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Factors associated with delays in time to treatment initiation in Colombian women with cervical cancer: A cross-sectional analysis

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ABSTRACT

Cervical cancer (CC) is one of the leading causes of morbidity in upper-middle income countries such as Colombia. Several studies have reported poor prognosis when treatment is delayed. We aimed to describe the factors associated with delays in time to treatment initiation (TTI) in Colombian women with CC. Cross-sectional analysis including newly diagnosed cases of CC during 2018 and reported to the National Administrative Cancer Registry. TTI was defined as days from diagnosis to the first treatment (chemotherapy, radiation, or surgery). Linear and multinomial logistic regression models were estimated to analyze the association of interest. 1,249 new cases of CC were analyzed (26.98% *in-situ* and 40.11% locally advanced). The median age was 46 years (IQR: 36–58). Median TTI was 71 days (IQR: 42–105), varying from 70 days (IQR: 43–106) among the surgery group to 76 days (IQR: 41–118) in women under chemotherapy. Only 12.41% were treated within 30 days from diagnosis. TTI was significantly longer in women with state insurance ($\beta = 18.95$ days, 95% CI: 11.77–26.13) compared with those insured by the third payer. Women from the Pacific and Eastern regions also had a significantly longer TTI than those living in the capital of Colombia. Age, health insurance, region of residence, and stage at diagnosis were associated with TTI longer than 45 days in the multinomial model. We concluded that demographic variables (age, region of residence, and health insurance) which are proxies of social disparities and poor access to quality health care services, were associated with delays in TTI.

1. Background

Cervical cancer (CC) is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women worldwide. In 2018, there were an estimated 569,847 new cases of CC and 311,365 deaths from the disease worldwide. WHO has called for action for the elimination of CC as a public health problem especially in low and middle Human Development Index (HDI) countries, where it is the second most common cancer, affecting significantly countries on the African continent, especially in sub-Saharan Africa, South-Eastern Asia, and Latin America and the Caribbean, while in countries with high HDI values, incidence and mortality rates are declining (WHO Iarc, 2018; Wild et al., 2020). However, even within countries, differences due to socioeconomic or racial disparities in disease burden and mortality have been observed, as in the United States, a country with a high HDI, where CC incidence and mortality among African American women is twice than in white women. These disparities are explained by the presence of inequalities in access to primary prevention, screening, and treatment services. Geographic location can also play a role. Women living in rural areas have the lowest screening rates and the highest incidence rates of CC in both, low and high HDI countries. It is known that women in countries and areas with lower HDIs are currently the least likely to have

Abbreviations: HDI, Human Development Index; GLOBOCAN, The Global Cancer Observatory; NACR, National Administrative Cancer Registry; CAC, Cuenta de Alto Costo (High Cost Diseases Fund); DANE, Departamento Administrativo Nacional de Estadística (Department for National Statistics); IQR, Interquartile range.

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access to or complete doses of HPV vaccine (Wild et al., 2020).

Delays in accessing timely and appropriate treatment are among the various conditions that result in poor prognosis (Ferreira da Silva et al., 2019; Ramey et al., 2018; Perri et al., 2014). Treatment of CC usually consists of chemoradiation or radical hysterectomy/trachelectomy with lymph node dissection in early stages and chemoradiation in advanced stages. Treatment may be adjusted according to the patient's health conditions, age, desire for parity, or comorbidities (Ferreira da Silva et al., 2019). Delays in access to treatment are given for different reasons such as second medical or pathological opinions, or geographical, administrative, economic, or cultural barriers, substantially affect the living conditions of women with this disease because time intervals are important to ensure the effectiveness of treatment (Ferreira da Silva et al., 2019; Chen et al., 2019). Delays of more than three months in therapeutic cancer care could decrease the prognosis and increase morbidity, reduction of survival is a subject of discussion due to differences in the results of several studies (Ferreira da Silva et al., 2019; Ramey et al., 2018; Perri et al., 2014), though, analyses of delay of treatment for women with CC have been more limited in scope (Ramey et al., 2018).

In Colombia, despite the progress made in the country and the high health coverage that exists, it is not unrelated to the situation mentioned above; it is a disease that continues to have a great impact on morbidity and mortality and is also the second most common type of cancer among women in the country. Further, according to The Global Cancer Observatory (GLOBOCAN), by 2018 CC was the sixth cause of cancer-related death in Colombia (GLOBOCAN, 2018).

The High Cost Diseases Fund (CAC, by its acronym in Spanish) is the entity responsible in the country for managing the National Administrative Cancer Registry (NACR), based on the information provided mainly by health insurers, as well as a small proportion of the uninsured population, which annually monitors the situation of CC, including the time that elapses once the diagnosis has been confirmed until treatment for CC begins. Therefore, we aimed to describe the associated factors to delays in time to treatment initiation (TTI) in Colombian women with CC during 2018.

2. Methods

2.1. Data sources

We performed a cross-sectional analysis using data provided by the NACR managed by the CAC. The NACR was established in 2012 by the Ministry of Health of Colombia (Ministry of Health and Social Protection R of C. Resolution 4496, 2012) to evaluate the demographic, clinical, and administrative situation of people with cancer through the annual report of 134 variables. It is an administrative and passive registry with a national scope due to the fact of ~97% of the Colombian population is insured to the national health system (Ministry of Health and Social Protection R of C. Health insurance coverage in Colombia [Internet]., 2020) and must be reported to the NACR by its health insurers (Ministry of Health and Social Protection R of C. Resolution 4496, 2012). Taking into account the above, it provides reliable information about real-life patterns of cancer distribution and risk management across the country.

Since its first measurement in 2015, 279,155 people with cancer have been reported. Each record is identified with a unique code to protect the personal information of the participants and allow the follow-up within the cohort. Data on prevalent cases are updated every year, while for new cases, full registration is completed.

On the other hand, the quality of the information was assured by a well-established data monitoring process, which was carried out in two steps: a prior identification of mistakes in the reporting process through a systematized algorithm, and once the structure and consistency of the variables were approved, the information was audited and compared with the health clinical records. All newly diagnosed and those previously diagnosed who were treated during the period were audited, otherwise, if they did not receive any treatment a random sample was taken.

2.2. Eligibility of participants

All women newly diagnosed with CC (International Classification of Diseases code 10 (ICD-10): C53 to D06) and reported to the NACR from January 2, 2018, to January 1, 2019, were eligible. CC diagnosis could be clinical or histopathological and it was confirmed by the data monitoring process previously described. A total of 1,930 new cases of CC were identified. Of these, 681 (35.28%) were excluded: 619 had no information about treatment (people diagnosed close to the cut-off date or the data was not available on clinical records) and 62 received palliative treatment rather than with curative purposes. Thus, the studied population included 1,249 women with CC.

2.3. Dependent variable

TTI was calculated from the date of diagnosis (clinical or histopathological) to the date of surgery, chemotherapy, or radiation. To establish the diagnosis, the date of the pathology report was considered as the first option, when it was not available, the date in which the physician made the clinical diagnosis and defined the treatment was used. TTI was analyzed both, as a continuous variable and as a categorical variable based on the literature: 30 days or less, 31–45 days and, more than 45 days (Perri et al., 2014).

2.4. Demographic and clinical variables

Demographic information included age, ethnicity, geographical region of residence, and health insurance. Regarding ethnicity, we used a proxy that classified women in indigenous, Romanis, blacks, or whites from the self-designation. Geographical regions were defined by the Department for National Statistics (DANE, by its acronym in Spanish), from Colombia's 32 departments according to the gross domestic product, identifying 6 regions: Bogotá C.D., Central, Eastern, Pacific, Caribbean, and Other departments (Fig. S1 of Supplementary Material). Moreover, health insurance was classified according to the funding source as follows: third payer, state insurance, especial and exception insurance and, a minimum proportion as uninsured. For this analysis, we reclassified the variable as third payer, state insurance, and other.

In respect of clinical data, the stage at diagnosis (0, I, II, III, and IV) was classified based on the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) system (Bhatla et al., 2018) and then were grouped as *in-situ* (0), local early stages/bulky (stages IA1 to IIA2), locally advanced (stages IIB2-IIIA) and metastatic (IIIB-IVB) (Marth et al., 2017). Histology was grouped as squamous carcinoma, adenocarcinoma/adenosquamous carcinoma, and no specified (Ferreira da Silva et al., 2019; Perri et al., 2014). Finally, treatment was grouped as surgery, radiation, or chemotherapy.

2.5. Statistical analysis

We performed a descriptive analysis summarizing continuous variables as medians and interquartile range (IQR) and categorical variables as absolute values and percentages. The differences in demographic and clinical variables according to the wait-time groups were evaluated using the Kruskal-Wallis test and X^2 test for continuous and categorical data, respectively. Associated factors were evaluated through both, bivariate and multivariate linear or multinomial logistic regression models, depending on the outcome (continuous or categorical, respectively). In the case of multinomial models, TTI $\leq$ 30 days was considered the reference category. Variables with less than 0.200 p-value, in the bivariate analysis, as well as those we considered important according to the directed acyclic graph method and the literature review were retained in the final models. R squared and Hosmer and Lemeshow tests

were used to verify the goodness of fit of linear and multinomial models, respectively. Adjusted coefficients (β) and odds ratio (OR) and their 95% confidence intervals were reported to determine the magnitude and direction of associations between covariates and the TTI. We also performed a sensitivity analysis excluding women diagnosed as *in-situ* to verify the consistency of our findings. *p*-values <0.05 (two-tailed) were considered statistically significant and all statistical analyses were performed in Stata version 13 (StataCorp LP, College Station, Texas, USA).

3. Results

3.1. Demographic and clinical characteristics of participants

A total of 1,249 women newly diagnosed with CC were analyzed. Demographic and clinical variables for all women as well as comparing by wait-time groups are presented in Table 1. The median age was 46 years (IQR: 36–58). Most women (94.16%) were self-identified as white, 50.04% belonged to the state insurance and 25.62% lived in the Central region followed by Bogotá, C.D. (21.86%). Regards clinical characteristics, 40.11%, and 27.86% were diagnosed in advanced and early stages, respectively. About 27.00% were classified as *in-situ* tumors and 56.20% were squamous cell carcinoma. The most frequent treatment was surgery (47.16%) followed by radiation (42.43%). The median TTI was 71 days (IQR: 42–105), varying from 70 days (IQR: 43–106) among the surgery group to 76 days (IQR: 41–118) in those women under chemotherapy. Only 12.41% were treated within 30 days from diagnosis. The shorter TTI according to the stage at diagnosis was observed in women with metastasis (median: 34 days, IQR: 19–58).

When comparing by wait-time groups, we found statistically significant differences in age, health insurance, stage at diagnosis, and type of treatment distribution. Also, by using the suitable hypothesis tests, women in the lowest TTI group, were slightly older, affiliated to the state insurance, diagnosed in advanced stages, and treated with surgery than those with the longest TTI (Table 1).

3.2. Factors associated with TTI (continuous outcome)

Age, health insurance, and region of residence were associated with the TTI in the multivariate linear regression model. TTI was significantly longer in women living in the Pacific region (β = 11.82 days, 95% CI: 1.48–22.16, $p = 0.025$), compared to Bogotá, the capital of Colombia. The same association was observed for women living in the Eastern region (β = 11.72 days, 95% CI: 0.11–23.34, $p = 0.048$). Furthermore, receiving attention under the state insurance was associated with a significantly longer TTI than those insured by the third payer (β = 18.95 days, 95% CI: 11.77–26.13, $p < 0.001$). On the other hand, age was associated with a slight but significant decrease in the TTI (β = 0.25 days, 95% CI: 0.01–0.48, $p < 0.039$) (see Table 2).

3.3. Factors associated with delays in TTI (categorical outcome)

In the final multinomial logistic regression model, age, health insurance, region of residence, and stage at diagnosis were significantly associated with a TTI longer than 45 days. We found that compared to women affiliated to the third payer insurer, those with state insurance had a significantly higher odds of delay in TTI (more than 45 days) relative to women who had a timely treatment (OR = 2.46, 95% CI: 1.59, 3.80, $p < 0.001$). Regarding region of residence, living in the Caribbean region rather than Bogotá was associated with a significant decrease of 59% in odds of having delays in TTI related to those who received a timely treatment (OR = 0.41, 95% CI: 0.23, 0.74, $p = 0.003$). Finally, we found a strong, negative, and significant association between metastasis at diagnosis and delays in TTI, related to women who were treated opportunely (OR = 0.10, 95% CI: 0.01, 0.86, $p = 0.036$) (see Table 3).

Fig. 1 shows the predicted probabilities of receiving treatment for each wait-time group, according to health insurance. As we previously mentioned, women under state insurance were above 80% more likely to receive the first treatment after an average of 45 days, compared with those affiliated to the third payer (~70%).

Finally, we repeated the analysis excluding women diagnosed with *in-situ* tumors, and important differences in the direction, magnitude, and statistical significance of the associations were not observed.

Table 1
Demographic and clinical characteristics of women newly diagnosed with cervical cancer by time to treatment initiation groups, Colombia 2018.

Variable[1]	Total (n = 1,249)	Time to treatment initiation			*p*-value[2]
		≤30 days (n = 155)	31–45 days (n = 140)	>45 days (n = 954)	
Age (years)	46 (36–58)	43 (34–54)	49 (36–63)	46 (37–57)	**0.004**
Ethnicity					0.199
White	1,176 (94.16)	147 (94.84)	130 (92.86)	899 (94.23)	
Indigenous	45 (3.60)	3 (1.93)	4 (2.86)	38 (3.99)	
Black	28 (2.24)	5 (3.23)	6 (4.28)	17 (1.78)	
Health insurance					**0.017**
State insurance	625 (50.04)	59 (38.06)	65 (46.43)	501 (52.52)	
Third payer	593 (47.48)	91 (58.71)	71 (50.71)	431 (45.18)	
Other	31 (2.48)	5 (3.23)	4 (2.86)	22 (2.30)	
Region of residence					0.168
Central	320 (25.62)	36 (23.23)	42 (30.00)	242 (25.37)	
Bogotá, C.D.	273 (21.86)	36 (23.23)	26 (18.57)	211 (22.12)	
Caribbean	245 (19.62)	41 (26.45)	33 (23.57)	171 (17.92)	
Pacific	232 (18.57)	21 (13.55)	20 (14.29)	191 (20.02)	
Eastern	139 (11.13)	18 (11.61)	15 (10.71)	106 (11.11)	
Other	40 (3.20)	3 (1.93)	4 (2.86)	33 (3.46)	
Stage at diagnosis					**0.044**
In-situ	337 (26.98)	34 (21.94)	27 (19.29)	276 (28.93)	
Local early/bulky	348 (27.86)	40 (25.81)	42 (30.00)	266 (27.88)	
Locally advanced	501 (40.11)	69 (44.52)	66 (47.14)	366 (38.36)	
Metastatic	5 (0.41)	2 (1.29)	1 (0.71)	2 (0.22)	
Unknown	58 (4.64)	10 (6.44)	4 (2.86)	44 (4.61)	
Histology					0.604
Squamous cell carcinoma	702 (56.20)	88 (56.77)	86 (61.43)	528 (55.35)	
Adenocarcinoma	204 (16.33)	24 (15.48)	21 (15.00)	159 (16.67)	
Other	330 (26.42)	42 (27.10)	30 (21.43)	258 (27.04)	
Unknown	13 (1.05)	1 (0.65)	3 (2.14)	9 (0.94)	
First treatment					**0.039**
Surgery	589 (47.16)	66 (42.58)	51 (36.43)	472 (49.48)	
Radiation	530 (42.43)	71 (45.81)	70 (50.00)	389 (40.78)	
Chemotherapy	130 (10.41)	18 (11.61)	19 (13.57)	93 (9.74)	

[1] Values are absolute values (percentages) or medians (IQR).
[2] Proportions were compared by a X^2 test and Kruskal-Wallis test was used for continuous variables.

4. Discussion

To the best of our knowledge, this is the first study focused on identifying factors associated with TTI in women newly diagnosed with

Table 2
Crude and multivariate-adjusted average changes in time to treatment initiation in women newly diagnosed with cervical cancer, Colombia 2018.

Variable[1]	Crude β (95% CI)	Adjusted[1] β (95% CI)
Age (years)	0.22 (−0.01, 0.44)	**0.25 (0.01, 0.48)**
Ethnicity		
Indigenous	Ref.	Ref.
White	−19.05 (−34.87, −3.23)	−7.89 (−23.75, 7.95)
Black	−14.04 (38.71, 10.64)	−2.72 (−27.42, 21.97)
Health insurance		
Third payer	Ref.	Ref.
State insurance	18.66 (12.48, 24.84)	**18.95 (11.77, 26.13)**
Other	−11.91 (−33.27, 9.45)	−11.25 (−32.78, 10.29)
Region of residence		
Bogotá, C.D.	Ref.	Ref.
Central	1.06 (−8.19, 10.31)	−1.08 (−10.47, 8.31)
Caribbean	4.74 (−4.89, 14.37)	−6.40 (−16.92, 4.13)
Pacific	19.78 (9.76, 29.78)	**11.82 (1.48, 22.16)**
Eastern	13.04 (1.36, 24.73)	**11.72 (0.11, 23.34)**
Other	25.30 (6.86, 43.74)	16.31 (−2.34, 34.97)
Stage at diagnosis		
In-situ	Ref.	Ref.
Local early/bulky	0.27 (−8.61, 9.15)	4.91 (−4.45, 14.27)
Locally advanced	−0.36 (−8.54, 7.81)	−1.12 (−12.41, 10.17)
Metastatic	−44.43 (−90.45, 1.59)	−39.74 (−85.49, 6.01)
Unknown	2.13 (−13.77, 18.03)	0.65 (−15.99, 17.29)
First treatment		
Chemotherapy	Ref.	Ref.
Surgery	−7.58 (−17.83, 2.66)	−2.41 (−14.81, 9.99)
Radiation	−10.51 (−20.59, −0.43)	−8.46 (−18.49, 1.57)

[1] Final model was adjusted by age (continuous), ethnicity (categorical), health insurance (categorical), region of residence (categorical), stage at diagnosis (categorical) and first treatment (categorical).

Table 3
Multivariate-adjusted odds ratio for wait-time groups in women newly diagnosed with cervical cancer, Colombia 2018.

Variable[1]	Adjusted OR (95% CI) [1]	
	TTI 31–45 days	TTI > 45 days
Age (years)	**1.03 (1.01, 1.05)**	**1.03 (1.01, 1.04)**
Health insurance		
Third payer	Ref.	Ref.
State insurance	1.50 (0.85, 2.64)	**2.46 (1.59, 3.80)**
Other	1.05 (0.26, 4.32)	1.02 (0.35, 2.93)
Region of residence		
Bogotá, C.D.	Ref.	Ref.
Central	1.41 (0.70, 2.84)	0.98 (0.58, 1.66)
Caribbean	0.67 (0.30, 1.49)	**0.41 (0.23, 0.74)**
Pacific	1.01 (0.44, 2.34)	0.99 (0.54, 1.83)
Eastern	1.16 (0.49, 2.76)	0.98 (0.52, 1.84)
Other	1.35 (0.26, 6.84)	1.14 (0.32, 4.09)
Stage at diagnosis		
In-situ	Ref.	Ref.
Local early/bulky	1.06 (0.51, 2.19)	0.87 (0.51, 1.49)
Locally advanced	0.69 (0.28, 1.65)	1.21 (0.62, 2.39)
Metastatic	0.31 (0.02, 4.14)	**0.10 (0.01, 0.86)**
Unknown	0.34 (0.09, 1.32)	0.49 (0.20, 1.15)
First treatment		
Chemotherapy	Ref.	Ref.
Surgery	0.65 (0.25, 1.69)	1.26 (0.60, 2.63)
Radiation	0.83 (0.39, 1.76)	1.07 (0.59, 1.93)

[1] Final model was adjusted by age (continuous), health insurance (categorical), region of residence (categorical), stage at diagnosis (categorical) and first treatment (categorical). Wait-time category of reference was TTI ≤ 30 days which is considered timely.

CC conducted in Colombia. The overall median TTI was 71 days, varying from 70 to 76 days in those who were treated with surgery or chemotherapy, respectively. Demographic variables (age, region of residence, and health insurance) which are proxies of social disparities and poor access to quality health care services, were associated with TTI in both linear and multinomial models. Regarding clinical characteristics, metastasis at diagnosis was associated with delays in TTI longer than 45 days in the multinomial model.

Our findings point out that less than 15% of the study population was treated within 30 days from diagnosis. The above represents a concerning scenario due to evidence suggests that delays in TTI have been associated with poor prognosis and worse survival (Chen et al., 2019; Choan et al., 2005; Nascimento and Azevedo e Silva, 2015) and their negative impact could be higher in low-middle income countries where research studies about this topic are also limited.

The median TTI estimated in our study was more than double the goal established in the protocol for public health surveillance and risk control of breast and cervical cancers in Colombia that is less than 30 days (Jimenez Herrera, 2018). This protocol was proposed within the framework of the 10-year cancer control plan to decrease cancer burden through early detection, treatment, rehabilitation, and palliation by reducing health disparities in access and treatment (Sardi et al., 2019). Despite the above, our results suggest that targeted interventions are required to guarantee a timeless treatment and prevent gaps in care from widening over time.

When comparing the median TTI we found, it was lower than the estimated in Brazil (114 days) (Ferreira da Silva et al., 2019) and Taiwan (Chen et al., 2019), but longer than the observed in Israel (Perri et al., 2014). Regards factors associated with delays in TTI, the evidence is limited. We identified demographic variables (age, region of residence, and health insurance) as the main predictors for TTI in Colombian women with CC. A strong direct and statistically significant association was found in women affiliated to state insurance when the outcome was analyzed as a continuous or categorical variable. However, in Taiwanese women with CC, health insurance was not associated with delays in TTI (Shen et al., 2016). In other contexts and types of cancer, such as breast cancer, there have been identified that women with public or no insurance and with low socioeconomic status tend to have longer treatment delay (Ramey et al., 2018; Smith et al., 2013; Ashing-Giwa and Rosales, 2013).

Delays in TTI observed in women with state insurance in Colombia are the result of a fragmented administrative health care system, which exhibits wider gaps in people with insurance subsidized by the government. It has been identified as the most significant barrier for an effective access to cancer diagnosis and treatment in the country (Sardi et al., 2019). Further, health insurance is a proxy of socioeconomic conditions, and it is well known that lower socioeconomic status contributes to and exacerbates healthcare problems and explains the wide variation in cancer access in the Americas and within the countries (Gribble et al., 1993).

Consistent with the above, the linear regression model showed strong, positive, and statistically significant associations between Pacific and Eastern regions with longer treatment delay. Taking into account that Colombian regions are grouped based on the gross domestic product, they are a proxy of social and economic development. In fact, in those regions, there are a limited number of centers and trained personnel and, usually, people have to be transfered to more specialized centers, mainly located in the center or north of the country.

In respect of age, our findings are consistent with the estimated in women with CC from Brazil (Ferreira da Silva et al., 2019) and Taiwan (Shen et al., 2016), where a direct association was observed. Comparable associations have been identified in previous studies concluding that the rate of treatment refusal increases with age (Jassem et al., 2014; Germann et al., 2005; Ward et al., 2013).

Despite we found differences in staging at diagnosis by wait-time groups, they were no longer significant when adjusting for potential

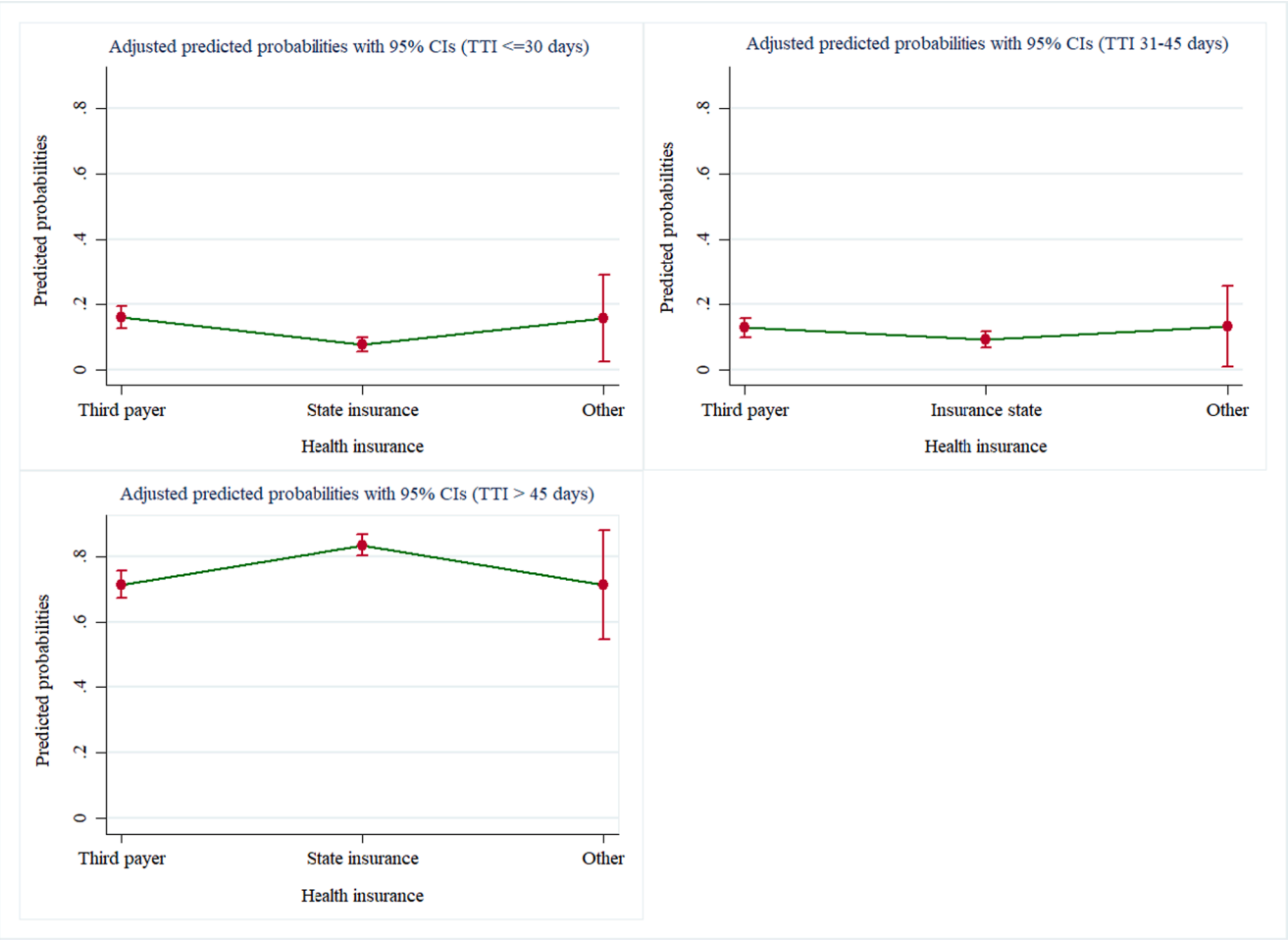

Fig. 1. Predicted probabilities of being in a wait-time group by health insurance in women newly diagnosed with cervical cancer, Colombia 2018. Predicted probabilities were estimated after the final multinomial logistic regression model for each wait-time group, according to health insurance. Predicted probability of having a time to treatment initiation longer than 45 days was higher in those women affiliated to the state insurance compared to those under the third payer o other insurance.

predictors, except for metastasis at diagnosis which was negatively associated with TTI longer than 45 days, related to TTI less than 30 days. Evidence from published studies has highlighted variables such as stage at diagnosis and treatment protocol as predictors for treatment delay (Ferreira da Silva et al., 2019; Shen et al., 2016). Shen et al. (2016) identified that the odds of treatment delay significantly increased with the increasingly advanced cancer stage. Otherwise, the evidence is inconsistent and some studies have found earlier stage was associated with longer TTI (Ramey et al., 2018). According to that, our findings did not show a homogeneous pattern across the stages of diagnosis.

When comparing the different types of treatment contemplated (surgery, chemotherapy, or radiotherapy), none was associated with longer TTIs than the other, taking into account that treatment depends on the stage of the disease. Similar findings are mentioned in the Brazilian publication, in which the median time from diagnosis to treatment initiation presented no significant variation according to the type of first treatment (surgery or radiation), although, the prevalence of treatment delay was greater than 80% in the surgery/radiation group. Likewise, the chemoradiotherapy protocol group had a higher probability of treatment delay than those treated with surgery alone or surgery plus radiation (Ferreira da Silva et al., 2019).

It is important to mention that treatment protocols may include one or more types of therapy and even different technologies which may shorten or lengthen times, an example of this is the study conducted in the United States which found that chemotherapy plus radiotherapy presented shorter times than radiotherapy alone, and in terms of techniques, intensity-modulated radiation therapy (IMRT) was associated with an increase in TTI versus non-IMRT (Ramey et al., 2018).

It is necessary to continue with similar studies that deepen in the different unique treatments or concurrent, as well as the inclusion of the various technologies available.

4.1. *Strengths and limitations*

The current analysis has important strengths, including the large completeness of the NACR, which guarantees the external validity and utility of our findings in the decision-making process at national and regional levels. This fact provides a unique opportunity to translate our findings directly into practice. Also, to our knowledge, it is the first approach to identify factors related to TTI in women with CC in Colombia using national data provided by health care insurers and providers, which allow the stakeholders to identify the gaps for effective cancer access and treatment within the framework of the real scenario of health care services. Furthermore, the accuracy and quality of the information of all new cases were verified by a data monitoring process.

On the other hand, considering that information was recorded for administrative purposes mainly, some limitations must be addressed. First, the passive case reporting by the health insurers could lead to under-reporting. In any case, it would be a small proportion because the reporting process is mandatory. The above means that the NACR data is

not collected directly from the patient or clinician; instead, it is reported by the insurers and later confirmed in medical records or other administrative sources (pharmacy, billing, and national databases). The cross-sectional nature of the analysis does not allow establishing the causality of the associations. Moreover, we lacked information about the socio-economic profile, lifestyle, comorbidities, as well as installed capacity of health services, instead, we included the best proxies available in the final models. Finally, information bias cannot be ruled out because clinical records are the primary data source and they may be subject to error.

4.2. Conclusions

Among women with a newly confirmed diagnosis of CC, treated within the framework of the Colombian health system we found a median TTI of 71 days and less than 15% had the first treatment within 30 days from diagnosis. Demographic variables (age, living in the Pacific or Eastern regions, and state insurance) which are proxies of social disparities and poor access to quality health care services, were positively associated with delays in TTI in our study population. These findings have public health relevance in providing an initial approach to identify gaps in cancer treatment access and their variability by region and health insurance. Our results should be confirmed by using longitudinal analysis, including variables related to sociodemographic, lifestyle, and healthcare access conditions instead of proxies.

Ethics approval and consent to participate

Because the present analysis was performed with secondary data sources, it has no risk for participants and informed consent or ethics approval was not required. Information was collected and analyzed following international standards (The Declaration of Helsinki, The Belmont Report and The International Guidelines prepared by the Council for International Organizations of Medical Sciences (CIOMS)), as well as national regulations (Resolution 8430 of 1993, stated by The Colombian Health Ministry) for conducting human research which stated that due the nature of the NACR and its direct regulation by the state, an ethics approval was not necessary. Confidentiality was guaranteed throughout the information processing (reporting, managing, analysis, and publication). All records were anonymized before the analysis. Furthermore, access to data was restricted to the research team and the results only can be used for approved research or academic purposes.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due they are owned and managed by the Colombian health system but are available from the corresponding author on reasonable request.

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Authors contributions

LA and AMV had the research idea. Analyses were performed by JAHV. The first draft of the manuscript was written by JAHV and PXRB. JAG wrote about the clinical aspects to support the discussion. All authors reviewed the final version.

This article is an original research work and all authors have seen and approved the final version of the manuscript. We declare that it hasn't been published before, as well as not being considered for publication in a different journal.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2021.100697.

References

Ashing-Giwa, K., Rosales, M., 2013. Evaluation of therapeutic care delay among Latina- and European-American cervical cancer survivors. Gynecol. Oncol. [Internet]. 128 (2), 160–165. Available from: https://doi.org/10.1016/j.ygyno.2012.11.015.

Bhatla, N., Aoki, D., Nand, D., Sankaranarayanan, R., 2018. Cancer of the cervix uteri. Int. J. Gynecol. Obs. 143 (2), 22–36.

Chen, C.P., Kung, P.T., Wang, Y.H., Tsai, W.C., 2019. Effect of time interval from diagnosis to treatment for cervical cancer on survival: A nationwide cohort study. PLoS One 14 (9), 1–15.

Choan, E., Dahrouge, S., Samant, R., 2005. Radical radiotherapy for cervix cancer: the effect of waiting time on outcome. Int. J. Radiat. Oncol. Biol. Phys. 61, 1071–1077.

Ferreira da Silva, I., Ferreira da Silva, I., Koifman, R.J., 2019. Cervical cancer treatment delays and associated factors in a cohort of women from a developing country. J. Glob. Oncol. 5, 1–11.

Germann, N., Haie-Meder, C., Morice, P., Al, E., 2005. Management and clinical outcomes of pregnant patients with invasive cervical cancer. Ann. Oncol. 16, 397–402.

GLOBOCAN, 2018. Cancer fact sheets: Colombia [Internet]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/170-colombia-fact-sheets.pdf.

Gribble, J., Preston, S., 1993. The epidemiological transition: policy and planning implications for developing countries—workshop proceedings. In: Press, N.A. (Ed.), Washington DC.

Jassem, J., Ozmen, V., Bacanu, F., Al, E., 2014. Delays in diagnosis and treatment of breast cancer: a multinational analysis. Eur. J. Public Heal. 24 (5), 761–767.

Jimenez Herrera, M.P., 2018. Cáncer de Mama y Cuello Uterino. Inf. Even [Internet] 03, 2–15. Available from: https://www.ins.gov.co/buscador-eventos/Informesdeevento/CÁNCER DE MAMA Y CUELLO UTERINO SEMESTRE I 2018.pdf.

Marth, C., Landoni, F., Mahner, S., McCormack, M., Gonzalez-Martin, A., Colombo, N., et al., 2017. Cervical cancer: ESMO clinical practice guidelines for clinical practice guidelines. Ann. Oncol. 28 (4), 72–83.

Ministry of Health and Social Protection R of C. Health insurance coverage in Colombia [Internet]. 2020. Available from: https://www.minsalud.gov.co/proteccionsocial/Paginas/cifras-aseguramiento-salud.aspx.

Ministry of Health and Social Protection R of C. Resolution 4496, 2012 [Internet]. Bogotá D.C.; 2012. 1–7 p. Available from: https://cuentadealtocosto.org/site/wp-content/uploads/2019/10/Resolucion-4496-de-2012.pdf.

Nascimento, M.I. do, Azevedo e Silva, G., 2015. Efeito do tempo de espera para radioterapia na sobrevida geral em cinco anos de mulheres com câncer do colo do útero, 1995-2010. Cad Saude Publica 31(11), 2437–2448.

Perri, T., Issakov, G., Ben-Baruch, G., Felder, S., Beiner, M.E., Helpman, L., et al., 2014. Effect of treatment delay on survival in patients with cervical cancer a historical cohort study. Int. J. Gynecol. Cancer 24 (7), 1326–1332.

Ramey, S.J., Asher, D., Kwon, D., Ahmed, A.A., Wolfson, A.H., Yechieli, R., et al., 2018. Delays in definitive cervical cancer treatment: An analysis of disparities and overall survival impact. Gynecol. Oncol. [Internet]. 149 (1), 53–62. https://doi.org/10.1016/j.ygyno.2017.12.010.

Sardi, A., Orozco-Urdaneta, M., Velez-Mejia, C., Perez-Bustos, A.H., Munoz-Zuluaga, C., El-Sharkawy, F., et al., 2019. Overcoming barriers in the implementation of programs for breast and cervical cancers in Cali, Colombia: A pilot model. J. Glob. Oncol. 2019 (5), 1–9.

Shen, S.C., Hung, Y.C., Kung, P.T., Yang, W.H., Wang, Y.H., Tsai, W.C., 2016. Factors involved in the delay of treatment initiation for cervical cancer patients: A nationwide population-based study. Med (United States) 95 (33).

Smith, E., Ziogas, A., Anton-Culver, H., 2013. Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. JAMA Surg. 148 (6), 516–523.

Ward, B.M.M., Ullrich, F., Matthews, K., Rushton, G., Goldstein, M.A., Bajorin, D.F., et al., 2013. Who does not receive treatment for cancer? J. Oncol. Pr. 9 (1), 20–26.
WHO Iarc, 2018. Cancer fact sheets: Cervix uteri. Globocan 2018 (876), 6–7.
Wild, C.P., Weiderpass, E., Stewart, B.W., 2020. World cancer report: cancer research for cancer prevention. World Health Organization, International Agency for Research on Cancer, 1–613 p.