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Free triiodothyronine and free thyroxine hormone levels in relation to breast cancer risk: a meta-analysis

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Abstract

Introduction: The conflict between breast cancer (BC) and thyroid hormone (TH) has been studied for years. The purpose of the study was to summarise and analyse the available data on the relationship between TH and BC.
Material and methods: The PubMed, EMBASE, Cochrane Library, and Google Scholar databases were searched to identify relevant studies. The mean difference (MD) with 95% confidence interval (CI) were calculated by fixed or random effects models to assess the effect sizes.
Results: Thirteen eligible studies with 5957 participants were included in the meta-analysis. The result of this study indicates that there is a significant risk relationship between BC and thyroid hormones [free triiodothyronine (FT3): MD = 1.01 pmol/L, 95% CI: 0.32–1.70, free thyroxine (FT4): MD = 0.26 ng/dL, 95% CI: 0.13–0.38].
Conclusions: Compared with healthy controls, the positive risk of FT3 and FT4 is higher in BC. **(Endokrynol Pol 2022; 73 (2): 309–315)**

Key words: *free triiodothyronine; free thyroxine; breast cancer; meta-analysis*

Introduction

Breast cancer (BC) is a hormone-dependent malignancy [1, 2], and it is one of the most common malignant tumours in women all over the world [3]. Apart from familial predisposition, environmental, age at menarche, menopause, first pregnancy, or hormonal factors, no clinically important risk factors for BC are known [2, 4, 5]. The relationship between thyroid hormone (TH) level and the occurrence and development of BC has been reported [6–8]. Some studies show high levels of free triiodothyronine (FT3) and free thyroxine (FT4) hormones are associated with BC [5, 9–11]. Studies have shown that FT3 and FT4 can promote the proliferation of BC cells [12–14], and thyroid receptors have been found in BC cells [15], but other results are in conflict with this [16–18].

Therefore, we have summarized studies related to BC and the level of TH (FT3 and FT4) to conduct a systematic review and meta-analysis to resolve the conflict.

Material and methods

Search strategy

We searched the PubMed, EMBASE, Cochrane Library, and Google Scholar databases using the medical subject heading keywords "Hyperthyroidism", "Hypothyroidism", "Thyroid hormone", "Thyroid disease", "Thyroxine", "Triiodothyronine", "Thyroid function test", "breast cancer", "breast neoplasm", and "breast carcinoma" and the individual corresponding free terms. The search was performed in October 2019 and restricted to English language. Furthermore, we checked manually the reference lists of relevant studies to ensure that no studies were lost.

Selection criteria

Selected studies must meet the following inclusion criteria: (1) The case group was a woman with BC, and the control group was a healthy woman without thyroid disease or breast disease. (2) Studies must include serum levels of FT_3 and FT_4 hormones. (3) Quantification of FT_3 and FT_4 was performed by thyroid function test. (4) The design was quantitative (mean and standard deviation). (5) Any studies failing to meet the above criterion were excluded from the meta-analysis.

Data extraction

The data were extracted by two independent investigators (L.Z.W. and Z.B.) and the coincidence rate was 95.3%. Subsequently the data were validated by other investigators. The quality of the studies was evaluated using the Agency for Healthcare Research and Quality (AHRQ) and the Newcastle-Ottawa Scale (NOS) by two investigators (GD and DQ). Data collection included the following information: author information, publication date, study type, country, number of cases and controls, and selected indexes (mean ± SD). If the information was missing and the unit was not unified, we contacted the author and unified the unit (FT3: pmol/L, FT4: ng/dL). Table 1 shows the data general situation of each study included in this study.

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Table 1. *Characteristics of the studies included in the meta-analysis*

Study	Year	Country	Study design	Case	Control	Quality score	Selected indexes	Summary of findings
Ali et al. [2]	2011	Kashmir	CS	100	75	4	FT_3, FT_4	Increased prevalence of BC
Brandt et al. [19]	2015	Sweden	CO	676	680	7	FT_3, FT_4	Increased prevalence of BC
Cengiz et al. [17]	2004	Turkey	CS	136	68	6	FT_3, FT_4	Increased prevalence of BC
Ditsch et al. [5]	2010	Germany	CC	79	38	6	FT_3, FT_4	Increased prevalence of BC
Giustarini et al. [20]	2006	Italy	CS	36	100	5	FT_3, FT_4	Not associated with BC incidence
Jiskra et al. [21]	2004	Czech Republic	CS	66	49	4	FT_4	Not associated with BC incidence
Jiskra et al. [22]	2007	Czech Republic	CS	84	49	7	FT_4	Not associated with BC incidence
Kuijpens et al. [16]	2005	Netherlands	CO	37	2738	8	FT_4	Decreased prevalence of BC
Saraiva et al. [14]	2005	Turkey	CS	22	22	6	FT_3, FT_4	Increased prevalence of BC
Szychta et al. [1]	2013	Poland	CC	9	490	7	FT_3, FT_4	Increased prevalence of BC
Takatani et al. [23]	1989	Japan	CS	39	36	6	FT_3, FT_4	Increased prevalence of BC
Turken et al. [18]	2003	Turkey	CS	149	100	5	FT_3, FT_4	Not associated with BC incidence
Valizadeh et al. [4]	2015	Iran	CS	41	38	10	FT_3, FT_4	Not associated with BC incidence

CC — case-control study design; CO — cohort study design; CS — cross-sectional study design; BC — breast cancer; FT4 — free thyroxine; FT3 — free triiodothyronine

Statistical analysis

Meta-analysis was conducted using Cochrane Review Manager, version 5.3 (Cochrane Library, Oxford, UK) and Stata version 12.0 (Stata Corp, College Station, TX, USA). A fixed or random-effect model [24] was used to obtain the pooled mean difference (MD) for the effect of FT3 and FT4 on the risk of developing BC. The heterogeneity of the study results was evaluated by Cochran Q statistic [25], p values, and I^2 statistics. The extent of heterogeneity was further quantified using the I^2 statistic with results of 25, 50, and 75% correlating with low, moderate, and high levels of heterogeneity, respectively. P values < 0.1 was indicative of statistically significant heterogeneity. Different environments and races may lead to high levels of heterogeneity; therefore, the areas were classified as "Europe" and "Asia" to investigate between-study heterogeneity, and the specific measure of sensitivity was analysed by evaluating whether the results were influenced by a single study. Moreover, Begg's adjusted rank correlation test [26] and Egger's regression asymmetry test [27] were used to assess the extent of publication bias.

Results

Description of studies

Based on the search strategy, we retrieved 10,862 studies and excluded 10,849 studies for various reasons, as shown in Figure 1. Thirteen studies [1, 2, 4, 5, 14, 16–23] were eventually included in this systematic review; among these, 10 [1, 2, 4, 5, 14, 17–20, 23] were about FT3 and 13 [1, 2, 4, 5, 14, 16–23] were about FT4. The systematic review contained 9 cross-sectional studies, 2 case-control studies, and 2 cohort studies. We summarized the main characteristics of the studies, as shown in Table 2.

Methodological quality assessment

All the selected articles were assessed for methodological quality. The quality score of each study is presented in Table 1. Five studies were of high quality and eight studies were of moderate quality. There were no articles with a low quality rating.

FT3 and BC risk

We found 10 studies with 2934 participants investigating FT3 hormones levels and the association of BC. In all the analyses, the overall pooled results of FT3 parameters demonstrated that the hormone levels of FT3 were significantly increased in patients with BC (MD = 1.01 pmol/L, 95% CI: 0.32–1.70, p = 0.004) with high levels of heterogeneity (I^2 = 100%, p < 0.00001). Hence, we used a random-effect model and classified the areas as "Europe" and "Asia" to assess the heterogeneity of the study. In the "Europe" subgroup [1, 5, 19, 20] the level of heterogeneity was low (I^2 = 6%, p = 0.36) and the results were significantly different (MD = 0.42 pmol/L, 95% CI: 0.34–0.50, p = 0.36), but in the "Asia" subgroup [2, 4, 14, 17, 18, 23], there was no significant difference in hormone levels between FT3 and BC (MD = 1.43 pmol/L, 95% CI: –0.69–3.55), and the heterogeneity (I^2 = 100%, p < 0.00001) was also high (Fig. 2).

FT4 and BC risk

A total of 13 articles with 5957 participants were used to ascertain the risks of FT4 hormone levels and BC. All 13

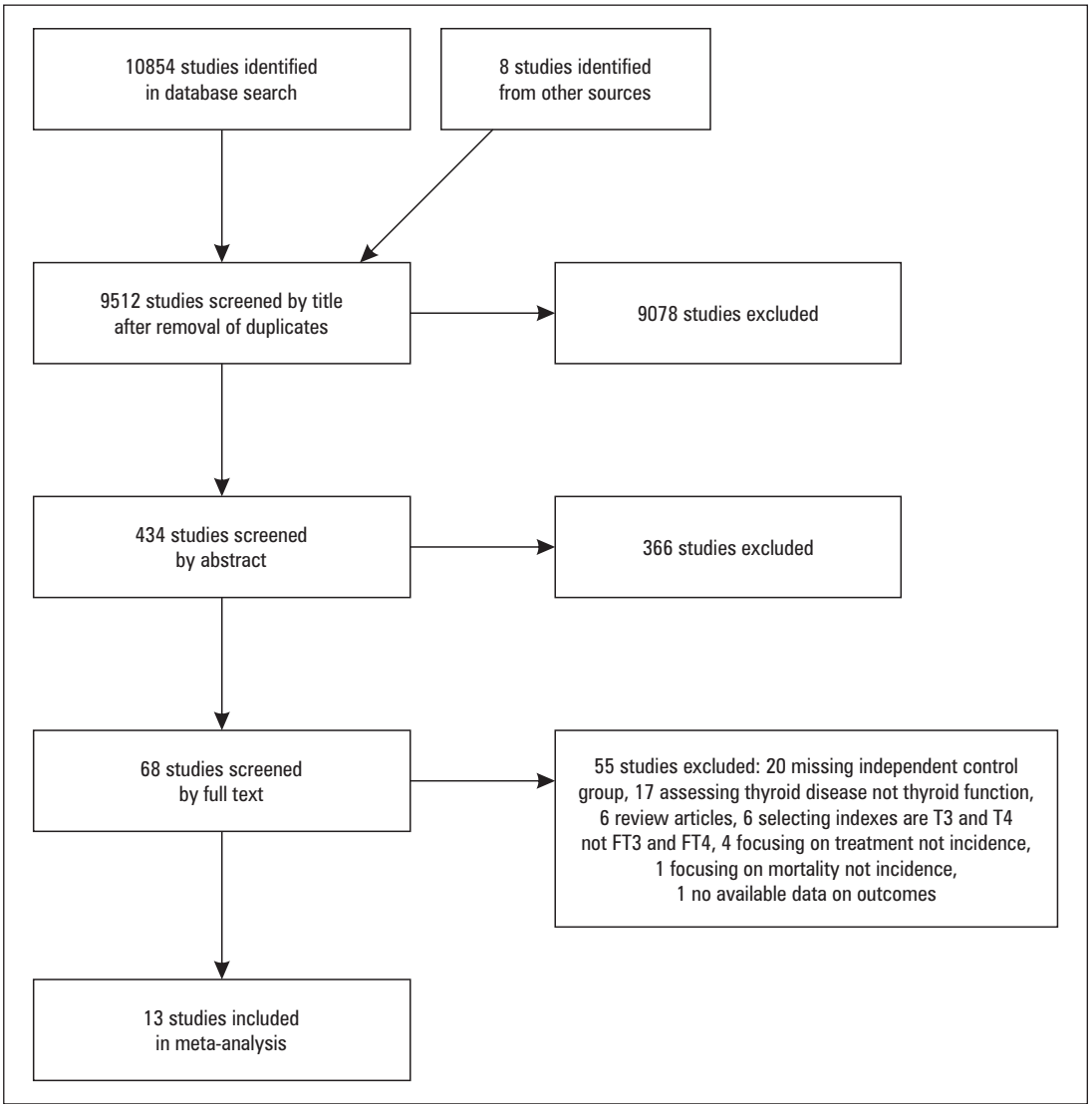

Figure 1. *Results of the literature search. T3 — triiodothyronine; T4 — thyroxine; FT3 — free triiodothyronine; FT4 — free thyroxine*

Table 2. ***The summary result for publication bias***

	Begg's test		Egger's test	
FT3	z = 0.72	p = 0.474	t = 0.73	p = 0.486
FT4	z = 0.55	p = 0.583	t = –0.53	p = 0.607

FT3 — free triiodothyronine; FT4 — free thyroxine

articles showed significant results of the hormone levels of FT4 and BC (MD = 0.26 ng/dL, 95% CI: 0.13–0.38, $p < 0.0001$) and high levels of heterogeneity ($I^2 = 99\%$, $p < 0.00001$). A random-effect and subgroup analysis (Europe and Asia) was used to investigate the hormone levels of FT4 and BC. Low heterogeneity ($I^2 = 26\%$, $p = 0.23$) and significant results (MD = 0.07 pmol/L, 95% CI: 0.04–0.10) were present in the "Europe" subgroup [1, 5, 16, 19–22]; however, there was high heterogeneity ($I^2 = 99\%$, $p < 0.00001$) in the "Asia" subgroup [2, 4, 14, 17, 18, 23] (Fig. 3).

Sensitivity analysis and publication bias

We implemented the specific measure of sensitivity analysis by evaluating whether the results were influenced by a single study. The meta-analysis was not

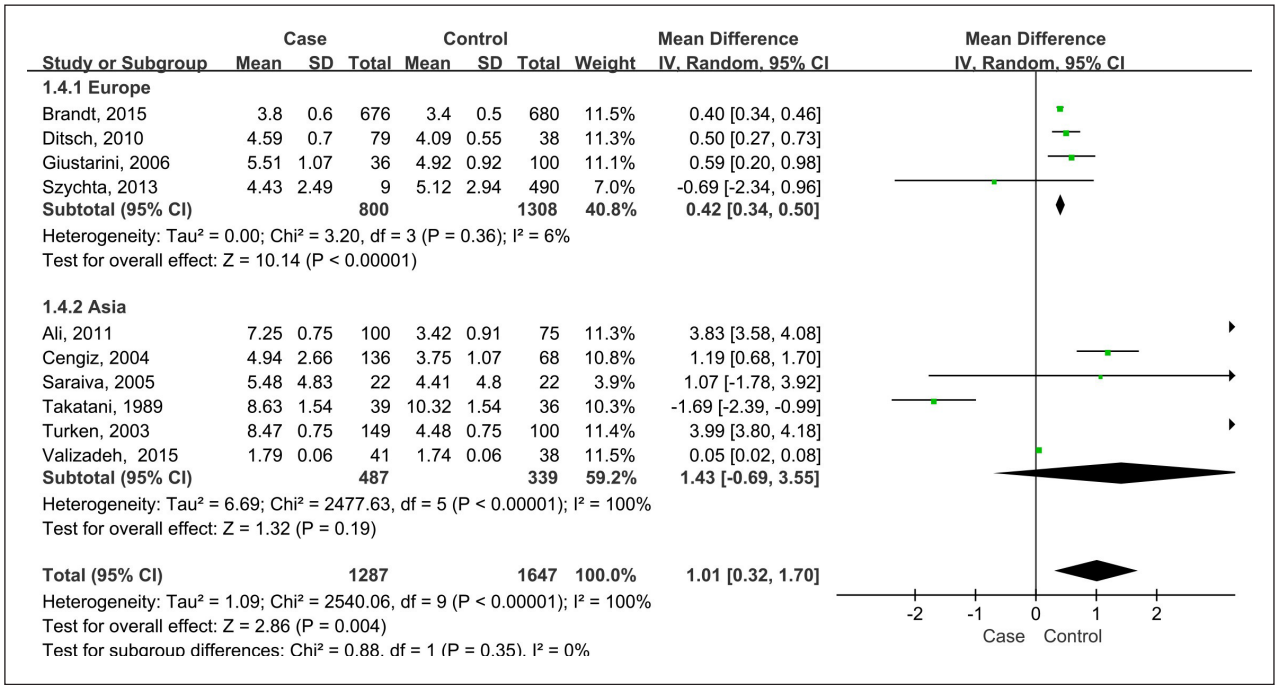

Figure 2. *Free triiodothyronine (FT3) and breast cancer (BC) risk*

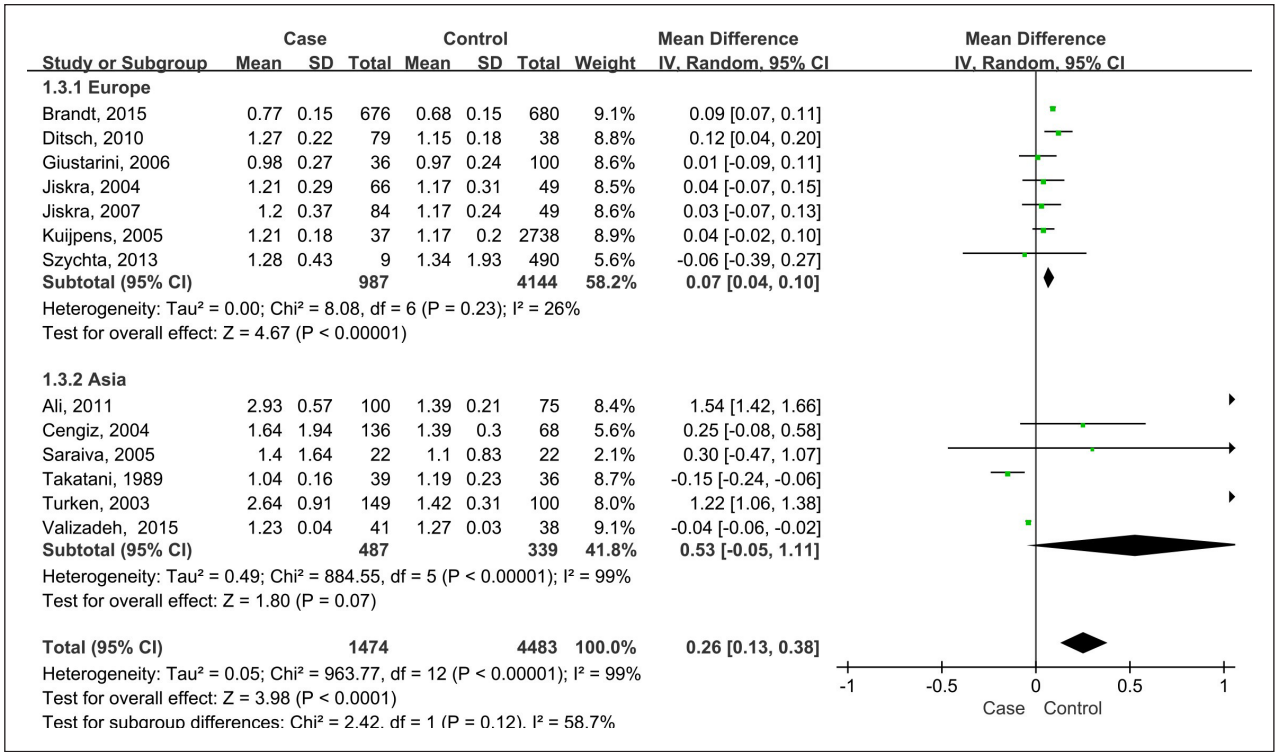

Figure 3. *Free thyroxine (FT4) and breast cancer (BC) risk*

dominated by any single study, and exclusion of any study at a time made no difference (figures not shown). The studies on FT3 and FT4 did not show publication bias as analysed by Begg's test and Egger's test (Tab. 2).

Discussion

Prospective studies have shown that high TH (FT3, FT4) levels increase the risk of BC, and no association was

found with thyroid stimulating hormone (TSH) [10, 28], so our meta-analysis investigated the risks of FT4 and FT3 in breast cancer. We found that the case group of BC patients had higher levels of FT3 and FT4 than controls. These results are consistent with the study by Ditsch et al. [5], which showed that high FT3 and FT4 hormone levels were related with BC ($p < 0.001$), and they contrast with the study by Kuijpens et al. [16], which showed low levels of FT4 correlated with a high risk of BC.

Giustarini et al. [20] reported no association between HT and BC. Subgroup analysis revealed the source of heterogeneity, but there was no clear explanation for the factors with high heterogeneity except for differences in environment and race.

A meta-analysis conducted in 2012 showed no relationship between hyperthyroidism and BC, there were few studies in this meta-analysis to explain that TSH was included in the diagnosis of hyperthyroidism. A meta-analysis conducted in 2014 showed no relationship between FT_4 and BC; the reason might be that the author only searched articles published from 2000 to 2014, so some articles were not included in the meta-analysis. Although the sample sizes of Søgaard et al. (n = 142,216) and Chen et al. (n = 25,125) were very large, they were excluded from our meta-analysis. There are 2 major reasons: (1) there were no healthy participants as a control group in the 2 studies, which does not satisfy the first principle of our selection criteria, and (2) the two studies used qualitative data to diagnose thyroid disease. To improve the quality of our meta-analysis, we developed precise inclusion criteria and used quantitative data, which are more sensitive and accurate than qualitative data, to analyse the level of TH, with no restrictions on the time and language of the articles published.

A broad study search and two or three independent participants analyzing data with high coincidence rate were the strengths of this meta-analysis. Most of the studies were cross-sectional studies with a lack of randomized controlled trial of high quality in this study. Thus, clearing the association between TH and BC, we may not definitively get causality.

Although the conflict between BC and TH has been studied for years [29], the mechanisms underlying the association between them are still unclear. TH and oestrogen play an important role in BC cell growth and development [9, 11, 14]. As a mitogen, they played a regulatory role in BC cell mitosis and apoptosis and increase the risk of BC [14, 29–32]. Biologically active TH has the function of significantly stimulating the proliferation and differentiation of breast tissue by promoting lobular growth [9, 33, 34], and it affects the expression of aromatase, oestrogen, and oestrogen receptor [35]. When TH and oestrogen are not balanced (the ratio increased significantly) there is an increased risk of BC [9].

Several hypotheses elucidate the risk of TH and BC:

1. TH was able to bind to the integrin $\alpha V\beta 3$, which is a plasma membrane protein that contains 2 TH binding sites (S1, S2) [36, 37]. The 2 TH binding sites translate different signals: one of the pathways, TH binding the integrin $\alpha V\beta 3$ site of S1, which activates the oncogenic phosphatidylinositol-3-kinase (PI3K) pathway [29], subsequently induces hypoxia-inducible factor (HIF-1α) gene expression. HIF-1α, as a prognostic marker, plays important role in BC cell invasion and metastasis [16, 38]. The other pathway, from site of S2, activates mitogen-activated protein kinase (MAPK) [39], subsequently inducing the oncogenic extracellular signal-regulated kinase 1/2 (ERK1/2) pathway. ERK1/2 not only induces the fibroblast growth factor 2, which can stimulate angiogenesis and tumour growth [29], but also stimulates the oestrogen response element (ORE) by activating oestrogen receptor α (ORα) to alter the transcriptional levels of key proteins involved in BC cell proliferation and survival [39];
2. TH can regulate the expression of anti-apoptotic genes and pro-apoptotic genes [40, 41], e.g. TH increases expression of programmed death-ligand 1 (PD-L1) gene, which can protect BC cells from T-cell-mediated destruction, in contrast, to reduce the activity of caspases to avoid DNA collapse. Other hypotheses about TH and solid tumours, such as lung cancer, are not discussed in this study, and future studies can clear the mechanisms underlying the association between TH and BC.

TH and BC are not only strongly related in our analysis, but also are related to mortality [42]. The lack of a large sample of participants and high-quality studies are the major limitations in our study. We implemented precise inclusion criteria to avoid bias, but confounding factors such as age, tumour size, tumour stage, etc. must be carefully considered in this meta-analysis. We cannot obtain data on the above confounding factors, so a large sample of participants and the various confounding factors should be included in future studies.

Conclusions

We found that FT3 and FT4 increased the risk associated with BC. Imperatively, physicians were aware of the clinical significance of this study and applied it to breast cancer screening. In the future, high-quality epidemiological studies and prospective studies should be carried out to provide evidence to help in the treatment of patients with hyperthyroxinaemia.

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Authors' contributions
Conception and design: Z.L., B.Z., L.W., Q.D., and D.G. Administrative support: D.G. and Q.D. Collection and assembly of data: D.G., Z.L., B.Z., and Q.D. Data analysis and interpretation: Z.L., B.Z., D.G., and Q.D. Manuscript writing: all authors. Final approval of manuscript: all authors.

Conflict of interest
The authors declare that they have no conflict of interest.

Ethics approval and consent to participate
Not applicable.

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Availability of data and materials
The datasets used and analysed for the present study are available from the corresponding author upon reasonable request.

ORIGINAL PAPER

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