



## Research paper

# Outcome of autologous hematopoietic stem cell transplant in older patients with B cell lymphoma when selected for fitness and chemosensitive disease

Christopher Lemieux, Imran Ahmad, Nadia M. Bambace, Léa Bernard, Sandra Cohen, Jean-Sébastien Delisle, Isabelle Fleury, Thomas Kiss, Luigina Mollica, Denis-Claude Roy, Guy Sauvageau, Jean Roy, Silvy Lachance\*

Hôpital Maisonneuve-Rosemont, Division of Hematology, Oncology and Hematopoietic Stem Cell Transplantation, Hematopoietic Stem Cell Transplant Program, Université de Montréal, Montréal, Québec, Canada

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## ABSTRACT

**Background:** Autologous hematopoietic stem cell transplantation (AHSCT) in the older population is associated with an increased risk of morbidity and mortality. Determination of the hematopoietic cell transplant comorbidity index (HCT-CI) has contributed to improve patient selection while allowing prediction of their non-relapse mortality (NRM). The goal of this study was to identify factors influencing both safety and efficacy of AHSCT in an older non-Hodgkin lymphoma (NHL) population to better select those who will benefit from this intervention in the Canadian context of a single-payer government healthcare program.

**Methods:** This single center, retrospective study, examined clinical outcomes in 90 consecutive older patients ( $\geq 60$  years old) with B-cell NHL treated with AHSCT between 2008 and 2014.

**Findings:** Median age was 63 (60–69) at time of transplantation. The HCT-CI risk score was low, intermediate and high in 34%, 40% and 26% of patients, respectively. NRM was 1% at 100 days and one-year post transplant and not influenced by age. At a median follow-up of 52 months, median progression-free survival (PFS) was 56 months while median overall survival (OS) was still not reached. Stable and progressive disease status at time of transplantation were associated with a lower PFS (HR 2.94) and OS (HR 3.91). BEAC conditioning and a graft cell dose  $5 \times 10^6$  CD34+ /kg led to faster recovery, decreased toxicity and resource consumption.

**Interpretation:** In the older population, AHSCT is safe and optimal when restricted to fit chemosensitive patients.

## 1. Introduction

High dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplantation (AHSCT) is considered standard of care in first-line treatment for mantle cell and T-cell NHL, as well as in primary refractory or relapsed chemosensitive lymphomas [1–3]. The benefit of AHSCT for chemosensitive relapsed NHL was initially demonstrated by the PARMA study [4] showing a 40% 2-year event-free survival (EFS) and was subsequently confirmed by Philip et al. who showed a 5-year EFS of 46% with AHSCT compared to 12% ( $p = 0.001$ ) [2] with chemotherapy alone. These studies positioned AHSCT as the standard of care for relapsed chemosensitive NHL patients. Both studies were conducted prior to the introduction of rituximab as standard therapy in B cell NHL and included only patients below the age of 60. More recently, the CORAL study showed comparable EFS for both R-ICE

and R-DHAP as salvage therapy followed by HDT and AHSCT for relapsed large B-cell lymphoma. Predictors of poor 3-year EFS were prior treatment with rituximab (21% compared to 47%,  $p < 0.001$ ) and relapse within 12 months after first-line treatment (20% compared to 45%,  $p < 0.001$ ) [5,6].

Over the last decade, a significant increase in the median age of AHSCT recipients has been observed [7]. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) revealed that the percentage of AHSCT in patients  $> 60$  years has increased from 10% between 2000–2006 to 22% between 2007–2015. Furthermore, from 2000 to 2014, the number of AHSCTs performed annually in the United States has also increased from about 7000 to 11,000 [8], explained in good part by inclusion of older patients. AHSCT over the age of 60 is currently considered safe and beneficial in selected patients [9]. Hermet et al. showed that age was not a limiting factor if clinical

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\* Corresponding author at: Hôpital Maisonneuve-Rosemont, Division of Hematology, Oncology and Hematopoietic Stem Cell Transplantation, 5415 boul. de l'Assomption, Montréal, Québec, H1T 2M4, Canada.

E-mail address: [silvy.lachance@umontreal.ca](mailto:silvy.lachance@umontreal.ca) (S. Lachance).

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condition was adequate [10]. Other retrospective studies have demonstrated the feasibility of AHSCT in older patients with divergent results [11–14].

The HCT-CI developed by Sorror et al. [15] for the evaluation of transplantation-related mortality in patients undergoing allogeneic transplantation has become an important tool to predict NRM and guide patient selection [16]. Subsequent studies have also validated HCT-CI in AHSCT cohorts [17].

The goal of this study was to identify clinical and disease-related factors that could predict toxicity and efficacy of AHSCT in an older NHL population ( $\geq 60$  years old), in order to better select those who will likely benefit from high-dose therapy and thus optimize resource utilization.

## 2. Methods

### 2.1. Study design

We report a single center, retrospective study examining outcomes of AHSCT in older rituximab exposed B-cell NHL patients ( $\geq 60$  years old) performed at hôpital Maisonneuve-Rosemont Hospital (HMR), affiliated to the Université de Montréal between January 1st, 2008 and January 1st, 2015. During this period, a total of 1080 HSCTs were performed at our center, including 565 autologous transplants. Among these, 90 (16%) older NHL patients met predefined inclusion criteria and are reported herein. Inclusion criteria were: age  $\geq 60$ , diagnosis of B cell NHL, eligibility for AHSCT according to our local HSCT program, chemosensitive disease, an estimated HCT-CI score  $\leq 3$  at time of transplant referral, if age 65 and older, based on patient's medical history. Most patients were treated with a BCNU containing preparative regimen. Indications for AHSCT, eligibility criteria, treatment and supportive care at time of transplant were identical for all patients according to standard operating procedures of our Foundation for the Accreditation of Cellular Therapy (FACT) accredited transplant program. All patients signed an informed consent. Our institution's ethics and research committee approved the study.

Older patients were classified into two age sub-groups: 60 to 64 and  $\geq 65$ . Treatment response at time of transplantation was evaluated based on the 2007 Revised Response Criteria for Malignant Lymphoma [18]. Time to neutrophil engraftment was defined as the first of three consecutive days on which neutrophils were  $\geq 0.5 \times 10^9/L$ . Time to platelet engraftment was defined as the first of three consecutive days with a platelet count  $\geq 20 \times 10^9/L$  and a minimum of 7 days after last platelet transfusion. We defined non-relapse mortality (NRM) as death from any other cause than relapse or progression of NHL. OS was calculated from the date of AHSCT to either the date of death from any cause or last follow-up. PFS was the duration from the date of AHSCT to progressive disease or death, regardless of the cause of death. HCT-CI was divided in three risk groups: low (score 0), intermediate (score 1–2) and high (score  $\geq 3$ ).

### 2.2. Statistical analysis

Descriptive statistics were used to characterize patient cohorts, describe engraftment, resource utilization (length of hospital stay, narcotic use, number of transfusions, intravenous (IV) antibiotic use and toxicity, which were all adjusted for age at time of transplantation, HCT-CI score, conditioning regimen and CD34<sup>+</sup> cell dose.

PFS and OS were calculated with the Kaplan-Meier method. The log-rank test was used to evaluate the differences between groups. PFS and OS were adjusted for the following factors: age, HCT-CI score, Karnofsky index, histology, stages of disease, number of prior treatment lines and disease status at time of AHSCT, conditioning regimen, number of CD34<sup>+</sup> cells/kg infused, engraftment time and lymphocytes count at 14 days post-transplantation. Cox proportional hazard method was used for this purpose.

**Table 1**  
Patients Characteristics.

	All cohort 90	60-64 years old 60	$\geq 65$ years old 30	p value
Number of patients				
Gender, n (%)				0.232
Male	52 (58)	32 (53)	20 (67)	
Female	38 (42)	28 (47)	10 (33)	
International prognostic index, n (%) (n = 58)				0.148
Low risk	18 (31)	14 (35)	4 (21)	
Intermediate risk	11 (19)	8 (21)	3 (16)	
High risk	29 (50)	17 (44)	12 (63)	
Histology at diagnostic, n (%)				0.290
Diffuse large B cell	34 (38)	24 (40)	10 (33)	
Follicular	32 (36)	19 (32)	13 (44)	
Mantle cell	18 (20)	12 (20)	6 (20)	
Other	6 (6)	5 (8)	1 (3)	
Ann-Arbor stage, n (%)				0.490
I	6 (7)	3 (5)	3 (10)	
II	9 (10)	7 (11)	2 (6)	
III	27 (30)	16 (27)	11 (37)	
IV	48 (53)	34 (57)	14 (47)	
Median age at transplantation, years old (range)	63 (60- 69)	62 (60- 64)	66 (65- 69)	<0.001
HCT-CI, n (%)				0.338
0	31 (34)	18 (30)	13 (44)	
1-2	34 (40)	26 (43)	10 (33)	
$\geq 3$	23 (26)	16 (27)	7 (23)	
Median Karnofsky index, % (range)	90 (70- 100)	90 (70- 100)	90 (80- 100)	0.480
Number of treatment line before AHSCT, n (%)				0.618
1-2	66 (73)	43 (72)	23 (77)	
$\geq 3$	23 (27)	17 (28)	7 (23)	
Disease status at transplantation, n (%)				0.304
Complete remission (CR)	49 (55)	33 (55)	16 (53)	
Partial remission (PR)	35 (39)	25 (41)	10 (33)	
Stable disease (SD)	3 (3)	1 (2)	2 (7)	
Progressive disease (PD)	3 (3)	1 (2)	2 (7)	
Conditioning regimen, n (%)				0.097
BEAM	40 (44)	30 (44)	10 (33)	
BEAC	45 (50)	26 (50)	19 (64)	
Busulfan-cyclophosphamide- etoposide	5 (6)	4 (6)	1 (3)	
Median CD34 <sup>+</sup> cell dose infused, x10 <sup>6</sup> /kg (range)	4.87 (1.84- 19.89)	5.05 (1.84- 19.89)	4.60 (2.50- 12.70)	0.752
Median lymphocyte count at 14-day post-transplantation, x10 <sup>9</sup> /L (range)	0.6 (0- 1.8)	0.4 (0- 1.8)	0.3(0.1- 1.3)	0.253

Cumulative incidences were estimated for NRM and relapse incidences, using each as mutually competing risk. Statistical significance was considered at  $p < 0.05$ . Analyses were run using the SPSS 25 (SPSS Inc., Chicago, IL) and R software (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

Between January 1st, 2008, and January 1st, 2015, 90 patients met inclusion criteria and are reported herein. Patients characteristics are summarized in Table 1. Patients were predominantly male (58%) and median age at transplantation was 63 years (range 60–69). A third of the cohort was  $\geq 65$  years old. NHL histology included: diffuse large B cell in 38%, follicular B cell in 36% and mantle cell lymphoma in 20%. Most patients were in advanced stages at diagnosis: 29% stage III and 53% stage IV. The HCT-CI risk score was low, intermediate and high in 34%, 40% and 26% of patients, respectively, at time of transplantation. Median Karnofsky index was 90% (70–100). Sixty-six patients (73%) received two treatment lines or less before AHSCT. Fifty-four (54) percent and 39% achieved a complete or partial remission prior to

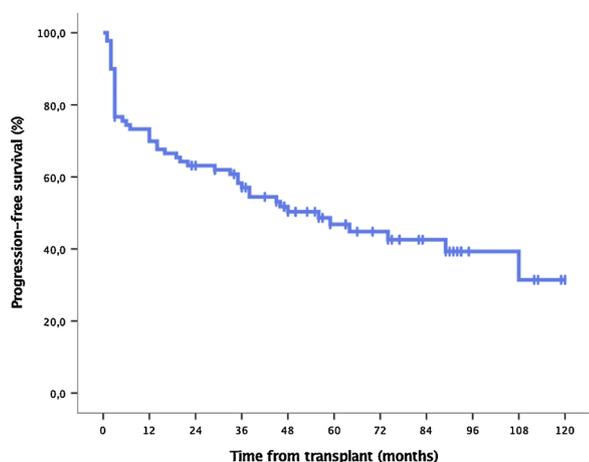


Fig. 1. Progression-free survival of older patients following AHST.

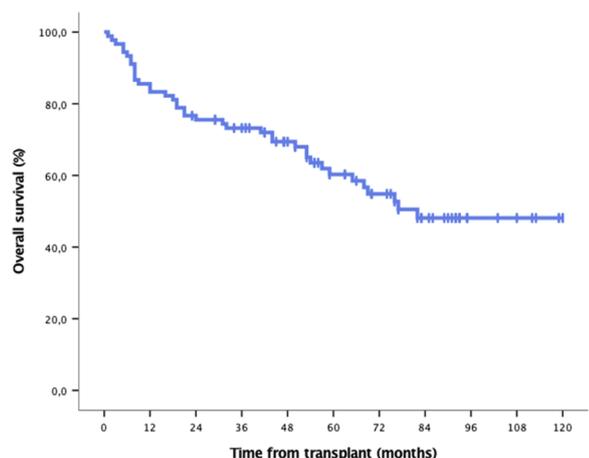


Fig. 2. Overall survival of older patients following AHST.

transplant, respectively.

BEAM (BCNU, Etoposide, Aracytine, Melphalan) and BEAC (BCNU, Etoposide, Aracytine and Cyclophosphamide) [8,19–24] conditioning regimens were used in 44% and 50% of patients, respectively. The median infused CD34<sup>+</sup> cell dose was 4.87 × 10<sup>6</sup>/kg (1.84–19.89). 92% of patients developed febrile neutropenia; only 1% had a septic shock and only 2% required admission to the intensive care unit (ICU). Grade 3–4 mucositis was seen in 16% of patients with a median duration of narcotic use of 2 days (0–34). A need for parenteral nutrition was present in 42% of our patients.

Median time to neutrophil and platelet engraftment were 10 (8–14) and 16 (11–43) days, respectively. Median lymphocyte count at day +14 was 0.6 × 10<sup>9</sup>/L (0–1.8). All patients required transfusion support. The median number of packed red blood cell units and platelet concentrates required per patient were 2 (0–8) and 3 (0–12),

respectively. Median duration of IV antibiotics was 8 (0–41) days, while median duration of hospitalization was 26 (19–65) days.

HCT-CI score was used upfront at time of referral to disqualify patients from transplantation. Despite this, 26% of patients had an HCT-CI score ≥ 3 at the time of transplant. These patients required more days of IV antibiotics compared to those with an HCT-CI < 3 (p = 0.028). Administration of the BEAM conditioning regimen was associated with a trend to a 4-day longer hospital stay (p = 0.12) despite a 1-day faster neutrophil engraftment (p = 0.04). An infused CD34<sup>+</sup> cell dose < 5.0 × 10<sup>6</sup>/kg was associated with delayed engraftment for both neutrophils (mean 11 vs 10 days; p = 0.01) and platelets (mean 19 vs 15 days; p = 0.001) and associated with a higher mean number of platelet transfusions (4 vs 3; p = 0.007). However, age alone had no influence on engraftment. The 60–64 years old cohort was more likely to receive BEAM conditioning and had an increased use of narcotics (6.32 days vs 2.43 days; p = 0.01) and of total parenteral nutrition (50% vs 28%; p = 0.046).

With a median follow-up of 52 months (1–120), the median PFS was 56 months (1–120) with no difference between the two age groups (p = 0.712). Median OS was not reached at time of study evaluation. The estimated 5-year PFS and OS was 47% and 60%, respectively (Figs. 1 and 2). No difference was observed between the two age groups. Cumulative incidence of NRM was remarkably low at 1% at 100 days. The only event was a cardiac arrest after hospital discharge. NRM remained low at 1% at 1 year and 5 years after transplantation. Age at time of transplantation, HCT-CI score, Karnofsky index, lymphoma histology, Ann-Arbor stage at diagnosis, number of lines before AHST, conditioning regimen, infused CD34<sup>+</sup> cell dose and lymphocyte count at day 14 post-transplantation showed no statistical association with PFS and OS in univariate analysis. However, having received > 2 lines of treatment prior to AHST was associated with a worse PFS (HR 2.0, 95%CI: 1.1–3.5) with a median PFS of 16 vs 74 months (p = 0.02). Nevertheless, this was not significant on multivariate analysis. Disease

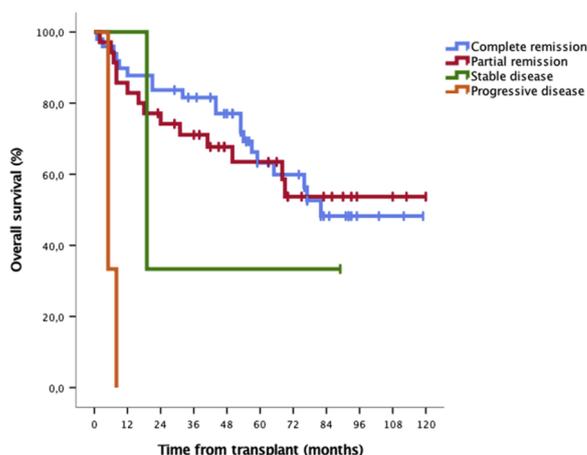


Fig. 3. Overall survival by disease status at transplantation comparing complete remission, partial remission, stable disease and progressive disease.

Table 2

Impact of disease status at time of transplantation on median Progression-free survival and Overall survival (univariate).

Disease status at transplantation, (%)	PFS (months)	Hazard ratio	Confidence interval	p value
Complete remission, (54)	66	1	–	–
Partial remission, (39)	61	1.18	0.65-2.16	0.58
Stable and progressive disease, (7)	17	3.16	1.19-8.38	0.02
Disease status at transplantation, (%)	OS (months)	Hazard ratio	Confidence interval	p value
Complete remission, (54)	80	1	–	–
Partial remission, (39)	78	1.10	0.56-2.19	0.77
Stable and progressive disease, (7)	24	4.07	1.51-10.98	0.01

status at transplantation did impact both PFS and OS (Table 2 and Fig. 3). Stable and progressive disease statuses were both associated with a worse outcome in terms of PFS (HR 2.94, 95%CI: 1.15–7.53) and OS (HR 3.91, 95%CI: 1.51–10.11). Disease status at time of AHST remained significant on multivariate analysis for both PFS (HR 5.00, 95%CI: 1.35–18.50) and OS (HR 6.52, 95%CI: 1.66–25.68).

#### 4. Discussion

This single center retrospective study demonstrates that AHST can be performed safely in selected older patients. In younger patients cohorts (<60 years old), studies have shown PFS and OS at 5 years of 43–51% and 53–77%, respectively, depending on histologic subtype [1–3]. Selection of transplant candidates must take into consideration comorbidities. Sorror's HCT-CI has become instrumental in excluding patients with multiple comorbidities from transplantation given an unacceptable high risk of NRM [15]. In contrast, the HCT-CI has only been used in a few studies in older patients; a statistical correlation between a high HCT-CI score and OS was demonstrated in only one small study with few patients [14]. Nevertheless, most of these studies were unable to correlate HCT-CI with OS, PFS or NRM [10,25–27] once patients were deemed eligible for transplant.

Our study of 90 older B cell NHL transplant recipients demonstrates clearly that toxicity is not increased in carefully selected older patients. Febrile neutropenia was almost universal but severe complications including septic shock and admission to the ICU were reassuringly rare events. Recipients between 60 and 64 years old required more narcotics and total parenteral nutrition. This might be related to the fact that a higher proportion of this subgroup received BEAM conditioning regimen. BEAM is well-known for its higher gastrointestinal toxicity compared to BEAC [28,29]. Jantunen et al. compared BEAM and BEAC in a retrospective study and indeed found no difference in PFS or OS but increased gastrointestinal adverse events with BEAM [28]. An interesting observation was that BEAM was associated with a longer hospital stay. Unfortunately, prospective randomized comparative studies do not exist for conditioning regimens in autologous transplantation. A recent study by Chen et al. compared the safety and efficacy of different conditioning regimens at time of AHST for lymphoma treatment and found that results varied according to histologic subtype [30]. Giving our results, we suggest that BEAC regimen should preferably be considered for conditioning in older patients because of its lower toxicity profile.

Age did not impact engraftment. Our results of 10 days for neutrophils and 16 days for platelets are very similar to that reported in the literature for younger patients [28,29]. In contrast to age, a CD34<sup>+</sup> cell dose < 5.0 × 10<sup>6</sup>/kg predicted a delayed engraftment of both neutrophils and platelets, as well as increased resource utilisation, but we could not show any association between engraftment and PFS or OS, as many larger studies have reported [31–35]. Similarly, rapid lymphocyte recovery has been reported as a prognostic factor influencing survival [36–40]. Our day 14 lymphocyte count recovery did not correlate with PFS or survival in our rituximab treated cohort, probably due to our small number of patients or, possibly, to pre-transplant rituximab related B cell depletion. Finally, our median hospital stay of 26 days was comparable to published reports of 20–23 days in younger patients (<60 years) [28,29,33,40].

With a median follow-up of 52 months, the estimated 5-year PFS and OS are 47% and 60%, compare favourably to a younger rituximab exposed cohort [1–3]. Staging, HCT-CI score, age at transplantation, Karnofsky index and histology did not impact on either PFS or OS. Interestingly, our study only identified two factors that influenced outcomes in this group of older patients. First, disease status at time of transplantation impacted PFS and OS. Our study shows dramatically worse PFS and OS when transplant is performed in presence of chemo resistant disease and further underlines the importance of chemosensitivity prior to transplantation. Our results confirm that older patients with stable or chemoresistant disease do not fare any better than their younger

counterparts. Most candidates with refractory disease to salvage therapy are excluded from transplantation studies regardless of age [41]. Limited data are therefore available on the outcome of this subgroup, especially in older patients. Hosing et al. have published results of their study, which included patients as old as 81 years. They found that having stable disease or progressive disease at the time of transplantation was associated with a significantly worse OS ( $p < 0.05$ ) [26]. Other studies, which included fewer patients with stable or refractory disease, were unable to report any impact of disease status [10,14,25,42,43]. Second, having received more than two lines of treatment before being considered for transplantation was associated with a higher rate of progression after transplantation (median of 16 vs 74 months;  $p = 0.02$ ). The latter reflects that patients with chemoresistant and more advanced disease are those who have received multiple lines of therapy.

NRM was very low at 1% both at 100 days and one year after transplant. Consequently, we were unable to identify risk factors for NRM in our cohort. These results are reassuring considering that high NRM is often feared when considering AHST in older patients. Our strategy to consider only fit older patients for transplantation based on their comorbidity index contributes to the low NRM observed. Those with significant comorbidities and deemed unfit were excluded upfront from the procedure. Using this strategy, our results compare favourably with those reported in the literature for older patients where NRM can be as high as 12% [9,12–14,26,27,42–45].

Relapse following transplantation remains the major hurdle and needs to be addressed in all patients regardless of age. Stiff et al. recently reviewed the role of AHST for lymphoma. Molecular classifications, novel therapies as well as the use of minimal residual disease (MRD) assessments are all discussed as potential tools to impact outcome [46]. Monitoring of MRD and maintenance therapy according to histology and risk factors will soon be part of an algorithm for personalized therapy of each transplant candidate. To better define the optimal treatment option in the older patient population, prospective studies including this population need to be conducted as this group has traditionally been excluded.

Our study has several limitations. First, we report on a single center retrospective study with a limited number of patients (90). However, when compared to other studies of AHST in older patients, our study is among the ones that included the most patients. Second, we selected fit older patients for transplantation to avoid NRM and to optimize resources utilisation in the Canadian context. Since there is a fear of increased risk of complications in this subgroup, transplant candidates older than 60 years are selected carefully and those with multiple comorbidities or unfit are excluded. Thus, our excellent results reflect this selection. Nonetheless, our study clearly demonstrates that high-dose chemotherapy followed by hematopoietic stem cell transplantation can be safely administered to a fit older population with a NRM similar to that of younger patients.

In summary, AHST is safe and effective in fit older patients with chemosensitive B-cell lymphoma. A BEAC conditioning regimen and a graft CD34<sup>+</sup> cell content  $\geq 5.0 \times 10^6$ /kg seem optimal in older patients. Patients with stable or progressive disease at the time of transplantation should be excluded from transplant and offered innovative clinical research therapies, in order to improve their PFS and OS.

#### Authorship

SL designs the study. CL and SL contributed to the execution and analysis of the study and wrote the manuscript. IA reviewed the statistical analysis. IA, NB, LB, SC, JSD, IF, TK, LM, GS, DCR and JR, contributed to the accrual of the trial, to patients care and provided reviews and suggestions for the manuscript.

#### Declaration of interests

None of the authors have any financial and personal relationships to disclose that could inappropriately influence this work.

## Ethic committee approval

All patients signed an informed consent. Our institution's ethics and research committee approved the study.

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