Clinical and epidemiological profile of Central-Western region of Brazil leprosy patients

Perfil clínico e epidemiológico dos pacientes com hanseníase da região Centro-Oeste do Brasil

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ABSTRACT

Leprosy is a chronic bacterial granulomatous disease that affects skin and peripheral nerves and shows slow progression. This study was to trace the epidemiological and clinical profile of leprosy among cases reported in the Information System for Notifiable Diseases in Anápolis, Goiás, Central-West region of Brazil. This is an epidemiological, descriptive and a cross-sectional study. Between January 2011 and December 2016, assistance was provided to 484 patients with leprosy. Among the patients, 59.5% male and the most prevalent age group was between 20-40 years old. Brown population in 47.3% of the cases and 51.7% of the patients completed elementary education. The majority of the cases were multibacillary and Virchowian clinical forms were prevalent, with zero degree of disability detected in 79.56% of the patients. There was no death due to leprosy during the study period. The epidemiological data indicates that a greater integration between the population and primary care must be encouraged, a crucial step for health education and strategies in order to combat the disease.

Keywords: Mycobacterium leprae, Hansen's disease.

1. INTRODUCTION
Leprosy (also called Hansen's disease) is a chronic bacterial granulomatous disease that affects skin and peripheral nerves and shows slow progression. The etiologic agent is the bacillus Mycobacterium leprae (Costa et al., 2019). This pathogen is an intracytoplasmic parasite of macrophages with high infectivity and low pathogenicity. The disease has great potential to cause physical disabilities that progress to severe deformities (Duarte-Cunha et al., 2012; Matos et al., 2018). Transmission occurs through direct person-to-person contact (Moreira et al., 2014). Physical disabilities lead to problems such as reduced work ability, limitation of social life and psychological problems (Baialardi, 2007; Miguel et al., 2017).

Leprosy is a public health problem in at least 10 countries, being endemic in India, Brazil, Madagascar, Mozambique, Nepal and Tanzania (Alencar et al., 2012; Gracie et al., 2017). Data from the World Health Organization (WHO, 2017; 2018) highlighted India and Brazil as the countries with the highest number of cases in the world. Brazil had a general detection coefficient of 15.44 cases per 100,000 inhabitants in 2013, which is high in comparison with other countries in the world (Brasil, 2018a). Brazil has the highest burden of the disease in the Americas, comprising 93.8% of the cases reported in the whole continent (Rodrigues, Lockwood, 2011; Freitas et al., 2017b; Brasil, 2018).

The transmission of leprosy occurs from intimate and prolonged contact of a susceptible individual with a bacilliferous patient through bacilli inhalation. The best way to stop transmission is early diagnosis and treatment (Porto et al., 2015; Anchieta et al., 2019). Leprosy manifests mainly through dermato-neurological signs and symptoms such as skin and peripheral nerves lesions, especially the medial, radial, ulnar, tibial, fibular and facial nerves (Duarte-Cunha et al., 2012). The initial symptoms are white and reddish spots, which appear on any part of the body (Barbosa, Freitas, 2017). M. leprae bacillus grows best on colder tissues such as skin, peripheral nerves, anterior chamber of the eye, upper respiratory tract, and testis and avoids warmer areas like armpits, groin, scalp and midline of the back (Miranzi et al., 2010; Barbieri et al., 2016).

WHO and the Brazilian Ministry of Health included leprosy among neglected and endemic diseases that is possible to be eradicated (WHO, 2018; Sampaio et al., 2019). Only 20% of patients in Brazil are diagnosed at initial stages of the disease and about 70% of patients present some degree of disability when leprosy is diagnosed (Goulart, Goulart, 2008; Dias et al., 2018). The best way to prevent disabilities due to leprosy is an early diagnosis followed by treatment (Ferreira et al., 2012; Porto et al., 2015). Patients should undergo neurological assessments at the beginning, during and at the end of
Self-care and exercising parts of the body such as eyes, nose, hands and feet are extremely requested (Duarte-Cunha et al., 2012; Brasil, 2018). Health care professionals indicate surgery and rehabilitation in case of disability development (Brasil, 2016; Freitas et al., 2017a).

According to Ridley and Jopling’s classification, the clinical forms of the disease depends on the clinical conditions of patients, pathological and neurological pathologies and the immune response of the host (Bernardes Filho et al., 2017; Costa et al., 2019). The disease falls under different categories such indeterminate, tuberculoid, Virchowian, dimorph-tuberculoid, dimorphic and dimorphic-Virchowian (Ferreira et al., 2012; Brasil, 2010; 2013; 2016, 2018b). WHO classified leprosy according to the bacilloscopic index in 1988 and for therapeutic reasons (WHO, 2018).

Paucibacillary (PB) leprosy, characterized by the presence of few cutaneous lesions and one nerve trunk involved and Multibacillary (MB) leprosy with more than five cutaneous lesions more than one nerve trunk affected (Goulart, Goulart, 2008; Ferreira et al., 2012; Costa et al., 2019). When bacilloscopic examination is available, patients with positive results are considered multibacillary regardless the number of lesions (Baialardi, 2007; Bernardes Filho et al., 2017).

In order to minimize the problems related to compulsory notification diseases, the Brazilian Ministry of Health launched the Information System for Notifiable Diseases (ISND) in the 90’s (Brasil, 2016). The project collects and processes data on notification of injury throughout the national territory and providing information for analyzing the morbidity profile. The overall results of the project are related to decision-making at the municipal, state and federal levels regarding diseases (Brasil, 2010). Therefore, the present study aimed to trace the epidemiological clinical profile of leprosy reported by ISND in Anápolis-GO, from 2011 to 2016.

2. METHODS

This is an epidemiological, observational, descriptive and cross-sectional study. The source of information was the notification/investigation formularies on leprosy from the ISND database from 2011 to 2016. The present study was carried out at the Department of Epidemiological Surveillance of the Municipal Health Center in Anápolis, state of Goiás, Brazil, which is linked to the University Center of Anápolis - UniEVANGÉLICA. The study was approved by the Human Research Ethics Committee (CEP/UniEvangélica, #75083-515).
The socio-demographic features assessed were gender, age, ethnicity, level of education and area of residence. The clinical epidemiological variables comprised the clinical forms of the disease (indeterminate, tuberculoid, dimorphic, Virchowian and unclassified); the operational classification (paucibacillary and multibacillary); the notification system input mode; closure (death, treatment abandonment or cure) and evaluation of the incapacity degree of patients with leprosy.

Microsoft® Excel program was used to tabulate the data and statistical analysis was performed by the SPSS® (version 16.0). The chi-square test ($\chi^2$) and Fisher's exact test were used to perform the descriptive statistical analysis. The level of significance was set to 5% ($p<0.05$).

3. RESULTS

According to the data obtained from the leprosy notification sheets registered in the ISND from January 2011 to December 2016, medical assistance was offered to 484 individuals with leprosy in the city of Anápolis-GO. Among those patients 59.5% were male (288/484) and 40.5% were female (196/484) (male/female ratio of 1:46:1120). The most prevalent age group was 20 to 40 years old with 38% of the cases, followed by 41 to 60 years old with 37.4% ($p=0.835$). The ethnic classification, the brown color skin was the most prevalent accounting for 47.3% of the cases. We found statistically significant difference regarding ethnicity ($p=0.0008$), which reflect the great ethnic diversity of the Brazilian population. Regarding the level of education 27.1% of the patients reported to have completed 1 to 5 years of elementary school and 24.6% completed the secondary school between 6th and 9th grades ($p=0.122$). Regarding the area of residence 96.9% of the cases were in the urban area ($p=0.087$). The socio-demographic characteristics of the leprosy cases are described in Table 1.

Table 2 shows gender distribution and clinical forms of leprosy patients during the period of the study. We found 38.8% of patients with the dimorphic form of leprosy; followed by 28.9% with Virchowian form; 12.6% with tuberculoid form; 11.6% with indeterminate form and 8.1% the classification was not possible to be performed. The proportion of leprosy was the same for males and females and the dimorphic form of the disease was prevalent in 2011 ($p=0.092$). In 2012 the number of patients with leprosy was higher males. The dimorphic form was prevalent in men while the Virchowian form of the disease was prevalent in women ($p=0.600$). In 2013 leprosy was prevalent in males and Virchowian was the most prevalent clinical form ($p=0.001$). In the year 2014 leprosy
cases were prevalent in men and the most prevalent form regarding gender was the dimorphic form (p=0.009). In 2015 most of the leprosy cases occurred in males, the dimorphic and Virchowian clinical forms were prevalent in the same proportion (p=0.600). Finally, in 2016, leprosy was prevalent in men and the Virchowian clinical form was more frequent (p=0.004).

The distribution of leprosy the patients according to the operational classification of leprosy during the period of the study (Table 3). We found that 73.1% of the study population had multibacillary leprosy while 26.9% had paucibacillary leprosy (p=0.001). Table 4 shows the relationship between the ISND entry and gender. There was no statistical significance and we found that the majority of the patients included in the notification system belonged to new cases of leprosy.

The results of treatment from January 2011 to December 2016 shows in Table 5. The majority of leprosy cases were cured after treatment. There was no death due to leprosy during the study years. The evaluation of the incapacity degree of patients with leprosy related to gender. The majority of patients 44.8% were classified as degree 0 and 4.4% of the patients were not evaluated.

4. DISCUSSION

At the epidemiological level, the data reveals similarities with the national reality of the disease once it is predominant in adult males with multibacillary leprosy. WHO set the goal of reducing the prevalence of leprosy to less than 1 case per 10,000 population (Brasil, 2010, 2013; Goiás, 2012, 2015; WHO, 2018). The average incidence rate of leprosy was above what is proposed by WHO showing the difficulty in controlling the disease. These results are in line with other national studies related to leprosy epidemiology (Sanches et al., 2007; Melão et al., 2011; Freitas et al., 2017a; Sampaio et al., 2019). Analyzing leprosy cases per year within the period of the study we found that the leprosy incidence remained above the WHO goal. However, in 2015 and 2016, leprosy rates decreased, showing the strengthening and expansion of disease control measures (Barbosa, Freitas, 2017; Matos et al., 2018).

During period of the study, leprosy was most prevalent in males affecting 59.5% of the individuals. This result is in accordance with the majority of the studies related to leprosy carried out in the Brazilian population (Ribeiro Júnior et al., 2012; Santo et al., 2012; Salles et al., 2015; Ribeiro et al., 2018), even though some studies present divergent results regarding the prevalence of leprosy and gender (Miranzi et al., 2010). Male gender
is predominant nationally and internationally, especially in countries such as India and Indonesia (Melão et al., 2011; Miguel et al., 2017). It seems that men have greater social contact in societies and less concerned with body health and medical aesthetics compared to women. Moreover, there are several specific medical programs aimed at the health of women. Therefore, women would have more chances of establishing an early diagnosis compared to men. Men take longer time to seek health care when the first manifestations of the disease appear and men are more careless than women regarding the treatment and the medical follow-up (Silva et al., 2010; Barbosa, Freitas, 2017).

In relation to ethnicity, there was a predominance of leprosy in brown color individuals, which reflects the historical process of colonization in Brazil and its misccegenation, migratory movements, dynamics of territorial occupation and spatial organization, as pointed out by other studies (Lima et al., 2009; Lima et al., 2010; Silva et al., 2010; Silva et al., 2017). The most prevalent age group was between 20 and 40 years old, which is in accordance with another study also carried out in the city of Anápolis (Nascimento et al., 2007). The observed increase in leprosy rates may be due to changes in the population age structure, marked by a relative decline in the younger population and a proportional increase in the number of young adults (Melão et al., 2011; Brasil, 2013; Gracie et al., 2017). In addition, aging is followed by decreased immunity, making the individual more susceptible to infectious diseases (Souza et al., 2018; Costa et al., 2019).

The most common leprosy clinical forms were dimorphic followed by Virchowian in this study. Similar results were observed in other studies with predominance of the late forms of the disease: dimorphic or Virchowian. Multibacillary leprosy was predominant regarding the operational classification (Gomes et al., 2005; Costa et al., 2019). In countries with the highest global incidence of leprosy, such as India, Brazil and Indonesia, multibacillary is the predominant form of the disease with frequency as high as 64.5%, 53.5% e 79.5%, respectively (Gomes et al., 2005; Mello et al., 2006; Sanches et al., 2007; Amaral, Lana, 2008; Lima et al., 2009; WHO, 2018).

The high rate of multibacillary cases may be related to a stabilization of the endemic disease since the most susceptible individuals are affected and the immunologically competent are not. Moreover, patients may be diagnosed late, with an under-informed population about the disease, an inefficient primary and epidemiological care system that helps perpetuate the focus of transmission (Penna et al., 2009; Matos et al., 2018). Therefore, the clinical disease is rare in spite of a high incidence of infection.
within the population (Campos et al., 2005; Monteiro et al., 2015; Sampaio et al., 2019). The increase in multibacillary cases also contributes to the maintenance of leprosy transmission since it represents the main group capable of infecting untreated individuals (Monteiro et al., 2017a; Anchieta et al., 2019). In addition, individuals diagnosed with multibacillary leprosy are more likely to develop physical disabilities, such as neural lesions, which is also explained by late diagnosis.

Regarding ISND entry into the system 84.3% represented new cases and 0.2% recurrence. Other studies corroborate our results regarding new cases and disease recurrence (Silva Sobrinho, Mathias, 2008; Freitas, Oliveira, 2008). Leprosy, is a public health problem due to the large number of cases, it has a high potential to cause physical incapacities, interfering with the productive phase and the social life of the patient (Bernardes Filho et al., 2017; Nazario et al., 2017). The disease also promotes economic losses and psychological traumas. These disabilities have been responsible for the stigma and discrimination of leprosy patients.

The most effective ways of assessing whether the diagnosis has been late is to identify the presence of physical disabilities at the time of diagnosis (Penna et al., 2009; Monteiro et al., 2017a). The degree of disability is determined from the neurological evaluation of the eyes, hands and feet, and the result is expressed in values ranging from 0 to II. Degree 0 means there is no neural impairment while degree I indicates loss of sensitivity and II indicates the presence of disabilities and deformities (Pereira et al., 2008; Monteiro et al., 2014; Barbosa, Freitas, 2017). The present study showed that the majority of the patients showed degree 0 of impairment after physical incapacity evaluation.

Leprosy patients do not present physical incapacity at the initial states of the disease (Alves et al., 2010; Dias et al., 2018). The later the diagnosis is performed, higher the risk of presenting deformities. An early diagnosis is the most effective way to avoid permanent damage, and the onset of deformity is more time-bound than the control actions of the disease (Porto et al., 2015; Monteiro et al., 2017b; Costa et al., 2019). Our results show that the leprosy diagnosis has been set earlier and the strategies of prevention and control of the disease are more effective than the past. There was a reduction in the number of leprosy cases in the study population in 2015 and 2016, due to a more efficient disease control programs. An expressive number of patients concluded the treatment and was cured. However, the goal of less than 1 case of leprosy per 10 thousand inhabitants proposed by WHO has not been reached (WHO, 2018).
order to reach that goal in the coming years, it is necessary to launch leprosy awareness campaigns, active case search and early and effective treatment (Barbieri et al., 2016; Nazario et al., 2017; Dias et al., 2018).

In Brazil, great achievements in public health assistance and economic development have taken place in recent years. However, leprosy remains an important public health problem, with 34,894 new cases reported in 2010 (WHO, 2018). Brazil presents significant levels of inequality and regional differences in leprosy detection. Leprosy is a major public health problem in Brazil and in several countries globally. The spatial distribution of leprosy is heterogeneous in Brazil (Bernardes Filho et al., 2017; Freitas et al., 2017b). Areas with high transmission of the disease remain in the North, Center-west and Northeast. Areas with high transmission of the disease remain in the Northern, Central-Western and Northeastern regions of the country.

Leprosy is a chronic infectious disease, thus greater integration between population and primary care should also be encouraged (Monteiro et al., 2017b; Matos et al., 2018). Preventive campaigns contribute to the clarification of the population's risk behaviors, stressing the importance of an individualized approach, in the sense of contextualizing the information provided with the reality experienced by each patient.

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| YEARS   | 2011  | 2012  | 2013  | 2014  | 2015  | 2016  | TOTAL |
|---------|-------|-------|-------|-------|-------|-------|-------|
| GENDER  |       |       |       |       |       |       |       |
| Male    | 54 (49.5) | 61 (58.7) | 57 (63.3) | 52 (59.0) | 35 (71.4) | 29 (66.0) | 288 (59.5) | 0.120 |
| Female  | 55 (50.5) | 43 (41.3) | 33 (36.7) | 36 (41.0) | 14 (28.6) | 15 (34.0) | 196 (40.5) |       |

| AGE     | 2011  | 2012  | 2013  | 2014  | 2015  | 2016  | TOTAL |
|---------|-------|-------|-------|-------|-------|-------|-------|
| 10-19   | 8 (7.3) | 6 (5.8) | 3 (3.3) | 6 (6.8) | 0     | 2 (4.5) | 25 (5.2) |       |
| 20-40   | 43 (39.4) | 41 (39.4) | 36 (40.0) | 31 (35.2) | 22 (44.9) | 11 (25.0) | 184 (38.0) | 0.835 |
| 41-60   | 35 (32.1) | 39 (37.5) | 35 (38.9) | 34 (38.6) | 19 (38.8) | 19 (43.2) | 181 (37.4) |       |
| 61-80   | 22 (20.2) | 16 (15.4) | 16 (17.8) | 15 (17.1) | 7 (14.3) | 10 (22.8) | 86 (17.7) |       |
| 81-85   | 1 (1) | 2 (1.9) | 0 | 2 (2.3) | 1 (2.0) | 2 (4.5) | 8 (1.7) |       |

| ETHNICITY | 2011  | 2012  | 2013  | 2014  | 2015  | 2016  | TOTAL |
|-----------|-------|-------|-------|-------|-------|-------|-------|
| White     | 34 (31.2) | 35 (33.7) | 33 (36.7) | 42 (47.7) | 16 (32.7) | 11 (25.0) | 171 (35.3) |       |
Table 2. Distribution of reported cases of leprosy according to the clinical form of the disease and gender.

| Clinical Form | Indeterminate | Tuberculoid | Dimorphic | Virchowian | Not assessed | p     |
|---------------|---------------|-------------|-----------|------------|--------------|-------|
|               | n (%)         | n (%)       | n (%)     | n (%)      | n (%)        |       |
| 2011          |               |             |           |            |              |       |
| Male          | 6 (5.5)       | 10 (9.2)    | 21 (19.3) | 15 (13.8)  | 2 (1.8)      | 0.092 |
| Female        | 12 (11.0)     | 5 (4.6)     | 27 (24.8) | 7 (6.4)    | 4 (3.6)      |       |
| 2012          |               |             |           |            |              |       |
| Male          | 9 (8.6)       | 10 (9.6)    | 21 (20.2) | 16 (15.4)  | 5 (4.9)      | 0.600 |
| Female        | 8 (7.7)       | 10 (9.6)    | 9 (8.6)   | 11 (10.5)  | 5 (4.9)      |       |
| 2013          |               |             |           |            |              |       |
| Male          | 2 (2.2)       | 4 (4.5)     | 19 (21.1) | 30 (33.3)  | 2 (2.2)      | 0.001 |
| Female        | 2 (2.2)       | 8 (8.9)     | 6 (6.7)   | 9 (10.0)   | 8 (8.9)      |       |
| 2014          |               |             |           |            |              |       |
| Male          | 2 (2.3)       | 2 (2.3)     | 27 (30.7) | 15 (17.0)  | 6 (6.8)      | 0.009 |
| Female        | 8 (9.1)       | 3 (3.4)     | 20 (22.7) | 5 (5.7)    | 0            |       |
| 2015          |               |             |           |            |              |       |
| Male          | 1 (2.0)       | 3 (6.1)     | 14 (28.6) | 14 (28.6)  | 3 (6.1)      | 0.027 |
| Female        | 5 (10.3)      | 1 (2.0)     | 5 (10.3)  | 2 (4.0)    | 1 (2.0)      |       |
| 2016          |               |             |           |            |              |       |
| Male          | 0             | 0           | 13 (29.5) | 14 (31.8)  | 2 (4.5)      | 0.004 |
| Female        | 1 (2.3)       | 5 (11.4)    | 6 (13.7)  | 2 (4.5)    | 1 (2.3)      |       |
| **Total**     | 56 (11.6)     | 61 (12.6)   | 188 (38.8)| 140 (28.9) | 39 (8.1)     |       |

EL: education level; RA: residential area.
Table 3. Distribution of leprosy cases and operational classification of patients diagnosed with leprosy from 2011 to 2016.

| Year | Paucibacillary | Multibacillary | p  |
|------|----------------|----------------|----|
| 2011 | 38 (29.2)      | 71 (20.1)      |    |
| 2012 | 40 (30.8)      | 64 (18.1)      |    |
| 2013 | 20 (15.4)      | 70 (19.8)      | 0.001 |
| 2014 | 16 (12.3)      | 72 (20.3)      |    |
| 2015 | 10 (7.7)       | 39 (11.0)      |    |
| 2016 | 6 (4.6)        | 38 (10.7)      |    |
| Total| 130 (26.9)     | 354 (73.1)     |    |

Table 4. Distribution of leprosy cases according to the type of INSD entry and year of registration in Anápolis–GO between 2011 and 2016.

| INSD entry | New case | Recurrent | Return | Transfer | p    |
|------------|----------|-----------|--------|----------|------|
|            | n (%)    | n (%)     | n (%)  | n (%)    |      |
| Male       | 51 (46.8) | 0         | 1 (0.9) | 2 (1.9)  | 0.353|
| Female     | 48 (44.0) | 0         | 1 (0.9) | 6 (5.5)  |      |
| Male       | 48 (46.1) | 0         | 7 (6.7) | 6 (5.8)  | 0.058|
| Female     | 41 (39.4) | 0         | 1 (1.0) | 1 (1.0)  |      |
| Male       | 40 (44.4) | 0         | 15 (16.7)| 2 (2.2) | 0.456|
| Female     | 27 (30.0) | 0         | 5 (5.6) | 1 (1.1)  |      |
| Male       | 42 (47.7) | 0         | 6 (6.8) | 4 (4.6)  | 0.612|
| Female     | 31 (35.2) | 0         | 4 (4.6) | 1 (1.1)  |      |
| Male       | 30 (61.2) | 0         | 4 (8.2) | 1 (2.0)  | 0.348|
| Female     | 13 (26.6) | 0         | 0      | 1 (2.0)  |      |
| Male       | 23 (52.2) | 1 (2.3)   | 1 (2.3) | 4 (9.1)  | 0.635|
| Female     | 14 (31.8) | 0         | 0      | 1 (2.3)  |      |
| Total      | 408 (84.3)| 1 (0.2)   | 45 (9.3)| 30 (6.2) |      |

ISND - Information System for Notifiable Diseases of the Brazilian Ministry of Health

Table 5: Distribution of leprosy cases and treatment results according to INSD entry in Anápolis – GO from 2011 to 2016.
| Treatment results | Cure | Interruption of treatment | Transfer | Death by leprosy | Death by other causes | p     |
|-------------------|------|--------------------------|----------|-----------------|-----------------------|-------|
|                   | n (%)|                          |          |                 |                       |       |
| 2011              |      |                          |          |                 |                       |       |
| Male              | 44 (40.4) | 10 (9.2) | 0 | 0 | 0 | 0.005 |
| Female            | 48 (44.0) | 2 (1.8) | 5 (4.6) | 0 | 0 |       |
| 2012              |      |                          |          |                 |                       |       |
| Male              | 55 (52.9) | 2 (1.9) | 4 (3.9) | 0 | 0 | 0.147 |
| Female            | 33 (31.7) | 2 (1.9) | 8 (7.7) | 0 | 0 |       |
| 2013              |      |                          |          |                 |                       |       |
| Male              | 49 (54.4) | 3 (3.3) | 4 (4.5) | 0 | 1 (1.1) | 0.548 |
| Female            | 26 (28.9) | 2 (2.2) | 5 (5.6) | 0 | 0 |       |
| 2014              |      |                          |          |                 |                       |       |
| Male              | 42 (47.7) | 4 (4.5) | 4 (4.5) | 0 | 2 (2.3) | 0.190 |
| Female            | 34 (38.7) | 0 | 2 (2.3) | 0 | 0 |       |
| 2015              |      |                          |          |                 |                       |       |
| Male              | 28 (57.1) | 2 (4.1) | 5 (1.2) | 0 | 0 | 0.366 |
| Female            | 10 (20.4) | 0 | 4 (8.2) | 0 | 0 |       |
| 2016              |      |                          |          |                 |                       |       |
| Male              | 25 (56.8) | 0 | 4 (9.1) | 0 | 0 | 0.317 |
| Female            | 13 (29.5) | 0 | 1 (2.3) | 0 | 1 (2.3) |       |
| Total             | 407 (84.1) | 27 (5.6) | 46 (9.5) | 0 | 4 (0.8) |       |