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Are contralateral parenchymal enhancement on dynamic contrast-enhanced MRI and genomic ER-pathway activity in ER-positive/HER2-negative breast cancer related?

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ABSTRACT

Purpose: To retrospectively explore the relation between parenchymal enhancement of the healthy contralateral breast on dynamic contrast-enhanced magnetic resonance imaging (MRI) and genomic tests for estrogen receptor (ER)-pathway activity in patients with ER-positive/HER2-negative cancer.

Methods: A subset of 227 consecutively included patients with unilateral invasive ER-positive/HER2-negative breast cancer underwent dynamic contrast-enhanced MRI prior to breast-conserving therapy between 2000 and 2008. Perfusion of the parenchyma in the healthy breast was assessed using a previously reported measure of contralateral parenchymal enhancement (CPE), consisting of the mean of the top-10% late enhancement. ER-pathway activity was assessed from the surgical resection specimen by the previously reported sensitivity to endocrine therapy (SET)-index and ER-factor. The SET-index is a genetic test to estimate survival benefit from endocrine therapy, consisting of genes related to the ESR1 gene. The ER-factor examines other factors as well including protein expression. The relation between CPE and ER-pathway activity was modeled using linear regression.

Results: Patients had a median age of 59 years. CPE was not significantly associated with the SET-index (R-squared = 0.005) nor the ER-factor (R-squared = 0.0002). The only variable significantly different between low and high CPE was age at diagnosis ($P < 0.001$).

Conclusions: Contralateral parenchymal enhancement on dynamic contrast-enhanced MRI was not associated with tumor-derived estrogen receptor pathway activity.

1. Introduction

Approximately three quarters of the breast cancer population are patients with estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer [1]. These patients often receive endocrine therapy, but less than 50% may benefit [2]. Moreover, endocrine therapy may have side effects including endometrial cancer, thromboembolic disease, and osteoporosis [3].

Risk stratification for personalized chemotherapy selection based on clinicopathological tests [4–6] and validated molecular assays [7–10] is routinely used. Options for patient-specific endocrine therapy selection are, however, limited. Recent studies show evidence that activation of the ER-pathway of the tumor is a prerequisite for effective endocrine therapy [11,12], independent of immunohistochemical staining of ER [11].

Healthy breast parenchyma is relatively underexposed in current

Abbreviations: BPE, background parenchymal enhancement; CPE, contralateral parenchymal enhancement; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; PR, progesterone receptor; RNA, ribonucleic acid; SER, signal enhancement ratio; SET, sensitivity to endocrine therapy

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research on prognostic and predictive biomarkers. The functional behavior of breast parenchyma can be assessed using dynamic contrast-enhanced magnetic resonance imaging (MRI). Background parenchymal enhancement (BPE) has been shown to be related to the risk of developing breast cancer [13–17]. In patients with breast cancer, the parenchymal enhancement of the contralateral breast has been linked to several prognostic factors, such as tumor grade and progesterone receptor (PR) status [18]. The contralateral parenchymal enhancement (CPE) has also been associated with long-term survival [19], and was recently validated in an independent cohort of ER-positive/HER2-negative breast cancer patients [20]. This association between CPE and survival was not explained by common prognostic variables [19], molecular assays [21], or ER/PR-staining percentages [20].

The question remains why various studies from different research groups have found associations between background parenchymal enhancement and prognostic factors of breast cancer. One of the yet unexplored hypotheses is that parenchymal enhancement might be indicative of the efficacy of local drug transport [20]: Pronounced contrast enhancement in parenchymal tissue is associated with higher microvessel density [22], hence it is a measure of the perfusion of healthy unaffected parenchymal breast tissue. Low contrast enhancement may indicate poorer transport of Tamoxifen in the breast, leading to poorer patient outcome. Local drug transport would be independent of the intrinsic receptiveness of the tumor to endocrine therapy, the latter indicated by ER-pathway activity derived from the tumor [11,12].

Given above rationale, it is of interest to investigate the potential relation between CPE and ER-pathway activity of the tumor. If CPE and ER-pathway activity are highly correlated, the hypothesis of drug transport may be rejected. If they are not, they may address different aspects of the efficacy of endocrine therapy, requiring future research.

Therefore, the purpose of this retrospective study was to explore the relation between parenchymal enhancement of the contralateral breast and ER-pathway activity in patients with ER-positive/HER2-negative cancer.

2. Material and methods

2.1. Data and study design

ER-positive/HER2-negative breast cancer patients who had a preoperative breast dynamic contrast-enhanced MRI were included. The association between CPE and survival was discovered in these patients [19]. In the current study, we added new data by extracting two measures of ER-pathway activity from fresh-frozen tumor tissue. We examined associations between CPE and this ER-pathway activity. The following paragraphs describe these steps in detail.

2.2. Patients

Data were acquired after approval of institutional review board and written informed patient consent. The patients participated in the prospective Multimodality Analysis and Radiological Guidance IN breast conServing therapy study (MARGINS, 2000–2008) performed at the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital. In short, patients eligible for breast conserving therapy were consecutively recruited for a preoperative breast MRI, proof of breast cancer was acquired using core biopsy or fine-needle aspiration, and treatment plans were established in consensus by a multidisciplinary team of breast cancer specialists.

Inclusion criterion for the current study was unilateral invasive ER-positive/HER2-negative breast cancer, regardless of progesterone receptor (PR) status. Patients who received neoadjuvant systemic therapy were excluded, since this is not compatible with analysis of treatment-naïve tumor tissue. Additional exclusion criteria were 1) previous surgery in the contralateral breast, 2) inadequate imaging data, 3) inadequate fresh-frozen tumor tissue, and 4) missing pathology data (Fig. 1).

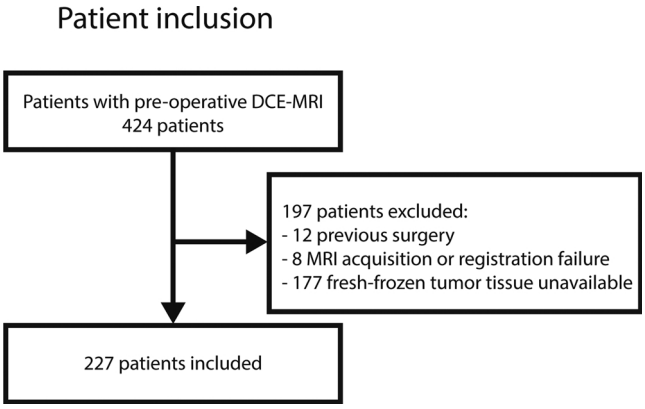

Fig. 1. Flowchart of patient inclusion.

2.3. Magnetic resonance imaging

The MR acquisition protocol was described elsewhere [19], and is summarized in Table 1. A dedicated breast MR imaging radiologist with more than 10 years of experience (C.E.L.) measured the largest tumor diameter on MRI in three orthogonal planes, after which the largest of the three measurements was recorded.

2.4. Tumor characteristics

2.4.1. Histopathology

Pathology characteristics determined on the surgical excision specimen were described elsewhere [19]. In short, ER and PR-status were positive if more than 10% of the cells stained positive on immunohistochemistry [23]. HER2 status was negative if it was scored 0 to 1+ on immunohistochemistry, or if it scored 2+ and in situ hybridization did not demonstrate ERBB2 gene amplification [23]. The histologic grade was determined using the Bloom and Richardson method [24]. The axillary load was stratified to three groups: zero, one to three, or four or more lymph nodes positive for malignancy [23].

2.4.2. Genomic analyses

Two signatures of genomic ER-pathway activation were recorded: The Sensitivity to Endocrine Therapy (SET)-index [11] and an ER-factor derived from multiomics data [25]. These measures were calculated on RNA sequence reads mapped to the human genome, which has been described extensively [21]. In short, fresh-frozen samples of the tumors were collected from the tissue bank of the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, RNA was extracted of samples with

Table 1
Magnetic resonance imaging protocol.

Variable	Value
Imaging unit	Magneton (Siemens, Erlangen, Germany)
Field strength	1.5 T
Contrast agent	Prohance (Bracco-Byk Gulden, Konstanz, Germany) at 0.1 mmol/kg body weight
Sequence name	FLASH (Fast Low Angle Shot)
Number of acquisitions	5
Acquisition time	90 s
Repetition time	8.1 ms
Echo time	4.0 ms
Flip angle	20°
Voxel size	1.35 × 1.35 × 1.35 mm^3
Field of view	310 mm
Fat suppression	No

30% or more tumor tissue, and mRNA was sequenced using Hiseq 2500 (Illumina, San Diego, California, USA) with 65-bp single-end reads. After cutting adapter sequences, RNA sequence reads were mapped to the human genome (GENCODE 23) with STAR 2.5.0a to quantify the RNA per gene [26]. Log2-transformed counts were scaled by gene length and normalized gene expression was calculated [21].

The SET-index comprises of 165 microarray probes associated with ESR1: 106 positively correlated and 59 negatively correlated genes [11]. We reapplied the SET-index signature as described by Symmans et al. to the samples in our dataset.

The multiomics ER-factor was developed on The Cancer Genome Atlas and reapplied to the current dataset [25]. In short, a sparse factor analysis aimed at identifying the driving factors in breast cancer was performed on RNA expression, protein expression, and DNA copy number aberrations. Afterwards, the biological processes underlying these factors were examined using a gene set enrichment analysis. The most dominant factor in the data was strongly associated with ESR1 RNA expression, ESR1 protein expression, and ESR1 copy number aberrations. Hence, this factor was named the ER-factor [25]. The ER-factor was calculated in the current dataset by applying the coefficients per gene identified on the The Cancer Genome Atlas dataset.

2.5. Parenchyma characteristics

The automatic processing of the MR images is described elsewhere in detail [19]. In short, a parenchymal tissue segmentation of the contralateral breast was acquired [27]. Time series were registered to each other using deformable registration to compensate for patient motion [28]. In the parenchymal tissue segmentation, CPE was calculated as the mean of the top-10% late enhancement voxels [19].

2.6. Statistical analysis

The primary aim of this study was to explore the relationship between CPE and ER-pathway activity. This was modelled using linear regression. To satisfy the criteria for linear regression, CPE was transformed using a Box-Cox transformation to more closely resemble a normal distribution. Differences in baseline characteristics such as PR-status were tested for significance using the Kruskal-Wallis rank sum test for continuous variables and Fisher's exact test for categorical variables. For all statistical tests, a two-tailed P-value < 0.05 was considered significant.

Statistical analysis was performed using R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient cohort

Four hundred and twenty-four patients were eligible for this study (Fig. 1). Twelve patients (3%) were excluded because of previous surgery, eight (2%) because of MR image acquisition or registration failure. Fresh-frozen tumor tissue was available for 227 of the remaining 404 patients (62%). The median age at diagnosis was 59 years (Table 2).

Patients of whom the fresh-frozen tumor tissue was available were on average 2 years older ($P = 0.017$) than patients of whom it was not available. The largest tumor diameter on MRI was on average 2.6 mm larger ($P < 0.001$) in patients with available frozen tissue, and harbored 6% more often a grade III tumor ($P = 0.005$) than tumors with tissue unavailable. Axillary load ($P = 0.124$) and PR-status ($P = 0.487$) did not significantly differ between these groups.

3.2. Relation of clinicopathological variables to CPE

CPE was normally distributed after the Box-Cox transformation (Shapiro-Wilk test: $P = 0.761$, before transformation: $P < 0.001$).

Of the clinicopathological variables, only age at diagnosis was significantly different between low and high CPE ($P < 0.001$). The largest tumor diameter on MRI, histologic grade, histologic tumor type, axillary load, and the PR status were not ($P > .523$, Table 2).

3.3. Relation of SET-index and ER-factor to CPE

CPE was not associated with the SET-index (R-squared = 0.005) or with the ER-factor (R-squared = 0.0002, Fig. 2). Patients with high CPE did not have a different SET-index or ER-factor than patients with low CPE ($P = 0.366$ and 0.395, respectively, Fig. 3). Examples of a patient with low CPE and a patient with high CPE with similar SET-index and ER-factor are shown in Fig. 4.

In the current study, the SET-index showed a trend with survival (hazard ratio (95% confidence interval) = 0.75 (0.53–1.05), $P = 0.095$), the ER-factor did not ($P = 0.652$).

4. Discussion

In 227 patients with unilateral invasive ER-positive/HER2-negative breast cancer, the parenchymal enhancement of the contralateral breast was not related to genetic ER-pathway activity of the tumor.

Previous studies reported that patients with high contralateral parenchymal enhancement show superior survival compared with patients with low enhancement [19,20]. Enhancement of parenchymal breast tissue is known to fluctuate with endocrine influences such as those related to the menstrual cycle and menopausal status [29,30]. Therefore, it is plausible that advanced tumor-derived ER-expression might provide additional information to explain these reported associations. The current study builds on this literature, using two different genomic signatures of ER-pathway activation: the SET-index and the ER-factor. We extracted these genomic signatures from fresh-frozen tumor tissue. The signatures were developed on independent datasets: the SET-index on patients from MD Anderson Cancer Center, and the ER-factor on patients from The Cancer Genome Atlas. After extracting these signatures from our dataset, the results do not indicate that they are related to parenchymal enhancement.

Another hypothesis for the association between parenchymal enhancement and survival is that the enhancement of the parenchymal tissue might be indicative of the efficacy of local drug transport [20]. Because the amount of contrast enhancement in parenchymal tissue is associated with the microvessel density [22,31], it is a perfusion measure of healthy parenchymal tissue. Therefore, low contrast enhancement may indicate poorer local drug transport, leading to poorer patient outcome after Tamoxifen. The genomic ER-pathway activity, represented by the SET-index and ER-factor, is a measure of intrinsic sensitivity of that tumor to endocrine therapy [11]. Since our results do not suggest parenchymal enhancement and ER-pathway activity to be interchangeable, they may be complementary. It would be interesting to investigate this hypothesis in a different datasets. This may, however, be a challenging task since MRI, RNA-sequencing, and long-term follow-up would have to be available.

In a recent study, Shin et al. were unable to reproduce the associations between contralateral parenchymal enhancement and patient survival [32]. It is difficult to compare these implementations of CPE in detail. A notable difference is, however, the much larger range of reported CPE values (0.22–172.66 in their study [32] vs 0.10–1.13 in the CPE biomarker-discovery study [19]). This might be due to differences in the algorithm or differences in the breast cancer population itself; The Adjuvant! Online model was also difficult to reproduce in the Asian population of breast-cancer patients [33,34].

A limitation of this study is that it focused on early breast cancer. It is unknown whether results can be extended to locally advanced breast cancer. This choice was made to avoid exposure of the surgically excised tumor to chemotherapy, which would influence the results of the

Table 2
Patient and tumor characteristics. All patients have unilateral estrogen receptor-positive/HER2-negative breast cancer.

Characteristic	All patients (N = 227)	Low CPE (N = 113)	High CPE (N = 114)	P-value
Age at diagnosis (years)‡	59 (51–65)	62 (56–67)	55 (48–62)	< .001
Largest tumor diameter on MRI (mm)‡	18 (14–25)	19 (13–25)	19 (14–25)	0.523
Histological grade (%)				0.957
Grade I	80 (35)	41 (36)	39 (34)	
Grade II	112 (49)	54 (48)	58 (51)	
Grade III	32 (14)	16 (14)	16 (14)	
Missing	3 (1)	2 (2)	1 (1)	
Histologic finding (%)				0.876
Invasive ductal carcinoma	168 (74)	84 (74)	84 (74)	
Invasive lobular carcinoma	42 (19)	17 (15)	25 (22)	
Other or mixed invasive carcinoma	17 (7)	12 (11)	5 (4)	
Progesterone receptor (%)				0.876
Positive	172 (76)	85 (75)	87 (76)	
Negative	54 (24)	28 (25)	26 (23)	
Missing	1 (0)	0 (0)	1 (1)	
Axillary load (%)				0.887
0 positive lymph nodes	143 (63)	72 (64)	71 (62)	
1 – 3 positive lymph nodes	66 (29)	32 (28)	34 (30)	
4 or more positive lymph nodes	16 (7)	7 (6)	9 (8)	
Missing	2 (1)	2 (2)	0 (0)	
Adjuvant systemic therapy (%)				0.254
No systemic therapy	122 (54)	67 (59)	55 (48)	
Chemotherapy only	1 (0)	0 (0)	1 (1)	
Endocrine therapy only	49 (22)	23 (20)	26 (23)	
Endocrine and chemotherapy	55 (24)	23 (20)	32 (28)	
Sensitivity to Endocrine Therapy-index ‡	2.80 (1.69–3.63)	2.76 (1.60–3.62)	2.85 (1.88–3.64)	0.294
Estrogen receptor-factor ‡	0.34 (0.07–0.57)	0.33 (0.03–0.55)	0.34 (0.09–0.59)	0.345

Data are numbers (percentages).
‡ Data are median (interquartile range).

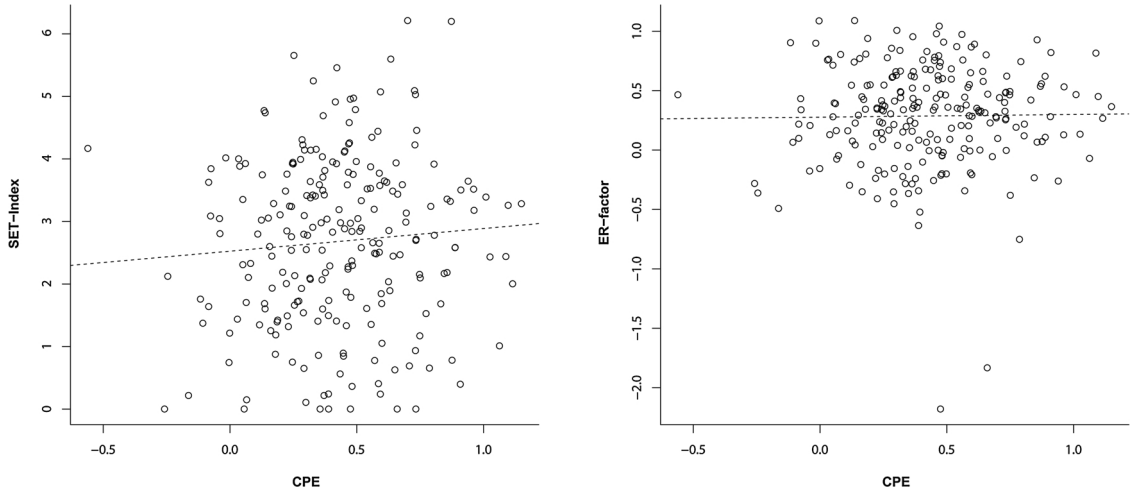

Fig. 2. Contralateral parenchymal enhancement (CPE) was not related to the sensitivity to endocrine therapy (SET)-index (left, R-squared = 0.006) and the estrogen receptor (ER)-factor (right, R-squared = 0.0002). CPE was transformed using a Box-Cox transformation to more closely resemble a normal distribution. The dashed lines represent the linear regression fit. All patients had ER-positive/HER2-negative breast cancer (N = 227).

genomic analysis. Another limitation of our study is that fresh-frozen tumor tissue was not available for analysis in all patients, which may lead to a potential bias. Given the distinct absence of a relation between CPE and ER-pathway activity in the current study, it would, however, be unlikely that we would have found a clear relation in the full patient cohort.

To conclude, contralateral parenchymal enhancement on dynamic contrast-enhanced MRI was not found to be related to tumor-derived estrogen receptor pathway activity in patients with ER-positive/HER2-negative breast cancer. Future research should address the potential complementary value of these biomarkers.

Contributions

Study concepts: BV KG
Study design: BV KG
Data acquisition: BV TB EL CL KG
Quality control of data and algorithms: BV TB
Data analysis and interpretation: BV TB CL KG
Statistical analysis: BV TB KG
Manuscript preparation: BV TB LW KG
Manuscript editing: BV TB CL EL JW MV LW KG
Manuscript review: BV TB CL EL JW MV LW KG

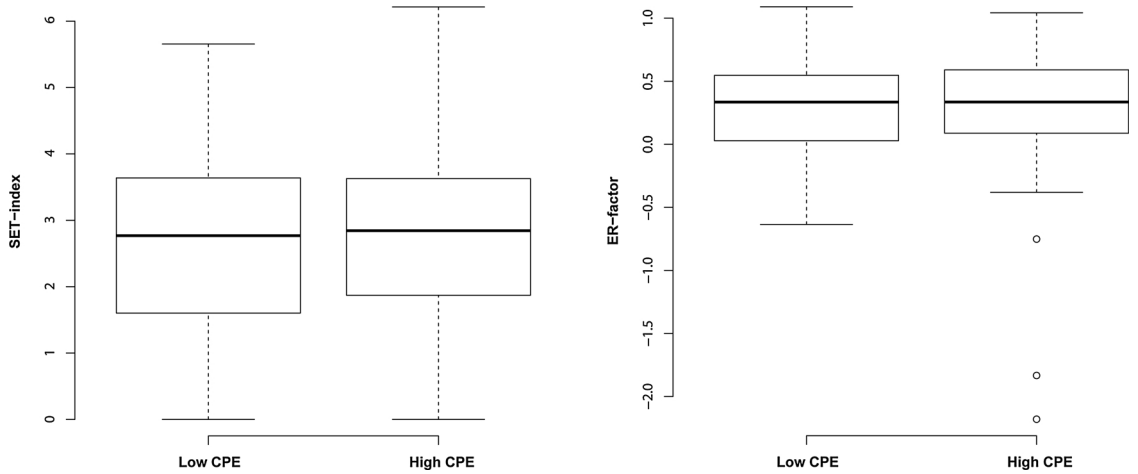

Fig. 3. There was no significant difference in the sensitivity to endocrine therapy (SET)-index (left, P = 0.366) and the estrogen receptor (ER)-factor (right, P = 0.395) between low and high contralateral parenchymal enhancement (CPE). CPE was divided in low and high CPE on the median. All patients had ER-positive/HER2-negative breast cancer (N = 227).

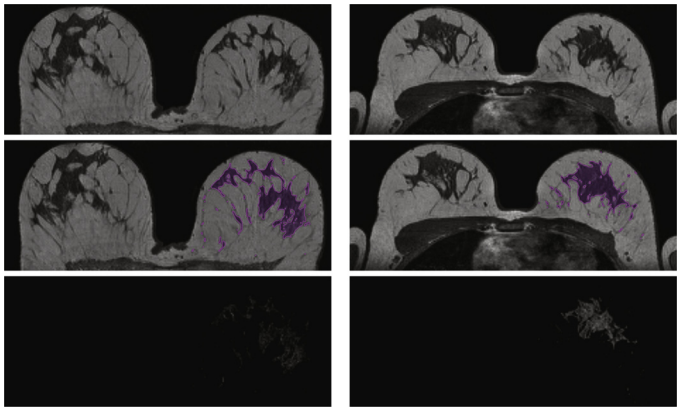

Fig. 4. Example of a patient with low contralateral parenchymal enhancement (CPE) on the left and a patient with high CPE on the right. Both the Sensitivity to Endocrine Therapy (SET)-index and estrogen receptor (ER)-factor are comparable, only patient age was substantially different between both patients.
Left: 70-year old patient with an ER-positive, progesterone receptor (PR)-positive, and HER2-negative invasive ductal carcinoma in the right breast. The tumor had a Sensitivity to Endocrine Therapy (SET)-index of 3.0, an ER-factor 0.55. CPE was 0.30.
Right: 32-year old patient with an ER-positive, PR-positive, and HER2-negative invasive ductal carcinoma in the right breast. The tumor had similar characteristics of hormonal activity as the patient on the left: the SET-index was 3.3, the ER-factor 0.54. CPE was 0.74.
Top row: the precontrast magnetic resonance images. Middle row: the same images with the contralateral parenchymal tissue segmentation overlaid in pink. Bottom row: the late enhancement voxels, calculated as described in [19], in the parenchymal tissue segmentation. The window and level are the same in the left and right image (center at 0.5, width at 1.0).

Ethical approval for research

Yes.

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The funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit.

Declaration of Competing Interest

None.

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