Review Article

Study on epidemiology, risk factors and clinical characteristics of triple negative breast cancer in Bangladesh

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ABSTRACT

Breast cancer is the second most common type of cancer in Bangladesh. Although significant improvement has been made in breast cancer treatment and management, Triple Negative Breast Cancer (TNBC) is still the least known breast cancer subtype in this country. TNBC is well known for its aggressive nature and limited therapeutic options when compared to other breast cancer subtypes. Several population-based studies indicated high prevalence of TNBC in African women in addition to few recent studies indicating a growing number of TNBC patients among Asian population. However, there is a lack of evidence on TNBC patients in Bangladesh due to limited knowledge and awareness. In this paper we review the epidemiology, general risk factors and clinical characteristics of TNBC to find out the correlation between TNBC and other conventional breast cancer subtypes in Bangladesh. Some diagnostic and therapeutic approaches as well as future novel solutions for TNBC are also discussed to understand the pathologic process and treatment strategies of TNBC. Literature review reveals that, there is a lack of TNBC studies in Bangladesh. Therefore, more investigations should be carried out to address the degree of vulnerability of TNBC in breast cancer patients of Bangladesh.

Keywords: Clinical characteristics, Epidemiology, Novel targets, Triple negative breast cancer, Risk factors

INTRODUCTION

Breast cancer is the most frequent type of carcinoma among Bangladeshi women. The complex and heterogeneous nature of breast cancer gives rise to distinctive subtypes that are different in cellular origin, mutation, histology, progression, metastatic potential, therapeutic response and clinical outcome. Triple negative breast cancer (TNBC) is a particular immunohistopathological subtype that lacks an effective therapeutic option presenting the worst prognosis.[1] Based on immunohistochemical analysis, ASCO and latest St Gallen consensus specified TNBC as a breast cancer subtype with no expression of estrogen receptor (ER-), progesterone receptor (PR-) and neither expression nor amplification of human epidermal growth factor receptor-2 gene (HER2-) thus having a unique molecular profile, aggressive nature, distinct metastatic patterns and lack of targeted therapies.[2,3] It is estimated that triple negative breast cancer accounts for approximately 10-20% of invasive breast cancers out of the worldwide breast cancer burden.[4] Currently approved targeted approaches such as hormone therapy or HER2 targeted drugs like trastuzumab are not effective in the treatment of TNBC compared to other breast cancer subtypes owing to its negative ER, PR and HER2 expression and therefore conventional cytotoxic chemotherapy remains the only option for TNBC treatment after surgery.

TNBC patients are considered to be more susceptible to neoadjuvant or, adjuvant chemotherapy involving anthracyclines, taxanes and alkylating agents. Neoadjuvant chemotherapy tends to show higher rate of complete pathologic remission (pCR) in TNBC patients than in other breast cancer subtypes.[5] Despite of being sensitive to adjuvant or, neoadjuvant therapy, TNBC patients have poorer outcomes and possess higher risk of early distant recurrence mostly in brain, lungs and soft tissue.[6,7] The most vulnerable time period for early recurrence in TNBC is first three years after initial treatment with survival rate shorter than in non-TNBC patients.[8]

However, there have been recent advancements on novel signalling pathways in the treatment of TNBC patients giving rise to novel chemotherapeutic approaches mostly focusing nano based solution that actively target this particular tumor. Use of agents targeting aberrant DNA repair is under clinical investigation showing a promising result improving the prognosis of the disease.

Epidemiologic studies of TNBC exhibit its close association with African ethnicity. A significant number of large scale population based studies were conducted on western population showing approximately three times higher occurrence of TNBC in African-American women than white Americans.[9] Compared to western population, Asian countries show much extensive diversity in terms of race and socio-economic status that can contribute to more complex outcomes and prognosis of breast cancer among Asian women. Developing countries from South Asia are particularly struggling with an increased breast cancer burden experiencing death of approximately half of their total breast cancer patients.[10]

However, prevalence of TNBC in developing countries from South Asia is still a lesser known fact. Although few studies relating Asian ethnicity indicate a rising number of TNBC patients, more precise and complete study is still needed to identify the proper distribution of TNBC in this region. Similarly, TNBC prevalence in Bangladesh is also an unidentified issue. Despite of being a resource-limited country, Bangladesh has made a significant improvement in public health sector in recent years especially dealing with infectious diseases. However, treatment and management of cancer and related research opportunities are still limited here. Adequate information on epidemiology, pattern and subtypes, clinical outcomes of breast cancer in Bangladesh is difficult to obtain as there is a lack of resource and necessary funding to conduct research works on this subject. In this paper, we aim to review the epidemiology, key risk factors and clinical characteristics of TNBC to understand their association with the common risk factors and pattern of other conventional breast cancer subtypes reported for Bangladeshi patients. In addition to the review of risk factors and molecular characteristics, we also intend to highlight some of the diagnostic and treatment approaches including some novel targets for the treatment of TNBC.

We systematically searched through some of the major online scientific databases such as, PubMed, Science Direct etc. to extract scientific papers of our key interest written in English language from the year 2005 to February 2018 published in reputed journals. The remainder of the paper includes six sections. In second section, we are going to discuss about the TNBC prevalence in Bangladesh by discussing an overall epidemiological statistics of TNBC in Asia. The third section deals with key risk factors of TNBC and their frequency among Bangladeshi breast cancer patients. In fourth section, we present molecular and clinical characteristics of TNBC. Brief highlights of diagnosis and current and future treatment approaches of TNBC are given in fifth and sixth sections respectively. Finally, a discussion part is included in the last section of the paper.

TNBC prevalence in Bangladesh

A little is known about the prevalence and distribution of TNBC in Bangladesh. Like many other South Asian countries, Bangladesh also lacks large-scale population based cancer registry or, a central cancer registry to provide a nationwide comprehensive data for cancer studies.[11] The only hospital based cancer registry in Bangladesh maintained by National Institute of Cancer Research and Hospital (NICRH) is also unable to keep record on TNBC patients since it lacks the necessary marker testing facilities for the detection of TNBC. Not only that, none of the public hospitals of Bangladesh is able to provide marker testing facility for estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor expression which is the main diagnostic approach for TNBC. There are only 3 private hospitals/clinics in Bangladesh that offer this particular marker testing facility which however, becomes very expensive to afford for mass people of the country.[12]

Our review has found two solid data on TNBC patients of Bangladesh. A cohort study involving 1042 cases of breast cancer in Bangladesh found 9% of the total cases to be triple negative after an immunohistochemical examination.[13] Another study on the patients of NICRH reported 20% (<40 years) and 26.6% (>40 years) TNBC patients during the period of November 2011 to February 2013.[14] These two studies show a huge difference in their respective results through which we cannot predict the actual scenario of TNBC in Bangladesh. However, TNBC prevalence may depend on several factors like race, age (premenopausal or, postmenopausal women), tumor grade and stage, family history etc.[9] For example, TNBC is generally said to be associated with African ethnicity. Several population based large scale studies confirmed the high prevalence of TNBC among African women or, African-American women compared to other races.

The study of TNBC distribution among Asian and South Asian population can help us to understand the racial influence on TNBC for Bangladeshi women. Frequency of triple negative hormone receptor among different ethnic groups were evaluated in UK and US where South Asian/Bangladeshi women were at higher risk of TNBC compared to White Americans which was the second highest (~19%) after African Americans (~25%).[15] Another institutional database study in US including patients diagnosed with invasive breast carcinoma found higher proportion of TNBC cases (12%) than non-TNBC (9%) among Asian population.[16] On the contrary, a cohort study comprising four ethnic groups- African, American, Hispanic and Asian women found that Asian women were at the lowest risk for TNBC occurrence compared to all three other groups.[17]

However, TNBC studies in Asian or, South Asian region reported a moderate to high proportion of TNBC patients among all breast cancer subtypes ranging from (15-25) % in most cases. A special mention to a study conducted in West Bengal (neighbouring state from India and very similar to Bangladesh in terms of race and culture) that found 22% of TNBC cases among all breast cancer patients attending a specialized breast cancer clinic in Kolkata.[18] Some study results showing TNBC prevalence among different Asian/South Asian countries are enlisted in Table 1.

Since most of the South Asian countries are similar in socio-economic, cultural, racial and other aspects, we can predict TNBC prevalence in Bangladesh from an overall study of TNBC in South Asian region.

Table 1: TNBC patients statistics in Bangladesh and some other Asian countries.

Study	Country	Region	TNBC patients (%)
Mostafa et al[13]	Bangladesh	South Asia	9%
Rahman et al[14]	Bangladesh	South Asia	(20-26.6) %
Jana et al[18]	India	South Asia	22%
Ambroise et al[19]	India	South Asia	25%
Gupta et al[20]	India	South Asia	~30%
Sharma et al[21]	India	South Asia	~32%
Teoh et al[22]	Malaysia	South-East Asia	15%
Tan et al[23]	Malaysia	South-East Asia	~18%
Ng et al[24]	Indonesia	South-East Asia	21%

TNBC risk factors for Bangladeshi women

All breast cancer subtypes are commonly linked with some reproductive and non-reproductive factors. Reproductive factors like age at menarche, menopause, parity, breastfeeding, age at first childbirth etc. play important role in the development of breast cancer. In addition to that, hormone therapy, oral contraceptives, familial history, BRCA1/2 gene mutation etc. are some non-reproductive factors that are thought to have close association with breast cancer. However, their effects can be different on TNBC and non-TNBC patients. BRCA 1 and 2 are tumor suppressing genes expressed in human breast cells and other tissues. BRCA gene mutation is one of the main causes for hereditary breast cancer. It has been reported that TNBC patients are the most common carriers of BRCA1 mutation among all breast cancer subtypes.[16] A study evaluating the BRCA mutation among different ethnic groups in a genetic counselling cohort reported 139 (30.8%) of total 469 TNBC patients confirming BRCA mutation where 106 of them had BRCA1 and 32 of them had BRCA2 mutation. BRCA mutation data according to race and age was also reported in the same study. 28.5% BRCA positive results were found in Asian patients which was the second highest among all races. African-American patients had the highest number of BRCA mutation. Among all age groups, BRCA mutation was most prevalent in women under the age of 40 (43.8%).[25] However, association of BRCA mutation in Bangladeshi breast cancer patients has not been studied profoundly. Little is known about the BRCA mutation but family history was taken into account for the development of hereditary breast cancer in Bangladeshi patients several times. In a study, about 15% patients were found to have a direct family history of breast cancer while a second study found the ratio to be quiet low for Bangladeshi breast cancer patients.[14,26] Though there is no significant correlation between family history and different breast cancer subtypes but a study reported approximately 28% TNBC patients with family history being highest among all subtypes.[27]

TNBC is repeatedly found to occur in premenopausal women. Early menarche, young age at first childbirth, increased parity, oral contraceptives, obesity these are some common risk factors for TNBC in general. Obesity has been reported to be strongly associated with the increased risk of TNBC. Increased body weight was found to contribute to increased risk of prognosis and poor survival for TNBC patients after surgery. The relation of TNBC with parity and breastfeeding is not clear. Increased parity is normally associated with lower risk of breast cancer in luminal subtypes however, some studies found the inverse effect of high parity in case of

TNBC while some studies did not find any correlation between TNBC and parity. Recurrence rate of TNBC was increased in patients with early age of first childbirth. Breastfeeding is considered to have protective effect for breast cancers. But a study in US found the adverse effect of breastfeeding while a Chinese study confirmed the protective effect of breastfeeding among TNBC patients.[28-30]

Studies confirmed these risk factors to prevail in Bangladeshi breast cancer patients. Breast cancer among premenopausal women is a characteristic for South Asian/Bangladeshi women. The common age group for breast cancer patients in Bangladesh was reported to be 40-49 years. The usual age of menarche is between 12-14 years for Bangladeshi girls. Bangladeshi women tend to give birth of their first child at a very young age. Increased parity is also a common feature for Bangladeshi women. Studies showed highest number of breast cancer patients giving birth before the age of 20 and having 3-4 full term pregnancies before breast cancer diagnosis in Bangladesh. Past history of any kind of hormone therapy or, oral contraceptive increases the risk of breast cancer regardless of any race. A study reported 47% patients who had a history of taking contraceptive pills. Obesity or, age higher than the BMI limit was also found in large number of breast cancer patients in Bangladesh.[14,26,31] Relation between various risk factors of TNBC and their prevalence in breast cancer patients of Bangladesh is simplified in Figure 1.
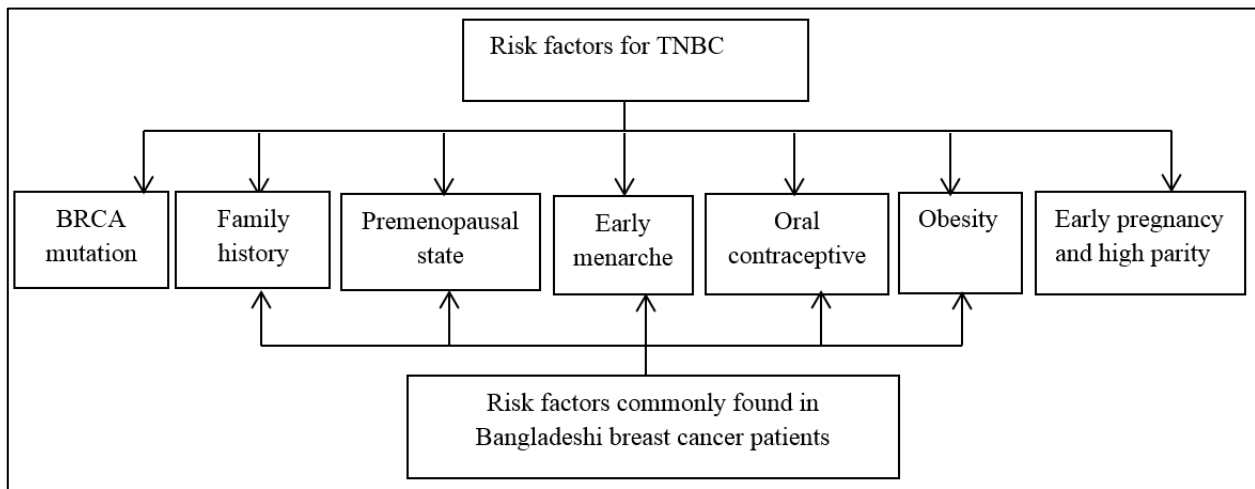
Figure 1: Frequency of TNBC risk factors among Bangladeshi breast cancer patients.

Molecular profile and clinical characteristics of TNBC

The underlying molecular mechanism of TNBC is much complex and distinct from other breast cancer subtypes. Previously, genomic studies have classified invasive breast tumors into 5 intrinsic subtypes- luminal A, luminal B, HER2 overexpressing, basal like and an additional normal breast like group.[4] Basal like subtype is the one which is considered to be particularly associated with TNBC. Although most TNBC tumors are basal like, they are not equivalent in terms of gene expression profiling and IHC analysis. Up to 30% basal like tumors differ from TNBC when they are subjected to IHC analysis because of expressing either ER receptor or, HER2 receptor gene.[32] The reasons behind the overlapping between TNBC and basal like tumors are mostly due to the overexpression of basal cytokeratins (CKs) 5, 7 and 17; epidermal growth factor receptor (EGFR/HER1) (in up to 60% of TNBC tumors). p-53, KIT, P-cadherin overexpression are also seen in both TNBC and basal like tumors.[33] Another important consideration regarding TNBC and basal like subtype overlapping is the association of both the subtypes with BRCA gene mutation. Apart from BRCA mutation, dysfunction of Hedgehog signalling pathway is also acknowledged in breast cancer progression. To observe the correlation between sonic hedgehog overexpression and TNBC, a study conducted on breast cancer patients from Bangladesh reported TNBC groups with higher sonic hedgehog expression compared to non-TNBC groups.[34] To understand the molecular features of TNBC more profoundly, tumors characterized by triple negative is further classified into at least six distinct molecular subtype upon gene expression profiling- basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) subtype.[35]

Histologically, majority of TNBC is of invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) but some other histological types are also presented such as, medullary, metastatic, apocrine and adenoid cystic carcinomas. Clinically TNBC is well known for its aggressive behavior and is characterized by onset at a younger age, high mean tumor size, higher grade tumors and sometimes, a higher rate of node positivity. In a retrospective study of clinicopathological study of TNBC

conducted on Chinese patients reported over 80% tumors to be IDC and approximately 13% to be ILC. Most of the tumors represented higher histological grade (grade II and III) where tumor size was also found to be more 2-5cm or, more.[36]

Data on molecular and clinical characteristics of breast cancer in Bangladesh is scarce. During the research, we found only one article regarding clinical and histopathological condition of breast tumors among 50 breast cancer of Bangladesh. The study revealed that most of the patients were in advanced stage of carcinoma (stage-III and IV); 82% of the tumors were histopathologically invasive ductal carcinoma (IDC). Other than IDC, 12% non-invasive ductal carcinoma, 4% invasive lobular carcinoma and 2% non-invasive carcinoma were reported in the study.[37]

TNBC diagnosis

Aggressive and metastatic nature of TNBC makes it difficult for an early and accurate diagnosis which is very much important in the establishment of an appropriate and adequate therapeutic intervention. Mammography is widely used method for detection of breast cancer but does not always give the accurate information about TNBC as most TNBC tumors lack the abnormal tissue features. Other existing radiological examinations such as ultrasonography, MRI etc. are also unable to detect the presence of TNBC in most cases.

That is why; TNBC diagnosis is mostly dependent on the IHC analysis of the biopsy samples of tissues identifying the absence of ER, PR and HER2 expressions. IHC analysis enables to identify those cell receptors using antibodies that specifically bind with antigens present in the tissue samples and this antibody-antigen binding can be detected usually by chemical or, enzymatic staining.[38,39] However, IHC analysis facility is very poor in Bangladesh thus presenting a poor diagnosis condition for TNBC in Bangladesh leading to patients having inappropriate treatment regimen in most cases.

Apart from these conventional methods, recent studies have shown some novel approaches for the diagnosis of TNBC to predict accurate early stage information as well as therapeutic outcome. Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (18 F-FDG) is a promising tool for the detection of TNBC with high level of accuracy. 18 F-FDG is a tracer molecule and a glucose analogue. Tumor cells in high level uptakes this tracer molecule (tumor cells uptake glucose in high level) while PET (an imaging method) constructs the 3-D images by measuring this radiolabelled tracer molecule in the body.[39] Molecular imaging technique is another promising diagnostic method for TNBC that uses novel and specific contrast agents. Here, molecular probes containing a signalling or, contrasting agent with targeting ligand that target overexpressed or, upregulated cell receptors to detect key

biological process. This allows a molecular examination of tumors rather showing only morphological view.[40]

TNBC current treatment approaches and novel targets for TNBC

Like other breast cancer subtypes, TNBC patients also undergo surgical excision (mastectomy and lumpectomy) and radiotherapy. This is one of the best approaches to achieve local control not only for TNBC but for any solid tumors. Other than surgery and radiotherapy, different adjuvant therapies like chemotherapy, hormone therapy, targeted therapy etc. are well-established treatment approaches to necessarily control tumor metastasis and improve overall survival. Breast cancer patients are currently subjected to anti-hormonal or HER2 targeted therapy based on the presence of cellular receptors for estrogen or, progesterone hormones or, HER2 receptor. However, TNBC do not possess these cellular receptors which limit the therapeutic option for TNBC to only chemotherapy. This limited therapeutic option and aggressive nature of TNBC eventually leads to a worse prognosis.

Historically, TNBC is well responded to cytotoxic chemotherapy. Cytotoxic combinations like anthracyclines (e.g. doxorubicin) and taxanes (e.g. docetaxel, paclitaxel) are commonly used as first line chemotherapeutic regimen. Capecitabine is given during the time of progression.[41-43] However, cytotoxic chemotherapies do not contribute to the reduction of recurrence or, mortality rate. Use of drugs like anthracyclines or, taxenes may develop a potential chance of resistance that limit the second line chemotherapy to a small number of non-cross resistant regimen.[44] Two non-taxane mitotic inhibitors-eribulin and ixabepilone are considered as alternative chemotherapeutics with improved mortality rate. Eribulin is reported to reduce the death risk upto 29% in patients pretreatd with anthracyclines or, taxanes but works better in capecitabine pretreated patients.[45] Ixabepilone is an epothilone-B analogue which is most effective when administered along with capecitabine after failure of anthracylines or, taxenes.[46]

Another important treatment regimen for TNBC is neoadjuvant chemotherapy. The term neoadjuvant chemotherapy stands for a therapeutic intervention that is given prior to the surgery to reduce the size of unresectable tumors that allows the surgery to be performed.[47] Clinically, neoadjuvant treatment has shown better clinical outcomes and survival in TNBC patients. Along with anthracyclines and taxenes, platinum based drugs like carboplatin or, cisplatin are also administered in neoadjuvant therapy.

Approved agents for breast cancer therapy have resulted in improvements of patient's outcome but the prognosis for metastatic TNBC patients remains poor. Much work has been aimed at improving this scenario. For this

reason many novel targets are being studied for a better outcome and for the establishment of newer therapeutic approach for TNBC. Administration of newer targeted therapies like poly ADP-ribose polymerase (PARP) inhibitors, epithelial growth factor receptor (EGFR) inhibitors, mTOR inhibitors, angiogenesis inhibitors, Src inhibitors etc. along with chemotherapeutics is showing promising results. Studies reported that when drugs like iniparib, cetuximab, bevacizumab, sorafenib etc. were administered in combination with conventional chemotherapy, progression free survival was demonstrated in patients having metastatic TNBC.[48] Some newer therapeutic approaches which are under clinical investigation in TNBC treatment are listed in Table 2.

Table 2: New TNBC treatment approaches.

Approach	Agents
Enhance aberrant DNA repair	Platinum drugs (e.g., cisplatin, carboplatin) PARP-1 inhibitors (e.g., olaparib, velaparib) Brostallicin
Block angiogenesis	Bevacizumab, Sunitinib
Block EGFR	Cetuximab, Erlotinib
Stabilize microtubules	Ixabepilone
Block signalling cascades	Src inhibitors (e.g., dasatinib) mTOR inhibitors (e.g., everolimus, rapamycine)

DISCUSSION

In this paper, a study of epidemiology, risk factors, molecular and clinical characteristics of TNBC as well as its diagnostic and treatment approaches have been compiled to understand the correlation between TNBC and other conventional breast cancer subtypes in Bangladesh. This understanding will eventually help us to predict an overall scenario of TNBC in Bangladesh. Studies conducted on different Asian ethnicities show a high prevalence of TNBC among Asian women. However, little is known about TNBC prevalence in Bangladesh. But from epidemiological studies conducted on other South Asian countries, we can predict a general scenario of TNBC in Bangladesh.

Our study also found a close association of TNBC risk factors with Bangladeshi breast cancer patients. The occurrence of TNBC differs from in terms of age and menopausal state. Studies have revealed the susceptibility of young premenopausal women towards TNBC which has also been found to be common for the breast cancer patients of South Asian/Bangladeshi women. However, shorter life expectancy of Bangladeshi or, other South Asian women may cause the incidence of breast cancer at an early age compared to their western counterparts. Again, very limited documentation on the molecular and clinical features of breast cancer in Bangladesh is an obstacle to the proper understanding of underlying mechanism of breast cancer incidence in Bangladesh.

Being a very densely populated country with a poor general health education, Bangladesh has been lacking the proper instrument to fight against cancer. For example, due to lack of awareness and social taboo, majority of women in Bangladesh often hesitate to see doctor for breast examination. Furthermore, there are very few specialized cancer hospitals in the country which make it almost impossible to provide proper medical healthcare for not only breast cancer patients but all other cancer patients in general. The quality of treatment of breast cancer in Bangladesh widely varies due to lack of proper guideline or, standard protocol. In many cases, the patients are going through surgical procedure such as mastectomy and lumpectomy without any appropriate diagnosis.

There is a very limited facility of proper histopathological analysis for breast cancer patients. It has been reported that almost 25% patients of breast cancer patients had undergone surgical procedure without any histopathological analysis in a teaching medical hospital of Bangladesh.[49] Commonly practiced diagnostic approach for breast cancer patients in Bangladesh are mammography, ultrasonography etc. However, without appropriate histopathological analysis TNBC cannot be detected which eventually leads to an inappropriate treatment strategy for TNBC patients demonstrating poorer prognosis.

As discussed above, TNBC is undeniably more aggressive than other breast cancer subtypes and therefore, worldwide research based on TNBC is being given much importance. It is high time to specify the condition of TNBC patients in Bangladesh as well. Early detection of TNBC is much important in the overall survival and prognosis. That is why we recommend the establishment and availability of proper histopathological analysis in every public and private hospitals of Bangladesh. A standard policy should be made and strongly followed to ensure correct diagnostic and treatment strategies for different breast cancer subtypes. Concurrently more scientific research should be carried out in this area that will help us to understand the degree and vulnerability of TNBC in Bangladesh as well as give us an opportunity of broad understanding of clinicopathological characteristics of TNBC.

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