Original Research Article

SAGE Open Medicine

SAGE Open Medicine
Volume 12: 1–6
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DOI: 10.1177/20503121241277498
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Femoral bone mineral density as a tool of personalized medicine for rheumatoid arthritis: Interleukin-6 inhibitors for patients with low density whereas tumor necrosis factor inhibitor for patients with preserved density?

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Abstract

Objectives: There is a lack of indicators to distinguish between interleukin-6 inhibitors responders and tumor necrosis factor inhibitors responders in the treatment of rheumatoid arthritis. Osteoporosis is a complication of rheumatoid arthritis and is closely related to inflammatory pathology. The purpose of this study was to evaluate whether bone mineral density can distinguish interleukin-6 inhibitors responders from tumor necrosis factor inhibitors responders in rheumatoid arthritis.
Methods: Either interleukin-6 inhibitors or tumor necrosis factor inhibitors was introduced as the first biologics to patients naïve to both corticosteroid and osteoporosis treatment. Correlations between baseline bone mineral density and Clinical Disease Activity Index after 3 months were analyzed.
Results: The subjects were 26 rheumatoid arthritis patients with a median age of 60 years old, disease duration of 1.4 years, Clinical Disease Activity Index of 13.7, and C-reactive protein of 1.69 mg/dL. The subjects were divided into two groups (high (H) and low (L)) according to their femoral bone mineral density with a cutoff of young adult mean of 80%. Six in group H and 11 in group L received interleukin-6 inhibitors, and nine in group H received tumor necrosis factor inhibitors. Clinical Disease Activity Index remission rate by interleukin-6 inhibitors was significantly greater in group L (8/11 (72.7%)) than in group H (1/6 (16.7%); $p < 0.05$). In the whole group H, significantly more patients obtained Clinical Disease Activity Index remission by tumor necrosis factor inhibitors (7/9, 77.8%) than by interleukin-6 inhibitors (1/6 (16.7%); $p = 0.04$).
Conclusions: In patients with rheumatoid arthritis, interleukin-6 inhibitors may be more beneficial for patients with low femoral bone mineral density, whereas tumor necrosis factor inhibitors may be advantageous for those with preserved bone mineral density.

Keywords

Biologic synthetic disease-modifying antirheumatic drugs, bone mineral density, interleukin-6, rheumatoid arthritis, tumor necrosis factor-α

Date received: 29 April 2024; accepted: 1 August 2024

Introduction

In treatment of rheumatoid arthritis (RA), optimal drug should be selected in a short period of time based on a treat-to-target strategy and safe treatment for high-risk patients.[1,2] If methotrexate (MTX) is not sufficiently effective, biologic disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi), interleukin-6 inhibitors (IL-6i), and abatacept are considered, but it is often difficult to decide which to choose. Shared epitope and anti-cyclic citrullinated peptide antibody (ACPA) are some

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of the indicators that predict whether abatacept is more effective,[3] but there is no clear indicator that can predict efficacy of IL-6 or TNF inhibitor in clinical practice.

Osteoporosis (OP) is an important complication of RA. It is classified as periarticular OP and generalized OP.[4,5] Periarticular OP occurs near affected joints of RA, and it is thought that osteoclast formation is activated by receptor activator of nuclear factor-kappa B (RANK), its ligand (RANKL), osteoprotegerin, and inflammatory cytokines such as IL-6, TNF-α, and IL-17.[5,6] On the other hand, generalized OP is caused by several factors such as systemic inflammation.[7] The pathogenesis of bone mineral density (BMD) reduction in RA patients involves various factors of the immune system, including overexpression of autoantibodies against citrullinated proteins, bone resorption by osteoclasts, and secretion of inflammatory cytokines.[7] Furthermore, in generalized OP, low bone density is more remarkable in load-bearing bones such as the calcaneus and femoral neck, which is associated with decreased activities of daily life (ADL).[4]

Although IL-6 is thought to be the main cytokine that causes generalized OP with RA patients,[8,9] rather than TNF, there is some article showing that treatment in RA with an IL-6i increase BMD and TNFi do not improve BMD.[10–12] In terms of improving BMD, IL-6i may be a treatment option for RA patients with reduced BMD. The objective of this study was to test the hypothesis that IL-6i are effective if BMD is reduced, and TNFi are effective if BMD is preserved in corticosteroid (CS)-naïve RA patients without treated OP.

Methods

Patients

Japanese patients with RA, classified by the 1987 American College of Rheumatology (ACR) and/or the 2010 ACR/European League Against Rheumatism (EULAR) criteria between January 2017 and May 2023, were extracted from the medical record of Kumamoto Shinto General Hospital. Selection criteria for this study included patients receiving IL-6i or TNFi as their first bDMARDs, and exclusion criteria were unmeasured BMD, history of treatment for OP, compression fractures, and CS medication in a retrospective analysis. Since beneficial treatment response to IL-6i in patients with reduced BMD was implicated from daily practice, it was considered clinically ethical that TNFi should be preferred only in patients with preserved BMD. For this reason, TNFi is not administered to RA patients with reduced BMD. The study was approved by the ethical review board of Kumamoto Shinto General Hospital (Approval No. 2023-01-001). Written informed consent for publication was obtained from all the patients by the corresponding author. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Clinical and laboratory assessments

RA disease activity was assessed by the Clinical Disease Activity Index (CDAI) and C-reactive protein,[13] while BMD was measured by dual-energy X-ray absorptiometry in both proximal left femoral neck (f-BMD) and average of second to fourth lumbar vertebrae (l-BMD) with young adult mean (YAM) values. The patients were divided into two groups: those with YAM values of f-BMD less than 80% (group L) and those with YAM values of f-BMD more than 80% (group H). Group H was divided into IL-6i (group $H_{IL\text{-}6i}$) and TNFi (group H_{TNFi}) groups, group L was compared to subgroup $H_{IL\text{-}6i}$, and subgroup H_{TNFi}. Patients were further divided into two groups: those with YAM values of l-BMD less than 80% (group L′) and those with YAM values of l-BMD more than 80% (group H′), and CDAI was also compared between these two groups.

Statistical analyses

Statistical analyses were performed using the statistical software "EZR" (Easy R).[14] Categorical variables are presented as percentages, and quantitative variables are presented as medians and interquartile ranges. We used the Mann–Whitney *U*-test for comparisons between independent medians, and the Fisher's exact test for the evaluation of the associations between categorical variables. p-Values <0.05 were considered as significant.

Results

Patients and background

The patient backgrounds are shown in Table 1. The subjects were 26 RA patients (Figure 1), with a median age of 60 years, 80.8% female, disease duration of 1.4 years, all rheumatoid factor positive as shown in Table 1. RA disease activity was generally moderate. The rate of MTX and other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are shown in Table 1.

All patients in group L received IL-6i, while group H was divided into group $H_{IL\text{-}6i}$ and group H_{TNFi} (Table 2). IL-6i were tocilizumab (TCZ) in all patients. In group L, 4 of 11 patients received 8 mg/kg intravenously every 4 weeks and 7 patients received 162 mg subcutaneously every 2 weeks, while all 6 patients in group $H_{IL\text{-}6i}$ received 8 mg/kg intravenously every 4 weeks (Table 2). The TNFi selection is also listed in Table 2, and all patients were treated with MTX in group H_{TNFi}.

There were no significant differences in background RA disease activity or inflammatory findings between each two groups except for BMD (Table 1). However, there were differences in treatment, with group L using more csDMARDs than group $H_{IL\text{-}6i}$, and moreover, the former used subcutaneous injections and the latter intravenous infusions ($p=0.03$).

Table 1. Patient characteristics.

Characteristic	All patients ($n=26$)	Group L ($n=11$)	p-Value between group L and $H_{IL\text{-}6i}$	Group $H_{IL\text{-}6i}$ ($n=6$)	p-Value between group $H_{IL\text{-}6i}$ and H_{TNFi}	Group H_{TNFi} ($n=9$)
Age, years (range)	60 (48–67)	65 (54–70)	1.00	63 (44–72)	0.53	51 (40–61)
Female, *n* (%)	21 (80.8)	8 (72.7)	1.00	4 (66.7)	0.14	9 (100)
Disease duration, years (range)	1.4 (0.5–5.4)	1.5 (0.7–6.0)	0.51	0.6 (0.3–3.6)	0.24	1.9 (0.8–2.8)
RF, IU/mL (range)	53 (38–140)	75 (28–248)	0.80	58 (48–179)	0.41	50 (45–106)
ACPA, U/mL (range)	172 (32–662)	172 (49–699)	0.91	298 (256–610)	0.70	114 (21–392)
CDAI (range)	13.7 (10.7–18.1)	12.6 (10.7–17.3)	0.73	13.0 (9.4–16.4)	0.46	14.2 (12.3–23.4)
CRP, mg/dL (range)	1.69 (0.72–4.40)	1.77 (1.21–5.87)	0.73	2.35 (1.63–4.76)	0.18	1.23 (0.62–2.34)
HAQ-DI (range)	1.13 (0.50–1.63)	1.25 (0.32–2.01)	0.92	1.13 (0.60–1.57)	0.95	1.0 (0.88–1.5)
HAQ-DI >0.5, *n* (%)	18 (69.2)	7 (63.6)	1.00	4 (66.7)	1.00	7 (63.6)
f-BMD, YAM (range)	82 (71–93)	71 (65–73)	<0.01	95 (85–97)	0.81	91 (87–106)
l-BMD, YAM (range)	84 (72–107)	72 (69–73.5)	0.03	97 (81–110)	0.46	105 (96–114)
csDMARDs use, *n* (%)	23 (88.5)	11 (100)	0.03	3 (50)	0.04	9 (100)
MTX use, *n* (%)	18 (69.2)	7 (63.6)	0.34	2 (33.3)	0.01	9 (100)
MTX dose, mg/week (range)	10 (6–12)	10 (7–12)	0.54	8 (7–9)	0.63	10 (6–12)
IGU use, *n* (%)	6 (23.1)	3 (27.3)	0.52	0	0.23	3 (33.3)
SASP use, *n* (%)	2 (7.7)	1 (9.1)	1.00	1 (16.7)	0.40	0
IGU plus SASP use, *n* (%)	4 (15.4)	2 (18.2)	0.52	0	0.49	2 (22.2)
IGU plus TAC use, *n* (%)	1 (3.8)	1 (9.1)	1.00	0	1.00	0

The data are median (interquartile range, Q1/4–Q3/4) or number (percentage). ACPA: anti-cyclic citrullinated peptide antibody; CDAI: clinical disease activity index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; f-BMD: femoral neck bone mineral density; HAQ-DI: Health Assessment Questionnaire-Disability Index; IGU: iguratimod; IL-6i: interleukin-6 inhibitors; l-BMD: lumbar 2–4 bone mineral density; MTX: methotrexate; RF: rheumatoid factor; SASP: salazosulfapyridine; TAC: tacrolimus; TNFi: tumor necrosis factor inhibitors; YAM: young adult mean.

CDAI remission 3 months after TCZ introduction was more common in the group L than in the group $H_{IL\text{-}6i}$

As shown in Table 3, after 3 months of TCZ treatment, only 1 of 6 patients (16.7%) in group $H_{IL\text{-}6i}$ achieved clinical remission, while 8 of 11 patients (72.7%) in group L achieved clinical remission ($p<0.05$). The median Health Assessment Questionnaire-Disability Index (HAQ-DI) after 3 months of TCZ treatment decreased from 1.13 only to 0.63 in group $H_{IL\text{-}6i}$, whereas in group L, it decreased from 1.25 to 0.19, with numerically greater difference in group L with marginal significance ($p=0.06$).

CDAI remission was more common after 3 months of introduction of TNFi (group H_{TNFi}) than IL-6i (group $H_{IL\text{-}6i}$) in patients with preserved femoral BMD

As shown in Table 4, after 3 months of bDMARDs, TNFi brought significantly greater remission rate (seven of nine patients (77.8%) in group $H_{TNF\text{-}i}$) than IL-6i did (only one of six patients (16.7%) in group $H_{IL\text{-}6i}$; $p=0.04$).

Discussion

We examined whether bDMARDs could be used in a small number of RA patients with relatively early disease duration of 2 years or less, but since most RA patients are generally female,[15] there seems to be no particular bias in this study. Although several articles have reported that IL-6i increases BMD[10,11] and TNFi does not improve BMD,[12] and there is little literature that examined the efficacy of these drugs as treatment of RA based on BMD results. In this study, we retrospectively illustrated the greater efficacy of IL-6i in RA patients with lower BMD. TNF and IL-6 are both cytokines related to OP and osteoclasts,[4,5] but this study was designed by estimating that IL-6 is not only an inflammatory cytokine but also has complex interactions with cells involved in bone remodeling and is closely related to OP in RA patients.[8,9] Consequently, the present analysis showed that group L, patients with reduced f-BMD, achieved clinical remission in greater rate as quickly as in 3 months of IL-6i compared to group $H_{IL\text{-}6i}$, patients with preserved BMD.

OP is a disease that reduces bone mass leading to fractures, and it is often complicated in patients with RA. Activated osteoclast formation is the dominant process leading to bone loss in the initial RA,[16] IL-6 is a cytokine involved

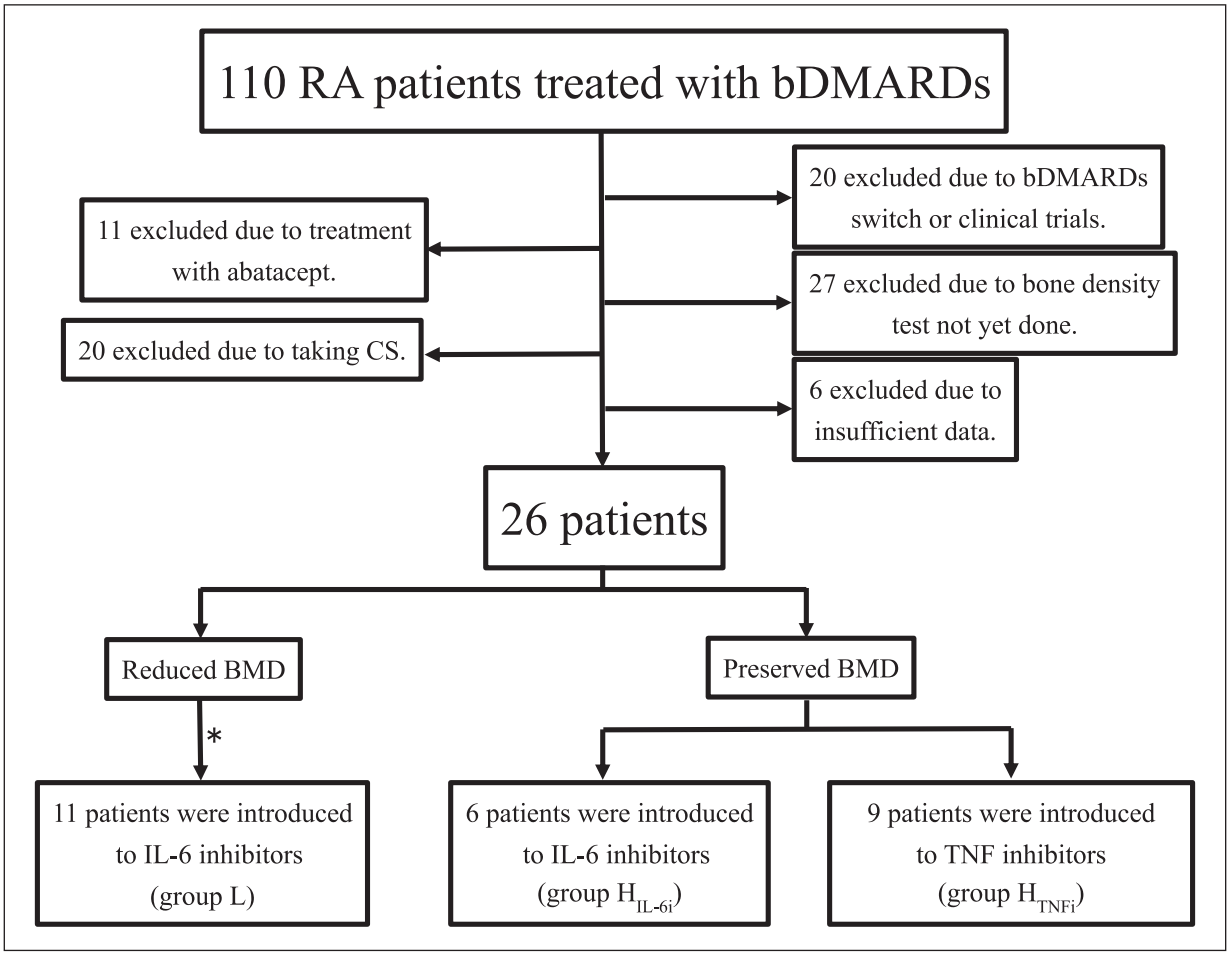

Figure 1. Selection of the study subjects. This study was restrospectively conducted on 26 cases treated with TNF inhibitors or IL-6 inhibitors as the first biologics. These cases were selected after excluding those with switched bDMARDs, treated with abatacept, taking CS, lacking bone density measurement in advance, and with insufficient data among 110 patients in whom bDMARDs were commenced between 2017 and 2023.
IL-6i: interleukin-6 inhibitors; bDMARDs: biologic disease-modifying antirheumatic drugs;CS: corticosteroid.
*Since beneficial treatment response to IL-6i in patients with reduced BMD was implicated from daily practice, it was considered clinically ethical that TNFi should be preferred only in patients with preserved BMD.

Table 2. Details of bDMARDs administered.

Dose	All patients ($n=26$)	Group L ($n=11$)	Group $H_{IL\text{-}6i}$ ($n=6$)	Group H_{TNFi} ($n=9$)
TCZ 8 mg/kg DIV use, *n* (%)	10 (38.5)	4 (36.4)	6 (100)	0
TCZ 162 mg SC use, *n* (%)	7 (26.9)	7 (63.6)	0	0
ADA 40 mg SC use, *n* (%)	3 (11.5)	0	0	3 (33.3)
GOL 50 mg SC use, *n* (%)	4 (15.4)	0	0	4 (44.4)
CZP 200 mg SC use, *n* (%)	1 (3.8)	0	0	1 (11.1)
ETN-BS 50 mg SC use, *n* (%)	1 (3.8)	0	0	1 (11.1)

The data are number (percentage). ADA: adalimumab; bDMARDs: biologic disease-modifying antirheumatic drugs; CZP: certolizumab pegol; DIV: dripped intravenous injection; ETN-BS: etanercept biosimilar; GOL: golimumab; IL-6i: interleukin-6 inhibitors; SC: subcutaneous; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitors.

in osteoclast formation activation and is also known to be associated with both RA and OP.[9] TNF is also associated with osteoclasts formation and is deeply involved in pathogenesis in RA. In general, TNF promotes osteoclast differentiation, stimulates bone resorption by increasing RANKL expression in T and B lymphocytes and osteoclasts, and RANK expression in osteoclast precursors, and also inhibits bone formation through stimulation of Dickkopf-1 production.[17] However,

Table 3. Parameters of disease activity and physical function (group L and $H_{IL\text{-}6i}$).

Parameter	Group L ($n=11$)	Group $H_{IL\text{-}6i}$ ($n=6$)	p Value
CDAI (range)	1.6 (1.5–2.5)	4.8 (3.3–6.5)	0.02
CDAI remission, *n* (%)	8 (72.7)	1 (16.7)	<0.05
CRP, mg/dL (range)	0.05 (0.04–0.05)	0.05 (0.05–0.05)	0.14
HAQ-DI (range)	0.19 (0.13–0.25)	0.63 (0.41–0.85)	0.06
HAQ-DI <0.5, *n* (%)	8 (72.7)	2 (33.3)	0.16

The data are median (interquartile range, Q1/4–Q3/4) or number (percentage). CDAI: clinical disease activity index; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index; IL-6i: interleukin-6 inhibitors.

Table 4. Parameters of disease activity and physical function (group H_{TNFi} and $H_{IL\text{-}6i}$).

Parameter	Group H_{TNFi} ($n=9$)	Group $H_{IL\text{-}6i}$ ($n=6$)	p Value
CDAI (range)	1.5 (0.8–2.4)	4.8 (3.3–6.5)	0.06
CDAI remission, *n* (%)	7 (77.8)	1 (16.7)	0.04
CRP, mg/dL (range)	0.06 (0.05–0.18)	0.05 (0.05–0.05)	0.32
HAQ-DI (range)	0.13 (0.13–0.38)	0.63 (0.41–0.85)	0.11
HAQ-DI <0.5, *n* (%)	7 (77.8)	2 (33.3)	0.13

The data are median (interquartile range, Q1/4–Q3/4) or number (percentage). CDAI: clinical disease activity index; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index; IL-6i: interleukin-6 inhibitors; TNFi: tumor necrosis factor inhibitors.

recent observations have shown that TNF-associated macrophages slow bone loss due to increased bone resorption in RA,[18] which explains why TNF inhibitors have only a limited effect on ameliorating bone loss in RA patients.[12] Furthermore, Nagase et al. prospectively evaluated the effects of TNFi plus bisphosphonates on BMD and bone and cartilage biomarkers at 1 year compared with BP alone in RA patients and found no effect on BMD at 1 year, although f-BMD was decreased in both groups.[19] This suggests that RA patients with reduced f-BMD will have further reduction in BMD with continued TNFi, and that treatment other than TNFi may be preferable for RA patients with reduced f-BMD in terms of OP progression. However, the thorough relationship between IL-6i and BMD is also unclear, with some reports showing an increase in BMD after treatment.[10] A report on ACPA-positive RA patients found that IL-6i treatment increased BMD,[11] so it may make sense to administer IL-6i to seropositive RA patients with decreased BMD, as in this study. In addition, all patients in the TNFi group were treated with csDMARDs such as MTX, while only 50% of patients in the IL-6i group were treated with csDMARDs, so the possibility that concomitant use of csDMARDs may have influenced the results cannot be denied. However, IL-6i is effective with or without MTX,[20] whereas TNFi is preferable with MTX, as shown in the ADACTA study comparing adalimumab and TCZ.[21] The difference in concomitant use of csDMARDs in the TNFi and IL-6i groups might be due to pharmacological differences in the treatment of RA.

The current study was able to predict clinical remission at 3 months in RA patients using f-BMD before induction of IL-6i, but not BMD of the lumbar spine (Supplemental Tables S1–S4). As mentioned above, systemic OP develops in the femoral neck, calcaneus, and other load-bearing regions in response to ADL decline, but BMD in the lumbar spine is less affected by ADL and is not considered to reflect disease activity in RA.[22] Although this study examined whether a decrease in BMD could predict the therapeutic efficacy of IL-6i, it does not suggest that the drug is less effective in RA patients who do not have a decreased BMD. In other words, we often experience that young RA patients, who are not generally considered to have reduced BMD, can benefit from IL-6i as first-line therapy. Rather, IL-6i may have a relatively early therapeutic effect in RA patients with reduced BMD.

There are several limitations to this study. First, the number of patients is small, so it is difficult to say that this study represents the entire picture of RA. Second, only YAM values were used as an index of bone loss in this study. Utilizing bone metabolism markers might bring more profound information as for the theme of this study. Third, in the present analysis, some of the significant differences in patient backgrounds, such as those in the prescription rates of concomitant csDMARDs including MTX, were observed. Although multiple logistic analysis had been attempted, they could not be performed effectively due to the small sample size, and power analysis for sample size calculation was not performed.

Conclusion

In patients with RA, IL-6i may be more beneficial for patients with low f-BMD, whereas TNFi may be advantageous for those with preserved BMD, and f-BMD is more useful than l-BMD for predicting response to IL-6i or TNFi.

Acknowledgements

None.

Author contributions

HT and TM contributed to the clinic and data collection; HT and KS analyzed the data and wrote the article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

The study was approved by the ethical review board of Kumamoto Shinto General Hospital (Approval No. 2023-01-001).

Informed consent

Written informed consent for publication was obtained from all the patient by the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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