

A retrospective comparative cohort study on the routine pre-engraftment use of granulocyte colony-stimulating factor in allogeneic hematopoietic stem cell transplantation

Muruvvet Seda Aydin^{1*}, Esra Cengiz¹, Ahmet Kursad Gunes¹, Mehmet Ali Ucar², Funda Ceran¹, Gulsum Ozet¹, Simten Dagdas¹

¹ Department of Hematology, Ankara City Hospital, Ankara, TR

² Department of Hematology, Faculty of Medicine, Cukurova University, Adana, TR

* Corresponding Author: Muruvvet Seda Aydin E-mail: drmseda84@gmail.com

ABSTRACT

Objective: Myeloid growth factors have been often used in allogeneic hematopoietic stem cell transplantation settings. There are some controversies about increased graft versus host disease, relapse, and delayed platelet engraftment with those growth factors in the pre-engraftment period. In this study, we aimed to compare the transplantation outcomes of allogeneic hematopoietic stem cell transplantation recipients according to their myeloid growth factor support status.

Materials and Methods: Sixty-seven adult acute myeloid leukemia/myelodysplastic syndrome and acute lymphoblastic leukemia patients who underwent allogeneic peripheral blood stem cell transplantation from HLA-identical matched sibling donors were analyzed retrospectively. All-cause mortality at day 100, day 180, and at 1-year were the primary outcome measures. Secondary outcome measures were the engraftment kinetics, length of hospital stay, and graft-versus-host disease incidences.

Results: Growth factor supported group was younger ($p=0.001$), and the first complete remission status at transplantation was seen more compared to the unsupported group ($p=0.04$). Myeloablative conditioning was used more in growth factor supported group ($p=0.004$). Faster neutrophil engraftment ($p=0.008$) and delayed platelet engraftment ($p=0.022$) were seen in growth factor supported group. Graft-versus-host disease, relapse incidences, and all-cause mortality at day 100, day 180, and at 1-year were not different between groups. Steroid-resistant graft-versus-host disease was the only factor related with relapse (OR: 0.196, $p=0.043$).

Conclusion: This real-life study shows colony-stimulating factors are safe in HLA-identical sibling allogeneic hematopoietic stem cell transplantation. Further prospective randomized controlled studies for different stem cell sources, different donors, and different conditioning and graft-versus-host disease prophylaxis regimens are mandatory.

Keywords: Acute Myeloid Leukemia, Colony-stimulating factor, Filgrastim, Hematopoietic stem cell transplantation, Lymphoblastic Leukemia

INTRODUCTION

Myeloid growth factors have been often used in the allogeneic hematopoietic stem cell transplantation setting with the aim of fastening neutrophil engraftment. Hematologists have some concerns about increased acute graft-versus-host disease (GVHD), relapse, and delayed platelet engraftment with those growth factors in the pre-engraftment period. Conflicting results of the previous studies and the paucity of the data in recent years encouraged us to study this issue (1, 2). Herein, we present transplantation outcomes of hematopoietic stem cell transplantation recipients by their pre-engraftment granulocyte colony-stimulating factor (G-CSF) support status.

Research Article

Received 04-08-2021

Accepted 14-08-2021

Available Online: 16-08-2021

Published 30-08-2021

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MATERIALS and METHODS

Patient Characteristics: Adult acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) and acute lymphoblastic leukemia (ALL) patients followed at a single tertiary transplantation center who underwent allogeneic peripheral blood stem cell transplantation from HLA-identical matched sibling donors between 31.01.2007-04.06.2020 were reviewed retrospectively for analysis. Patients whom data were accessible as printed or electronic records are included in the study. Patients who underwent a second transplant were excluded from the study.

Predictive models: Sorror risk index was used for hematopoietic stem cell transplantation comorbidity scoring (HCT-CI). This score analyzes 17 comorbidities as well as their degree, and is predictive for non-relapse mortality after stem cell transplantation (3). Patients were stratified as low-intermediate risk (0-2 points) or high risk (3 or more points). European Society for Blood and Marrow Transplantation (EBMT) score was employed to determine the disease risk status. This score is a validated score that predict approximately the 5-year probability of overall survival and the transplantation related mortality (4).

Conditioning regimens, graft versus host disease prophylaxis and management: Conditioning regimens were recorded as either myeloablative or non-myeloablative/reduced intensity conditioning. Cyclosporin A plus methotrexate on days +1,+3, +6, +11 (may be omitted according to toxicity) were used for GVHD prophylaxis. Anti-thymocyte globulin was not used in any of the recipients. Diagnosis and grading of acute GVHD were based on the original Glucksberg score (5). Chronic GVHD was defined according to 2014 National Institute of Health criteria (6). GVHD was treated according to institutional protocols.

Engraftment: Neutrophil engraftment was defined as the first of the three consecutive days with absolute neutrophil count of $\geq 0.5 \times 10^9/l$. Platelet engraftment was defined as the first of the three consecutive days with platelet count $>20 \times 10^9/l$ with free of transfusion requirements. Febrile neutropenia was defined as the fever $\geq 38^\circ C$ during neutropenia. G-CSF support protocol was as $5 \mu g/kg/day$ filgrastim beginning from day +5 until absolute neutrophil count $\geq 1.5 \times 10^9/l$.

Relapse: Morphological relapses were analyzed. Morphological relapse was defined as the $\geq 5\%$ blasts in the bone marrow or peripheral blood (7).

Statistics: Statistical analyses were performed using the Statistical Packages for the Social Sciences software version 20. Quantitative data was defined as median (minimum and maximum value). "Student's t test" was used for normally distributed quantitative data and "Mann Whitney U" was used if the quantitative data was not normally distributed. Univariate analyses were performed via "Chi-square test" for qualitative data (or "Fisher exact test" when Chi-square assumptions do not hold due to low expected cell counts). Multivariate analyses were done by "Cox regression" analysis. A p-value of less than 0.05 was considered to show a statistical significant result.

Ethics: This study was approved by the ethics committee of our institution before the study began (E1-20-914 approval number) and the protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration. Informed consent was not required as the study reports observational, retrospective data obtained from hospital records.

RESULTS

Sixty-seven patients were included in the study with median age 36 (ranging 19-67). Median follow-up time was 19 months (ranging 0.9-165 months) in the whole study group. Males (n=41), were more than the females (n=26). Cytomegalovirus statuses were all seropositive for the donors and the recipients. In the whole study group, eighty percent of the patients were AML/MDS and the remaining were ALL. Conditioning intensity was mostly myeloablative (59 of 67 patients). G-CSF was administrated to twenty-nine patients.

Patients of the growth factor supported group were younger (32 vs. 42) than the unsupported (p=0.001). Two groups were similar for sex and disease distribution, for HCT-CI grading and the median EBMT scores. First complete remission (CR1) status at transplantation was seen more in the growth factor supported group (p=0.040). Myeloablative conditioning was used more in the growth factor supported group (p=0.008). Growth factor support was mostly applied in transplantation procedures earlier than 2014 (p=0.000) and median follow-up period was longer in the growth factor supported group (51 vs. 15 months) (p=0.024). Those demographic and transplantation related clinical factors of patient groups were given in Table 1.

In the growth factor supported group, time to platelet engraftment was longer (14 vs. 12 days) (p=0.022), but time to neutrophil engraftment was shorter (14 vs. 16.5 days) (p=0.004). Febrile neutropenia incidence, days with fever, and length of hospital stay from transplantation day 0 were not different between the two groups. Those engraftment kinetics related outcomes of the patient groups were given in Table 2. In the whole study group, median time to neutrophil engraftment was faster in myeloablative conditioning versus non-myeloablative/reduced intensity conditioning (15 vs. 17 days) (p=0.027) but conditioning intensity was not related with median time to platelet engraftment (p=0.640).

Acute or chronic or both GVHD incidences were similar between the two groups. Also, growth factor support was not associated with steroid resistant GVHD. Grade I-II and grade III-IV GVHD incidences were also similar between the two groups. There was a less relapse risk tendency in the growth factor supported group without statistical significance (17.2% vs. 36.8%) (p=0.084). Mortality incidences at day 100 and day 180 in the growth factor supported group were not different from the unsupported group (Table 3).

For determining the impact of growth factor support over 1 year mortality, cases whose transplantation was in the first year of the analysis were excluded. Sixty-one cases were evaluated and there was no statistically significant 1-year mortality difference (Table 4). Kaplan-Meier analysis was performed; there was a not statistically significant overall survival difference between the growth factor supported and the unsupported group (p=0.190) which was represented in Figure 1.

Table 1: Demographic and transplantation related clinical factors of patient groups

	No GF support (n=38)	GF support (n=29)	p
Age Mean±SD (Median)	42.05±13.06 (41)	32.21±9.44 (32)	0.001
Sex (Female/Male)	14/24	12/17	0.706
Disease MDS-AML/ALL	81.6% vs. 18.4%	79.3% vs. 20.7%	0.816
Conditioning regimen intensity MAC vs. RIC/NMA	78.9% vs. 21.1%	100% vs. 0%	0.008
Disease status at transplantation CR1 vs. >CR1	73.7% vs. 26.3%	93.1% vs. 6.9%	0.040
HCT-CI Low/Intermediate vs. High	94.6% vs. 5.4%	100% vs. 0%	0.502
EBMT score Mean±SD (Median)	2.54±1.12 (2)	2.04±0.922 (2)	0.060
Follow-up, mo (range)	14.6 (2.1-100.7)	50.6 (0.89-164.5)	0.024

AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, CR1: First complete remission, EBMT: European Society for Blood and Marrow Transplantation, GF: Growth factor, HCT-CI: Hematopoietic stem cell transplantation comorbidity index, MAC: Myeloablative conditioning, MDS: Myelodysplastic syndrome, NMA/RIC: Non-myeloablative conditioning/ reduced intensity conditioning, SD: Standard deviation

Table 2: Comparison of engraftment kinetics and related outcomes between the two groups

	No GF support (n=38)	GF support (n=29)	p
Febrile neutropenia	94.7%	100%	0.502
Days with fever Mean±SD (Median)	5.21±5.63 (3.50)	4.93±2.44 (4)	0.079
Time to neutrophil engraftment Mean±SD (Median)	16.87±3.74 (16.5)	14.45±3.63 (14)	0.004
Time to platelet engraftment Mean±SD (Median)	13.16±4.15 (12)	15.14±4.03 (14)	0.022
Hospital stay Mean±SD (Median)	35.34±15.7 (32)	43.59±28.68 (37)	0.084

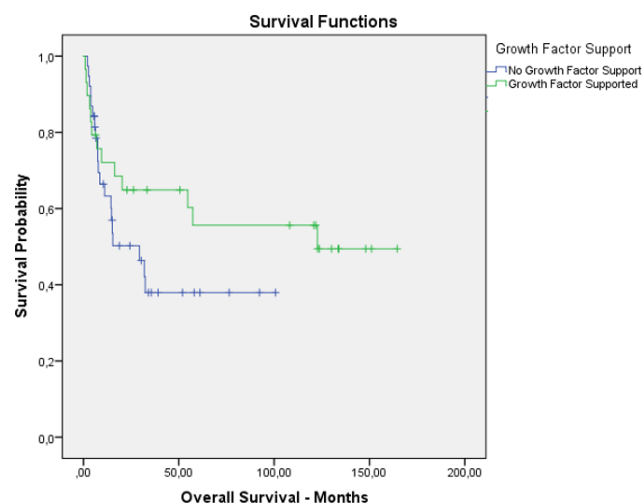
GF: Growth factor

Table 3: Univariate analysis for growth factor support and transplantation outcomes

	No GF support (n=38)	GF support (n=29)	OR	95% CI	p
GVHD (Yes)	55.3%	34.5%	0.420	0.157-1.155	0.094
aGVHD (Yes)	34.2%	24.1%	0.612	0.207-1.807	0.374
cGVHD (Yes)	39.5%	20.7%	0.400	0.132-1.213	0.105
srGVHD (Yes)	31.6%	27.6%	0.825	0.285-2.391	0.724
GVHD grade (I-II/III-IV)	12/9	5/5	1.333	0.294-6.043	0.709
Relapse (Yes)	36.8%	17.2%	0.357	0.111-1.148	0.084
Day 100 relapse (Yes)	15.8%	6.9%	0.395	0.074-2.120	0.279
Day 100 mortality (Yes)	7.9%	13.8%	1.867	0.384-9.085	0.440
Day 180 mortality (Yes)	18.4%	20.7%	1.155	0.342-3.900	0.816

Table 4: Growth factor support and 1 year mortality

	No GF support (n=32)	GF support (n=29)	OR	95% CI	p
Day 365 mortality (Yes)	37.5%	27.6%	0.635	0.215-1.877	0.412

**Figure 1:** Kaplan-Meier analysis for overall survival according to growth factor support status

Relapse incidence was found to be inversely related with steroid resistant GVHD ($p=0.040$). Other transplantation related factors in Table 5 were found to be unrelated with relapse.

Table 5: Factors affecting relapse after transplantation

	OR	95% CI	p
Age	1.006	0.964-1.050	0.778
Sex (Female vs. male)	1.123	0.375-3.364	0.836
Conditioning intensity	0.824	0.151-4.493	0.823
Leukemia type	1.156	0.309-4.325	0.830
Disease status	1.333	0.350-5.087	0.674
HCT-CI	2.937	0.173-49.74	0.455
EBMT score	1.467	0.874-2.464	0.147
GVHD (Yes)	0.791	0.270-2.310	0.667
aGVHD (Yes)	1.571	0.508-4.856	0.433
cGVHD (Yes)	0.313	0.080-1.223	0.095
srGVHD (Yes)	0.196	0.040-0.949	0.043
Transplantation period (Earlier)	1.625	0.556-4.753	0.375

aGVHD: Acute graft versus host disease, cGVHD: Chronic graft versus host disease, CI: Confidence interval, EBMT: European Society for Blood and Marrow Transplantation, GVHD: Graft versus host disease HCT-CI: Hematopoietic stem cell transplantation comorbidity index, OR: Odds ratio, srGVHD: Steroid resistant graft versus host disease

DISCUSSION

Granulocyte colony-stimulating factors are cytokines enhancing neutrophil production with safe usage in acute leukemia and myelodysplastic syndrome (8). Expectation from myeloid growth factors in allogeneic hematopoietic stem cell transplantation setting is faster neutrophil engraftment (9) but it should be noted that the engraftment kinetics is influenced by several factors such as the stem cell source, graft composition, the underlying disease, the conditioning regimen, and the type of GVHD prophylaxis (10). Limited up-to-date data exist in the literature regarding the efficacy and safety of myeloid growth factors after allogeneic stem cell transplantation. The increasing numbers of patients older than 60 years undergoing stem cell transplantation and increased reduced intensity conditioning encourage the researchers to study pre-engraftment myeloid growth factors and its effects in the era of improved supportive care relevant to infectious complications (11). Since 2014 our institutional guideline was changed regarding the empiric use of filgrastim after allogeneic stem cell transplantation based on concurrent guidelines and studies demonstrating increased GVHD and mortality (1, 12-14). This change in practice was the reason for the transplantation timeline difference between groups.

There have been studies evaluating the effects of myeloid growth factors on engraftment kinetics. Bishop et al. found faster neutrophil engraftment (11 vs. 15 days for placebo, $p=0.008$) with filgrastim (10 $\mu\text{g}/\text{kg}/\text{day}$) versus placebo in a double blind placebo-controlled study in 2000. In this study with fifty-four recipients filgrastim was started at day of transplantation. There were no significant differences for red blood cell transfusion and time to platelet engraftment (15). In a randomized trial of Prepizioka et al. with forty-two adult recipients of allogeneic blood stem cells from human leukocyte antigen-matched related donors, 10 $\mu\text{g}/\text{kg}/\text{day}$ filgrastim subcutaneously from day 1 through neutrophil recovery was compared with no growth factor support after transplantation.

The group receiving filgrastim had a shorter time to neutrophil engraftment (12 vs. 15 days, $P=0.002$) and a trend for earlier discharge (16 vs. 20 days, $p=0.05$). There were no significant differences for the number of transfusions, time to platelet engraftment, and infections (16). In 2001, in a retrospective comparative trial of Ozcan et al., fifty-six allogeneic stem cell transplantation recipients with different hematological neoplasms were involved. Both the neutrophil and platelet engraftments were faster with myeloid growth factor administration. Besides, less febrile episodes and less mucositis were seen (17). In a retrospective trial of Remberger et al., in matched related donors with various hematological neoplasms, neutrophil engraftment was fastened without an effect on platelet engraftment, red blood cell transfusion burden, and infections (12). Ringden et al., retrospectively analyzed myeloid growth factors effects in matched related (14) or matched unrelated (13) bone marrow and peripheral blood stem cell transplantation recipients and showed faster neutrophil but delayed platelet engraftment. In the meta-analysis by Dekker et al., the studies were heterogeneous regarding transplantation setting (allogeneic/autologous), stem cell sources (bone marrow/peripheral blood), age group (adult/pediatric), and cytokines G-CSF or granulocyte and monocyte colony-stimulating factor (GM-CSF). Fewer infections and parenteral antibiotic use accompanied fastened neutrophil engraftment with both G-CSF and GM-CSF, but infection-related mortality risk was comparable between the groups (18). Following those studies, Khoury et al. showed faster neutrophil engraftment (16 vs. 20 days, $p<0.001$) with myeloid growth factors administration. In this retrospective trial, the stem cell source was unrelated donor bone marrow, related donor bone marrow, or peripheral blood (19). A phase III trial with filgrastim after HLA-matched related bone marrow transplantation with various hematological neoplasms showed faster neutrophil engraftment, although days with neutropenic fever and antibiotic usage durations were not affected (20).

Authors conducted a prospective randomized controlled trial of filgrastim 5 µg/kg/day from day +7 until neutrophil recovery in HLA-identical allogeneic bone marrow transplantation in various hematological neoplasms and showed accelerated neutrophil recovery (16 vs. 23 days for placebo, $p < 0.001$), reduced intravenous antibiotic therapy (18 vs. 26 days, $p = 0.001$) and reduced hospitalization (27 vs. 34 days, $p = 0.017$) but platelet recovery rate was not affected (21). One of the most recent largest studies demonstrated shorter hospitalization with myeloid growth factors administration for HLA-matched unrelated donor stem cell transplantation in acute leukemia and myelodysplastic syndrome (11), and the most recent retrospective study demonstrated earlier neutrophil engraftment and shorter post-transplant hospital stay in peripheral blood stem cell transplantation for various hematological neoplasms including lymphomas (22).

G-CSF has effects on the immune system, mainly exerting Th2 polarization and anti-inflammatory profile and might alter the risk of GVHD. Some authors recommend using of the myeloid growth factors in allograft recipients with leukopenia persisting for 3 weeks after transplantation (23). The first meta-analysis in the field, searching for GVHD, was done by Ho et al. at 2003. A total of 1198 allogeneic hematopoietic stem cell transplantation recipients were analyzed. In this meta-analysis, the studies were heterogeneous regarding stem cell sources (bone marrow/peripheral blood), age group (adult/pediatric), cytokines (G-CSF/GM-CSF), and trial design (randomized controlled/retrospective cohort). There was not a significant difference in the risk of grade 2-4 acute GVHD, grade 3-4 acute GVHD, and chronic GVHD when hematopoietic growth factors were used (24). A double-blind placebo-controlled study by Bishop et al., demonstrated comparable incidences of acute GVHD and 100-day mortality with filgrastim (15). In the retrospective comparative trial of Ozcan et al., pre-engraftment filgrastim support was not associated with increased acute GVHD, relapse, disease free survival, and overall survival (17). There were trials resulting with unfavorable results. One of them, was conducted in 2003, was a retrospective analysis of various hematological neoplasms with matched related donors and with bone marrow or the peripheral blood as the stem cell source. In this trial, there was an increase in the risk of grade 2-4 acute GVHD (34% vs. 9%, $P < 0.001$) without a detrimental effect on chronic GVHD, relapse, and survival (12). In the retrospective analysis of Ringden et al., there was a 1.33 times more grade 2-4 acute GVHD, 1.29 times more chronic GVHD, increased transplantation related mortality, and decreased survival with G-CSF in bone marrow transplant recipients. These detrimental effects were not seen when peripheral blood stem cells were used (14). In 2010, Ringden et al. demonstrated 1.52 times more grade 2-4 acute GVHD and 1.51 times more chronic GVHD with G-CSF; however equal non-relapse mortality, relapse, and survival were seen with G-CSF. The interesting result of this study was that the G-CSF increases the risk of acute GVHD, especially with peripheral blood stem cell transplantation and chronic GVHD with bone marrow transplantation (13). In the aforementioned meta-analysis by Dekker et al., colony-stimulating factors were not found to be detrimental on grade 2-4 acute GVHD and transplantation related mortality (18). Contemporaneous

with those studies, American Society of Clinical Oncology 2006 guidelines recommended the use of G-CSF after autologous, but not after allogeneic HSCT (2). In Khoury et al. cohort of acute myeloid leukemia and chronic myeloid leukemia, G-CSF use was not a determinative factor for day 30 and day 100 mortality, acute GVHD, chronic GVHD, and survival in the multivariate analysis (19). Randomized placebo-controlled trial of Ernst et al., showed comparable GVHD, mortality, and relapse rate with 2 years follow-up (20). A randomized clinical trial with long-term follow up, demonstrated less non-relapse mortality and comparable GVHD and relapse incidences. In this trial, the age range was 16 to 49 (younger than our cohort), myeloablative conditioning was used, and the stem cell source was bone marrow (21). American Society of Clinical Oncology revised recommendations on the use of G-CSFs in 2016, as they may be administered after allogeneic stem-cell transplantation to reduce the duration of severe neutropenia with low quality of evidence and weak strength of recommendation (1).

G-CSF administration was not related with overall survival neither in matched sibling donor nor matched unrelated donor peripheral blood stem cell transplantation in a recent and large retrospective multicenter cohort transplantation of acute leukemia and myelodysplastic syndrome patients (11). Unlike the aforementioned studies, a recent study with peripheral blood stem cell transplantation for various hematological neoplasms showed G-CSF use was associated with higher rate of extensive chronic GVHD (22). This study was also similar to our study by more myeloablative conditioning usage in the G-CSF supported recipients.

Filgrastim dosage can have an impact on transplantation outcomes. In a study with mycophenolate mofetil for GVHD prophylaxis, higher doses of G-CSF was/were associated with higher acute GVHD incidence with cord blood and bone marrow as the stem cell sources and decreased progression free survival with cord blood stem cell transplantation (9). One of the recent interests is the difference between biosimilar versus originator filgrastim and a study showed similar transplantation outcomes (25).

Our study clearly showed faster neutrophil recovery with growth factor administration but delayed platelet engraftment. Faster neutrophil recovery did not provide less neutropenic fever incidence or days with fever. Likewise, faster neutrophil recovery did not translate into shorter length of hospital stay after transplantation. However, mucositis or severe mucositis incidence, invasive fungal infections were not evaluated in our study. In this study, we clearly demonstrated the safety of pre-engraftment growth factor in terms of GVHD. Our study shows a trend through less early (day 100) relapse and cumulative relapses with growth factor administration, although statistically insignificant. Only the steroid resistant GVHD was a better factor for relapse in the univariate analysis. This can be related to the graft versus leukemia effect. We found the growth factor support was safe in terms of day 100, day 180 and 1-year mortality. Mortality incidences have a tendency to be higher at day 100 and day 180 in growth factor supported group, but mortality at 1-year showed a tendency for decreased mortality favoring G-CSF use.

There are limitations of this study. First of all due to the institutional protocol switch by 2014, growth factor supported recipients had a shorter follow-up duration. Median age, disease status at transplantation and conditioning regimen intensities were not comparable between groups as this is a real-life data. In our study, molecular relapses, measurable residual disease determination and loss of chimerism are not considered as relapse due to lack of patient records transplanted in the earlier times.

CONCLUSION

This study shows colony-stimulating factors are safe in HLA identical allogeneic hematopoietic stem cell transplantation. Heterogeneity between randomized trails and lack of up-to-date meta-analyses mandate further prospective randomized controlled studies to be performed in order to make routine suggestions regarding pre-engraftment growth factor administration for different stem cell sources, different donors, and different conditioning and GVHD prophylaxis regimens.

Acknowledgments: None

Author Contributions: MSA, EC, AKG, MAU, FC, GO, SD: project development, data collection, literature review, manuscript writing, MSA: statistics, manuscript review

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Financial & competing interest's disclosure: The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Local Ethical Committee

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