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Mortality and Comorbidities of Tuberculosis in Rheumatoid Arthritis – A Retrospective Clinicopathologic Study of 161 Autopsy patients

Miklós Bély[1*] and Ágnes Apáthy[2]

[*1]*Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary.*

[2]*Department of Rheumatology, St. Margaret Clinic, Budapest, Hungary.*

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ABSTRACT

Tuberculosis (TB) is one of the most important diseases accompanying rheumatoid arthritis (RA).The aim of this study was to determine the prevalence and *mortality* of post-primary fibrous or fibrocaseous TB (fTB or fcTB) with or without miliary dissemination (**mTB**), to analyze the relationship between fTB, fcTB or mTB and mortality or clinical diagnosis of TB, and to assess the possible influence of fTB, fcTB or mTB on the prevalence and mortality of comorbidities: atherosclerosis (Ath), hypertension (HT) or adult type 2 diabetes mellitus (DM) in a random autopsy population of RA patients.

Patients (autopsy population) and methods: At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 with RA which were autopsied. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR). TB was detected at autopsy and specified histologically, all available clinical and pathological reports were retrospectively reviewed. Demographics of different patient cohorts were compared with the Student (Welch) t-probe.

The relationships were analyzed between fTB**,** fcTB**,** mTB and comorbidities (Ath, HT or DM) with Pearson's chi-squared (χ^2) test.

Results: Post-primary TB localized to the lungs accompanied RA in 21 (13.04% of 161) patients. TB was inactive fTB or fcTB in 15 RA patients and was complicated with active military dissemination (mTB) in further 6 patients. fcTB complicated by mTb led to death in 2 female patients; the cases were not recognized clinically (clinically only 2 not fatal fTB was diagnosed). The chance of survival decreased significantly in RA patients with fcTB or mTB; the fTB did not influence statistically the lifespan of RA patients. The link between clinical diagnosis and mortality of TB was not significant, indicating the incidental nature of diagnosis. TB (fTB, fcTB or mTB) and comorbidities (Ath, HT or DM) were sovereign associated diseases in RA, which were present at the same time; TB and Ath led to death independently from each other.

Discussion and Conclusions: The prevalence of post-primary TB was higher in RA autopsy patients compared to the general population of Hungary. Inactive fTB or fcTB (n=15) and active mTB (n=6) developed at any time in the course of RA. The presence of fcTB or mTB did increase the risk of mortality of RA patients, while consolidated anthracotic scars (fTB) did not. Women were more likely to be affected by TB in RA, in contrast to to the European general population, where more males died of TB, than females. The risk of active miliary dissemination (mTB) and fatal outcome was particularly high in women, who died earlier then women without mTB. The onset, and duration of RA did not influence the prevalence and mortality of inactive or active TB.

Keywords: Rheumatoid arthritis, Latent tuberculosis, Mortality, Clinical diagnosis, Comorbidities

ABBREVIATIONS

RA: Rheumatoid Arthritis; ACR: American College of Rheumatology; TB: Tuberculosis; fTB: Fibrous TB; fcTB: Fibrocaseous TB; mTB: Miliary TB; **csDMARDs**: **C**onventional **S**ynthetic **D**isease **M**odifying **A**ntirheumatic **D**rugs; **bDMARDs** or **boDMARDs**: **B**iological **O**riginal **D**isease **M**odifying **A**ntirheumatic **D**rugs; Ath: Atherosclerosis; HT: Hypertension; DM: Diabetes Mellitus; RhV: Rheumatoid Vasculitis; AAa: Amyloid A Amyloidosis; SI: Septic Infection; PA: Purulent Arthritis; Pr n/y – Protocol Number /Year; Cl+: Clinically Diagnosed; Cl-: Clinically Not Recognized; **SD: S**tandard **D**eviation; **ND**: **N**o **D**ata; **NS**: **N**ot **S**ignificant; HE: Hematoxylin-Eosin Staining; c – Coefficient of Colligation; IGRAs: Interferon-Gamma (γ) Release Assays

Corresponding author: Miklós Bély, Department of Pathology, Hospital of the Order of the Brothers of Saint John of God, H-1027 Budapest, Frankel L. 17-19, Hungary, Tel: (06-30) 2194142; E-mail: dr.bely.miklos@gmail.hu

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INTRODUCTION

Tuberculosis (TB) is one of the most important diseases accompanying rheumatoid arthritis (RA) beside atherosclerosis (Ath), hypertenson (HT), and adult type 2 diabetes mellitus (DM) [1]. The risk of TB is higher in patients with RA than in the general population [2 – 6] and especially high when the patients are treated with steroids, and conventional or biological disease-modifying antirheumatic drugs (cDMARDs or bDMARDs) [7].

Introduction of bDMARDs (TNF inhibitors, etc.) increases the risk of reactivation of dormant TB in RA [8–9].

OBJECTIVE

The subject of this study was to assess the risk of clinically latent (not diagnosed) indolent TB in RA in the era of steroid and cDMARDs, before introduction of the bDMARDs. The aim was to determine the prevalence and mortality of post-primary inactive fibrous or fibrocaseous TB (fTB or fcTB) with or without miliary dissemination (mTB), to analyze the relationship between fTB, fcTB or mTB and mortality or clinical diagnosis of TB, to assess the possible influence of fTB, fcTB or mTB on the prevalence and mortality of comorbidities (Ath, HT or DM) in a non selected (random) autopsy population of RA patients.

Patients (autopsy population) and methods

Of special significance is the fact that until the end of the 20th century all patients who died in a hospital in Hungary were autopsied. This study is based on this unique autopsy population of our Pathology Department [1]. At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 non-selected patients with RA. All patients who died with RA were treated in one institute in an era of steroid and csDMARDs, before introduction of bDMARDs. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [10]. TB was detected at autopsy and specified histologically, retrospectively reviewing all available clinical and pathological reports. From each patient a total of 50-100 tissue blocks of 16 organs (heart, lungs, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal gland, skeletal muscle, peripheral nerve, skin, brain, bone and synovial membrane of hip- and knee-joint) were studied microscopically [1].

The tissue blocks were fixed in an 8% aqueous solution of formaldehyde at pH 7.6 for >24 hours at room temperature (20 C^{o}) and embedded in paraffin. Serial sections (5 microns) were stained with hematoxylin-eosin (HE) [11]. In case of fTB, fcTB or mTB additional histological sections were stained according to Ziehl-Neelsen [12] using a positive control in each case. Atherosclerosis (Ath) was diagnosed in RA patients only when it was present macroscopically as a "severe" atherosclerotic process (characterized by occlusive thrombosis or sclerotic ulcers) or, when it was the basic disease leading to death. Moderate changes like hyaline or sclerotic plaques – without causal role in death – were not mentioned as "atherosclerosis"; such changes are frequent in elderly RA patients. The diagnosis of HT and DM were based on clinical data.

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [13]. The difference between two samples was regarded "significant" at an alpha level of 0.05. The relationships were analyzed with person's chi-squared (χ^2) test [13] comparing fTB, fcTB or mTB and mortality of TB, fTB, fcTB or mTB and clinical diagnosis of TB, furthermore fTB, fcTB or mTB and prevalence and mortality of comorbidities (Ath, HT or DM) in RA.

RESULTS

Prevalence of TB, fTB, fcTB or mTB

Post-primary fTB (n=12) or fcTB (n=9) localized to the lungs accompanied RA in 21 (13.04% of 161) patients.

One of 12 fTB and 5 of 9 fcTB were complicated by disseminated mTB in 6 (3.7% of 161; 28.57% of 21) RA patients. Miliary epitheloid granulomatous inflammation was not observed without post-primary fTB or fcTB.

There was a significant and positive association between fibrocaseous character of post-primary tuberculotic foci and mTb (c=0.9895, χ^2 =56.8924, p < 0.000000000000046). fTb did not favor (promote) the military dissemination; the link between fTb and mTb was not significant (c=0.4472, χ^2 = 0.0070, p <0.9333 – NS).

Table 1 summarizes the demographics, onset and duration of RA in patients with TB (n=21), inactive fTB or fcTB (n=15) and active mTB (n=6), with (n=2) and without (n=19) fatal outcome, furthermore without TB (n=140).

Comparing the age, onset, and duration of RA at the time of death there was no significant difference in lifespan (p <0.870 – NS), onset (p< 0.321 – NS) or duration of RA (p< 0.109 – NS) between patient cohorts with inactive (fTB, fcTB: n=15) and active (mTB: n=6) TB. We found that miliary dissemination (mTB) could have developed at any time in the course of RA accompanying with TB. In our autopsy population only, female patients were involved with mTB. Comparing the age, onset of RA, and duration of disease in women at death, there was no significant difference in lifespan (p <0.614 – NS), onset (p <0.434 – NS), or duration of RA (p <0.133 – NS) between women with inactive (fTB, fcTB n=9) and active tuberculosis (mTB n=6); mTB developed in women at any time in the course of RA accompanying with TB. Duration of RA was significantly shorter in patients who died in mTB (n=2) compared to the patients who did not die in mTB (n=19) (7.50 years versus 15.58 years, p <0.016). Duration of RA was significantly shorter in women who died in mTB (n=2)

compared to the women who did not die in mTB (n=13) (7.50 years versus 16.92 years, p <0.044).

Table 1. Sex mean age with SD, range, onset and disease duration of 21 RA patients with TB, inactive fTB, fcTB and active mTB, with or without fatal outcome, and without TB.

Sex	Number of autopsies	Mean age in years at death ± SD	Range (in years)	Mean age at onset of disease ± SD	Disease duration (in years) ± SD
RA patients (total)	**161**	**65.32±12.95**	**16 – 88**	**50.83±16.96**	**14.43±10.51**
Female	116	64.95±11.79	16 – 87	50.19±15.70	14.79±10.65
Male	45	66.27±15.50	19 – 88	52.57±19.88	13.46±10.08
with TB	**21 of 161**	**69.00±9.70**	**50 – 84**	**54.19±16.39**	**14.81±12.41**
Female	15	70.20±10.18	50 – 84	54.53±17.88	15.67±13.82
Male	6	66.00±7.59	50 – 78	53.33±11.80	12.67±7.45
without TB	**140 of 161**	**64.77±13.28**	**16 – 88**	**50.22±16.99**	**14.36±10.13**
Female	101	64.17±11.81	16 – 87	49.42±15.15	14.64±9.97
Male	39	66.31±16.38	19 – 88	52.42±21.08	13.61±10.51
Inactive fTB, fcTB	**15 of 21**	**69.27±9.07**	**56 – 84**	**52.40±18.37**	**16.87±13.84**
Female	9	71.44±9.32	57 – 84	51.78±21.65	19.67±16.20
Male	6	66.00±7.59	56 – 78	53.33±11.80	12.67±7.45
Active mTB	**6 of 21**	**68.33±11.09**	**50 – 82**	**58.67±8.24**	**9.67±4.85**
Female	6	68.33±11.09	50 – 82	58.67±8.24	9.67±4.85
Male	0	–	–	–	–
Fatal fcTB with mTB	**2 of 21**	**64.50±6.50**	**58 – 71**	**57.00±7.00**	**7.50±0.50**
Female	2	64.50±6.50	58 – 71	57.00±7.00	7.50±0.50
Male	0	–	–	–	–
Not fatal fTB, fcTB or mTB	**19 of 21**	**69.47±9.86**	**50 – 84**	**53.89±17.05**	**15.58±12.81**
Female	13	71.08±10.36	50 – 84	54.15±18.99	16.92±14.44
Male	6	66.00±7.59	50 – 78	53.33±11.80	12.67±7.45

Figure 1.1 demonstrates the mean age, onset and duration of RA in patient cohorts, and **Figure 1.2** in women with TB (n=21), inactive fTB or fcTB (n=15), active mTB (n=6), with fatal outcome of TB (n=2), and without TB (n=140) at death.

Table 2 summarizes the statistical correlations ("p" values) between female and male RA patients with inactive fTB, fcTB and active mTB, with and without fatal outcome.

Figures 2.1a-f – 2.2a-f demonstrates the mean age, onset and duration of RA in patient cohorts with TB (n=21), inactive fTB or fcTB (n=15), active mTB (n=6), and without TB (n=140) at death.

Mortality of TB, **fTB**, **fcTB** or **mTB**

fcTB complicated by mTb led to death in 2 (9.52% of 21; 1.24% of 161) female patients; TB without mTb was not

fatal. There was a significant correlation between TB and mortality of TB (c=1, χ^2=6.8539, p<0.009), fcTB and mortality of TB (c=1, χ^2=18.4871, p<0.000017) or mTB and mortality of TB (c=1, χ^2=28.6735, p<0.00000009); the chance of survival decreased significantly in RA patients with TB, fcTB or mTB. There was no relation between fTB and mortality of TB (c=-1*, χ^2=0.9039, p<0.3417 – NS); the fTB did not influence statistically the lifespan of RA patients, even the relationship was inverse.

Table 2. Relationship between patient cohorts with inactive fTB, fcTB and active mTB, with and without fatal outcome.

"p" values – Level of significance: p <0.05	**Age**	**Onset of RA**	**Duration of RA**
RA patients n=161 versus pts. with TB n=21 of 161	**0.136**	**p <0.402**	**p <0.898**
Female n=116 of 161 versus n=15 of 21	0.090	p <0.400	p <0.822
Male n=45 of 161 versus n=6 of 21	0.950	p <0.905	p <0.837
With TB n=21 of 161 pts. versus without TB n=140 of 161	**0.093**	**p <0.329**	**p <0.880**
Female n=15 of 21 versus n=101 of 140	0.056	p <0.326	p <0.792
Male n=6 of 21 versus n=39 of 140	0.944	p <0.891	p <0.811
Inactive fTB, fcTB n=15 of 21 vs active mTB n=6 of 21	**0.870**	**0.321**	**0.109**
Female n=9 of 15 versus n=6 of 6	0.614	0.434	0.133
Male n=6 of 15 versus n=0 of 6	-	-	-
InactivefTB, fcTB n=15 of 21 vs without TB n=140 of 161	**0.108**	**p <0.679**	**p <0.521**
Female n=9 of 15 versus n=101 of 140	0.064	p <0.771	p <0.412
Male n=6 of 21 versus n=39 of 140	0.944	p <0.891	p <0.811
With active mTB n=6 of 21 vs without TB n=140 of 161	**0.905**	**p <0.402**	**p <0.159**
Female n=6 of 6 versus n=101 of 140	0.750	p <0.502	p <0.177
Male n=0 of 6 versus n=39 of 140	-	-	-
fatal fcTB-mTB n=2 of 21 vs not fatal TB n=19 of 21	**0.580**	**0.742**	**0.016**
Female n=2 of 21 versus n=13 of 21	0.484	0.773	0.044
Male n=0 of 2 versus n=6 of 21	-	-	-
fatal fcTB-mTB n=2 of 21 vs without TB n=140 of 161	**0,974**	**0,506**	**0.000004**
Female n=2 of 21 versus n=101 of 140	0,968	0,469	0.000003
Male n=0 of 2 versus n=39 of 140	-	-	-
not fatal TB n=19 of 21 versus without TB n=140 of 161	**0,080**	**0,704**	**0.404**
Female n=13 of 21 versus n=101 of 140	0,047	0,604	0.422
Male n=6 of 21 versus n=39 of 140	0,944	0,811	0.891

There was no significant difference between RA patients with inactive fTB or fcTB (n=15) and active mTB (n=6) in mean age, onset or disease duration of RA. Duration of RA was shorter in patients with fatal outcome of TB (n=2), than in patients without fatal outcome of TB (n=19) (7.50 years versus 15.58, p <0.016).The women with fatal outcome of TB (n=2) died earlier then the women without fatal outcome of TB (n=13) (7.50 years versus 16.92, p <0.044).Compering the patient cohorts of TB with fatal outcome (n=2) to the patients without TB (n=140) the duration of RA was also significantly shorter (7.50 years versus 14.36, p <0.000004).Women died significantly earlier with TB of fatal outcome (n=2) then women without TB (n=101) (7.50 years versus 14.64, p <0.000002)

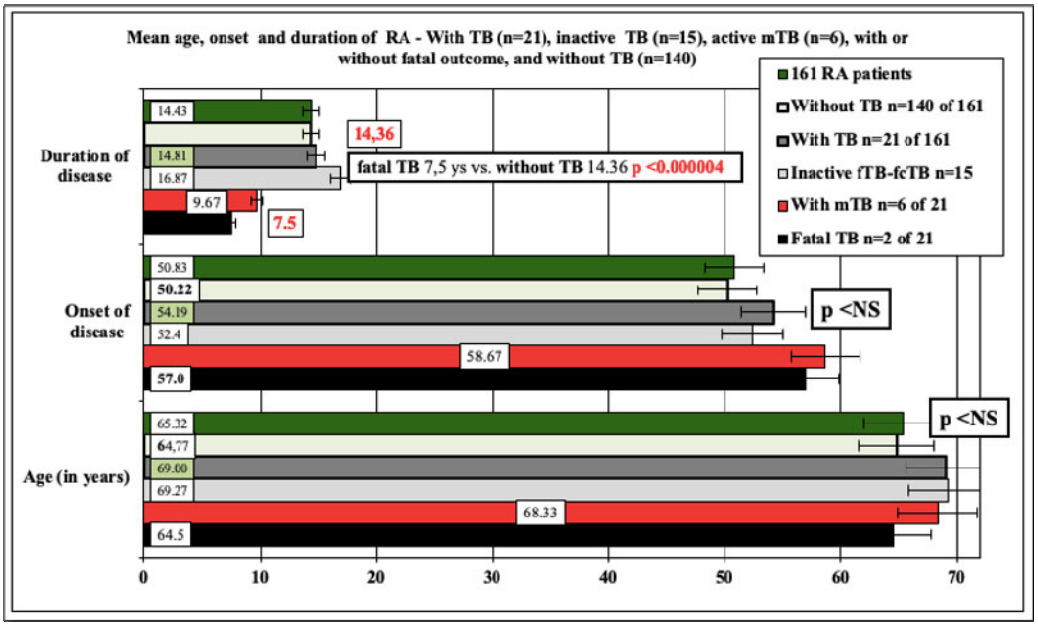

Figure 1.1. Mean age, onset and duration of RA in patient cohorts with TB, inactive fTB or fcTB, active mTB, with fatal outcome of TB, and without TB at death (error bars in %).

The difference in mean age was not significant between patient cohorts with TB, inactive TB, with fatal outcome of TB and without TB; "p" values were higher than 0.05. The onset and duration of RA in patient cohorts did not influence basically the miliary dissemination of coexistent TB (fTB, fcTB, mTB). The patients with active mTB (9.67 years) died earlier than the patients without TB (14.36 years); but these differences were also not significant (p <0.159). The lifespan of patients with fatal outcome of TB was significantly shorter (7.50 years) than that of patients without TB (14.36; p< 0.000004)

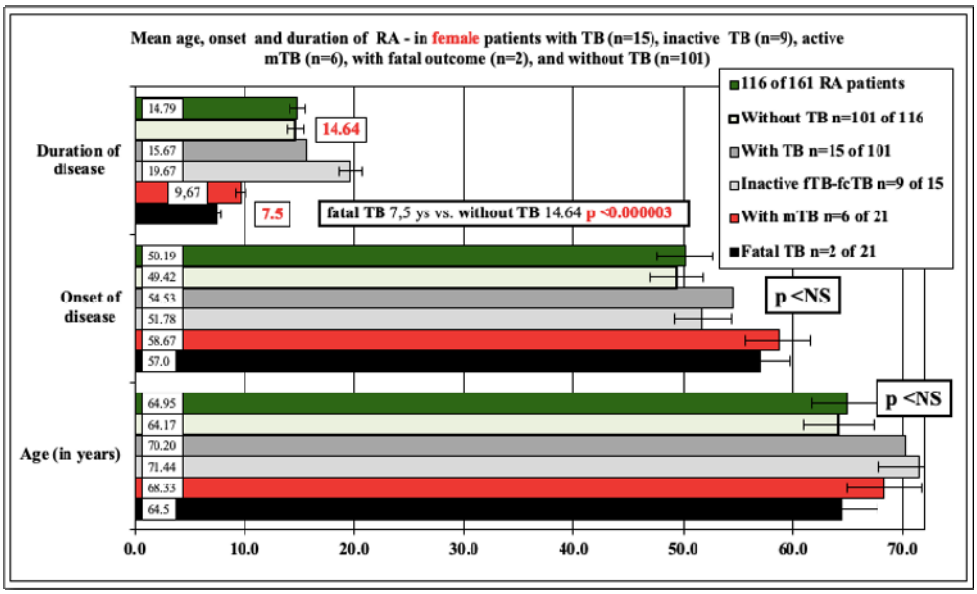

Figure 1.2. Mean age, onset and duration of RA in women with TB, inactive fTB or fcTB, active mTB, with fatal outcome of TB, and without TB at death (error bars in %).

Comparing the age, onset, and duration of RA in women at death, there was no significant difference in lifespan, onset or duration of RA between women with TB, inactive TB, with fatal outcome of TB and without TB; "p" values were higher than 0.05. The women with active mTB died earlier (9.67 years) than the women without TB (14.64 years); but these differences were also not significant (p <0.177). The lifespan of women with fatal outcome of TB was significantly shorter (7.50 years) than the lifespan of women without TB (14.64; p< 0.000003

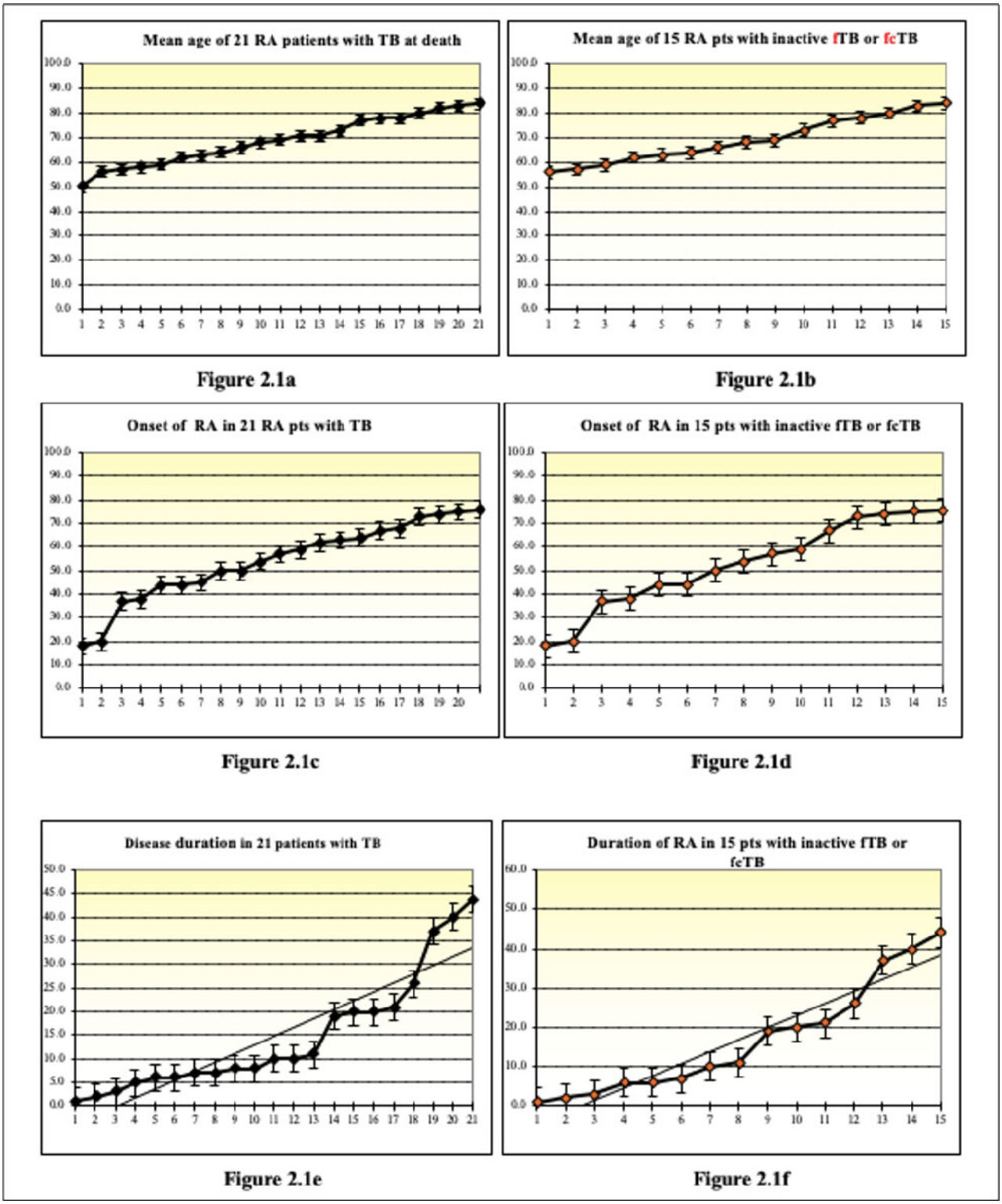

Figure 2.1a-f. Mean age, onset and duration of RA in patient cohorts with TB, and with inactive fTB or fcTB at death (error bars in %).

There was no significant difference in mean age, onset and duration of RA between patient cohorts with TB (n=21) and with inactive TB (n=15)

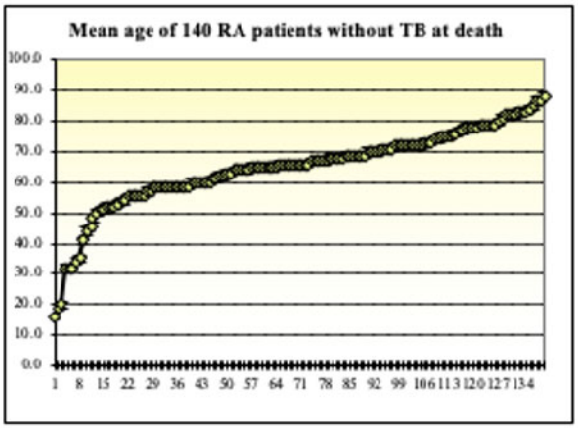

Figure 2.2a

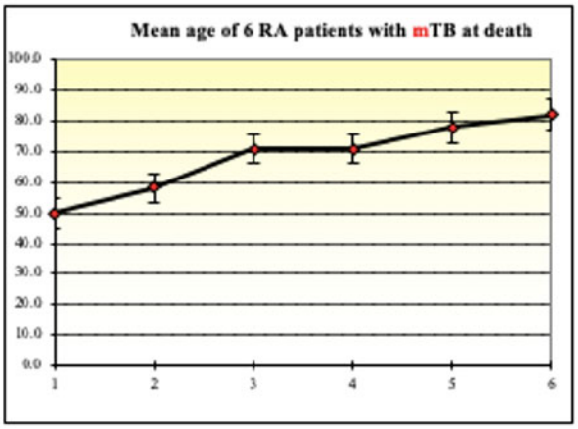

Figure 2.2b

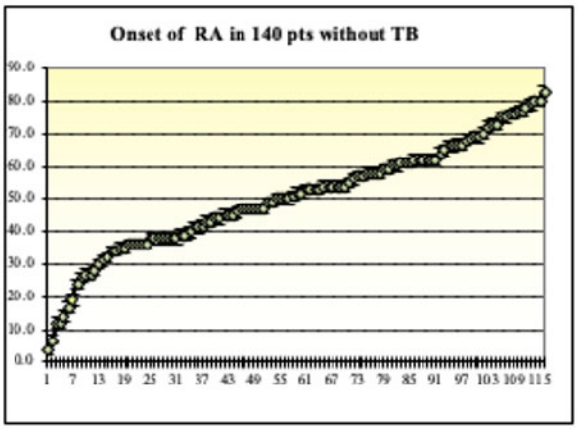

Figure 2.2c

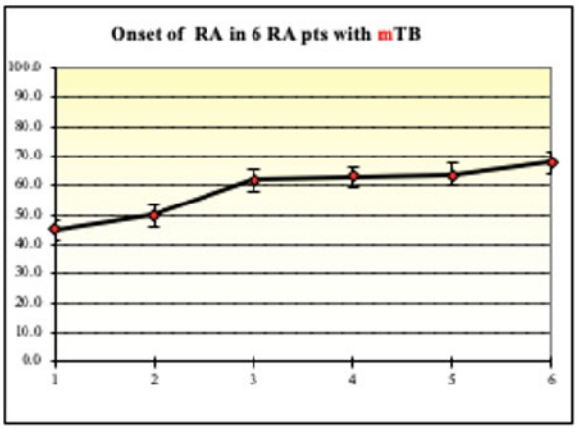

Figure 2.2d

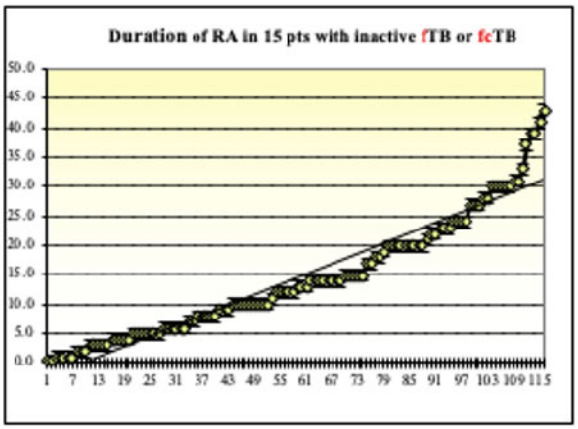

Figure 2.2e

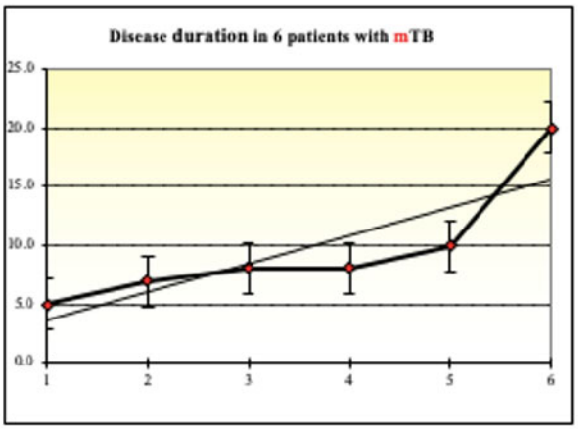

Figure 2.2f

Figure 2.2. A-F. Mean age, onset and duration of RA in patients without TB, and with active mTB (error bars in %).
*The mean age of RA patients at death was higher with active mTB (n=6) than without TB (n=140), but the difference was not significant (68.33 years vs 64.77 years; p<0.905) (**Tables 1** and **2**). The differences regarding the onset (p<0.402) and duration of RA p<0.159) were also not significant **(Table 2)***

Clinical diagnosis of TB, fTB, fcTB or mTB

fTB was mentioned only in 2 (9.52% of 21; 1.24% of 161) patients with consolidated fibrous tubercular scars (the two cases of fcTB complicated by mTB with fatal outcome were not diagnosed clinically). fTB or fcTB was clinically latent (not recognized and/or not mentioned in clinical reports) in 19 (90.48% of 21; 11.80% of 161) patients. The links between clinical diagnosis and mortality of fTB (c=1, χ^2=0.2878, p<0.5916 – NS), fcTB (c=-1*, χ^2=0.2878, p<0.5916 – NS) or mTB (c=-1*, χ^2=0.0138, p<0.9064 – NS) were not significant; the histological appearance or characteristics of fTB, fcTB or mTB did not influence statistically the clinical recognition of TB; the lifespan or mortality did not influence the positive clinical diagnosis (the positive clinical diagnosis was independent from the lifespan or mortality). Prevalence, mortality and clinical diagnosis of TB, fTB, fcTB with or without mTB are summarized in **Table 3** and **Figures 3.1-3.5**.

Figure 3.1 demonstrates the distribution of inactive fTB or fcTB (n=15) and active mTB (n=6) in 21 RA patients with TB.

Mortality of TB with miliary dissemination (mTB) (n=2 of 6) is demonstrated in **Figure 3.2**.

Figure 3.3 demonstrates the prevalence of fTB or fcTB post-primary tuberculotic foci in the lungs with or without miliary dissemination (mTB) in 21 RA patients with TB.

Figure 3.4 demonstrates the distribution of fTB, fcTB or mTB with or without fatal outcome in 21 RA patients with TB.

Figure 3.5 demonstrates the clinical diagnosis of fTB, fcTB or mTB with or without fatal outcome in 21 RA patients with TB.

Table 3. Prevalence, mortality and clinical recognition of TB, fTB, fcTB with or without mTB in 21 of 161 RA patients.

RA population n=161	**Inactive fTB or fcTB without mTB**	**fTB or fcTB with active mTB**	**Lethal outcome**	**Clinically diagnosed**
TB n=21 (13.04%) of 161	**n=15** of 21 (9.32%) of 161 (71.43%) of 21	**n=6** of 21 (3.72%) of 161 (28.57%) of 21	**n=2** of 21 (1.24%) of 161 (9.53%) of 21	**n=2** of 21 (1.24%) of 161 (9.53%) of 21
fTB n=12 (7.45%) of 161 (57.14%) of 21	**n=11** of 12 (6.83%) of 161 (52.38%) of 21	**fTB with mTB n=1 of 12** (0.62%) of 161 (4.76%) of 21	**n=0** of 12	**n=2** of 12
fcTB n=9 (5.59%) of 161 (42.86%) of 21	**n=4** of 9 (2.48%) of 161 (19.05%) of 21	**fcTB with mTB n=5 of 9** (3.11%) of 161 (23.81%) of 21	**n=2** of 9	**n=0** of 9

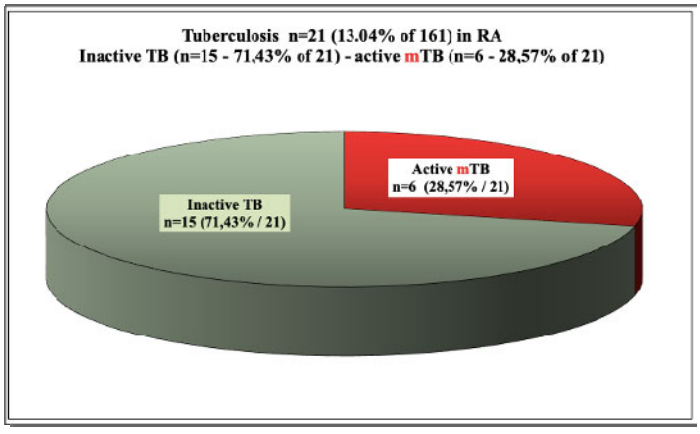

Figure 3.1. Inactive (fTB or fcTB) and active mTB in 21 RA patients with TB.
TB (fTB or fcTB) was inactive in 15 (71.43%) of 21 patients, and was complicated with active miliary dissemination (mTB) in 6 (28.57%) of 21 patients

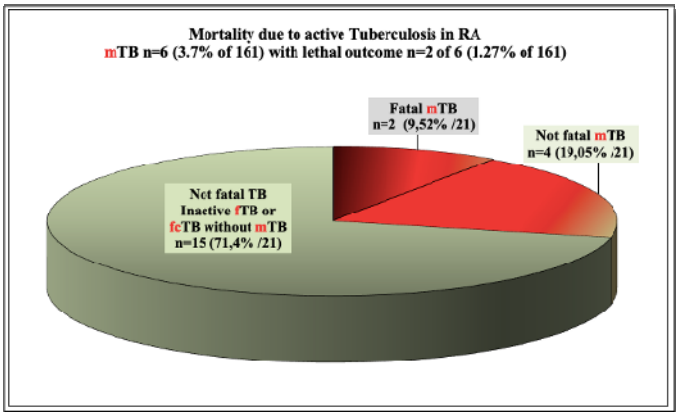

Figure 3.2. Mortality due to active mTB in RA.
Miliary dissemination complicated TB in 6 (28.57% of 21) and led to death in 2 (9.52% of 21) patients. In all other patients post-primary TB was limited or disseminated only terminally, and the patients died of other complications of RA or atherosclerosis ***(see Table 4)***

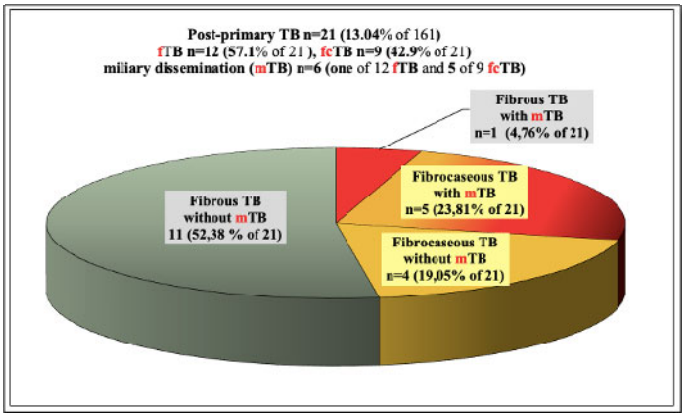

Figure 3.3. Distribution of fTB, fcTB or mTB in 21 RA patients with TB.
There was a significant and positive association between fibrocaseous character of post-primary tuberculotic foci and mTb (c=0.9895, χ^2 =56.8924, p < 0.000000000000046). fTb did not favor (promote) the military dissemination; the link between fTb and mTb was not significant (c=0.4472, χ^2 = 0.0070, p <0.9333 – NS)

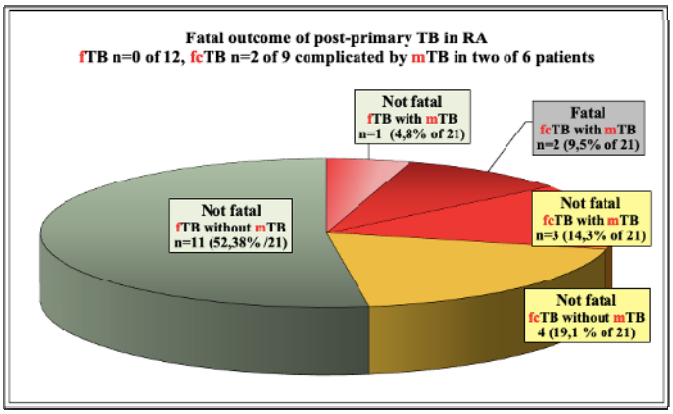

Figure 3.4. Mortality of fTB, fcTB, mTB in 21 RA patients with TB.
There was a significant and positive association between fcTB and mortality of TB (c=1, χ^2 =18.4871, p <0.000017). fTB did not influence the mortality of TB; the association was not significant even negative (c=-1, χ^2 = 0.9039, p <0.3417 – NS).*
**Asterisk indicates negative value of association's coefficient*

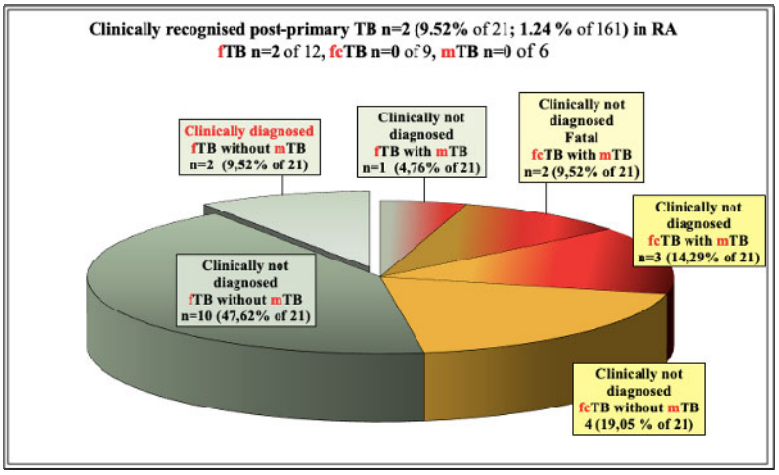

Figure 3.5. Clinical diagnosis of fTB, fcTB or mTB in 21 RA patients with TB.
There was no association between clinical diagnosis and mortality of fTB (c=1, χ^2=0.2878, p<0.5916 – NS), fcTB (c=-1, χ^2=0.2878, p<0.5916 – NS) or mTB (c=-1*, χ^2 =0.0138, p <0.9064 – NS); the fatal outcome or histological character of post-primary tuberculotic foci did not influence the clinical recognition of TB.*
**Asterisk indicates negative value of association's coefficient*

Basic diseases, complications and accompanied disorders in 21 RA patients with fTB, fcTB or mTB

In our autopsy population 2 (1.24% of 161) RA patients died of circulatory failure due to fibrocaseous tuberculosis complicated by miliary dissemination; in one case the extended miliary dissemination and in the second one the involvement of the pituitary gland and collapsed regulation system led to circulatory insufficiency and fatal outcome **(Tables 1 and 2)**. The hematogenous dissemination of post-primary TB was limited in all other patients and involved only a few organs; the patients died of other complications of basic diseases: RA or atherosclerosis (Ath) **(Table 4)**. The most important complications and associated diseases in 21 RA patients with fTB, fcTB or mTB, and the clinical recognition of TB are summarized in **Table 4**.

Ath* was diagnosed in RA patients only when it was present macroscopically as a "severe" atherosclerotic process or when it was the basic disease leading to death. HT** only atherosclerosis related hypertension was listed; RA related hypertension caused by glomerulonephritis or renal AAa, RhV, Cushing syndrome, etc. were not considered. The diagnosis of HT and DM*** was based on clinical data.

Proliferative or exudative epithelioid granulomas (mTB) existed side by side in the same or in different organs, such as lungs, liver, spleen, adrenal glands, synovial membrane, vertebrae, pituitary gland, and lymph nodes.

The organs involved by disseminated military tuberculosis are listed in **Table 5**.

Possible influence of TB (fTB, fcTB or mTB) on comorbidities (Ath, HT or DM) of RA with and without lethal outcome

Atherosclerosis (Ath) accompanied RA in 75 (46.58%) of 161 patients and led directly to death in 37 (22.98% of 161 and 49.33% of 75) cases; Ath in 38 (23.60% of 161 and 50.6 7% of 74) cases was only concomitant (associated disease) without direct causal role in death. TB was associated with Ath in 13 of 75 patients: fTB in 9, fcTB in 4 (one of them complicated by mTB) cases. TB was associated with fatal Ath in 6 patients of 37 patients: fTB in 6, fcTB or mTB in none of 37 patients. TB was associated with concomitant Ath in 7 of 38 patients: fTB in 3, fcTB in 4 (one of them complicated by mTB) cases. The correlations were not significant between TB (fTB, fcTB or mTB) and prevalence of Ath (n=75), TB (fcTB or mTB) and mortality of Ath (n-37) or TB (fTB, fcTB or mTB) and concomitant Ath (n=38). There was a positive and significant correlation between fTB and mortality of Ath (c=0.58, χ^2=5.3478, p<0.0207). Hypertension (HT) was observed in 24 (14.91%) of 161 RA patients; the HT was controlled in all cases and did not lead to death. TB was assotiated with HT in 2 of 24 patients: fTB in 1, fcTB in 1 case (complicated by mTB). The correlations were not significant between TB (fTB, fcTB or mTB) and HT. Adult type 2 diabetes mellitus (DM) was found in 30 (18.63%) of 161 RA patients; the DM was controlled in all cases and did not lead to death. TB was assotiated with DM in 7 of 30 patients: fTB in 5, fcTB in 2 (in one case complicated by mTB). The correlations were not significant between TB (fcTB or mTB) and DM, except fTB and DM, where the relationship was positive and significant (c=0.56, χ^2=4.5372, p<0.0331). Fatal mTB (n=2) was associated with DM in one of two patients and was not with Ath or HT; the

correlations were not significant. The statistical links between TB (fTB, fcTB or mTB) and comorbidities (Ath, Hy or DM) are summarized in **Table 6**.

Figures 4 and 10 demonstrate TB (fTB, fcTB, mTB) with traditional HE is staining, viewed by light microscopy. Original magnifications correspond to the 24x36 mm transparency slide; the correct height: width ratio is 2:3. The printed size may be different; therefore, it is necessary to indicate the original magnifications.

Table 4. Basic disease, complications, cause of death and associated diseases in 21 RA patients with fTB, fcTB or mTB.

	f/m	Basic disease	Complication(s)	Cause of death	Associated disease	Cl + Cl-	Pr n°/year
1	f	fcTB	mTB	Circulatory failure	RA–DM	Cl-	*61/70*
2	f	fcTB	mTB	Circulatory failure	RA	Cl-	*140/70*
3	f	RA	RhV –AAa	Myocardiocytolysis	fcTB–mTB	Cl-	*395/76*
4	f	RA	RhV –AAa	Myocardiocytolysis	fTB–mTB	Cl-	*240/88*
5	f	RA	RhV	Myocardiocytolysis	fcTB–mTB–HT	Cl-	*227/89*
6	f	RA	RhV –Pancarditis	Circulatory failure	fcTB–mTB-Ath	Cl-	*87/90*
7	m	RA	RhV	Circulatory failure	fTB	Cl+	*174/72*
8	m	RA	Fibrinous pericarditis	Circulatory failure	fTB-Ath	Cl-	30/75
9	f	RA	Purulent arthritis	Septic infection	fcTB	Cl-	*287/75*
10	f	RA	Interstitial pneumonitis-ILyH	Multifocal pneumonia	fTB-DM-Ath–HT	Cl-	*115/84*
11	m	RA	RhV	Circulatory failure	fTB-Ath	Cl-	*36/86*
12	f	RA	RhV	Multiple brain necrosis	fTB–CAA–DM	Cl-	*279/87*
13	m	RA	Purulent arthritis	Septic infection	fcTB-Ath	Cl-	*169/89*
14	f	RA	RhV–Pancarditis	Circulatory failure	fcTB–DM-Ath	Cl-	*41/90*
15	f	RA	RhV–Coronary thrombosis	Myocardial necrosis	fcTB–Ca-Ath	Cl-	*65/90*
16	f	Ath	Myocardial fibrosis	Bronchopneumnia	RA–fTB	Cl-	*318/76*
17	f	Ath	Myocardial fibrosis	Circulatory failure	RA–fTB	Cl+	*208/77*
18	f	Ath	Myocardial fibrosis	Circulatory failure	RA–fTB	Cl-	*257/80*
19	m	Ath	Coronary thrombosis	Myocardial necrosis	RA–fTB–DM–G	Cl-	*283/80*
20	m	Ath	Cerebral artery sclerosis	Multiple brain necrosis	RA–fTB–DM–G	Cl-	*62/83*
21	f	Ath	Coronary thrombosis	Myocardial necrosis	RA–fTB–DM	Cl-	*121/87*

Basic Disease: Underlying disease related to death (fcTB complicated by mTb in 2, RA in 13, and Ath in 6 of 21 cases)
Complication: consequence of basic disease leading directly to death (RhV in 8, AAa in 2, SI with PA in 2 of 21 cases, etc.
Associated (Accompanying) disease: important disorder without direct causal role in death (Ath in 7, DM in 7, HT in 2 of 21 cases, etc)
Cl+: Clinically diagnosed, Cl-: Clinically not recognized fTB, fcTB or mTb
Pr n^0/y – Protocol number/year

Table 5. Organs involved by disseminated miliary tuberculosis.

Pr n/year	Post-primary tuberculotic focus in:	Histological character of TB: Fibrous (fTB) or fibrocaseous (fcTB)	Disseminated military TB (mTB) exudative or proliferative granulomas side by side in:
61/70	Lung	fcTB	Lung, liver, spleen, adrenal gland, synovial membrane, vertebrae
140/70	Lung	fcTB	Lung, pituitary gland
395/76	Lung	fcTB	Lung, liver
240/88	Lung	fTB	Lung, spleen
227/89	Lung	fcTB	Lung, lymph node, liver
87/90	Lung	fcTB	Lymph node

Table 6. Relationships between coexistent TB (fTB, fcTB or mTB) and comorbidities (Ath, HT or DM) in 161 RA patients.

Ath, HT or DM vs TB, fTB, fcTB or mTB	Prevalence of Ath n=75 of 161	Mortality of Ath n=37 of 75	Concomittant Ath n=38 of 75	Prevalence of HT n=24 of 161	Prevalence of DM n=30 of 161
TB n=21 of 161	c=0.58, χ^2=3.0642, p<0.0800	c=0.17, χ^2=0.4264, p<0.5137	c=0.27, χ^2=0.2682, p<0.2601	c=-0.28*, χ^2=0.1716, p<0.6787	c=0.44, χ^2=3.4419, p<0.0635
fTB n=12 of 21	c=0.58, χ^2=3.0642, p<0.0800	**c=0.58, χ^2=5.3478, p<0.0207**	c=0.04, χ^2=0.0551, p<0.8143	c=-0.34*, χ^2=0.0592, p<0.8077	**c=0.56, χ^2=4.5372, p<0.0331**
fcTB n=9 of 21	c=-0.05*, χ^2=0.0175, p<0.8946	c=-1.00*, χ^2=1.6355, p<0.2009	c=0.47, χ^2=2.2965, p<0.1296	c=-0.18*, χ^2=0.0233, p<0.8787	c=0.12, χ^2=0.0243, p<0.3760
mTB n=6 of 21	c=-0.64*, χ^2=1.1668, p<0.2800	c=-1.0*, χ^2=0.7555, p<0.3847	c=-0.22*, χ^2=0.0068, p<0.9345	c=0.07, χ^2=0.2123, p<0.6449	c=-0.07*, χ^2=0.1666, p<0.6831
mTB (fatal) n=2 of 6	c=-1.0*, χ^2=0.3791, p<0.5380	**	c=-1.0*, χ^2=0.0022, p<0.9626	c=-1.0*, χ^2=0.6781, p<0.4102	c=-0.6352, χ^2=0.0541, p<0.8160

Bold indicates significant values of association (the difference was regarded significant between two samples at an alpha level of 0.05)
**Asterisk indicates a negative value of association's coefficient.*
The negative association coefficient refers to an inverse link, and the positive association coefficient shows a parallel correlation.
Controlled HT and adult type 2 DM were not fatal in our autopsy population.
***One patient can have only one cause of death*

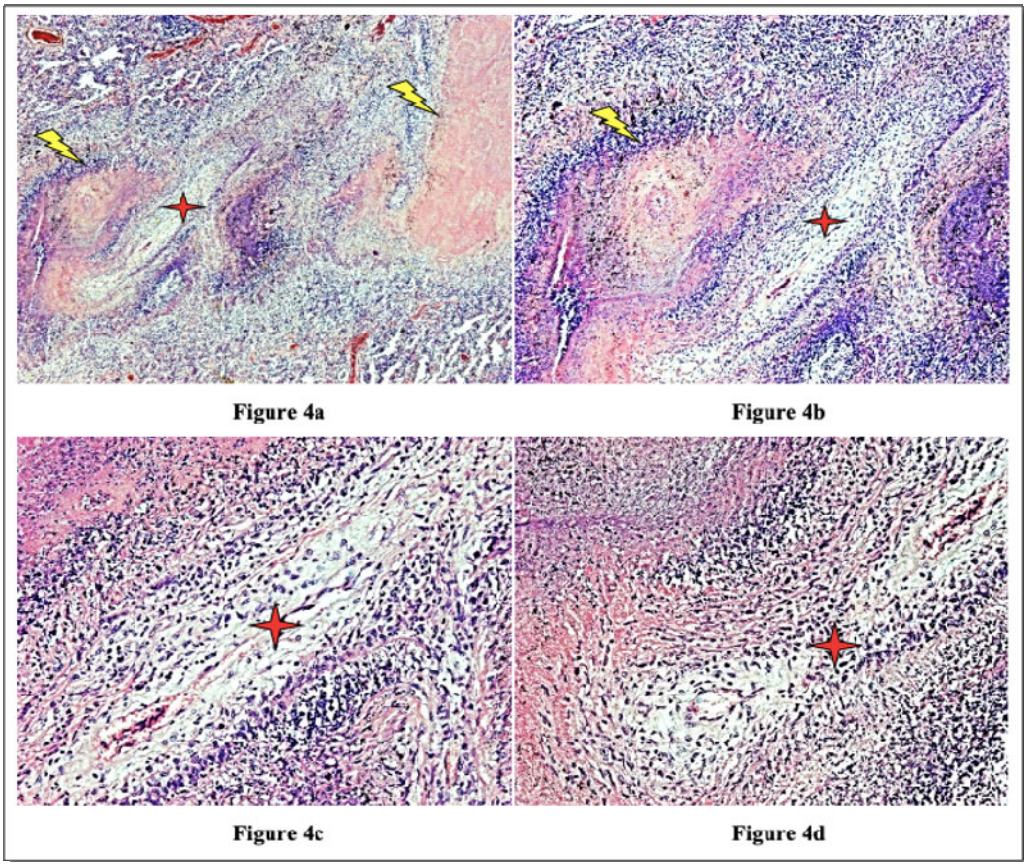

Figure 4a-d. Post-primary fibrocaseous tuberculotic foci (yellow arrows) in the lung with concomitant occlusive arteritis of a small artery (red star), **a**: HE, x 20, **b**: same as (a) x40, **c**: same as (a) HE, x 100, **d**: same as (a) x100.

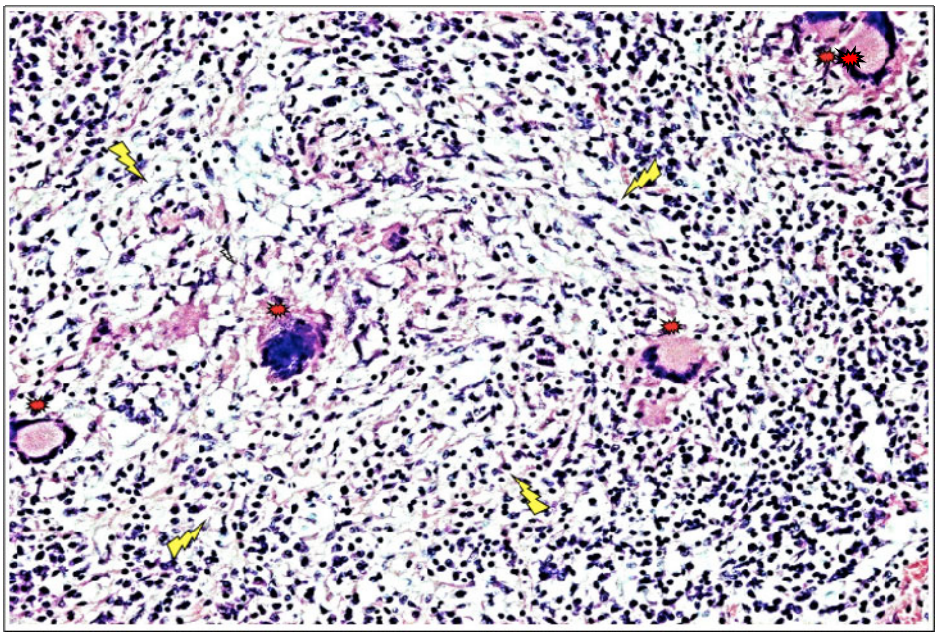

Figure 5. Incipient exudative (yellow arrows) miliary granuloma with giant cells of Langhans (red point) in the lung, **a**: HE, x 100.

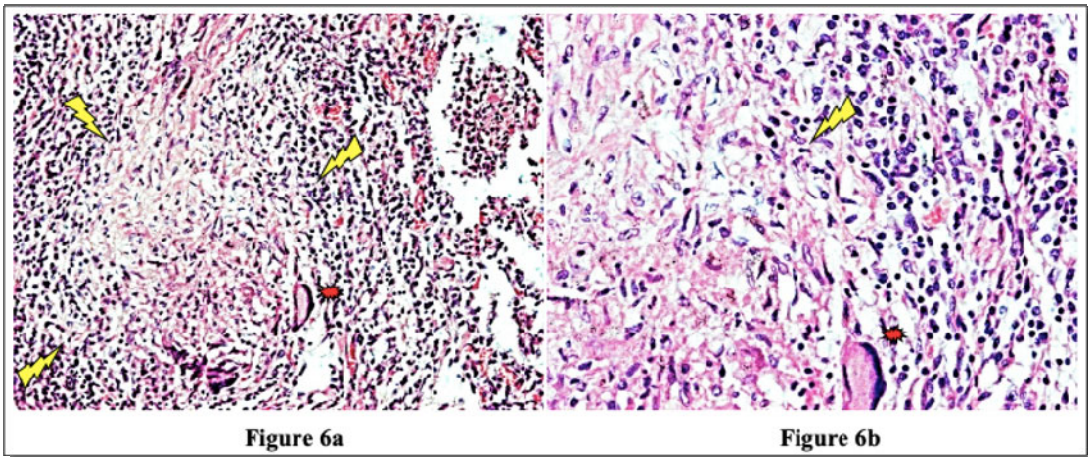

Figure 6a-b. Proliferative miliary granuloma (yellow arrows) with giant cell of Langhans (red point) in the lung a: HE, x 40, b: HE, x 100.

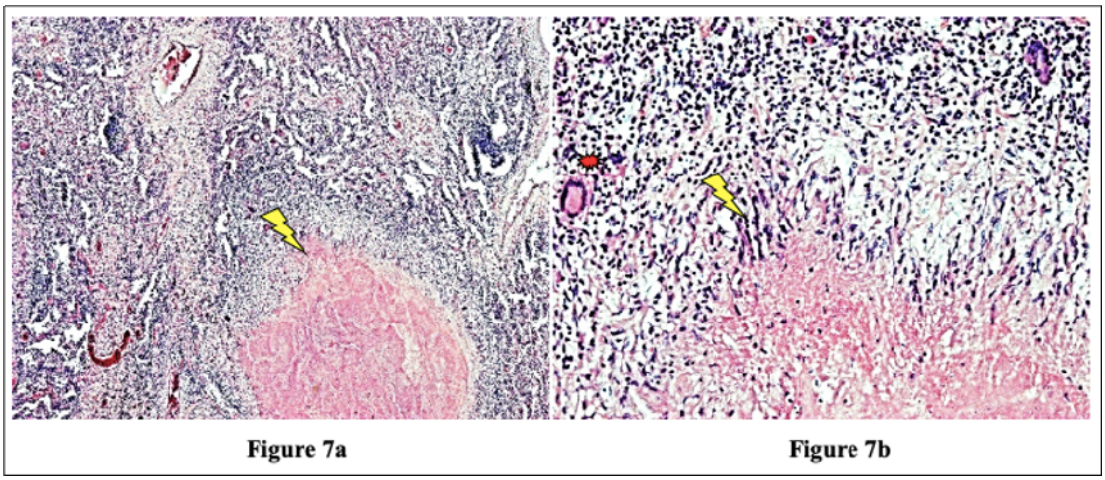

Figure 7a-b. Moderatelly caseous proliferative miliary granuloma (yellow arrows) with giant cell of Langhans (red point) in the lung **a**: HE, x 40, **b**: HE, x 100.

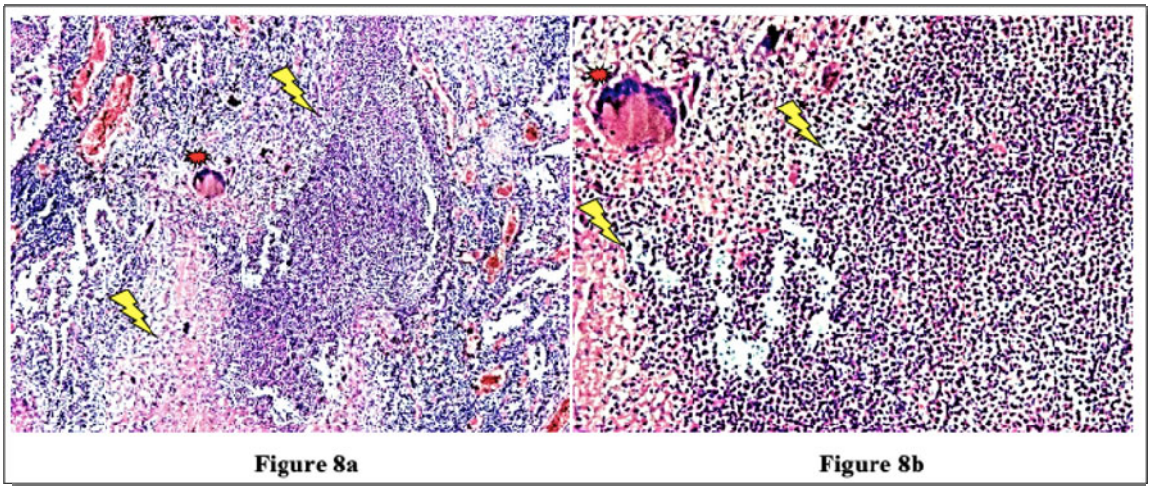

Figure 8a-b. Coalescent miliary granuloma (yellow arrows) with giant cell of Langhans (red point) in the lung **a**: HE, x 40, **b**: HE, x 100.

DISCUSSION

Many studies confirm that the incidence of TB is higher in RA than in the general population [2–6].

The prevalence and mortality of latent TB was also higher in our autopsy population with RA compared to the general population of Hungary [14–16]. Data of the U.S. Department of Health, Tuberculosis Control Division supported this statement as well [17]. Lowell's [17] data roughly refers to the 4th quarter of the 19th century and are comparable to our data of RA patients who died between 1969-1992. The prevalence and mortality of TB is much higher in autopsy population compared to the general population [18]. The risk of encountering TB is reduced with decreasing incidence in the general population; however, it still can be found at autopsy [19]. Histopathology remains one of the most important methods for diagnosing tuberculosis [20]. The histology of tuberculosis is quite characteristic but stage dependent, therefore it is not always easy to make a correct diagnosis e.g. it may be problematic to distinguish fibrocaseous necrotic foci of TB in the lungs from rheumatoid nodules. The diagnosis of latent TB in RA is a great challenge for the rheumatologist mainly due to the limited response in elderly autoimmune patients. Despite the presence of TB, patients may have no clinical complaints or radiological abnormalities, and the value of the tuberculin skin test may be also limited due to inadequate or poor response of the patients [21 – 22], as well as the QuantiFERON blood test [23 – 24]. A positive Interferon-Gamma (γ) Release Assays (IGRA) result may not necessarily indicate TB infection with tuberculous mycobacteria [23]. A negative IGRA does not rule out active TB disease [24].

Detailed medical history and targeted X-ray examination, as well as the tuberculin skin test, and the QuantiFERON blood test (despite their limitations) are key factors in the clinical diagnosis of latent TB with or without subclinical or atypical miliary exacerbation [25 – 27]. Microbiologic culture may be necessary, but takes time (may be critical premortem), the results are often false negative, and in clinically latent TB it appears not indicated. In our total autopsy population with RA (n=161) the proportion of female (n=116) to male (n=45) patients was: 2.57, and it was similar in RA patients with TB (n=21) as well; the rate of women (n=15) to men (n=6) was: 2.5. In Europa (including Hungary) more male (9647 persons) died of TB (rate: 63.8/100000), than females (3103 persons) (rate: 15.2/100000); the male: female ratio among of deceased people was 9647:3103 = 3.1089 [17]. In our autopsy population exclusively women (n=2 of 21) died of TB; the female: male ratio was 2:0 in contrast to to the European general population, where more males died of TB, than females [17]. According to our data women were more likely to be affected by TB in RA than in the European general population. The risk of active miliary dissemination (mTB) was particularly high in women; only females were involved by miliary dissemination of TB (all of 6 RA patients with mTB were women), the female: male ratio was 6:0) [18]. Miliary dissemination of tuberculosis (mTB) may be considered as a terminal phenomenon in our autopsy population, because of the limited numbers of granulomas involved only a few organs, except one patient with more extended dissemination **(Table 5)**. The exudative (more serous, less cellular) and proliferative (more or less cellular) miliary foci without caseous necrosis or fibrous transformation and calcification also support the assumption that hematogenous dissemination was terminal i.e. premortem [18]. The exudative characters, beside proliferative epithelioid granulomas are consecutive stages of a basic pathological process, and in reverse order they may be regarded as histological evidence of an impaired and gradually decreasing immune reactivity [18]. The coalescent caseous cores of tuberculotic foci also support the poor reactivity of the patients; solid caseous necrosis or fibrous consolidated stages of miliary dissemination were not detected. The presences of exudative granulomas are unfavorable prognostic sign in elderly patients. The risk of death (probability of fatal outcome) in RA patients associated with fcTB or mTB is increased compared to the RA patients without TB, certified (proved, showed) by the significant and positive correlation between fcTB or mTB and mortality of TB. Consolidated anthracotic scars did not increase the risk of lethal outcome; the probabilitiy of death in RA patients with fTB was the same as that of RA patients without TB. The onset, and duration of RA did not influence the prevalence and mortality of inactive or active TB; inactive fTB or fcTB (n=15) and active mTB (n=6) developed at any time in the course of RA.

RA itself or its treatment modify the clinical symptoms of associated diseases and present atypical clinical manifestations leading to late recognition or missed diagnosis. The limited immune reactivity of elderly patients, the autoimmune character of RA, steroid and/or immunosuppressive drugs, and nowadays biological therapy may also play a role in missing the diagnosis of fcTB or mTb, including lethal cases. In our autopsy population only two cases of fTB were diagnosed; one of them was recognized by the patient's detailed history, and the second one by the goal-oriented x-ray examination. The link between between clinical diagnosis and mortality of fTB or mTB was not significant, indicating the incidental nature of diagnosis. Clinical diagnosis of latent TB remains one of the main challenges of rheumatologists. In most cases the correlatios were not significant between TB (fTB, fcTB or mTB) and comorbidities (Ath, HT or DM), except fTB and mortality of Ath (c=0.58, χ^2=5.3478, p <0.0207) or fTB and prevalence of DM (c=0.56, χ^2=4.5372, p <0.0331) **(Table 6).** The lack of correlation between TB (fTB, fcTB or mTB) and comorbidities (Ath, HT or DM) indicate that these are sovereign phenomena (associated diseases) in RA, which may be present at the same time, and can lead to death independently from each other. This assumption is supported by the not significant "p" values, moreover by the

negative values of association coefficients between them. The high values of association coefficient and the positive and significant correlation between fTB and mortality of Ath (c=0.58, χ^2=5.3478, p <0.0207) or fTB and DM (c=0.56, χ^2=4.5372, p <0.033) refer to a very close connection, but this does not necessarily mean a causal relationship; coincidence of parallel phenomena seems more likely. The strong positive correlation between fTB and mortality of Ath or fTB and prevalence of DM may be due to the equally high prevalence of fTB, fatal Ath or DM in aged RA patient cohorts. In our opinion fTB, Ath or DM are coincident comorbidities of elderly RA patients. This is supported by the fact that the mean age of RA patients with fTB, fatal Ath or DM was significantly higher, than the mean age of RA patients without fTB, Ath or DM: fTB: 70.92 years versus 64.87, p <0.046 [18]; fatal Ath: 73.1 years versus 59.7, p <0.0000000010 [1]; or DM: 69.10 years versus 64.82, p <0.038 [28]. The incidence of co-morbidities (including hypertension, dyslipidemia, myocardial infarction or angina, stroke, osteoarthritis, lung cancer, colon cancer, pulmonary tuberculosis, asthma, diabetes, depression, thyroid disease and chronic kidney disease") is higher in RA than in the general population [6]. The prevalence of latent and/or clinically not diagnosed TB was also higher in our autopsy population with RA compared to the general population of Hungary [14 – 16]. According to our data the prevalence of DM (n=30/161) was equal with the general population of Hungary [29]; the RA did not increase the rate of controlled adult type 2 DM [30]. Atherosclerosis is a leading cause of vascular disease worldwide [31]. Ruscitti et al. [31] reported an increased prevalence of subclinical and clinical atherosclerosis in RA [32]. Agca et al. [32] found a double rate of cardiovascular events in RA compared to the general population [33]. Cardiovascular disease may be regarded as the major comorbidity associated with mortality in RA [34]. The incidence of ischaemic cardiovascular disease (myocardial infarction or stroke) in Hungary is 17% in the general population [27]. In our autopsy population the prevalence of atherosclerosis was 46.58 % (n=75 of 161), and nearly half of the cases (n=37 of 75) led to death (22,42% of 161; 49.33% of 75), both morbidity and mortality were higher compared to the general population.

CONCLUSION

The prevalence of post-primary TB was higher in RA autopsy patients compared to the general population of Hungary. Inactive fTB or fcTB (n=15) and active mTB (n=6) developed at any time in the course of RA.

The presence of fcTB or mTB increased the risk of mortality of RA patients, while consolidated anthracotic scars (fTB) did not. Women were more likely to be affected by TB in RA compared to the European general population. The risk of active miliary dissemination (mTB) and fatal outcome was particularly high in women; women with mTB died earlier then women without mTB. The onset, and duration of RA did not influence the prevalence and mortality of inactive or active TB.

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