ARTICLE - Non-Hodgkin Lymphoma

Optimizing bone health in lymphoma survivors: denosumab superiority to alendronate for R-CHOP-like therapy (the DENOSULY phase III randomized controlled trial)

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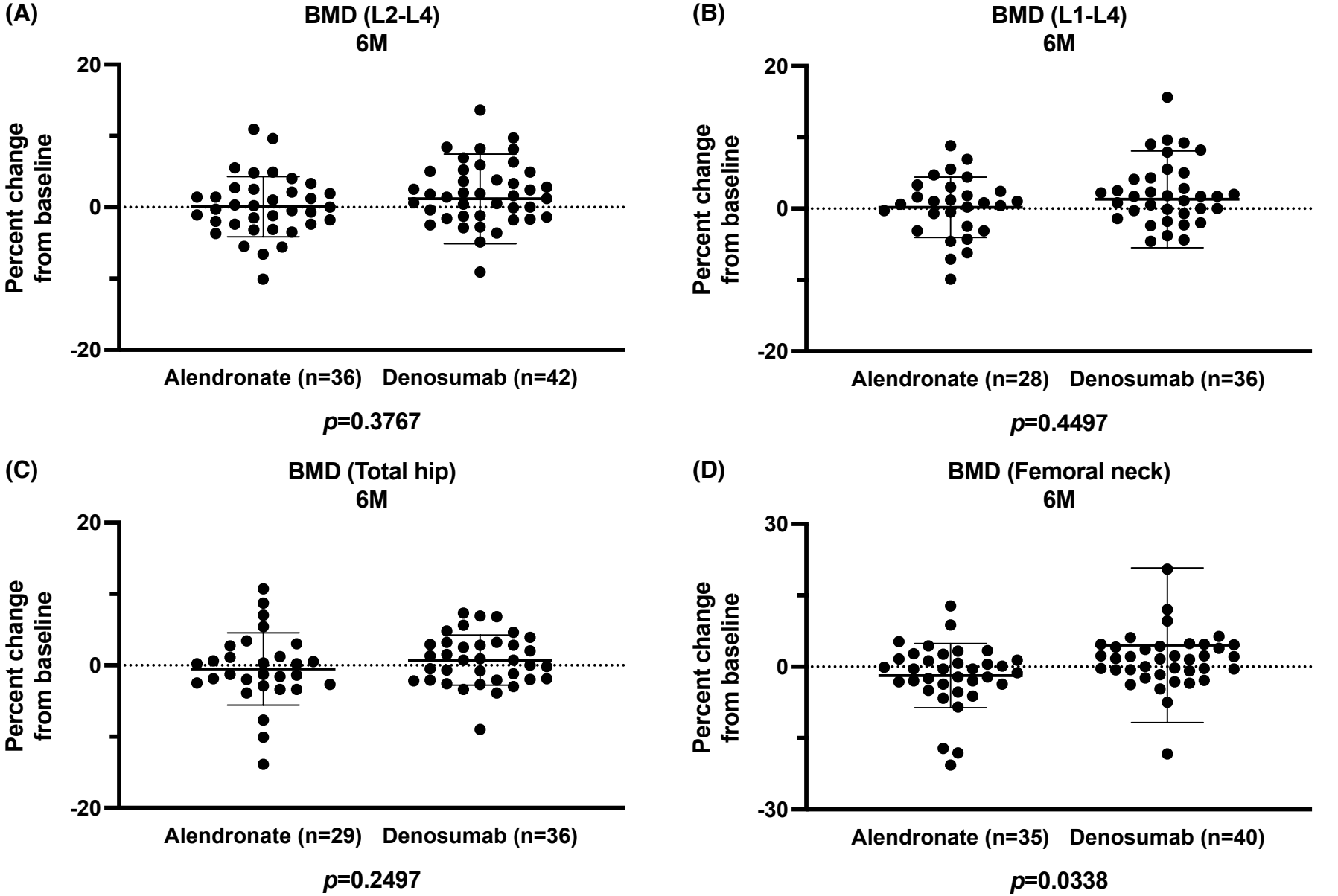
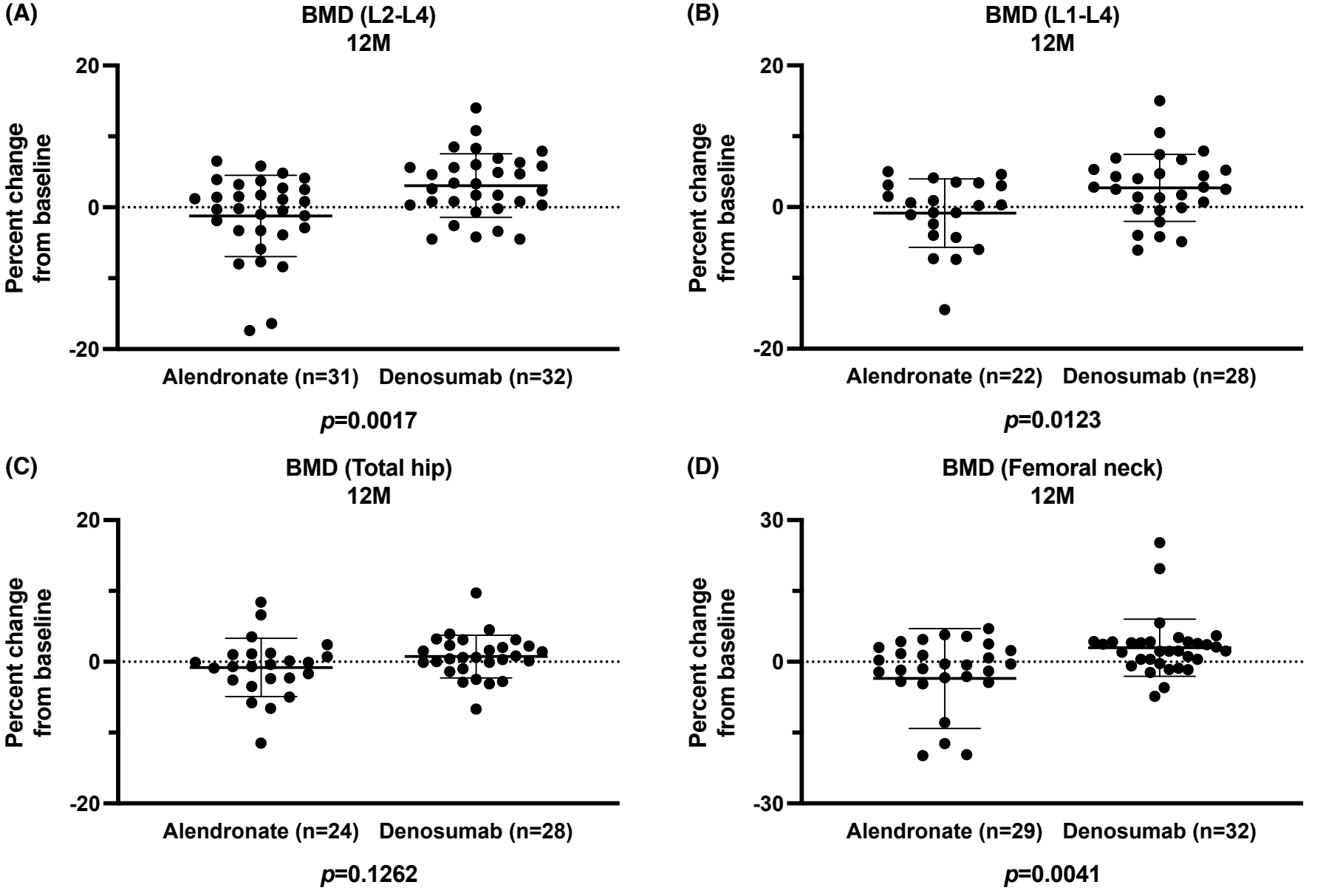
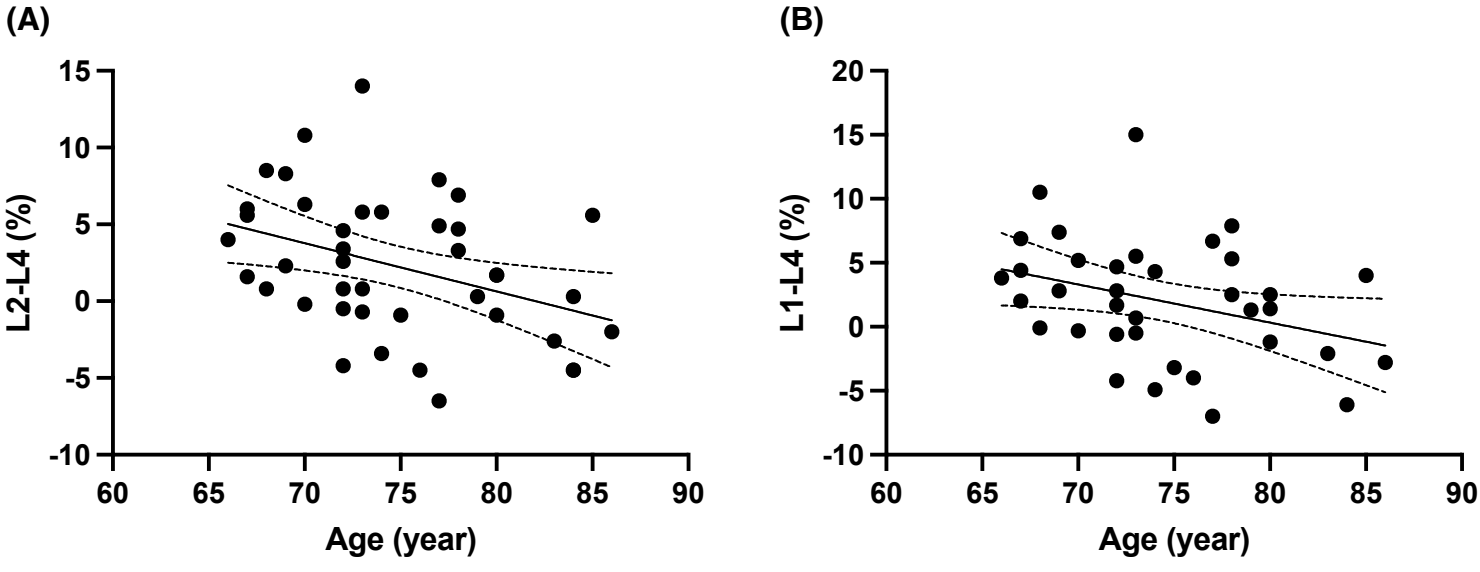


Supplementary Figure 1. Comparison of percentage changes in bone mineral density (BMD) at 6 months.
Percentage change from baseline between the alendronate and denosumab groups at (A) L2–L4; (B) L1–L4; (C) total hip; and (D) femoral neck.



Supplementary Figure 2. Subgroup analysis of percentage change in bone mineral density (BMD) in patients with DLBCL at 12 months.

Comparison between the alendronate and denosumab groups at (A) L2–L4; (B) L1–L4; (C) total hip; and (D) femoral neck.



Supplementary Figure 3. Correlation between patient age and percentage change in bone mineral density (BMD) at 12 months.

Spearman's correlation analysis evaluating the association between age and BMD change at (A) L2–L4 and (B) L1–L4.

Supplementary Table 1. Histology and regimen.

		Histology					
		DLBCL (n=89)	PTCL (n=4)	FL (n=2)	IVLBCL (n=2)	AITL (n=2)	BL (n=1)
Regimen	R-CHOP (+ RT)	67 (7)	0	1 (0)	0	0	0
	Pola-R-CHP (+ RT)	7 (1)	0	0	2 (0)	0	0
	R-CVP (+ RT)	6 (0)	0	0	0	0	0
	BV-CHP (+ RT)	0	2 (0)	0	0	1 (0)	0
	CHOP (+ RT)	0	2 (0)	0	0	0	0
	DA-EPOCH-R (+ RT)	0	0	0	0	0	1 (1)
	CVP (+ RT)	0	0	0	0	1 (0)	0
	None	9	0	1	0	0	0

DLBCL, diffuse large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; FL, follicular lymphoma; IVLBCL, intravascular large B-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; BL, Burkitt lymphoma. R, rituximab; Pola, polatuzumab vedotin; BV, brentuximab vedotin; DA, dose-adjusted; CHOP, cyclophosphamide + hydroxydaunorubicin + vincristine + prednisolone; CHP, cyclophosphamide + hydroxydaunorubicin + prednisolone; CVP, cyclophosphamide + vincristine + prednisolone; EPOCH, etoposide + prednisolone + vincristine + cyclophosphamide + hydroxydaunorubicin; RT, radiation therapy.

Supplementary Table 2. Adverse events of interest.

	Alendronate (n=48)	Denosumab (n=52)
Event	n (%)	n (%)
Hypocalcemia (Grade ≥ 3)	0 (0)	0 (0)
Skin infection (cellulitis) (Grade ≥ 3)	0 (0)	0 (0)
Eczema (Grade ≥ 3)	0 (0)	0 (0)
Anaphylaxis (Grade ≥ 3)	0 (0)	0 (0)
Secondary malignancy (Grade ≥ 3)	0 (0)	0 (0)
Hip fracture (atypical) (Grade ≥ 3)	0 (0)	0 (0)
Osteonecrosis of jaw (Grade ≥ 3)	0 (0)	0 (0)
Fracture healing complication	0 (0)	0 (0)

Supplementary Methods

Study design and objective

This study is a prospective, interventional, multi-center, open-label, randomized trial. Its objective is to compare the efficacy and safety of denosumab versus alendronate in newly diagnosed malignant lymphoma patients undergoing corticosteroid-containing chemotherapy. The primary endpoint was defined as the percentage change in lumbar spine BMD (comparison between baseline and 12 months post-treatment initiation). Secondary endpoints included the percentage change in lumbar spine BMD (comparison between baseline and 6 months), the percentage change in femoral BMD (comparison between baseline and 6 and 12 months), and the percentage change in Bone Turnover Marker (BTM) (comparison between baseline and 6 months). BMD was measured using Dual energy X-ray absorptiometry (DXA). Measurements were performed using Hologic (Bedford, MA, USA) or GE Lunar (Madison, WI, USA) densitometers at each participating center, with daily calibration performed using a standard phantom to ensure precision. The BTMs measured were Tartrate-resistant acid phosphatase 5b (TRACP-5b) and total type I procollagen N-terminal propeptide (total P1NP). The study protocol was approved by the Institutional Review Board of Toyama University Hospital (protocol no. R2019137) and monitored annually by the Data Safety Monitoring Committee of the Toyama University Hospital. All trial participants provided written informed consent. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; ID: UMIN000038881).

Patients

The inclusion criteria for participation in this study were as follows: 1) patients newly diagnosed with malignant lymphoma, 2) patients aged 65 years or older, 3) patients scheduled to receive steroid-containing chemotherapy, such as R-CHOP or similar regimens, and 4) patients who provided written informed

consent for study participation. Exclusion criteria included a history of hypersensitivity to denosumab, the presence of hypocalcemia, pregnant or possibly pregnant women, the presence of esophageal transit disorders, the inability to remain upright for 30 minutes or more, hypersensitivity to bisphosphonates, the presence of hypercalcemia or vitamin D intoxication, current or prior treatment for osteoporosis with denosumab or bisphosphonates, or any patient deemed ineligible by the study investigator.

Treatment

Patients were stratified by two factors: age (80 years or older) and sex and were randomly allocated to either the alendronate group or the denosumab group using a permuted block method. The denosumab group received a total of two subcutaneous injections of denosumab 60 mg, at the initiation of treatment and 6 months later. The alendronate group received oral alendronate 35 mg once weekly for 12 months starting from the initiation of treatment. Both groups received oral calcitriol preparation 0.25 μg once daily for 12 months starting from the initiation of treatment. Regarding the steroid protocol, in each cycle of R-CHOP-like therapy, patients typically received oral prednisolone (100 mg/body/day) for 5 days. However, intravenous administration of water-soluble prednisolone was permitted. Depending on the patient's clinical status, salvage chemotherapy or additional corticosteroid doses could be administered at the discretion of the investigator. Ultimately, all corticosteroids administered during the 1-year study period were converted into prednisolone equivalents and reported as the total cumulative dose.

Adverse events

Adverse events were considered "serious" if they met the following criteria: 1) resulted in death, 2) were life-threatening, 3) required inpatient hospitalization or prolongation of existing hospitalization, 4) resulted in persistent or significant disability/incapacity, or 5) resulted in a congenital anomaly or birth

defect in the offspring. For adverse events highly predicted to occur frequently in the target population due to chemotherapy for malignant lymphoma—such as myelosuppression, febrile neutropenia, gastrointestinal symptoms, hepatic or renal dysfunction, and electrolyte abnormalities—reporting was not required if they were not deemed serious. Conversely, the following items, which are considered characteristic adverse events of denosumab or alendronate, required reporting as "adverse events of interest" if they were Grade ≥3: 1) hypocalcemia, 2) skin infection (cellulitis), 3) eczema, 4) anaphylaxis, 5) secondary malignancy, 6) hip fracture (atypical), 7) osteonecrosis of the jaw (ONJ), and 8) fracture healing complication. For the assessment of calcium status, serum calcium levels were measured at the laboratory of each participating institution. Calcium values were corrected for hypoalbuminemia. The severity of hypocalcemia was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Rationale for target sample size

The sample size was determined by referencing a comparative study of denosumab and alendronate for steroid-induced osteoporosis in patients with nephritis. In that report, the percentage change in lumbar spine BMD when comparing baseline with 12 months post-treatment was +5.3% in the denosumab group. The standard error (SE) was 1.0%, the number of analyzed cases was 14, and the standard deviation (SD) was 3.7%. In the alendronate group, the percentage change was +2.0%, the SE was 1.2%, the number of analyzed cases was 14, and the SD was 4.5%. Therefore, for the current trial, we hypothesized a difference in the percentage change between the two groups of 3.0% and a SD of 5.0%. Performing a two-sided test with a significance level alpha of 0.05 and a statistical power of 80%, the required number of cases calculated using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was 44 patients per group. Assuming a 12% dropout rate due to withdrawal of participation, disease progression, adverse events, or loss to

follow-up, the target sample size was set at 50 patients per group, totaling 100 patients.

Statistical methods

All statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software, La Jolla, CA). All values are presented as mean ± SD. Statistical significance was determined using the student's t-test in the case of normally distributed data, otherwise the Mann-Whitney U test was performed. For comparisons of data from the same patient, the paired Student's t-test was used. The Fisher exact test was used to evaluate the association between two categorical variables. The Spearman correlation coefficient was used to estimate the correlation between two continuous variables. All tests were two-sided. p values < 0.05 were considered statistically significant.