Analysis of the treatment of pulmonary tuberculosis in elderly patients at a university hospital in Rio de Janeiro, Brazil*

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Abstract
Objective: To describe the clinical and therapeutic aspects of pulmonary tuberculosis and compare the adverse effects of the treatment and its outcome in elderly and nonelderly patients. Methods: This was a case-control study of 117 elderly individuals (over the age of 60 years) and 464 nonelderly individuals (aged 15-49 years). All subjects presented pulmonary tuberculosis that had been diagnosed and treated at the Thoracic Diseases Institute of the Federal University of Rio de Janeiro between 1980 and 1996. Results: In the elderly group, pulmonary tuberculosis was found to be correlated with diabetes (OR = 3.98; 95% CI = 2.07-7.65; p = 0.001), lung disease (OR = 7.24; 95% CI = 3.64-14.46; p = 0.001) and heart disease (OR = 5.86; 95% CI = 2.88-11.95; p = 0.001). Smoking (OR = 2.07; 95% CI = 1.26-3.42; p = 0.002) and alcohol abuse (OR = 1.63; 95% CI = 1.01-2.68; p = 0.041) were also more common in the elderly group. In the elderly group, the treatment more frequently resulted in adverse reactions (OR = 1.62; 95% CI = 1.04-2.54; p = 0.024), especially gastrointestinal reactions (OR = 1.64; 95% CI = 1.01-2.77; p = 0.047), and treatment efficacy was lower: cure rate, 51%; mortality rate, 24%. Treatment adherence was low (approximately 77%) in both groups. Conclusions: In the elderly group, adverse reactions were more common, treatment outcomes were less favorable, there was a greater frequency of clinical complications and deaths related to drug toxicity, and the prevalence of concomitant diseases was higher.

Keywords: Tuberculosis, pulmonary; Aged; Drug therapy; Treatment outcome.

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Introduction

The geographic distribution of pulmonary tuberculosis is directly related to the low socioeconomic indices of the individual countries. Nevertheless, it remains a major public health problem of global interest. In Latin America alone, approximately 250,000 cases are reported annually, with an incidence of 68/100,000 inhabitants and 20,000 deaths.\(^1\)

In 1950, there were 240,000,000 elderly individuals. In 2050, a world population of 1,900,000,000 elderly individuals is expected,\(^3\) considerably increasing their risk of exposure to and development of infectious diseases such as pulmonary tuberculosis.

The Brazilian population has also grown older. In the year 2000 census, the population over the age of 60 years was 14,536,029 people, representing 8.6% of the population. The mean age of the elderly people in Brazil is 69 years, and the life expectancy of women is 8 years greater than that of men. Among the capital cities, Rio de Janeiro and Porto Alegre are the ones with the greatest proportions of elderly individuals: 12.8 and 11.8%, respectively.\(^2\)

The interest for pulmonary tuberculosis in the elderly patient is already a reality in Europe and the United States, and it is increasing in Brazil. Therefore, in the last few years, various studies on clinical presentation, diagnostic methods, chemoprophylaxis, and antituberculosis chemotherapy in old age were organized to help understand this phenomenon.\(^4-9\)

Finally, although the treatment does not differ from that for young adults, some measures should be taken into consideration during chemotherapy: dosage proportional to the weight; monitoring of the hepatic and renal functions; drug interactions; and direct or indirect supervision of the treatment.\(^4,9\)

The objective of this study was to increase the knowledge of the principal therapeutic aspects of pulmonary tuberculosis in elderly patients. To that end, we describe the frequency of smoking/alcoholism, the occurrence of concomitant diseases, and the severity of the adverse effects of treatment with regimen I (two months of rifampicin+isoniazid+pyrazinamide followed by four months of rifampicin+isoniazid), as well as the clinical profiles and treatment outcomes, in elderly and nonelderly pulmonary tuberculosis patients monitored at a referral university institution in the city of Rio de Janeiro, Brazil.

Methods

This study adopted the retrospective case-control model and was conducted using data collected from the medical charts registered in the nosological files at the Thoracic Diseases Institute of the Federal University of Rio de Janeiro in the period from January of 1980 to December of 1996. Of the total of 581 patients, 117 cases (elderly patients over the age of 60) and 464 controls (nonelderly individuals between the ages of 15 and 49 years) were selected, which represents a ratio of 1:4. Each control was consecutively selected in the period of 30 days before or after each case appeared, without another type of matching.

In this study, we included patients with pulmonary tuberculosis who met the following criteria: confirmed or probable diagnosis of pulmonary tuberculosis, in accordance with the norms of the National Ministry of Health,\(^10,11\) although we also considered histopathologic findings consistent with pulmonary tuberculosis, such as granulomatous chronic inflammatory process with caseous necrosis and histiocytic infiltrate of multinucleated giant cells; exclusive outpatient monitoring at the IDT-UFRJ; and use of regimen I. The two study groups consisted of patients from 15 to 49 years of age (nonelderly group) and patients over the age of 60 (elderly group).\(^10,11\)

The following exclusion criteria were defined to ensure the homogeneity of the sample studied: altered diagnosis; initial suspicion of nontuberculous mycobacteriosis or of multidrug resistance of *Mycobacterium tuberculosis*; HIV co-infection; being between 50 and 59 years of age. We opted for the exclusion of this age bracket because the highest incidence of the disease in the Brazilian population is in the age brackets up to 49 years.\(^1,2\) In addition, exclusion allows a clear distinction to be drawn between elderly and nonelderly, with a 10-year gap between the two groups.

All data were collected from medical charts. The following biological and social characteristics were described: gender (male and female); age; race (white, black, or mixed); city of origin (region); and...
residence (state capital or its greater metropolitan area, rural area, or other states). The following variables were statistically tested: presenting diabetes mellitus; presenting another lung disease (asthma, chronic obstructive lung disease, sarcoidosis, silicosis, carcinoid tumor, bronchial carcinoma, or pulmonary embolism); presenting a cardiovascular disease (systemic arterial hypertension, cerebral vascular accident, coronary artery disease, or heart failure); presenting a neurological disease (epilepsy, parkinsonism, brain paralysis, senile dementia, or mental retardation); use of medications that interact with chemotherapy (hypoglycemic agents, corticosteroids, anticonvulsants, or anovulatory drugs); being a smoker; suffering from alcoholism; presenting adverse effects, including gastrointestinal reactions (appetite loss, nausea, vomiting, epigastic pain, diarrhea, or abdominal pain), neurological reactions (paresthesia, hyperesthesia, convulsion, or scintillating scotoma), immunological (pruritus, exanthema, urticaria, drug-induced hepatitis, coagulation disorders, or anasarca), and metabolic reactions (hyperglycemia or adrenal insufficiency); being in a follow-up treatment program for the identification/clinical evaluation of therapeutic complications and the subsequent management thereof (temporary suspension of chemotherapy or change in the therapeutic regimen), as well as of missed visits and treatment outcomes (cure, noncompliance, treatment failure, or death).

Odds ratios (ORs) were used as a measure of the strength of the association of the various degrees of exposure between the elderly and nonelderly groups. We also used the level of significance of 5% (p < 0.05) with a confidence interval of 95% (95% CI).

The chi-square test and Fisher’s test were used for the comparison of proportions of categorical variables. The statistical analysis was made using the SAS program (Statistical Analysis System, Cary, NC, USA).

The study was approved by the Ethics Committee of the IDT-UFRJ, in accordance with the stipulations set forth in Brazilian National Health Council Resolution no. 196/96.

Results

The socio-epidemiological characteristics of the elderly and nonelderly patients are described in Table 1. Of the 581 patients with pulmonary tuberculosis, 391 (67.3%) were male and 190 (32.7%) were female.

The mean age of the total population was 38.5 years (range, 15-87 years). The elderly group consisted of patients from 60 to 87 years of age (mean, 66.6 ± 16.5 years). The nonelderly group consisted of patients from 15 to 49 years of age (mean, 31.4 ± 9 years). Among the elderly patients, the age bracket with the greatest number of representatives was the one from 60 to 69 years, with 81 individuals (69.2%). In the nonelderly group, the age bracket with the greatest number of representatives was the one from 20 to 29 years, with 177 individuals (38.2%).

There were no great differences among the ethnic groups within the population studied, with a majority of whites and mixed.

In both groups, there was a predominance of individuals born in states located in the southeast region, followed by those born in states located in the northeast region. However, the great majority (98.2% of the elderly patients and 97.2% of the nonelderly patients) were residents of the state capital or of its greater metropolitan area.

Concomitant diseases were identified in 154 (26.9%) of the 573 patients evaluated, 44 (7.7%) of which reported suffering from other respiratory diseases. In the elderly group, 59.6% presented concomitant diseases, compared with 19% in the nonelderly group. Table 2 shows a statistical association of this variable with the elderly individuals (OR = 6.41; 95% CI = 4.03-10.22; p = 0.001), subdivided into diabetes mellitus, lung disease, cardiovascular disease, and neurological disease. Except for the neurological diseases, all of the diseases investigated are related to being elderly.

In Table 3, it can be seen that the use of medications was also relatively common among the 557 patients who provided data regarding this variable. Of the elderly patients, 28 (26.2%) reported the regular use of some medication, compared with 9.3% of the nonelderly patients, a significant association (OR = 3.44; 95% CI = 1.95-6.08; p = 0.001). Tobacco intake, expressed as the median, was markedly different between the age groups. Among the elderly patients,
8.8% of the patients reported complications such as the need for treatment modification. These, when they occurred, were more common in the older patients, especially the change in chemotherapy, which occurred in 13 (11.1%) of the elderly patients and in 16 (3.5%) of the nonelderly patients. Another significant complication was the temporary suspension of the triple-treatment regimen, in 10 (8.6%) of the elderly patients and 12 (2.6%) of the nonelderly patients. The determination of the presence (or absence) of both therapeutic difficulties is shown in Table 5. There, one can see the positive association of this variable with the elderly group (OR = 3.81; 95% CI = 2.02-7.19; p = 0.001). It is also seen that the proportion of missed visits did not differ significantly between the groups: 23.9% in the elderly group versus 27.2% in the nonelderly group.

In terms of treatment outcome, there were differences between the two groups. Among the nonelderly patients, the cure rate was 70%, the rate of noncompliance with treatment was approximately 24%, the treatment failure rate was 2.8%, and the median cumulative tobacco consumption was 50 pack-years, compared with 15 pack-years among the nonelderly patients (p = 0.0001). Alcoholism was reported for 311 patients: 72 (70.6%) of the elderly patients and 239 (59.6%) of the nonelderly patients (Table 3). Its quantification, however, could not be measured by objective criteria and, therefore, it was not considered.

As can be seen in Table 4, although the adverse effects of chemotherapy were common in elderly and nonelderly patients alike (45.9% and 34.3%, respectively), the difference between the two groups was statistically significant (OR = 1.62; 95% CI = 1.04-2.54; p = 0.024). When discriminating such effects - gastrointestinal; neurological; and metabolic - it was observed that they were always more strongly associated with the elderly group, and only those of gastrointestinal origin, which were identified in 25%, reached statistical significance (OR = 1.64; 95% CI = 1.01-2.77; p = 0.047). Nevertheless, the drug treatment was well accepted by the majority of patients. In the sample as a whole,
mortality rate was 3%. Among the elderly patients, however, the cure rate was 51%, and the rate of noncompliance with treatment was 23%, whereas the mortality rate was near 25%, much higher than that seen among the nonelderly patients. In studying the outcome strictly in terms of cure versus no cure (Table 5), we found that better results were obtained in the nonelderly than in the elderly (OR = 0.45; 95% CI = 0.29-0.69; p = 0.001).

**Discussion**

In the present study, gender distribution differed between the elderly and nonelderly groups. Among the nonelderly patients, the proportions of males and females (64.4% and 35.6%, respectively) followed the pattern of the pulmonary tuberculosis population treated at all Municipal Health Centers, as estimated by the Municipal Secretary of Health. When we studied the elderly group, we noticed a predominance of males (approximately 80%), which reflects an apparent epidemiological paradox, since, in the general population, the life expectancy of females is approximately 8 years greater than that of males. The male predominance in the elderly group suggests two hypotheses: a greater predisposition to tuberculosis in males, due to biological mechanisms that remain unconfirmed; and greater exposure to *M. tuberculosis* in this cohort when they were still young and the circulation of men exposed them to the etiological agent more frequently. In other countries, there is evidence of predominance of the male gender and its association with greater risk of disease.  

Despite the difficult racial definition of the Brazilian population, due to its great miscegenation, we opted for simplification and classified individuals as one of three racial types: white, black, or mixed. Such classification defined the groups with a majority of whites and a minority of black; however, the nonelderly group had a greater proportion of blacks (20%). Although we recognize the fact that our sample is not representative of the general population, there is no reason to believe that this difference between the two groups in terms of their racial makeup influenced decisions regarding referral to the IDT-UFRJ. Therefore, although this difference was not statistically significant, it is plausible to consider that the greater proportion of white individuals in the elderly population reflects the fact that whites have historically enjoyed better socioeconomic conditions in Brazil.

The description of the place of birth of the elderly and nonelderly patients is similar and reflects the heavy migration of individuals from the northeast region to Rio de Janeiro. The finding that great numbers of these individuals resided in the greater metropolitan area of the city (i.e., in the periphery) suggests difficulties in accessing health care facilities near their place of residence. However, it is important to remember that the IDT-UFRJ, as it is a referral facility and, as such, has always treated complex cases that primary care facilities were unable to solve. Therefore, it would be expected

### Table 2 - Associated diseases among patients with pulmonary tuberculosis, IDT-UFRJ, 1980-1996.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Elderly (n = 573)</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated diseases</td>
<td>Present</td>
<td>68 (59.6)</td>
<td>86 (18.7)</td>
<td>6.41</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>46 (40.4)</td>
<td>373 (81.3)</td>
<td>(4.03-10.22)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>22 (19.3)</td>
<td>26 (5.7)</td>
<td>3.98</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92 (80.7)</td>
<td>433 (94.3)</td>
<td>(2.07 -7.65)</td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td>Yes</td>
<td>26 (22.8)</td>
<td>18 (3.7)</td>
<td>7.24</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>88 (77.2)</td>
<td>441 (96.3)</td>
<td>(3.64-14.46)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>Yes</td>
<td>22 (19.3)</td>
<td>18 (3.7)</td>
<td>5.86</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92 (80.7)</td>
<td>441 (96.3)</td>
<td>(2.88-11.95)</td>
</tr>
<tr>
<td>Neurological diseases</td>
<td>Yes</td>
<td>4 (3.5)</td>
<td>11 (2.4)</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>110 (96.5)</td>
<td>448 (97.6)</td>
<td>(0.39-5.15)</td>
</tr>
</tbody>
</table>

95% CI: 95% Confidence Interval; *Asthma, chronic obstructive lung disease, sarcoidosis, silicosis, bronchial carcinoma, carcinoid, or pulmonary embolism; °Arterial hypertension, cerebral vascular accident, coronary artery disease, or heart failure; and †Epilepsy, parkinsonism, brain paralysis, senile dementia, or mental retardation.
tuberculosis was also naturally more common in the elderly patients (26%), although, proportionally, it was not equal to the percentage of elderly patients presenting concomitant diseases (60%). However, such use should not be automatically interpreted as indicative of a causal association. This group includes drugs that, although having no immunosuppressive effect, compete with the hepatic metabolic site of the antituberculosis chemotherapeutic agents, generating adverse effects.\(^{(22)}\)

Although the prevalence of smoking was high in both groups, it was highest among the elderly patients (73%). It is interesting, however, to notice the dissociation between this high prevalence and the much lower number of patients with lung diseases (22%), as previously mentioned. Naturally, tobacco intake was much higher among the smokers in the elderly group than among those in the nonelderly group, since this value can be related to a longer history of smoking. However, its contribution in the genesis of pulmonary tuberculosis has not been confirmed. Nevertheless, the median smoking history of 50 pack-years contributes to a critical analysis of the number of pulmonary tuberculosis patients described in the sample.

Within this context, we found that more diseases associated with the elderly, especially diabetes, lung diseases, and cardiovascular diseases, which is in accordance with the findings of other authors.\(^{(16-20)}\) Other lung diseases, present in 38% of the elderly patients with concomitant diseases, might be confounding factors in the diagnosis of pulmonary tuberculosis, since they present similar symptoms. Diabetes mellitus was also found to be strongly associated with advancing age, in accordance with the findings of other authors,\(^{(19,20)}\) who include this disease in the list of those which increase the susceptibility to pulmonary tuberculosis, even causing alterations in the usual radiological aspect of the disease, such as involvement of the lower lobes.\(^{(5,20,21)}\) The cardiovascular diseases evaluated in the present study were also strongly associated with being elderly, although no causal relation with pulmonary tuberculosis was established. This might be another confounding factor, since such diseases are quite frequently present in any elderly population and not only in that with pulmonary tuberculosis. As for the neurological diseases, it was not possible to establish an association, since there is no known relationship with pulmonary tuberculosis, and since, in the sample studied, there were very few patients with neurological diseases.

The use of drugs of pharmacological interest in relation to the triple chemotherapy for pulmonary tuberculosis was also naturally more common in the elderly patients (26%), although, proportionally, it was not equal to the percentage of elderly patients presenting concomitant diseases (60%). However, such use should not be automatically interpreted as indicative of a causal association. This group includes drugs that, although having no immunosuppressive effect, compete with the hepatic metabolic site of the antituberculosis chemotherapeutic agents, generating adverse effects.\(^{(22)}\)

Table 3 - Medication use, smoking and alcoholism among patients with pulmonary tuberculosis. IDT-UFRJ, 1980-1996.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Elderly n (%)</th>
<th>Nonelderly n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of medication(^{a})</td>
<td>Yes</td>
<td>28 (26.2)</td>
<td>42 (9.3)</td>
<td>3.44 (1.95-6.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>(n = 557)</td>
<td>No</td>
<td>79 (73.8)</td>
<td>408 (90.7)</td>
<td>2.07 (1.26-3.42)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>78 (73.6)</td>
<td>241 (57.4)</td>
<td>1.63 (1.01-2.68)</td>
<td>0.041</td>
</tr>
<tr>
<td>(n = 526)</td>
<td>No</td>
<td>28 (26.4)</td>
<td>179 (42.6)</td>
<td>1.63 (1.01-2.68)</td>
<td>0.041</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Yes</td>
<td>72 (70.6)</td>
<td>239 (59.6)</td>
<td>1.63 (1.01-2.68)</td>
<td>0.041</td>
</tr>
<tr>
<td>(n = 503)</td>
<td>No</td>
<td>30 (29.4)</td>
<td>162 (40.4)</td>
<td>1.63 (1.01-2.68)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

95% CI: 95% Confidence Interval; and \(^{a}\)Oral hypoglycemic agents, insulin, corticosteroids, anticonvulsants, or anovulatory drugs.
The treatment with regimen I was also evaluated. Due to the toxicity of the chemotherapy, the elderly patients were naturally more vulnerable to the adverse effects and, therefore, subject to difficulties such as temporary suspension of or a change in the regimen. Similarly, the adverse effects were also more common in the elderly patients in nearly half of the sample. Gastrointestinal effects were found to be associated with being elderly. This finding revealed that the treatment toxicity associated with the continuous use of other drugs and the presence of other diseases elevate the frequency of side effects in this age bracket.20,21 Studies have shown the need for clinical and laboratorial monitoring of hepatic function in elderly patients with a history of alcoholism or liver disease.22

Other difficulties during outpatient treatment were inferred by the irregularity of the monitoring and missed visits. In this variable, the results were similar, the number of missed visits being high in both groups. This explains the high rate of noncompliance with treatment, which was estimated at 23%. It is of note that, despite the fact that the difficulty of access might cause a greater tendency towards interruption of the outpatient monitoring among the elderly, the rate of noncompliance with treatment, although high in both groups, was not higher among the elderly patients. The comparison between elderly and nonelderly patients revealed a much higher proportion of deaths in the former group and of cure in the latter. Epidemiological surveys conducted in other countries also revealed an increase in mortality among elderly patients with pulmonary tuberculosis in last years, principally when accompanied by extensive disease.23 In Brazil, a study of mortality among elderly pulmonary tuberculosis patients showed an increase in the contribution of this age bracket to the overall mortality rate in the last 50 years.18 This means that the delay in the diagnosis of a patient previously debilitated by organic aging and by the presence of other diseases resulted in low efficacy of the treatment. It is important to pay attention to the characteristics of the population studied, referred to a referral center for presenting a greater degree of diagnostic or therapeutic difficulty. Therefore, it might be believed that this poor outcome in the elderly patients studied does not represent the general population of this age bracket.

The biological and social aspects that maintained a positive correlation with pulmonary tuberculosis in elderly patients were smoking and alcoholism.

We can conclude that, based on the clinical findings, regimen I presents higher toxicity, principally of gastrointestinal nature, and lower efficacy in elderly patients. This lower efficacy, related to the elevated mortality of the disease, is also due to comorbidities, especially diabetes mellitus, lung diseases, and cardiovascular diseases, which are naturally more advanced in this age bracket. Likewise, these comorbidities require more frequent use of other drugs, thereby increasing the probability of interaction with the chemotherapy and the consequent adverse effects.

Table 4 - Adverse reactions among patients with pulmonary tuberculosis. IDT-UFRJ, 1980-1996.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Elderly n (%)</th>
<th>Nonelderly n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reactions</td>
<td>Present</td>
<td>50 (45.9)</td>
<td>154 (34.3)</td>
<td>1.62 (1.04-2.54)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>59 (54.1)</td>
<td>295 (65.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal reactiona</td>
<td>Yes</td>
<td>28 (25.7)</td>
<td>78 (17.4)</td>
<td>1.64 (1.01-2.77)</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>81 (74.3)</td>
<td>371 (82.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological reactionb</td>
<td>Yes</td>
<td>7 (6.4)</td>
<td>21 (4.7)</td>
<td>1.40 (1.01-2.77)</td>
<td>0.454</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>102 (93.6)</td>
<td>428 (95.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunological reactionc</td>
<td>Yes</td>
<td>17 (15.6)</td>
<td>50 (11.1)</td>
<td>1.47 (0.52-3.59)</td>
<td>0.198</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>92 (84.4)</td>
<td>399 (88.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic reactiond</td>
<td>Yes</td>
<td>6 (5.5)</td>
<td>9 (2)</td>
<td>2.85 (0.88-8.98)</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>103 (94.5)</td>
<td>440 (98)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% CI: Confidence Interval 95%; aAnorexia/appetite loss, nausea, vomiting, epigastric pain, diarrhea, or abdominal pain; bParesthesia, hyperesthesia, convulsion, or scintillating scotoma; cPruritus, exanthema, urticaria, drug-induced hepatitis, coagulation disorders, or anasarca; and dHyperglycemia or adrenal insufficiency.
The elevated number of missed visits and the high rate of noncompliance with treatment, among the elderly and nonelderly patients, suggest the existence of similar factors related to the public health system, which were not addressed in this study and merit attention in future studies.

References