, as demonstrated by the survival curves; the median OS was 68.9 years for men versus not reached for women ($P = 0.3246$), although the difference was not statistically significant, likely as a result of the low number of patients. However, in this subgroup, the PFS survival curves
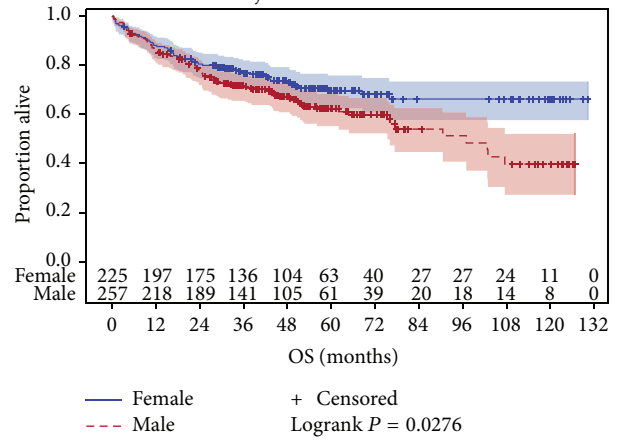
PFS according to gender (patients with normal BMI between 18.5 and 25)
with number of subjects at risk and 95% confidence interval
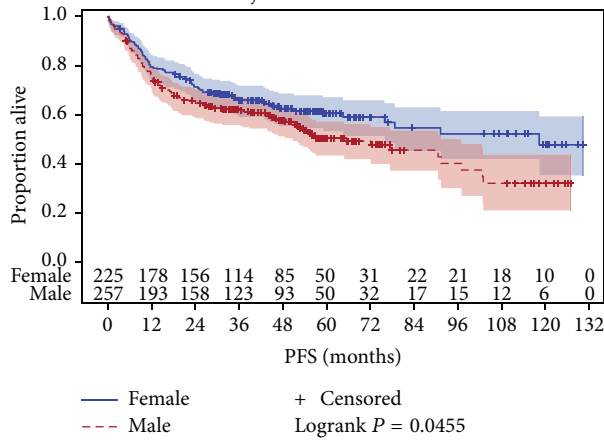
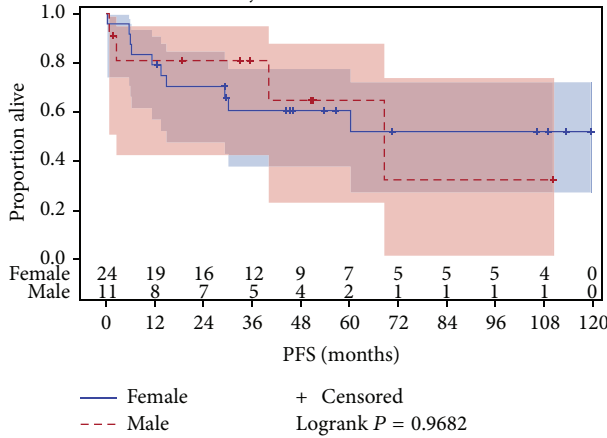|	Number of subjects	Event	Censored	Median survival (95% CI)
Female	225	38.7% (87)	61.3% (138)	118.3 (75.9; NA)
Male	257	47.1% (121)	52.9% (136)	64.8 (50.7; 97)

(a)

OS according to gender (patients with normal BMI between 18.5 and 25)
with number of subjects at risk and 95% confidence interval

	Number of subjects	Event	Censored	Median survival (95% CI)
Female	225	28% (63)	72% (162)	NA (NA; NA)
Male	257	37.4% (96)	62.6% (161)	97 (75.4; NA)

(b)

FIGURE 4: PFS and OS according to gender in the subgroup of patients with a BMI between 18.5 and 25: females had a longer OS ($P = 0.0276$, median OS 97 months versus NR for men and women, resp., HR = 1.427, 95% CI (1.038–1.962)) and PFS ($P = 0.0455$, median PFS 64.8 months versus 118.3 for men and women, resp., HR = 1.32, 95% CI (1.00–1.74)) than males.
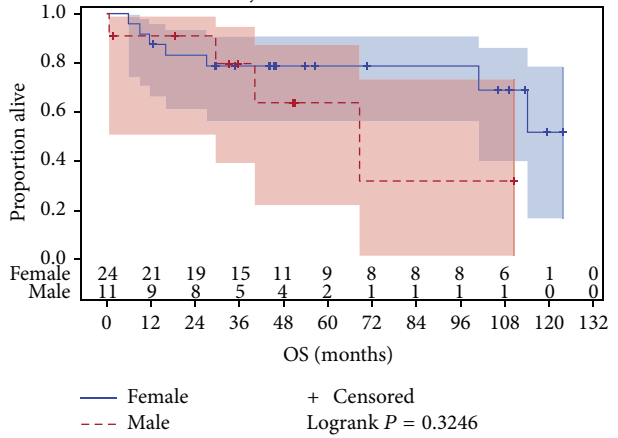
PFS according to gender (patients with BMI <18.5)
with number of subjects at risk and 95% confidence interval

	Number of subjects	Event	Censored	Median survival (95% CI)
Female	24	41.7% (10)	58.3% (14)	NA (14.9; NA)
Male	11	36.4% (4)	63.6% (7)	68.6 (2.5; NA)

(a)

OS according to gender (patients with BMI <18.5)
with number of subjects at risk and 95% confidence interval

	Number of subjects	Event	Censored	Median survival (95% CI)
Female	24	29.2% (7)	70.8% (17)	NA (101; NA)
Male	11	36.4% (4)	63.6% (7)	68.6 (29.6; NA)

(b)

FIGURE 5: PFS and OS according to gender in the subgroup of patients with a BMI < 18.5: female patients tended to have a longer OS (median 68.9 versus NR for men and women, resp., $P = 0.3246$), as shown by the survival curves, although the difference was not significant, most likely due to the low number of patients. However, in this subgroup, the PFS survival curves were totally stackable ($P = 0.968$, median OS 68 months versus NR for men and women, resp., HR = 1.024, 95% CI (0.32–3.27)).

TABLE 3: Statistical analysis for OS and PFS in the global population.

	PFS $N = 985$	OS $N = 985$
Univariate analysis		
	$P = 0.3528$	$P = 0.2253$
	$P = 0.18$	$P = 0.12$
BMI (<18.5/18.5–25/>25)*	HR = 1.1	HR = 1.18
>25 versus ≤25	95% CI (0.94–1.37)	95% CI (0.95–1.46)
<18.5 versus ≥18.5	$P = 0.74$	$P = 0.63$
	HR = 0.9	HR = 0.86
	95% CI (0.53–1.57)	95% CI (0.47–1.59)
	P = 0.0262	$P = 0.0681$
Gender (male versus female)	**HR = 1.237**	HR = 1.218
	95% CI (1.025–1.493)	95% CI (0.985–1.505)
	P < 0.0001	**P < 0.0001**
aaIPI (2-3 versus 0-1)	**HR = 1.967**	**HR = 2.407**
	95% CI (1.62–2.38)	**95% CI (1.92–3.01)**
	P = 0.0011	**P > 0.0001**
Age (≥60 y versus <60)	**HR = 1.61**	**HR = 2.021**
	95% CI (1.207–2.148)	**95% CI (1.409–2.898)**
Cox model		
	$P = 0.78$	$P = 0.82$
BMI > 25 versus normal	HR = 1.097	HR = 0.917
	95% CI (0.56–2.11)	95% CI (0.4162.00)
	$P = 0.31$	**P = 0.048**
BMI < 18.5 versus normal	HR = 1.16	**HR = 1.394**
	95% CI (0.86–1.55)	**95% CI (1.00–1.94)**
	$P = 0.14$	$P = 0.07$
Gender (male versus female)	HR = 1.226	HR = 1.342
	95% CI (0.93–1.61)	95% CI (0.97–1.84)
	$P = 0.57$	$P = 0.33$
Age (≥60 y versus <60)	HR = 1.096	HR = 1.215
	95% CI (0.79–1.51)	95% CI (0.81–1.80)
	P < 0.0001	**P < 0.0001**
aaIPI (>1 versus 0-1)	**HR = 1.926**	**HR = 2.287**
	95% CI (1.55–2.38)	**95% CI (1.78–2.93)**
	$P = 0.58$	$P = 0.93$
BMI and gender	HR = 0.716	HR = 1.055
	95% CI (0.21–2.36)	95% CI (0.29–3.76)

*The test was performed using the 3 BMI classes: <18.5, 18.5–25, and >25. When 16.5 and 30 were used as the cut-offs, BMI had no impact on OS or PFS ($P = 0.69$ and 0.71, resp.).
In a Cox regression model including BMI, gender, age, aaIPI score, and the interaction between BMI and gender as covariables, a high aaIPI score was the only factor associated with a worse PFS and OS. Low BMI significantly impacted OS but not PFS.

TABLE 4: Impact of gender stratification on BMI.

Gender (male versus female)	BMI < 18.5	BMI 18.5–25	BMI > 25
	$P = 0.9682$	$P = 0.0455$	$P = 0.312$
PFS	HR = 1.024	HR = 1.324	HR = 1.147
	95% CI (0.32–3.27)	95% CI (1.00–1.74)	95% CI (0.88–1.49)
	$P = 0.3246$	$P = 0.0276$	$P = 0.9899$
OS	HR = 1.88	HR = 1.427	HR = 1.00
	95% CI (0.52–6.82)	95% CI (1.038–1.96)	95% CI (0.747–1.344)

The impact of gender varied with BMI. Gender had no impact on PFS in the subgroup of patients with a low BMI (<18.5); however, men with a low BMI tended to have a shorter OS than women with a BMI < 18.5. Male gender was a relevant bad prognostic factor for OS and PFS in the subgroup of patients with BMI scores between 18.5 and 25. Finally, gender was not a relevant prognostic factor in patients with a BMI > 25.
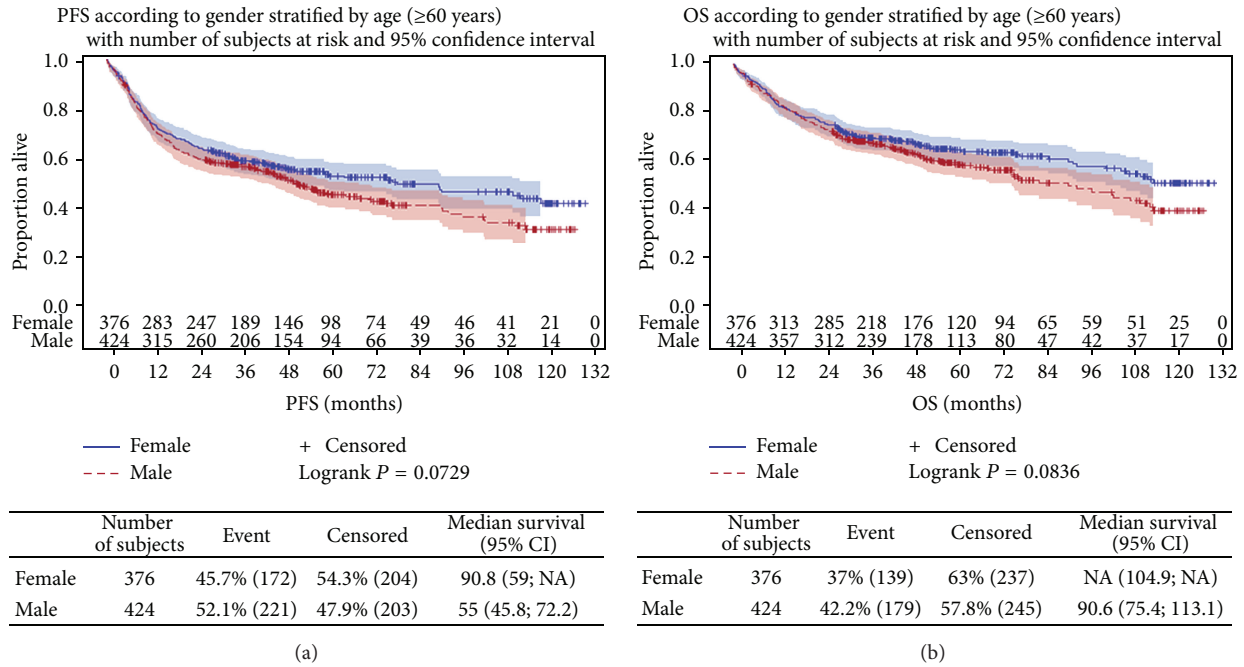
FIGURE 6

were comparable; the median PFS was 68 months for men and indeterminate for women ($P = 0.968$, HR = 1.024, 95% CI (0.32–3.27)). The survival analysis according to BMI and gender demonstrated that although the difference was not significant, male patients with a BMI < 18.5 had a shorter OS; the median OS of men with a BMI < 18.5 was 69 months compared with 97 months for men with a normal BMI, 111 months for men with a BMI > 25, 106 months for women with a BMI > 25, and not reached for women with a normal BMI or a BMI < 18.5 (data not shown).

Finally, if females always exhibited a longer PFS and OS than males, the difference in PFS and OS observed between males and females was most significant in the elderly population. However, this difference was not statistically significant. Indeed, male over 60 years had a median PFS and OS of 55 months and 90.6 months, respectively, whereas women had a median PFS of 90.6 months and median OS was not reached (Figures 6(a) and 6(b)).

3.3. Multivariate Analysis. In a Cox regression analysis including gender, BMI, age, aaIPI score, and interaction between gender and BMI as variables, a high aaIPI score was the strongest factor independently associated with shorter OS and shorter PFS ($P < 0.0001$, HR = 2.287 and $P < 0.0001$, HR = 1.926 for OS and PFS, resp.). A low BMI (<18.5) was also associated with a shorter OS ($P = 0.048$, HR = 1.394, 95% CI (1.00–1.94)) but not with a shorter PFS ($P = 0.31$). Neither age nor gender had any significant impact on OS or PFS in this multivariate analysis. The interaction between BMI and gender was also not statistically significant (Table 3).

4. Discussion

To our knowledge, this is the largest study evaluating the impact of gender and BMI independently of aaIPI score and age in patients with DLBCL who were prospectively treated with R-CHOP in phase III trials. In a univariate analysis, the aaIPI score was the only predictive factor for both OS and PFS. Gender was a relevant prognostic factor for PFS and exhibited a strong trend for OS. Interestingly, the impact of gender on PFS and OS varied with BMI. Indeed, the differences in OS and PFS were completely nonexistent in overweight women. Underweight women tended to have a longer OS than men with a BMI < 18.5 but exhibited a similar PFS.

In multivariate analysis, gender was not anymore a relevant prognostic factor for PFS and OS (even the difference was almost significant for OS, $P = 0.07$), and aaIPI remained the strongest prognostic factor for both OS and PFS. Nevertheless, a low BMI was a relevant prognostic factor for OS independent of the aaIPI score but had no significant impact on PFS. These results emphasise the potential role of confounding factors in explaining the impact of low BMI or gender on survival. Those patients with a low BMI may die from causes not related to the lymphoma and/or from the complications of the treatment. Interestingly, male patients with a lower BMI exhibited lower albumin levels and higher creatinine levels at diagnosis, which may be the source of treatment-related toxicities. Furthermore, the population of males with a BMI < 18.5 exhibited the worst median OS (68.6 months), even if the difference was not statistically significant, most likely due to the low number of patients. These patients also more frequently exhibited low albumin levels or high creatinine levels compared with the

other patients (data not shown), promoting a higher rate of complications and treatment-related toxicities.

Our results partially corroborate those from the RICOVER-60 of the DSHNHL [3]. In this study, the advantage in PFS provided by the rituximab was smaller in men than in women [22]. The authors also reported that men but not women might benefit from extended rituximab exposure [23]. Relying on this data, the German group is currently recruiting patients in a clinical trial (DSHNHL 2004-1) in which men receive a higher dosage of rituximab than do women. As in the present analysis, the CORAL study reported an effect of BMI on the impact of gender. Indeed, in their study, young women or slim women seemed to benefit more from rituximab maintenance salvage after ASCT than did men or overweighted postmenopausal women. The authors explain this difference with the hormone-related rituximab pharmacokinetic variation [24]. Other retrospective studies reported the impact of gender on the outcomes of patients treated with rituximab and chemotherapy for DLBCL or follicular lymphoma [15, 25].

One explanation for this observed difference in outcomes between males and females may be the clearance of rituximab, which is more rapid in heavy or male patients [16, 26]. This variation has been described with other monoclonal antibodies [27–32]. One explanation for the changes in pharmacokinetics with hormonal variation and the slower elimination of monoclonal antibodies observed in women could be an inhibition of antibody production and/or uptake for degradation by oestrogen alpha receptor stimulation [33–36]. However, rituximab pharmacokinetics may not be the only key point, as this difference in outcome according to gender existed before the rituximab era and as anthracycline has also been reported to exhibit a different elimination schema according to gender [37].

Although male gender is commonly known as an independent poor prognostic factor in haematological malignancies [38–40] and also in solid tumors [41–43], it does not yet influence therapeutic choices. The absence of a clear relationship between worse outcomes and gender and the presence of many confounding factors may be the reason for this.

In the literature, the relationship between BMI and cancer incidence has been frequently studied. A recent review suggested a relationship between the secretion of cytokines in obese adipose tissue and the development of a microenvironment favorable to cancer proliferation and aggressiveness [44]. A prospective US study reported that the incidence of DLBCL was higher in obese patients [14, 45]. However, the impact of BMI on outcomes in NHL is not clear, as demonstrated by the controversial results in the literature. Indeed, a recent retrospective analysis in 2534 male United States veterans demonstrated that being overweight or obese was associated with a prolonged OS, even in the rituximab era [46]. This result corroborates a former retrospective study of NHL patients [18]. On the contrary, the RICOVER [3, 16] study reported that, in patients with a lower body weight, the addition of rituximab to CHOP resulted in a significant improvement in PFS but not in patients with a higher body weight. Furthermore, in a large prospective study including more than 900 000 [17] patients free from cancer and in a meta-analysis of different prospective studies [12], a higher BMI was associated with a higher risk of death from NHL, including DLBCL.

In conclusion, male gender and low BMI may impact outcomes in DLBCL. The main message of this analysis is that based on large prospective data, gender or BMI may influence the outcomes of DLBCL patients treated with R-CHOP in the context of other confounding factors. The strongest prognostic factor impacting OS and PFS remains the aaIPI score. Therefore, relying on these data, it is too early to consider a gender- or BMI-specific therapeutic approach in DLBCL.

Conflict of Interests

The authors report no potential conflict of interests.

Authors' Contribution

Bertrand Coiffier, Clémentine Sarkozy, and Nicolas Mounier designed the study. Bertrand Coiffier, Clémentine Sarkozy, Nicolas Mounier, Alain Delmer, Achiel Van Hoof, Jean Michel Karsenti, Emmanuel Fleck, Marie Maerevoet, Jean Claude Eisenmann, and Michel Fabbro included patients in the study. Bertrand Coiffier, and Clémentine Sarkozy controlled the database. Bertrand Coiffier and Clémentine Sarkozy wrote the paper. All of the authors reviewed and approved the paper.

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