INTRODUCTION

The Global Burden of Cancer (GLOBOCAN) states that breast cancer is one of the most common cases of cancer in 2020 with 2.26 million cases and deaths occurring in 685 thousand cases worldwide[1]. One of the molecular subtypes of breast cancer is Triple Negative Breast Cancer (TNBC) which is characterized by Immunohistochemistry (IHC) of Estrogen Receptor (ER) and Progesterone Receptor (PR) less than 1% and the absence of overexpression or amplification of Human Epidermal Growth Factor Receptor 2 (HER2) [2,3].

Breast cancer cases with TNBC subtypes account for approximately 15–20% which equates to 200.000 new cases worldwide each year [2,4]. The National Cancer Data Base (NCDB) shows that 13% of breast cancer patients are TNBC, ranging from 23,7% African-Americans to 8,9% Filipino patients. In Southeast Asia, a study found that TNBC accounted for 10,5% of 1.227 breast cancer patients. Epidemiological data in Indonesia, from a study at Dr. Sardjito Hospital, Yogyakarta reported that 25% of breast cancer cases recorded were TNBC [5]. Research in West Sumatra with data collected from 2008 to 2017 at Dr. M. Djamil Hospital, Padang, found that the most common subtype in young women was TNBC which was 80,3% of 71 breast cancer cases [6].

Triple Negative Breast Cancer is highly invasive, with distant metastasis occurring in about 46% of patients.
Distant metastasis usually occurs 3 years after diagnosis and metastasis, which affects the brain and internal organs, such as the lung. After metastasis, the median survival is only 13.3 months, with a postoperative recurrence rate of 25% [7,8]. Triple Negative Breast Cancer has a more aggressive clinical course than other breast cancer phenotypes. Triple Negative Breast Cancer can recur early, 1–3 years after diagnosis and death occurs within the first 5 years after therapy [9]. Only about 60% of patients survive for 5 years [10].

According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, the determinants of breast cancer prognosis are size, lymph node involvement, histopathological grading of the tumor, and receptor statuses such as ER, PR, and HER-2 [11,12]. The degree of differentiation or histological grading of the tumor considers morphology and proliferation in its determination so that it has prognostic significance in breast cancer [13]. Histological grading of the tumor is associated with decreased survival. Grade III is associated with poor prognosis and higher mortality than grade I [14].

The presence of tumor cells in the lumen of the lymphatic or vascular system at the site of tumor origin is known as Lymphovascular Invasion (LVI) [15]. LVI not only occurs in large and advanced tumors but is also found in early-stage Breast Cancer (BC) with varying degrees of differentiation [16]. Studies by Ozer et al. [17] and Mittal et al. [18] suggest a significant association between molecular subtypes with histological grading and LVI. The majority of TNBC cases have a high histopathologic grade of grade II or grade III, and LVI is commonly found in TNBC.

Research by Agarwal et al. [19] comparing the outcome of TNBC patients and non-TNBC patients found that the incidence of LVI occurred as much as 20.4% in TNBC patients, which is higher than in non-TNBC patients, 13.5% [19,20]. Research conducted at Dr. M. Djamil Padang Hospital found TNB data with a large number of LVI, 37.8% [21]. Research on 21,704 BC patients by Zhong et al. [22] found that BC patients with positive LVI had worse Overall Survival (OS), Loco-Regional Recurrence (LRR), Distant Metastases (DM), Breast Recurrence (BR), Disease Specific Survival (DSS), Breast Cancer Specific Survival (BCSS), and Local Recurrence (LR) after receiving breast conservative surgery than LVI negative patients.

Based on the description above, researchers are interested in conducting this study because the degree of differentiation and LVI that occurs in triple-negative breast cancer can affect the prognosis and survival of patients, and there is still a lack of research and updated data regarding the relationship between the degree of differentiation and LVI in TNBC conducted in Indonesia, especially in Padang, West Sumatra.

METHODS

The ethical review permit number in this study is 760/UN.16.2/KEP-FK/2022 issued by the Ethics Committee of the Faculty of Medicine, Andalas University in 2022, and LB.02.02/5.7/216/2022 issued by the Ethics Committee of Dr. M. Djamil Hospital, Padang.

Data Collection

This type of research is analytic observational research with a cross-sectional approach. The population of this study were breast cancer patients diagnosed with the molecular subtype Triple Negative Breast Cancer on IHC examination characterized by ER-negative, PR-negative, and HER2-negative as stated in the medical records at the Ropanasuri Surgical Hospital, Ibnu Islamic Special Hospital, and Dr. M. Djamil Hospital from 2016 to 2021. The samples of this study were TNBC patients who met the inclusion criteria, namely patients who had been diagnosed with TNBC from the first IHC examination onwards and had data on the degree of differentiation and LVI from the results of anatomical pathology examination and exclusion criteria, namely male patients and patients with bilateral breast cancer.

Statistical Analysis

Utilizing the Lemeshow formula, we arrived at a minimum sample size of 36. Purposive sampling was used where the sample size was selected based on the specific aims and objectives of the population. The data analysis technique used was univariate analysis to present data on the frequency distribution of TNBC patients based on their age, histopathological type, and metastasis, which affects the brain and internal organs, such as the lung. After metastasis, the median survival is only 13.3 months, with a postoperative recurrence rate of 25% [7,8]. Triple Negative Breast Cancer has a more aggressive clinical course than other breast cancer phenotypes. Triple Negative Breast Cancer can recur early, 1–3 years after diagnosis and death occurs within the first 5 years after therapy [9]. Only about 60% of patients survive for 5 years [10].

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RESULTS

In this analytical study, 44 samples were selected from a pool of 111 Triple Negative Breast Cancer (TNBC) patient samples (Figure 1). Based on Table 1, the majority of 35 TNBC patients, or 79.5% had a histopathology type of Invasive Carcinoma Mammam of No Special Type (NST). Conversely, Adenoid Cystic Carcinoma Mammam, Invasive Papillary Carcinoma Mammam, and Ductal Carcinoma In Situ had the lowest frequency, with each accounting for just 1 person (2.3%).

According to the data presented in Table 1, out of the 44 TNBC patients in West Sumatra, the highest age bracket is those above 60 years, totaling 19 individuals (43.2%), while the youngest age bracket, consisting of individuals less than 30 years, had only 1 person (2.3%). The most common age detected was 52 years with the mean age of patients in this study as a whole being...
Table 1. Clinicopathology of triple-negative breast cancer patients

<table>
<thead>
<tr>
<th>Clinicopathology</th>
<th>n=44</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histopathology Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive Lobular Carcinoma Mammae</td>
<td>4</td>
<td>9,1</td>
</tr>
<tr>
<td>Invasive Carcinoma Mammae</td>
<td>2</td>
<td>4,5</td>
</tr>
<tr>
<td>Invasive Carcinoma Mammae of No Special Type</td>
<td>35</td>
<td>79,5</td>
</tr>
<tr>
<td>Adenoid Cystic Carcinoma Mammae</td>
<td>1</td>
<td>2,3</td>
</tr>
<tr>
<td>Invasive Papillary CarcinomaMammae</td>
<td>1</td>
<td>2,3</td>
</tr>
<tr>
<td>Ductal Carcinoma In Situ</td>
<td>1</td>
<td>2,3</td>
</tr>
<tr>
<td>Invasive Lobular Carcinoma Mammae</td>
<td>4</td>
<td>9,1</td>
</tr>
<tr>
<td>Invasive Carcinoma Mammae</td>
<td>2</td>
<td>4,5</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>1</td>
<td>2,3</td>
</tr>
<tr>
<td>31–40 years</td>
<td>8</td>
<td>18,2</td>
</tr>
<tr>
<td>41–50 years</td>
<td>6</td>
<td>13,6</td>
</tr>
<tr>
<td>51–60 years</td>
<td>10</td>
<td>22,7</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>19</td>
<td>43,2</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>55 ± 13.754</td>
<td></td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>56 (26–77)</td>
<td></td>
</tr>
<tr>
<td><strong>Modus</strong></td>
<td>52</td>
<td></td>
</tr>
<tr>
<td><strong>Degree of Differentiation (Grade)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>2</td>
<td>4,5</td>
</tr>
<tr>
<td>Grade II</td>
<td>33</td>
<td>75</td>
</tr>
<tr>
<td>Grade III</td>
<td>9</td>
<td>20,5</td>
</tr>
<tr>
<td><strong>Lymphovascular Infiltration (LVI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positif</td>
<td>15</td>
<td>34,1</td>
</tr>
<tr>
<td>Negatif</td>
<td>29</td>
<td>65,9</td>
</tr>
</tbody>
</table>

55 years, and the median age of occurrence was 56 years. Based on the research data, it can be concluded that among the 44 samples studied, the most common histopathological differentiation degree for TNBC patients in West Sumatra was grade II (indicating a moderate degree of differentiation), with 33 individuals (75,0%). On the other hand, patients with grade I (representing a low degree of differentiation) were the least common, accounting for only 2 individuals (4,5%). The table indicates that 29 of the TNBC patients (65,9%) did not exhibit LVI (lymphovascular infiltration), while 15 TNBC patients (34,1%) in this study were identified to have LVI during the examination.

Table 2 shows the results of bivariate statistical tests using the chi-square test. The table indicates that the results of the statistical data testing show a significant relationship between the degree of differentiation and the incidence of LVI (lymphovascular infiltration) in TNBC. This relationship is evident from the p-value, which is less than 0,05, specifically 0,000.

Table 2. Relationship between Degree of Differentiation and Incidence of Lymphovascular Infiltration in Triple Negative Breast Cancer Patients in West Sumatera

<table>
<thead>
<tr>
<th>Lymphovascular Infiltration (LVI)</th>
<th>Degree of Differentiation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I &amp; II</td>
<td>Grade III</td>
</tr>
<tr>
<td>Positive</td>
<td>7</td>
<td>15,9</td>
</tr>
<tr>
<td>Negative</td>
<td>28</td>
<td>63,6</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>79,5</td>
</tr>
</tbody>
</table>
**DISCUSSION**

Most of the histopathological types found in TNBC patients in this study were Invasive Carcinoma Mammae of No Special Type (NST) as much as 79.5%. Similar results were also obtained in the study by Koleckova et al. [23] in 2021 in Czech who obtained results that most of the histopathology from TNBC was of the high grade of No Special Type (NST). Another study by Sanges et al. [24] in 2020 found that 78.1% of the 1,009 TNBC patients studied had the histopathological type of NST invasive carcinoma.

TNBC patients in this study had a limited number of specific histological features, and only 7 types of histopathology were detected, namely Invasive Lobular Carcinoma Mammae, Adenoid Cystic Carcinoma Mammae, Invasive Papillary Carcinoma Mammae, Ductal Carcinoma In Situ, Invasive Carcinoma Mammae, and Invasive Carcinoma Mammae of No Special Type. Balkenhol et al. [25] in 2020 also arrived at similar findings, noting that the prevalence of TNBC with specific histological features was relatively low. In their study, out of 14 histological subtypes of TNBC, the invasive carcinoma of no special type (NST) was the most dominant, accounting for as much as 88.4% of cases and being the most frequently observed subtype within TNBC. Anna et al. [26] in 2022 also conducted research in Jakarta and obtained the results for the most types of histopathology in breast cancer patients, namely the NST type as much as 87.6% and TNBC ranked third with this type of histopathology.

Determining the histopathological type of cancer, alongside factors such as tumor size, biomarkers, and the presence of metastatic events, plays a crucial role in shaping treatment strategies, predicting therapeutic responses, and assessing the overall prognosis of cancer. These factors collectively inform medical decisions and impact the course of treatment for cancer patients [27]. NST invasive carcinoma is a category of tumors or cancers that do not have significant histological characteristics to be categorized as certain special types [28]. Triple-negative breast Cancer with the NST type has clinicopathology and molecular genetic changes that are different from the “Special types” of TNBC. This affects the biological behavior and clinical course [24].

The distribution of TNBC cases based on age reveals that the majority of cases, amounting to 43.2%, fall into the age category of over 60 years. This corresponds with the findings of a study conducted by Rayson et al. [29] in 2018, which included 412 TNBC patients, and revealed that 46.3% of them were over 60 years old. A study by Aapro et al. [30] reported that in the United States, approximately 15% of elderly breast cancer patients have TNBC. Additionally, a study in China found that TNBC accounted for 18.4% of all breast cancer cases in patients aged over 70 years. Zhai et al. [31] research results showed that among TNBC patients, those in the age range of 50–70 years were the most numerous, with 4,328 patients, and the second-highest group was those aged above 70 years, with 1,715 patients out of a total of 7,739 TNBC patients studied. These findings differ from Prasad et al. [32] study in the United States, where more than half (59%) of the patients were in the age range of 41–60 years, while those aged 61 years or older accounted for only 23%.

The variation in age at breast cancer diagnosis can be attributed to several factors, including delays in patients seeking healthcare, which may be influenced by factors such as education, knowledge, socioeconomic status, and the availability and accessibility of treatment facilities. These factors can impact the timing of diagnosis and subsequent treatment. Hikmanti et al. [33] in their research stated that delays in the diagnosis and treatment of breast cancer are mostly caused by feelings of fear of costs and the absence of drugs, surgery, or chemotherapy without sufficient information. Another cause is the patient’s ignorance of breast cancer itself so a lump in the breast is considered normal.

The average age in this study was 55 years with the most common age being 52 years. This is in line with the research of Subiyanto et al. [34] in 2021 in East Java with an average age of TNBC patients above 52.8 years. Labert et al. [35] also mentioned in their research that the average age of TNBC patients was 53 years. Hermansyah et al. [36] in 2021 conducted a study in Medan, North Sumatra, and obtained results from 79 TNBC patients studied. The age range in which the most clinical manifestations of cancer appeared was 41–50 years with an average age of 50 years. Triple Negative Breast Cancer varies in an age range. The high mean age of TNBC patients is thought to be related to the family history of breast cancer and the use of endocrine therapy [37]. The relationship between age and Disease-Free Survival (DFS) and Overall Survival (OS) is not well understood. This can be attributed to differences in tumor biological characteristics such as tumor histological subtypes although other biological factors may influence such as BRCA gene mutations which are more common in young adults and often associated with TNBC subtypes [30].

A significant amount of research has been dedicated to studying triple-negative breast cancer (TNBC) in young patients who have been diagnosed with breast cancer. TNBC is more commonly found among younger patients compared to older ones. It has been found that up to 20% of TNBC cases are associated with a BRCA mutation, especially in the BRCA1 gene, and the risk of having a BRCA mutation is higher in younger TNBC patients [38]. Kartini et al. [39] in their research stated that information regarding risk factors and early detection of breast cancer using the Periksa Payudara Sendiri (SADARI) which is breast self-examination method is not widely distributed.
in the community, while programs for early detection of breast cancer have developed in other countries.

In this study, 75% of TNBC patients were classified as grade II, and 20.5% were classified as grade III. These results are supported by the research of Sanges et al. [24] who found the majority of TNBC patients with grade II and grade III were 21.3% and 77.6%. Research by Sejati et al. [40] in 62 TNBC patients showed that as many as 25 people (65.8%) had a grade II degree of differentiation, 12 people (31.6%) had grade III, and 1 person (2.6%) had grade I. The level of aggressiveness of the cancer is indicated by its degree of differentiation (Grade). Research by Vashit et al. [21] in Padang, West Sumatra, found that the grade associated with the molecular subtype of cancer characterized by grade III was found more in TNBC than other subtypes. Similar results were also found by Anna et al. [26] in 2022 in Jakarta where grade III is the most common grade found in the TNBC molecular subtype. In their study, it was also stated that there was a significant relationship between the molecular subtype of breast cancer and histopathological grade. Subiyanto et al. [34] study in East Java reported different results, with grade I being the most commonly found grade, in contrast to the findings of this study.

The degree of differentiation in breast cancer is assessed based on the extent of cellular abnormalities, considering cell morphology and proliferation. This grading system is significant in predicting cancer prognosis, as the grade reflects the speed at which the tumor grows and its potential to spread. It is influenced by various factors, including genetic mutations, growth factors produced by the tumor, and signaling pathways related to cell growth and division [41]. This difference is also influenced by the expression of hormone receptors such as ER, PR, HER2, and Ki67. In tumors with lower histological grades, there was a higher prevalence of ER and PR expression, whereas in tumors with higher histological grades, an increased expression of HER2 and Ki67 was detected [34]. In breast cancer, histopathological grading also influences molecular subtypes. In the TNBC subtype, grade III is commonly observed, while in molecular subtypes like Luminal A and Luminal B, grade I is typically associated with the well-differentiated classification [21].

Differences in grades in breast cancer are also influenced by nutritional status and family history. People with higher Body Mass Index (BMI) are at an increased risk of developing high-grade cancers. Additionally, those with a family history of cancer tend to have a predisposition for grade III cancer due to the presence of genetic mutation [42]. Research in Asia shows that breast cancer is often found at different levels and stages and is associated with the level of knowledge and services of cancer screening [38].

Out of the 44 TNBC patient data analyzed in this study, 29 samples (65.9%) tested negative for LVI, while 15 samples (34.1%) exhibited positive results for LVI. These findings align with the results obtained by Houvenaeghel et al. [43] in 2021. Their study, which included data from 17,322 early-diagnosed breast cancer patients, revealed that only 4.205 (24.3%) of the patients showed positive LVI in their anatomic pathology examination. Lymphovascular infiltration is also associated with clinical characteristics as well as hormone receptor status. Similar studies were also seen in the study by Richa et al. [44] in 2021 in India who received results from 249 samples studied, 198 (79.5%) of whom had negative LVI. Research by Sanges et al. [24] in 2020 had the same result, namely negative LVI was the most common in 427 (55%) of the 1,009 TNBC patients studied. The absence of LVI may explain the good prognosis of carcinoma, which may be related to the downregulation of genes involved in cell invasion.

The difference in the results obtained by Hermansyah et al. [36] in 2021 who studied 79 TNBC patients found 60.8% of them were positive for LVI. This is the same as the study by Vashit et al. [21] in 2016 of the 19 TNBC samples studied, 14 samples (37.8%) had LVI. In addition to a high mitotic rate and elevated nuclear grading, the TNBC subtype exhibits other distinguishing features such as pushing the invasion border, tumor necrosis, and the presence of a large central acellular zone. While TNBC typically doesn’t metastasize through the lymphatic system, it often follows a hematogenous route for metastasis. However, it’s important to note that lymphoid invasion can also be a characteristic of TNBC [7].

Tumor cells are capable of producing growth factors themselves and forming a variety of other tumor cells that are capable of infiltrating the angiolymphatic vessels. This LVI is also influenced by the S100A8 gene which plays a role in the formation and metastasis of cancer cells. Overexpression of this gene may indicate tumor differentiation leading to lymphovascular infiltration [11]. Tumor cells that invade the stroma around the tumor mass can occur because these cells lose adhesion to each other. Adhesion between cells is regulated by a transmembrane protein called E-cadherin. This protein acts as a tumor suppressor in various tissues. In TNBC, there was a significant decrease in E-cadherin expression. This will have an impact on the spread of cancer cells locoregionally and systemically after the invasion of cancer cells into the blood vessels and lymphatic channels. The absence of LVI in the examination results of this study may be attributed to the predominance of grade II differentiation in most of the detected cancers. Grade II tumors typically exhibit higher levels of E-cadherin protein, which aids in cell adhesion compared to grade III tumors. This phenomenon could explain the low
incidence of LVI detected in the study [45]. The risk of recurrence in the TNBC subtype is higher than in the other subtypes due to the presence of LVI [46].

Analysis of the results of this study showed a significant relationship between the degree of differentiation and LVI (p < 0.001). Indira et al. [41] in their research found a relationship between histopathological grading and a significant incidence of LVI (p = 0.039) in breast cancer in Bandung, West Java. Houvenaeghel et al. [43] in 2021 also found that the incidence of LVI was significantly related to hormone receptor status, tumor subtype, and grade. Sejati et al. [40] also stated that the higher the degree of cancer differentiation, the higher the likelihood of LVI occurrence.

Hermansyah et al. [36] examined the clinical characteristics of TNBC patients and found that gene changes and molecular differences between low-grade and high-grade histology in TNBC had an impact on the process of angioinvasion. The process of rapid vasculogenesis in embryos is similar to the activity of vasculogenesis reported in TNBC. At a high degree of histological differentiation, many mitoses, nuclear pleomorphism, and tubular gland structures are found. These nuclear changes in cancer are caused by a high rate of mitosis compared to normal cells. At a poor degree of differentiation, the tubular appearance tends to disappear due to weakened inter-cell bonds caused by decreased adhesion between cells which makes it easier for tumor cells to metastasize both lymphovascular and distant organs. The decrease in the presence of LVI, along with the increase in tumor aggressiveness, suggests a heightened risk of tumor metastasis [40]. The presence of LVI is a poor prognostic factor in cancer. The significant relationship between LVI and tumor size, cell proliferation, and expression of p-53 (tumor suppressor gene) tends to trigger the process of angiogenesis and accelerate metastasis. Further research is needed to analyze additional factors that influence lymphovascular grading and infiltration, including delays in patients seeking medical care, cancer tissue characteristics, and metastasis rates [21].

CONCLUSIONS

Triple Negative Breast Cancer patients in West Sumatra predominantly exhibit the histopathological type of Invasive Carcinoma of No Special Type (NST). Moreover, the majority of these patients are over 60 years of age, and the most common degree of differentiation among them is grade II. The majority of these patients do not exhibit lymphovascular invasion (LVI) based on examination results. Furthermore, a significant relationship between the degree of differentiation and the incidence of LVI in Triple Negative Breast Cancer patients in West Sumatra has been established.

DECLARATIONS

Competing Interest
The authors declare no competing interest in this study.

Ethics Approval
The ethical review permit number for this study is 760/UN.16.2/KEP-FK/2022 issued by the Ethics Committee of the Faculty of Medicine, Andalas University in 2022, and LB.02.02/5.7/216/2022 issued by the Ethics Committee of RSUP Dr. M. Djamil Padang.

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