Global Distribution of Idiopathic Granulomatous Mastitis: A Scoping Review

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ABSTRACT

Background: Idiopathic granulomatous mastitis (IGM) is a challenging exclusion diagnosis for breast lesions, manifested as benign, chronic inflammation of the breast tissue. Although some evidence suggest that IGM cases are not uniformly distributed worldwide, few investigations have specifically addressed this topic. This study aims to examine the distribution of IGM cases among countries and races/ethnicities based on reported cases.

Methods: A review of studies with a report of at least one IGM patient published from 2011 to 2020 inclusive was conducted. The search was performed in MEDLINE, and citations were filtered in two stages by title/abstract and full text. Those cases with a positive growth of pathogens, male granulomatous mastitis and review articles were excluded.

Results: Among 365 retrieved publications, 218 were finally included based on the inclusion and exclusion criteria, comprising 7161 patients from 34 different countries. Turkey, the United States, and China were the countries where the most publications (including case reports) originated. Considering the number of patients within papers, Turkey, Iran, and China were the pioneers.

Conclusion: Based on the published literature, some populations seem to be more prone to IGM. Further investigations may reveal the genetic and environmental factors associated with this disease in different geographic areas.

INTRODUCTION

For more than 50 years, researchers have been investigating granulomatous mastitis (GM) from different perspectives. GM is a benign, chronic granulomatous inflammation of the breast tissue which mimics breast cancer, and thus, its diagnosis may be challenging and vital.
autoimmunity. The diagnosis of IGM is confirmed by excluding infectious and autoimmune etiologies, followed by histopathological examination. The biopsy can be extracted by fine-needle aspiration, core needle, or excisional/incisional surgery. It is worth mentioning that neither ultrasonography nor mammography can differentiate GM from other benign or malignant lesions.

IGM mainly involves women at a median age of 30 years (mostly in childbearing age) with a history of breastfeeding. Although the patients may suffer from a wide variety of signs and symptoms, the typical presentation is a painful unilateral mass which can be accompanied by erythema, swelling, fistula, or areolar retraction in the involved breast.

IGM is an uncommon disease. For instance, the United States has an estimated incidence of 2.4 per 100,000 women aged 20-40 years. Hence, the limited evidence has caused controversy, especially regarding its pathogenesis and management. For instance, no definite treatment modality is accepted for IGM and various treatment modalities such as immunosuppressive therapy, antibiotics, and wide surgical excision have been implemented.

Some evidence suggest that IGM may have a higher incidence and prevalence in specific geographical areas. This is not the first time the difference in the incidence of a disease according to geographical factors is being investigated. Previously, several communicable and non-communicable conditions have been shown to be related to the region, such as Behcet’s Disease in the Silk Road countries, Malaria in tropical African countries, and Crohn's disease in North America and Western Europe.

In the case of IGM, few researchers have addressed distribution among different regions and countries. Although the disease has been found worldwide, it seems the distribution is not the same across the globe. A narrative literature review has shown that most publications, particularly more extensive case reports, originate from Mediterranean countries, the United States, Asia, and the Middle East. Also, a higher prevalence of IGM among African-American and Hispanic ethnicities has been reported. Nevertheless, there remains a need for assessing the connection between the place of residence, ethnicity/race, and IGM disease.

Race is defined as "a family, tribe, people, or nation belonging to the same common stock, or a class or kind of people unified by shared interests, habits, or characteristics". On the other hand, ethnicity focuses on societal differences related to cultural heritage, language, and other social and geo-political factors. However, in epidemiology, the terms ethnicity and race, despite having distinct definitions, have been used interchangeably to represent a combination of cultural, socioeconomic, and genetic factors.

This study intends to review the evidence on the distribution of IGM among countries and ethnicities based on the reported cases past ten years. Understanding this potential association can serve as an essential step in elucidating the etiology and also in developing appropriate preventive and treatment approaches.

METHODS

This scoping review was conducted using the methodology introduced by Levac et al. which was an advancement for an earlier version. The reporting of this study complies with Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). No protocol was registered for this scoping review.

Eligibility Criteria

To be included in this review, articles needed to contain at least one patient with granulomatous mastitis confirmed through pathological examination. No limitation was set for study type and language. The cases were excluded if the explorations showed a bacterial, viral, or fungal infection as the underlying cause, especially those with positive growth tests for Mycobacterium or Corynebacterium species. Reviews, letters to the editor, or other correspondence which did not introduce new cases and discussed previously introduced patients were also excluded from the study.

Search and Information Sources

A literature search was conducted in August 2021 and included papers that were indexed in MEDLINE between 2011 to 2020 inclusive, with ‘Granulomatous Mastitis’ as the medical subject heading (MeSH) keyword or within the title/abstract.

Study Selection

One reviewer (MK) independently filtered the records (titles and abstracts) to double-check their eligibility based on the mentioned criteria and remove potential duplications. Any conflicts about eligibility were resolved by discussing them with the second reviewer (AK). Afterward, full-texts of the papers were retrieved and reviewed. Non-English publications were checked after translating them into English using Google Translate.

Data Charting Process

Based on a pilot study on IGM publications in 2010 (not included in this paper), we developed a data-extraction form that comprised the following variables: the first author, year of publication, title, the country where the study was performed (in case of multiple
countries, the country mentioned in the first author’s affiliation), classification of country’s income, number of reported cases, age, ethnicity/nationality, number of those with parity history, number of those with lactation history, number of those with OCP consumption history, and IGM confirmation. The country of the first author was charted as the patient’s ethnicity/nationality, if authors did not indicate the ethnicity or race of the reported patient(s) explicitly. In order to identify the country’s income classification, the latest evaluation of the World Bank was used. In this regard, countries were categorized into four groups: Low-income economies (LIC), Lower-middle-income economies (LMIC), Upper-middle-income economies (UMIC), High-income economies (HIC). In some papers, a number of the patients studied were diagnosed with GM secondary to gram-positive bacteria, and others were categorized as IGM; in these instances, the numbers being secondary to infections were removed from the total number of the patients who were included. The data were charted by at least one reviewer and double-checked by a second reviewer (MK or SM).

**Synthesis of Results**

We grouped the cases by nationality and summarized the count, parity history, lactation history, OCP consumption history, and reported ethnicities for each group. Data were synthesized both narratively and by the table. The number of included and excluded documents was summarized in a flow diagram.

**RESULTS**

The records retrieved from Pubmed included 365 publications; no duplicates were observed upon the initial assessment. These papers were screened, and 50 records were excluded as they were a letter or commentary (n=22) or reviews that did not present new patients (n=28). After examining the full text of the remaining 315 records, 96 papers were further excluded. The most common reasons for exclusion at this stage were evidence of Corynebacterium as the underlying causes of GM (n=20), tuberculosis mastitis (n=15), male GM (n=8), and cystic neutrophilic granulomatous mastitis (n=4). The final database for this study consisted of 218 papers. Due to the reference number constraints, papers with a higher sample size are referenced here: The complete list of included studies can be found in Supplementary 1. A flow diagram of the study selection process is presented in Figure 1.

![Figure 1. Flow diagram of the study selection process](image)
In the following paragraphs, we will present the data in regard to four different aspects: the number of published articles, the number of patients, the classification by income, and the ethnicity/race of patients.

First, 218 articles were included. As can be seen in Table 1, Turkey had the highest share of the papers (29.4%), followed by the United States (18.3%), China (8.3%), India (7.3%), and Iran (5.5%).

### Table 1. Characteristics of studies based on the country of the first author and sorted by the number of studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Classification by Income *</th>
<th>Included Articles (n=218)</th>
<th>Included Patients (n=7161)</th>
<th>Weighted Mean of Age (n=195)</th>
<th>Patients with Parous History (n=2952)</th>
<th>Patients with Lactation History (n=2103)</th>
<th>Patients with OCP Usage History (n=403)</th>
<th>Race / Ethnicity † (n=686)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey</td>
<td>UMIC</td>
<td>64 (29.4)</td>
<td>2801 (39.1)</td>
<td>36.1</td>
<td>1034 (35)</td>
<td>931 (44.3)</td>
<td>211 (52.4)</td>
<td>NR</td>
</tr>
<tr>
<td>United States</td>
<td>HIC</td>
<td>40 (18.3)</td>
<td>787 (11)</td>
<td>35.8</td>
<td>239 (8.1)</td>
<td>153 (7.3)</td>
<td>26 (6.4)</td>
<td>Hispanic (452, 65.9%), Afro-American (39, 5.7%), Caucasian (16, 2.3%), Asian (15, 2.2%), Pacific Islander (2, 0.3%), Native American (2, 0.3%), Ukranian (1, 0.1%), Turkish (1, 0.1%)</td>
</tr>
<tr>
<td>China</td>
<td>UMIC</td>
<td>18 (8.3)</td>
<td>956 (13.4)</td>
<td>33.2</td>
<td>239 (8.1)</td>
<td>183 (8.7)</td>
<td>2 (0.5)</td>
<td>NR</td>
</tr>
<tr>
<td>India</td>
<td>LMIC</td>
<td>16 (7.3)</td>
<td>160 (2.2)</td>
<td>33.2</td>
<td>73 (2.5)</td>
<td>5 (0.2)</td>
<td>40 (9.9)</td>
<td>NR</td>
</tr>
<tr>
<td>Iran</td>
<td>LMIC</td>
<td>12 (5.5)</td>
<td>1294 (18.1)</td>
<td>33.1</td>
<td>942 (31.9)</td>
<td>690 (32.8)</td>
<td>97 (24.1)</td>
<td>NR</td>
</tr>
<tr>
<td>Japan</td>
<td>HIC</td>
<td>8 (3.7)</td>
<td>38 (0.5)</td>
<td>36.8</td>
<td>10 (0.3)</td>
<td>6 (0.3)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>France</td>
<td>HIC</td>
<td>7 (3.2)</td>
<td>42 (0.6)</td>
<td>46.6</td>
<td>17 (0.6)</td>
<td>0 (0.05)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Spain</td>
<td>HIC</td>
<td>6 (2.8)</td>
<td>12 (0.2)</td>
<td>43.2</td>
<td>5 (0.2)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>HIC</td>
<td>4 (1.8)</td>
<td>29 (0.4)</td>
<td>39.6</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>Caucasian (1, 0.1%)</td>
</tr>
<tr>
<td>Morocco</td>
<td>LMIC</td>
<td>4 (1.8)</td>
<td>33 (0.5)</td>
<td>39.3</td>
<td>1 (0.03)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Italy</td>
<td>HIC</td>
<td>4 (1.8)</td>
<td>137 (1.9)</td>
<td>44.5</td>
<td>1 (0.03)</td>
<td>11 (0.5)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Egypt</td>
<td>LMIC</td>
<td>4 (1.8)</td>
<td>132 (1.8)</td>
<td>34.2</td>
<td>73 (2.5)</td>
<td>60 (2.9)</td>
<td>7 (1.7)</td>
<td>NR</td>
</tr>
<tr>
<td>Australia</td>
<td>HIC</td>
<td>3 (1.4)</td>
<td>19 (0.3)</td>
<td>43.7</td>
<td>14 (0.5)</td>
<td>1 (0.05)</td>
<td>0 (0)</td>
<td>Caucasian (10, 1.4%), Middle Eastern (3, 0.4%), Chinese (3, 0.4%)</td>
</tr>
<tr>
<td>Country</td>
<td>Classification by Income *</td>
<td>Included Articles (n=218)</td>
<td>Included Patients (n=7161)</td>
<td>Weighted Mean of Age (n=195)</td>
<td>Patients with Parous History (n=2952)</td>
<td>Patients with Lactation History (n=2103)</td>
<td>Patients with OCP Usage History (n=403)</td>
<td>Race / Ethnicity † (n=686)</td>
</tr>
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<td>-----------------------------</td>
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<td>-------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>South Korea</td>
<td>UMIC</td>
<td>3 (1.4)</td>
<td>142 (2.0)</td>
<td>36.0</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>NR</td>
</tr>
<tr>
<td>Mexico</td>
<td>HIC</td>
<td>3 (1.4)</td>
<td>62 (0.9)</td>
<td>36.4</td>
<td>3 (0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Taiwan</td>
<td>HIC</td>
<td>2 (0.9)</td>
<td>2 (0.03)</td>
<td>35.5</td>
<td>1 (0)</td>
<td>1 (0.05)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Jordan</td>
<td>UMIC</td>
<td>2 (0.9)</td>
<td>112 (1.6)</td>
<td>37.8</td>
<td>80 (2.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Belgium</td>
<td>HIC</td>
<td>2 (0.9)</td>
<td>2 (0.03)</td>
<td>31.5</td>
<td>1 (0.03)</td>
<td>0 (0)</td>
<td>1 (0.2)</td>
<td>NR</td>
</tr>
<tr>
<td>Tunisia</td>
<td>LMIC</td>
<td>1 (0.5)</td>
<td>2 (0.03)</td>
<td>41.4</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Thailand</td>
<td>UMIC</td>
<td>1 (0.5)</td>
<td>44 (0.6)</td>
<td>38</td>
<td>30 (1)</td>
<td>0 (0)</td>
<td>14 (3.5)</td>
<td>NR</td>
</tr>
<tr>
<td>Slovakia</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>39 (0.5)</td>
<td>37</td>
<td>39 (1.3)</td>
<td>12 (0.6)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Singapore</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>113 (1.6)</td>
<td>36.2</td>
<td>96 (3.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>21 (0.3)</td>
<td>NR</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Qatar</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>1 (0.01)</td>
<td>36</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Oman</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>20 (0.3)</td>
<td>37.5</td>
<td>20 (0.7)</td>
<td>20 (1.0)</td>
<td>2 (0.5)</td>
<td>NR</td>
</tr>
<tr>
<td>Malaysia</td>
<td>UMIC</td>
<td>1 (0.5)</td>
<td>1 (0.01)</td>
<td>23</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Lebanon</td>
<td>UMIC</td>
<td>1 (0.5)</td>
<td>2 (0.03)</td>
<td>38</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Kuwait</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>10 (0.1)</td>
<td>38</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>Middle Eastern (1, 0.1%)</td>
</tr>
<tr>
<td>Hungary</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>2 (0.03)</td>
<td>NR</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>102 (1.4)</td>
<td>33</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Canada</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>11 (0.2)</td>
<td>38.7</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Brazil</td>
<td>UMIC</td>
<td>1 (0.5)</td>
<td>1 (0.01)</td>
<td>38</td>
<td>1 (0.03)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Bahrain</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>29 (0.4)</td>
<td>39</td>
<td>29 (1)</td>
<td>29 (1.4)</td>
<td>2 (0.5)</td>
<td>Middle Eastern (26, 3.8%)</td>
</tr>
<tr>
<td>Austria</td>
<td>HIC</td>
<td>1 (0.5)</td>
<td>3 (0.04)</td>
<td>30.3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: Data are reported in frequency (percent). NR, not reported.

* Based on classification presented by The World Bank which categorizes countries into four groups: Low-income economies (LIC), Lower-middle-income economies (LMIC), Upper-middle-income economies (UMIC), High-income economies (HIC).

† Data in the parentheses are the count and percentage among the total count of patients in the study, respectively. Only those explicitly indicated the race/ethnicity of their patient(s) were reported.

Second, taking the number of included patients into account (totally, 7161 women), rankings were slightly changed: Turkey had the highest share (39.1%), followed by Iran (18.1%), China (13.4%), the United States (11%), and India (2.2%). Third, the data were analyzed based on classification by income. Countries within HIC,
Fourth, the ethnicity/race of the patients was analyzed. Obviously, considering the nationality of the patients, Turkish people had the most reported cases, followed by Iranian and Chinese. In these studies, authors took it for granted that the reported patient(s) was from the country the study was conducted, without further details regarding ethnicity. However, as a limitation, only 36 papers explicitly indicated the ethnicity/race of the patient(s) in their reports. Of these studies, 27 were from the United States (the country with the fourth-highest share of reported cases), with Hispanics (n=452, 65.9% of cases reported from the United States) as the most common reported ethnicity of GMs from that country. Amongst other reported ethnicities/races within the studies, Chinese (n=82, 12%) and African-American (n=40, 5.8%) were the most common.

Besides, some additional analyses were also performed. The age of the GM patients was reported in 196 papers, with the mean age being 35.9 years. Parity status was reported in 88 papers: of 3231 patients in these articles, 2952 had a history of parity (parity ≥1), with the parity rate being around 91.4%. Some papers had reported the average parity for their series, which could not be included in this estimation. The history of lactation was reported in 62 papers: of 2932 GM patients in these records, 2103 had a history of lactation (71.7%). Some authors had reported whether GM had occurred during or shortly after breastfeeding and had not included the information on how many of the patients had ever experienced lactation. The history of OCP use was mentioned in 57 articles: of 3023 patients in these records, 1649 had previously used OCP (54.5%).

**DISCUSSION**

This scoping review showed that most of the published articles on IGM belongs to Turkey, the United States, and China. Concerning the number of patients included, Turkey had the highest share in the number of patients, followed by Iran and China. Hispanic, Chinese and African-American ethnicities were among the three most reported races/ethnicities for IGM. Also, we found that the majority of GM patients had a history of parity or lactation.

A systematic review of 70 articles by Martinez-Ramos et al., showed that Turkey had more publications concerning IGM than other countries. This finding is relatively compatible with the narrative review of Wolfrum et al., in which they reported that most publications originate from Mediterranean countries, the United States, Asia, and the Middle East. Our review confirmed the contribution of Turkey, Iran, and the United States in this regard, but simultaneously showed that more attention should be paid to China and India - which is justifiable considering the large population - as countries with the most reported IGM cases.

With regard to the ethnicity of the individuals, the results reported herein should be considered in the light of some limitations. Only 36 papers had reported the ethnicity/race of the patients. This was more common among publications from the United States, as a country composed of individuals from different ethnicities. Most authors from other countries had not specifically reported the patients’ ethnicity/race, based on a priori assumption that they were of the dominant ethnic/racial group of the country in which the study was conducted, except otherwise specified. Therefore, the possibility that this assumption could have been violated in some cases must be considered. Also, some articles focused on the ethnicity of the participants, while others reported their race. Therefore, due to a lack of consistency in the literature, a combination of the two variables was considered in this review. This is not the first study that has considered the combined impact of race and ethnicity on disease susceptibility, incidence, diagnosis, and mortality. For instance, Caucasians and African Americans have been shown to be more likely to develop Multiple Sclerosis than individuals of Asian and Hispanic ethnicity. Also, it has been shown that breast cancer in African-American women develops ten years earlier than in Caucasian women. Further, the presentation of breast cancer in African American women has been of a higher stage with more positive lymph nodes. In this review, the Hispanic ethnicity was shown to be the most common ethnicity from which GMs were reported. The Chinese ethnicity was found to have the second-highest number of reported cases and the African-American ethnicity to be in third place. The relatively high prevalence rate found among the Hispanic, and African-American ethnicities were also confirmed by Pandy et al., However, to our knowledge, this is the first report that has pointed out the position that Chinese ethnicity holds within this ranking. Also, another important issue that pertains to the ranking of ethnicities based on IGM prevalence is that even though Turkey had the highest number of published articles on IGM and it also had the highest share in the number of patients followed by Iran, Turkish and Persian ethnicities have not been indicated in studies that focused on the association of race/ethnicity with the relative prevalence of IGM. This study, by collectively looking at the distribution of IGM among countries and ethnicities, showed that
even though Hispanic, Chinese, and African-American ethnicities were among the three most 'reported' races/ethnicities for IGM, these reports accounted for a small proportion of the eligible papers. Thus, considering the highest share of Turkey and Iran regarding the number of patients, these ethnicities must also be considered among the ethnicities with a relatively high prevalence rate. As a result, these findings suggest that conclusions should not be drawn merely based on the ethnicities that were more frequently reported, but rather a more holistic view needs to be taken when it comes to reporting the distribution of IGM.

Furthermore, concerning the parity and lactation history of the patients as risk factors for IGM, it must be taken into consideration that breastfeeding intentions can vary among individual populations, which can act as a confounding factor in the association of GM with different populations. According to a study by Bonuck et al., women born outside the US were more likely to have an intention of breastfeeding than women born inside the US. In addition, several studies have shown that parity and breastfeeding rates correlate with the individuals’ ethnicity and race.

Nonetheless, this study is subject to several limitations. First, it was performed only in one database - however the most inclusive one - due to time constraints. Secondly, we used the first author's country as the country of reported patients' residence, which might not be true in all instances. Furthermore, most studies (especially those conducted out of the US) did not explicitly indicate the race/ethnicity of their participants, as a distinct variable within the article.

This should be taken into account in generalizability of the findings. In this regard, we suggest researchers report the ethnicity/race of their patients in future works. Finally, publication bias should also be considered before interpreting the findings, as some countries might have been overrepresented due to the higher publication rate of their IGM patient reports or even some cases may be republished in several articles.

CONCLUSION
Understanding the distribution of IGM cases among countries and races/ethnicities can provide helpful insight for elucidating the etiology of IGM, as ethnic/geographical differences in incidence and prevalence of the disease are reflective of cultural, socioeconomic, and genetic factors. In future works, by systematically analyzing the impact of culture, socioeconomic status, and genetic factors separately, the uneven distribution of this disease can be better explained, and the underlying causes of IGM can be more easily understood.

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CONFLICT OF INTEREST
All authors declare that they have no conflict of interest.

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