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Five-year survival of triple-negative breast cancer and the associated clinicopathological factors: a study in an Indonesian tertiary hospital

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ABSTRACT

BACKGROUND Triple-negative breast cancer (TNBC) has a worse rate of recurrence, survival, and overall survival. This study aimed to find the survival of TNBC and its clinicopathological factors at Cipto Mangunkusumo Hospital.

METHODS This study used survival analysis based on clinicopathology in 112 TNBC cases at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, diagnosed from 2009 to 2019. Kaplan–Meier and log-rank tests were used for the analysis. Bivariate and multivariate analyses using Cox regression were performed to obtain the hazard ratios (HRs).

RESULTS Most patients were diagnosed at the locally advanced stage (40.2%) compared to the early (33.0%) and metastatic stages (17.9%). The 5-year survival of TNBC was 81.2% with an HR value of 1.372 (p = 0.239) compared to luminal A. Bivariate analyses showed that the older age group with an HR of 6.845 (p = 0.013; CI 1.500–31.243), larger tumor size and extension (T) with an HR of 11.826 (p = 0.001; CI 2.707–51.653), broader regional lymph node involvement (N) with an HR of 8.929 (p = 0.019; CI 1.434–55.587), farther distant metastases (M) with an HR of 3.016 (p = 0.015; CI 1.242–7.322), more lymphovascular invasion with HR of 3.006 (p = 0.018; CI 1.209–7.477), and not operated-on cases with an HR of 9.165 (p<0.001; CI 3.303–25.434) significantly shortened the survival of TNBC. Multivariate analysis found that the only factor worsening the survival was not having surgery, with an HR of 6.175 (p<0.001; CI 1.518–34.288).

CONCLUSIONS The 5-year survival rate of TNBC patients was 81.2%. Not having surgery was a clinicopathological factor that worsened survival outcomes in TNBC.

KEYWORDS breast cancer, Indonesia, prognosis, survival, triple-negative breast cancer

Breast cancer is the second most common cancer worldwide and the most common cancer in women. It is the fifth leading cause of cancer-related deaths worldwide, especially in women.[1] In Indonesia, breast cancer is the most common cancer, with 39,831 reported cases and 20,052 deaths in 2008. Data collected from Cipto Mangunkusumo Hospital from 2008 to 2012 showed that most breast cancer cases were at advanced stages (stage II and IV), which are difficult to treat.[2,3] Breast cancer not only causes problems in terms of remission and life expectancy but also imposes a psychosocial burden on patients from aesthetic and emotional perspectives.

The diagnosis and classification of breast cancer are not limited to histopathological type. Breast cancer is currently classified at the molecular level owing to its heterogeneity. Perou et al[4] first proposed this classification in 2000; it refers to molecular markers in breast cancer cells through immunohistochemical examinations. It is divided into luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-overexpressing, basal-like, and normal-breast-like

breast cancers.[5] However, since 2005, a new group of triple-negative breast cancer (TNBC) has been introduced, which has a poor prognosis, shorter overall survival (OS) rates, and is difficult to treat.[5,6] Qiu et al[7] conducted a study comparing the TNBC and non-TNBC groups. The results showed that the OS and disease-free survival (DFS) in the TNBC and non-TNBC groups were 72.05% *versus* 86.52% (p = 0.003) and 88.51% *versus* 95.46% (p = 0.031), respectively.

TNBC is an important issue in managing breast cancer in Indonesia. However, only a few studies have been conducted on TNBC. Basic research on TNBC in Indonesia should be conducted and published to serve as guidelines for future research on similar topics. This study aimed to determine the survival of patients with TNBC and its clinicopathological factors at Cipto Mangunkusumo Hospital as an initial description of the magnitude of this problem in Indonesia.

METHODS

This retrospective cohort study and a survival analysis involved patients with TNBC. The database used as the data source was breast cancer registration from the Division of Surgical Oncology, Department of Surgery, Cipto Mangunkusumo Hospital. The inclusion criteria were female patients diagnosed with TNBC using an immunohistochemical test between January 2009 and December 2019 and undergoing therapy at Cipto Mangunkusumo Hospital. The outcome was OS. The censoring criteria were patients who did not complete the follow-up period (lost to follow-up), did not experience an outcome by the end of the observation period, whose outcome was unknown, or whose experience was unclear.

The clinicopathological factors examined were age, tumor, node, metastasis (TNM) stage, clinical stage, histopathological type, histopathological grade, lymphovascular invasion (LVI), and surgical type. Age was defined as the patient's age at diagnosis and categorized as <40, 41–60, and >60 years. The TNM and clinical stages used the 8th American Joint Committee on Cancer classification in 2017.[3] Histopathological types were described according to the number of findings. However, the data were divided into invasive ductal carcinoma and others (invasive lobular, tubular, medullary, and mucinous carcinoma) for analysis. The Nottingham combined histological grade classification system comprising G1, G2, and G3 was used for histopathological grading.[7] LVI was defined as the presence or absence of lymphatic and vascular involvement on histopathological examination. The surgery was performed for curative purposes. This was also described according to the findings, but the data analysis was divided into those who underwent surgery and those who did not.

All data are presented as characteristic data. Each clinicopathological factor was statistically analyzed for association with TNBC survival. Survival analysis was performed using the Kaplan–Meier estimator. Bivariate analyses using the log-rank test and Cox regression were performed to determine the hazard ratio (HR). Multivariate analysis was performed to determine clinicopathological factors influencing TNBC survival, with p<0.25 was considered significant. Data processing was performed using the SPSS software version 20.0 (IBM Corp., USA). This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No: KET-602/UN2.F1/ETIK/PPM.00.02/2019).

RESULTS

Participant characteristics

Of the 1,309 patients with breast cancer who visited Cipto Mangunkusumo Hospital between 2009 and 2019, only 944 were treated, and 365 (27.9%) did not undergo therapy at the hospital because they were only referred for immunohistochemical examinations and continued therapy at the referring hospital. In total, 815 patients with immunohistochemical data were included in this study. The numbers of patients with molecular subtypes luminal A, luminal B, HER, and triple-negative were 243 (29.8%), 319 (39.1%), 141 (17.3%), and 112 (13.7%), respectively. The mean follow-up period was 60 months.

Of the 112 patients with triple-negative molecular subtypes, 21 (18.8%) died, 37 (33.0%) survived, and 54 (48.2%) were lost to follow-up. Clinicopathological factors related to survival in all patients (n = 112) were analyzed. The characteristics of the patients with TNBC and the incidence of events at TNBC based on their clinicopathological factors are shown in Table 1.

TNBC survival

The incidence of death was 18.8% in the TNBC group. The median survival rate of patients with TNBC was 49 months. Survival rates were compared based

on the molecular subtypes of breast cancer. These data were obtained by analyzing the immunohistochemical examination results of all patients with breast cancer (n = 815). The incidences of mortality in the luminal A, luminal B, and HER2 groups were 16.9%, 27.6%, and 30.5%, respectively. The median survival rates for patients with luminal A, luminal B, HER2, and triple-negative tumors were 51, 46, 43, and 49 months, respectively. The Kaplan–Meier curve of breast cancer according to molecular subtype is shown in Figure 1.

Cox regression analysis was performed for four molecular subtypes: luminal A, luminal B, HER2, and triple-negative. Luminal A was used as the reference. This analysis showed that luminal B (HR = 1.841; 95% confidence interval [CI] = 1.271–2.667; p = 0.001) and HER2 (HR = 2.221; 95% CI = 1.447–3.410; p<0.001) had significant correlation. Meanwhile, TNBC cases were 1.372 times more likely to experience an event but not statistically significant (95% CI = 0.810–2.322; p = 0.239).

TNBC survival based on its clinicopathological factors

Based on the Kaplan–Meier curves, none of the clinicopathological factors met the proportional hazards. However, the clinicopathological factors T, N, M, clinical stage, LVI, and type of surgery had a log-rank value of <0.05 (Figure 2).

DISCUSSION

The number of patients with breast cancer in our study differed from that in other studies. Abubakar et al[8] conducted a 13-year breast cancer survival study with a follow-up period of 10 years in 3,352 breast cancer patients in Malaysia. This was a single-center study rather than a national referral hospital or cancer center. Additionally, they had a better registration system that minimized the excluded data, with only 2% incomplete immunohistochemical data and a loss to follow-up rate of approximately 5%.[8]

Table 1. Characteristics of TNBC patients and incidence of TNBC mortality based on its clinicopathological factors, bivariate, and multivariate analyses

Clinicopathological factors	n (%), (N = 112)	Died, n (%)	Bivariate analysis			Multivariate analysis		
			HR	95% CI	*p*	HR	95% CI	*p*
Age (years)								
≤40	10 (8.9)	4 (40)	6.845	1.500–31.243	**0.013**	4.58	0.911–23.029	**0.065**
41–60	75 (67.0)	14 (19)	1.923	0.552–6.699	0.305	1.16	0.291–4.598	0.835
>60	27 (24.1)	3 (11)	-	1.00	-	-	1.00	-
Tumor size and extension (T)								
T1	2 (1.8)	0 (0)	-	-	-	-	-	-
T2	23 (20.5)	0 (0)	-	-	-	-	-	-
T3	20 (17.9)	2 (10)	-	1.00	-	-	1.00	-
T4	56 (50.0)	18 (32)	11.826	2.707–51.653	**0.001**	1.268	0.221–7.287	0.790
Tx*	11 (9.8)	1 (9)	1.647	0.149–18.169	0.684	0.316	0.027–3.679	0.358
Regional lymph node involvement (N)								
N0	48 (42.9)	3 (6)	-	1.00	-	-	1.00	-
N1	43 (38.4)	13 (30)	5.945	1.691–20.902	**0.005**	2.872	0.737–11.197	**0.129**
N2	16 (14.3)	3 (19)	3.588	0.723–17.800	0.118	0.647	0.115–3.649	0.621
N3	5 (4.5)	2 (40)	8.929	1.434–55.587	**0.019**	1.998	0.262–15.259	0.505
Distant metastases (M)								
M0	92 (82.1)	13 (14)	-	1.00		-	1.00	-
M1	20 (17.9)	8 (40)	3.016	1.242–7.322	**0.015**	0.322	0.079–1.306	**0.113**
Lungs	8 (40.0)	-	-	-	**-**	-	-	**-**
Bone	7 (35.0)	-	-	-	**-**	-	-	**-**

Continued on next page

Table 1. (continued)

Clinicopathological factors	n (%), (N = 112)	Died, n (%)	Bivariate analysis			Multivariate analysis		
			HR	95% CI	*p*	HR	95% CI	*p*
Heart	1 (5.0)	-	-	-	-	-	-	-
Bones and lungs	2 (10.0)	-	-	-	-	-	-	-
Lungs and liver	1 (5.0)	-	-	-	-	-	-	-
Lungs and brain	1 (5.0)	-	-	-	-	-	-	-
Clinical stage								
Early	37 (33.0)	0 (0)	-	-	-	-	-	-
Locally advanced	45 (40.2)	12 (27)	-	1.00	-	-	-	-
Metastatic	20 (17.9)	8 (40)	1.154	0.471–2.828	0.754	-	-	-
Unstageable	10 (8.9)	1 (10)	0.184	0.024–1.430	0.306	-	-	-
Histopathological type								
Invasive ductal	93 (83.0)	19 (20)	-	-	-	-	-	-
DCIS	3 (2.7)	1 (0.33)	-	-	-	-	-	-
Invasive lobular	2 (1.8)	-	-	-	-	-	-	-
Mixed	3 (2.7)	1 (0.33)	-	-	-	-	-	-
Others[†]	11 (9.8)	-	-	-	-	-	-	-
Histopathological grade								
G1	8 (7.1)	0 (0)	-	-	-	-	-	-
G2	59 (52.7)	13 (22)	-	-	-	-	-	-
G3	45 (40.2)	8 (18)	-	-	-	-	-	-
LVI								
No	61 (54.5)	7 (11)	-	1.00		-	1.00	-
Yes	51 (45.5)	14 (27)	3.006	1.209–7.477	**0.018**	3.116	0.814–11.292	**0.097**
Type of operation								
Operated	68 (60.7)	5 (7)	-	1.00	-	-	1.00	-
MRM	51 (45.5)	-	-	-	-	-	-	-
CRM	11 (9.8)	-	-	-	-	-	-	-
SM	1 (0.9)	-	-	-	-	-	-	-
BCS	5 (4.5)	-	-	-	-	-	-	-
Not operated	44 (39.3)	16 (36)	9.165	3.303–25.434	**<0.001**	6.175	1.518–34.288	**0.001**
Chemotherapy								
Yes	38 (33.9)	-	-	-	-	-	-	-
No	74 (66.1)	-	-	-	-	-	-	-
Radiotherapy								
Yes	17 (15.2)	-	-	-	-	-	-	-
No	95 (84.8)	-	-	-	-	-	-	-
Status								
Censor[‡]	91 (81.3)	-	-	-	-	-	-	-
Event	21 (18.8)	-	-	-	-	-	-	-

BCS=breast-conserving surgery; CI=confidence interval; CRM=classic radical mastectomy; DCIS=ductal carcinoma in situ; HR=hazard ratio; LVI=lymphovascular invasion; MRM=modified radical mastectomy; SM=simple mastectomy; TNBC=triple-negative breast cancer

*The primary tumor cannot be assessed; [†]others were invasive tubular, medullary, and mucinous carcinoma; [‡]censoring criteria were patients who did not complete the follow-up period (loss to follow-up), did not experience an outcome by the end of the observation, whose outcome was unknown, or whose experience was unclear

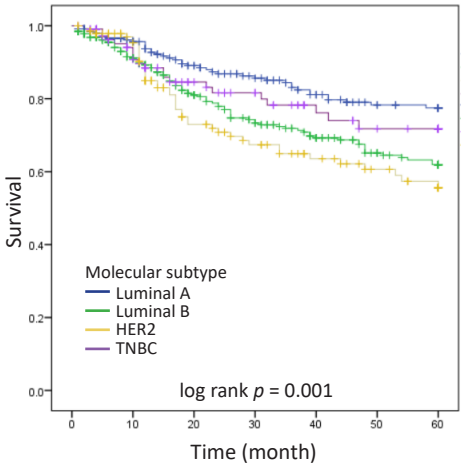

Figure 1. Kaplan–Meier of breast cancer based on molecular subtypes. Molecular subtypes had significant lower correlation with survival ($p<0.05$). HER2=human epidermal growth factor receptor 2; TNBC=triple-negative breast cancer

Abubakar et al[8] found that the percentages of breast cancers based on the molecular subtypes of luminal A, luminal B, HER2, and triple-negative were 34%, 33%, 13%, and 20%, respectively. This differs from other studies where TNBC is typically less common and ranges from 10% to 17%.[9] Furthermore, the present study had different characteristics of TNBC compared with previous studies.[8] Most patients in this study were diagnosed at a locally advanced stage, unlike other studies where most patients were diagnosed at T1 and early stage.[8] Other studies also suggested that most TNBCs were diagnosed at T2 and an early stage.[10] The tumor size and stage at diagnosis certainly influence the outcome.[11] Based on the results, the 5-year survival of TNBC was 81.3%. This is lower than in similar studies where the 5-year survival rate of TNBC

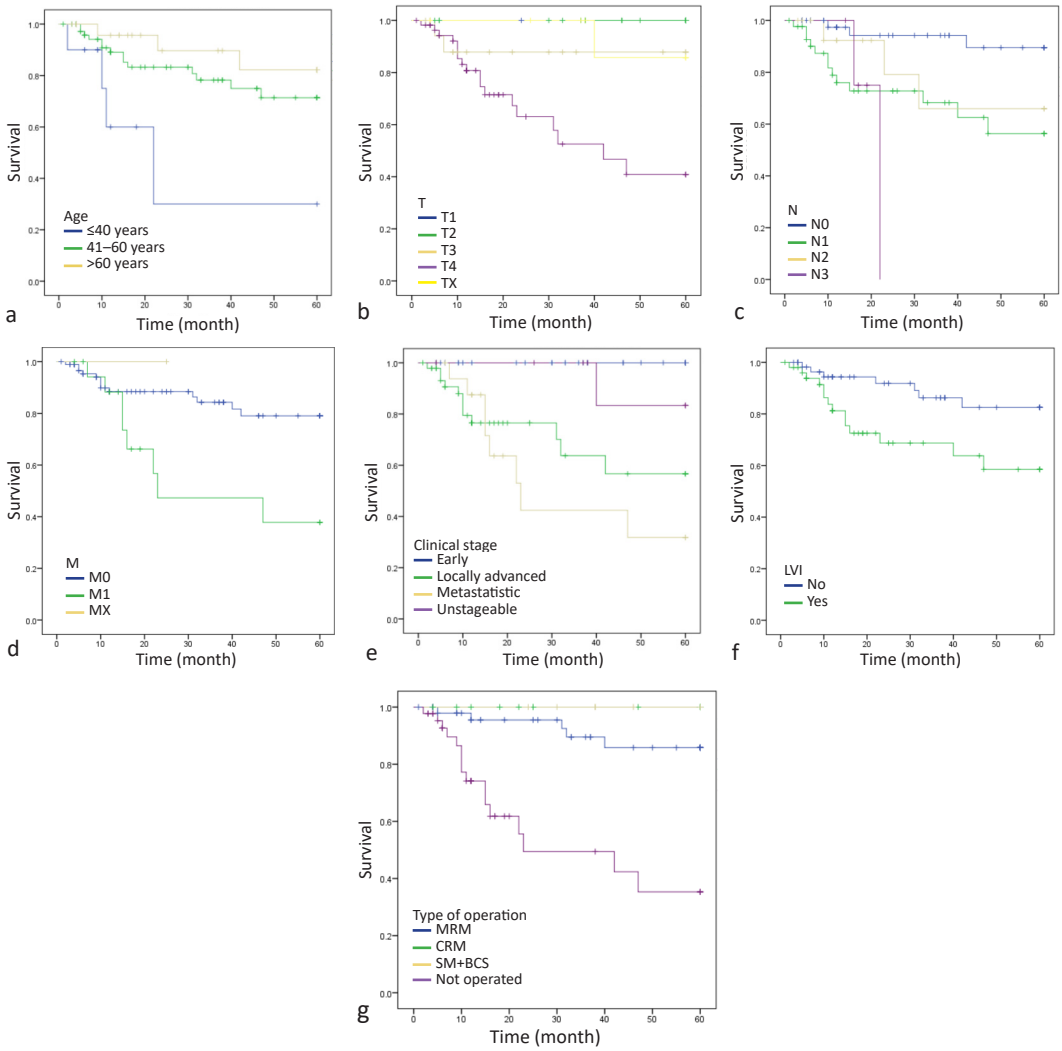

Figure 2. Kaplan–Meier TNBC curves based on: (a) age group; (b) tumor size and extension (T); (c) regional lymph node involvement (N); (d) distant metastases (M); (e) clinical stage; (f) LVI; and (g) type of operation. All clinicopathological factors, except histopathological type and grade, had a significant correlation with survival ($p<0.05$). BCS=breast-conserving surgery; CRM=classic radical mastectomy; LVI=lymphovascular invasion; MRM=modified radical mastectomy; SM=simple mastectomy; TNBC=triple-negative breast cancer

was above 85%, and the patients were diagnosed earlier.[8,12,13] This difference may be due to differences in the characteristics of the research participants.

This study also investigated the survival rates of all breast cancers based on their molecular subtypes. Previous studies have revealed that TNBC is an aggressive molecular subtype with worse outcomes than other molecular subtypes.[9,14] Notably, this study found that TNBC provided better survival results than the luminal B and HER2 subtypes, where HER2 had the worst survivability. However, the difference was not statistically significant. The poor survival of luminal B cells may be due to their high proliferation index, although this characteristic is also present in TNBC. The poor survival of HER2 patients could be due to the targeted therapy for HER molecular subtypes at the hospital, which is restricted to patients with metastases. However, this was not proven in the present study, emphasizing the need for further research.

Based on bivariate analysis, the clinicopathological factors influencing the survival of patients with TNBC were age, tumor size and extension (T), regional lymph node involvement (N), distant metastases (M), LVI, and type of surgery. In this study, most patients were in the 41–60 age group, with the highest mortality rate (30.8%) in the <40 age group. This is also supported by the survival analysis, where the <40 age group was the only group with a rate exceeding 50%. These data indicated that younger patients experienced poorer survival outcomes. This result aligns with previous studies, where breast cancer diagnosed at a young age has worse characteristics and properties,[15–17] such as a higher histopathological grade, the absence of hormone receptors, and a higher proliferation index.[15] This results in a higher mortality rate than the older age groups.[16,17]

In the present study, patients with TNBC were diagnosed at stage T4, and only a few were diagnosed when the tumor was small. This contrasts with similar studies in which TNBC cases were found when smaller, and only a few were found at sizes greater than 5 cm.[7,8] Based on the analysis of survival data, a statistically significant difference in survival was observed based on clinical stage T. The multiplied size and extension of T4 tumors result in poor survival outcomes. Previous studies reported similar results.[11]

Regional lymph node involvement affects TNBC survival and is a strong predictor.[11] However, the highest incidence of death occurred in N3, indicating cross-locoregional infiltration that allows for a long spread, thereby affecting survival outcomes. One study revealed that TNBC survival was influenced by the number of lymph nodes involved and the presence or absence of lymph node involvement (p<0.001).[18] Similar to the present study, patients with lymph node involvement (regardless of the number of lymph nodes) had a 5-fold worse survival rate than patients without lymph node involvement. Several recent studies have also revealed that the lymph node ratio (ratio of the pathological lymph nodes to the evaluated lymph nodes) is more accurate in predicting prognostics.[19–22] This is also supported by a survival study with a large sample size, which revealed that the lymph node ratio is a better predictor of clinical and pathological lymph nodes, providing a better picture of survival.[11] However, the lymph node ratio has not been used at Cipto Mangunkusumo Hospital.

Patients with distant metastases (M1) also showed poorer survival rates. In the present study, 82.1% of the patients had M0. However, the incidence of death was significantly higher in the M1 group. This indicates that distant metastatic conditions had a clinically significant effect on the survival of the TNBC (p = 0.010), supported by a statistical analysis showing 3 times worse survival in the M1 stage compared with the M0, with a significant value. Clinically, in the present study, most patients with TNBC experienced metastases to the lungs, followed by the bone, liver, and brain. The results of our study align with those of previous studies.[11,23] Poor survival in M1 could be because TNBC is 4 times more likely to metastasize to the viscera than the other subtypes.[24,25]

LVI is an invasion of the lymphatic space, blood vessels, or both peritumoral areas due to tumor embolism, indicating metastasis. It is a strong predictor of lymph node metastasis[26] and a predictor for the outcome of patients with breast cancer.[27] Furthermore, LVI could improve outcome predictions in TNBC patients.[28] In the present study, the incidence of events in the LVI group was higher than in those without this invasion. In addition, patients with TNBC with LVI had worse survival than those without this invasion, as evidenced by a statistically significant value.

In the present study, patients who did not undergo surgery had poorer survival rates. No events occurred in the classic radical mastectomy and simple mastectomy + breast-conserving surgery groups, which did not

indicate that the two choices of operation type resulted in better survival outcomes than modified radical mastectomy (MRM). However, the type of surgery performed had an insignificant effect on the survival of patients with TNBC. A study showed that MRM surgery had better DFS than other types of surgery but did not show a significant difference (p = 0.150).[7] This is in line with the research of Abdulkarim et al,[28] who revealed no difference in the survival of patients with TNBC based on the type of operation. The present study only analyzed surgery as a management treatment for TNBC. However, surgery alone is insufficient, especially for patients with locally advanced and metastatic stages who require chemotherapy. There was also a discrepancy between the number of locally advanced and metastatic stages and the number of patients receiving chemotherapy. Although TNBC has the worst prognosis among other molecular subtypes, it is more responsive to chemotherapy.[29] The suitability of management also influences breast cancer survival.[30] Notably, one study also reported that radiotherapy is important in locoregional recurrence instead of surgery.[28] This aspect could serve as valuable information for future studies.

The clinical stage in this study did not show a statistically significant difference in the survival of patients with TNBC, which is consistent with the results of previous studies. The survival prognosis of TNBC, in terms of both mortality and recurrence, cannot be linked to the clinical stage. Park et al[11] showed that the clinical stage of TNBC was unrelated to recurrence. Furthermore, the present study showed that the locally advanced stage of the HER2 subtype group had a worse outcome than TNBC, although the difference was not statistically significant. However, Li et al[31] compared TNBC and non-TNBC at each stage and showed that TNBC cases had significantly worse survival than non-TNBC cases. The clinical stages were categorized as T, N, and M. In most breast cancer cases, the increase in tumor size is directly proportional to the number of positive lymph nodes.[32] However, for TNBC, it is not accompanied by an increase in the number of positive lymph nodes or metastatic behavior and is ultimately unrelated to the outcome of the nasopharyngeal carcinoma.[33] TNBCs of small size and without positive lymph nodes have a poor prognosis and different metastatic behavior from non-TNBCs.[34] These may explain why the clinical stage did not provide a significant difference in survival.

In multivariate analysis, whether or not the patient underwent surgery was the only statistically significant factor for TNBC survival. Patients who did not undergo surgery had 6 times worse survival risk factors than those who underwent surgery. No other clinicopathological factors were statistically significant. Therefore, surgery was a clinicopathological factor that affected survival.

This was the first TNBC survival study at Cipto Mangunkusumo Hospital involving a long follow-up examination of the associated clinicopathological factors. However, this study had several limitations. This study had limited chemotherapy data and the available follow-up data on the management pattern, type, and timing of administration, making it challenging to analyze the survival of TNBC; therefore, manual data collection from medical records was required. Many patients did not complete the study period or had no known outcomes (loss to follow-up). The number of high losses to follow-up that occurred randomly (missing at random) was negligible, even when the loss to follow-up rate reached 60%. We conducted a statistical test of clinicopathological factors on survival in the study participants who were lost to follow-up, and the results showed no statistically significant findings (p>0.05). Therefore, losses to follow-up occurred randomly (missing at random).

In conclusion, the 5-year survival rate of patients with TNBC in this study was 81.2%. Surgery type was a clinicopathological factor that influenced survival. Active surveillance should be conducted in patients with breast cancer or in prospective follow-up survival studies to minimize the loss to follow-up rate.

Conflict of Interest
The authors affirm no conflict of interest in this study.

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