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Research Article

MULTIVARIATE ANALYSIS WITH EMPHASIS OF HER2/NEU EXPRESSION ON OVARIAN TUMORS IN A TERTIARY CARE HOSPITAL

PRAVEENA T*, PAVITRA K, MADHAVI K

Department of Pathology, Gitam Institute of Medical Sciences and Research, Visakhapatnam and Government Medical College, Srikakulam, Andhra Pradesh, India.
***Corresponding author: Praveena T; Email: tpraveena354@gmail.com**

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ABSTRACT

Objectives: The objective of the study was to evaluate immunohistochemical expression of HER2/NEU in ovarian tumors. Whether we can correlate HER2/NEU expression with the age of the patient, tumor size, histopathological type, and histopathological grade of the tumor.

Methods: Retrospective study was carried out for 2 years, ovarian specimens were received, grossing was done and evaluated with hematoxylin-eosin staining on 40 cases, and immunostaining with HER2/NEU was done on 32 cases of surface epithelial tumors.

Results: Out of 32 cases, HER2/NEU positivity was seen in 18 (56.5%) cases, and negativity was seen in 14 (43.5%) cases. Fifteen cases (46.8%) were serous type and 17 cases (53.2%) were mucinous ovarian tumors. In serous tumors, 0/+1 score was seen in 5(15%) benign (serous cystadenomas + serous adenofibromas) tumors, and in 1(3.1%) borderline, +2 score was seen in 2 (6.3%) borderline and +3 score was seen in 7 (21.8%) serous cystadenocarcinomas. In mucinous tumors, 6 (18%) benign (mucinous cystadenomas) and 2(6.3%) borderline tumors showed 0/+1 score. Score +2 was assigned to 5 (13.8%) benign (mucinous cystadenomas) tumors, 2(6.3%) mucinous cystadenocarcinomas and 2 (6.3%) mucinous cystadenocarcinomas shown +3 positivity

Conclusion: HER2/neu expression needs further evaluation to emerge as a prognostic indicator, which indicates disease progression, survival rate, and whether its overexpression can be correlated with the staging of the tumor or not in the near future. Prognostic significance of HER2/NEU is well established in breast carcinomas, unlike in ovarian carcinomas, which warranted further studies to establish its role.

Keywords: Ovarian tumors, HER2/neu expression, Histopathological grade.

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INTRODUCTION

Ovarian tumors are a diverse group of malignancies arising from various cell types like epithelial, sex cord stromal, and germ cells [1]. Epithelial ovarian cancer is one of the leading causes of death from gynecological cancers. There is an urgent need to better understand the molecular mechanisms of ovarian tumors, to identify new targets and biomarkers for early detection and treatment [1,2]. The HER2/NEU oncogene on chromosome 17q21 encodes a protein that functions as a tyrosine kinase growth factor receptor. HER2/NEU overexpression serves as a predictive and prognostic marker in various carcinomas, mostly in breast carcinomas, approximately in 15–30% cases and in 10–30% gastric or gastroesophageal carcinomas, so in these carcinomas HER2/NEU directed therapies are giving promising results regarding the survival. Its overexpression is also seen in carcinomas of the head and neck, lung, bladder, colon, lung, endometrium and ovary. However, targeted therapies are not up to the mark in these carcinomas associated with different outcomes and survival. Expression of HER2/NEU in surface epithelial ovarian tumors is associated with varied clinical outcome [3]. Epithelial ovarian carcinomas are the important and one of the most common causes of postmenopausal bleeding. Immunohistochemical study of cytokeratins, epidermal growth factor receptor (EGFR), Ki67, and p53 were evaluated to study the outcome in ovarian carcinomas [3,4].

In our study, we evaluated the HER2/NEU expression in surface epithelial tumors.

"HER2/NEU expression according to CAP guidelines":

- Tumors that show strong circumferential staining (referred to as +3 staining) in >30% of cells by Immunohistochemistry (IHC)
- Tumors that show moderately strong circumferential membrane staining (referred to as +2 staining)
- Tumors that show little or no protein expression by IHC (referred to as 0 or +1 staining) [5].

Aims and objectives

1. To evaluate immunohistochemical expression of HER2/NEU in ovarian tumors
2. Whether we can correlate HER2/NEU expression with the age of the patient, tumor size, histopathological type, and histopathological grade of the tumor.

Inclusion criteria

Ovarian tumors with a size >3 cm diameter were included in the study.

Exclusion criteria

- Endometriotic cysts, tumors <3 cm diameter, polycystic ovaries, simple cysts, and tubo-ovarian masses excluded
- Insufficient tissue samples
- Patients with previous treatment history
- Cases with inadequate clinical data.

METHODS

It is a retrospective study carried out in the tertiary care hospital for 2 years from 2019 to 2021. The present study was approved by the ethical committee. A total of 40 cases were selected, taking the inclusion and exclusion criteria.

All specimens were fixed in neutral buffered formalin, subjected to hematoxylin-eosin staining, and IHC (peroxidase-antiperoxidase method) of HER2/NEU was done using polyclonal Anti-HER2/NEU Antibody (AN471/5ME). Breast carcinoma with HER2/neu positive expression taken as control for the evaluation of scoring and intensity in surface epithelial ovarian tumors. Immunohistochemical study of HER2/NEU expression was evaluated by two independent pathologists, and each one assigned different scores and the average value was taken into consideration.

Interpretation

Qualitative assessment

Intensity is assessed qualitatively with a focus on the cytoplasmic membrane staining of tumor cells. For qualitative assessment, strong staining can be easily seen on lower magnification (×4), while faint cytoplasmic membrane staining that could only be detected using higher magnification (×40) is taken into consideration.

Scoring system

Dark brown membrane staining was taken as positive immunoreaction. The intensity of staining is evaluated by counting the number of positive cells among 100 malignant cells at the total magnification of ×40. The percentage of immunoreactive cells is calculated relative to the total number of malignant cells. Each sample was scanned for at least five fields with a high power magnification.

We followed the HER2/NEU scoring method by Sophia *et al*. at objective 40 and as follows:

- Scoring 0 (negative): No staining or only faint, incomplete membrane staining that is barely perceptible in <10% of tumor cells, indicates no overexpression
- Score +1 (negative): Incomplete membrane staining that is faint or perceptible in more than 10% of cancer cells indicates no overexpression
- Score +2 (equivocal): Complete circumferential moderately intense membranous staining observed in more than 10 % of the tumor cells, suggesting equivocal overexpression

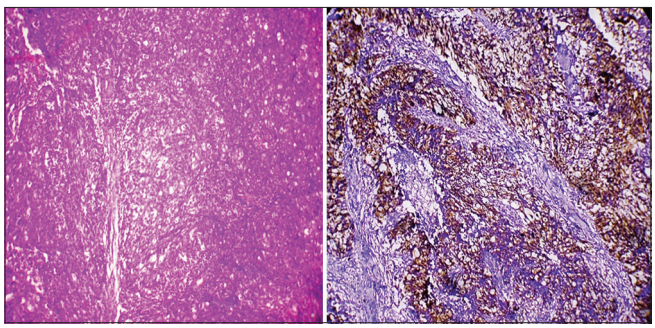

Fig. 1: Poorly differentiated serous cystadenocarcinoma, Grade 3, HER2/NEU positivity score +3

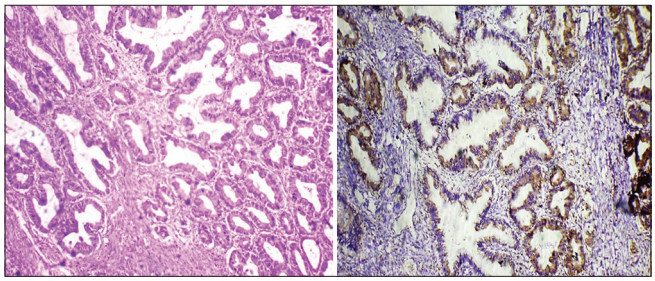

Fig. 2: Mucinous cystadenocarcinoma, Grade 3, HER2/NEU positivity score +3

- Score +3 (positive): Circumferential membrane staining that is complete and intense involving more than 10 % of tumor cells, suggesting overexpression *o*f the HER2 gene [6].

Intensity and proportion of cells with cytoplasmic membrane staining were taken into consideration for our scoring. Only well-preserved and well-stained slides were assessed.

Evaluation criteria

Only cytoplasmic membrane staining was evaluated, as cytoplasmic staining was considered to have uncertain biological significance. So tumors showing +2 and +3 positivity were taken into consideration. Gene amplification or gene expression by fluorescence *in situ* hybridization technique was not evaluated in this study. +2 and +3 scores are taken as HER2/NEU positivity and score 0/score +1 is taken as negative.

Statistical analysis

All cases were entered in a Microsoft Excel sheet. Quantitative analysis was done on relative frequencies and percentages.

RESULTS AND DISCUSSION

HER2/NEU is an oncogene associated with malignant transformation and may significantly contribute to the development of various cancers, including ovarian carcinomas**.** However, the prognostic significance of HER2/NEU in ovarian tumors, evaluated in multiple studies, demonstrates varied expression across different individuals and studies due to differing sample sizes [5,7,9].

Table 1: Distribution of ovarian tumors

Type of the tumor	Number of cases (%)
Surface epithelial tumors	32 (80)
Non-surface epithelial tumors	8 (20)
Total	40

40 cases were subjected to Hematoxylin and eosin staining out of which 32 (80%) cases were surface epithelial tumors and 8 cases (20%) were non-surface epithelial tumors, which include germ cell tumors, metastatic deposits, and sex cord-stromal tumor

Table 2: Comparison of our study with Goel *et al*. according to histopathological type

Type of ovarian tumor	Our study	Goel *et al.*
Surface epithelial tumors	32	26
Non-surface epithelial tumors	8	11
Total	40	37

Table 3: Distribution of HER2/NEU expression according to size of the tumor

Tumor size	HER2/NEU positive (%)	HER2/NEU negative (%)
<10 cm	6 (18.8)	7 (21.8)
>10 cm	12 (37.6)	7 (21.8)

Tumor size <10 cm seen in 6 cases (18.8%) of HER2/NEU positive and 12 cases (37.6%) of HER2/NEU positivity shown tumors size >10 cm. In HER2/NEU negative cases, tumor size <10 cm is seen in 7 cases (21.8%) and 7 cases (21.8%) are showing size >10 cm

Table 4: Comparison of HER2/NEU positivity for size with other studies

Size of the tumor	Our study	Goel *et al.*	Sueblinvong *et al.*
<10 cm	6	9	6
>10 cm	12	9	17

Table 5: HER2/NEU expression according to age of the patient

Age of the patient (in years)	Number of HER2/ NEU positive and percentage	Number of HER2/ NEU negative and percentage
<50	6 (18.8)	7 (21.8)
>50	12 (37.6)	7 (21.8)

In HER2/NEU positive cases, 6 cases (18.8%) were <50 and 12 cases (37.6%) were >50 years of age. In HER2/NEU negative cases 7 cases (21.%) fall into <50 and 7 cases (21.8%) were >50 years of age

Table 6: Comparison of HER2/NEU positivity for age with other studies

Age in years	Our study	Goel *et al.*
<50	6	6
>50	12	12

Table 7: HER2/NEU expression in surface epithelial ovarian tumors

HER2/NEU immunostaining	Number of cases and percentage
HER2/NEU positive	18 (56.5)
HER2/NEU negative	14 (43.5)

HER2/NEU Immunostaining was carried out on surface epithelial tumors only. HER2/NEU positivity was seen in 18 (56.5%) cases and negativity was seen in 14 (43.5%) cases

Table 8: Relative frequencies of surface epithelial tumors according to histological type

Type of the tumor	Number of cases (%)
Serous	15 (37.5)
Mucinous	17 (52.5)
Total	32 (100)

15 (37.5%) cases were serous tumors and 17 (52.5%) cases were mucinous tumors

Table 9: HER2/NEU positivity score in serous tumors

Histological type	Score 0/+1 (%)	Score +2 (%)	Score +3 (%)
Benign	5 (15)	-	-
Borderline	1 (3.1)	2 (6.3)	-
Malignant	-	-	7 (21.8)

A total number of serous tumors showing HER2/NEU positivity (score+2 and score+3) equals to 9. In serous tumors, 0/+1 score was seen in 5 (15%) benign (serous cystadenomas+serous adenofibromas) tumors, and in 1 (3.1%) borderline, +2 score was seen in 2 (6.3%) borderline and +3 score was seen in 7 (21.8%) serous cystadenocarcinomas

Table 10: HER2/NEU positivity score in mucinous tumors

Histological type	Score 0/+1 (%)	Score +2 (%)	Score +3 (%)
Benign	6 (18)	5 (13.8)	-
Borderline	2 (6.3)	-	-
Malignant	-	2 (6.3)	2 (6.3)

9 mucinous tumors are showing HER2/NEU positivity (score+2 and score+3). In mucinous tumors, 6 (18%) benign (mucinous cystadenomas) and 2 (6.3%) borderline tumors showed 0/+1 score. Score +2 was assigned to 5 (13.8%) benign (mucinous cystadenomas) tumors, 2 (6.3%) mucinous cystadenocarcinomas, and 2 (6.3%) mucinous cystadenocarcinomas shown +3 positivity

Table 11: Histological grading of malignant tumors

Type of tumor	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Serous (7)	3 (9.3)	2 (6.3)	2 (6.3)
Mucinous (4)	2 (6.3)	0	2 (6.3)

Under serous tumors, there are 3 cases of Grade 1, 2 cases of Grade 2, and 2 cases of Grade 3 serous cystadenocarcinomas. Whereas 2 cases of Grade 1 and 2 cases of Grade 3 mucinous cystadenocarcinomas are included in mucinous category

Table 12: HER2/NEU positivity in our study in comparison to other studies according to histological type

Name of the study	Benign	Borderline	Malignant
Our study	5	2	11
Kacinski *et al.*	1	-	23
Goel *et al.*	0	0	16

Table 13: HER2/NEU positivity and histological grading of tumors

Histopathological grade	Score 0/+1	Score +2 (%)	Score +3 (%)
Grade1	-	3 (9.3)	2 (6.3)
Grade2	-	2 (6.3)	-
Grade3	-	2 (6.3)	2 (6.3)

Score +2 was assigned to 3 cases of Grade 1, 2 cases of Grade 2, and 2 cases of Grade 3. Score+3 was assigned to 2 cases of Grade 1 and 2 cases of Grade 3

Table 14: HER2/NEU positivity in serous cystadenocarcinomas according to grade of the tumor

Histopathological grade	Score 0/+1	Score +2 (%)	Score +3 (%)
Grade 1	-	3 (9.3)	-
Grade 2	-	2 (6.3)	-
Grade 3	-	-	2 (6.3)

In serous cystadenocarcinomas, 3 cases of Grade 1 and 2 cases of Grade 2 are showing HER2/NEU positivity with score +2.2 cases with Grade 3 are showing score +3 HER2/NEU positivity

Table 15: HER2/NEU expression in serous tumors in our study compared with Goel *et al.* study

Tumor category	Our study	Goel *et al.* study
Benign	0	0
Borderline	2	0
Malignant	7	13

Table 16: HER2/NEU positivity in mucinous cystadenocarcinomas according to grade of the tumor

Histopathological grade	Score 0/+1	Score +2 (%)	Score +3 (%)
Grade 1	-	-	-
Grade 2	-	-	-
Grade 3	-	2 (6.3)	2 (6.3)

Score +2 was seen in 2 cases of Grade 3 mucinous cystadenocarcinomas. Score +3 was seen in 2 cases of Grade 3 mucinous cystadenocarcinomas

Table 17: HER2/NEU positivity of Grade3 in comparison to Goel *et al*. study

Histological type	Our study	Goel *et al.*
Mucinous cystadenocarcinomas (grade3)	2	2

HER2/NEU expression was evaluated in our study, taking into consideration only surface epithelial ovarian tumors, and its expression is correlated with various clinicopathological parameters, such as age, size, histopathological type, and histopathological grade, similar to breast carcinomas.

In the present study, we also evaluated the grading of ovarian tumor with HER2/NEU overexpression and whether it can be of prognostic value in benign tumors showing its expression and to assess whether such a relation could be used as a prognostic factor for the early diagnosis of the malignancy [5,9,11].

The overexpression of HER2/NEU in ovarian tumors remains a topic of discussion for many years. Overexpression of HER2/NEU in various studies ranges from 5% to 30% based on sample size and other parameters (Hellstrom *et al.* 2001) [5,7,12,13].

As shown in Table 1, histopathological examination was done on 40 cases of ovarian tumors, among these, 32 cases were surface epithelial tumors and eight cases included germ cell tumors, metastatic deposits, and sex cord-stromal tumors, but we evaluated HER2/NEU positivity in surface epithelial tumors only, in contrast to the study done by Goel *et al*., in which other non-epithelial tumors were included in the study [12] as shown in Table 2.

Our study shows a significant association between the size of the tumor (>10 cm) and HER2/NEU positivity with malignant tumors showing a size >10 cm as seen in Table 3 and intensity of staining in malignant tumors is more when compared to intensity in benign and borderline tumors in contrast to Goel *et al*. and other studies as observed in Table 4 [5,7,8,12].

In our study, in Table 5 most HER2/NEU positivity was seen in patients older than 50 years in contrast to other studies (Goel *et al*.) [12] as noted in Table 6.

In Nielsen *et al*. study, a total of 783 malignant ovarian tumors were evaluated, and found no significant association between the size of the tumor and age of the patient. In this multivariate analysis with age, FIGO staging, tumor grade, and histopathological type were carried out along with p53, HER2/NEU, and EGFR expression were carried out along with consideration [14]. However, as shown in Table 3 in our study, all malignant tumors are showing size >10 cm in contrast to the previously mentioned studies, and the intensity of staining also increased in these tumors.

Skírnisdóttir *et al*. also analyzed the expression of HER2/NEU in ovarian carcinomas and found that it does not correlate with clinicopathological prognostic parameters [15].

Sueblinvong *et al*. 2007 found no correlation between HER2/NEU and clinicopathologically analyzed factors for 74 cases of surface malignant ovarian tumors [8]. However, in our study, most of the tumors with HER2/NEU positivity show size >10 cm and age of the patient >50 years as observed in Table 4.

As shown in Tables 7 and 8 out of 32 cases, 15 serous and 17 mucinous ovarian tumors were identified. HER2/NEU positivity was observed in 9 serous, along with 9 mucinous ovarian tumors. Score +2 and score +3 were taken as positive, and score 0 and score +1 were taken as negative as observed in Tables 9 and 10.

As seen in Tables 9-11 we observed HER2/NEU positivity in benign and borderline tumors along with malignant tumors.

The present study was compared with Kacinski *et al*. [5]and Goel *et al*. [12], studies with respect to histological type as shown in Table 12.

As observed in Table 12 in Kacinski *et al*.' study, out of 24 ovarian tumors evaluated, positivity was seen in 23 malignant tumors along with one benign tumor showing positivity [5]. However, in Goel *et al*. study only malignant tumors are showing HER2/NEU positivity, none of the benign and borderline HER2/NEU positivity.

From the Tables 13, 14 and 15 we observed that 7 serous cystadenocarcinomas are HER2/NEU positivity with scores +2 and score +3. Poorly differentiated serous cystadenocarcinomas are associated with score +3 when compared to other differentiated tumors. Even 2 borderline serous tumors are showing score +2 positivity in contrast to Goel *et al*. study in which HER2/NEU positivity was seen in serous cystadenocarcinomas only.

Regarding HER2/NEU expression in serous tumors, most of the benign tumors are showing HER2/NEU negativity while most malignant tumors exhibit HER2/NEU positivity. This indicates that HER2/NEU overexpression is significantly associated with serous malignant tumors. Our research was in concordance with Goel *et al*. [12] study which shows positivity in 13 malignant tumors as seen in Table 15.

In our study, moreover, Grade 3 serous cystadenocarcinomas are showing intense positivity when compared to Grade 1 and Grade 2 tumors as shown in Fig. 1. In contrast to our study, Rubin *et al*. [16] observed no difference in HER2/NEU expression based on tumor type.

In our study, not more than two cases of Grade 3 mucinous cystadenocarcinomas show a score +3 for HER2/NEU expression as shown in Fig. 2 and Table 16.

As seen in Table 10, the present study is compared to Goel *et al*. [12] study, which shows positivity in two cases of mucinous cystadenocarcinomas; however, Rubin *et al*. [16] study shows no significant association between malignancy and HER2/NEU expression.

Regarding intensity of HER2/NEU positivity in malignant tumors irrespective of histological type, Grade 3 malignant tumors are showing intense positivity when compared to Grade 1 and Grade 2. Score +3 was assigned to most of the Grade 3 malignant tumors. Our study as shown in Tables 14, 16 and 17, when compared to other studies, which shows no relationship between HER2/NEU expression and histopathological grade of the malignant tumor [13,16].

In Hellstrom *et al*. study, some of the cases which were negative on IHC are positive for this marker on cell lines [13]. No significant association was found between HER2/NEU expression and clinicopathological parameters in Rubin *et al*.' study, even after evaluation of 105 patients [16].

Plotkin *et al*. observed that none of the malignant (serous tumors) showed HER2/NEU expression [17]. However, as seen in Tables 14 and 11, serous cystadenocarcinomas showed HER2/NEU positivity in our study.

In Garcia-Velasco *et al*. study, even after evaluation of 72 samples of malignant tumors, HER2/NEU overexpression was seen in 4 samples (5%) only [11], in contrast to HER2/NEU expression in our study. This may be due to variation in the size of the samples taken in the study.

In Verria *et al*. study in 2005, even though 13.9% were intensely positive (score +2–+3), no remarkable association was noted between malignancy and immunostaining [18].

In Peethambaram *et al*. study (2003) out of 43 samples, sensitivity is 2% for HER2/NEU expression. Among them, 30 patients showed a score of 0, score of +1 in 12 patients, and one patient showed +3 positivity with no difference [19].

There are varied proportions of sensitivity for expression of HER2/NEU in studies ranging from 2% Peethambaram *et al*., 2003 to 32% Berchuck *et al*., 1990 [9,19].

As observed from the Table 10, in our study, even 5 benign (mucinous cystadenomas) tumors showed HER2/NEU positivity with score +2 along with cystadenocarcinomas and borderline tumors. In contrast to other studies in which borderline and malignant tumors showed HER2/NEU positivity, benign tumors in this study also showed HER2/NEU positivity which may indicate that expression of HER2/NEU in benign tumors may be related to its progression to malignancy in the future, however, most of the malignant tumors showed HER2/NEU positivity.

FIGO Staging of the tumor, levels of Cancer Antigen-125, tumor laterality, parity of the patient, lymph node status, and metastasis were not evaluated in our study. Role of certain biomarkers like EGFR and Ki-67 [20] is somewhat established in the evaluation of ovarian tumors but HER2/NEU marker needs further evaluation.

CONCLUSION

When compared with the other studies, in our study, we conclude that there is an association between different clinicopathological parameters such as age, tumor type, and expression of HER2/NEU in ovarian tumors. HER2/NEU overexpression in ovarian tumors needs further studies to arise as a predictive and prognostic marker, moreover, in our study, we have not evaluated the HER2/NEU expression with the most important prognostic indicator like FIGO staging of the tumor unlike in other studies (Høgdall *et al*. study carried out on Danish patients demonstrated that the HER2/NEU overexpression together with the stage of the tumor, tetranectin level and age of the patient) [21].

The intensity of HER2/NEU positivity was higher in malignant tumors (serous + mucinous cystadenocarcinomas) compared to benign tumors.

Some of the studies mentioned above found that there was no significant association between HER2/NEU expression and the age of the patient and tumor type. However, in our study, most of the malignant tumors show a size greater than 10cm with solid areas with scores+2 and +3, in contrast to other studies.

Even benign tumors, especially mucinous cystadenomas, also showed HER2/NEU positivity in concordance with the malignant tumors, indicating that the HER2/NEU expression was not related to the tumor malignancy.

Most of the Grade 3 cystadenocarcinomas showed intense positivity (score +3) in contrast to Grade 1 and Grade 2 (score +2).

HER2/NEU expression needs further evaluation to emerge as a prognostic indicator, which indicates disease progression, survival rate, and whether its overexpression can be correlated with the staging of the tumor or not in the near future. Prognostic significance of HER2/NEU is well established in breast carcinomas, unlike in ovarian carcinomas, which warranted further studies to establish its role.

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AUTHOR'S CONTRIBUTION

This original research article equally contributed by all authors to the concept, data collection, analysis, drafting, and manuscript.

CONFLICTS OF INTEREST

None.

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