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Matrix-associated stem cell transplantation (MAST) in chondral defects of the 1st metatarsophalangeal joint is safe and effective—2-year-follow-up in 20 patients

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ABSTRACT

The aim of the study was to assess the 2-year-follow-up of matrix-associated stem cell transplantation (MAST) in chondral defects of the 1st metatarsophalangeal joint (MTPJ).

In a prospective consecutive non-controlled clinical follow-up study, 20 patients with 25 chondral defect at the 1st MTPJ that were treated with MAST from October 1st, 2011 to March, 30th, 2013 were analysed. The size and location of the chondral defects range of motion (ROM), and the Visual-Analogue-Scale Foot and Ankle (VAS FA) before treatment and at follow-up were registered.

Stem cell-rich blood was harvested from the ipsilateral pelvic bone marrow and centrifuged (10 min, 1500 RPM). The supernatant was used to impregnate a collagen I/III matrix (Chondro-Guide). The matrix was fixed into the chondral defect with fibrin glue.

The age of the patients was 42 years on average (range, 35–62 years). The VAS FA before surgery was 50.5 (range, 18.3–78.4). The defects were located as follows, dorsal metatarsal head, $n = 12$, plantar metatarsal head, $n = 5$, dorsal & plantar, $n = 8$ (two defects, $n = 5$). The defect size was 0.7 cm^2 (range, .5–2.5 cm^2). ROM was 10.3/0/18.8° (dorsal extension/plantar flexion). All patients completed 2-year-follow-up. VAS FA improved to 91.5 (range, 74.2–100; *t*-test, $p < .01$). ROM improved to 34.5/0/25.5 ($p = .05$).

The surgical treatment including MAST led to improved clinical scores and ROM. Even though a control group is missing, we conclude that MAST is a safe and effective method for the treatment of chondral defects of the 1st MTPJ.

1. Introduction

The optimal treatment for chondral defects at foot and ankle is debatable. The current options are distraction, debridement, abrasion, microfracture, antegrade or retrograde drilling, mosaicplasty or osteochondral autograft transfer system (OATS), autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), autologous matrix-induced chondrogenesis (AMIC), allologous stem cell transplantation, allograft bone/cartilage transplantation, or matrix-associated stem cell transplantation (MAST) [1–11]. MAST was described as a modification of AMIC with a potentially higher concentration of stem cells in the implanted matrix, and also as a completely new method [3,12]. Most of these methods have been used for chondral defects at the ankle [3]. MAST was also used for the 1st metatarsophalangeal joint (MTPJ) with encouraging initial results [3]. The aim of the study was to assess the 2-year-follow-up of MAST in chondral defects of the 1st MTPJ.

2. Methods

2.1. Technique

MAST was performed as single open procedure associated with other procedures. The other procedures included the standard joint preserving surgical management for hallux rigidus like cheilectomy, synovectomy, arthrolysis and tenolysis [13–15]. Stem cell-rich blood was harvested during the procedure from the ipsilateral pelvic bone marrow with a Jamshidi needle (10 × 3 mm, Cardinal,

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Dublin, OH, USA) and a special syringe (Arthrex-ACP®, Arthrex, Naples, FL, USA) through a stab incision. The syringe was centrifuged (10 min, 1500 rotations per minute). The supernatant was used to impregnate a collagen I/III matrix (Chondro-Guide®, Geistlich, Baden-Baden, Germany) that was cut to the size of the cartilage defect before. The cartilage defect was debrided until stable surrounding cartilage was present. Microfracturing with a 1.6 mm Kirschner wire was performed. The matrix with stem cells was fixed into the chondral defect with fibrin glue (Tissucoll, Deerfield, IL, USA). An 8Ch drainage was inserted without suction. Closure was performed following the local standard with layer wise closure (joint capsule, subcutaneous, skin). The postoperative treatment included full weight bearing without orthosis or splint. Motion of the joint with MAST was restricted for two days, and physiotherapy with motion of this joint was started at day three after surgery. The patients were instructed to perform motion of the joints with MAST 10 times a day for 10 min. Postoperative consultations were performed at 6 weeks, 3, 12 and 24 months. Figs. 1–3 show a typical case.

2.2. Study design

In a prospective consecutive non-controlled clinical follow-up study, 20 patients with 25 chondral defect at the 1st MTPJ that were treated with MAST from October 1st, 2011 to March, 30th, 2013 were analysed. The single inclusion criteria for the study was the described procedure. Patients with bilateral treatment ($n = 15$) or with corrective osteotomies for hallux valgus correction or others ($n = 57$) were excluded. No other exclusion criteria were defined. Range of motion (ROM) was measured clinically with a goniometer. All patients had radiographs (bilateral views (dorso-plantar and lateral) full weight bearing). The degenerative changes were classified in four degrees [13]. Pedography was performed as described below. There were no limitations in terms of patient's age and defect size. There was no clear and objective definition regarding the combination of defect size, location and age. The indication for the procedure was based on patient history, clinical investigation and radiographic findings (Stage 1–3) [13]. Stage 4 was considered as contraindication for the procedure. Visual Analogue Scale Foot and Ankle (VAS FA) was registered [16,17]. The defect size and location was assessed intraoperatively. The defects were classified as dorsal when located above a virtual horizontal line at 50% of the metatarsal head height or diameter; plantar when located below that line, or both when crossing the line. The following parameters were registered at 2-year-follow-up: VAS FA, ROM, radiographic hallux rigidus stage and pedographic parameters.

2.3. Pedography

Standard dynamic pedography (three trials, walking, third step, mid stance force pattern) was performed as described before [18–20]. A standard platform (Emed AT®, Novel Inc., Munich, Germany & St. Paul, MN, USA) and software (Emed ST®, version 12.3.18, Novel Inc., Munich, Germany & St. Paul, MN, USA) was used. Both sides were measured. Computerised mapping to create a distribution into the following foot regions was performed with the standard software (Automask, version 12.3.18, Novel Inc., Munich, Germany & St. Paul, MN, USA): hindfoot, midfoot, 1st metatarsal head, 2nd metatarsal head, 3rd metatarsal head, 4th metatarsal head, 5th metatarsal head, 1st toe, 2nd toe, 3rd–5th toe. This mapping process does not include manual determination of landmarks [21]. Parameters of 1st metatarsal head and 1st toe were compared preoperative versus follow-up [20].

A paired t-test was used for statistical comparison of VAS FA and maximum pedographic pressures preoperatively and at follow-up, and a Chi2-test for all other parameters. Before using the paired t-test, the data were investigated regarding the distribution and the data were proven to be normally distributed.

3. Results

Twenty patients with 25 defects were included in the study. The age at the time of surgery was 42 years on average (range, 35–62 years), 14 (70%) were male. The VAS FA before surgery was 50.5 on average (range, 18.3–78.4). In 12 cases (60%), the right foot was affected. Table 1 shows the radiographic hallux rigidus stage. The most common stage was 2 ($n = 9$, 45%). Mean ROM was

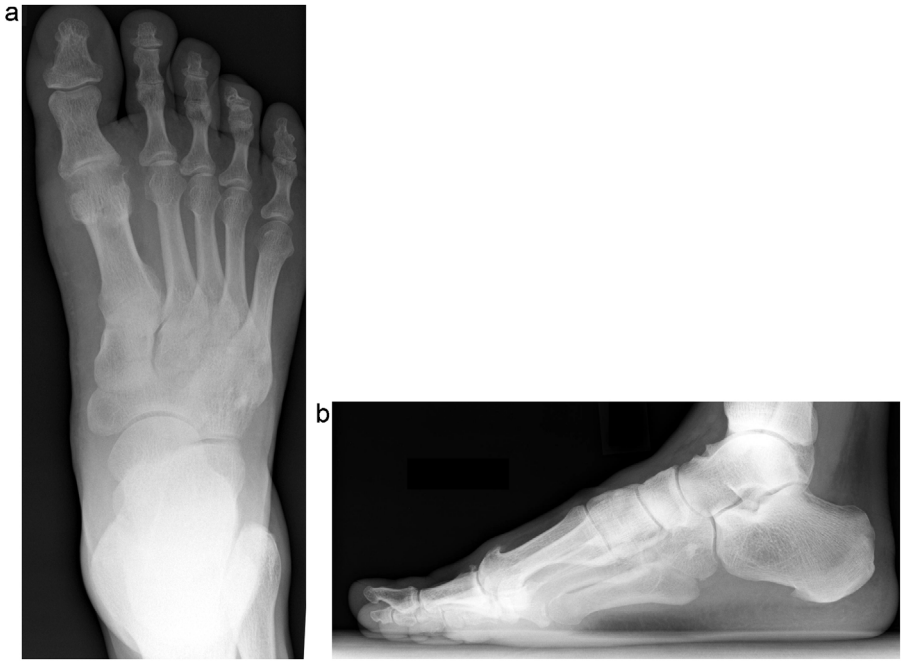

Fig. 1. (a and b) Case with hallux rigidus stage 2. 45-year-old female; VAS FA 56.2; ROM dorsal extension/plantar flexion 10/0/20°.

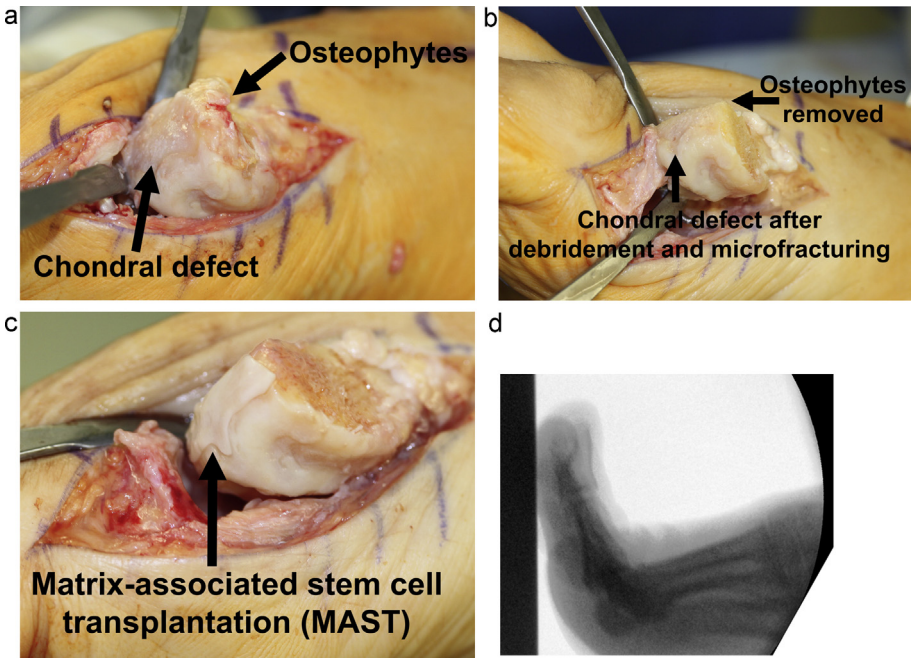

Fig. 2. (a–d) Hallux rigidus stage 2 (same case as Fig. 1) with typical dorsal osteophytes and dorsally located chondral defect (1 × 2 cm = 2 cm^2; (a)). Subpart b shows the situs after removal of the osteophytes (medial and cheilectomy), debridement of the chondral defect and microfracturing. Subpart c shows the implanted MAST. Subpart d shows a lateral intraoperative fluoroscopic image with possible 90° dorsal extension in the MTPJ.

10.3/0/18.8° for dorsal extension/plantar flexion. Table 2 shows the pedographic parameters. The maximum pressure was 237.7 kPA at the MTPJ and 807.1 kPa at the 1st toe on average. The defects were located as follows, dorsal metatarsal head, $n = 12$, plantar metatarsal head, $n = 5$, dorsal & plantar, $n = 8$ (two defects, $n = 5$). The defect size was 0.7 cm^2 (range, .5–2.5 cm^2). No complications or consecutive surgeries were registered until follow-up, i.e. no patient was converted to fusion or total joint replacement. All patients completed 2-year-follow-up. VAS FA improved to 91.5 (range, 74.2–100; *t*-test, $p < .01$). ROM improved to 34.5/0/25.5 (dorsal extension & plantar flexion, $p < .01$). The radiographic hallux rigidus stage decreased (Chi2-test, $p < .01$) Stage 2 was the most common preoperatively, and stage 1 at 2-year-follow-up (Table 1). The maximum pressure and the percentage of maximum force of the maximum force of the entire foot increased at the 1st MTPJ and decreased at

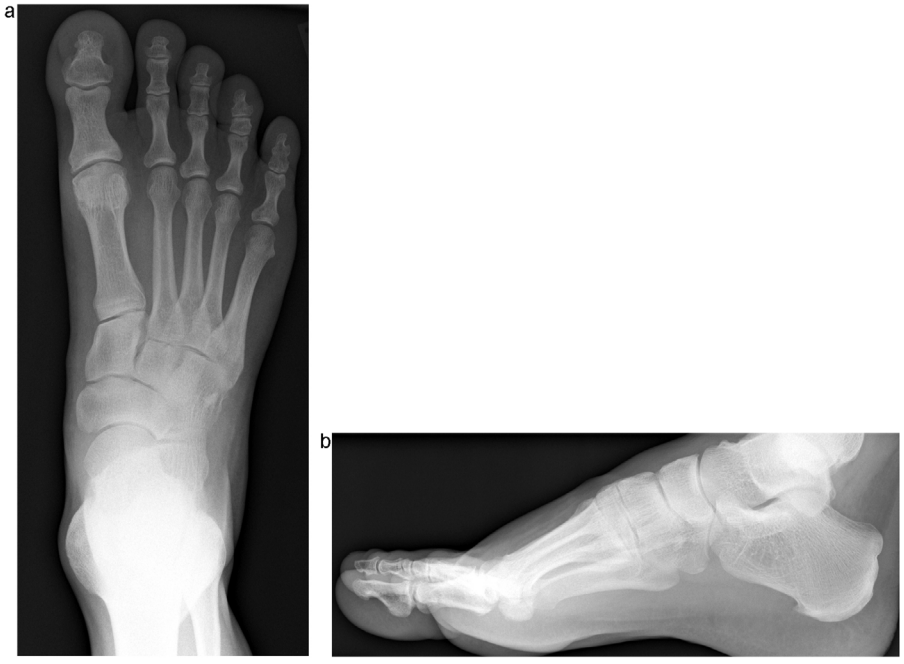

Fig. 3. (a and b) Case with preoperative hallux rigidus stage 2 at two-year-follow-up (same case as Figs. 1 and 2). 47-year-old female; VAS FA 92.4; ROM dorsal extension/plantar flexion 40/0/30°. Hallux rigidus stage was classified 0 at follow-up.

Table 1
Radiographic hallux rigidus stage preoperatively and at 2-year-follow-up.

Stage	Preoperatively	2-year-follow-up
0	0	5 (25%)
1	5 (25%)	8 (40%)
2	9 (45%)	6 (30%)
3	6 (30%)	1 (5%)
4	0	0

the 1st toe (Table 2, all $p < .01$) when comparing preoperative with 2-years-follow-up.

4. Discussion

Cheilectomy, synovectomy, arthrolysis and tenolysis are the standard procedure for joint preserving surgery in hallux rigidus [13–15,22]. These studies have shown good but not optimal results [14,15,22]. Reasons for suboptimal results were remaining pain and functional restrictions [14,15,22]. Later conversion to arthrodesis were described in up to 16% in the short- to midterm follow-up [22]. As attempt to improve the outcome, we added MAST for the chondral defect(s) based on our previous experience with MAST and hallux rigidus surgery [3]. Despite many studies focused on treatment of cartilage defects at the ankle, no such methods were utilised for the MTPJ so far [3]. Furthermore, the use of these methods in other joints of the foot have not been described so far [3]. Very recently, one study dealing with implantation of synthetic cartilage in the 1st MTPJ was published showing good results [23].

4.1. Technical issues

We consider MAST as a combination of stem cell transplantation and AMIC [3]. An almost similar method was introduced for the ankle as completely novel method [12]. The advantage in comparison with AMIC which uses peripheral blood is the higher concentration of pluripotent cells or stem cells. No one knows the exact concentration of stem cells which varies for different age and location [3,24]. Rough estimations name 0.1% stem cells as concentration in the peripheral blood and 3% in the pelvic bone marrow in young adults [3,24,25]. This deduces that the cells should be harvested from the pelvic bone marrow which is part of MAST [3]. Centrifugation is a useful method to double the concentration of the cells, and the MAST includes a typical centrifugation (1500 RPM for 10 min) that potentially doubles the concentration of stem cells in the supernatant to 6% [3]. As in MACI, MAST uses a carrier or scaffold for the cells [3]. Different scaffold are available, some with hyaluronic acid, and others with collagen [3]. The introduced method includes a collagen matrix (Chondro-Guide®, Geistlich, Baden-Baden, Germany) [3]. This scaffold is manufactured out of denaturated collagen from the pig, and contains collagen I and III. The matrix has two layers (bilayer). The superficial layer is water proof, and the deep layer is porous [3]. The superficial, water proof layer should maintain the cell fluid in the defect, and the deep, porous layer should contain and maintain the cells, and should integrate in part with the underlying subchondral bone [3]. The microfracturing is added to add cells and supply from the underlying bone (marrow), as use in microfracture alone [3]. The fibrin glue is added to give sufficient initial stability for early functional after treatment [3]. Our strategy is to fit the matrix as exact and as stable as possible [3]. The main advantage of MAST in comparison with ACI and MACI is the single procedure methodology and lower cost [3]. The advantage in comparison with AMIC is the potential higher concentration of stem cells [3]. The advantage of the Chondro-Guide® in comparison with other scaffolds/matrices used (hyaluronic acid) is the more physiological content and structure [3]. This matrix gives the initial stability to allow the early stimulation of the transplanted cells by motion which induces the determination of the transplanted stem cells into chondrocytes [3]. Furthermore, it gives the collagen scaffold which seems to be extremely difficult to determine from stem cells by an in vivo stimulation [3].

Table 2
Pedographic parameters preoperatively and at 2-year-follow-up.

Parameter	Preoperatively Mean (range)	2-year-follow-up Mean (range)	Test p
MTPJ, percentage maximum force of entire foot (%)	29	67.9	Chi2
	3–67	45–86	<.01
MTPJ, maximum pressure (kPa)	237.7	777.1	t-test
	29–763	456–987	<.01
1st toe, percentage maximum force of entire foot (%)	87.6	18.6	Chi2
	45–100	12–45	<.01
1st toe, maximum pressure (kPa)	870.1	245.4	t-test
	734–987	38–753	<.01

MTPJ, 1st metatarsophalangeal joint. The individual percentages of the maximum force of the entire force represent the percentage of the maximum force measured in the in the corresponding area (MTPJ or 1st toe) of the maximum force of the entire force (100% means that the maximum force of the corresponding area is similar to the maximum force of the entire foot). The individual maximum pressure values represent the mean values of the maximum pressure measured in the three different trial in the corresponding area (MTPJ or 1st toe).

4.2. Outcome

Our results are favourable and no adverse effects have been registered. The scores improved, ROM increased, and the pedographic parameters were normalised. This is the first study including validated functional investigation based on pedography as far as we are aware, and improvement of the investigated function (gait stance phase) was shown. The radiographic hallux rigidus stage as proposed by Shereff was decreased at follow-up when compared with the preoperative stage [13]. This classification is based on radiographs, and is focused on extent of osteophytes and joint space. It is not surprising at all that removal of osteophytes and cheilectomy changes the extend of osteophytes which is part of the classification. However, the width of the joints space which is also part of the classification was also changed, i.e. widened on average at 2-year-follow-up (example Figs. 1 and 3). We think that the MAST procedure and not the osteophyte removal/cheilectomy is the reason for the joint space widening. The widening of joint space after implantation of "scaffold and cells" was not described for the ankle, 1st MTPJ and other joints before as far as we know. The used classification does not give any direct information about the cartilage as such as sufficient MRI with thin slice thickness could give. We would be extremely interested in histological specimens of the transplants. However, no patient was undertaken surgery again so far in which histological specimens could have been harvested. Earlier histological assessment from specimens from the talus gave anecdotal but clear evidence that the transplanted cells could develop or better determine into chondrocytes, and that the implanted collagen matrix stayed in place and acts as a scaffold for the chondrocytes as in "real" cartilage [3].

Only one of the above mentioned studies dealing with cartilage restoration addressed the 1st MTPJ, and none included a validated outcome score which makes a comparison with our results difficult from a scientific point of view [23]. The single study addressing the 1st MTPJ compared implantation of "synthetic cartilage" with arthrodesis, and the conclusion of the study was that implantation

of "synthetic cartilage" and arthrodesis were equivalent. When comparing length and rate of follow-up, our results have the same typical 2-year-follow-up with a 100% follow-up rate [23]. The score based results seem to be comparable based on the fact that different scores were used [23]. Regarding functional assessment, we would again like to point out that this is the first investigation including validated pedographic parameters. We registered improvement of function, i.e. pressure/force distribution in the gait stance phase which was not shown by the above mentioned study. Our results seem to be better than with cheilectomy alone which was the main goal of the introduced method [14,15,22]. Especially, improvement of validated score, validated functional assessment and low conversion rate to arthrodesis (0%) is superior to previously reported results of cheilectomy alone [14,15,22].

4.3. Limitations

Limitations of the study are: small patient number, unclear indication for treatment, associated procedures, no control group, short follow-up, and missing outcome parameter for the created tissue. All patients with corrective osteotomies at the forefoot and combination with MAST at the 1st MTPJ were excluded from the study because we wanted to exclude any effect of a correction on the result. More patients ($n = 57$) were excluded from the study due to corrective osteotomies than patients ($n = 20$) included without corrective osteotomies. Furthermore patients with bilateral treatment ($n = 15$) were excluded comprising almost as many patients as included with unilateral treatment ($n = 20$).

A missing control group is always a methodological shortcoming as in many other studies that we cannot invalidate. The follow-up time of 2 years for a modified or new technique seems appropriate. Nevertheless a longer follow-up would be desirable. When indicating MAST, we did not follow a clear and objective definition regarding the combination of defect size, location and age. The indication was finally made intraoperatively and subjectively by the surgeon. Regarding assessment of the created tissue, we did not obtain histological specimens which would be optimal from a scientific point of view. Giannini et al. suggested to use special MRI protocols (T2) for the ankle for evaluation of the tissue at follow-up and created a score from that [26]. They suggested that an integration of both T2 mapping and Magnetic Resonance Observation of Cartilage Repair scoring permitted adequate evaluation of the repair site in the ankle [26]. Based on our experience regarding MRI based assessment of chondral lesions at the ankle, we would like to discuss the diagnostic value of MRI for chondral defects even if we did not investigate the imaging as such. In our earlier study, we noticed a high incoherence between MRI findings and intraoperative (arthroscopic) findings when focusing on the cartilage and not on the subchondral bone situation at the ankle [3]. This was also described earlier and for other joints [27–30]. So it seems clear that MRI is able to detect subchondral bone abnormalities but it is much less clear why the investigation of the cartilage is not optimal [30,31]. After having changed from "standard" MRI imaging with slice thickness of 3 mm to so-called "Cartilage-mapping" with slice thickness of 0.4 mm, we immediately realised the reason is simply technical. The normal cartilage thickness at the ankle is around 1 mm, and the same is true for the 1st MTPJ. Using an investigating method with a larger slice thickness ("standard" MRI with 3 mm slice thickness) is technically not able to correctly picture cartilage. The created pictures show a full image but the displayed structures between the slices are calculated means from the neighbouring slices. This might be sufficient for subchondral bone structure with a diameter of 3 mm or more but not for cartilage with thickness of less than 2 mm. When we obtained "slices" of 0.4 mm from the ankle after modifying the MRI at our institution, we immediately noticed the difference. The cartilage was clearly pictured. Furthermore, fluid content could be measured and displayed. Even lacking a scientific investigation, the qualitative interpretation of changed MRI methods with smaller slice thickness implies that the modified technique is much better. We conclude that only MRI with slice thickness of 1 mm or less is able to correctly picture ankle cartilage. Based on our conclusion, we did not include MRI findings in because MRI with sufficient technical specifications (thin slice thickness) was not available at our institution for the entire follow-up period. Therefore, we used our validated score as principal outcome parameter and not MRI findings [17].

In conclusion, surgical treatment including MAST led to improved clinical scores, ROM, pedographic parameters and decreased radiographic hallux rigidus stage. Even though a control group is missing, we conclude that MAST is a safe and effective method for the treatment of chondral defects of the 1st MTPJ.

Conflict of interest

None of the authors or the authorś institution received funding in relation to this study.

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