

CLINICAL AND HISTOPATHOLOGIC CHARACTERISTICS ASSOCIATED WITH PATIENTS WITH TRIPLE NEGATIVE BREAST CANCER OF A NATIONAL HOSPITAL DEL PERU, 2012 - 2018

CARACTERÍSTICAS CLÍNICAS E HISTOPATOLÓGICAS ASOCIADAS A PACIENTES CON CÁNCER DE MAMA TRIPLE NEGATIVO EN UN HOSPITAL DE REFERENCIA PERUANO, 2012- 2018

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ABSTRACT

Objective: To determine the clinical and histopathological characteristics associated to patients with triple negative breast cancer of the Hipólito Unanue National Hospital between June 2012 to June 2018. **Methods:** Cross-sectional, analytical study. We reviewed the medical records of all patients treated at the Hipólito Unanue National Hospital during the period from June 2012 to June 2018. **Results:** 134 patients were included, out of which 36 (26.9%) were TN and 98 No TN. Of the histopathological characteristics, the most frequent CD was III and II for the two groups. The histological type that predominated was the infiltrating ductal type in both groups. The high histological grade was characteristic in NT (58%) unlike non TN. The NTs were larger 5.75 cm in contrast to the TNs with 3 cm, and the Ki 67 was higher in the TN 35% in contrast to the NON TN with 15%. In the bivariate analysis the size (RP: 1.4, CI: 1.17-1.68, p = 0.0001), Ki 67 (RP: 1.05, CI: 1.03-1.07, p = 0.001), BMI ≥ 25 kg / m² (RP: 1.14, CI: 1.23-6.22, p = 0.014), Histological Grade 3 (RP: 3.87, CI: 1.74-8.63, p = 0.001), size ≥ 5 cm (RP: 2.94, CI: 1.33-6.48, p = 0.008) were significant. In the multivariate analysis it was found that grade 3 (PR: 1.74, CI: 1.01-3, p = 0.0046) and Ki 67 (RP: 1.02, CI: 1.01-1.03, p = 0.0001) were histopathological characteristics associated with CMTN. **Conclusion:** There are histopathological characteristics associated with triple negative breast cancer particularly high histological grade and Ki67 value.

Key words: Breast cancer; Triple negative breast cancer; Ki 67. (source: MeSH NLM)

RESUMEN

Objetivo: Determinar las características clínicas e histopatológicas asociadas a las pacientes con cáncer de mama triple negativo (CMTN) en un Hospital peruano de referencia. **Métodos:** Estudio transversal, analítico. Se revisaron las historias clínicas de todas las pacientes atendidas en el Hospital Nacional Hipólito Unanue durante el periodo de junio del 2012 a junio del 2018. **Resultados:** Se incluyeron 134 pacientes de los cuales 36 (26,9%) correspondieron a CMTN, el estadio clínico más frecuente fue el III y II para los dos grupos. El tipo histológico que más predominó fue el tipo ductal infiltrante en ambos grupos. El grado histológico elevado fue característico en los casos de CMTN (58%) a diferencia de los No TN. Los CMTN fueron de mayor tamaño (5,75 cm vs 3cm en no TN), y el Ki 67 fue más elevado en el TN (35% en comparación con el No TN con 15%). Se determinó en el análisis bivariado que el tamaño (RP: 1,4, IC: 1,17-1,68, p= 0,0001), Ki 67 (RP: 1,05, IC: 1,03-1,07, p= 0,001), IMC ≥ 25 kg/m² (RP: 1,14, IC: 1,23-6,22, p= 0,014) y el Grado Histológico 3 (RP:3,87, IC: 1,74-8,63, p= 0,001) se asociaron significativamente a la presencia de CMTN. En el análisis multivariado se encontró que el grado 3 (RP: 1,74, IC: 1,01-3, p= 0,0046) y el Ki 67 (RP: 1,02, IC: 1,01-1,03, p= 0,0001) fueron las características histopatológicas asociados al CMTN. **Conclusión:** Las características más consistentemente asociadas al cáncer de mama triple negativo en fueron el elevado grado histológico y mayor valor de Ki67.

Palabras clave: Cáncer de mama; triple negativo; Ki 67. (fuente: DeCS BIREME)

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INTRODUCTION

Negative triple-type breast cancer is a public health problem that is on the rise due to its high incidence and mortality in the world population and especially in Latin America^{2,3}.

Since this type of breast cancer does not have a TARGET treatment because it does not have estrogen and progesterone receptors, and lack of overexpression of Her-2, it would not benefit from endocrine and biological treatment with trastuzumab. It will only respond to chemotherapy: neoadjuvant chemotherapy being the best outcome. So that currently it is a reason for continuous and ongoing research to find patterns that help classify their treatment or risk factors that improve survival. It is also known that the CMTN is the most aggressive and with the highest recurrence rate. It has high mortality in contrast to the other subtypes, so it is important to know what clinical and histopathological characteristics are associated in this subtype of breast cancer, so that patients can be treated efficiently.

It is also important to mention that there are few studies of the triple negative type of breast cancer at the national level, which highlights the value of conducting this study.

Therefore, it is important to consider and perform additional research, such as studies that consider the prognostic and predictive factors.

METHODS

A cross-sectional analytical observational study was performed. The population was made up of patients treated in the breast cancer and breast pathology unit of the Gynecology and Obstetrics Service of the National Hospital Hipólito Unanue, during the period June 2012- June 2018, with a diagnosis of breast cancer. As for the sample, all the medical records corresponding to the study period were included

Patient data were selected according to the inclusion and exclusion criteria.

Those cases with incomplete and illegible medical records, patients without histological diagnosis or immunohistochemistry, medical records of pregnant patients, and under 18 years were excluded.

For the statistical analysis, Pearson's χ^2 tests were used, considering a p value <0.05 as significant; Likewise, the ratios of crude and adjusted prevalences with their respective 95% confidence intervals were found.

RESULTS

The study included 134 clinical records of patients diagnosed with breast cancer, of which 26.9% (n = 36) were of the Triple Negative type and 73.1% (n = 98) were the triple negative, selected by inclusion and exclusion criteria in Hospital Nacional Hipólito Unanue. (Table 1)

Table 1. Description of mammary carcinomas according to their HNNU recipients from June 2012 to June 2018.

	RECEIVER					n	%
	E	P	Her 2	Ki 67			
TN	-	-	-	High		36	26,87
Lum A	+	+	-	<14%		66	49,25
Lum B	-	+	-	≥ 14%		3	2,24
Lum B	+	-	-	≥ 14%		5	3,73
Her 2	-	-	+	High		10	7,46
Lum B Her 2	+	-	+	High		6	4,48
Lum B Her 2	+	+	+	High		8	5,97

The median age of the TN patients was 54.5 ± 12.03 , while the non-TN was 52.2 ± 12.46 years. And that the patients older than 50 years were more of the group Non-triple negative (68.3%) in contrast to the TN (31.2%). In the case of BMI, both in the TN

group with a median BMI of 26.62 kg / m^2 (SD: 4.31) and No TN with 28.54 kg / m^2 of IMC (SD: 5.3). With respect to the Clinical Stages, stages III, II were more frequent in patients with NT, as in non-TN patients. The infiltrating Ductal histological type was the most

frequent for both groups. The histological grade 3 was the most frequent of the TN, as opposed to the grade 2 of the non TN. Regarding the tumor size, TN patients presented larger tumors at diagnosis 5.75 (IR: 2-13) cm vs 3 cm (1.2-10) of the No TN group ($p = 0.002$). In addition, in the categorized size, the tumors <5 cm were, for the most part, the non-TN group (80.7%) compared to the TN group (19.3%). Regarding Ki 67, a statistically significant difference was found between both groups, TN were represented by an average value

of 35% (RI: 5-90) compared to No TN with only 15% (RI: 1-90) with $p = 0.0001$. In the categorized measurement, the Ki 67 value of less than 20% was higher in the No TN group (95%) than the TN (5%) as well as the Ki67 value of 20 to 50%, where the group No TN was 68.6% in contrast to TN (31.8%). The most significant case occurs with the Ki 67 value greater than 50%, where TN is 74% compared to Non TN with 26%. ($p = 0.0001$). See table 2.

Table 2. Clinical and histological characteristics of the TN and non-TN patients of the HNHU June 2012 to June 2018.

	Breast cancer (N = 134)		P Value
	Triple Negative n = 36 (26.9%)	No Triple Negative n = 98 (73.1%)	
Age	54,14 DE:12,03	52,20 DE: 12,46	0,423
Categorized age			0,192
<50 years	12 (21,05)	45 (78,95)	
≥50 years	24 (31,17)	53(68,83)	
IMC	26,62 DE:4,31	28,54 DE: 5,3	0,053
IMC			0,012
≥25 kg/m ²	20 (20,83)	76(79,17)	
<25 kg/m ²	16 (42,11)	22 (57,89)	
Clinical stage			0,045
I	1 (10)	9(90)	
II	12 (23,53)	39 (76,47)	
III	18 (27,27)	48 (72,73)	
IV	5 (71,43)	2 (28,57)	
Histological type			0,61
CDI	33 (26,83)	90 (73,17)	
CDL	3 (27,27)	8 (72,73)	
Histological grade			0,002
1	1 (6,67)	14 (93,33)	
2	14 (19,44)	58 (80,56)	
3	21 (45,65)	25 (54,35)	
Histological Grade			0,001
1 – 2	15 (17,24)	72 (82,76)	
3	21 (44,68)	26 (55,32)	
Size	5,75 RI: 2-13	3 RI: 1,2-10	0,002
Categorized size			0,006
<5cm	17(19,32)	71 (80,68)	
≥5cm	19 (41,30)	27 (58,70)	
Ki-67	35 RI: 5-90	15 RI:1-90	0,0001
Ki-67 categorized			0,0001
<20 %	3 (5)	57 (95)	
20 -50 %	16 (31,37)	35 (68,63)	
>50 %	17 (73,91)	6 (26,09)	

Table 3. Assigned treatment of each group studied.

	Breast cancer		p
	Triple negative n=36 (26,9%)	No negative triple n=98 (73,1%)	
Treatment			
1. Chemotherapy	36 (28.57)	90 (71.43)	0.076
Neoadjuvant chemotherapy	26 (34.21)	50 (65.79)	0.028
Chemotherapy adjuvant	11 (20)	44 (80)	0.135
2. Surgical Tto			
Yes	36 (26.87)	98 (73.13)	
No	2 (100)	0	
Type of surgery		0.732	
Conservative	6 (30)	14 (70)	
Not conservative	28 (82.35)	84 (17.65)	
3. Radiotherapy	22 (25)	66 (75)	0.317
4. Hormonotherapy	1 (1.23)	80 (98.77)	0.0001
5. Biological therapy	0	19 (100)	0.002

ORIGINAL ARTICLE

All TN patients received systemic treatment with chemotherapy (n=36) and most of the TNTs, in addition to surgical treatment. The most frequent treatment of the TN group was Neoadjuvant Chemotherapy, the most used scheme in chemotherapy was AC (adriamycin and cyclophosphamide) with taxanes (paclitaxel), as well as in Non TN (34.2% vs 65.8%, p = 0.028). Followed by local treatments, such as surgery, being the non-conservative type the most frequent in NT than in non-TN (82.35% vs. 17.65%, p = 0.732) and radiotherapy (p = 0.317). Hormone therapy was another more frequent treatment of Non-TN, in addition to chemotherapy and surgical treatment, unlike TN. (98.8% vs 1.24%, p = 0.0001). See Table N ° 3

Of the TN patients who received QTn (n = 26) only 2 of them achieved CPR (7.6%). And of the group No TN that received QTn (n = 50) achieved 7 RPC (14%) with p = 0.29. See table 4.

Table 4. Response to neoadjuvant chemotherapy treatment of each group studied.

	Breast cancer		P
	Yes Triple Negative	No Triple Negative	
Pathological response			0,295
Complete answer	2 (22,22)	7(77,8)	
Partial answer	19(35,85)	34(64,15)	

In the bivariate analysis, significant associations of the following variables were found: tumor size (p = 0.0001), Ki67 (p = 0.001), BMI (p = 0.014), histological grade (p = 0.001) and size categorized (p = 0.008). With these significant variables the multivariate analysis was performed.

Table 5. Bivariate analysis of the CMTN.

	Triple Negative		
	RP	IC(95)	p
Size	1,4	1,17-1,68	0,0001
Ki-67	1,05	1,03-1,07	0,001
BMI (≥25 kg/m ² / <25 kg/m ²)	1,14	1,23-6,22	0,014
Histological Grade (3/ 1 y 2)	3,87	1,74-8,63	0,001
Size (≥5cm/<5cm)	2,94	1,33-6,48	0,008

For the multivariate analysis, the statistically significant variables of the bivariate analysis that appear in Table 5 were used. It was found that the histological grade and Ki67 are associated with TN: those patients with histological grade 3 had 1.74 times the probability of having TN with IC 95%: 1.01-3; p = 0.046, in comparison grade 1, 2; as the Ki 67 increases, the probability of TN is 1.02 times with IC95%: 1.01-1.03, p = 0.0001, being in all cases adjusted for the other variables. (Table N ° 6)

Table 6. Multivariate Analysis of Triple Negative Breast Cancer.

	Triple Negative		
	RP _a	IC(95)	p
BMI (≥25 kg/m ² / <25 kg/m ²)	1.32	0.78-2.25	0.301
Clinical Stadium	1.18	0.74-1.87	0.493
Histological grade (3/ 1 y 2)	1.74	1.01-3	0.046
Size(≥5cm/<5cm)	1.13	0.62-2.05	0.699
KI67	1.02	1.01-1.03	0.0001

DISCUSSION

Breast cancer is one of the most common malignancies and causes of mortality in women worldwide^{3,4}. being the first cause of death in Peruvian women^{1,3}, the Triple Negative type has a high incidence in the Afro-American population⁵, with a frequency of 21.3% in Peru^{4,5}. In addition, the CMTN has high morbidity and mortality, and does not have target treatment unlike other types of breast cancer, being only a beneficiary of systemic treatment with chemotherapy^{1,3}.

In our study, patients with CMTN were 26.9% of patients with breast cancer, a figure similar to that reported in the national literature, where it was found that TN tumors were 20-25%⁶. In 2015, it is described that 21.3% of breast cancer are TN in Peru⁴. The study in 2015 in Arequipa, where the prevalence of the CMTN of its study was 30.8%⁷ and in a study in Chiclayo a frequency of 32.5% of CMTN⁸.

The median age of triple negative patients in our study was 54.14 years, similar data found in a study in Argentina in 2014 where the median age at diagnosis of TN was 54.9 years⁹ and another study in Argentina In 2017, the average age was 51 years¹⁰. However, national studies indicate an earlier age in the diagnosis of CMTN as described in the study in 2015 where the median presentation is 48 years, with 53% of cases diagnosed before 50 years⁴. A similar finding was found in the study, where the median age at diagnosis was 40 years in CMTN⁶. The difference in the age of diagnosis found in the literature regarding our study may be due to several factors, one of them would be the lack of knowledge of the age for screening this disease or the accessibility to hospital centers for early diagnosis. which would entail in the delay of the diagnosis.

Regarding the BMI, in the national study conducted at the National Institute of Neoplastic Diseases, it was found that of the 89 patients who had CMTN, 67.4% were overweight and obese⁶. Another study carried out in our country describes that the role of overweight in the CMTN would be controversial since it is a non-hormonal cancer, finding that premenopausal and obese women have 1.4 times the risk of presenting CMTN⁵. Similar data were found in the present study, since most of the patients had a BMI ≥ 25 kg / m² both in the TN (26.6 kg / m², SD: 4.31) and in the non-TN group (28.5 kg / m², DE: 5.3). Likewise, it was found that overweight and obesity were associated with a 14% higher risk of having CMTN compared to those of low and normal weight (RP: 1.14; 95% CI: 1.23-6.22; p: 0.014). However, in a study conducted in Mexico, it mentions that there was no significant relationship with overweight (BMI ≥ 25 kg / m²; p: 0.423) or obesity (BMI ≥ 30 kg / m²; p: 0.103)¹¹.

Regarding the tumor size, it was determined that the patients with CMTN were larger at the time of diagnosis, in the bivariate analysis it was found that the tumor size of the TN type was 5.75 cm (IR: 2-13) unlike those not TN that was 3 cm (IR: 1.2-10) with p: 0.002, however in the multivariate analysis it was not statistically significant (RP: 1.13; 95% CI: 0.62-2.05; p: 0.699). It is known that CMTN is associated with larger carcinomas, unlike other tumor types. In an article

about CMTN in Peru, it is mentioned that the average tumor size was 36mm⁴. In an Argentine study, the tumor size found in patients with CMTN was 5 cm at diagnosis¹⁰.

The ductal histological type was the most frequent in both TN (91.6%) and Non-TN (91.8%). Although this characteristic was not associated with the presence of MMTN, the information is consistent with what was reported in the literature where the histological type was 96.6% of the cases, ductal carcinoma⁶. The same was reported in Argentina, where it was found that the ductal type was the most frequent^{9, 12-14}.

The clinical stages were another variable that was not statistically significant, with stages III and II being the most frequent at the time of diagnosis, both in TN and non-TN, with Stage III and II being 50% in TNs and 33.3% respectively. Similar findings were found in several studies where locally advanced clinical stages (II and III) accounted for 95.5% of cases⁶. In another study, a higher incidence of stages III and IV was also found in patients with TN9 tumors and in another study there were greater cases in stage II (49.9%) and III (31.1%)¹⁵.

The international literature reports that the CMTN is associated with larger size and high histological grade, as identified in our study regarding histological size and grade III. The association of the histological grade (3 / 2-1) with the CMTN (RP: 1.74, 95% CI: 1.01-3, p: 0.046) was found in the multivariate analysis and that in addition the histological grade 3 was more frequent in the TN (58%) than in the non-TN group (26%). Which is consistent with a national study, where histological grade III was the most frequent, representing 68.5% of patients with CMTN⁶. Slightly higher figures report another article, where histological grade 3 was the most frequent in TN compared to non-TN (73.5% vs. 41.8%; p: 0.0008)⁹. And in another study it also reveals that grade 3 was the most frequent, with 74% of cases of TN¹⁰.

The value of Ki 67, a marker of cell proliferation and also a predictive factor and prognosis, was the one that attracted the most attention in the present study, where in the univariate analysis of categorized Ki 67, that is to say greater than 50%, it was found that in TN patients were 74%, compared to non-TN patients being only 26% (p = 0.0001). And in the multivariate analysis we found statistical significance where the value of Ki 67 was associated with a 2% increase in prevalence for each increase in a percentage unit of the marker (RP: 1.02; 95% CI: 1.01-1, 03; p: 0.0001). These findings are consistent with international studies, such as that of 2014 in Spain, where they indicate the significant

relationship between Ki 67, histological grade 3 and larger tumor size¹⁶. Several studies indicate the association of the value of Ki 67 with the CMTN, as in the study (REF)¹⁷ in which they focus on the predictive value and prognosis of Ki 67 in CMTN who received neoadjuvant chemotherapy, where in the multivariate analysis in the patients who did not have R_{Pc} had an independent prognostic value for disease relapse (HR: 0.986; 95% CI: 0.988-0.994; p: 0.001), it was also indicated that primary Ki 67 can help classify CMTN in subtypes with different responses to chemotherapy¹⁷. In another study, the association of high levels of Ki 67 with CMTN was also identified, in addition to having a good response to neoadjuvant chemotherapy¹⁸. Like in the study where they determine that patients with TN are associated with high levels of Ki 67 ($\geq 10\%$) and also associated with high rates of R_{Pc} to neoadjuvant chemotherapy¹⁹.

Only two decades ago, breast cancer was considered a simple disease, with a special focus on knowing whether it was estrogen positive or not, a situation that has remained for more than a century.

In current times, breast cancer is characterized by its molecular and clinical heterogeneity.

More population-based studies are required to have the frequency of breast cancer subtypes in Latino populations and even in various ethnic groups.

Finally, this new classification of triple negative breast cancer presents a real opportunity to improve treatments and therapeutic options and will lead to a greater understanding of the role of lifestyle factors in the etiologies of breast cancer. Triple negative breast cancer represents a special challenge for epidemiologists, oncologists and pathologists.

CONCLUSION

In conclusion, our study shows that the factors significantly associated with the presence of CMTN were BMI greater than 25, tumor size greater than 5 cm, histological grade and Ki 67 value, the latter two being the only factors associated in Multivariate analysis.

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