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Article

Shorter delay to treatment by integrated diagnostic services and NGO-provided support among breast cancer patients in two Brazilian referral centres

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Abstract

Background: The diagnosis of breast cancer requires a complicated series of diagnostic exams. The present study addressed the delay of patients who used publicly and privately financed diagnostic services. Non-governmental organizations (NGOs) donated diagnostic mammograms and biopsies.

Design and Methods: Data from 304 patients were obtained from two Brazilian referral centres. In one referral centre (FAP), diagnostic mammography, clinic-histopathological exam and immunohistochemistry were outsourced, whereas in the other centre (HNL), these services were integrated. Cox regression, Kaplan-Meier analysis and non-parametric tests were used to compare variables and time intervals.

Results: If diagnostic mammography was financed privately and covered by private health insurance, the likelihood of a delay of >90 days between the first medical visit and the initiation of treatment decreased 2.15-fold (95%CI: 1.06- 4.36; p=0.033) and 4.44-fold (95%CI: 1.58-12.46; p=0.004), respectively. If the clinic-histopathological exam was outsourced (FAP) and publicly or privately financed, the median time between diagnostic mammography and the diagnostic result was 53 and 65 days in the integrated (HNL) and outsourced public system, compared to 29 days in the outsourced private system (p<0.050). The median time between the first medical visit and the diagnostic results of patients who were supported by NGOs, who financed their diagnostic services privately, and who used exclusively public diagnostic services was, respectively, 28.0, 48.5 and 77.5 days (p<0.050).

Conclusion: Patients who used privately financed health services had shorter delays. Compared to outsourcing, the integration of the publicly financed clinic- histopathological exam diminished the delay. The support of patients by NGOs accelerated patient flow.

Introduction

Breast cancer is the most common cancer worldwide, and between 2005 and 2015, the incidence of disease increased by 33% from 1.7 to 2.4 million cases worldwide.[1] Incidence and mortality rates remained stable or even declined in developed countries, whereas they increased in developing countries mainly due to prolonged life expectancy and changing lifestyle and reproductive patterns.[2] Of all regions in the world, Latin America and the Caribbean had the highest-increasing mortality trend between 1990 and 2015, with a slope of 1.48 per 100,000 women.[1]

Brazil has approximately 209 million inhabitants, making it the largest Latin American country, and breast cancer currently contributes to 29.5% of all neoplasms among women.[3] The incidence of disease has developed differentially in distinct regions of the country: in the South, Southeast and Centre-West regions, which also include the two largest urban centres of the country, namely, São Paulo and Rio de Janeiro, the incidence has stabilized over the last ten years.[3,4] In contrast, in the Northeast region, the incidence of breast cancer has increased between 2005 and 2018 from 27.23 to 63.98 new cases per 100,000 women.[3,4]

The diagnosis and treatment of breast cancer is complex and requires a series of diagnostic and therapeutic procedures. These successive diagnostic and therapeutic steps require time and can lead to delays in the time to treatment initiation (TTI). Long waiting times for diagnostic procedures, poor disease management, barriers to access and a high number of services used before treatment initiation were often identified as causal factors of TTI.[5,6] Furthermore, low income, low educational level, no private health insurance, poor communication and ethnic origin can hinder the orientation of patients within the health system and negatively influence the speed of treatment decisions by physicians.[5] Additionally, the misinterpretation of symptoms by physicians can be associated with the TTI.[7]

Significance for public health

In many developing countries the incidence of breast cancer is increasing due to changing lifestyles and longer life expectancies. In Brazil, like in many other developing countries, this increase is characterized by high mortality to incidence ratios. The complex diagnostic procedures of breast cancer can lead to time delays from diagnosis to start of treatment. Previous Brazilian studies compared the time delays of diagnostic services and treatment between public and private health service centres. The present Brazilian study is the first one that compared treatment delay between two public referral centres of breast cancer treatment, one with integrated and the other one with outsourced diagnostic services. Results argue in favour of the integration of diagnostic services into the referral centre, instead of outsourcing them. The study also documents the successful work of the two Brazilian non- governmental organizations "Mulheres de Peito" and "Americas Amigas" that donate biopsies and diagnostic mammographies to low-income women.

Delays in the TTI were associated with advanced stage (stages III and IV) of disease and poor prognosis.[6,8,9] A recent study based on data from more than 1.3 million cases of breast cancer from the National Cancer Database of the United States showed that delays in the TTI increased the mortality risk of stage I and stage II breast cancer by 1.8%, respectively, or 1.2% per week.[10] Delays in the TTI of breast cancer are a major problem in low- and middle-income countries, leading to high incidence-mortality rates.[6]

In Brazil, a high number of studies performed in the South, Southeast and Centre-West regions of the country have addressed causal factors of TTI.[11-22] Some other studies have been performed in the Northeast region.[23-25] Few studies have compared the TTI of breast cancer between public and private health services.[21] One factor that hampers direct comparison between private and public health services is that many breast cancer patients who receive treatment in a public health service centre also receive private services.[26,27] Approximately 25% of the Brazilian population has access to private health services financed by individual health insurance.[26,27] Additionally, each service can be paid for directly by a private individual. The Brazilian public "Sistema Único de Saúde (SUS)" provides access to health facilities for all Brazilians, regardless of their income. This means that in the case of disease, patients have the option to combine self-financed private and free public health services for diagnosis and treatment. In addition, the SUS is a decentralized system that allows cooperation between the public and private health sectors, affording the possibility of contracts between municipal governments and private health care providers.[27] In the case of cancer diagnosis, this means that there are public referral centres for treatment that offer all diagnostic services within a hospital, whereas other centres outsource these diagnostic services in part or in full.

The present study addressed the TTI of patients from two referral centres of breast cancer treatment in north-eastern Brazil. In the hospital *Fundação Assistencial da Paraíba* (FAP), diagnostic mammography, clinic-histopathological exam, and immunohistochemistry were outsourced, whereas in the *Hospital Napoleão Laureano* (HNL), these diagnostic services were integrated. First, we examined which socio- economic variables were associated with a longer TTI. Second, specific time intervals from first medical visit to treatment initiation were compared between both referral centres. Third, the time intervals of both referral centres were compared among patient groups who financed one or more health services on their own during patient flow and among patients who received all diagnostic services within the public health system. Fourth, the effect of integration and outsourcing of a clinical histopathological exam on patient flow was analysed. Fifth, the impact of biopsies and diagnostic mammograms donated by two non-governmental organizations (NGOs) on the TTI was analysed.

Design and Methods

Study population

The present study was performed in João Pessoa and Campina Grande, two urban centres in the Northeast region of Brazil. João Pessoa, the capital of the state of Paraíba, has approximately 800,000 inhabitants and is located on the coast.[28] Campina Grande, with approximately 400,000 inhabitants, is the second-most populated urban centre in Paraíba and is located approximately 120 km away from the capital in the interior of the state.[28] Paraíba has a mixed-ethnic population of indigenous, African and European ancestry.

Patients of two different referral centres

Patient data were obtained from two Brazilian cancer treatment referral centres: the HNL in João Pessoa and the FAP hospital in Campina Grande. Both referral centres together treat more than 90% of all breast cancer patients in the state of Paraíba. Patients come from as far as 400 km away to the HNL and FAP. The HNL has an integrated pathology section. Therefore, anatomic-histopathological and immunohistochemical exams can be performed within the referral centre. Furthermore, diagnostic mammography can also be performed in the referral centre. The FAP, by contrast, does not have a pathology section, and their patients did not undergo diagnostic mammography at the referral centre. In the case of the FAP, diagnostic mammography and clinic-histopathological and immunohistochemical exams were financed by the public SUS or were financed privately but were always performed by private laboratories and medical centres in Campina Grande.

Participating women

All data were collected between October 2016 and March 2019. A total of 304 women participated in the study, of which 107 (35.2%) and 197 (64.8%) were patients from the FAP and HNL, respectively. Only patients with invasive tumours who received treatment in one of the two referral centres (FAP or HNL) were included in the study. Furthermore, only patients who received a diagnosis of disease within the last three years from the beginning of data collection were included in the study. The recruitment of patients was initiated with an interview (see below).

In 199 (65.5%) cases, treatment was initiated during the time interval of data collection. In 105 (34.5%) cases, treatment was initiated before the data collection began. Patients with recurring disease and patients with cognitive problems were excluded from the study.

Data sampling from medical records

Authors of the study extracted data of medical records. Clinical and histopathological data were obtained from medical records in the medical archives of both hospitals. The following

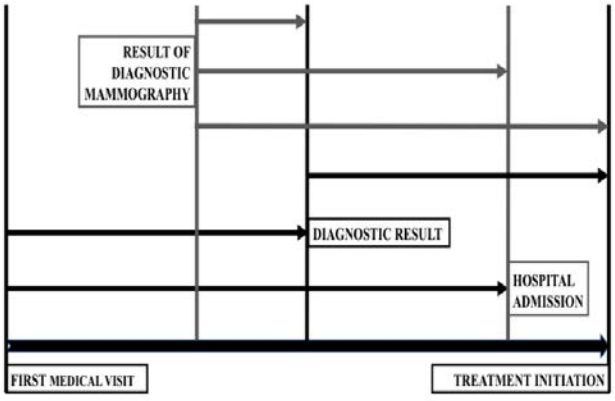

Figure 1. A schematic representation of patient flow and the analysed time intervals. Following time intervals are shown from the bottom to the top: First medical visit-> treatment initiation; First medical visit-> hospital admission; First medical visit-> diagnostic result; Diagnostic result-> treatment initiation; Result of diagnostic mammography-> treatment initiation; Result of diagnostic mammography-> hospital admission; Result of diagnostic mammography-> diagnostic result.

data were also obtained from medical records: date of each diagnostic service before and after hospital admission; date of hospital admission and treatment initiation; public or private health care service used at first medical visit; date of first medical visit; type of health care service used at first medical visit; private or public coverage of costs of diagnostic services, including mammography, ultrasonography, clinical breast examination and biopsy; and type of first treatment in the FAP or HNL.

The date of the first medical visit was defined based on reason for attendance; we included consultations for symptoms of breast cancer or screen-detected tumours. Of all 304 patients, 272 (90.5%) sought medical help because of symptoms, whereas in 32 (9.5%) cases the tumour was detected by mammography screening. The diagnostic result was defined as the date when the result of the clinical-histopathological exam was obtained. Treatment initiation was defined as the date of the first therapeutic treatment, including surgery, chemotherapy and radiotherapy.

If the date of the usage of a particular medical and/or diagnostic service was not documented in the medical record, the corresponding patient was excluded from the analysis of the time interval that included this service as a starting point or endpoint of a defined time interval. The data of medical records in both referral centres were not digitalized and were incomplete in many cases. Therefore, in general, for each analysed time-interval, only the dates of a portion of all 304 patients were available, which explains the heterogeneity of the numbers of patients within identical patient groups in different time intervals. Figure 1 is a schematic representation of patient flow and analysed time intervals.

Interview of women

To obtain information about socio-demographic characteristics and medical visits, all patients in this study were interviewed. The interviews included questions referring to the following variables: civil state; education level; occupation status; income; health insurance status; first discovery of disease symptoms; and health care services used before breast cancer diagnosis. A structured questionnaire was administered to patients within the chemotherapy and radiotherapy units of both hospitals. A similar questionnaire has been established and used in previous studies.[29] All interviews were performed by one of the authors. The selection of patients for interviews always occurred by direct face-to-face contact and in a stochastic manner. All patients during a determined chemotherapy and radiotherapy session were interviewed. Breast cancer patients who were never present in the chemotherapy or radiotherapy units during interviews were excluded from the study. Educational level was defined as follows: Having no schooling was defined as "no formal schooling". The basic education level was defined as ≤8 years of basic school education. The middle education level was defined as >8 years of school education. Minimum wage and its multiples were used to characterize income. This is a popular and well-known method used to define economic level among low- and middle-class subjects.[30] Minimum wage or less was defined as "low" income, whereas incomes equivalent to two and three times the minimum wage were defined as "basic" and "middle" income, respectively. An income of four times the minimum wage was defined as "high" income. The minimum wage in 2018 was R$ 954.00/month (US$ 281.60/month; 1st January 2018). Women were asked about quality of health care accessibility and the types, as well as the frequency, of health service use before and after the diagnosis of their disease. Additionally, women were asked about their adherence to the mammography- screening programme. Of all 304 women, 123 (40.5%) reported undergoing regular mammography.

Organizations that donated diagnostic mammograms and biopsies

The two NGOs (*Mulheres de Peito* in Campina Grande and *Amigos do Peito* in João Pessoa), or, respectively, "Women of the breast" (http://mulheresdepeito.com) and "Friends of the breast" (http://amigosdopeitojampa.blogspot.com/p/o-grupo-amigos- dopeito.htm), have been in operation since 2016 and 2006, respectively, in the state of Paraíba. In the present study, both NGOs paid for biopsies and breast examinations by mastologists. Furthermore, they mediated direct contact with medical staff and diagnostic laboratories. The work and donations of the NGOs were financed by private initiatives and by the sales of a doll called *Boneca Maria*, which is offered throughout the year but primarily during the public mammography screening campaign in October (October Rosa). With the cash receipts from the doll sales, the *Mulheres de Peito* recently started to pay for mammography services as well.

The third NGO, called *Américas Amigas* (https://americasamigas.org.br/), was founded in 2009 and is active in 12 Brazilian states. The group donates preventive and diagnostic mammography and supports the education of specialized mammography staff. In the present study, *Américas Amigas* donated mammography services as well as needles for biopsies. In 2017, *Mulheres de Peito* donated 400 mammograms in cooperation with the *Américas Amigas*, who provided financial resources. In 2018, *Américas Amigas* continued to donate mammograms for women in Campina Grande. Private initiatives and company foundations support the work of *Américas Amigas*. In April 2018, they received the certificates *ONG Transparente* and the *Selo Doar* for administrative and financial transparency. In the present study, 30 women received help from one of the NGOs.

Statistical analysis

Data were tabulated in Excel® software (version 10; MICROSOFT, 2010). Cox regression analysis was performed with R software (version 3.4.3; R Core Team, 2017) using the Therneau T package (version 2.38; R Core Team, 2015). Univariate Cox regression analysis was performed to identify significant variables using the Wald test. Significant variables of univariate regression analysis were used for stepwise Cox regression modelling with multiple adjusted variables applying the criterion of Akaike. The fit of the final model was tested using the Wald test.

Student's *t*-tests, Pearson's chi-square (χ^2) test, non- parametric tests and Kaplan-Meier analysis were performed with SPSS STATISTICS™ software (SPPS; IBM company; version 24). Mean, median values and 75th percentiles were calculated to compare total time intervals between groups without censoring data using Student's *t*-test and non- parametric tests. The fit of Kaplan-Meier analysis was tested using the Breslow (Generalized Wilcoxon)- test and Log Rank (Mantel-Cox)-test.

Results

Socio-economic and clinical characteristics

The mean age of all 304 patients was 54.56 (s=11.92) years, and 108 (35.53%) of them were under 50 years old (Table 1). Patients from the HNL and FAP were characterized by several differences. Of all patients, 26 (24.5%) and 74 (37.6%) patients from the FAP and HNL were employed (p=0.020; Table 1). In the HNL, 82 (56.59%) patients had grade III tumours compared to 29 (29.29%) in the FAP (p=0.010; Table 1). Metastases were detected

in 34 (37.36%) patients in the HNL and in 19 (20.21%) patients in the FAP (p=0.010; Table 1). All together, 46 (48.9%) and 56 (61.6%) patients of the FAP and HNL presented at an advanced stage (III, IV) of disease (p=0.077; Table 1). Mammography screening led to tumour detection in 6 (5.6%) and 26 (13.2%) cases in the FAP and HNL (p=0.000; Table 1), respectively.

Patient-level characteristics associated with prolonged TTI

To identify variables that were associated with prolonged TTI, the time interval of 90 days between the first medical consultation and treatment initiation was compared in univariate analysis among patients in different categories of socio-economic and clinical characteristics (Table 2). Patients with middle education level, respectively income, had a 1.93 (95%CI: 1.06-3.52) and 1.95- fold (95%CI: 1.15-3.30) increased chance of prompt TTI compared to those ones with basic education and income (p=0.030 and p=0.012; Table 2). Women were asked which types of health services and providers they used before the diagnosis of their disease and at the initiation of patient flow: women who used public and private health care services or who used only private services had, respectively a 1.88-fold (95%CI: 1.09-3.23) or a 2.57-fold (95%CI: 1.00- 6.63) increased chance of prompt TTI compared to women who used exclusively public services (p=0.021 and p=0.049, respectively; Table 2). Women who started patient flow in a primary service had a 3.85-fold (HR=0.26; 95%CI: 1.83-14.80) increased chance of delay compared to those who started patient flow with a diagnostic service (p<0.001 for both; Table 2).

Table 1. Socio-economic and clinical characteristics of the 304 patients from the FAP (n=107) and HNL (n=197) referral centres.

	FAP	HNL	Total	p*
Age				
Mean (years)	54.6 (s= 11.92)	54.6 (s= 11.71)	54.6 (s= 12.06)	0.100
	n (%)	n (%)	n (%)	
20- 29 years	0	1 (0.5%)	1 (0.3%)	0.910
30- 39 years	9 (8.4%)	21 (10.6%)	30 (9.9%)	
40- 49 years	26 (24.3%)	51 (25.9%)	77 (25.3%)	
50- 59 years	37 (34.6%)	61 (30.9%)	98 (32.2%)	
60- 69 years	24 (22.4%)	38 (19.3%)	62 (20.4%)	
≥70 years	11 (10.3%)	25 (12.8%)	36 (11.9%)	
Living place				
Urban centre	35 (32.7%)	85 (43.1%)	120 (39.5%)	0.090
Rural region	72 (67.3%)	112 (56.9%)	184 (60.5%)	
Marital status				
In a relationship	62 (57.9%)	104 (52.8%)	166 (54.6%)	0.401
Single	45 (42.1%)	93 (47.2%)	138 (45.4%)	
Education level				
No formal schooling	7 (6.5%)	14 (7.1%)	21 (6.9%)	0.780
Basic	64 (59.8%)	77 (39.1%)	141 (46.4%)	
Middle	36 (33.6%)	106 (53.8%)	142 (46.7%)	
Occupation status				
Employed	26 (24.5%)	74 (37.6%)	100 (32.9%)	0.020
Unemployed	81 (75.7%)	123 (62.4%)	204 (67.1%)	
Income				
Low	5 (4.7%)	1 (0.5%)	6 (2.0%)	0.020
Basic	65 (60.7%)	131 (66.5%)	196 (64.5%)	
Middle	25 (23.4%)	54 (27.4%)	79 (26.0%)	
High	12 (11.2%)	11 (5.6%)	23 (7.5%)	
Private Health Insurance				
Yes	18 (16.8%)	19 (9.6%)	37 (12.2%)	0.100
No	89 (83.2%)	178 (90.4%)	267 (87.8%)	
Histological grade				
I	2 (2.0%)	4 (2.3%)	6 (2.2%)	0.010
II	68 (68.7%)	90 (90.9%)	158 (57.5%)	
III	29 (29.3%)	82 (82.8%)	111 (40.3%)	
Missing	8	21	29	
Metastases				
Yes	19 (20.2%)	34 (37.4%)	53 (28.6%)	0.010
No	75 (79.8%)	57 (62.3%)	132 (71.5%)	
Missing	13	106	119	
TNM				
I	19 (20.2%)	15 (16.5%)	34 (18.4%)	0.077
II	29 (30.9%)	20 (21.9%)	49 (26.5%)	
III	27 (28.7%)	22 (24.2%)	49 (26.5%)	
IV	19 (20.2%)	34 (37.4%)	53 (28.6%)	
Missing	13	106	119	

s=standard deviation; **t-test* was used to compare the mean of age and Pearson's chi- square (χ^2) test was applied to analyse categorical variables.

Financing of diagnostic mammography by the public health system increased the chance of delay 2.38-fold (HR= 0.42; 95%CI: 0.23 – 0.78), compared to direct private payment (p<0.001; Table 2). Similarly, patients who privately covered the costs of biopsy had a 1.80-fold (95%CI: 1.01-3.19) increased chance of prompt TTI compared to those whose costs were covered by the public health system (p=0.045; Table 2). Of all 304 patients, 10 (3.3%) covered the costs of most diagnostic services by private health

Table 2. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) of single variables are shown in univariate Cox regression analysis. The HR was calculated as the likelihood of hospital treatment initiation within 90 days after the first medical consultation (n= 76).

	Missing	N (%)	Median	HR (CI 95%)	p*
Marital status					
In a relationship	1	92 (52.6%)	118.0	Ref	
Single		83 (47.4%)	116.0	1.39 (0.85-2.29)	0.192
Education level					
Basic	-	138 (78.4%)	120.5	Ref	
No formal schooling		13 (7.4%)	180.0	0.37(0.09-1.56)	0.179
Middle		25 (14.2%)	75.0	1.93 (1.06-3.52)	0.030
Occupation status					
Unemployed	-	119 (67.6%)	122.0	Ref	
Employed		57 (32.4%)	102.0	1.54 (-0.07 - 0.94)	0.090
Income					
Basic	2	111 (63.8%)	122	Ref	
Low		6 (3.4%)	196	1.20 (0.28 – 5.00)	0.801
Middle		47 (27.0%)	89	1.95 (1.15-3.30)	0.012
High		10 (5.8%)	118	1.09 (0.33-3.57)	0.880
Private health insurance					
No	-	156 (88.6%)	118.5	Ref.	
Yes		20 (11.4%)	107.5	1.33 (0.65-2.70)	0.439
Histological grade					
II	7	94 (55.6%)	110.0	Ref	
III		74 (43.8%)	124.0	0.74 (0.43 – 1.26)	0.272
I		1 (0.6%)	45.0	6.45 (0.86 – 48.40)	0.069
Metastases					
No	87	60 (67.4%)	118.5	Ref	
Yes		29 (32.6%)	99.0	1.61 (0.81 – 3.22)	0.172
First discovery of symptoms of disease					
Patient	5	151 (68.8%)	116.0	Ref.	
Mammography		20 (14.2%)	68.5	2.15 (0.01- 1.12)	0.083
Health care services used before diagnosis of breast cancer					
Public	3	114 (64.8%)	82.5	Ref	
Public and private		49 (27.8%)	102.0	1.88 (1.09-3.23)	0.021
Private		10 (5.7%)	125.5	2.57 (1.00-6.63)	0.049
Public or private health care service used at first medical visit					
Public	27	90 (60.4%)	144.0	Ref	
Private		59 (39.6%)	71.0	3.52 (2.03-6.12)	<0.001
Type of health care service used at first medical visit					
Diagnostic service	27	73 (41.5%)	86.0	Ref	
Primary health service		68 (38.6%)	165.5	0.26 (0.13 – 0.49)	<0.001
Hospital		8 (4.5%)	71.5	1.35 (0.53 – 3.45)	0.520
Financing of diagnostic mammography					
Direct private payment	13	78 (47.8%)	103.0	Ref	
Public health system		74 (45.4%)	139.0	0.42 (0.23 – 0.78)	<0.001
Health insurance		7 (4.3%)	69.0	2.46 (1.02 – 5.90)	0.040
Donated by NGO		4 (2.5%)	131.0	1.40 (0.33 – 5.87)	0.630
Coverage of costs of biopsy					
Public health system	15	73 (45.3%)	139.0	Ref	
Health insurance		6 (3.7%)	87.0	2.26 (0.67-7.63)	0.190
Direct private payment		70 (43.5%)	102.0	1.80 (1.01-3.19)	0.045
Donated by NGO		12 (7.5%)	97.0	1.86 (0.69-4.98)	0.217
Type of first treatment in the FAP or HNL					
Neoadjuvant chemo	-	97 (55.1%)	118.0	Ref	
Surgery		78 (44.3%)	112.5	1.09 (0.66-1.81)	0.728
Immunotherapy		1 (0.6%)	44.0	8.57 (1.14-64.73)	0.037

*Wald test.

insurance. All other patients financed these diagnostic services privately by direct payment, or they were financed by the public SUS.

To identify a model of independent variables, multivariate analysis was performed (Table 3). In this model the coverage of costs of diagnostic mammography by the public health system decreased chance of prompt TTI 2.38-fold (HR=0.42; 95%CI: 0.19-0.90), compared to direct private payment (p=0.025; Table 3). Furthermore, women who initiated patient flow with a primary health service had a 2.86-fold (HR=0.35; 95%CI: 0.16-0.76) decreased chance of prompt TTI compared to those who started patient flow with a diagnostic service (p=0.008; Table 3).

Time intervals and comparison of delays between patients in the FAP and HNL

The median time between the first medical visit and the diagnostic result was 56.0 days, and 54 (34.8%) out of 155 patients had a delay of >90 days (Table 4). The median time between the first medical visit and hospital admission and between first medical visit and treatment initiation for 173 and 176 patients, respectively, was 91.0 and 116.5 days, respectively (Table 4). Of these 173 and 176 patients, 87 (50.3%) and 114 (64.8%) patients had a delay of >90 days (Table 4). The median time between diagnostic results and treatment initiation was 54.0 days for 236 patients, and 99 (42.0%) of them delayed >60 days (Table 4).

In general, the time intervals were shorter for patients in the HNL compared to those in the FAP. The median time between the first medical visit and the diagnostic result was 136.0 and 52.0 days for patients in the FAP and the HNL, respectively (p<0.050; Table 4). The median time for patients in the FAP and the HNL who had a delay of >60 days during the latter time interval was 180.0 and 158.0 days, respectively (p=0.032; Table 4). The median time between the first medical visit and the treatment initiation was 148.0 and 110.0 days for patients in the FAP and the HNL, respectively (p<0.050; Table 4). The median time between the results of diagnostic mammography and diagnostic results was 79.0 and 38.5 days for patients in the FAP and the HNL, respectively (p<0.05; Table 4).

To clarify this difference between the two referral centres, patients were subdivided into two groups: patients in both referral centres who financed one or more health services (FAP_{PRIV} and HNL_{PPRIV}) and patients who performed all diagnostic and medical exams within the public health system (FAP_{PUB} and HNL_{PUB}), excluding all those who received help from one of the NGOs. The analysis indicated that most patients had financed a minimum of one health service: Between the first medical visit and the initiation of treatment of 128 patients in the HNL, 85 (66.4%) financed a medical service on their own (HNL_{PRIV}), whereas 43 (33.6%) received all diagnostic services in the public system (HNL_{PUB}; Table 4). In the case of the FAP, all 29 patients with available data for this time interval had financed health services privately (FAP_{PRIV}; Table 4). The median time between the first medical visit and treatment initiation was 172.0, 101.0 and 135.0 days for FAP_{PRIV}, HNL_{PRIV}, and HNL_{PUP}, respectively (p<0.050; Table 4).

Patients in the FAP and HNL used, on average, 4.49 (s=1.8) and 3.85 (s=1.4) health services, respectively, from their first medical visit until the initiation of treatment (p>0.050). If only patients were considered who financed a minimum of one or more diagnostic services, the median value for privately financed diagnostic services was 3.0 and 2.0 for patients in the FAP and HNL, respectively (p≥0.050). The mean number of private services used was 3.1 (s=1.6 for FAP patients; s=1.9 for HNL patients) for patients in both the FAP and the HNL (p=0.993).

Delay of the integrated and outsourced clinic-histopathological exam in the FAP and HNL

As the clinic-histopathological exam was integrated in the HNL and outsourced in the FAP hospital to private laboratories, we asked if there exists a relevant difference in the delay of the clinic-histopathological exam between the outsourced and integrated system. First, the time interval between diagnostic mammography and the diagnostic result was compared among patients of both referral centres who used exclusively public services. The median time between the result of diagnostic mammography and the diagnostic result of FAP_{PUB} and HNL_{PUB} was 122.0 and 41.0 days, respectively (p≥0.05; Table 4). Next, the delay between diagnostic mammography and the diagnostic result was compared among the following groups of patients, independent of whether they had privately financed any diagnostic service other than the clinic-histopathological exam (Table 4). Patients in the FAP who performed the clinic-histopathological exam outsourced in a private laboratory and financed it with the public health system (FAP_{OUTPUP}) or those who financed it privately ($FAP_{OUTPRIV}$); and all patients who performed the histopathological exam within the HNL, financed by the public health system (HNL_{INT}). Together, the FAP_{OUTPUP}, $FAP_{OUTPRIV}$ and HNL_{INT} groups encompassed 60, 77 and 45 patients, respectively (Table 4). The median time between the results of diagnostic mammography and the diagnostic results for FAP_{OUTPUP}, $FAP_{OUTPRIV}$ and HNL_{INT}, was 65.0, 29.0 and 53.0 days, respectively (p<0.050; Table 4).

Time intervals for patients who were supported by one of the NGOs

We asked if support by NGOs could accelerate patient flow. Therefore, patients of both referral centres who received support

Table 3. Hazard ratios (HRs) and confidence intervals (CIs) are shown for a model of multivariate Cox regression analysis. The HR was calculated as the likelihood of hospital treatment initiation within 90 days after the first medical consultation.

	HR* (95%CI)	p#
Financing of diagnostic mammography		
Direct private payment	Ref.	
Public health system	0.42 (0.19-0.90)	0.025
Health insurance	2.15 (1.06- 4.36)	0.033
Donated by NGO	0.74 (0.14-3.93)	0.731
Type of health care service at first medical visit		
Diagnostic service	Ref.	
Primary health service	0.35 (0.16- 0.76)	0.008
Hospital	1.60 (0.48- 5.29)	0.441

*Adjusted with histological grade; #Wald test.

Table 4. Time intervals are shown in days for groups of patients for descriptive and Kaplan-Meier analysis. Numbers and mean and median values are shown for all patients and those ones with time intervals >90 and >60 days of each group. Numbers, percentages and mean and median values of Kaplan-Meier analysis refer to patients who delayed >90 days and >60 days for a determined time interval. The 25th percentile of Kaplan-Meier analysis defined the time (in days) after which 75% of these patients delayed. Diagnostic results were defined as the date of the result of the clinic- histopathological exam.

	All					Time interval >90 days				
	N	Mean	75%	Median	p	N_{DELAY} (%)	Mean	25%	Median (95%CI)	p
First medical visit – Diagnostic result										
All	155	128.8 (s=493.3)	136.0	56.0		54 (34.8%)	298.8(s=110.6)	260.0	160 (151.6- 168.4)	
FAP	31	324.8 (s=1082.9)	229.0	136.0	<0.050*	17 (54.8%)	562.8 (348.5)	284.0	180.0 (88.6- 271.4)	0.032^
HNL	124	79.8 (s=80.9)	107.8	52.0	<0.050*	37 (29.8%)	177.5 (14.0)	183.0	158.0 (139.1- 176.9)	0.032^
FAP_{PRIV}	25	374.7 (s= 204.5)	260.5	110.0	<0.050*	14 (56.0%)	640.8 (s=423)	334.0	180.0 (29.7- 330.3)	0.118$
HNL_{PRIV}	75	70.3 (70.3)	93.0	41.0	<0.050*	19 (25.3%)	172 (s= 5.2)	183.0	160.0 (157.2- 162.8)	0.118$
HNL_{PUB}	38	114.3 (s=101.6)	142.3	114.3		17 (44.7%)	196.1 (s=24.7)	260.0	161.0 (103.2- 218.8)	
NGO	17	58.0 (s=99.0)	99.0	28.0	<0.050°	4 (23.5%)	140.0 (s=6.2)	144.0	144.0 (125.3- 162.7)	
Public	38	114.3 (s=142.3)	142.3	77.5	<0.050°	17 (44.7%)	196.1 (s=24.7)	260.0	161.0 (103.2- 218.8)	0.319$
Private	100	146.4 (s=139.8)	139.8	48.5	<0.050°	33 (33.0%)	370.9 (s=110.6)	255.0	162.0 (148.5- 168.4)	0.022$
First medical visit - Hospital admission										
All	173	375.5 (s=3238.4)	168.0	91.0		87 (50.3%)	704.5 (s=488.4)	249.0	167.0 (147.7- 186.3)	
FAP	35	1345.2 (s=7085.3)	255.0	142.0	<0.050*	25 (71.4%)	1924.4 (s= 697.9)	333.0	190.0 (170.4- 209.6)	0.055^
HNL	138	120.69 (s=170.6)	151.5	79.0	<0.050*	62 (44.9%)	212.7 (s= 27.7)	269.0	156.0 (125.1- 186.9)	0.055^
First medical visit - Treatment initiation										
All	176	396.7 (s=3211.9)	193.5	116.5		114 (64.8%)	583.2 (s= 373.2)	248.0	167.0 (144.0- 190.0)	
FAP	36	1319.7 (s=148)	217.5	148.0	<0.050*	28 (77.8%)	1742.3 (s= 1517.6)	314.0	186.0 (134.1- 237.9)	0.094$
HNL	140	151 (s=166.7)	184.0	110.0	<0.050*	86 (61.4%)	205.8 (s= 20.5)	227.0	162.0 (134.7- 189.3)	0.094$
FAP_{PRIV}	29	1659.1 (s=7896.8)	294.5	172.0	<0.050°	22 (75.9%)	2170.6 (s= 1930.7)	341.0	186.0 (155.0- 217.0)	0.173$
HNL_{PRIV}	85	146.0 (s=195.6)	173.0	101.0	<0.050°	47 (50.3%)	218.3 (s= 35.0)	252.0	165.0 (130.3- 199.7)	0.173$
HNL_{PUB}	43	172.16 (s=114.5)	222.0	135.0	<0.050°	33 (76.7%)	207.8 (s= 18.7)	248.0	179 (137.4- 220.6)	0.173$
NGO	18	105.17 (s=55.0)	141.3	101.5	<0.050*	12 (66.7%)	134.6 (s= 12.2)	148.0	113.0 (85.8- 140.2)	0.006$
PUBLIC	44	168.27 (s=116.1)	221.5	132.0	<0.050*	33 (75.0%)	207.8 (s= 18.7)	248.0	179.0 (137.4- 220.6)	0.006$
PRIVATE	114	530.9 (s=3989.8)	192.5	112.5		69 (60.5%)	840.8 (s= 616.3)	272.0	173.0 (152.1- 193.9)	0.006$
	All					**Time interval >60 days**				
Result of diagnostic mammography - Diagnostic result										
All	219	101.6 (s= 65.5)	121.3	45		91 (41.6%)	209.3 (s= 22.6)	274.0	134 (109.9- 158.2)	
FAP	71	153.5 (s=239.9)	160.0	79.0	<0.050*	44 (62.0%)	246.3 (s= 42.0)	288.0	154.0 (120.4- 187.6)	0.135$
HNL	148	77.5 (s=106.9)	85.0	38.5	<0.050*	47 (31.8%)	174.7 (s= 18.2)	252.0	127.0 (112.2-141.8)	0.135$
FAP_{PUB}	11	185.7 (s=176.9)	311.0	122.0	≥0.050*	8 (72.7%)	247.5 (s= 59.9)	311.0	125.0 (0.000- 355.1)	0.580$
HNL_{PUB}	45	99.8 (s=130.8)	127.5	41.0	≥0.050*	19 (42.2%)	205.3 (s= 33.5)	301.0	134.0 (0.000-286.2)	0.580$
FAP_{OUTPUP}	60	149.5 (s=247.9)	154.8	65.0	<0.050°	32 (53.3%)	255.8 (53.6)	288.0	149.0 (107.4- 190.6	0.227$
$FAP_{OUTPRIV}$	77	71 (s=103.9)	77.5	29.0	<0.050°	25 (22.5%)	171.2 (s= 27.0)	188.0	126.0 (73.8- 178.2)	0.227$
HNL_{INT}	45	95.1 (97.5)	127.5	53.0	<0.050°	22 (48.9%)	169.2 (s= 19.6)	264.0	127.0 (97.6- 156.4)	0.227$
Result of diagnostic mammography - Hospital admission										
All	229	132.7 (s= 167.8)	164.0	79.0		142 (62.0%)	194.3 (s= 15.7)	224.0	141.0 (122.5- 159.6)	
FAP_{PRIV}	48	204.2 (s= 255.6)	235.8	119.0	<0.050#	39 (81.3%)	282.5 (s= 54.4)	314.0	164.0 (139.2- 188.8)	0.028$
HNL_{PRIV}	91	123.8 (s= 128.4)	164.0	74.0	<0.050#	78 (85.7%)	176.4 (s= 17.7)	225.0	125.0 (77.7- 172.3)	0.028$
FAP_{PUB}	14	89.6 (s= 49.1)	141.5	76.0	≥0.050*	12 (85.7%)	117.0 (s= 12.9)	146.0	135.0 (50.3- 219.7)	0.136$
HNL_{PUB}	51	103.3 (s= 106.9)	132.0	74.0	≥0.050*	44 (86.3%)	164.0 (s= 21.1)	198.0	118.0 (95.18- 140.8)	0.136$
Result of diagnostic mammography - Treatment initiation										
All	241	153.1 (s= 163.2)	179.0	111.0		191 (79.3%)	182.3 (s= 12.4)	94.0	131.0 (119.9- 142.1)	
Diagnostic result - Treatment initiation										
All	236	62.39 (s= 47.9)	79.8	54.0		99 (42.0%)	101.3 (s= 5.0)	113.0	86.0 (79.04- 93.0)	
NGO	30	53.2 (s= 24.9)	66.8	56.5	≥0.050°	14 (46.7%)	76.6 (s= 4.5)	88.0	69.0 (61.7- 76.3)	0.004$
PUBLIC	61	62.8 (s= 42.1)	79.0	56.0	≥0.050°	23 (37.7%)	102.0 (s= 8.6-)	151.0	86.0 (76.7- 95.3)	0.004$
PRIVATE	145	64.1 (s= 53.5)	85.0	54.0	≥0.050°	62 (42.8%)	106.7 (s= 7.2)	116.0	93.0 (82.4- 103.6)	0.004$

ALL, all patients; FAP, all patients from the FAP; HNL, all patients from HNL; NGO, patients who received help from one of the NGOs; PUBLIC, FAP_{PUB}, HNL_{PUB}, all patients and patients of the FAP and the HNL who performed all diagnostic and other medical exams within the public health service system; patients who received help from one of the NGOs were excluded from the analysis; PRIVATE, FAP_{PRIV}, HNL_{PRIV} all patients and patients of the FAP and the HNL who privately financed a minimum of one diagnostic or other medical service. Patients who received help from one of the NGOs were excluded from this analysis; FAP_{OUTPUP}, patients of the FAP who performed the clinical histopathological exam outsourced in a private laboratory financed by the public health system; $FAP_{OUTPRIV}$, patients of the FAP who privately financed the clinical histopathological exam that was performed in a private laboratory; HNL_{INT}, patients who performed the clinical histopathological exam in the HNL, financed by the public health system; s=standard deviation; p-values for analysis of time intervals of all patients: *Mann-Whitney (U-Test); °Kruskal-Wallis test; #Kolmogorov-Smirnov test; for Kaplan-Meier analysis (Time interval >60 days and >90 days): ^Breslow (Generalized Wilcoxon)-test; $Log Rank (Mantel-Cox)-test.

from NGOs were compared with those who had privately financed one or more diagnostic or medical exams (PRIVATE) and those who exclusively performed these exams within the public health system (PUBLIC; Table 4). Patients who were supported by one of the NGOs and those who used exclusively public diagnostic services without the help of NGOs had a median time of 28.0 and 77.5 days, respectively, between the first presentation and the diagnostic result ($p<0.05$; Table 4). The median time of patients who delayed >60 days during the latter time interval was 144.0 days for the NGO and 162.0 days for the PRIVATE patient groups ($p=0.022$; Table 4). The median time between the first medical visit and the initiation of treatment for the NGO, PUBLIC and PRIVATE groups was 101.05, 132.0 and 112.5 days, respectively ($p<0.05$; Table 4). The median time for patients with a delay of >60 days for the latter time interval was 113.0, 179.0 and 173.0 days for the NGO, PUBLIC and PRIVATE patient groups, respectively ($p=0.006$; Table 4). For the time interval between the results of diagnostic mammography and treatment initiation, the median time for patients with a delay of >60 days was 69.0, 86.0 and 93.0 days for the NGO, PUBLIC and PRIVATE patient groups, respectively ($p=0.004$; Table 4). Other time intervals were not significantly different but were generally shorter for patients who received support from one of the NGOs.

Discussion

To the best of our knowledge this is the first Brazilian study that compared delay of cancer treatment between two public referral centres with integrated and outsourced diagnostic services. Data indicated that publicly financed diagnostic mammography and clinical- histopathological exam are performed faster in the integrated system of the HNL referral centre, compared to the outsourced system of the FAP hospital. There is an ongoing debate in Brazil regarding the privatization of the public health care services.[27] The present study is a contribution to this debate.

Variables that were associated with TTI

Cox regression analysis indicated that prolonged TTI was generally associated with the use of public health services. Women who used principally public health services before disease discovery and at the beginning of patient flow had an increased chance of delay of >90 days between the first medical visit and the initiation of treatment. This finding was also underlined by the observation that women who covered the costs of diagnostic mammography and biopsy on their own had a decreased risk of delay compared to women who used public health services for these exams. In most cases, those women who used a diagnostic service at the beginning of patient flow financed this service on their own. Consequently, the usage of a diagnostic service at the beginning of patient flow also reduced the risk of delay compared to the usage of a public health service. Furthermore, patients who started treatment in a private hospital and continued it in one of both public referral centres also had a decreased delay.

Time intervals and prolonged TTI of all patients

For patients in both referral centres combined, the median time interval between the first medical visit and diagnostic results was 56.0 days. This finding is in contrast to those of earlier studies performed in the states of Rio de Janeiro and Minas Gerais that reported median and mean waiting times of 6.5 months and >6 months, respectively, between the first medical visit and diagnostic confirmation.[16,18] Similar, a study performed in Malaysia revealed a median time interval of 5.5 months for the time between the first medical visit and diagnosis.[31] The present value of 56.0 days was within the median time span ranging from 0.9 to 5.0 months for the time interval between the first medical visit and the completed diagnosis of nine studies from low- and middle-income countries.[32] The present results indicated a delay of >90 days between the first medical visit and the diagnostic results for 34.8% of the patients. In contrast, a recent study performed in Rio de Janeiro revealed a delay of 68.8% among 526 patients ≥90 days between the first medical visit and the diagnosis.[33] Similar to the present results, a study performed in Thailand reported a delay of >90 days for 42% of all patients for this time interval.[34] The median time between the first medical visit and hospital admission and treatment initiation was 91.0 and 116.5 days, respectively. This is in contrast to a recent Portuguese study of 282 patients who had a shorter median delay of 44 days between the first diagnosis and treatment initiation.[35]

The median time between the result of diagnosis and treatment initiation was 54.0 days for 236 patients of both referral centres. Lower median values for this time interval of 0.6 to 1.2 months were reported in eight studies from low- and middle-income countries.[32] A recent study performed in the USA revealed median values of 62.0 and 35.5 days for breast cancer patients of African and Caucasian ancestry.[36] Similar to the present results, in a recent study performed in the state of Ceará, north-eastern Brazil, the median time between diagnosis and hospital admission was 39 and 71.5 days for patients referred by the private and public health system, respectively.[25]

Different time intervals for public and privately financed health services

Consistent with the results of Cox regression analysis, the comparison of time intervals among different patient groups indicated a faster patient flow for women who financed a minimum of one health care service on their own. A prolonged TTI associated with a lack of financial resources was also perceived in recent studies of Mexican breast cancer patients.[7,37] Previous Brazilian studies reported delays in the public health care system compared to privately financed health care.[15,16,19,20] Studies performed in the states of Minas Gerais and in Rio de Janeiro also suggested that the usage of public versus private health services was associated with an advanced stage of disease and a decreased chance of five-year survival.[16,21] In a study that included data from 56,094 women in various Brazilian regions, the authors reported increased delays with respect to the time between diagnosis and treatment initiation for public referrals compared to private one.[33] Long waiting times for specialized medical consultations and diagnostic exams were among the main problems in cancer treatment by public health services.[25,38] These long waiting times can often be the result of a lack of specialized services: waiting times of up to 30 days for specialized services after the detection of the first symptoms were reported.[23] Furthermore, guidelines for referrals or requests for subsidiary exams by health professionals are often missing.[25,38]

Different time intervals among patients in both referral centres

The results indicated remarkable differences in the delays among breast cancer patients in two referral hospitals in urban centres within the same state, located approximately 120 km from each other. Time intervals were generally shorter for patients in the HNL in João Pessoa than for patients in the FAP in Campina Grande.

The comparison of patients who used exclusively public ser-

vices indicated that the chance of prompt TTI was increased among women in the HNL compared to those in the FAP. Furthermore, the patients who performed the clinic-histopathological exam within the public health service system of the HNL had a significantly decreased delay compared to patients in the FAP who also performed it within the public health service system. This finding indicated that the integrated public diagnostic service of the HNL was indeed faster than the outsourced service of the FAP. In the latter case, oncologists of the FAP had to communicate with the staff of private laboratories, whereas in the HNL, the clinic-histopathological exam was directly performed in the pathological sector of the hospital.

Differences in delays between patients of both referral centres were also obvious for patient groups who used one or more privately financed health services. These differences may be attributed to two main explanations. First, in the case of the patients in the HNL, which is in the capital (João Pessoa), services could be more concentrated, such that single health care providers could offer several diagnostic services. Previous studies also found associations between diagnostic delay and an increased number of health care providers used before admission to a specialized health care centre.[6,37] On the one hand, this argument was supported by the fact that patients in the FAP generally used more health care providers on average than those in the HNL. On the other hand, the mean number of privately financed services was nearly identical between both groups of patients. Second, waiting times could be longer in Campina Grande than in João Pessoa due to a lower number of private health care providers. The increased number of health care providers in the capital compared to in Campina Grande could cause shorter waiting times for exams and corresponding results.

NGOs accelerated patient flow

The present data indicated that the work of the three NGOs accelerated patient flow. The median and mean time intervals between the first medical visit and diagnostic results and between the first medical visit and treatment initiation were significantly shorter for patients who received support from the NGOs. As the NGOs paid for biopsies and diagnostic mammograms, this result indicated that the delay observed was primarily a diagnostic delay and that the work of the NGOs reduced it. Members of the NGOs also communicated with oncologists within both referral centres, and the time between the diagnostic result and treatment initiation was shorter for patients who were supported by the NGOs. Therefore, it is plausible that patients who were supported by one of the NGOs also obtained treatment earlier because of better communication mediated by the NGOs. The authors of a previous Brazilian study that focused on the time interval between screening mammography and the treatment initiation of patients in São Paulo identified the absence of coordination of patient flow and social assistance for patients as organizational problems and principal reasons for delays.[12]

Method limitations

The most severe limitation of the present study was the small amount of data. The small numbers increased uncertainty of patient group associated time delays. This issue also hindered the resolution of detailed differences among patients in the FAP and HNL who exclusively used public health care services. Low resolution was further aggravated by missing dates of diagnostic health services, thus reducing the amount of available data for the analysis of each defined time interval. The latter problem was due to the fact that medical records were incomplete and the patient data of both referral centres were not digitalized. Errors may have occurred during the registration of these data in the pathological reports. A further source of error may be attributed to recall bias among the interviewed women about the dates and types of health services. Recall bias may also have been reinforced by the chemotherapeutic treatment of patients. The recruitment of patients was stochastic, but the possibility of a selection bias cannot be eliminated.

The study did not determine in detail why prolonged TTI was less pronounced for patients who used private health care services than for those who used only public services. The performance of privately financed diagnostic services obviously resulted in a remarkable difference in prolonged TTI among patients in the FAP and HNL. The present data did not include information about the specific private health care provider that was used for a determined diagnostic process. Therefore, it was not possible to attribute longer waiting times for a diagnostic service to specific private health care services, and the real cause of different delays among patients in the FAP and HNL who financed diagnostic services privately remained unclear.

Conclusions

The present data indicated that patients who used public diagnostic services had prolonged TTI compared to those who financed these services privately. The TTI was shorter for patients who used private health care services before the diagnosis of disease and at first medical visit and who financed privately diagnostic mammography and biopsy. In general, delay was increased among patients in the FAP compared to those in the HNL in the capital João Pessoa. The results indicated that the integrated clinical histopathological exam in the HNL accelerated patient flow compared to the outsourced exam in the FAP. Furthermore, the difference in the delay among patients of both referral centres was also caused by distinct patient flow within the privately financed health sector. The results clearly indicated that the NGOs' donation of biopsies and diagnostic mammograms and strong communication skills accelerated patient flow.

The present data indicated that there could be a reduction in TTI via the concentration of diagnostic services in the state of Paraíba. The design of future studies should further address the question of whether the concentration of diagnostic services in public referral centres and private laboratories can reduce TTI among breast cancer patients. Furthermore, it should be elucidated whether an increased number of private health care providers can help to reduce the waiting time for diagnostic services.

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Key words: Breast cancer; patient flow; treatment delay; public and private diagnostic services; outsourced diagnostic services.

Contributions: LSSA, TTMS, MECO, KALG and ARAPS collected data from medical records, conducted the interviews and tabulated the data. TAO and MW performed the data analysis. MW designed the study and drafted the manuscript. LSSA critically reviewed the manuscript. All authors read and approved the final manuscript.

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