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Original article

Characteristics and prognosis of stage I-III breast cancer subtypes in Brazil: The AMAZONA retrospective cohort study

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ABSTRACT

Objective: To describe stage I-III breast cancer (BC) molecular subtypes and outcomes among a cohort of patients from Brazil.
Methods: AMAZONA study is a retrospective cohort conducted from June 2008 to January 2009 including women of at least 18 years old, with histologically proven breast cancer, diagnosed in 2001 (n = 2198) and 2006 (n = 2714). In this analysis, we included patients who underwent surgery, had stage I-III disease and available pathological information (n = 2296). We estimated molecular subtypes by local immunohistochemical stains. Data was obtained from medical charts and public databases.
Results: Mean age at diagnosis was 54 years and 41.1% were younger than 50 years. 23.3% were diagnosed in stage I, 53.5% in stage II and 23.2% in stage III. 80.8% were treated in the public health system. 71.3% had hormonal receptor positive disease, 15.7% were HER-2 positive and 21.1% had triple-negative breast cancer. 55.6% were treated with mastectomy and 96.2% received adjuvant treatment (82.2% chemotherapy). 13.4% of HER-2 positive patients received adjuvant trastuzumab. Overall survival rate at 5 years was 96.84% for stage I, 94.16% for stage II and 70.48% for stage III. Molecular subtypes were independent prognostic factor in stages II and III patients.

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Conclusions: Brazilian women have a higher risk of being diagnosed with late stage breast cancer and younger age than in high-income countries. Luminal-like disease is the most common molecular subtype in the country. Triple negative and HER-2 positive had the worst prognosis.

1. Introduction

Breast cancer (BC) is the second most common cancer in the world and, by far, the most frequent cancer in women, as well as the fifth cause of death from cancer overall [1]. In 2012, there were 1.67 million new cases of disease and 522,000 deaths worldwide [1]. In Brazil, BC is the most prevalent cancer in women with approximately 57,960 new cases (56.20 for every 100,000 women) estimated in 2016 [2]. Available mortality data is based on estimates from high-income countries, such as USA and European ones; therefore, it is biased by the population characteristics and healthcare in those regions, which are remarkably different from low and middle-income countries (LMIC).

Few data on the clinical characteristics, treatment and outcomes of patients diagnosed with BC are available in Brazil. The AMAZONA Study, an initiative of the Grupo Brasileiro de Estudos em Câncer de Mama (GBECAM), the most comprehensive observational study so far, included more than 3000 patients and showed discrepancies according to health care coverage (public vs. private) in terms of stage at diagnosis, relapse and survival [3,4].

Molecular classification of BC subtypes is used to guide systemic therapy and is a prognostic factor associated with survival. Largely, available data describing prevalence, patients characteristics and survival associated with the different BC subtypes is based mostly in studies from European and North American populations, therefore there is a need to describe characteristics and outcomes of Brazilian patients, that may show differences due to the recognized unique population miscegenation [5].

The aim of this study is to describe the patients' characteristics, estimated molecular subtypes, treatments and outcomes of patients diagnosed with stages I-III BC in Brazil.

2. Methods

2.1. Study design

The AMAZONA is an observational retrospective cohort study which enrolled 4912 patients within 28 Brazilian institutions. The study included patients diagnosed with BC in the years of 2001 (n = 2198) and 2006 (n = 2714). Data collection for baseline variables was performed from June 2008 to January 2009. Additionally, follow-up was collected from November 2011 to April 2012, thus for the current analysis we evaluated 5-year survival data. The study was approved by the ethics committee of each participating institution before start of data collection.

2.2. Patients

AMAZONA eligibility criteria were women with at least 18 years old, diagnosed with invasive breast cancer and who have been registered as new cases in the participating institutions during the period of study accrual (2001 and 2006). For this analysis, only patients who underwent surgery for BC, had clinicopathological stage I-III disease and had available information on hormonal receptors, Human Epidermal Growth Factor Receptor 2 (HER-2) status and tumor grade were included (n = 2296).

2.3. Data collection and variables

Baseline and follow-up data were collected from medical charts and information inserted in an electronic case report form database. Information regarding tumor stage, both clinical and pathological, was collected from pathological reports or medical records and classified using the UICC TNM Classification of Malignant Tumors, 6th edition [6]. Hormone Receptors (HR) [estrogen and progesterone receptors], HER-2 status and tumor grade were performed in local laboratories in each institution. Results were collected as positive or negative for HR and HER-2, and 1 to 3 for tumor grade. For the estimation of BC molecular subtypes by immunohistochemistry we used the following classification [7]: *Luminal A*-like tumors - HR positive, HER-2 negative and grade 1 or 2; *Luminal B/HER-2 negative*-like tumors - HR positive, HER-2 negative and grade 3; *Luminal B/HER-2 positive*-like tumors - HR positive, HER-2 positive, any grade; *HER-2-positive (nonluminal)*-like tumors – HR negative, HER-2 positive, any grade; *Triple-negative* tumors - HR negative, HER-2 negative, any grade. *Luminal-like* comprises *Luminal A* and both *Luminal B* subtypes. Public health system is defined as the insurance covered by the Sistema Único de Saúde, funded by the Brazilian government. Private health system is defined as health insurance funded by patients or employers, not related to the government.

2.4. Statistical analysis

The results of this study are exploratory and descriptive; therefore, no sample size was calculated. For descriptive analysis, quantitative variables are presented as mean and standard deviation, while the qualitative variables are presented by their absolute and relative frequencies. Overall survival (OS) was defined as the time between date of surgery and date of death for any cause and analyzed using the Kaplan-Meier method for data description. All analyses were performed using SAS version 9.4.

3. Results

3.1. Baseline characteristics

2296 women were included in this study. Baseline characteristics of patients are described in Table 1. Mean age was 54 years, 39.1% were premenopausal and 80.8% were insured by public health system. Most patients had stage II (53.5%) and *Luminal A* (49.4%) BC subtype.

Table 2 shows the clinical and pathological patients' characteristics according to different BC subtypes. Age was similar between subgroups. There were a high proportion of *HER-2 positive (nonluminal)* and *Triple-negative* subtypes diagnosed with clinical stage III (32.3% and 30.6%, respectively). Stage I BC was more common in *Luminal A* subtype patients (29.0%). The prevalence of *HER-2 positive (nonluminal)* BC was 20.4% overall and 32.9% in patients who had private health insurance. We also found that prevalence of BC subtypes was different among the regions of the country. In the North and Northeast, there was a high proportion of patients with *Triple-negative* subtype (18.3% and 7.3%, respectively), whereas in

Table 1
Study participants' demographic and clinical-pathological characteristics. Amazona Study. Brazil.

Characteristic[a]	All patients (n = 2296)
Age (years)	54 (±12.9)
<40	278 (12.1%)
40–50	739 (32.2%)
>50	1279 (55.7%)
Brazilian region	
Southeast	1268 (55.3%)
South	333 (14.5%)
Northeast	267 (11.6%)
North	256 (11.1%)
Center-west	171 (7.5%)
Health coverage	
Public	1109 (80.8%)
Private	264 (19.2%)
Menopausal status	
Pre	801 (39.1%)
Post	1246 (60.9%)
Breast cancer family history[b]	
Yes	282 (15.5%)
No	1539 (84.5%)
Ovarian cancer family history[b]	
Yes	28 (1.6%)
No	1674 (98.4%)
Histology	
Invasive ductal carcinoma	1573 (92.0%)
Invasive lobular carcinoma	111 (6.5%)
Medullary carcinoma	25 (1.5%)
Clinical stage	
I	504 (23.3%)
II	1160 (53.5%)
III	502 (23.2%)
Tumor grade	
G1 – well differentiated	248 (10.8%)
G2 - moderately differentiated	1302 (56.7%)
G3 – poorly differentiated	516 (22.5%)
GX	38 (1.7%)
Unknown	192 (8.3%)
Estrogen receptor status	
Positive	1464 (63.8%)
Negative	680 (29.6%)
Unknown	152 (6.6%)
Progesterone receptor status	
Positive	1261 (54.9%)
Negative	851 (37.1%)
Unknown	184 (8.0%)
HER-2 status	
Positive	360 (15.7%)
Negative	1437 (62.6%)
Unknown	499 (21.7%)
Molecular subtype classification	
Luminal A	838 (49.4%)
Luminal B/HER-2 negative	147 (8.7%)
Luminal B/HER-2 positive	223 (13.2%)
HER-2 positive	131 (7.7%)
Triple-negative	357 (21.0%)

[a] Continuous variables expressed as mean (±standard deviation) and categorical variables expressed as n (%).
[b] Considered only first-degree relatives.

the South and Southeast regions we found a greater prevalence of *Luminal A* (11.9% and 65%) and *HER-2 positive (nonluminal)* (14.5% and 58%) subtypes. Regardless of BC subtype, most patients were from Southeast region of the country (higher than 50% for each region). In addition to that, the North region was the one with second higher frequency of *Triple-negative* BC subtype (18.8%), while the South region had the second higher percentage of *Luminal B/HER-2 positive* BC subtype (20.2%).

3.2. Treatment

Table 3 describes types of treatment by BC subtypes. About 56% of patients received mastectomy as surgical treatment, without clinical relevant differences between BC subtypes. The most frequent adjuvant chemotherapy regimen used was anthracycline-based in all subgroups. In all HER-2 positive BC patients with available data, only 13.4% received adjuvant trastuzumab. Neo-adjuvant treatment was administered in less than one third of patients (18.8%); however, it was more commonly performed in the *HER-2 positive (nonluminal)* and *Triple-negative* subtypes.

3.3. Survival outcomes

Median follow-up for all study participants was 60 months (using reverse Kaplan-Meier estimator). The 5-year overall survival (OS) rate for all patients was 88.74% (95% CI: 87.23%; 90.25%) – 96.84% in stage I, 94.16% in stage II and 70.48% in stage III. For patients with stage I disease, OS was not different among BC subtype Fig. 1.

On the other hand, for patients with stage II and III there was a difference among molecular subtypes in terms of OS, despite the low number of events. In stage II breast cancer (Fig. 2), patients with *HER-2 positive (nonluminal)* had a 5-year OS rate of 82.34%; conversely, for patients with *Luminal A* subtype, it was 97.59%. Moreover, patients with *Triple-negative* disease also had inferior prognosis when compared to *Luminal A* patients in stage II BC (86.8%). For women with stage III BC (Fig. 3), *Triple-negative* tumors had worst OS (56.12%), followed by *HER-2 positive* (*nonluminal*) disease (64.10%). The highest OS was in patients with *Luminal B/HER-2 negative*, which had a 5-year OS rate of 85.83%.

4. Discussion

AMAZONA is the first large, multi-center, retrospective cohort study describing characteristics and survival of BC in Brazil.

Many known factors can affect clinical outcomes of BC patients, as screening frequencies, pathological characteristics of tumors and access to medical care. Specifically in Brazil, health coverage status is associated with worse stage at diagnosis and, therefore, worse overall survival [4]. In our study, we found a 5-year OS rate for all patients of 88.74%. Noteworthy, this is quite similar to what is seen in high-income countries. In England and Wales, during 2010-11, the 5-year survival rate was 86.6% [8] and in the European Union, 83.7% [9]. Moreover, it is slightly lower than what is seen in USA, where 5-year OS rate is 89.7% [10]. Despite limitations in Brazil's healthcare, these data highlight that access to adequate local treatment and common, less-expensive adjuvant therapies may improve BC survival, despite low access to BC screening and expensive drugs. Furthermore, we found a relevant difference in overall survival according to BC subtypes in stage II and III patients. In stage III, *Triple-negative* BC subtype had the worst prognosis (60% 5-years OS) which is similar to data from developed countries; in contrary, in stage II BC, *Luminal HER2 positive* had the worse prognosis, which highlights the lack of access to optimal care [11–14]. Patients with Hormone Receptor positive BC had the best prognosis regardless of stage, which is in line with what is found in the U.S. and Europe [15,16].

We found that a considerable proportion of patients are diagnosed with BC under 50 years old (41.1%), which is slightly higher than cohorts from high-income countries, as US [17] and Germany [12] for example. This difference may be due to discrepancies between age distributions, female median age in Brazil and European Union is 32.8 and 44.4 years-old, respectively [18] or different disease patterns. Nonetheless, these results highlight the importance of generating local data, as the current national BC screening guideline recommends mammography starting at 50 years old. In addition, the majority of patients in our study were diagnosed with

Table 2
Demographic and clinical-pathological characteristics by molecular subtype.[a] Amazona Study. Brazil.

Characteristic	*Luminal A*	*Luminal B/HER-2 negative*	*Luminal B/HER-2 positive*	*HER-2 positive (nonluminal)*	*Triple-negative*
Age at diagnosis - valid n = 1696 (73.9%)					
<40	87 (10.4%)	22 (15.0%)	38 (17.1%)	20 (15.3%)	52 (14.6%)
40–50	297 (35.4%)	42 (28.6%)	75 (33.6%)	37 (28.2%)	110 (30.8%)
>50	454 (54.2%)	83 (56.4%)	110 (49.3%)	74 (56.5%)	195 (54.6%)
Mean	54	54	52	52	53
Missing = 600 (26.1%)					
Clinical stage - valid n = 1601 (69.7%)					
I	229 (29.0%)	18 (13.1%)	50 (23.5%)	29 (23.4%)	52 (15.4%)
II	420 (53.2%)	83 (60.6%)	111 (52.1%)	55 (44.3%)	182 (54.0%)
III	141 (17.8%)	36 (26.3%)	52 (24.4%)	40 (32.3%)	103 (30.6%)
Missing = 695 (30.3%)					
Brazilian region - valid n = 1695 (73.8%)					
Southeast	544 (65.0%)	102 (69.4%)	128 (57.4%)	76 (58.0%)	199 (55.7%)
South	100 (11.9%)	16 (10.9%)	45 (20.2%)	19 (14.5%)	30 (8.4%)
Northeast	28 (3.3%)	7 (4.8%)	10 (4.5%)	9 (6.9%)	26 (7.3%)
North	106 (12.7%)	18 (12.2%)	11 (4.9%)	11 (8.4%)	67 (18.8%)
Center-west	59 (7.1%)	4 (2.7%)	29 (13.0%)	16 (12.2%)	35 (9.8%)
Missing = 601 (26.2%)					
Health Coverage - valid n = 905 (39.4%)					
Public	364 (80.9%)	57 (79.2%)	97 (76.4%)	51 (67.1%)	151 (83.9%)
Private	86 (19.1%)	15 (20.8%)	30 (23.6%)	25 (32.9%)	29 (16.1%)
Missing = 1391 (60.6%)					
Menopausal status - valid n = 1513 (65.9%)					
Pre	302 (40.1%)	55 (42.3%)	86 (46.2%)	51 (42.1%)	123 (38.1%)
Post	451 (59.9%)	75 (57.7%)	100 (53.8%)	70 (57.9%)	200 (61.9%)
Missing = 783 (34.1%)					
Breast cancer family history[b] - valid n = 1385 (60.3%)					
Yes	92 (13.7%)	22 (18.0%)	29 (15.4%)	23 (21.5%)	56 (18.9%)
No	579 (86.3%)	100 (82.0%)	159 (84.6%)	84 (78.5%)	241 (81.1%)
Missing = 911 (39.7%)					
Ovarian cancer family history[b] - valid n = 1328 (57.8%)					
Yes	4 (0.6%)	2 (1.7%)	5 (2.8%)	2 (2.1%)	2 (0.7%)
No	643 (99.4%)	119 (98.3%)	173 (97.2%)	95 (97.9%)	283 (99.3%)
Missing = 968 (42.2%)					

[a] Maximum number of patients equal to 2296.
[b] Considered only first-degree relatives.

locally advanced disease (53.5% stage II and 23.2% stage III) which is significantly higher than developed countries [19] and consequently impacts patients outcomes.

In our study, the most frequent BC subtype identified was *Luminal A*, with an estimated prevalence of 49.4%, which is lower than the prevalence found in high-income countries. Spitale and cols [20] detected a frequency of 73.2% of *Luminal A* in a population-based study from Switzerland. Moreover, Carey et al. [21] found a prevalence of almost 60% in post-menopausal women included in a cancer registry from North Carolina, USA and Yang et al. [22] found a prevalence of 69% in a population from Poland. On the other hand, data from a Peruvian hospital found a prevalence of 49.3% of *Luminal A* BC subtype, similar to what we identified in Brazil [23]. These differences may result from discrepancies in age distribution across different countries, genetic variances between populations, criteria of BC subtype classification and patient selection. Nonetheless, we found a 21.0% *Triple-negative* BC rate, similar to the one identified in high income countries as USA and Western Europe, despite age- and ethnic-related heterogeneity [24–27]. The prevalence of *Triple-negative* was higher in the north and northeast regions of the country, where there are a larger proportion of women from African ancestry. These findings are similar to what is described in other countries regarding differences between molecular subtypes and race, and may be associated with health disparities [28,29].

Almost 81% of patients were insured by public health system where there are several limitations in drug access. For instance, trastuzumab was approved as adjuvant or neoadjuvant treatment for early BC only in 2013 [30]. In our study, only 13.4% of HER-2 positive patients received adjuvant trastuzumab, which certainly impacted our estimates of survival in these subjects; therefore, we need to consider that the estimated survival rates do not translate to current status in Brazil, as BC treatment has improved in the past ten years. Notwithstanding, we fear that, in near future, with the development of new, expensive drugs, BC survival differences between Brazil and high-income countries may increase if the access to new agents is not improved. This is true for *HER-2 positive (nonluminal)* and *Luminal-like* BC patients, where recent studies showed benefit with new target therapies that lower recurrence and progression, as CDK4/6 inhibitors [31] and TDM-1 [32].

Our study has some limitations. This cohort included patients diagnosed in 2001 and 2006, i.e., before some adjuvant therapies entered into current practice in Brazil, as adjuvant anthracycline-taxane chemotherapy and trastuzumab. Moreover, selection bias may have occurred as selected subjects were not consecutive cases treated in participating institutions as well as missing data due to retrospective data capture. Additionally, molecular subtypes were estimated by immunohistochemical stains, which do not have strict correlation with molecular classification by genomic tests; pathological evaluation was performed in local laboratories without central review, hence quality was not assured by investigators. Despite some limitations inherent to the study design AMAZONA is the most comprehensive BC study to date in Brazil and we consider that the results reflects the scenario of breast cancer care in the country.

In conclusion, breast cancer is diagnosed at younger age and in more advanced stages in Brazil. *Luminal-like* BC is the most prevalent tumor type (71.3%) and, with exception of *Luminal A*, the proportion of BC subtypes is similar from those in developed countries. Moreover, immunohistochemical stains commonly

Table 3
Treatments performed according to molecular subtype.* Amazona Study. Brazil.

	Luminal A	*Luminal B/HER-2 negative*	*Luminal B/HER-2 positive*	*HER-2 positive (nonluminal)*	*Triple-negative*	Total
Surgery - valid n = 1686 (73.4%)						
Breast conservative	401 (48.2%)	58 (39.7%)	93 (41.7%)	51 (38.9%)	146 (41.2%)	749 (44.4%)
Mastectomy	431 (51.8%)	88 (60.3%)	130 (58.3%)	80 (61.1%)	208 (58.8%)	937 (55.6%)
Missing = 610 (26.6%)						
Adjuvant treatment - valid n = 1696 (73.9%)						
Yes	816 (97.4%)	144 (98.0%)	217 (97.3%)	120 (91.6%)	334 (93.6%)	1631 (96.2%)
No	22 (2.6%)	3 (2.0%)	6 (2.7%)	11 (8.4%)	23 (6.4%)	65 (3.8%)
Missing = 600 (26.1%)						
Type of adjuvant treatment - valid n = 1531 (93.9%)						
Chemotherapy only	44 (5.5%)	13 (9.3%)	20 (9.3%)	98 (100.0%)	279 (100.0%)	454 (29.7%)
Endocrine therapy only	204 (25.5%)	25 (18.0%)	44 (20.6%)	0 (0.0%)	0 (0.0%)	273 (17.8%)
Chemotherapy + Endocrine Therapy	553 (69.0%)	101 (72.7%)	150 (70.1%)	0 (0.0%)	0 (0.0%)	804 (52.5%)
Missing = 100 (6.1%)						
Chemotherapy regimen - valid n = 1226 (97.5%)						
CMF	195 (33.7%)	32 (29.6%)	53 (31.9%)	25 (26.3%)	75 (26.8%)	380 (31.0%)
Anthracycline-based	302 (52.3%)	55 (50.9%)	80 (48.2%)	36 (37.9%)	148 (53.1%)	621 (50.6%)
Taxane-based	51 (8.8%)	15 (13.9%)	22 (13.3%)	23 (24.2%)	36 (12.9%)	147 (12.0%)
Other	30 (5.2%)	6 (5.6%)	11 (6.6%)	11 (11.6%)	20 (7.2%)	78 (6.4%)
Missing = 32 (2.5%)						
Endocrine therapy regimen - valid n = 1051 (97.6%)						
Tamoxifen	658 (88.9%)	113 (91.9%)	162 (86.2%)	0 (0.0%)	0 (0.0%)	933 (88.8%)
Aromatase inhibitor	33 (4.5%)	7 (5.7%)	14 (7.4%)	0 (0.0%)	0 (0.0%)	54 (5.1%)
Sequential treatment (TMX -> AI)	49 (6.6%)	3 (2.4%)	12 (6.4%)	0 (0.0%)	0 (0.0%)	64 (6.1%)
Missing = 26 (2.4%)						
Adjuvant trastuzumab - valid n = 261 (16.0%)						
Yes	0 (0.0%)	0 (0.0%)	16 (9.1%)	19 (22.1%)	0 (0.0%)	35 (13.4%)
No	0 (0.0%)	0 (0.0%)	159 (90.9%)	67 (77.9%)	0 (0.0%)	226 (86.6%)
Missing = 1370 (84.0%)						
Neoadjuvant treatment - valid n = 1696 (73.9%)						
Yes	122 (14.6%)	30 (20.4%)	43 (19.3%)	37 (28.2%)	86 (24.1%)	318 (18.8%)
No	716 (85.4%)	117 (79.6%)	180 (80.7%)	94 (71.8%)	271 (75.9%)	1378 (81.2%)
Missing = 600 (26.1%)						
Neoadjuvant regimen - valid n = 317 (99.7%)						
Chemotherapy	114 (93.4%)	29 (96.7%)	39 (90.7%)	36 (100.0%)	86 (100.0%)	304 (95.9%)
Endocrine therapy	8 (6.6%)	1 (3.3%)	4 (9.3%)	0 (0.0%)	0 (0.0%)	13 (4.1%)
Missing = 1 (0.3%)						

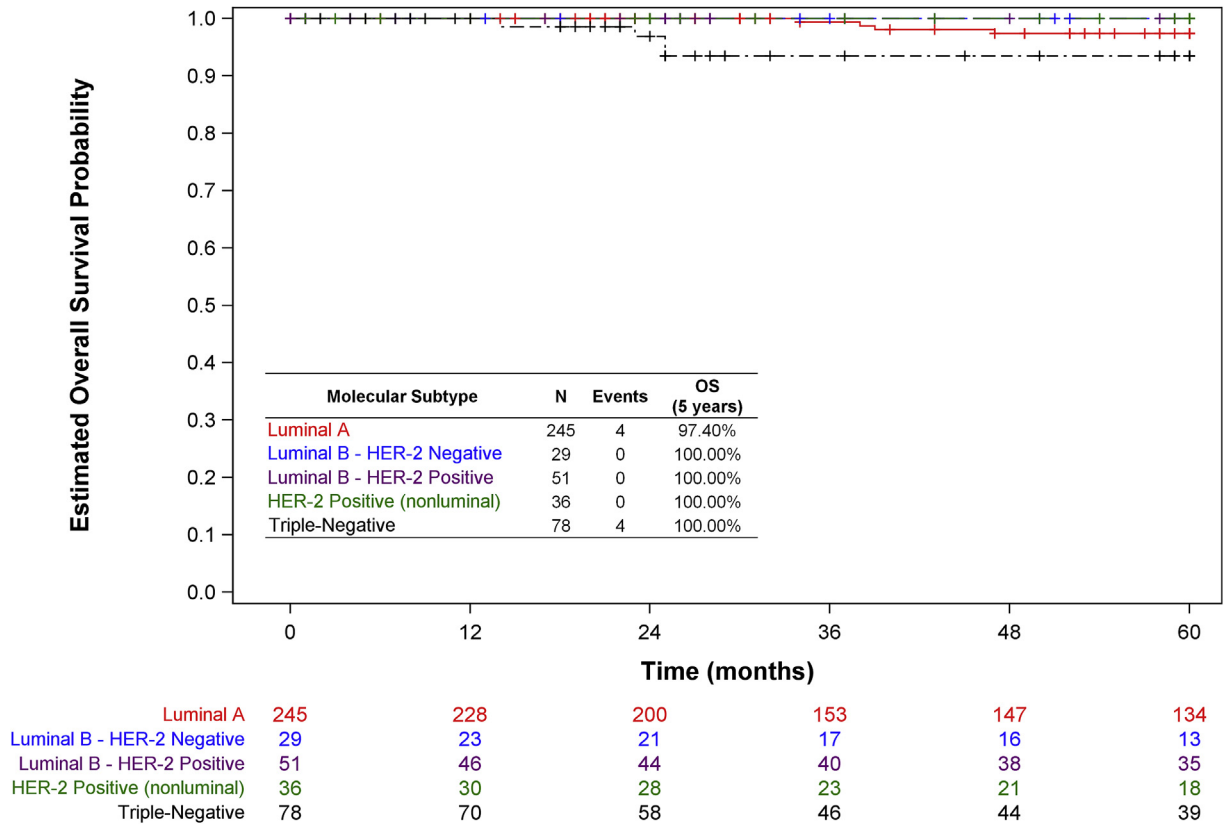

Fig. 1. Overall survival by molecular subtype, according to pathological stage I. Amazona Study. Brazil.

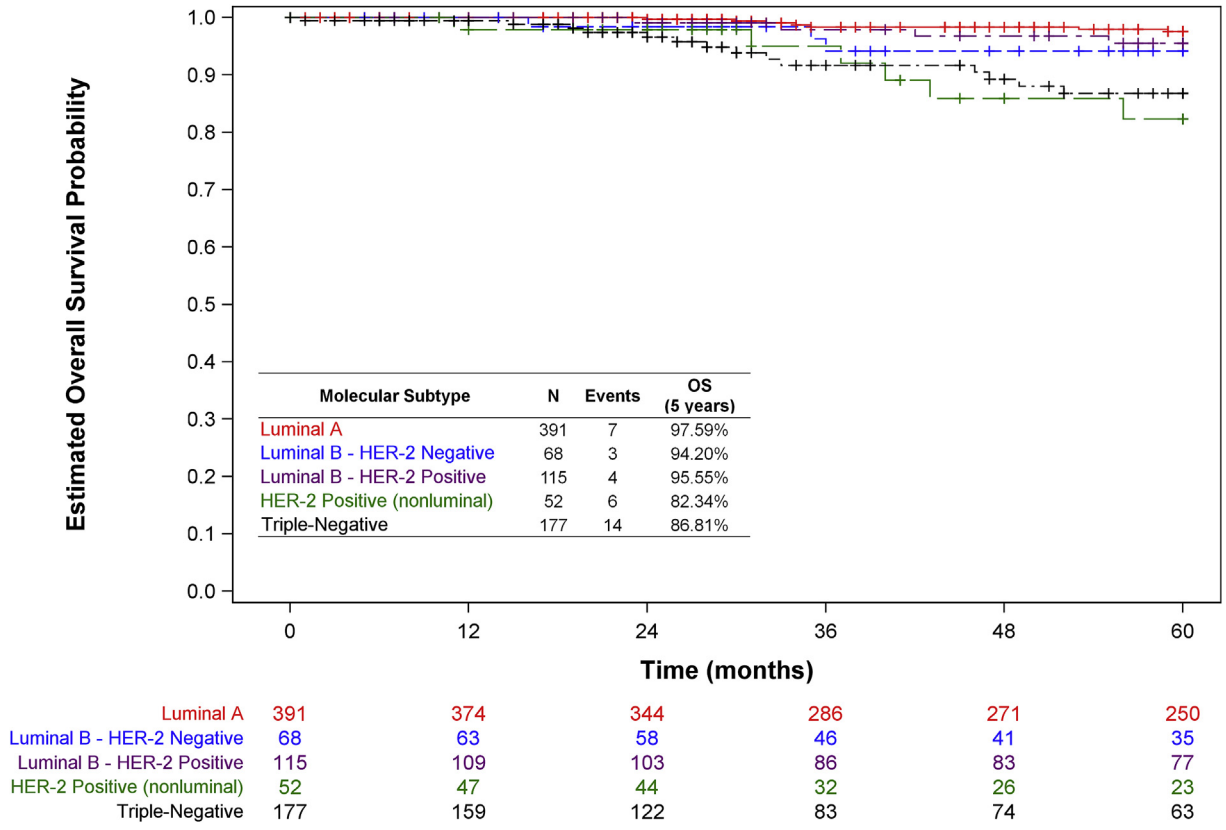

Fig. 2. Overall survival by molecular subtype, according to pathological stage II. Amazona Study. Brazil.

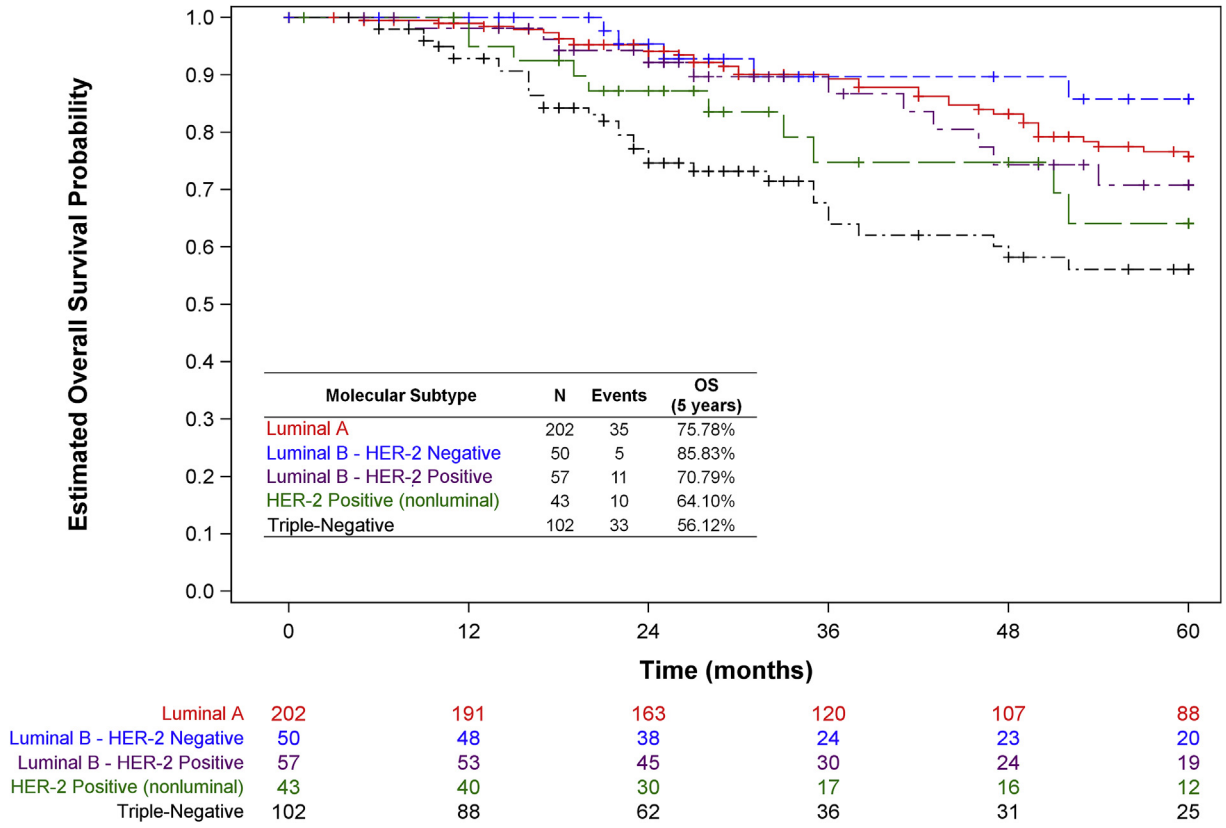

Fig. 3. Overall survival by molecular subtype, according to pathological stage III. Amazona Study. Brazil.

available in low resource settings create distinct groups with different prognosis. Of note, our study shows that five-year survival rates by BC subtypes are similar to the data described in the literature from high-income countries.

Authors contributions

SDS, JB, GW, JMM and CHBE conceived and designed the study and participated in data collection. JSN, FCP, JGG, AJSG, BMHRAVE, DLG, SC, RFJ, LDL, GSQ, SJA, DDR, GD, GSB, YVN were principal investigators and collected data. FZ and JMM performed statistical analysis. All the authors have read and approved the final version of this manuscript.

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Conflicts of interest

Declaration of interests: none.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.01.008.

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