Is sarcopenia a missed factor in the management of patients with metastatic breast cancer?

Elise Deluche*a, Denis Lachatreb, Mario Di Palmac, Hélène Simon, Valentin Tissote, Damien Vansteene, Philippe Meingan, Alexis Mohebi, Grégory Lencznerr, Francois Pigneuri, Francois Goldwasser, Bruno Raynard, the SCAN Study Group

*Department of Medical Oncology, Limoges University Hospital, Limoges, France
bDepartment of Radiology, Limoges University Hospital, Limoges, France
cMedical Oncology, Gustave Roussy Cancer Campus, Paris Saclay University, Villejuif, France
dDepartment of Medical Oncology, Morvan Hospital, Brest, France
eDepartment of Radiology, Morvan Hospital, Brest, France
fDepartment of Medical Oncology, Institut de Cancérologie de l'Ouest Pays de la Loire, Nantes, Saint Herblain, France
gDepartment of Radiology, Institut de Cancérologie de l'Ouest Pays de la Loire, Nantes, Saint Herblain, France
hDepartment of Radiology, RPO, Institut du sein Henri Hartmann, Neuilly-sur-Seine, France
iDepartment of Radiology, Henri Mondor University Hospitals, AP-HP, Créteil, France
jDepartment of Medical Oncology, Cochin Hospital, AP-HP, CARPEM, Paris Descartes University, Paris, France
kTransversal Unit of Dietetics and Nutrition, Gustave-Roussy, Villejuif, France

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A B S T R A C T
Background: Sarcopenia has emerged as an important parameter to predict outcomes and treatment toxicity. However, limited data are available to assess sarcopenia prevalence in metastatic breast cancer and to evaluate its management.

Methods: The SCAN study was a cross-sectional multicenter French study that aimed to estimate sarcopenia prevalence in a real-life sample of metastatic cancer patients. Sarcopenia was identified by low muscle mass (estimated from the skeletal muscle index at the third lumbar, via computed tomography) and low muscle strength (defined by handgrip strength). Three populations were distinguished based on EWGSOP criteria: a sarcopenic group with low muscle mass AND strength, a pre-sarcopenic group with low muscle mass OR strength and a normal group with high muscle mass AND strength.

Results: Among 766 included patients, 139 patients with breast cancer and median age of 61.2 years (29.9 – 97.8 years) were evaluable; 29.5% were sarcopenic and 41.0% were pre-sarcopenic. Sarcopenic patients were older ($P < 0.01$), had a worse PS-score ($P < 0.05$), and a higher number of metastatic sites ($P < 0.01$), the majority being hepatic and bone. A moderate agreement between the oncologist’s diagnosis and sarcopenia evaluation by muscle mass and strength was recognized (Cohen’s kappa = 0.45). No associations were found between sarcopenia and adverse event occurrence in the 12 patients for whom these were reported. Sarcopenic patients were underdiagnosed and nutritional care and physical activity were less proposed.

Conclusion: It is necessary to evaluate sarcopenia due to its impact on patient prognosis, and its utility in guiding patient management in metastatic breast cancer.

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1. Introduction

While being overweight and obese were shown to be strong risk factors for breast cancer [1], the relationship between body mass index (BMI) and metastatic breast cancer (MBC) survival is still in a debate [2–5]. We recently showed in UNICANCER Epidemiology-Strategy-Medical-Economical-MBC national cohort that...
overweight and obesity are not associated with poorer outcomes in MBC, while underweight appears as an independent adverse prognostic factor [6]. A way to improve the identification of patients at risk of death could be to analyze body composition instead of BMI. Prado et al. were the first to demonstrate the utility of body composition (BC) analysis on survival and treatment toxicities in cancers [7]. Since then, it has emerged as predictive factor of survival outcomes and toxicity in different type of cancers [8,9].

Computed tomography (CT) for the evaluation of BC has been validated, and a major advantage is that it could allow BC assessment simultaneously with tumor staging, monitoring and tumor response evaluation [10]. Sarcopenia has emerged as an interesting parameter for the assessment of BC features and the European Working Group on sarcopenia defined it as a progressive and generalized loss of skeletal muscle mass and strength, that may increase the risk of adverse outcomes [11].

Previous reports have highlighted that sarcopenia affects the efficacy and toxicity of chemotherapy in patients with non-metastatic [12,13] and metastatic breast cancers [14,15]. Sarcopenia was also associated with negative prognosis in adjuvant and metastatic breast cancers [16-18]. However, no data are available to assess the sarcopenia prevalence in MBC according to international consensus (including both low muscle mass with low muscle strength or performance) [19] and only one prospective study was conducted but with a small population of 55 [15].

The SCAN study is the first prospective investigation to measure sarcopenia (including both low muscle mass with low muscle strength) prevalence in a large group of real-life metastatic cancer patients, using CT-scan, biologic and anthropometric measurements. Other aims were to assess the impact and management of sarcopenia in real-life. Only results of breast cancer cohort are presented in this article.

2. Material and methods

2.1. Study design and patients

This cross-sectional study was performed in 29 private and public hospitals in France between September and October 2017. Patients were included if they were 18 years or older, had a confirmed diagnosis of metastatic lung, prostate, breast, colon, or kidney cancer, were undergoing chemotherapy, targeted therapy or hormonotherapy that was initiated since at least one cycle of treatment or for at least one month, irrespective of the line of ongoing treatment. Patients had a CT scan performed (for any reason) between 6 weeks before or 4 weeks after the inclusion study and included an L3 cross-section suitable for SMI evaluation of low muscle mass (Fig. 1). More details are available in the main publication [20]. In this present study, we present only the data from the breast cancer cohort.

2.2. Assessments and procedures

2.2.1. Clinical and biological characteristics

Oncologists, who were blinded to the CT-scan results, recorded information on clinical, demographic and pathological characteristics, treatments and toxicities, nutritional status and management, physical activity, food intake, biological data and anthropometric measures.

BMI was used to describe underweight, normal weight, overweight and obesity thresholds, as per the World Health Organization guidelines [21]. Weight prior to cancer diagnosis, at the study visit and at 1 and 6 months prior to the visit was also collected. Malnutrition was defined as weight loss >10% in 6 months, weight loss >5% in 1 month, BMI \(< 18.5\) kg/m² or \(< 21\) kg/m² if patients were 70 years old and older or serum albumin \(< 30\) g/l or \(< 35\) g/l if patients were 70 years old and older [22].

The mid-upper arm circumference (MUAC), thigh circumference and quadriceps atrophy was assessed by the oncologist. Muscle strength was assessed by handgrip strength of the dominant arm and quadriceps atrophy was assessed by the oncologist. Muscle strength was assessed by handgrip strength of the dominant arm was measured using a JAMAR hydraulic hand dynamometer [20].

2.2.2. CT scan imaging

Radiologists were trained by a radiologist member of the SCAN study scientific committee in the measurement of the L3 total muscular surface area (TMS, cm²) using a standardized approach [23]. TMS was measured from the axial section of the third lumbar vertebra (L3). Skeletal muscle was identified and quantified by use of Hounsfield unit (HU) between thresholds (−29 to +150). Manual segmentation of residual structures that did not correspond to muscle was performed. The SMI at L3 (cm²/m²) was calculated as follows: SMI = TMS/height².

2.2.3. Study end-points

The primary objective was to evaluate the prevalence of sarcopenia in MBC based on the EWGSOP criteria, defined by low muscle mass and strength.

In this study, we defined three populations (Fig. 2) [11]: (1) population A or sarcopenic group with both low muscle mass (via the SMI at L3) and muscle strength (defined by handgrip strength) (2) population B or pre-sarcopenic group with low muscle mass or low muscle strength (3) population C or normal group with both high muscle mass and strength.

The cut-off for low muscle mass was SMI < 55 cm²/m² for men and < 39 cm²/m² for women [24]. Low muscle strength was defined by handgrip strength < 30 kg for men and < 20 kg for women [11].

Secondary objectives were to evaluate the correlation between sarcopenia and the following variables: subjective assessment of sarcopenia by the oncologist (yes/no), MUAC (low if < 21.1 cm for men and < 19.9 cm for women) [25] and thigh circumference (low if < 38.8 for men and < 38.9 for women) [26], quadriceps atrophy assessed visually by the oncologist (yes/no). Objectives also included the evaluation of: the relationship between anthropometric characteristics and nutritional status, the impact of...
Sarcopenia on cancer therapy tolerance, the relationship between sarcopenia and nutritional status, nutritional care, and physical activity for each patient.

2.2.4. Ethical statement

All patients were informed about the study and data collection. Clinical data were collected according to French bioethics laws regarding patient information and consent. The protocol was in line with the French data protection committee (CNIL, approval no. 2066086) regulations and was approved by the French ethical research committee, “Le Comité de Protection des Personnes” (CPP), on the July 6, 2017 (approval no. 2017-A01648-45).

2.2.5. Statistical analysis

Data management and statistical analyses were performed by Kantar Health (Paris, France). Statistical analyses were performed using DAISIE (version 2.4.25 & 2.4.45) and R (386 3.0.1). For continuous variables, descriptive analyses (means, SD, median and range) were provided, and the Z-test or t-test was used for comparisons between the sarcopenic and non-sarcopenic groups. Data are presented as percentages for categorical variables. The Cohen’s kappa coefficient (κ) was used to assess the reliability of the oncologists’ subjective assessment of sarcopenia diagnosis. All statistical tests had a level of significance established at P < 0.05.

3. Results

3.1. Clinical characteristics of the patients

Among 766 included patients, 139 patients (2 men and 137 women) with breast cancer having available data for SMI and hand-grip strength were analyzed. Patient demographics and cancer characteristics are presented in Table 1. The median age was 61.2 years (29.9–97.8 years). Most patients (83.5%) had a PS of 0 or 1. The median time between primary diagnosis and discovery of the first metastasis was 40.3 months (0.0–329.0 months); 23.7% were metastatic at diagnosis. The median time between the onset of primary diagnosis and current chemotherapy was 62.0 months (0.0–285.0 months).

The main metastatic sites were bone (73.4%), liver (46.0%), lymph nodes (38.8%), lung (36.0%) or brain (7.9%). Patients presented a median of 1.6 metastatic sites (1.0–7.0). At diagnosis of metastatic disease, 21 patients had bone-only metastases (15.1%); 91 (65.5%) had visceral metastases (excluding brain metastases) while 11 had brain metastases at diagnosis (7.9%).

Most patients (45.3%) were on their first line of treatment, 14.4% received 2 treatment lines and 37.4% were undergoing a third or higher line of treatment. The main treatment was chemotherapy (45.3%) followed by targeted therapy (17.3%) and hormonotherapy (9.4%). In 28.1% of cases, patients had a combination treatment.

Generally, sarcopenic patients were older (P < 0.01 vs the normal group), had a worse PS-score (P = 0.03 vs the normal group), more bone metastases (P = 0.02 vs the normal group) and a higher number of metastatic sites (P < 0.01 vs the normal group) (Table 1).

3.2. Sarcopenia prevalence and anthropometric characteristics

According to the EWGSOP criteria, 29.5% of patients (n = 41) were sarcopenic and 41.0% of patients (n = 57) were pre-sarcopenic, among whom 63.2% (n = 36) had low SMI and 36.8% (n = 21) had low muscle strength (Fig. 2).

In the sarcopenia group, sarcopenia was correctly assessed by physicians in 61.0% of cases, whereas patients in the normal group were correctly assessed as non-sarcopenic in 78.0% of cases by oncologists. A Cohen’s kappa index of 0.45 indicated a moderate level of agreement between oncolist assessment and sarcopenic evaluation as per EWGSOP criteria.

In the sarcopenia group, atrophy of the quadriceps was noted in 46.3% of patients, contrary to pre-sarcopenic or normal group (19.3% and 7.3% respectively, P < 0.01). In the sarcopenia group, 29.3% had a low thigh circumference versus 1.8% in the pre-sarcopenic group and 0.0% in the normal group (P < 0.01). There was no difference in the mean brachial circumference of the dominant arm between the sarcopenia and normal groups. Pearson’s correlation coefficients (r) indicated a moderate correlation between sarcopenic status and low thigh circumference (r = 0.55) and low MUAC (r = 0.52).

3.3. Sarcopenia, nutritional status and care

Table 2 shows the nutritional status and characteristics of patients. Mean BMI at inclusion was 24.3 ± 4.2 kg/m², of which 30.2% were overweight and 9.4% were obese. A weight loss of 5% in the previous month was found in 5.0% of patients. In sarcopenic group, BMI was lower at initial cancer diagnosis (P = 0.01 vs the normal group) and at study inclusion (P < 0.01). Sarcopenic patients tended to be malnourished or underweight with low serum albumin. A poor correlation was found between sarcopenia status and dietary assessment (r = 0.13).

Personalized nutritional counselling was proposed only in 27.3% of cases, regardless of the patient’s nutritional status (Table 3). More sarcopenic patients with counselling were consulting dieticians (19.5%) and 17.0% used oral nutritional supplements or...
Sarcopenia prevalence was 29.5%, taking into account muscle mass and muscle strength measurements as recommended [11]. Our work is the first large-scale study in metastatic situation which established sarcopenia according muscle mass and muscle strength criteria [19] and by using cut-off defined by the international consensus [24].

Until now, data on the prevalence of sarcopenia are limited in breast cancer compared to others cancers [9,27], with most reports being retrospective. Three studies report the prevalence of low muscle mass in MBC in patients with a similar median age to our cohort [19]. The median age of our cohort is also similar to the ESME cohort [19]. The median age of our cohort is also similar to the ESME cohort [19]. The median age of our cohort is also similar to the ESME cohort [19].

The prevalence of low muscle mass varied from 25% (cut-off: 87 cm²/m²) [28] to 66.9% (cut-off: 41 cm²/m²) in metastatic breast cancer (MBC) [15,19].

3.4. Impact of sarcopenia on cancer therapy tolerance

Adverse events (AEs) were reported in 12 patients. Since the initiation of treatment and specifically in the last month of its administration, AE of grade 3 or higher included hematomatological abnormalities, gastrointestinal side effects and hand and foot syndrome. No impact of sarcopenia status on anti-cancer treatment related toxicities and treatment management was noticed in this small population (Table 4).

4. Discussion

In the present study, we evaluated for the first time the prevalence of sarcopenia and its impact in real-life MBC patients. Sarcopenia prevalence was 29.5%, taking into account muscle mass and muscle strength measurements as recommended [11]. Our

### Table 1

Breast cancer patient and cancer characteristics with and without sarcopenia.

| Table 1 | Breast cancer patient and cancer characteristics with and without sarcopenia. |
|---------|------------------------------------------------------------------------------|
| Female, n (%) | Total (n = 139) | Population A (n = 41) | Population B (n = 57) | Population C (n = 41) | Pop A vs. B p-value | Pop A vs. C p-value | Pop B vs. C p-value |
| Age (yrs) | 137 (98.6%) | 40 (97.6%) | 56 (98.2%) | 41 (100.0%) | NS | NS | NS |
| Mean ± SD | 60.4 ± 13.4 | 67.3 ± 13.3 | 57.6 ± 12.7 | 57.5 ± 11.8 | P < 0.01 | P < 0.01 | NS |
| > 70 years, n (%) | 34 (24.5%) | 17 (41.5%) | 10 (17.5%) | 7 (17.1%) | P < 0.01 | P < 0.03 | NS |
| Performance status, n (%) | | | | | | | |
| 0 | 59 (42.4%) | 10 (24.4%) | 29 (50.9%) | 20 (48.8%) | P < 0.01 | P < 0.04 | NS |
| 1 | 57 (40.1%) | 20 (48.8%) | 22 (38.6%) | 15 (36.6%) | NS | NS | NS |
| 2 | 17 (12.2%) | 10 (24.4%) | 5 (8.8%) | 2 (4.9%) | P < 0.05 | P < 0.03 | NS |
| 3 | 3 (2.2%) | 1 (2.4%) | 1 (1.8%) | 1 (2.4%) | NS | NS | NS |
| Number of metastatic sites | | | | | | | |
| Mean ± SD median (range) | 2.2 ± 1.1 | 2.5 ± 1.2 | 2.3 ± 1.2 | 1.9 ± 0.9 | P < 0.01 | NS | NS |
| Main metastatic sites, n (%) | | | | | | | |
| Bones | 102 (73.4%) | 32 (78.0%) | 40 (70.2%) | 30 (73.2%) | NS | NS | NS |
| Liver | 64 (46.0%) | 24 (58.5%) | 24 (42.1%) | 16 (39.0%) | NS | NS | NS |
| Lymph nodes | 54 (38.8%) | 16 (39.0%) | 25 (43.9%) | 13 (31.7%) | NS | NS | NS |
| Lung | 50 (36.0%) | 17 (41.5%) | 24 (42.1%) | 9 (22.0%) | NS | NS | P < 0.05 |
| Brain | 11 (7.9%) | 3 (7.3%) | 7 (12.3%) | 1 (2.4%) | NS | NS | NS |
| Current metastatic sites, n (%) | | | | | | | |
| Bone-only metastasis | 21 (15.1%) | 3 (7.3%) | 6 (10.5%) | 12 (29.3%) | NS | P < 0.02 | P < 0.04 |
| Visceral metastases (excluding brain metastases) | 91 (65.5%) | 31 (75.6%) | 36 (63.2%) | 24 (58.5%) | NS | NS | NS |
| Non-visceral metastases (skin, lymph nodes and ovaries) | 54 (38.8%) | 17 (41.5%) | 23 (40.4%) | 14 (34.1%) | NS | NS | NS |
| Brain metastases | 11 (7.9%) | 3 (7.3%) | 7 (12.3%) | 1 (2.4%) | NS | NS | NS |
| Visceral metastasis (excluding brain)* | | | | | | | |
| Yes | 91 (65.5%) | 31 (75.6%) | 36 (63.2%) | 24 (58.5%) | NS | NS | NS |
| No | 48 (34.5%) | 10 (24.4%) | 21 (36.8%) | 17 (41.5%) | NS | NS | NS |
| Current therapies, n (%) | | | | | | | |
| Chemotherapy alone | 63 (45.3%) | 23 (56.1%) | 21 (36.8%) | 19 (46.3%) | NS | NS | NS |
| Targeted therapy alone | 24 (17.3%) | 3 (7.3%) | 15 (26.3%) | 6 (14.6%) | P < 0.03 | NS | NS |
| Hormonotherapy alone | 13 (9.4%) | 3 (7.3%) | 5 (8.8%) | 5 (12.2%) | NS | NS | NS |
| Chemotherapy and Targeted therapy | 24 (17.3%) | 9 (22.0%) | 11 (19.3%) | 4 (9.8%) | NS | NS | NS |
| Targeted therapy and hormonotherapy | 14 (10.1%) | 3 (7.3%) | 7 (11.7%) | 4 (9.8%) | NS | NS | NS |
| Chemotherapy and hormonotherapy | 1 (0.7%) | 0 (0.0%) | 1 (1.8%) | 0 (0.0%) | NS | NS | NS |
| Number of treatment lines | 2.5 ± 2.0 | 2.9 ± 2.5 | 2.4 ± 1.8 | 2.4 ± 1.7 | NS | NS | NS |
| Mean ± SD median (range) | 1.2 (1–10) | 1.0 (1–10) | 1.3 (1–8) | 1.4 (1–7) | NS | NS | NS |
| Current line of treatment, n (%) | | | | | | | |
| 1st line | 63 (45.3%) | 20 (48.8%) | 25 (43.9%) | 18 (43.9%) | NS | NS | NS |
| 2nd line | 20 (14.4%) | 2 (4.9%) | 12 (21.1%) | 6 (14.6%) | P < 0.05 | NS | NS |
| 3rd line and more | 52 (37.4%) | 16 (39.0%) | 19 (33.3%) | 17 (41.5%) | NS | NS | NS |

Results are presented by N (%) or mean ± SD. NS: not significant.

*Unknown responses and non-responses are not reported in the Table.

†Patients with at least one site of visceral metastases (liver, lung, pleural effusion peritoneum, adrenal gland, pancreas, retinal, mediastinum, breast, epididymis).
found to be related to sarcopenia status, a single method on its own was insufficient to conclusively determine sarcopenia status. The most effective way to identify sarcopenia would thus be to combine screening tools, including CT-scan. The relationship between handgrip strength and muscle mass that was previously explored in early adjuvant breast cancer confirms the above comment [30]. We also showed that the rate of sarcopenia was independent of the treatment line. There is little data on this in breast cancer but this is consistent with another publication in pancreatic cancer [31].

Although previous studies showed a link between sarcopenia and treatment intolerance in breast cancer [12–15], we could not confirm this because a small number of AEs had occurred in the sample. In our study, AEs has occurred in less than 10% of patients, compared to 33% of patients in a study by Shachar et al. [13] or to 50% of patients described by Prado et al. [15]. The differing percentage of toxicities could be related to the design of our study, which had a cross-sectional design, in contrast to these two studies that were especially designed to evaluate the relation between toxicities and sarcopenia. Another explanation is the use of treatments different from chemotherapy or a less toxic chemotherapy than in previous studies.

Finally, we showed that nutritional care and physical activity were under-proposed to sarcopenic patients. It is well known that sarcopenia is linked to poor prognosis [16–18,32–34] and that using simple tools to screen early for sarcopenia and to propose a nutritional management plan could help to counter sarcopenia worsening. One explanation is the lack of knowledge about a patient's sarcopenic status through inadequate assessment, but even correctly assessed sarcopenic patients did not receive adequate nutritional support and physical exercise management. A French study previously highlighted the difficulty of assessing nutrition status and its management in elderly patients with cancer [35].

Proper nutrition and exercise have been shown to have a synergistic effect in the prevention and improvement of sarcopenia
Results are presented by N (%). NS not significant.

**Exercise** improves lean body mass and muscular strength in BC patients. These improvements have been associated with improved quality of life (QoL). One randomized trial highlighted that exercise had a positive effect on muscle mass in cancer patients [39]. Exercise improves lean body mass and muscular strength in BC patients. These improvements have been associated with improved quality of life (QoL). One randomized trial highlighted that exercise had a positive effect on muscle mass in cancer patients [39].

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**Results** are presented by N (%). NS not significant.

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### Table 4

Impact of sarcopenia on anti-cancer treatment related toxicities and treatment management.

|                      | Total (n = 139) | Population A (n = 41) | Population B (n = 57) | Population C (n = 41) | Pop A vs. B p-value | Pop A vs. C p-value | Pop B vs. C p-value |
|----------------------|----------------|----------------------|----------------------|----------------------|--------------------|--------------------|--------------------|
| **Dose reduction due to toxicities** |                |                      |                      |                      |                    |                    |                    |
| Yes                  | 15 (10.8)      | 5 (12.2)             | 5 (8.8)              | 5 (12.2)             | NS                 | NS                 | NS                 |
| No                   | 121 (87.1)     | 36 (87.8)            | 51 (89.5)            | 34 (82.9)            | NS                 | NS                 | NS                 |
| **Treatment interruptions due to toxicities** |                |                      |                      |                      |                    |                    |                    |
| Yes                  | 13 (9.4)       | 4 (9.8)              | 4 (7.0)              | 5 (12.2)             | NS                 | NS                 | NS                 |
| No                   | 123 (88.5)     | 37 (90.2)            | 52 (91.2)            | 34 (82.9)            | NS                 | NS                 | NS                 |
| **Treatment delay due to toxicities during the previous month** |                |                      |                      |                      |                    |                    |                    |
| Yes                  | 17 (12.2)      | 7 (17.1)             | 5 (8.8)              | 5 (12.2)             | NS                 | NS                 | NS                 |
| No                   | 119 (85.6)     | 34 (82.9)            | 51 (89.5)            | 34 (82.9)            | NS                 | NS                 | NS                 |
| **Adverse events (AE), ≥ grade 3 during the previous month** |                |                      |                      |                      |                    |                    |                    |
| Yes                  | 12 (8.6)       | 3 (7.3)              | 4 (7.0)              | 5 (12.2)             | NS                 | NS                 | NS                 |
| No                   | 122 (87.8)     | 38 (92.7)            | 50 (87.7)            | 34 (82.9)            | NS                 | NS                 | NS                 |

Results are presented by N (%). NS not significant.

*Unknown responses and non-responses are not reported in the Table.*

### Ethics approval

This study, conducted in accordance with the Declaration of Helsinki, was approved by the French ethical research committee, "Le Comité de Protection des Personnes" (CPP), on the July 6, 2017 (approval no. 2017-A01648-45). National data protection regulations were also met (CNIL, approval no. 2066086).

### Consent to participate

All persons provided their informed consent prior to enrollment.

### Consent for publication

All persons were informed that this study would be submitted for publication.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

All authors were remunerated for their participation as...
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