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# Clinicopathological characteristics of young patients with breast cancer in a cancer center in Medellin.

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## Abstract

Introduction: Breast cancer is the main neoplasm in women, and an increased incidence has been reported in young people under 40 years of age. The objective of the present study was to describe the clinical and pathological characteristics of patients with invasive breast cancer, ≤40 years old, treated at a reference oncology center in Medellín-Colombia.

Methodology: A cross-sectional study was carried out by the statistics department of the Vida Clinic (Colombian Cancer Foundation) from January 2015 to December 2019. The sample was nonprobabilistic of patients with an oncological diagnosis of invasive breast cancer. Age, type of cancer, family history, recurrence, and mortality were recorded. Descriptive statistics are used.

Results: Of 2332 cases of new invasive breast cancer, 261 were identified in women ≤49 years, 11.19% (95% CI 11.17-11.22%), age 34.2±4 years. 16.5% in those under 30 years of age, 40.2% in women between 30 and 45 years of age, and 42.2% in women between 35 and 40 years of age. The main presentation was a self-detected palpable mass. The molecular subtypes luminal A 16%, luminal B 48.3%, Her2 enriched 11.2%, and triple-negative 21.6%. A total of 27% had a family history. Recurrence was 14%, and mortality was 14.9%.

Conclusion: Eleven percent of patients with breast cancer in this series were young women, with a presentation in more advanced stages and unfavorable molecular biology, which requires more aggressive and radical management. This highlights the importance of timely diagnosis in young women with breast injuries.

Keywords:
MESH: Breast neoplasms, adult, neoadjuvant treatment, molecular biology

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## Introduction

Breast cancer is the most common tumor in women of all ages globally [1]. According to data from Globocan 2019, it corresponds to 11.7% of the total cases, including men and women, with 2.3 million new cases, with an incidence in women of 24.5% and a mortality of 15.5% [2]. Reports of breast cancer survival are highly heterogeneous, with rates less than or equal to 40% in low-income countries, 60% in middle-income countries, and greater than or equal to 80% in North America, Sweden, and Japan [3]. Among women under the age of 40 at diagnosis, considered young according to the guidelines of the Breast Cancer in Young Women - BCY1 [4], incidences of 7% have been reported in developed countries and up to 12% in Latin America [5].

According to estimates from the International Agency for Research on Cancer - IARC, in 2018 in Colombia, there were 13,380 new cases of breast cancer and 3,702 deaths from it, with an age-adjusted incidence rate of 44.1 per 100 thousand inhabitants [6].

Regarding the clinical characteristics in general, young women are diagnosed with larger tumors and with greater lymph node involvement [5], probably due to the presence of more glandular and nodular tissue. In addition, benign lesions are common and can act as distractors. at the time of diagnosis. The main form of presentation of cancer is a mass that must be studied by ultrasound and biopsy, and if malignancy is found, a mammogram will be performed. This form of diagnosis differs from older patients, where mammography is the first approach to the disease [7].

Breast cancers in young women have traditionally been considered to be etiologically driven by genetic/inherited factors, and although they are more likely to be associated with increased familial risk, less than 10% of cases are attributable to inherited variations in genes such as BRCA1/BRCA2 and are higher in women with a very strong family history of breast or ovarian cancer. Factors such as lifestyle, sedentary lifestyle, obesity, and other epidemiological variables, such as age and molecular biology of the tumor, can significantly affect recurrence and survival in these patients [8].

Young patients with breast cancer have a higher burden of disease due to the frequent delay in diagnosis and are generally diagnosed at advanced stages [9]. This cancer causes psychosocial distress, as young women often find themselves at a time in their lives when they have multiple roles that are difficult to replace, such as raising young children or educating them. Additionally, physical appearance and fertility are relevant elements that influence the delay of primary health care [10].

In Colombia, there are morbidity and mortality data from official statistics and studies such as Globocan [11]. For the local literature, 2 studies were identified: one was carried out in Bucaramanga on the incidence of cancer in women under 40 years of age between 2000 and 2004 [11], and another was conducted in the city of Medellin from the Institute of Cancerology between 2007 and 2016, where the overall survival of women aged less than or equal to 40 years was described as the main objective; as a secondary objective, the clinical and pathological characteristics of the patients were described [12]. To provide local information for

decision-making, the purpose of this study is to describe the clinical, pathological, and survival characteristics of young women with invasive breast cancer.

## Materials and methods

### Study design

The present study is observational, from a retrospective cohort.

### Study area

The study was conducted in the statistics service of the Colombian Foundation for Clinical Cancer Life in the city of Medellin - Colombia. The study period was the files registered from January 1, 2015, to December 31, 2019. Data collection was carried out from March 20 to December 18, 2020. The study ended on December 27, 2020. February 2021.

### Universe and sample

The population was made up of all the patients registered in the institution. The sample size calculation was nonprobabilistic, census type, in which all incident cases in the study period that met the admission criteria were included.

### Participants

Cases of women aged 40 years or younger admitted for the first time with a diagnosis of invasive breast cancer were included. Cases of patients with in situ neoplasms, phyllodes tumors, and pathologies derived from connective tissue (sarcomas) were excluded, and records with incomplete data were excluded.

### Variables

The variables collected included sociodemographic variables, marital status, number of children, place of residence, and occupation. Clinical variables: height, weight, characteristics of the disease, initial presentation of the disease, tumor size, axillary involvement, distant metastases, stage, molecular subtype classified as luminal A (estrogen receptors (ER) and progesterone (PR) strongly positive and HER2 negative, Ki67 less than 14%; luminal B (ER-positive, PR low or absent, HER2 negative or positive and Ki67 unspecified) Her2 enriched (ER and PR negative HER2 positive, Ki67 unspecified and triple-negative (ER, PR and HER2 negative, ki67 unspecified), treatment,

### Procedures, techniques, and instruments.

The data were collected from the clinical history in a form designed exclusively for that purpose. The institutional electronic system was used for case investigation. The following codes from the ICD-10 international classification were used: (C50) Malignant neoplasms of the breast and their derived diagnoses according to the topographical location:
C50.11 (Central portion of breast) C50.111, C50.112, C50.119,
C50.2 (Upper inner quadrant of breast), C50.21, C50.211, C50.212, C50.219,
C50.3 (Lower Inner Quadrant of Breast), C50.31, C50.311, C50.312, C50.319,
C50.4 (Upper outer quadrant of breast), C50.41, C50.411, C50.412, C50.419,

C50.5 (Lower outer quadrant of the breast, C50.51, C50.511, C50.512, C50.519,
C50.6 (Axillary tail of breast), C50.61, C50.611, C50.612, C50.619,
C50.8 (Contiguous breast sites), C50.81, C50.811, C50.812, C50.819,
C50.9 (location not specified), C50.91, C50.911, C50.912, C50.919.
The database was coded with serial numbers, thus protecting the confidentiality of the information and identity of the patients.

### Bias avoidance

To guarantee the reliability of the information, the researchers were trained on data collection. A double checklist was used to include all cases. The data were validated and curated by two researchers: ACA and AUC.

### Statistical analysis

Initially, a descriptive univariate analysis of the sample is performed. In a secondary analysis, the population was arbitrarily divided into 3 groups: under 30 years of age, between 30 and 35, and over 35. For scaled variables, the mean and standard deviation are used. Qualitative variables are presented as frequencies and percentages. A 95% confidence interval is presented for relevant proportions. The chi-square test was used to compare cancer characteristics by subgroups (less than 30 years old, between 30 and 35 years old, and older than 35 years). A P-value <0.05 was considered statistically significant. The statistical package used was SPSS version 21.0 for PC (Armonk, NY: IBM Corp.) licensed by CES University.

## Results

### Study participants

The study included 261 analyzable cases (Figure 1). Cases of invasive breast cancer in women ≤ 40 years represented 11.19% (95% CI 11.17-11.22%).

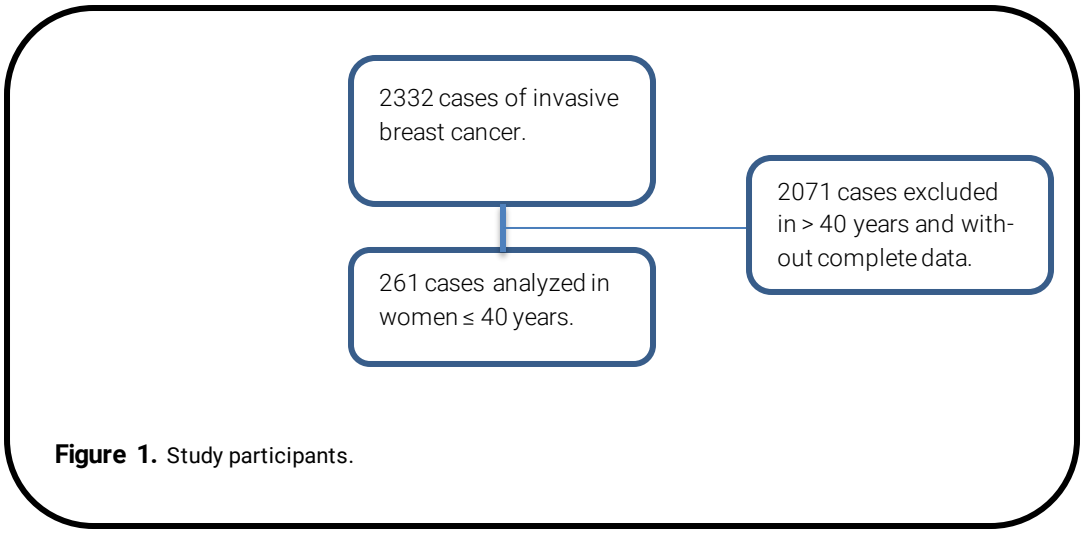


**Figure 1.** Study participants.

## Sample characterization

The mean age of the group was 34.2 ± 4 years (Table 1). Regarding the clinical characteristics of the patients, 73.94% had children, 42.1% had a total body mass index within normal limits, 43% were obese and overweight, 57.9% had a partner, and 75.9% resided in the Medellin metropolitan area.

The presentation of breast cancer in 81.2% was mass and 3.1% pain. A predominance of laterality was not identified in this cohort. The predominant histology with 90.8% was ductal carcinoma and only 4.2% was lobular and 4.2% other histology such as mucinous and 0.8% without data. A total of 48.7% of tumors had nuclear grade 3, and 30.7% had nuclear grade 2. A total of 81.3% of tumors at presentation were larger than 2 cm (T2-T4), and 52.5% of cases had ipsilateral axillary lymph node involvement. A total of 8.8% of the cases presented with metastases at the time of diagnosis, which were mostly bone (42.8%) and visceral (33.3%). Regarding the characteristics of the tumor, 48.3% had a luminal B subtype, followed by triple-negative 21.6% luminal A with 16.

**Table 1.** Demographic and clinical characteristics of the studied sample.

| | n=261 | Percentage |
|---|---|---|
| Age | 34.2± 4 years | * |
| | Civil status | |
| Married/Commonwealth | 151 | 57.9% |
| Single woman | 78 | 29.9% |
| Separated | 10 | 3.8% |
| Widow | two | 0.8% |
| No data | 19 | 7.6% |
| | body mass index | |
| Under | 5 | 1.9% |
| Normal | 110 | 42.1% |
| Overweight | 74 | 28.4% |
| Obesity | 38 | 14.6% |
| No data | 3. 4 | 13% |
| | Obstetric-gynecological history | |
| Sons | 193 | 73.9% |
| Nulliparity | 56 | 21.4% |
| No data | 12 | 4.5% |
| | Family history of breast cancer | |
| Yes | 72 | 27.6% |
| No | 158 | 60.5% |
| No data | 31 | 11.9% |
| | Clinical presentation | |
| Mass | 212 | 81.2% |
| Pain | 8 | 3.1% |
| Incidental | 3 | 1.1% |
| Screening | 2 | 0.8% |
| Others | 7 | 2.7% |
| No data | 29 | 11.1% |

*Average and standard deviation are presented.

**Table 2.** Pathological and treatment characteristics of the study group.

| | n=261 | Percentage |
|---|---|---|
| Histological grade | | |
| 1 | 33 | 12.6% |
| 2 | 80 | 30.7% |
| 3 | 127 | 48.7% |
| No data | 21 | 8.1% |
| Metastasis | | |
| Present | 23 | 8.8% |
| Absent | 233 | 89.3% |
| No data | 5 | 1.9% |
| Molecular subtype | | |
| Luminal A | 42 | 16.1% |
| Luminal B | 126 | 48.3% |
| Enriched Her2 | 29 | 11.2% |
| Triple-negative | 56 | 21.6% |
| No data | 6 | 2.6% |
| Primary treatment | | |
| Neoadjuvant | 190 | 72.8% |
| Surgery | 59 | 22.6% |
| Hormone therapy | 1 | 0.4% |
| No data | eleven | 4.2% |
| Type of surgery | | |
| BCS | 96 | 36.8% |
| Mastectomy | 122 | 48.7% |
| Without surgery | 19 | 7.3% |
| No data | 24 | 9.2% |
| Recurrence | | |
| Yes | 37 | 14.2% |
| No | 210 | 80.5% |
| No data | 14 | 5.3% |
| Death | | |
| Yes | 39 | 14.9% |
| No | 222 | 85.1% |

BCS: Breast-Conserving Surgery

**Table 3.** Bivariate analysis of molecular subtype related to relapse and mortality

| | | Luminal A n=42 | Luminal B n=126 | Her2 Enriched n=29 | Triple-negative n=56 | *P* |
|---|---|---|---|---|---|---|
| **Recurrence** | Yes | 0 (0%) | 13 (10.3%) | 6 (20.7%) | 18 (32.1%) | <0.0001 |
| | No | 41 (97.6%) | 108 (85.7%) | 22 (75%) | 34 (60.7%) | |
| | No data | 1 | 5 | 1 | 0 | |
| **Mortality** | Yes | 2 (4.8%) | 12 (9.5%) | 7 (24.1%) | 16 (28.6%) | 0.001 |
| | No | 40 (95.2%) | 114 (90.5%) | 22 (75.9%) | 40 (71.4% | |

A total of 27.6% of the patients reported having a family history of breast cancer, most of the relatives were third-degree relatives, such as maternal and paternal aunts, and 26.8% were first-degree relatives, such as their mother and sister.

Genetic testing was requested in 67% of cases. The most frequent types of mutations were BRCA2 (35.7%), TP53 (35.7%), and PALB2 (21%). The main treatment of the patients in 72.8% was neoadjuvant chemotherapy, and 22.8% was primary surgery. Mastectomy was the main technique in 46.7% and breast-conserving surgery in 36.8%; in the axilla, sentinel lymph node biopsy and axillary dissection were performed in similar percentages. Mortality was identified in 14.9% of patients at the time of the study, and recurrence was identified in a similar percentage (Table 2).

## Bivariate analysis

When evaluating the clinical results of recurrence and mortality with the molecular subtype grade 1, the majority were luminal A subtype with 31%; and in grade 3, the subtypes with the worst prognosis stand out, such as triple-negative (69.6%), HER2-enriched (62%) and luminal B (46%). Considering all the subtypes in this cohort, the triple-negative subtype tended to have fewer metastases at diagnosis, but it is the molecular subtype that relapsed the most over time, up to 32%. Mortality in this series showed an upward trend when associated with the molecular subtype. The triple-negative molecular type had the highest mortality, and the luminal A type had the lowest mortality (Table 3).

**Table 4.** Analysis by age subgroups.

| | | <30 years n=43 (16.5%) | 30-35 years n=126 (40.2%) | >35 years n=113 (42.2%) | *P* |
|---|---|---|---|---|---|
| histological grade | 1 | 5 (11.6%) | 14 (13.3%) | 14 (12.4%) | 0.70 |
| | two | 10 (23.3%) | 35 (33.3%) | 35 (31%) | |
| | 3 | 24 (55.8%) | 46 (43.8%) | 57 (50.4%) | |
| | No data | 4 | 31 | 7 | |
| Metastasis | M0 | 38 (8.4%) | 95 (90.5%) | 100 (88.5%) | 0.085 |
| | M1 | 2 (4.7%) | 9 (8.6%) | 12 (10.6%) | |
| | No data | 3 | 22 | 1 | |
| Mortality | Luminal A | 6 (14%) | 16 (15.4%) | 20 (17.9%) | 0.034 |
| | Luminal B | 17 (39.5%) | 54 (51.9%) | 55 (49.1%) | |
| | Her2 Enr | 6 (14%) | 7 (6.7%) | 16 (14.3%) | |
| | Triple-negative | 10 (23.3%) | 26 (25%) | 20 (17.9%) | |
| | No data | 4 | 23 | two | |
| Family history | Yes | 16 (37.2%) | 20 (19%) | 36 (31.9%) | 0.024 |
| | No | 23 (53.5%) | 66 (62.9%) | 69 (61.1%) | |
| | No data | 4 (9.3%) | 19 (18.1%) | 8 (7.1%) | |
| Genetic mutation | BRCA1 | 0 (0%) | 1 (14%) | 0 (0%) | <0.0001 |
| | BRCA2 | 1 (16%) | 4 (57%) | 0 (0%) | |
| | TP53 | 5 (83%) | 0 (0%) | 0 (0%) | |
| | PALB2 | 0 (0%) | 0 (0%) | 0 (0%) | |
| | Other | 0 (%) | 2 (28.5%) | 0 (0%) | |
| | No data | 0 (%) | 0 (0%) | 1 (100%) | |
| | no mutation | 37 | 119 | 112 | |
| Recurrence | | 8 (18.6%) | 17 (16.2%) | 12 (10.76%) | 0.798 |
| Death | | 5 (11.6%) | 20 (19%) | 14 (12.4%) | 0.310 |

### Analysis by age

The analysis by age group shows that, from the age of 30, there are more women diagnosed with invasive breast cancer. In the subgroup of >35 years, lesions are already identified in mammography screening. In the age subgroups, there was no predominance in terms of laterality. In the subgroup of >35 years, it was shown that obesity begins to make a difference in terms of BMI. The subgroup <30 years had the PALB2 genetic mutation more frequently identified. Mastectomy was performed similarly in the <30-year-old and >35-year-old groups. In the subgroup of 30 to 35 years, more breast-conserving surgeries were performed. There were no significant differences in mortality and recurrence between the subgroups divided by age (Table 4).

## Discussion

The incidence of breast cancer in women aged ≤40 years was 11.9%, which is above the 7% reported in developed countries and is closer to the data published in Latin America [5]. Although evidence has been reviewed that breastfeeding could reduce the risk of breast cancer among women, especially for some molecular subtypes [13], in the present study, 74% of the patients had children; however, we do not have information about breastfeeding specifically. Body mass index (BMI) is one of the modifiable factors involved in the development of breast cancer, and although most studies have been described in postmenopausal patients, in young women, BMI could also become a risk factor due to its proinflammatory action [14].

The majority of patients presented with symptoms related to the topographical area of the breast in 87.8%, with a palpable lesion in 81%, pain in 3.1%, and nipple discharge in 2.7%, as has already been described in series such as the John Hopkins group [15], which contrasts with postmenopausal women in whom the diagnosis is usually made with smaller tumors and in earlier stages [16]. Regarding tumor characteristics, the vast majority were larger than 2 centimeters (81%) and had axillary lymph node involvement (52%), similar to that described in a review by Mount Sinai Medical Center [17]. Tumor grades 2 and 3 were predominant in this series. More advanced and adverse tumor characteristics were also evidenced in previous studies [15, 16].

In the present series, 80% of the patients had locally advanced disease, and 8.8% had distant metastases at the time of diagnosis. This is possible because in young patients, there is a delay in diagnosis due to the greater frequency of benign disease, delays in medical attention, or worse, ignorance of the possibility of cancer in this age group [18 ].

The triple-negative molecular subtype was more common in this group of patients than in the general population, 21% vs 12%, respectively, and this difference was more noticeable in patients under 36 years of age. Furthermore, as has been identified in other series, the luminal B subtype was also increased in these age groups [19, 20]; this has led some authors to state that breast cancer in young patients is a poor prognostic factor [21]. Contrary to some published studies, the enriched Her2 molecular subtype was not as common in this group of patients (11.2%); probably if we take into account that in other studies they classified as Her2 enriched patients with positive hormone receptors and Her2 positive, which in this series are included as Luminal B, it could explain this difference [22].

The vast majority of patients received neoadjuvant treatment (73%) due to both stage and adverse tumor molecular biology; however, surgery has been reported as the main primary treatment in different series, probably due to diagnosis in earlier stages than in this study [23], as established in the 4th ESO-ESMO International Consensus Guideline for the management of cancer in young women (BYC) [24]. The main surgical treatment performed in this series was mastectomy; it was not possible to assess the causes; probably many patients did not obtain the expected response to neoadjuvant therapy and were not candidates for breast conservation [25].

A meta-analysis by He et al. of 19 observational studies examined the relationship between young age and breast conservation, finding a higher risk of local recurrence in younger women vs. older women who underwent breast conservation surgery at 5 and 10 years [26]. In this study, younger patients (under 30 years of age) showed an even higher percentage of relapse during the study despite receiving mastectomy.

Breast cancer in young women is associated with family history and genetic mutations more frequently than in older patients [27]. 27% of this series referred to family history and of these almost 30% of the first degree; however, it must be taken into account that these data are subject to memory bias. The proportion of women who underwent genetic testing in this study was 67%, and we do not know what proportion had prior genetic counseling. National and international guidelines suggest genetic counseling in patients younger than 50 years or if they have triple-negative breast cancer [28].

A relationship between young age and the possibility of genetic mutations has been identified [28]. In the present study, some type of genetic mutation was identified in 9.9% of the patients studied (14/141), with TP53 and BRCA2 being the most common in this group, similar to that identified in other series [28]. When analyzed by subgroups, TP53 was more common in those under 30 years of age, and in those over 36 years of age, none had a mutation. This suggests that the younger the patients are, the more likely they are to have a genetic mutation.

Recurrence was more common in patients with the triple-negative molecular subtype and Her2-enriched breast cancer, 32% and 21%, respectively, reflecting the aggressive nature of these two molecular subtypes, unlike a Brazilian cohort [29] in which recurrence was more prevalent in the luminal B molecular subtype. The behavior of mortality in this group of patients was similar to recurrence, with a higher percentage of deaths from breast cancer in patients with triple-negative and HER2-enriched subtypes, 28% and 24%, respectively, being higher than that observed in postmenopausal women, probably due to its diagnosis in late stages and adverse molecular biology, similar to that identified in this Brazilian series [29].

This study has several limitations. The results from a single reference institution are presented, which limits the generalizability of the findings. This was a retrospective review, and the variables were obtained from medical records with a variety of different information between them. These types of descriptive and retrospective studies have an inherent limitation in controlling for selection bias. In addition, there are self-reported data, such as family history, that were subject to the memory of the participants; therefore, there may be recall bias. It cannot be established whether the request for genetic tests was conditional on prior genetic counseling or if they were requested directly. What can also be considered information bias?

Regarding the strengths of this study, the low cost, the speed of preparation, a different perspective to approach this population group, and the formulation of new hypotheses for

later studies are identified. As a proposal for future research, the importance of genetic counseling in these patients can be taken into account to define treatment and prognosis, in addition to family follow-up.

## Conclusions

The young patients diagnosed with breast cancer aged 40 years or younger reviewed in this study presented a high percentage of unfavorable molecular subtypes, especially luminal B and triple-negative subtypes. Usually, in these patients, the diagnosis of breast cancer is underestimated as it presents a low index of suspicion, so its diagnosis occurs in advanced stages, which implies more aggressive treatments, but despite this, with worse outcomes is survival.

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## Abbreviations

BCS: Breast-Conserving Surgery.

## Administrative information

### Additional Files

None was declared by the authors.

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### Author contributions

Ángela Cala-Ayala: conceptualization, validation, visualization, methodology, project management, writing: review and editing.

Alejandro Uribe-Castaño: conceptualization, data curation, formal analysis, fundraising, research, resources, software, writing - original draft.

Néstor Llinás-Quintero: conceptualization, data curation, formal analysis, fundraising, research, resources, software.

Elsa Vásquez- Trespalacios: conceptualization, data curation, formal analysis, fundraising, research, resources, software.

Luis Gallón-Villegas: conceptualization, data curation, formal analysis, fundraising, research, resources, software.

All authors read and approved the final version of the manuscript.

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Availability of data and materials

Data availability is available upon request to the corresponding author. No other materials were reported.

## Statements

Ethics committee approval

It does not apply to observational studies with a review of databases or medical records.

Consent to publication

This does not apply to studies that do not publish explicit images, such as CT scans, MRIs, and physical exam images.

Conflicts of interest

The authors declare that they have no conflict of interest or competence.

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