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# Prevalence and factors associated with diabetes mellitus among tuberculosis patients: a nationwide cohort

*To the Editor:*

The association between diabetes mellitus (DM) and tuberculosis (TB) has been a matter of study worldwide, since it is assumed that DM triples the risk of TB [1]. Recent studies have found discrepant prevalence of DM among TB patients, ranging from 5.3% in Denmark [2] to 44% in India [3]. There is an urgent need to control both epidemics in order to achieve the World Health Organization (WHO) TB elimination goal [4]. To reach this goal, an integrated approach between TB elimination strategies and control of noncommunicable diseases that perpetuate the risk for TB is fundamental [5].

Portugal has an intermediate incidence rate of TB and an estimated prevalence of DM of 7.4% (estimated underdiagnosed prevalence of 5.7%) [6]. There are no official recommendations to actively screen for DM in TB patients (there is only a provisional recommendation from the WHO Collaborative Framework for Care and Control of Tuberculosis and Diabetes [7]). A previous systematic review estimated that if TB patients were screened for DM, the DM prevalence would range widely, from 1.9% to 35% [8]. This study aims to assess DM prevalence among the Portuguese TB population and to identify which factors are associated with it. This is a Portuguese nationwide retrospective cohort study of a 6-year period (2008–2013).

Data were collected from the national TB database, SVIG-TB (Sistema de Vigilância da TB em Portugal (System for Surveillance of TB in Portugal)) [9]. All patients diagnosed with TB in Portugal are mandatorily recorded through this registry. We included all patients with newly diagnosed pleural-pulmonary TB who finished treatment between January 2008 and December 2013. Exclusion criteria were age <18 years, previous TB diagnosis, isolated extrapulmonary TB, multidrug- or extensively drug-resistant TB and unknown outcome (abandonment/emigration).

The following definitions were used. TB diagnosis: positive culture or both smear and nucleic acid amplification test positivity in a pleural or respiratory specimen; DM diagnosis: self-reported by the patient and/or based on clinical data; TB compliance: ⩾80% of prescribed treatment; unsuccessful treatment: death, lack of microbiological conversion and/or incomplete treatment (<80% of prescribed treatment); drug consumer: regular consumer of illicit drugs. All the comorbidities analysed (including DM itself) were reported to the Portuguese surveillance system, SVIG-TB [9].

For the statistical analysis, categorical variables were described by absolute (relative) frequencies, while continuous variables were described by the median (interquartile range (IQR)). For all variables, a comparative analysis between patients with and without DM was performed: Chi-squared or Fisher test (as adequate) for the study of independence among categorical variables, and the Mann–Whitney test for the assessment of statistically significant differences between two independent continuous variables.

DM prevalence (6.0%) and the number of possible predictors hindered a straightforward application of a multiple logistic regression model. Initially, random oversampling of the DM class, until the two classes had exactly the same number of observations, was performed and for each oversample, a classification tree was created. As all trees exhibited essentially the same structure, the tree considered was the one obtained from the repetition of the DM class until the achievement of exact balance. This procedure reduced the number of predictors to a smaller subset. Then a logistic regression model was performed, considering the variables assigned with a predictive importance greater than zero. The imbalance was then dealt with as follows: 1) oversampling of the DM class using full-size random selection with replacement; 2) logistic regression with the obtained dataset and saving of the estimated coefficients; 3) repetition of the procedure 1000 times. A regression coefficient was considered to be statistically significant if its values did not include zero, disregarding the adequate lower and upper percentiles.

Statistical analyses were carried out using the R language and software environment for statistical computation, version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at 0.05.

Ethical approval was not required since data were already anonymised according to national data protection rules.

TABLE 1 Factors associated with diabetes mellitus in the Portuguese population with tuberculosis from 2008 to 2013

| | Patients n | Diabetes mellitus | | Bivariate analysis | | Multiple analysis | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No n (%) | Yes n (%) | OR (95% CI) | p-value | OR (95% CI) | Estimate# | Lower bound# | Upper bound# |
| **Sex** | 11317 | | | | 0.440 | 1.044 (0.999–1.088) | 0.044 | −0.001 | 0.084 |
| Male | 7894 | 7410 (69.7) | 484 (71.1) | 1.070 (0.902–1.269) | | | | | |
| Female | 3423 | 3226 (30.3) | 197 (28.9) | Reference | | | | | |
| **Foreign origin** | 11317 | | | | 0.001 | | | | |
| Yes | 1787 | 1709 (16.1) | 78 (11.5) | 0.676 (0.531–0.860) | | | | | |
| No | 9530 | 8927 (83.9) | 603 (88.5) | Reference | | | | | |
| **Alcohol dependence** | 10661 | | | | 0.474 | | | | |
| Yes | 1650 | 1557 (15.5) | 93 (14.5) | 0.921 (0.734–1.154) | | | | | |
| No | 9011 | 8462 (84.5) | 549 (85.5) | Reference | | | | | |
| ***i.v.* drug user** | 10680 | | | | <0.001 | 0.603 (0.494–0.729) | −0.505 | −0.706 | −0.316 |
| Yes | 746 | 734 (7.3) | 12 (1.9) | 0.241 (0.135–0–429) | | | | | |
| No | 9934 | 9303 (92.7) | 631 (98.1) | Reference | | | | | |
| **Other drug user** | 10647 | | | | <0.001 | 0.643 (0.557–0742) | −0.442 | −0.586 | −0.299 |
| Yes | 880 | 862 (8.6) | 18 (2.8) | 0.306 (0.191–0.491) | | | | | |
| No | 9767 | 9143 (91.4) | 624 (97.2) | Reference | | | | | |
| **Reclusion** | 10854 | | | | 0.342 | | | | |
| Yes | 201 | 192 (1.9) | 9 (1.4) | 0.723 (0.369–1.417) | | | | | |
| No | 10653 | 10004 (98.1) | 649 (98.6) | Reference | | | | | |
| **Homelessness** | 10851 | | | | 0.213 | | | | |
| Yes | 181 | 174 (1.7) | 7 (1.1) | 0.620 (0.290–1.326) | | | | | |
| No | 10670 | 10020 (98.3) | 650 (98.9) | Reference | | | | | |
| **Communitarian shelter** | 10805 | | | | 0.651 | | | | |
| Yes | 329 | 307 (3.0) | 22 (3.3) | 1.107 (0.713–1.719) | | | | | |
| No | 10476 | 9839 (97.0) | 637 (96.7) | Reference | | | | | |
| **HIV** | 11317 | | | | <0.001 | 0.497 (0.432–0.564) | −0.700 | −0.840 | −0.573 |
| Yes | 1123 | 1097 (10.3) | 26 (3.8) | 0.345 (0.232–0.513) | | | | | |
| No | 10194 | 9539 (89.7) | 655 (96.2) | Reference | | | | | |
| **Haematological malignancies** | 11317 | | | | 0.448 | | | | |
| Yes | 33 | 30 (0.3) | 3 (0.4) | 1.564 (0.476–5.139) | | | | | |
| No | 11284 | 10606 (99.7) | 678 (99.6) | Reference | | | | | |
| **Lung cancer** | 11317 | | | | 0.708 | | | | |
| Yes | 117 | 109 (1.0) | 8 (1.2) | 1.148 (0.558–2.364) | | | | | |
| No | 11200 | 10527 (99.0) | 673 (98.8) | Reference | | | | | |
| **Other cancers** | 11317 | | | | <0.001 | | | | |
| Yes | 298 | 262 (2.5) | 36 (5.3) | 2.210 (1.546–3.159) | | | | | |
| No | 11019 | 10374 (97.5) | 645 (94.7) | Reference | | | | | |
| **COPD** | 11317 | | | | 0.014 | | | | |
| Yes | 286 | 259 (2.4) | 27 (4.0) | 1.654 (1.104–2.478) | | | | | |
| No | 11031 | 10377 (97.6) | 654 (96.0) | Reference | | | | | |
| **Liver disease** | 11317 | | | | 0.182 | | | | |
| Yes | 425 | 393 (3.7) | 32 (4.7) | 1.285 (0.889–1.859) | | | | | |
| No | 10892 | 10243 (96.3) | 649 (95.3) | Reference | | | | | |
| **Renal failure¶** | 11317 | | | | <0.001 | | | | |
| Yes | 109 | 92 (0.9) | 17 (2.5) | 2.934 (1.739–4.952) | | | | | |
| No | 11208 | 10636 (99.1) | 664 (97.5) | Reference | | | | | |
| **Silicosis** | 11317 | | | | 0.639 | | | | |
| Yes | 138 | 131 (1.2) | 7 (1.0) | 0.833 (0.388–1.789) | | | | | |
| No | 11179 | 10505 (98.8) | 674 (99.0) | Reference | | | | | |

Continued

TABLE 1 Continued

| | Patients n | Diabetes mellitus | | Bivariate analysis | | Multiple analysis | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No n (%) | Yes n (%) | OR (95% CI) | p-value | OR (95% CI) | Estimate# | Lower bound# | Upper bound# |
| **Sarcoidosis** | 11317 | | | | 1.000 | | | | |
| Yes | 12 | 12 (0.1) | 0 (0) | | | | | | |
| No | 11305 | 10624 (99.9) | 681 (100) | | | | | | |
| **Other diffuse lung disease** | 11317 | | | | 0.411 | | | | |
| Yes | 28 | 28 (0.3) | 0 (0) | | | | | | |
| No | 11289 | 10608 (99.7) | 681 (100) | | | | | | |
| **Inflammatory joint disease** | 11317 | | | | 0.022 | | | | |
| Yes | 58 | 50 (0.5) | 8 (1.2) | 2.517 (1.188–5.330) | | | | | |
| No | 11259 | 10586 (99.5) | 673 (98.8) | Reference | | | | | |
| **Abnormal radiograph** | 10685 | | | | 0.137 | | | | |
| Yes | 10319 | 9671 (96.5) | 648 (97.6) | 1.466 (0.883–2.434) | | | | | |
| No | 366 | 350 (3.5) | 16 (2.4) | Reference | | | | | |
| **Cavitation** | 10685 | | | | 0.226 | | | | |
| Yes | 5132 | 4798 (47.9) | 334 (50.3) | 1.102 (0.942–1.289) | | | | | |
| No | 5553 | 5223 (52.1) | 330 (49.7) | Reference | | | | | |
| **Fatal adverse drug reaction** | 9031 | | | | 0.099 | | | | |
| Yes | 297 | 273 (3.2) | 24 (4.5) | 1.430 (0.933–2.191) | | | | | |
| No | 8734 | 8228 (96.8) | 506 (95.5) | Reference | | | | | |
| **Isoniazid resistance** | 7348 | | | | 0.632 | | | | |
| Yes | 450 | 419 (6.1) | 31 (6.6) | 1.097 (0.752–1.599) | | | | | |
| No | 6898 | 6462 (93.9) | 436 (93.4) | Reference | | | | | |
| **Rifampicin resistance** | 7349 | | | | 0.697 | | | | |
| Yes | 93 | 88 (1.3) | 5 (1.1) | 0.836 (0.338–2.067) | | | | | |
| No | 7256 | 6794 (98.7) | 462 (98.9) | Reference | | | | | |
| **Ethambutol resistance** | 7342 | | | | 0.607 | | | | |
| Yes | 65 | 60 (0.9) | 5 (1.1) | 1.229 (0.491–3.076) | | | | | |
| No | 7277 | 6815 (99.1) | 462 (98.9) | Reference | | | | | |
| **Pyrazinamide resistance** | 5681 | | | | 0.707 | | | | |
| Yes | 102 | 96 (1.8) | 6 (1.6) | 0.853 (0.371–1.958) | | | | | |
| No | 5579 | 5198 (98.2) | 381 (98.4) | Reference | | | | | |
| **Streptomycin resistance** | 7260 | | | | 0.793 | | | | |
| Yes | 713 | 666 (9.8) | 47 (10.2) | 1.043 (0.763–1.425) | | | | | |
| No | 6547 | 9132 (90.2) | 415 (89.8) | Reference | | | | | |
| **Treatment success** | 10403 | | | | <0.001 | | | | |
| Yes | 9655 | 9107 (93.2) | 548 (86.3) | 0.457 (0.360–0.581) | | | | | |
| No | 748 | 661 (6.8) | 87 (13.7) | Reference | | | | | |
| **Mortality** | 10403 | | | | <0.001 | 1.098 (1.031–1.172) | 0.094 | 0.031 | 0.159 |
| Yes | 746 | 659 (6.7) | 87 (13.7) | 2.194 (1.727–2.789) | | | | | |
| No | 9657 | 9109 (93.3) | 548 (86.3) | Reference | | | | | |
| **Age years** | | 43.0 (33.0–56.0)+ | 60.0 (50.0–72.0)+ | 1.044 (1.039–1.048) | <0.001 | 1.047 (1.046–1.049) | 0.046 | 0.045 | 0.047 |
| **Time from symptoms to diagnosis days** | | 60.0 (36.0–102.0)+ | 66.0 (39.0–112.0)+ | 1.000 (1.000–1.001) | 0.209 | | | | |

COPD: chronic obstructive pulmonary disease. #: results from the logistic regression methodology; the "Estimate" column corresponds to the mean of all estimates obtained within the procedure, while the "Lower bound" and "Upper bound" columns correspond to the 0.025 and 0.975 quantiles, respectively; if 0 is not within the given interval, then the variable is statistically significant for a 0.05 significance level. ¶: haemodialysis. +: median (interquartile range).

During the studied period, 11 317 TB patients were recorded (median (IQR) age 44 (33–58) years; 69.8% males). The global prevalence of DM in the present cohort was 6.0% and stable during the studied period. There was a male predominance in patients both with and without DM (71.1% and 69.7%, respectively). Patients with DM were significantly older ($p<0.001$), with half being aged >60 years (table 1). Moreover, they had a significantly higher rate of malignancies other than haematological or lung cancer (OR 2.210, 95% CI 1.546–3.159), of chronic obstructive pulmonary disease (OR 1.654, 95% CI 1.104–2.478), of renal failure under haemodialysis treatment (OR 2.934, 95% CI 1.739–4.952) and of inflammatory joint disease (OR 2.517, 95% CI 1.188–5.330). Patients with DM also had a significantly lower rate of HIV infection (OR 0.345, 95% CI 0.232–0.513), consumption of intravenous (OR 0.241, 95% CI 0.135–0.429) or other drugs (OR 0.306, 95% CI 0.191–0.491) and were less often foreign born (OR 0.676, 95% CI 0.531–0.860). No differences were identified in TB radiological manifestation or in the delay from symptoms to TB diagnosis. Patients with DM presented a significantly lower rate of treatment success (OR 0.457, 95% CI 0.360–0.581) and a higher rate of death during treatment (OR 2.194, 95% CI 1.727–2.789).

In the multiple analysis, the odds for DM among TB patients increased by 4.7% per year of age (OR 1.047, 95% CI 1.046–1.049) but decreased by ~50% in HIV-positive patients (OR 0.497, 95% CI 0.432–0.564), 39.7% in *i.v.* drug consumers (OR 0.603, 95% CI 0.494–0.729) and 35.7% in drug consumers other than *i.v.* (OR 0.643, 95% CI 0.557–0.742). Moreover, the odds for DM among those who died were 9.8% higher (OR 1.098, 95% CI 1.031–1.172).

The factors associated with DM among TB patients identified in this study were older age, no drug consumption and no HIV infection. Death occurred more often among DM patients. No other clinical, radiological or sociodemographic factor predicted DM.

DM, particularly type 2 DM, is strongly related to older age in developed countries where most patients are above the retirement age, whereas in developing countries those most frequently affected are aged 35–64 years [10]. In developed countries most TB patients tend to be younger than the retirement age. This might explain why DM prevalence among TB patients is significantly lower in countries like Portugal (6.0%), Spain (5.9%) [11] and Denmark (5.3%) [2], in comparison with developing countries where, however, increasing age is also related to the presence of DM in TB [3].

Being HIV positive was related to a lower DM prevalence among TB patients even when controlled for age. Similar results were found in other studies [11]. In the same way, being a consumer of *i.v.* or other drugs was associated with a lower risk of DM even when controlled for age and HIV status. There are no known protective factors for DM among those who are HIV positive or drug consumers. More studies are needed to clarify why these TB patients present a lower risk for DM.

This study showed that death during TB treatment was 9.8% higher in patients with DM. These results are in line with some other studies [12–15] but in conflict with a recently published article [11]. Advanced age, comorbidities and drug interactions are reasonable factors that may be related to death. Nevertheless, it is still unknown if there is any pathological mechanism between TB and DM that explains the poorer outcomes.

In previous studies, foreign origin [16], changes in chest radiography [11, 13, 14, 17], adverse drug reactions [11] or sex [18] were significantly associated with DM among TB patients. In the present study, none of these factors were related to DM comorbidity.

The present study has limitations, especially due to its retrospective nature: 1) DM could not be actively confirmed; 2) death causes could not be determined. Nevertheless, because of the nationwide nature of our study, the size of our sample and the constantly improving TB registry, we are confident that these results clarify the role of DM among Portuguese TB patients. To our knowledge, a systematic nationwide survey concerning DM among TB patients has never previously been conducted, which reinforces the importance of this study's results to the comprehension of the TB–DM relationship.

To conclude, in this nationwide Portuguese TB cohort, DM was associated with older patients, lack of HIV infection and lack of drug consumption. Further studies should analyse the causes of mortality among this group in order to define new strategies to improve outcomes.

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**In a Portuguese TB cohort, diabetes mellitus was associated with older age and no HIV infection or drug consumption** http://ow.ly/10EoN1

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