Journal of Bone and Mineral Metabolism (2019) 37:886–892
https://doi.org/10.1007/s00774-019-00990-5

ORIGINAL ARTICLE

Incidence of osteonecrosis of the jaw in Japanese osteoporosis patients taking minodronic acid

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Received: 8 December 2018 / Accepted: 21 January 2019 / Published online: 4 February 2019

Abstract

Osteonecrosis of the jaw (ONJ) associated with bisphosphonate therapy is a rare but severe side effect in osteoporosis patients. Recently, the number of osteoporosis patients with ONJ has dramatically increased in Japan. This has contributed to an increase in the number of patients avoiding extractions. However, there has been no prospective study providing definitive incidence data for ONJ in Japanese patients. The purpose of this study was to elucidate the true as well as suspected incidence of ONJ. A total of 3229 subjects (1612 subjects in the minodronic acid group and 1617 subjects in the raloxifene group) in the Japanese Osteoporosis Intervention Trial protocol number 4 participated in this study. ONJ was diagnosed by experienced dentists. Suspected Stage 0 and 1 (bone exposure of the jaw) ONJ was assessed by a structured questionnaire at baseline and at 6, 12, 18, and 24 months. No established ONJ cases were diagnosed during the study. The incidence of suspected Stage 0 and/or Stage 1 ONJ was 6.14 per 1000 patient-years in the minodronic acid group and 3.38 per 1000 patient-years in the raloxifene group [hazard ratio (95% confidence interval) = 1.82 (0.84–3.93), $P = 0.13$]. Approximately 50–60% of bone exposures that appeared during the study had disappeared at the next observation. Although the subjects in this study may have developed a greater interest in the health of the oral cavity, the incidence of ONJ after minodronic acid treatment would be lower than the expected incident rate.

Keywords Osteonecrosis · Jaw · Osteoporosis · Antiresorptives · Bone exposure

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Introduction

In 2003, Marx first presented a new adverse event, avascular necrosis of the jaws, in oncology patients who had taken high-dose intravenous bisphosphonates (BPs) [1]. The following year, Ruggiero et al. found this adverse event in osteoporosis patients who had a history of chronic low-dose BP therapy, and named this condition osteonecrosis of the jaw (ONJ) associated with the use of BP [2]. Subsequently, many studies about bisphosphonate-related ONJ (BRONJ) have been published in both basic and clinical fields to elucidate the pathogenesis of BRONJ. However, the definitive pathogenesis of BRONJ is still debated [3]. This has been a serious limitation in the treatment of osteoporosis. Because it has been reported that osteoporosis patients who take BPs and who undergo surgical dental procedures such as tooth extraction are at high risk of developing BRONJ [4], there is widespread confusion regarding BRONJ among physicians, dentists, and osteoporosis patients throughout Japan. Dentists in Japan have become reluctant to provide dental treatment for osteoporosis patients under BP treatment. In addition to these concerns about BPs, recent reports have proposed that a RANKL inhibitor, denosumab (Dmab), may also be associated with an increased incidence of ONJ [5].

A Japanese position paper regarding BRONJ was first released by the Japanese Society for Bone and Mineral Research (JSBMR) in 2010 [6]. A minor revised version in 2012 added a flow diagram for the discontinuation of BP at the time of minor oral surgery such as extractions. These position papers were developed according to those released by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2009 [7]. However, despite a reduction in the use of BPs in Japan, the number of patients with BRONJ increased markedly after 2009 [8, 9]. This caused concern for dentists and for osteoporosis patients who had been prescribed BPs and contributed to a reluctance to extract teeth without drug discontinuation in osteoporosis patients [10]. The practice of discontinuation of BP before tooth extraction has produced discord between physicians and dentists in Japan [10].

The incidence of BRONJ in patients undergoing treatment for osteoporosis ranges from 0 to 90 per 100,000 patient-years worldwide [3]. However, because there has been no prospective study regarding the incidence of BRONJ in Japan, the true incidence of BRONJ in Japan remains unknown. Bone exposure/necrosis is not always induced by BPs. Bone exposure may occur in the absence of BP therapy, with attendant oral ulceration and bone sequestration (OUBS) [3]. Furthermore, Stage 0 ONJ, in which there is no bone exposure, was added in a Japanese position paper revised in 2016 according to the AAOMS position paper [11]; however, the international ONJ taskforce has expressed concern that the Stage 0 classification may lead to over-diagnosis of ONJ [3]. Over-diagnosis of ONJ could lead to detrimental effects in patients' skeletal health, especially if it results in discontinuation of BP medication. To date, the incidence of suspected Stage 0 ONJ remains unknown in patients on BP therapy. A lack of precise information regarding the incidence of true as well as suspected ONJ may contribute to increased controversy and reduced cooperation between physicians and dentists, as well as an increased number of patients refusing to undergo tooth extractions and to continue BP therapy [10].

Minodronic acid, a Japanese-made bisphosphonate, and raloxifene, a member of the class of selective estrogen receptor modulators (SERMs), have demonstrated their efficacy in fracture prevention [12, 13]. With regard to inhibition of bone resorption, minodronic acid is 10–100 times more effective than alendronic acid. A recent review revealed that the proportion of minodronic acid users was similar to that of alendronate in Japan [14]. Both medications are classified as anti-bone-resorbing agents, although ONJ was observed in osteoporosis patients on BP therapy, but not those on SERM therapy in Japan. The purpose of this study was to elucidate the incidence of true as well as suspected ONJ in osteoporosis patients on BP therapy in a Japanese multicenter, open-label, randomized controlled, head-to-head trial comparing minodronic acid and raloxifene in osteoporosis patients.

Materials and methods

Study protocol and participants

The Japanese Osteoporosis Intervention Trial protocol number 4 (JOINT-04 trial) is a multi-center, open-label, randomized controlled trial in Japan; it is registered at the University Hospital Medical Information Network—Clinical Trials Registry (UMIN-CTR) under trial identification number UMIN000005433. The protocol was approved by the Central Ethical Committee for the Adequate Treatment of Osteoporosis (A-TOP) group (Dr. Rikushi Morita, Chairman) and was reviewed by the institutional review board of each participating institution. The trial was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained prior to patient enrollment after a thorough explanation of the trial objectives, duration (2 years), and procedures. Study design, eligibility criteria, assessment of clinical data, and sample size calculations were described in our recent report [15]. The primary endpoints of JOINT-04 are osteoporotic (vertebral, humeral, femoral, and radial), vertebral, and major osteoporotic (clinical vertebral, humeral, femoral, and radial) fractures.

In addition to the primary endpoint, dental health was followed as one of the secondary endpoints [15]. A total of 3229 subjects (1612 subjects in the minodronic acid group and 1617 subjects in the raloxifene group) finally participated in the study which evaluated the incidence of true as well as suspected ONJ (Fig. 1).

Estimated incidence of ONJ, and determination of ONJ and suspected ONJ cases

The Japanese Society of Oral and Maxillofacial Surgeons (JSOMS) survey of 501 institutions found that approximately 2200 patients undergoing BP treatment for osteoporosis were diagnosed with BRONJ during 2011–2013 [9]. Given that 1.5–2 million osteoporosis patients are prescribed BPs, the incidence of BRONJ is estimated to be 40–50 per 100,000 patient-years. Because the response rate of their survey was 70.3%, the estimated incidence of BRONJ would be as high as 57–71 per 100,000 patient-years if the response rate had been 100%. Additionally, taking into account that there were 923 institutions in Japan that advocated oral and maxillofacial surgery and which ONJ patients were likely to attend for a consultation in 2015, the final estimated incidence of BRONJ was calculated as 105–131 per 100,000 patient-years. This means that at least three to four ONJ patients were likely to appear in the minodronic acid group during the study, although it is likely that this number may be higher because there were approximately 71,400 dental clinics in Japan in 2015.

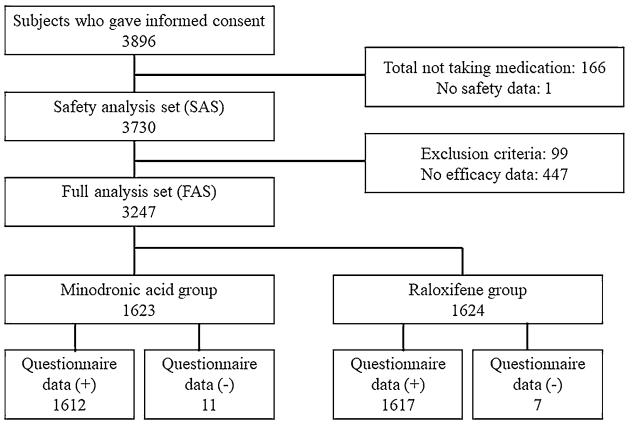

Fig. 1 Subject registration chart showing the number of subjects participating in screening, randomization, questionnaire administration and completion, and discontinuation in this clinical study. The reasons for exclusion were counted multiple times

The incidence of ONJ was determined by experienced dentists during the 2-year study in accordance with the definition of ONJ stated in a Japanese position paper revised in 2016 [16]. Before the study, the participating physicians had explained the possibility of having ONJ during the study to the subjects. Oral health status was assessed using a structured questionnaire with a photograph of bone exposure of the jaw at baseline and at 6, 12, 18, and 24 months after baseline. The content of the questionnaire is shown in Table 1. According to the Japanese position paper revised in 2016 [16], patients at Stage 0 have clinical symptoms such as deep periodontal pockets, loose teeth, oral mucosal ulceration, swelling, abscess formation, trismus, hypoesthesia/numbness of the lower lip, and non-odontogenic pain. However, because some patients provided ambiguous responses in the questionnaire, we defined the presence of clinical symptoms related to questions 8, 9, and 10 (see Table 1) as suspected Stage 0 to reduce the risk of over-diagnosis. We counted one case as a suspected Stage 0 case, although clinical symptoms related to questions 8, 9, and 10 disappeared during the study. We also defined bone exposure of the jaw (question 11) as a suspected Stage 1 case. We did not count cases as suspected Stage 1 if the bone exposure of the jaw disappeared during the study. However, we counted cases

Table 1 Content of the structured questionnaire to assess oral health status

1. How many teeth do you have now?
2. How many of your teeth have been extracted (not counting wisdom teeth)?
3. How many teeth were extracted during the last year (not counting wisdom teeth)?
4. Do you have persistent bleeding, swelling and/or pain in your gums?
5. Do you have any loose teeth?
6. For subjects who have dental implants:
(1) Do you have persistent bleeding, swelling and/or pain in your gums around your dental implants?
(2) Do you have any loose dental implants?
7. Do you have persistent pain caused by rubbing of your dentures?
8. Do you have numbness of the lower lip and lower jaw?
9. Do you have persistent dull pain in the jaws?
10. Do you have persistent pus discharge from an intraoral fistula of your gums?
11. Do you have any bone exposure of the jaw?

A photograph showing bone exposure of the lower jaw was attached to the questionnaire

as suspected Stage 1 if bone exposure of the jaw remained at the final observation at 24 months because we could not continue follow-up of the bone exposure thereafter. If bone exposure of the jaw (question 11) or pus discharge from an intraoral fistula of the gingiva (question 10) persisted beyond 8 weeks during the study, the subjects were referred to experienced dentists, including an oral surgeon, and had a thorough oral and maxillofacial examination to determine the presence of ONJ. Finally, the presence of ONJ of the subjects was confirmed clinically and radiographically by experienced dentist (AT) for ONJ. Subjects who already had suspected Stage 0 and/or Stage 1 at baseline were excluded from the analysis of the incidence of suspected Stage 0 and/or Stage 1 ONJ.

Statistical analysis

Oral health status as evaluated by the questionnaire at baseline was compared between subjects in the minodronic acid and raloxifene groups by *t* test or Fisher's exact test. Clinical symptoms that appeared at least once and were related to questions 8, 9, 10, and 11 were also compared between subjects in both groups by Fisher's exact test during the study period, excluding those at baseline. The incidence of established ONJ or suspected Stage 0 and/or Stage 1 ONJ was calculated using a Poisson regression model. Additionally, the hazard ratio (HR) and 95% confidence interval (CI) in the incidence between subjects in both groups were calculated. All comparisons were two-sided and performed at a $P = 0.05$ level of significance. Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

No established ONJ cases were observed during the 2 years of the study. Oral health status, as evaluated by questionnaire at baseline, was compared between subjects in the minodronic acid and raloxifene groups (Table 2). There were no significant differences between groups in any of the oral health conditions at baseline. There were no significant differences in suspected ONJ cases corresponding to questions 8, 9, 10, and 11 in the questionnaire between subjects in the minodronic acid and raloxifene groups at baseline (Table 2) or during the 2 years of the study (Table 3).

Bone exposure of the jaw that appeared during the study disappeared at the next observation period in seven (58%) of 12 subjects in the minodronic acid group and four (50%) of the eight subjects in the raloxifene group. This indicated that five (0.3%) subjects in the minodronic acid group and four (0.3%) in the raloxifene group had suspected Stage 1 ONJ during the study (Table 4). The person time for each subject was calculated as the time from randomization to the day of the last visit. The incidence of suspected Stage 0 and/or Stage 1 ONJ was 6.14 per 1000 patient-years in the minodronic acid group and 3.38 per 1000 patient-years in the raloxifene group. The HR (95% CI) was 1.82 (0.84–3.93) ($P = 0.13$) (Table 4). The incidence of suspected Stage 0 ONJ was 4.44 per 1000 patient-years in the minodronic acid group and 2.37 per 1000 patient-years in the raloxifene group. The HR (95% CI) was 1.87 (0.75–4.69) ($P = 0.18$). The incidence of suspected Stage 1 ONJ was 1.71 per 1000 patient-years in the minodronic acid group and 1.35 per 1000 patient-years in the raloxifene group. The HR (95% CI) was 1.26 (0.34–4.70) ($P = 0.73$).

Table 2 Difference in oral health status evaluated by questionnaire at baseline between subjects in the minodronic acid and raloxifene groups

	Minodronic acid (1612 subjects)	Raloxifene (1617 subjects)	*P* value
Number of teeth present	13.15 ± 10.45 (1370)	13.31 ± 10.63 (1386)	0.69
Number of teeth extracted last year	2.48 ± 3.71 (187)	2.39 ± 3.42 (185)	0.79
Persistent gingival bleeding, swelling and/or pain (+)	77 (4.8%)	73 (4.5%)	0.74
Loose tooth (+)	123 (7.6%)	111 (6.9%)	0.41
Persistent gingival bleeding, swelling and/or pain around dental implant (+)	2 (0.6%)	6 (1.7%)	0.29
Loose dental implant (+)	4 (1.3%)	2 (0.6%)	0.44
Persistent pain caused by dentures (+)	64 (4.9%)	82 (6.2%)	0.15
Hypoesthesia of the lower lip and jaw (+)	15 (0.9%)	13 (0.8%)	0.85
Persistent dull pain in the jaw (+)	6 (0.4%)	5 (0.3%)	1.00
Persistent discharge of pus from the gingiva (+)	6 (0.4%)	5 (0.3%)	1.00
Bone exposure of the jaw (+)	11 (0.7%)	6 (0.4%)	0.33

Mean ± SD or number of subjects. Brackets show the number of all subjects who answered each question or % subjects for all subjects who answered the question

Table 3 Difference in oral health status evaluated by questionnaire during the study between subjects in the minodronic acid and raloxifene groups who did not have these conditions at baseline

	Minodronic acid		Raloxifene		*P* value
	Yes	No	Yes	No	
Hypoesthesia of the lower lip and jaw	13 (0.81%)	1595 (99.19%)	10 (0.62%)	1601 (99.38%)	0.54
Persistent dull pain in the jaw	16 (1.00%)	1601 (99.00%)	11 (0.68%)	1608 (99.32%)	0.34
Persistent discharge of pus from the gingiva	6 (0.37%)	1600 (99.63%)	5 (0.31%)	1607 (99.69%)	0.77
Bone exposure of the jaw	12 (0.75%)	1598 (99.25%)	8 (0.50%)	1603 (99.50%)	0.38

Number of subjects. Brackets show % subjects for all subjects who answered the question

Table 4 Incidence of suspected Stage 0 and 1 osteonecrosis of the jaw in the minodronic acid and raloxifene groups, and hazard ratios between them

	Yes	No	Incidence (1000 patient-years)	HR	95% CI	*P* value
Stage 0 and 1						
Minodronic acid	18 (1.1%)	1560 (98.9%)	6.14	1.82	0.84–3.93	0.13
Raloxifene	10 (0.6%)	1582 (99.4%)	3.38			
Stage 0						
Minodronic acid	13 (0.8%)	1565 (99.2%)	4.44	1.87	0.75–4.69	0.18
Raloxifene	7 (0.4%)	1585 (99.6%)	2.37			
Stage 1						
Minodronic acid	5 (0.3%)	1573 (99.7%)	1.71	1.26	0.34–4.70	0.73
Raloxifene	4 (0.3%)	1588 (99.7%)	1.35			

Number of subjects. Bracket shows % subjects for all subjects who answered the question

HR Hazard ratio, *CI* Confidence interval

Discussion

This is the first prospective study that has focused on the incidence of true as well as suspected ONJ in Japan. Before the study, we estimated that at least three to four cases of BRONJ may appear in the minodronic acid group during the study. However, no established ONJ was diagnosed in this group in our study. Although the short observation period (2 years) may have contributed to this result, it has been reported that the time to onset of BRONJ in patients prescribed minodronic acid ranged from 196 days to 742 days with a median of 432 days [17]. Additionally, in the recent Japanese multicenter retrospective study regarding BRONJ by oral surgeons, there was no significant difference in the prevalence of BRONJ between the duration of oral BP administration more and less than 3 years ($P = 0.142$) and between more and less than 4 years ($P = 0.319$) [18].

The incidence of suspected Stage 0 ONJ was relatively high (6.14 per 1000 patient-years) in the minodronic acid group in our study. However, there was no significant difference in the incidence of suspected Stage 0 ONJ between subjects in the minodronic acid and raloxifene groups, implying that the definition of Stage 0 may result in over-diagnosis of ONJ. Bedogni et al. reported that the AAOMS staging system including Stage 0 does not correctly identify the extent of bony disease in patients with ONJ, even if advanced imaging modalities such as computed tomography are used [19].

There was no significant difference in the prevalence of suspected Stage 1 ONJ between subjects in the minodronic acid and raloxifene groups at baseline. Subjects who had taken BPs within the previous 6 months were excluded from this study [15], and it is unlikely that previous BP treatment more than 6 months prior to the study would have contributed to the occurrence of suspected Stage 1 ONJ at baseline. Kwon et al. indicated in their case–control study that the adjusted odds ratios for the presence of BRONJ in past BP users (non-cancer) and current continuous BP users (non-cancer) were 1.26 (95% CI 0.54–2.96) and 3.87 (95% CI 2.27–6.58), respectively, when compared with non-BP users [20].

A new finding of this study was that approximately 50–60% of bone exposures of the jaw that appeared during the study had disappeared at the next observation. As in suspected Stage 0 ONJ, the definition of Stage 1 ONJ may include many misdiagnoses. Generally, in the patients who were diagnosed as having ONJ, the treatment of osteoporosis had been stopped in accordance with the

ONJ position paper released by JSBMR in 2010. We did not know whether subjects who had bone exposure had any treatment. However, there were no subjects who had discontinued osteoporotic treatment, suggesting that there were no subjects with established ONJ. We calculated the incidence of suspected Stage 1 cases in this study using the number of patients with bone exposures that could not be re-assessed at the end of the study; these cases also may have disappeared after the last observation of the study, resulting in the incidence of 0 per 1000 patient-years. Bone exposure had continued from 12 to 24 months observation only in 1 subject aged 73-years-old. She had no gingival bleeding, swelling, pain, and tooth mobility. She had numbness of the lower lip and lower jaw at 24 months. It is likely that she may have established Stage 1 ONJ; however, she belonged to the raloxifene group.

There are limitations in this study. The estimated incidence of BRONJ in Japan was 105–131 per 100,000 patient-years based on the data from the JSOMS report [9], but the incidence of established BRONJ was 0 per 1000 patient-years in our current study. Because all subjects voluntarily participated in this study, it is possible that they were interested in their general health as well as their dental health. Recent studies have demonstrated the usefulness of maintaining oral health to reduce the risk of ONJ in oncology patients [21, 22]. It is likely that the incidence of ONJ may differ between osteoporosis subjects with and without an interest in their general health. Additionally, because subjects were asked about their oral health status using the questionnaire at baseline and at 6, 12, 18, and 24 months, they may have developed a greater interest in the health of the oral cavity.

The fact that the incidence of BRONJ induced by minodronic acid among intravenous or oral BP users in 2004–2014 was the lowest among all BPs in Japan may have influenced our results [17]. However, with regard to inhibition of bone resorption, minodronic acid is 10–100 times more effective than alendronic acid. In addition, in our study, mean medication possession ratio (MPR) was estimated to be approximately 83% and 85% at 6 months and 74–78% at 2 years in the minodronic acid and the raloxifene groups, respectively (unpublished data). Eiken et al. recently described that adherent users (MPR > 50%) were at two to threefold increased risk of ONJ compared to low adherence (MPR < 50%) [23]. These imply the possibility that increased risk of ONJ may be expected in our prospective study. Furthermore, 239 teeth from 101 subjects were extracted during the first year, and 231 teeth from 110 subjects were extracted between the first and second year in the minodronic acid group in this study. Because tooth extraction largely increases the risk for developing ONJ [3, 9, 24], it is possible that more patients with established ONJ might have appeared in our study.

This study was conducted during the short follow-up period (2 years) only for minodronic acid. The results of our study were limited to monodronic acid. It also is possible that longer follow-up period more than 2 years may influence the results. Additionally, in this study, there was lack of data demonstrating balance between efficacy (fracture prevention) and safety (ONJ).

No established ONJ cases were confirmed during the JOINT-04 study. The incidence of suspected Stage 0 and/or Stage 1 ONJ cases was 6.14 per 1000 patient-years in the minodronic acid group, but no significant difference in incidence was observed between the minodronic acid and raloxifene groups. Approximately 50–60% of bone exposures that appeared during the study had disappeared at the next observation. The definition of Stage 0/1 ONJ may result in many misdiagnoses. This is the first prospective study to focus on the incidence of true as well as suspected ONJ in Japanese patients. The incidence of ONJ among Japanese patients is estimated to be substantially lower than that expected from previous studies.

Acknowledgements The authors express their thanks to the chairman, Dr Rikushi Morita, and the members of the ethics committee, Ms Mamiko Matsumura, Dr Tetsuro Inoue, Dr Isao Yoshimura, Dr Mitsuyoshi Nakajima, Tooru Ebihara RPh, and Mr Shinya Hattori. The authors would also like to thank those who participated as clinical investigators in JOINT-04. This JOINT study was sponsored by the Public Health Research Foundation. This study was also supported in part by funding from the Project Promoting Clinical Trials for Development of New Drugs (17lk0201061h0002) from the AMED (Japan Agency for Medical Research and Development) to ST. We thank Helen Jeays, BDSc AE, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Compliance with ethical standards

Conflict of interest AT received consultancy or lecture fees from Asahikasei Pharmaceutical Co., Teijin Pharma, Ono Pharmaceutical Co., Chugai Pharmaceutical Co., Takeda Pharmaceutical Co., and Daiichi Sankyo Co. YU received a consultancy fee from Teijin Pharma. ST has received lecture fees from Astra-Zeneca, Taiho, and Ono Pharmaceutical Co. He has received consultation fees from DeNA Life Science and CanBus. He has received outsourcing fees from Satt and Asahi Kasei Pharma. His wife has been engaged in a research project for Bayer. HO received fees from Pfizer Japan Inc. TS has received research grants from Astellas Pharma, Eisai, Daiichi Sankyo, Chugai Pharmaceutical, and Eli Lilly Japan as well as consulting and/or lecture fees from Asahi Kasei Pharma and Daiichi Sankyo. SS received lecture and consultancy fees from Asahikasei Pharmaceutical Co., Astellas Pharma, Chugai Pharmaceutical Co., Daiichi Sankyo Co., Eisai Co., Eli Lilly Japan, Ono Pharmaceutical Co., Pfizer Co., and Takeda Pharmaceutical Co. MS received lecture and consultancy fees from Asahikasei Pharma and Teijin Pharma. TI, TN, and HO declare that they have no conflict of interest.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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