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The extrapulmonary dissemination of tuberculosis: A meta-analysis

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ABSTRACT

Background and objective: The epidemiology of the forty percent of tuberculosis patients who present with disseminated and/or extrapulmonary disease is in need of further study. Further study of such dissemination using published data from international indices may provide data which assist with control of tuberculosis.

Methods: For each clinical or epidemiologic factor studied, summary odds ratios and corresponding 95% confidence intervals were calculated showing associations between such factors and documented extrapulmonary dissemination of tuberculosis.

Results: Eighteen studies fulfilled criteria for study of the clinical factors and nine for the cytokine studies. Significant factors associated with a greater risk of extrapulmonary dissemination were female gender (summary odds ratio, 1.92 (95% confidence intervals, 1.72–2.13), *I*-squared 86.9), age under 45 (1.37, 1.18–1.60, 63.7), and as well the absence of smoking, drinking and diabetes but not HIV infection (1.10, 0.91–1.32, 80.5). Among cytokines, the macrophage receptor protein P2X7 was associated most strongly associated with extrapulmonary dissemination of tuberculosis (2.28, 0.88–5.90, 92.9).

Conclusion: Young age, female gender, and the macrophage purinergic receptor protein P2X7 were major factors associated with extrapulmonary dissemination of tuberculosis.

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Introduction

The extrapulmonary dissemination of tuberculosis (TB) is the result of pathogen, host genetic and environmental factors. The relative importance of these factors is a debatable topic. The known pathogen factors include the particular virulence of certain types, such as the Beijing strain, which is associated with extrapulmonary disease [1], as well as biologic properties of disseminating pathogens as shown by mice studies in which variants of a heparin-binding hemagglutinin are associated with an increased risk of disseminated disease [2].

Is it possible to answer questions about risk factors for extrapulmonary disease simply by referring to published data from international indices? Data provided by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) provide widely disparate values for the incidence of extrapulmonary tuberculosis [3–5]. For example, Cambodia reports that 37% of their reported (TB) cases are extrapulmonary, while China reports only 7% [4]. The overall rate is 11.6% for high-risk nations and 13.1% for all nations in this WHO report, while a CDC report for the same period lists a rate of 19% for extrapulmonary disease [3]. Age and

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sex disaggregated data, however, are not typically available as cited in the most recent WHO report [4]. The recognized fact that up to 40% of extrapulmonary cases also contain pulmonary disease complicates any analysis [6].

Host factors are also important in extrapulmonary dissemination and traditionally suggested by the fact that the human immunodeficiency virus (HIV)-infected [7,8] and patients with other immunosuppressive diseases such as systemic lupus erythematosus [9] show an increased risk of extrapulmonary dissemination when infected with *Mycobacterium tuberculosis*. The biologic basis for this host susceptibility is the subject of many studies, dating back to early NIH studies when the then-classified HLA group Bw15 ("w" for "working") was found in a small series to be associated with extrapulmonary dissemination of TB [10].

To assess the correlates which are most strongly associated with extrapulmonary dissemination of TB, meta-analyses of published series of TB were performed. This article presents the findings of these meta-analyses.

Materials and methods

Searching for studies

PubMed database and Google Scholar were searched for studies comparing extrapulmonary tuberculosis (EPTB) to pulmonary tuberculosis (PTB) controls. The search terms used were: extrapulmonary OR extrathoracic AND pulmonary AND tuberculosis within the title or abstract. Searches were limited to the English language although all languages with English translations were included. Abstracts and titles of articles were scanned for key words ("epidemiology," "demographics," "risk factors") indicating a comparative analysis. The bibliographies of the first set of articles were reviewed to locate additional articles.

Selecting studies and collecting articles and data

Studies were included if they: (a) compared data for EPTB and PTB cases; (b) were published within the last 10 years (because of the scarcity of earlier studies); and (c) provided calculated odds ratios or sufficient data for the calculation of such odds ratios. Studies were excluded if: (a) cases in which clinically both EPTB and PTB were reported as part of either group; (b) pleural TB cases were included in the PTB group (because the convention is to include them as EPTB); or (c) studies contained duplicate data from a larger study. Due to large differences in available resources and health care protocols between study sites, no studies were excluded based on method of TB confirmation. When duplicate papers using the same data were encountered, the larger study was chosen. A sample search would include the above variables, and examining the individual articles, for example, for data on gender and then collating the relevant articles.

Factors studies by meta-analysis

These meta-analyses were performed on analyzed factors present in sufficient frequency for statistical analysis. These included gender, age, HIV status, African ancestry, smoking and drinking history, the presence of diabetes, and the presence of polymorphisms in five cytokines, including interferon-gamma (γ), tumor necrosis factor-alpha (α), interleukin 10, toll-like receptor 2, and the macrophage protein P2X7.

Limitations of factors used in meta-analysis

HIV-negativity was assumed when HIV status was reported as unknown because without this restriction, few studies were usable. Smoking, diabetes and excess alcohol drinking habits were generally reported based on the authors' assessments, usually without specific definitions. Race was rarely reported with detail. In the end, only African or non-African ancestry reports were present in sufficient number or detail to justify analysis. Age was reported with diverse stratification and the most often used age for stratification (age 45, 4 studies) was used for this meta-analysis. The use of other age cutoffs did not provide sufficiently large samples for analysis.

Statistical analyses

Characteristics of patients reported in at least 2 eligible studies were analyzed using STATA software (version 11.0, College Station, TX [11] and "metan" commands [12]). Meta-analysis was performed using random effects analysis, and heterogeneity was measured using the I^2 statistic. The studies were analyzed with graphs produced with best fit lines showing the odds ratio for extrapulmonary vs. pulmonary disease given the presence of a studied demographic, trait, behavior, or polymorphism. For cytokine and molecular polymorphisms, absolute allele numbers and associated proportions were used rather than specific genotypes, and the search criteria were limited by the paucity of polymorphism articles related to dissemination of TB.

Results

From 1257 articles generated in the initial search, 27 met the inclusion criteria and 3 additional articles were found using bibliographies in the 27; among the 30 articles, 11 were excluded for combining pulmonary and extrapulmonary disease, 3 were excluded for equating pleural with pulmonary disease, 1 was excluded for duplicate data, an additional 3 were located in reviewing data, and the final 18 were suitable for inclusion in the meta-analysis. Large public health databases (CDC, WHO) did not typically contain sufficient detail regarding combined pulmonary and extrapulmonary cases and thus did not fit the inclusion criteria for the study.

The proportion of cases confirmed by culture varied by study and this proportion was often not reported. The remaining cases were confirmed by a variety of methods including microscopy, histology, and clinical decision-making.

The data analyzed on cytokines and immune polymorphisms were based on reviews of 30 recent publications, and data from 9 articles met criteria for the study.

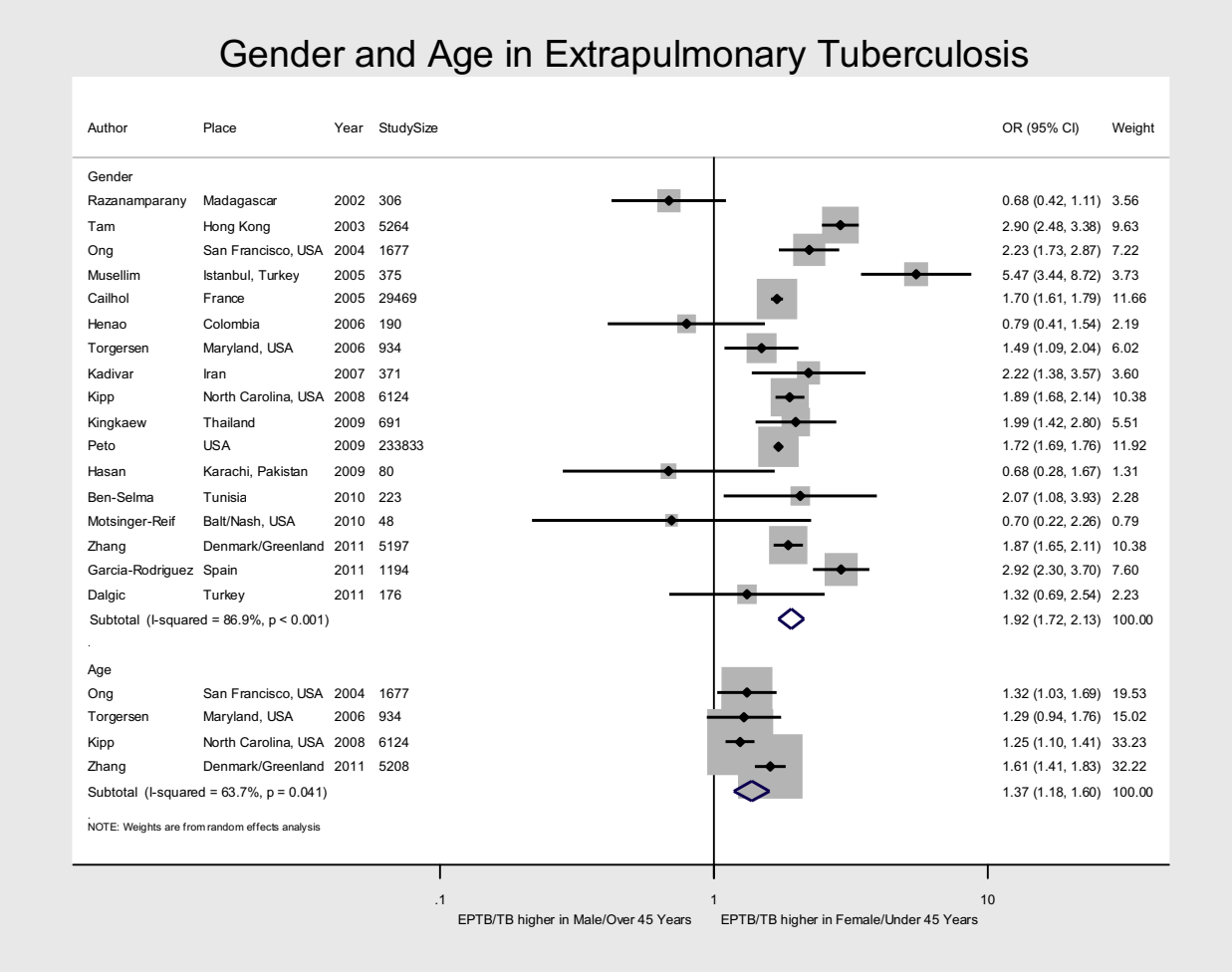

Fig. 1 – The odds ratio of extrapulmonary to pulmonary disease (EP/P) with 95% confidence intervals for female gender and age (divided at 45 years). Subtotal, *I*-squared = 86.9% and 63.7% respectively, *P* < 0.001 (gender), and *P* = 0.041 (age) for models, random effects model.

Table 1 – Assessing odds ratios of dissemination (defined as EPTB/PTB >1) by epidemiologic and host factors.

Risk factor	N	Odds ratio	I^2 Value
Female gender	17	1.92 (1.72–2.13)	86.9
HIV positive	7	1.10 (0.91–1.32)	80.5
Black African ancestry	4	0.97 (0.95–0.99)	0.00
Age under 45	4	1.37 (1.18–1.60)	63.7
History of diabetes	3	0.52 (0.14–1.97)	94.8
History of smoking	2	0.28 (0.22–0.36)	11.6
History of heavy alcohol use	2	0.24 (0.15–0.39)	77.8
Interferon-γ 874T/A	4	1.03 (0.53–2.01)	83.0
Toll-like receptor-2 Arg753Gln	2	0.71 (0.38–1.33)	0.00
Tumor necrosis factor-α 308G/A	3	1.21 (0.82–1.79)	0.00
Macrophage protein P2X7 1512A/C	3	2.28 (0.88–5.90)	92.9
Interleukin-10 1082G/A	4	0.88 (0.65–1.19)	38.2

The data show that the factors associated with a statistically higher proportion of extrapulmonary to pulmonary desease are female gender or age under 45 while the factors associated with a statistically lower proportion of extrapulmonary to pulmonary disease are African ancestrage and a history of smoking or alcohol usage (Table 1).

The largest number of studies available for meta-analyses were for gender (17), followed by HIV positivity (7), black African ancestry (4), age cutoff at 45 (4), and interferon-γ

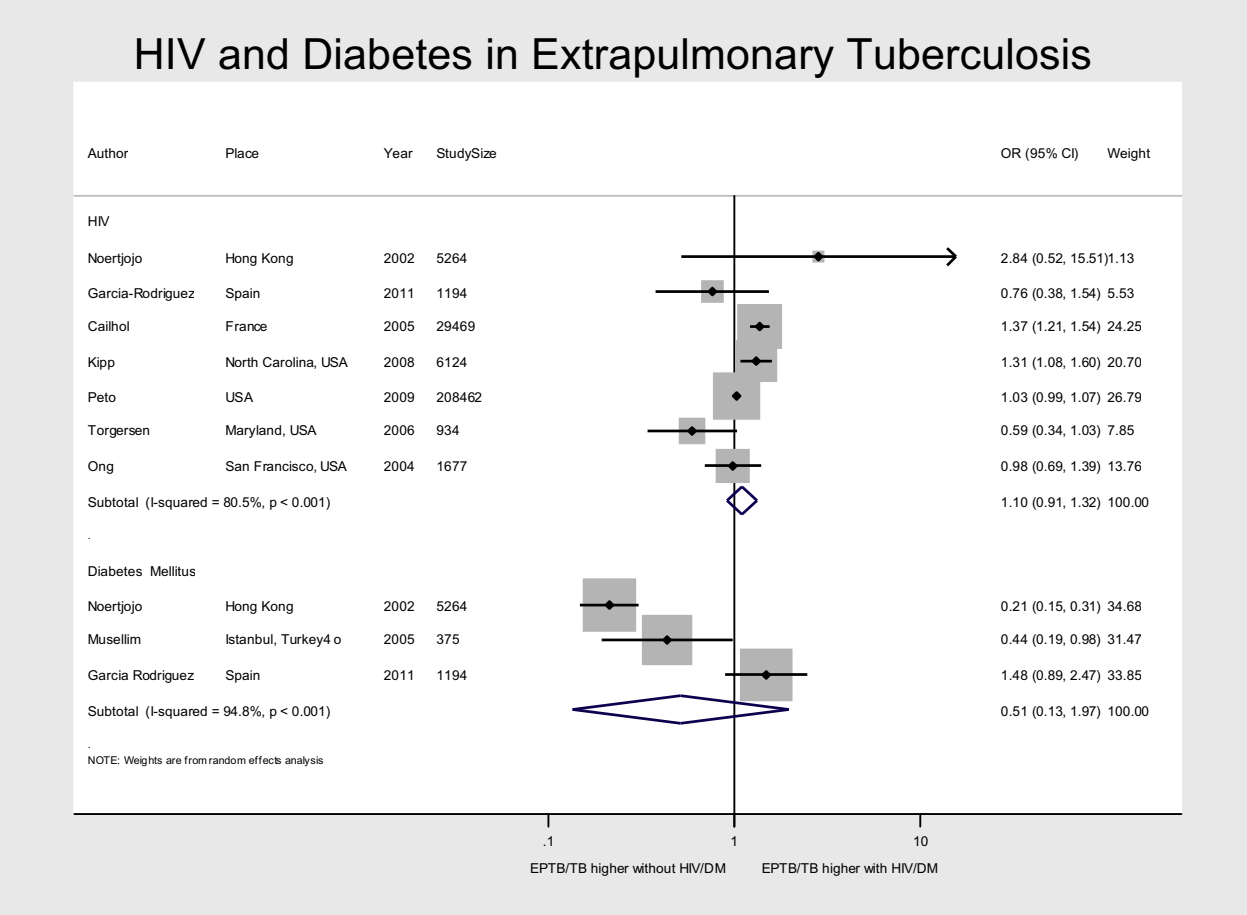

Fig. 2 – The odds ratio of extrapulmonary to pulmonary disease (EP/P) with 95% confidence intervals for human immunodeficiency virus (HIV) infection status and diabetes. Subtotal *I*-squared = 80.5% and 94.8%, respectively, *P* < 0.001 for both for models, random effects model.

874T/A and interleukin-10 1082G/A polymorphisms (4). A smaller number of studies were available for meta-analyses for a history of diabetes (3), a history of heavy drinking (2) or a history of smoking (2), and with the polymorphisms in P2X7 1512A/C (3), tumor necrosis factor-α 308G/A (3), and toll-like receptor -2 Arg753Gln (2).

Both female gender and youth were significantly associated with a higher ratio of extrapulmonary to pulmonary disease (Table 1, Fig. 1) with HIV-positivity showing a weak association (Table 1, Fig. 2). A history of diabetes, heavy alcohol usage or smoking was all associated with a lower ratio of extrapulmonary to pulmonary disease. Among the immunologic factors assessed in this study, the P2X7 (-1513 A/C) and TNF-α (-308 G/A) polymorphisms showed a higher ratio of EPTB to PTB, whereas the TLR-2 (-753 Arg/Gln) and IL-10 (-1028 G/A) polymorphisms showed trends toward lower EPTB to PTB ratios. There was no detected association between the interferon-gamma (IFN-γ) polymorphism examined and the EPTB/PTB ratio (Table 1, Fig. 3).

The random-effects model was applied with the presence of significant heterogeneity among studies showing high *I*-squared value for all but four factors: black African ancestry history of smoking, and two of the cytokine/immune polymorphisms (the TLR-2 and TNF-α reported polymorphisms) (Table 1).

Discussion

The extrapulmonary dissemination of TB is the subject of multiple past reviews. These reviews include variables showing a greater predilection by female gender, HIV infection, race, age and personal history of diabetes, alcoholism and smoking. The more recently recognized role of multiple biologic pathogen factors is much harder to analyze, for while at least 10 such factors are now identified (including interleukin-1 receptor polymorphisms [13–16], IFN-γ [13,16,17], interleukin-6 [13,14,16], interleukin-12 [18], toll-like receptor 2 [15,17,19–21], CCL2 [22,23], and NRAMP [now called solute carrier family 11A1 or SLC11A1] [24–26]), there are few studies examining their role in the pathogenesis of the different forms of TB.

Gender was identified in an assessable fashion in 17 studies [8,14,15,19,23,27–36]. As emphasized in the large CDC review [33], men are at greater risk for both pulmonary and extrapulmonary TB, but the male to female ratio is lower for extrapulmonary disease. This is evident in Fig. 1 where the

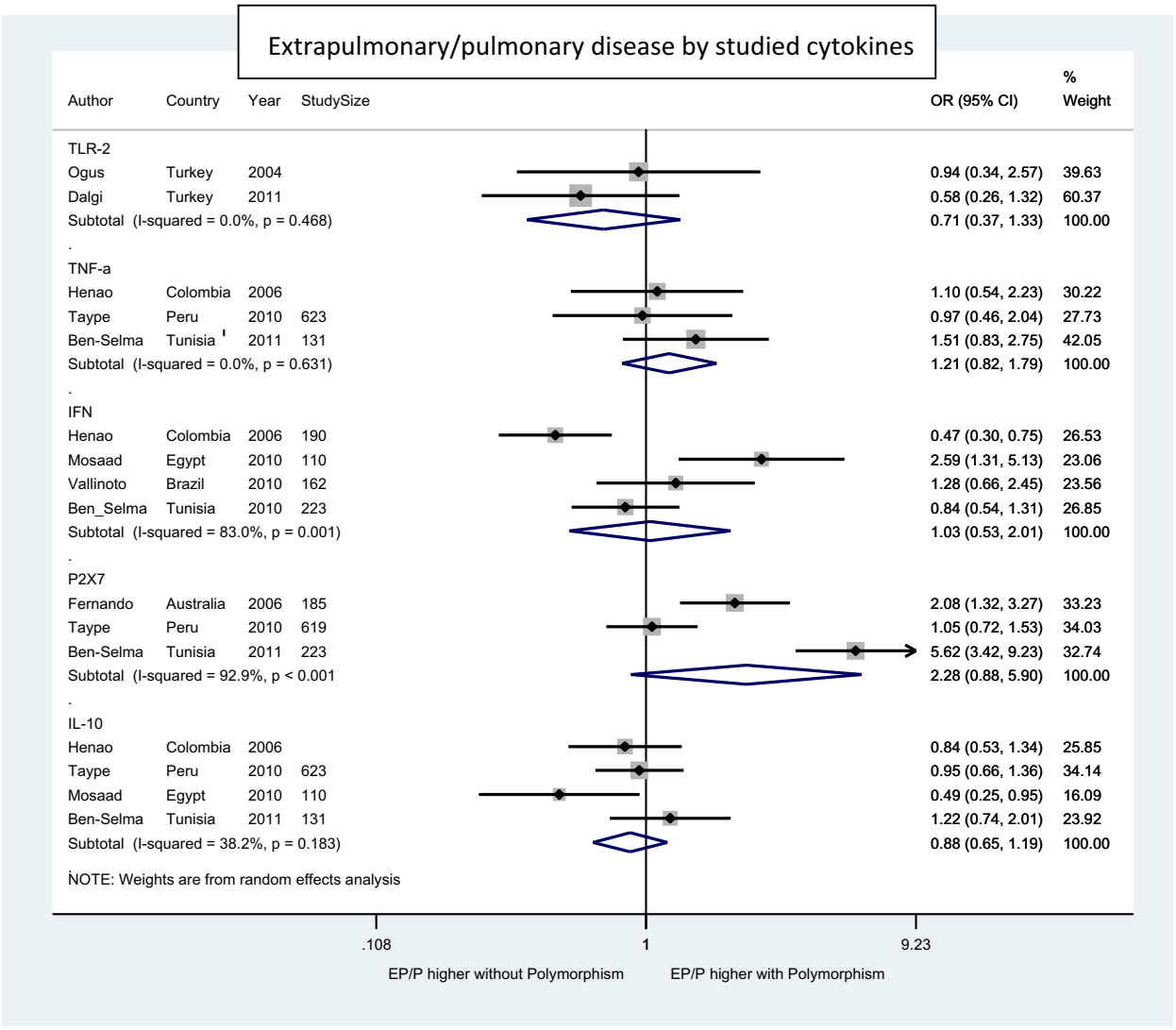

Fig. 3 – The odds ratio of extrapulmonary to pulmonary disease (EP/P) with 95% confidence intervals for five selected cytokine and immunologic polymorphisms. TLR, toll-like receptor; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; P2X7, purinoreceptor 7; *I*-square and *P* values given on chart, random effects model.

ratio of extrapulmonary to pulmonary disease is shown to be higher in women.

HIV infection is the classic immunosuppressive state thought to be associated with extrapulmonary dissemination although the reports from Turkey of the association with systemic lupus erythematosus [9] predate this. In compiling the seven studies in a meta-analysis [8,28,29,32,33,35,37], the combined odds ratio suggests that the extrapulmonary dissemination occurs at only a slightly increased level with HIV infection.

The diversity of races makes race a difficult factor to study. Because a group of articles report African ancestry in comparison with other races, the racial analysis was limited to the four studies [15,32,33,35], which include mention of black African vs. other ancestry. The large CDC study [33] is allotted nearly the entire weight in this meta-analysis (99%) and therefore it is not surprising that the meta-analysis odds ratio corresponds closely with that of the large CDC study. Thus, while African ancestry is known to predispose to TB, there is only a minimal black racial predilection towards EPTB based on this analysis.

Age is another factor difficult to study because of the inconsistency of age grouping or cutoffs. The use of age 45 in a dichotomous fashion does not allow for assessing a gradation with age. The four articles with this age [8,32,35,36] cutoff showed as expected a lower odds ratio for extrapulmonary/pulmonary disease among patients older than 45.

A new set of articles shows the importance of diabetes mellitus in predilection toward TB, but only three were included in the meta-analysis [29,31,37] due to exclusion criteria. The results suggest a lower predilection for extrapulmonary disease in diabetics although the severity of diabetes could not be assessed and the anticipated confounding effect of age complicates any analysis.

With respect to the habits of drinking or smoking, the small number of studies included in the meta-analysis showed higher rates of extrapulmonary disease in those not

engaged in these habits. Again, such factors would in a large, future study need analysis of co-factors, including especially age and gender.

The impacts of various immunologic factors on the clinical form of TB are studied in but a few papers to date.

The strongest association was with the purinoceptor 7 (P2X7) receptor polymorphism. This protein receptor is a selective cation channel found in high concentration on macrophages. Its activation induces apoptosis and activates phospholipase D, which promotes mycobacterial killing in macrophages [38]. The inability of such macrophages to appropriately kill mycobacteria might predispose one to disseminated disease.

The role of TNF-α in controlling TB in humans is recognized from the high incidence of TB in rheumatoid arthritis patients taking anti-TNF-α monoclonal antibodies [14]. TNF-α is also implicated in host-mediated lung damage [14,39]. The -308 G/A polymorphism upregulates TNF-α production and is known to be associated with severe forms of other infectious diseases [14,40]. There are mixed data on whether this polymorphism increases susceptibility to TB [14,39,40], but higher serum concentrations of TNF-α are seen in association with severe vs. mild TB [40]. High levels of TNF-α may damage host tissues and impair containment of mycobacteria.

The TLR-2 (-753 Arg/Gln) polymorphism showed the lowest ratio of EPTB to PTB (yet not statistically significant) among biologic factors studied. TLR-2 activates macrophages in response to mycobacteria [19,41] and leads to further cytokine production, including TNF-α [19]. Several TLR-2 polymorphisms are implicated in TB disease, and it is reported that a number of these polymorphisms may be associated with extrapulmonary disease [21]. The TLR-2 polymorphism examined herein leads to decreased macrophage response and is found more often in patients diagnosed with TB [41]. This same polymorphism is implicated in susceptibility to other infectious diseases, including group A hemolytic Streptococcal infections [19]. The impaired recognition of mycobacteria with this TLR-2 polymorphism is consistent with the data reported herein showing a lower EPTB/PTB ratio.

The anti-inflammatory cytokine IL-10 down-regulates the Th1 immune response and lowers levels of IFN-γ. Previous studies show varied associations between IL-10 polymorphisms and susceptibility to TB [14,39,42]. IL-10 can "deactivate" macrophages and reduce mycobacteria-induced apoptosis of macrophages. IL-10 deficient mice show improved immunity to mycobacteria [14]. This studied polymorphism is associated with a low IL-10 state [14,42] which can lead to an increase in macrophage activity. This improved immune response may help to contain the infection at the initial infection site in the lungs and prevent dissemination, leading to a lower EPTB/PTB ratio as seen in these data. (Table 1).

IFN-γ is an important cytokine down-regulated by IL-10, also involved in the activation of macrophages and subsequent destruction of mycobacteria [14,27,42,43]. The -874 T/A polymorphism studied herein reduces IFN-γ levels, a state associated with a higher frequency of TB when compared with healthy controls [27,42,43]. The low IFN-producing allele is reportedly seen more often both in EPTB [43] and PTB [14]. Differences in populations and therefore a myriad of other co-factors likely account for this discrepancy and these data do not suggest a significant association between IFN-γ and the ratio of EPTB/PTB.

Is there a specificity of organ system involvement based on immunologic factors? In former reports, systemic cases of TB showed a predilection for HLA type DQB1*03 [44]. The tendency of TB to manifest itself in non-respiratory tissue dates to historical discussions, particularly those of Johns Hopkins pathologist Arnold Rich, who described central nervous system TB as the breakdown of a granulomatous focus (later called a "Rich focus") [45]. Today, the many manifestations of TB suggest that a variety of pathogenic mechanisms can be associated with extrapulmonary dissemination, especially among the immunosuppressed. It is not unreasonable that tissue specificity may be impacted by HLA status, but most extrapulmonary disease is not associated with unique HLA loci.

The summary odds ratio table (Table 1) provided shows that demographic, epidemiologic, and clinical factors are to date strong factors in increasing the risk for extrapulmonary dissemination of TB. Whether or not select polymorphisms of cytokines and immunologic factors will be more important in the future remains speculative. Because most of these latter studies were only carried out in the last three to four years and at a limited number of institutions, it will be important to reassess their relative importance in determining the risk of the dissemination of TB in the future.

Some of the data assessed in the meta-analysis are limited by the number of studies available for inclusion. In many excluded studies, the data were reported in sufficient detail, but the definition of what constitutes an extrapulmonary case would not allow inclusion. Other useful data were excluded because pulmonary and extrapulmonary diseases were counted only as part of the EPTB group or the two were reported together. Such differences in definitions between and within countries suggest the need for more uniform and international standardized definitions in TB epidemiology.

Several I^2 values calculated to assess heterogeneity among studies included in meta-analysis are above 75%, a substantial amount of heterogeneity [12]. Given that included studies varied considerably in terms of design, purpose, size and geography, the authors feel this level of heterogeneity was inevitable. The ideal meta-analysis contains large numbers of non-heterogeneous studies, and these data point to the need for improved data collection and the surveillance of existing scientific data, especially in the emerging field of cytokines.

Other factors that need assessment are the considerable geographic variability for extrapulmonary disease, a variability that may be a function of different assays, of immunogenetic factors, of socioeconomic factors, or of selective reporting characteristics (why do rates of reported extrapulmonary disease range from 7% in China to 22.3% in Afghanistan, and 37% in Cambodia?) [4]. Immigrants in several studies show higher rates of extrapulmonary disease than do native populations, and the proportion of immigrants may also explain geographic foci of higher prevalence of extrapulmonary disease [30,46,47]. The role of TB resistance is also important and shows that many factors other than the ones listed here may be important in determining the risk for extrapulmonary dissemination [33,48].

In summary, the results here suggest that the prototype for extrapulmonary TB is a young woman who is HIV-infected,

but does not have diabetes mellitus and who does not smoke or drink excess alcohol, while the prototype for TB that does not disseminate is an elderly male who smokes and drinks excess alcohol, but who is not HIV-infected. The former patient is more likely to show lower levels of functional, active protein P2X7 receptor. Future studies of the extrapulmonary dissemination of TB should in particular concentrate on this molecular factor. The presence and use of such clinical and molecular factors may in the future be prognostic in determining which patients are likely to show or to develop disseminated disease.

Conflict of interest

The authors declare no conflicts of interest.

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