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Clinical characteristics of breast cancer patients admitted to academic surgical wards in Tehran, Iran: an analytical cross-sectional study

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Abstract

Background Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer death among women. Knowledge of the clinical characteristics of BC in a population may be informative for disease prediction or diagnosis and for developing screening and diagnostic guidelines. This study aimed to evaluate the clinical characteristics of female patients with BC who were admitted to academic surgical wards in Tehran, Iran.

Methods In this cross-sectional study, demographic information and clinical characteristics of Iranian females with BC who had undergone breast surgery from 2017–2021 in four academic Breast Surgery Units were extracted from medical files and recorded via a pre-designed checklist.

Results A total of 1476 patients with a mean age of 48.03 (\pm 11.46) years were enrolled. Among them, 10.4% were aged less than 35. In younger patients, Triple-negative and Her2-enriched subtypes of BC were significantly higher compared to older ones. Overall, 85.7% of tumors were invasive ductal carcinoma, 43.3% were grade 2, 41.4% were located in the UOQ, and 65.2% had presented with mass palpation. The mean pathologic tumor size was 28.94 mm, and the most common subtype was luminal B.

Conclusions Many characteristics of breast cancer in this study were similar to other countries and previous studies in Iran. However, a higher proportion of young BC compared with Western countries, and even with older studies in Iran, suggest a trend toward lower age for BC in recent years. These results indicate the need for preventive measures and screening in Iranian women at a younger age.

Keywords Breast Cancer, Cross-Sectional study, Multicenter study, Prevalence, Iran

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Background

According to the World Health Organization (WHO) in 2019, cancer is the first or second leading cause of death before the age of 70 in 112 of 183 countries and ranks third or fourth in a further 23 countries [1]. Based on the estimates of the GLOBOCAN 2020, breast cancer (BC) is the most commonly diagnosed cancer and leading cause of cancer death among women and its incidence in developed communities is higher than in developing ones. This may reflect the higher frequency of risk factors related to breast cancer such as low parity, higher age at first pregnancy, use of oral contraceptive pills (OCP), use of hormone replacement therapy (HRT), high-calorie diet, and alcohol consumption in developed countries [2, 3].

In comparison to Europe and the United States, the incidence and prevalence of BC are lower in Asia. However, the mortality rate of BC in low-income countries is higher than in high-income ones [4–6]. Based on previous studies, BC occurs sooner in Asia (around 40–50 years old) than in Western countries (about 60–70 years old) [7]. In addition, the proportion of young patients aged less than 35 years is about 10% in developed nations, vs. 25% in developing areas [8]. In Iran, BC accounts for about 32 percent of all women diagnosed with cancer, and it is defined as the sixth major cause of death [3]. According to the Iranian National Cancer Registry (INCR), the age-standardized incidence rate (ASIR) of primary BC is 27.4 per 100,000 persons per year in Iran [9].

The nature, incidence, and prognosis of BC vary in accordance with the patient's characteristics, such as the patient's age, menopausal status, and family history; as well as the tumor characteristics [10]. Recent studies conducted in Iran demonstrate that family history of BC, low parity, employment, and oral use of contraceptives are associated with an elevated risk of BC [5, 9].

Knowledge of the distribution and frequency of clinical characteristics of BC in a population may be informative for disease prediction or diagnosis, and assists in decision-making for treatment purposes, or developing screening and diagnostic guidelines [10]. Furthermore, BC would be a more serious health issue and may put a strain on the healthcare systems of middle-income countries like Iran in the near future [5, 9].

This study aimed to evaluate the clinical characteristics of female patients with BC in Iran. As Tehran University of Medical Sciences is the leading academic and referral center in the country, we gathered data of all patients who had undergone breast cancer surgery during a recent 4-year period in all Breast Surgical Units of the University to report the surgical approach and evaluate their main clinical and histological features; and explore the proportion and characteristics of young BC.

Methods

Study design

This multicenter cross-sectional study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1400.006) and was conducted on women diagnosed with BC who had undergone breast surgery from 2017 to 2021. Informed consent had been obtained from all breast cancer patients before surgery in order to use the information for research projects. The project was run according to the ethical principles of the Declaration of Helsinki. All active Breast Surgery Units of the University, which include four academic hospitals (Imam Khomeini Hospital, Cancer Institute, Arash Women's Hospital, and Sina Hospital) affiliated with Tehran University of Medical Sciences, Tehran, Iran, have participated in the present study.

Participants' characteristics

In this study, data of 1476 females with BC who had undergone breast surgery were extracted. The sources of this information were medical files, pathologic results as well as the electronic archive system available in some hospitals. A similar pre-designed checklist was used in all centers. The checklist contained three parts. The first part variables included demographic and reproductive characteristics, the second comprised breast cancer information, and the last part covered breast surgery data.

Age, weight, height, smoking habit and alcohol consumption, age at menarche, age at first pregnancy, parity, menopausal status, age and cause of menopause, OCP use, history of abortion and family history of breast and ovarian cancer were extracted. Clinical characteristics of the disease consisted of presenting symptoms, tumor size, axillary lymph node status, core needle biopsy results, metastasis status and sites, findings of breast and axillary lymph node surgeries, tumor grade, and treatment types.

Tumors had been examined histologically by board-certified pathologists dedicated to breast diseases in the four academic centers. The histologic type had been assigned according to the 5th edition of the WHO Classification of Tumors of the Breast, in 2019 [11]; tumor grade had been classified as G1, G2, or G3 according to the Modified Bloom-Richardson Grading System [12]. BC was categorized into four molecular subtypes, including Luminal A (estrogen receptor (ER) /progesterone receptor (PR) +, Her2 negative, Ki 67% ≤ 15%), Luminal B (ER + and/or PR +, HER2 + or HER2 – with Ki67 > 15%), triple-negative/basal-like (ER –, PR –, HER2 –), and HER2-enriched type (ER –, PR –, HER2 +) [13].

In this study, the tumor sites have been categorized as the upper outer quadrant (UOQ), the upper inner quadrant (UIQ), the lower outer quadrant (LOQ), the lower

inner quadrant (LIQ), as well as multicentric tumors defined as tumors in different quadrants or more than 5 cm apart in one breast [14, 15]. BC surgeries have been categorized as breast-conserving surgery (BCS), mastectomy, and others, which include flap reconstructions, nipple reconstructions, and excisional biopsy.

In cases with incomplete information, the patient's records were obtained and completed through a telephone interview. Patients with incomplete medical records that could not be retrieved by phone calls were excluded from the study.

Statistical analysis

Statistical analyses were conducted using SPSS software version 22 for Windows (IBM Inc, NY). Continuous data are presented as mean \pm standard deviation (SD) and categorical data as frequency counts (percentages). Patients were categorized into two age groups: patients less than 35 years old, and those above or equal to 35 years old; with the purpose of comparing the tumor and clinical characteristics of BC in these two age populations. The Chi-square test was used to determine the differences between the qualitative variables of the two groups. The normality of Ki-67% was tested using Kolmogorov–Smirnov Test. The results showed the Ki-67% level was not normally distributed (p -value < 0.001). Therefore, a comparison of Ki-67% between the two groups was conducted using Mann–Whitney U-test. P values < 0.05 were considered statistically significant.

Results

The final analysis of 1476 female patients showed a mean age of 48.03 (± 11.46) years (range: 17 to 86 years). The baseline information of the patients is presented in Table 1, in detail. Our results showed that about half (50.9%) of the patients were postmenopausal, and about 31% of these women had experienced menopause naturally. About 50% of these women had a history of abortion and 39.8% had a previous history of OCP usage. Also, 24.1% of women had a family history of breast or ovarian cancer.

Table 2 presents the clinical characteristic of breast cancer in the study sample. At the time of diagnosis, 968 patients (85.7%) had invasive ductal carcinoma (IDC). Regarding tumor locations, the most frequent site was the UOQ (474 cases, 41.4%) and 98 cases (8.5%) had multicentric tumors. The most frequent symptom was mass palpation ($n=962$, 65.2%) followed by nipple retraction (70 cases, 4.7%). The mean pathologic tumor size was 28.94 (± 21.76), and the majority of patients (43.7%) were diagnosed when the pathologic size of the tumor was between 20–50 mm. The most frequent tumor grade was G2 (43.3%).

Out of 948 tumors, in order of prevalence, 439 (46.3%) were Luminal B, 279 (29.4%) were Luminal A, 132 (14%) were triple-negative (TN) and 98 (10.3%) were Her2-enriched. Out of 1476 cases, 126 (8.7%) had at least one metastatic site. The most common sites of metastasis were bone (64 cases, 4.6%), liver (28 cases, 2%), lung (27 cases, 1.9%), skin (21 cases, 1.5%), and other sites (14 cases, 1%).

More than half of the 1476 recorded patients ($n=760$, 51.5%) had received chemotherapy, and 451 (30.5%) had undergone radiotherapy. The most frequent surgery was BCS ($n=833$, 56.4%) followed by mastectomy in 42.6% ($n=629$) and the remaining had undergone mastectomy with reconstruction ($n=71$, 4.8%). Axillary lymph node dissection (ALND) had been performed for 610 (46.7%) and sentinel lymph node biopsy (SLNB) for 696 subjects (53.3%).

Our results represented that 154 patients (10.4%) were aged less than 35, and there was a significant difference between the molecular subtype of BC considering patients' age (P value: 0.009). In triple-negative and Her2-enriched BC, the proportion of patients aged less than 35 was higher than those 35 years of age or above (Table 3). Furthermore, Ki67% was significantly higher in younger BC patients. Pregnancy-associated BC (PABC) was diagnosed in 17 women (1.2%).

Discussion

The review of medical records of 1476 breast cancer patients who had undergone breast surgery in four academic hospitals of the largest university (TUMS) in Iran, between 2017–2021 showed, the mean age of BC patients who undergo surgery is lower than 50 years old and about 10% of patients were aged less than 35. Palpation of the mass, between 20 and 50 mm, was the most common symptom in patients at the time of diagnosis. More than half of the patients had BCS surgery. The luminal subtype of BC was more prevalent in the total population. However, triple-negative and Her2-enriched BC were the most prevalent subtypes in younger patients. Since these hospitals are considered referral centers, it seems that the results of the current study have high generalizability.

BC is characterized by several clinical and histological types. Large differences have been reported in the age of onset, stage at presentation, clinical manifestations, and prognosis of BC between various countries, mainly between BC patients from the Middle East or North Africa, and those from the Western populations [16, 17]. According to the American Cancer Society, BC mainly occurs in women middle-aged and older, with a median age at the time of diagnosis of 62 years (available on: www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html). Our study

Table 1 Baseline Characteristics of Patients

| Baseline Characteristics (Quantitative Variables) | | | |
|---|-------------------|-----------|-------------------|
| | Minimum | Maximum | Mean ± SD |
| Age (yrs) | 17 | 86 | 48.03 ± 11.46 |
| BMI (kg/m ²) | 13.71 | 52.34 | 27.20 ± 4.54 |
| Age at menarche (yrs) | 9 | 22 | 13.39 ± 1.54 |
| Age at first pregnancy (yrs) | 12 | 47 | 22.26 ± 5.45 |
| Parity (n) | 0 | 16 | 2.74 ± 2.11 |
| Breastfeeding duration (mo) | 0 | 264 | 44.80 ± 41.83 |
| Baseline Characteristics (Qualitative Variables) | | Frequency | Valid Percent (%) |
| Menopausal status | Menopausal | 602 | 50.9 |
| | Premenopausal | 580 | 49.1 |
| | Total | 1182 | 100 |
| Causes of menopause | Natural menopause | 322 | 31.1 |
| | Surgical | 71 | 6.9 |
| | Medical | 83 | 8 |
| | Unknown reason | 558 | 54 |
| | Total | 1034 | 100 |
| Abortion | Yes | 191 | 49.7 |
| | No | 193 | 50.3 |
| | Total | 384 | 100 |
| OCP consumption | Yes | 422 | 39.8 |
| | No | 639 | 60.2 |
| | Total | 1061 | 100 |
| Smoking ^a | Yes | 105 | 11.8 |
| | No | 782 | 88.2 |
| | Total | 887 | 100 |
| Hormone replacement therapy | Yes | 32 | 3.3 |
| | No | 705 | 95.7 |
| | Total | 737 | 100 |
| Family history of BC or OC | Yes | 303 | 24.1 |
| | No | 953 | 75.9 |
| | Total | 1256 | 100 |

BMI Body mass index, SD Standard deviation, BC Breast Cancer, OC Ovarian cancer

^a Active and passive smokers

result supported a previous report which showed that BC incidence peaks among women in their forties in Iran, whereas in the United States and Europe, it peaks among women in their sixties [17]. In the present study, the mean age of the patients was 48 years, however, the previous study by Taghipour et al. reported a mean age of 50 ± 12.9 years among 566 Iranian BC patients between 2008 and 2014 [18]. Comparing the average age in the present study and Taghipour's study raises the possibility that the average age of breast cancer in our country is decreasing, and this point shows the necessity of preventive strategies and breast cancer awareness in our country. Furthermore, another study on very young BC in Tehran, Iran from 1979 to 2012 by Alipour et al. [19] revealed that 1.17% of BC

patients attending a referral center throughout 33 years were 25 years old or less; whereas in our study, 1.4% of patients were in these ages at the time of BC diagnosis. Thus, the proportion of BC patients aged less than 25 years was higher in the present study compared with the findings of Alipour et al.; this also is in favor of the decreasing age of BC in Iran.

Based on the present study results, about one-fourth of patients reported a positive history of OCP usage. In addition, more than one-third of recruited patients had a positive familial history of BC or OC. In a nested case-control study derived from the Golestan Cohort., long-term use of OCP and a positive familial history were reported in 28.3% and 34.3% of BC patients, respectively [16]; these findings are consistent with the present study.

Table 2 Clinical characteristics of breast cancer disease in study population

| Variables | Categories | N (%) |
|------------------------------|-----------------------------|------------|
| Breast cancer side | Right | 719 (48.7) |
| | Left | 745 (50.5) |
| | Bilateral | 2 (0.1) |
| | Missing | 10 (0.7) |
| Pathologic tumor size | Less than 20 mm | 455 (36.3) |
| | 20 – 50 mm | 547 (43.7) |
| | More than 50 mm | 251 (20) |
| Symptoms | Mass palpation | 962 (65.2) |
| | Nipple retraction | 70 (4.7) |
| | Dimpling | 48 (3.3) |
| | Edema | 39 (2.6) |
| | Erythema | 35 (2.4) |
| Tumor site | UOQ | 474 (41.4) |
| | UIQ | 154 (13.4) |
| | LOQ | 98 (8.5) |
| | LIQ | 62 (5.4) |
| | Multicentric | 98 (8.5) |
| Grade | G1 | 216(16.4) |
| | G2 | 571 (43.3) |
| | G3 | 300 (22.7) |
| LVI | Yes | 582 (51) |
| | No | 560 (49) |
| Histologic type | IDC | 968 (85.7) |
| | DCIS | 91 (8) |
| | ILC | 49 (4.3) |
| | Others | 21 (2) |
| Molecular Subtype | Luminal B | 439 (46.3) |
| | Luminal A | 279 (29.4) |
| | Triple-negative (TN) | 132 (14) |
| | Her2-enriched | 98 (10.3) |
| Metastatic site | Bone | 64 (4.6) |
| | Liver | 28 (2) |
| | Lung | 27 (1.9) |
| | Skin | 21 (1.5) |
| | Other | 14 (1) |
| Breast surgery type | Breast-conserving surgery | 833 (56.4) |
| | Mastectomy | 629 (42.6) |
| | Mastectomy + reconstruction | 71 (4.8) |
| Axillary surgery type | ALND | 610 (46.7) |
| | SLNB | 696 (53.3) |
| Adjuvant treatment | Chemotherapy | 760 (51.5) |
| | Radiotherapy | 451 (30.5) |

Data are presented as number with percentages in parenthesis

UOQ Upper outer quadrant, UIQ Upper inner quadrant, LOQ Lower outer quadrant, LIQ Lower inner quadrant, IDC Invasive ductal carcinoma, DCIS Ductal carcinoma in situ, ILC Invasive lobular carcinoma, ALND Axillary lymph node dissection, SLNB Sentinel lymph node biopsy

In consistence with our results, many studies reported that the left breast is at greater risk of developing cancer and the UOQ is the most common location of breast cancer [20–22]. It might be important to pay attention to the area of primary involvement because some evidence showed that the survival of BC patients with UOQ involvement is significantly better than tumors located elsewhere in the breast [23–25].

Globally, IDC constitutes about 70–80 percent of all BCs [25]. The results of our study also show that IDC is the most common type of BC in our population. Similar to our study, a previous study in Iran reported that grade 2 BC is the most prevalent grade, and that grade 1 is the least commonly seen [18].

The most common subtype of BC in the present study was Luminal B, followed by Luminal A, TNBC, and Her2-enriched. The frequency of molecular subtypes in our study followed the same order as those of Mighri et al. [22], Al Tamimi et al. [26], and Caldarella et al. [27]. However, these results are inconsistent with some previous studies conducted in Algeria, Egypt, Japan, and the USA [28–31]. These controversies may be due to different cut-off values set for Ki-67 in the stratification of luminal BCs.

In our study, 8.7% percent of patients were diagnosed with metastatic BC. Bone metastasis was reported as the most common site, followed by metastasis to the skin, liver, lung, and brain. A recent study was performed by Anwar et al. on 1,329 females with BC to investigate risk factors, patterns, and distribution of bone metastases and skeletal-related events in high-risk BC patients [31]. Their findings showed a rate of about 18.5 percent for metastatic BC (higher than ours), but like our results, bones were the most common site of metastasis in their analysis. As our population consisted of women admitted to surgical wards, the rate of metastatic BC is not demonstrative for all BCs. Bone metastasis has the best prognosis among metastatic sites [32], and curative surgery is considered in many cases. The non-expected high rate of skin metastases is because these patients are occasionally referred for surgical excision of the skin lesions.

Worldwide, BCS is defined as the most common surgical procedure for early-stage BC [33]. An institutional review board in the United States reported that the mastectomy rate (including bilateral mastectomy and reconstruction) has increased slowly during 1994–2007 (33%–44%) [34]. A cohort study in the USA on 21,869 BC patients from 1998 to 2007 also showed an increased rate of mastectomy for early-stage BC treatment in all age groups [35]. In our study, BCS was more commonly performed (56.4% for BCS vs. 42.6% for mastectomy). The rate of mastectomy in our country is similar to the US report in 2007 (44%) [34] and is lower than Saudi Arabia

Table 3 Comparison of variables between patients based on age groups (< 35 vs ≥ 35 years)

| Variables | | <35 years (n=154) | ≥35 years (n=1322) | P-value |
|-------------------------------|-----------------|----------------------|--------------------|--------------|
| Family history of BC or OC | Positive | 28 (21.5%) | 275 (24.4%) | 0.47 |
| | Negative | 102 (78.5%) | 851 (75.6%) | |
| Grade | G1 | 15 (15.3%) | 201 (20.3%) | 0.055 |
| | G2 | 46 (46.9%) | 525 (53.1%) | |
| | G3 | 37 (37.8%) | 263 (26.6%) | |
| LVI | Yes | 57 (53.8%) | 525 (50.7%) | 0.54 |
| | No | 49 (46.2%) | 511 (49.3%) | |
| Pathologic size category (mm) | ≤20 | 45 (36.6%) | 410 (36.3%) | 0.25 |
| | 21-50 | 47 (38.2%) | 500 (44.2%) | |
| | >50 | 31 (25.2%) | 220 (19.5%) | |
| Histologic type | IDC | 94 (87.9%) | 874 (85.4%) | 0.54 |
| | DCIS | 9 (8.4%) | 84 (8.2%) | |
| | Others | 4 (3.7%) | 66 (6.4%) | |
| Molecular subtype | Luminal A | 14 (15.2%) | 265 (28.8%) | 0.009 |
| | Luminal B | 41 (44.6%) | 398 (43.3%) | |
| | Luminal X | 5 (5.4%) | 59 (6.4%) | |
| | Her2-enriched | 16 (17.4%) | 82 (8.9%) | |
| | Triple negative | 16 (17.4%) | 116 (12.6%) | |
| Ki-67 (%) | | 30.86 ± 22.13 | 24.88 ± 19.28 | 0.01* |

Luminal X means ER and/or PR positive, Her-2 negative, Unknown Ki-67%. *US* Ultrasonography, *BC* Breast Cancer, *OC* Ovarian Cancer, *LVI* Lymphovascular Invasion, *CNB* Core Needle Biopsy, *IDC* Intra-ductal carcinoma, *DCIS* Ductal Carcinoma Insitu, *ILC* Intra-Lobular Carcinoma, *LCIS* Lobular Carcinoma Insitu

P-value refers to Chi-square test in categorical variables. Mann–Whitney U-test was used for comparison of Ki-67% between two-groups

(62.4%) [33]. In BC women of Saudi Arabia, the predictor of mastectomy was increased tumor size, stage, and HER-2 positivity [33]. This worldwide increasing trend of mastectomy emphasizes the urgent need for early detection screening protocol to move towards BCS. The geographical difference in the decision for BCS or mastectomy in early-stage BC has been observed in other studies as well. One study in Iran has indicated that Iranian general surgeons avoided BCS and their major reason (46.3%) was uncertainty about the result of conservative therapy [36]. It seems that the rate of mastectomy is still high; therefore, holding breast surgery fellowship courses and training classes for general surgeons and taking advantage of consultation in a multidisciplinary team (MDT) breast is highly recommended.

One study showed that the risk of death from breast cancer has increased sharply in women younger than 35 years. Therefore, they recommended that age less than 35 years is a reasonable cut-off for defining young age-onset breast cancer [37]. In the present study, we compared the clinical characteristics of BC patients younger or older than 35. Our results showed that tumor size was larger in younger patients and Ki-67% as a proliferative factor of breast cancer was significantly higher in those patients. Furthermore, the rate of good prognosis tumors (Hormone-receptor positive) was lower in patients

younger than 35. These results are consistent with several previous studies [38–40].

The current study has the advantage that it was conducted in several academic and active referral hospitals, and its results seem to be generalizable, although, this study is ongoing on a wider scale with a large sample size. However, this study had some limitations. Despite the young age of patients, data about genetic testing were scarce and therefore were not included in this study. Also, we did not have information about the ethnicity of the patients, but this could provide interesting findings.

Conclusions

This study highlights the epidemiological and clinical characteristics of BC in Iranian women, with a special focus on factors that were not well defined in previous records in the Iranian population. In line with previous studies, invasive ductal carcinoma was the most common histologic type, grades 2 and 3 constituted the highest proportion of tumors. Luminal B was the most frequent molecular subtype, followed by Luminal A. Young women constituted a higher proportion of cases compared with older studies, suggesting a trend toward lower age for BC in recent years. These results indicate the need for more attention and preventive measures and screening in Iranian women before 50 years.

Abbreviations

| | |
|------|---------------------------------|
| WHO | World Health Organization |
| BC | Breast cancer |
| OCP | Oral contraceptive pills |
| HRT | Hormone replacement therapy |
| NCR | National Cancer Registry |
| ASIR | Age-standardized incidence rate |
| ER | Estrogen receptor |
| PR | Progesterone receptor |
| UOQ | Upper outer quadrant |
| UIQ | Upper inner quadrant |
| LOQ | Lower outer quadrant |
| LIQ | Lower inner quadrant |
| BCS | Breast-conserving surgery |
| SD | Standard deviation |
| IDC | Invasive ductal carcinoma |
| ALND | Axillary lymph node dissection |
| SLNB | Sentinel lymph node biopsy |
| PABC | Pregnancy-associated BC |
| MDT | Multidisciplinary team |

Acknowledgements

We would like to thank Mrs. Afsaneh Norouzi for her assistance in completing questionnaires and active follow-up of patients.

Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection was performed by SA, LH, NM, AYK, MM, MT, MMZ, ShH, SSh, FM, MMG. Statistical analysis was conducted by BE. The first draft of the manuscript was written by RP and RO. All authors read and approved the final manuscript.

Funding

The study was funded by a grant from Research Deputy of Tehran University of Medical Sciences (TUMS) (Grant Number: 99–3–101–50918).

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1400.006). Informed consent was obtained from all participants. The project was run according to the ethical principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 10 June 2023 Accepted: 6 September 2023

Published online: 25 September 2023

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