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ORIGINAL ARTICLE

The Detection of *BRCA1* and *BRCA2* Mutations in Saudi Females with Breast Cancer in Al-Madinah Province by Next Generation Sequencing

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ABSTRACT

Background: **Breast cancer has the highest incidence among Saudi women and is often diagnosed at a younger age with distinct genetic features. This study aimed to determine the prevalence and mutation of germline *BRCA1* and *BRCA2* mutations in Saudi women in Al-Madinah Province with breast cancer.**
Methods: **This cross-sectional study included 54 Saudi females with a median age of 46.5 years (IQR 39.0 - 53.7 years). Genomic DNA from peripheral blood was screened using high-depth next-generation sequencing (NGS), which encompassed all coding exons and splice regions of *BRCA1* and *BRCA2*. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Clinical information, such as age at diagnosis, cancer subtype, staging, treatment response, and overall survival, was collected from patients' medical files to assess them against mutation status.**
Results: **Pathogenic or likely pathogenic BRCA variants were found in eight patients (14.8%): five had *BRCA1* mutations (62.5%), four of which were pathogenic variants including a large exon 16 deletion in one patient and one was likely a pathogenic variant. Three patients had *BRCA2* mutations (37.5%); all of which were pathogenic variants. Most mutation carriers (62.5%) developed the disease at a relatively young age, particularly in *BRCA2* carrier ER-positive patients, although the difference between carriers and non-carriers was not statistically significant (p = 0.6). Carriers were significantly more likely to have a positive family history (p = 0.001). The mortality rate was higher in carriers (25%) than in non-carriers (2.2%); however, this difference was statistically non-significant (p = 0.05), a finding that may be related to the small sample size.**
Conclusions: **Mutations of *BRCA1* and *BRCA2* were detected; the prevalence was 14.8%. These mutations are associated with a relatively young age at diagnosis, a positive family history, and a lower survival rate. The findings highlight the need for robust BRCA mutation screening and genetic counseling for female breast cancer patients to enable appropriate risk assessment and clinical intervention.**
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KEYWORDS

BRCA1 and *BRCA2* mutations, TNBC: triple-negative breast cancer, NGS: next-generation sequencing

INTRODUCTION

Breast cancer is the most prevalent cancer among women and a primary cause of cancer-related mortality, making it a significant global health concern. The disease is caused by the uncontrolled proliferation of abnormal cells in the breast, predominantly in the milk-se-

creting cells and duct cells [1]. Key risk factors include age and gender, with a higher incidence in women; genetic factors, such as family history and specific gene mutations like those in *BRCA1* and *BRCA2*; and lifestyle choices, including obesity and hormone replacement therapy [2].

Saudi women often receive a diagnosis at considerably younger ages than women in Western countries, which may point to genetic and environmental factors. They also frequently present with later-stage, high-grade breast cancer when first diagnosed [3]. Convincing evidence suggests that the existence of genetic modifications in *BRCA1* and *BRCA2* leads to a heightened risk for breast and ovarian cancer. Women, especially younger women, who possess these genes are more likely to develop breast cancer [4].

BRCA1 was the first gene linked to familial breast and ovarian cancer syndrome. Its location is on the long arm of chromosome 17 and encodes a protein of 1,863 amino acids [5]. This protein has ubiquitous expression and is critical for myriad cellular functions, including cell cycle regulation, DNA damage repair, transcription, and proteolytic degradation by ubiquitination. The *BRCA2* gene is located on the long arm of chromosome 13 and encodes a protein containing more than 3,400 amino acids [6,7].

Various damaging loss-of-function mutations can occur in active regions, including nonsense mutations, small insertions or deletions, splices, large rearrangements, and even the entire *BRCA1* gene. Three breast cancer clusters have been discovered: c.179 to c.505, c.5261 to c.5563, and c.4328 to c.4945 [8]. Some large-scale genomic rearrangements, such as deletions or insertions spanning several kilobases, have also been documented in breast cancer cases involving *BRCA1* and *BRCA2* genes [9].

While numerous potential breast cancer cluster regions have been designated, particularly toward the 3′ end of the gene, pathogenic *BRCA2* mutations that cause a loss of function can occur throughout the entire gene, similar to *BRCA1* [9]. This was underscored by the identification of two other damaging mutations, *BRCA2* c.5964 delT and *BRCA2* c.771_775del, which are reported to account for a significant percentage of breast cancer families [10].

Individuals with a *BRCA2* mutation have a markedly higher risk of developing breast cancer during their lifetime and can develop it at a relatively young age. A recent article specified that a notable proportion (70 to 80 percent) of patients with breast cancer have positive ER and assumes the dominant positive role. Unlike self-occurring ER-positive tumors, *BRCA2*-mutated ER-positive breast cancers tend to have worse clinicopathological aggressiveness [11]. An analysis of 263 mutations across 51 genes found an infection prevalence of 11.7% for *BRCA2* and 10.2% for *BRCA1*. The study also identified 46 other variants in 22 genes that were previously deemed pathogenic, which undermines their value in genetic discrimination [12]. Thus, Saudis may have some unique genetic features that complicate the treatment of breast cancer. Survivorship analysis suggests that patients with *BRCA1* and *BRCA2* mutations had worse survival rates than the general patient population [12].

Despite the existence of numerous genetic indicators that predict the onset and management of breast cancer, a knowledge gap remains regarding BRCA mutations among Saudi Arabian women. It has been over a decade since the first report on the occurrence of *BRCA1* and *BRCA2* mutations in breast cancer patients in Saudi Arabia was published, yet very few studies have attempted to assess the prevalence of these mutations [13].

This study aimed to determine the prevalence and mutation of germline *BRCA1* and *BRCA2* mutations in Saudi women in Al-Madinah Province with breast cancer.

MATERIALS AND METHODS

Study design and participant recruitment

This cross-sectional study aimed to determine the clinical value and the prevalence of *BRCA1* and *BRCA2* mutations in breast cancer among Saudi females. Study participants were recruited from the Oncology Center at King Salman Bin Abdulaziz Medical City (KSAMC) in Al-Madinah in the western region of Saudi Arabia. The study included women aged 18 years and older with a diagnosis of breast cancer. Participants were excluded if they had received prior BRCA-altering therapies. All participants provided written informed consent after researchers explained the study's purpose, methodology, and associated risks. Researchers took a full history, including age, menstruation status, and family history of breast, ovarian, or colorectal cancer. Histopathological examinations, tumor grades, and metastasis were extracted from the medical records of each patient.

Sample collection and preparation

For each participant, 5 to 10 mL of blood was collected in EDTA tubes and stored at 4°C until processing. Samples were sent to the central lab within 24 hours for DNA extraction. Clinical data, such as tumor grade, stage, treatment history, menopausal status, and temporal data (e.g., age and family history of breast or ovarian cancer), were derived from health records. Genomic DNA was extracted from blood leucocytes using the Qiagen QIAamp DNA Blood Mini Kit according to the manufacturer's instructions. A NanoDrop spectrophotometer assessed the purity of the extracted DNA by measuring standard ratios at 260/230 nm and 260/280 nm (Algebaly et al., 2021; Alhuqail et al., 2018). DNA samples required an ideal ratio of 1.8 - 2.0 to be classified as high quality. Some samples were run on a 1% agarose gel to test DNA integrity; clear, distinguishable bands indicated that the samples met the quality standards set for later stages of the procedure.

Next-generation sequencing assay for *BRCA1* and *BRCA2* genes

Genomic DNA from 30 - 100 ng samples was loaded and analyzed using the Ion GeneStudio S5™ System (Thermo Fisher Scientific) following the manufacturer's instructions. The assay provided approximately 100% exon coverage across both *BRCA1* and *BRCA2* genes, with high uniformity and read counts across all exons, allowing for over 99% confidence in detecting 5% somatic variants. Torrent Suite™ v 5.14 software processed the raw data and performed signal processing.

Statistical analysis

Statistical analyses were performed using SPSS (version 25.0). Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as mean with standard deviation or median with IQR. The Shapiro-Wilk test assessed normality. The Chi-squared and Fisher's exact tests evaluated associations between BRCA mutations and categorical clinicopathological features, as appropriate. Independent *t*-tests or Mann-Whitney U tests analyzed continuous variables. Survival analyses were conducted using Kaplan-Meier methods, and survival curves were compared using the log-rank test. Cox proportional hazards regression analysis calculated hazard ratios (HR) with 95% confidence intervals (CIs). A p-value less than 0.05 was considered statistically significant.

RESULTS

Prevalence of BRCA mutations in the studied patients

Participants enrolled in the current study comprised 54 Saudi female patients with breast cancer. The median age at diagnosis was 46.5 years (IQR 39.0 - 53.7 years). Researchers screened all patients for BRCA gene mutations.

BRCA gene mutations were found in 14.8% (8 out of 54) of the patients (Figure 1, Table 1). *BRCA1* mutations accounted for 62.5% (5 out of 8), and *BRCA2* mutations accounted for 37.5% (3 out of 8) (Figure 2, Table 1). Non-carriers of BRCA mutations constituted the remaining 85.2 percent (46 out of 54) (Table 1) and (Figure 1, Figure 2).

Mutation spectrum and functional impact

Nearly 5 patients have *BRCA1* mutations, most of them are deletions (3 out of 5), while three patients have *BRCA2* mutations as illustrated in (Table 2). Demographic and clinicopathological data in carrier patients are summarized in (Table 3). All our detected variants were reported previously in ClinVar and HGMD.

The overall survival rate was significantly lower in patients with BRCA mutations compared to those without (log-rank p = 0.034). In Cox-regression analysis, the presence of a BRCA mutation was associated with a higher risk of mortality (HR = 2.8; 95% CI: 1.05 - 7.72; p = 0.04). In Figure 3, the comparison of survival between patients with BRCA mutations and those without. And in Figure 4, the mutations of both BRCA were stratified.

DISCUSSION

BRCA1 and *BRCA2* are DNA repair genes that produce proteins to help repair damaged DNA. Mutations in these genes increase the risk and influence the severity of the function of cancer and interfere with the cell cycle due to their role in maintaining orderly cellular processes [6].

More than 60% of women who inherit a harmful *BRCA1* or *BRCA2* mutation will develop breast cancer during their lifetime. By contrast, about 13% of women in the general population will develop breast cancer during their lifetime. Women, especially younger ones, possessing these mutations are more likely to develop breast cancer [4].

This study aimed to determine the prevalence of *BRCA1* and *BRCA2* mutations in females diagnosed with breast cancer in Al-Madinah province, Saudi Arabia, and establish the influence of these genetic alterations on the course and prognosis of the disease in this population. In the studied cohort, two *BRCA2* carrier patients had invasive ductal carcinoma at 49 and 52 years of age and were ER-positive. This finding matches previous reports that individuals with a *BRCA2* mutation have a markedly higher risk of developing breast cancer during their lifetime and can develop it at a relatively young age. Li and his colleagues specified that a notable proportion (70 to 80 percent) have breast cancer that is positive for ER [15]. As Al-Moghrabi et al. reported, *BRCA2*-mutated ER-positive breast cancers tend toward greater clinicopathological aggressiveness [11].

This can also be attributed to the high rate of consanguinity in Al-Madinah. One study suggests that the high levels of consanguinity in the western part of the Kingdom of Saudi Arabia are likely to result in the increased accumulation of some harmful genetic traits [7]. This, alongside lifestyle changes, may explain why there is a rise in the frequency of BRCA mutations and the lower average age of first symptoms of breast cancer within this population sample [16].

In the present study, BRCA mutation carriers had a median age of 50.5 years, which is distinctly younger than Western and Caucasian cohorts, where the median age is recorded to be over 63 years. Intriguingly, five out of eight patients were diagnosed before the age of 60 (62.5%), and one (12.5%) was diagnosed below the age of 30, highlighting the necessity for early employment of BRCA mutation genetic screening in Saudi Arabia. Furthermore, although age alone did not significantly associate with BRCA variants, a highly significant difference existed between BRCA carrier and non-carrier patients regarding familial history (p = 0.001). This indicates the importance of screening for BRCA muta-

Table 1. Distribution of BRCA mutation in the studied patients (n = 54).

Variable	Statistic
Age Median	46.5 years
IQR	39.0 - 53.7 years
Non-Carriers for BRCA mutations	46 patients (85.2%)
Carriers for BRCA mutations	8 patients (14.8%)
Positive (*BRCA1*)	5 patients (62.5%)
Positive (*BRCA2*)	3 patients (37.5%)

Table 2. *BRCA1 and BRCA2* variant types.

Gene	cDNA change	Protein change	Variant type	Significance
BRCA1	c.5030_5033del	p.Thr1677IlefsTer2	frameshift	pathogenic
BRCA1	c.5363G>C	p.Gly1788Ala	missense	likely pathogenic
BRCA1	c.5530del	p.Leu1844SerfsTer11	frameshift	pathogenic
BRCA1	exon 16 deletion	non	large deletion	pathogenic
BRCA1	c.5095C>T	p.Arg1699Trp	missense	pathogenic
BRCA2	c.1813del	p.Ile605TyrfsTer9	frameshift	pathogenic
BRCA2	c.7234_7235insG	p.Thr2412SerfsTer2	frameshift	pathogenic
BRCA2	c.7480C>T	p.Arg2494Ter	nonsense	pathogenic

Table 3. Demographic and clinicopathological data of carrier patients.

Characteristic	*BRCA1* Carrier 1	*BRCA1* Carrier 2	*BRCA2* Carrier 3	*BRCA2* Carrier4	*BRCA2* Carrier 5	*BRCA1* Carrier 6	*BRCA1* Carrier 7	*BRCA1* Carrier 8
Age (years)	26 years	37 years	65 years	49 years	52 years	46 years	67 years	66 years
Premenopausal onset	✓	✓	-	✓	-	✓	-	-
Menoposal onset	-	-	✓	-	✓	-	✓	✓
Family history	positive (mother& sister)	positive (sister)	negative	positive (mother)	negative	negative	positive (sister)	positive (cousins)
Pathological diagnosis	IDV	IDV	IDV	IDV	IDV	IDV	IDV	IDV
Tumor grade	1	3	2	2	2	3	3	2
Metastasis	✖	✓	✓	✖	✓	✓	✓	✓
Survival	alive	alive	died	alive	alive	died	alive	alive
Chemotherapy. Response	good	good	not good	good	not good	good	good	good

IDV: Invasive Ductal Carcinoma.

tions in high-risk individuals, as the guidelines of the National Comprehensive Cancer Network recommend [17].

Some identified variants in the present study included frameshift deletions, nonsense mutations, and class genomic rearrangements, all considered pathogenic or

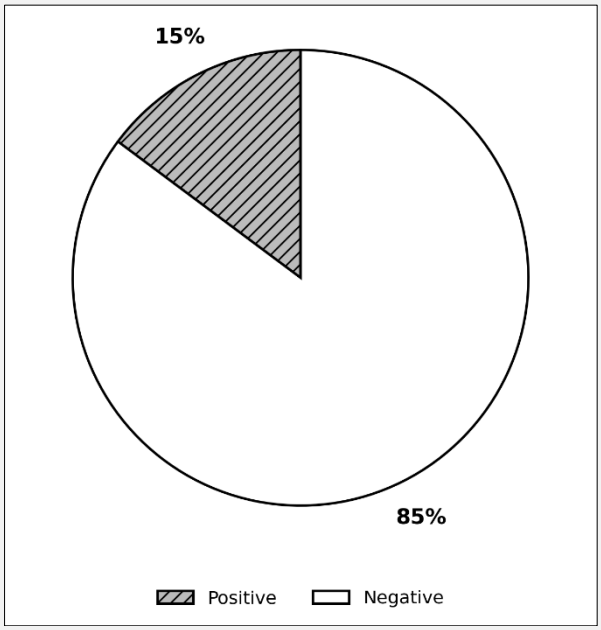

Figure 1. Prevalence of the BRCA Mutations.

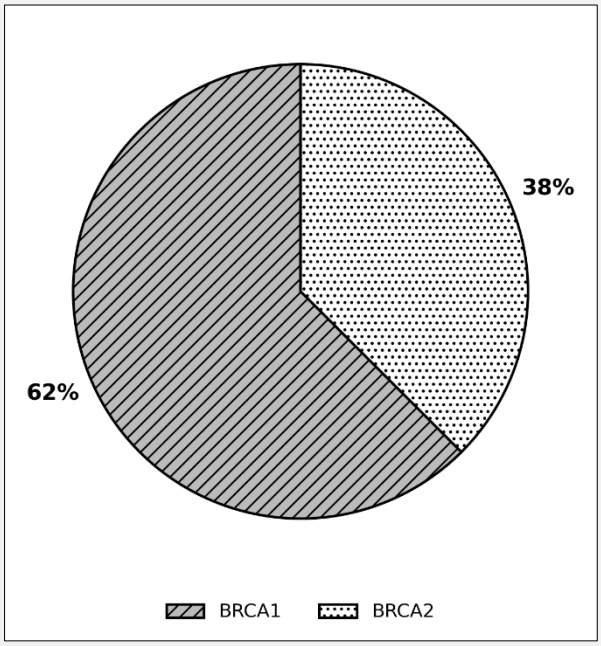

Figure 2. Distribution of BRCA gene mutation in carrier patients.

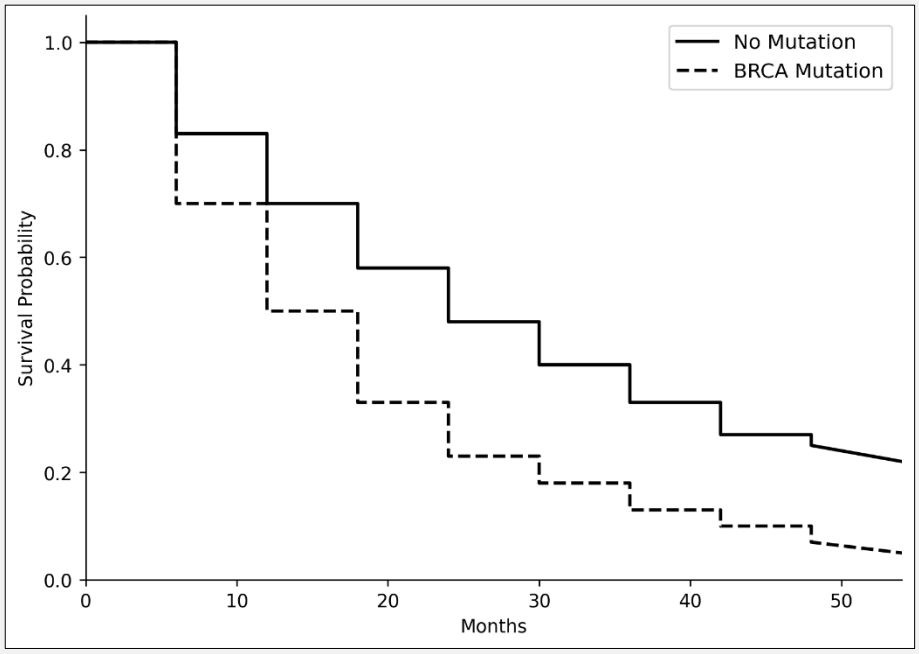

Figure 3. Kaplan-Meier survival curve (BRCA mutation against no mutation).

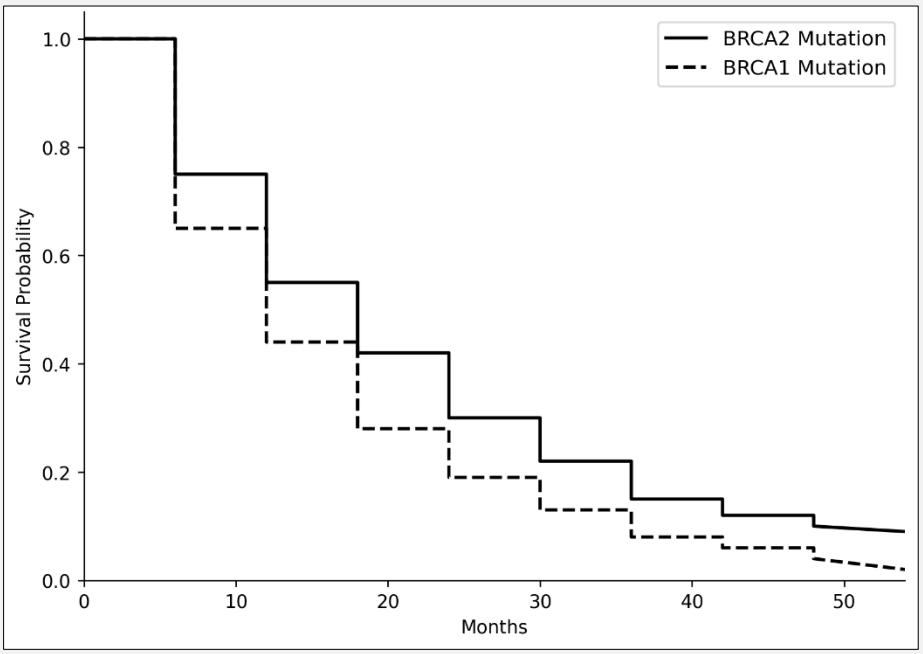

Figure 4. Kaplan-Meier survival curve (*BRCA1* against *BRCA2*).

likely pathogenic. For *BRCA1*, recurrent truncating mutations were c.5530del (p.Leu1844SerfsTer11) and an exon 16 deletion, both known to hinder homologous recombination repair. In line with findings from global databases such as ClinVar and ENIGMA, the *BRCA1* variant c.5363G>C (p.Gly1788Ala) was deemed likely pathogenic. This was classified as a missense change impacting a conserved residue within the C-terminal domain of *BRCA1*. Other identified *BRCA2* mutations included c.7480C>T (p.Arg2494Ter), a nonsense variant, and c.1813del (p.Ile605TyrfsTer9), a frameshift deletion.

Finally, we found that two out of five (40%) *BRCA1* carrier patients enrolled in the study had TNBC. TNBC is an aggressive subtype with limited treatment options and is common in women with a *BRCA1* gene mutation [17]. Supporting this, a 2018 Saudi study by Abulkhair et al. showed a strong correlation between TNBC and BRCA mutations. Out of those with mutations, 86% had TNBC and *BRCA1* mutations, which was more frequent than previously reported [18]. When comparing overall survival rates in the present study, carriers had a lower survival rate than non-carriers (25% versus 2.2%); however, the small sample size rendered this difference statistically non-significant ($p = 0.0542$).

CONCLUSION

In conclusion, this study sets the stage for precision oncology tailored to the region's needs. It highlights the importance of implementing genetic screening in breast cancer protocols in Saudi Arabia to improve early detection, treatment customization, and patient survival rates.

By focusing on the identification and implications of *BRCA1* and *BRCA2* mutations, this study sheds light on the genetic basis of breast cancer in Saudi women. The findings reveal a high prevalence of pathogenic variants of *BRCA1* and *BRCA2* in younger patients, suggesting an indigenous early-onset breast cancer phenotype that differs from what is documented in Western populations. Our data corroborate other studies stating that the aggressive disease in our cohort may partly explain the predominance of *BRCA1* mutations, mainly those associated with TNBC, underscoring the need for early genetic screening.

The study reaffirmed that *BRCA1* and *BRCA2* mutations greatly impact the clinical picture and prognosis of breast cancer among Saudi women in terms of their tumor features. These results reinforce the argument for the integration of genetic testing into routine diagnostic evaluations, particularly for defined high-risk groups.

These findings have both clinical and public health implications. Clinically, the presence of specific BRCA mutations opens new options for tailored treatment strategies. From a public health perspective, the findings advocate for incorporating genetic counselling, tailored screening questionnaires, and family-based risk evaluation strategies into proactive, population-wide measures for managing breast cancer on a national scale.

Despite its contributions, this study was constrained by an insufficient sample size, single-center participant recruitment (the cohort of n = 54 was from Al-Madinah province), and gaps in clinical documentation; these should be foci of further investigations.

Future research requires larger, multicentric coverage areas from other parts of Saudi Arabia to achieve better population representation. Furthermore, adding other multigene panels such as TP53 and PALB2 to *BRCA1* and *BRCA2* screening would increase the predictive value. Prospective long-term follow-up studies are also necessary to elucidate further the prognostic implications of different mutations and inform treatment strategies.

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Ethical Approval:
The local ethics committee at King Salman Medical City granted ethical approval (IRB log No.: 2i005). All participants signed a written informed consent form. The study protocol adhered to the guidelines of the Declaration of Helsinki (1975, revised in 2000).

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Declaration of Interest:
The author has no conflicts of interest to declare, and the work was not supported or funded by any drug company. The work was not presented at any conference.

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