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# Predictors of mortality in patients with rheumatoid arthritis in Lithuania: Data from a cohort study over 10 years

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ABSTRACT

*Background and objective:* Increased mortality and shorter survival among rheumatoid arthritis (RA) patients are recognized but not fully explained. This cohort study aimed to identify predictors of mortality among RA patients at a tertiary clinical setting.

*Materials and methods:* Patients with RA were recruited during 1998–2003 and followed up until April 1, 2012, or death whichever happened first. Baseline variables included socio-demographic and disease characteristics, and comorbidities. Cox regression and hazard risk (HR) were computed to estimate risks for mortality.

*Results:* One hundred ninety-one patients were included into the study, 186 patients were eligible for the analysis and of these 131 patients (70.4%) completed the entire period of followed-up while 55 patients (29.6%) died. The average follow up period was equivalent to 9.24 year per person. A Cox regression model identified four major factors having an impact on survival. History of a stroke at baseline was identified as a major factor (HR = 5.33; 95% CI, 2.13–13.32). Statistically significant risk factors were also age over 50 years (HR = 4.59; 95% CI, 2.04–10.30); education less than 11 years (HR = 3.3; 95% CI, 1.72–6.33) and angina pectoris (HR = 1.98; 95% CI, 1.03–3.80).

*Conclusions:* Higher age, lower education and cardiovascular comorbidities were identified as predictors of mortality in this prospective cohort study while disease-related variables were not independent predictors of mortality.



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## 1. Introduction

There are evident trends in improvement of disease activity and radiological damage by introducing new treatment modalities in rheumatoid arthritis (RA) management schemes but not for mortality and life expectancy [1]. Mortality rates are still higher in RA patients if compared to the general population although RA patients are now living longer than decades ago. The mean age at RA diagnosis and of prevalent cases is increasing, but with increasing life span of a population, RA patients stay far behind them and the gap between those two groups is continuing to widen [2,3]. Increased mortality and shorter survival are recognized but not fully explained and population death registry databases are not helpful because RA is rarely reported as a primary cause of death in death certificates conversely to major cardiovascular diseases and malignancies or trauma. For example, RA as a cause of death was reported only in 18 cases among all 41 511 death cases in Lithuania in 2013 and 10 000 suffering from this disease. Therefore, the prospective cohort studies have a study design to unclose RA-related mortality and morbidity. In the prospective inception cohort study conducted in the Netherlands with 1094 participants followed for up to 23 years after diagnosis the excess mortality occurred after 10 years of follow-up. The authors of that study reported that absolute survival rates did not improve in the last 23 years and a trend toward a widening mortality gap between RA patients and the general population was visible [4]. This trend is accompanied by an increasing prevalence of co-morbidities, in particular cardiovascular disease, malignancy and infections. It may be assumed that due to the named reasons prevalent in the RA cohort the life span of RA patients is reduced and they die prematurely [5]. Along with cardiovascular and other comorbidities, the disease characteristics, sociodemographic and economic factors are discussed as possible predictors for worth survival and mortality [6]. According to our knowledge no longitudinal cohort of RA patients has ever been reported from neighboring or Eastern European countries and followed up for a sufficient long period as it is presented in this study. Although the overall tendency of excess of cardiovascular morbidity is comparable between the European countries, some sociodemographic factors may differ from country to country because specialized care and social systems are different. This cohort study was carried out to identify the predictors of mortality among RA patients with disease duration up to 4 years and followed up for almost 10 years at a tertiary clinical setting of the university hospital.

## 2. Materials and methods

### 2.1. Study design

This was a prospective cohort study designed to evaluate the predictors of mortality of RA patients. Patients with RA were recruited from the rheumatology outpatient and inpatient clinic during 1998–2003 with approval by the regional Bioethics Committee. Inclusion criteria were patients older than 18 years, diagnosed with RA according to the 1987 American College of Rheumatology and with disease duration less than 4 years. A total of 191 patients were included in the initial cohort while 5 patients were excluded from the final analyses since the diagnosis changed during the follow-up period. The mean age at the first interview of the eligible cohort was 54.11 (SD 13.82, range 22–82) and 145 (78%) were women. The demographical social and clinical characteristics of the eligible cohort are presented in Table 1.

### 2.2. Study variables

A structured questionnaire was administered during the first interview to assess the following aspects that may be related to the outcome:

A. Demographic and social characteristics, including age, gender, RA in close family, marital status (married currently versus otherwise), years of education and qualification achieved, mental job opposed to manual job or staying without job, smoking status ever, alcohol abuse.
B. Disease features at the time of the cohort onset included: health assessment questionnaire score for functioning (HAQ) 0–3 (3 worth), visual analog scale for pain (pain VAS) 0–100 mm, patient global disease assessment 1–10, disease activity according to physician 1–5, modified disease activity score, laboratory – rheumatoid factor present, radiological index by Sharp modified by van der Heidje (hand, feet and global) [7].
C. Comorbid diseases included cardiovascular diseases, diabetes, bronchial asthma, kidney diseases, cancer, surgical operations, and overall evaluation of comorbidities present or in the past. The cardiovascular diseases included myocardial infarction, stroke in the past, documented angina pectoris ever and hypertension if present before inclusion into the study.
D. Disease modifying antirheumatic drugs (DMARDs) taking at the time of enrolment into the study.

### 2.3. Follow-up strategy and outcome variable

Patients were followed up on a routine clinical basis by a rheumatologist once per year until April 1, 2012, or death which ever happened first. Vital status and the death date if happened were obtained from The Lithuanian Statistics Office.

### 2.4. Statistical analysis

Qualitative variables are expressed as numbers and percentages, while quantitative variables are expressed as means (standard deviation (SD)). Quantitative comparisons were computed with independent Student *t*-test or Mann–Whitney test where appropriate and Pearson chi-square test or Fisher exact test used for qualitative variables in a univariate analysis. Unadjusted relative risks were obtained for qualitative variables dividing the incidence of the outcome (death) among the exposed by the incidence of the outcome among nonexposed. 95% confidence intervals (95% CI) for each relative risk were calculated.

**Table 1 – Characteristics of rheumatoid arthritis (RA) patients who completed the entire follow-up period and those who developed a fatal outcome.**

| Variables[a] | Total ($n$ = 186) | Survived ($n$ = 131) | Died ($n$ = 55) | $P$ |
|---|---|---|---|---|
| Female, $n$ (%)[b] | 145 (78) | 107 (81.7) | 38 (69.1) | 0.059 |
| Age at first interview years, mean (SD) | 54.11 (13.82) | 49.43 (12.19) | 65.27 (10.79) | <0.001 |
| RA in close family, $n$ (%) | 43 (23.1) | 27 (20.6) | 16 (29.1) | 0.211 |
| Married currently, $n$ (%) | 116 (62.4) | 84 (64.1) | 32 (58.2) | 0.445 |
| Smoking ever | 50 (26.9) | 32 (24.4) | 18 (32.7) | 0.244 |
| Cigarettes per day (median, range) | 10 (1–30) | 10 (1–30) | 7 (2–20) | 0.739 |
| Alcohol abuse | 6 (3.3) | 2 (1.5) | 4 (7.7) | 0.056 |
| Education in years (SD) | 11.73 (4.14) | 12.88 (3.53) | 8.98 (4.23) | <0.001 |
| High school education, $n$ (%) | 42 (22.6) | 36 (27.5) | 6 (10.9) | 0.013 |
| Mental job performed, $n$ (%) | 63 (33.9) | 54 (41.2) | 9 (16.4) | 0.003 |
| Pain VAS during the last week, 0–100 (SD) | 56.69 (22.3) | 56.07 (21.00) | 58.18 (25.31) | 0.56 |
| Global Sharp/van der Heidje radiology index (SD) | 21.79 (19.39) | 21.45 (20.30) | 22.84 (16.44) | 0.702 |
| Health assessment questionnaire score, 0–3 worth (SD) | 1.15 (0.69) | 1.13 (0.64) | 1.20 (0.80) | 0.548 |
| Patient global, 1–10 (SD) | 5.35 (2.15) | 5.31 (2.1) | 5.44 (2.28) | 0.714 |
| Disease activity according the physician, 1–5 (SD) | 3.04 (0.87) | 3.0 (0.82) | 3.13 (0.96) | 0.362 |
| Modified disease activity (SD) | 5.05 (1.25) | 5.08 (1.18) | 5.00 (1.40) | 0.720 |
| Rheumatoid factor positive, $n$ (%) | 158 (84.9) | 109 (83.2) | 49 (89.1) | 0.318 |
| Comorbidities present, $n$ (%) | 130 (69.9) | 85 (64.9) | 45 (81.8) | 0.022 |
| Hypertension, $n$ (%) | 40 (21.5) | 20 (15.3) | 20 (36.4) | 0.002 |
| Angina pectoris ever, $n$ (%) | 19 (10.2) | 7 (5.3) | 12 (21.8) | 0.002 |
| Myocardial infarction in the past, $n$ (%) | 14 (7.5) | 3 (2.3) | 11 (20.0) | <0.001 |
| Stroke in the past, $n$ (%) | 7 (3.8) | 1 (0.8) | 6 (10.9) | 0.003 |
| Disease modifying antirheumatic drugs used, $n$ (%) | 148 (79.6) | 106 (80.9) | 42 (76.4) | 0.486 |

[a] Hand and feet radiology index, kidney diseases, bronchial asthma, diabetes prevalence within the groups is not shown as they appear similar between the groups.
[b] Data for nominal variable are presented in counts and percentages out of column counts; data for continuous variables are presented by means and standard deviations.

Kaplan–Meier analysis and the log rank test were used to estimate the difference in survival time between patients with presence of a risk factor compared with patients without risk factors. The model included factors that were significant in the univariate analysis. A multivariate Cox regression forward stepwise data entering model was build and hazard ratio (HR) with 95% CI were computed to estimate the adjusted risks for the development of a fatal outcome. Statistical significance was set up at level below 5%. Statistical analysis was performed using PASW Statistics 18 and relative risk was estimated using an Internet-based OpenEpi calculator.

## 3. Results

One hundred ninety-one patients were included into the study; to five of them the diagnosis was changed during the follow-up and they were excluded from the final analysis. A total of 186 patients were eligible for analysis and of these 131 patients (70.4%) completed the entire period of follow-up while 55 patients (29.6%) died during the study period.

The cumulative number of years of follow-up on this cohort of patients was 1,718.78 years, equivalent to 9.24 year average follow-up period per person.

The median disease duration before entering the study was 19 months. At the beginning of the study the average value of HAQ was 1.15 (SD 0.69) and disease activity was 5.05 (SD 1.25). Positive RF was found in 85.1% of the patients. Comorbid diseases were observed in 130 (69.9%) and among those, 14 patients (7.5%) recovered from MI and seven (3.8%) from stroke while five patients (2.7%) were ill with diabetes mellitus at the first interview. One hundred forty-eight patients were already taking DMARDs or they were prescribed for long-term use during the inclusion visit.

Univariate comparison of baseline characteristics between those who survived versus passed away is shown in Table 1. Patients who passed away during the follow-up period were older at the beginning of the study (65.27 (SD 10.79) vs 49.43 (SD 12.19), $P < 0.001$), they were less educated (8.98 (SD 4.23) vs. 12.88 (SD 3.53), $P < 0.001$), less often obtained high school diploma (10.9% vs. 27.5%, $P < 0.013$) and also performed mental job less often (16.4% vs. 41.2%, $P < 0.003$). We found no difference in clinical variables during the first examination, while the comorbidities reported during the first examination increased the risk of a fatal outcome almost twofold, i.e., 1.94 (95% CI, 1.05–3.57). Among cardiovascular disorders myocardial infarction and stroke increased threefold the risk for fatal outcome i.e., 3.07 (95% CI, 2.11–4.46) and 3.13 (95% CI, 2.13–4.46), respectively. Hypertension and angina pectoris played a significant role related to the outcome in this univariate model, although less important. Hypertension and angina pectoris increased the risk of fatal outcome twofold: 2.09 (95% CI, 1.37–3.19) and 2.45 (95% CI, 1.60–3.80), respectively. High school education and white collar job performance were strong factors protecting against fatal outcome, 0.42 (95% CI, 0.19–0.91) and 0.35 (95% CI, 0.18–0.67), accordingly.

Kaplan–Meier analysis showed nine predictors associated with poor survival of this cohort of patients (Table 2). Factors associated with lower survival time were age greater than 50 years ($P < 0.001$), education ≤ 11 years ($P < 0.001$), and lower

**Table 2 – Kaplan–Meier analysis of variables associated with the fatal outcome in rheumatoid arthritis patients cohort.**

| Variable | N (%) | Mean survival time (years) | P Log rank (Mantel–Cox) test |
|---|---|---|---|
| Age at first interview, years | | | <0.001 |
| Age ≤50 (*n* = 79) | 7 (8.9) | 12.57 | |
| Age >50 (*n* = 107) | 48 (44.9) | 10.28 | |
| Education, years | | | <0.001 |
| ≤11 (*n* = 94) | 43 (45.8) | 10.10 | |
| >11 (*n* = 92) | 12 (13.0) | 12.31 | |
| High school education | | | 0.02 |
| Yes (*n* = 42) | 6 (14.3) | 11.32 | |
| No (*n* = 144) | 49 (34.0) | 11.16 | |
| Mental job performed | | | 0.001 |
| Yes (*n* = 63) | 9 (14.3) | 12.19 | |
| No (*n* = 123) | 46 (37.4) | 10.80 | |
| Comorbidities present/past | | | 0.043 |
| Yes (*n* = 130) | 45 (34.6) | 11.21 | |
| No (*n* = 56) | 10 (17.9) | 11.71 | |
| Hypertension | | | 0.002 |
| Yes (*n* = 40) | 20 (50.0) | 9.10 | |
| No (*n* = 146) | 35 (24.0) | 12.03 | |
| Angina pectoris ever | | | 0.001 |
| Yes (*n* = 19) | 12 (63.2) | 8.57 | |
| No (*n* = 167) | 43 (25.8) | 11.83 | |
| Myocardial infarction | | | <0.001 |
| Yes (*n* = 14) | 11 (78.6) | 6.87 | |
| No (*n* = 172) | 44 (25.6) | 11.91 | |
| Stroke | | | <0.001 |
| Yes (*n* = 7) | 6 (85.7) | 5.55 | |
| No (*n* = 179) | 49 (27.4) | 11.75 | |

than high school education ($P = 0.02$); mental job performed less often ($P = 0.001$); comorbidities present or in the past ($P = 0.043$); hypertension present ($P = 0.002$); angina pectoris ever ($P = 0.001$); myocardial infarction and stroke survived before entering the study ($P < 0.001$ and $P < 0.001$, respectively). No other predictors including functioning, disease activity, radiological indexes and DMARDs prescribed had no impact on survival. The survival curves for nine significant predictors are shown in Fig. 1.

For investigating the effect of several variables acting simultaneously and during the time course, Cox regression analysis was performed and all variables significant in Kaplan–Meier analysis were included into the model. The Cox regression model identified four major factors having an impact on survival (Table 3). Stroke was identified as a major factor with fivefold hazard ratio on those who survived it in the beginning of RA (HR = 5.33; 95% CI, 2.13–13.32). Less important but still significant factors were age over 50 years (HR = 4.59; 95% CI, 2.04–10.30); education in years ≤ 11 (HR = 3.3; 95% CI, 1.72–6.33) and angina pectoris (HR = 1.98; 95% CI, 1.03–3.80). Other variables that were significant in Kaplan–Meier analysis did not remain important in this adjusted model that initially included high school education, mental job performed, overall comorbidities, hypertension and myocardial infarction.

Fig. 2 shows the cumulative hazard curves from three subgroups of patients according to a construct in number of risk factors for the development of a fatal outcome. At the beginning of the study 48 (25.8%) patients had no risk factors identified as important in Cox regression, 125 (67.2%) patients had 1–2 factors and 13 (7%) had 3–4 factors present. Using the patients who had no risk factors (HR = 1) at all as a reference group, the subgroup with 1 or 2 factors had a significant increase in HR = 6.08 (95% CI, 1.88–19.68), and the subgroup with 3–4 factors was extremely under the risk of dying HR = 29.90 (95% CI, 8.35–107.0).

## 4. Discussion

This first longitudinal prospective inception cohort study of RA patients in Lithuania followed up in average for 9.24 years per person elucidated several sociodemographic and comorbid diseases being in relation to the fatal outcome. Lower education, being older at the beginning of the disease and a history of angina pectoris or stroke significantly reduced the probability of survival and increased the probability of a fatal outcome.

In general, the studies agree that RA is associated with an increased mortality rate and the expected survival of RA patients is likely to be shorter for 3–10 years if compared to the general population [8–10]. Despite new disease-modifying antirheumatic drugs and substances introduced during the last 15 years into a daily practice, it is still unclear if the survival of the patients can be prolonged and comorbidities intervened [11]. The meta-regression analysis performed by Meune et al. showed no change in the standardized mortality rate from 1960 to 2008, and RA patients had a 60% increase in risk of cardiovascular death compared with the general population [9]. The acute attributed causes of death in overall are similar to the general population, with cardiovascular diseases being the most common cause of death, and with more infection, pulmonary and renal disease in RA than in the general population. According to the systematic review by Symmons and Gabriel, overall survival in persons with RA is significantly reduced compared to the general population and the mortality gap between RA and the general population appears to be widening over time [12]. According to the authors, this is because mortality in persons with RA has remained unchanged while mortality in the general population has improved over the past several decades.

The possible predictors are also widely described in the systemic reviews and the predictors of mortality can be categorized in several groups. First, patients with RA tend to have higher risk of cardiovascular morbidity if compared to their counterparts in the general population. Accelerated atherosclerosis in RA patients is due to inflammatory origin of the disease and numerous innovative studies trying to elucidate underlying mechanisms evolved in recent years and innovative methods followed them according to the review of Gkaliagkousi et al. [3]. The prevalence of cardiovascular comorbidity is difficult to assess accurately, because cardiovascular disease has a tendency to remain silent in RA according to the review by Goodson [13]. A systematic review of the literature conducted by Levy et al. found that the risk of myocardial ischemia in RA patients was about 1.63 compared to the general population but no excess was found for the risk of stroke event in RA patients [14]. Although some disparities

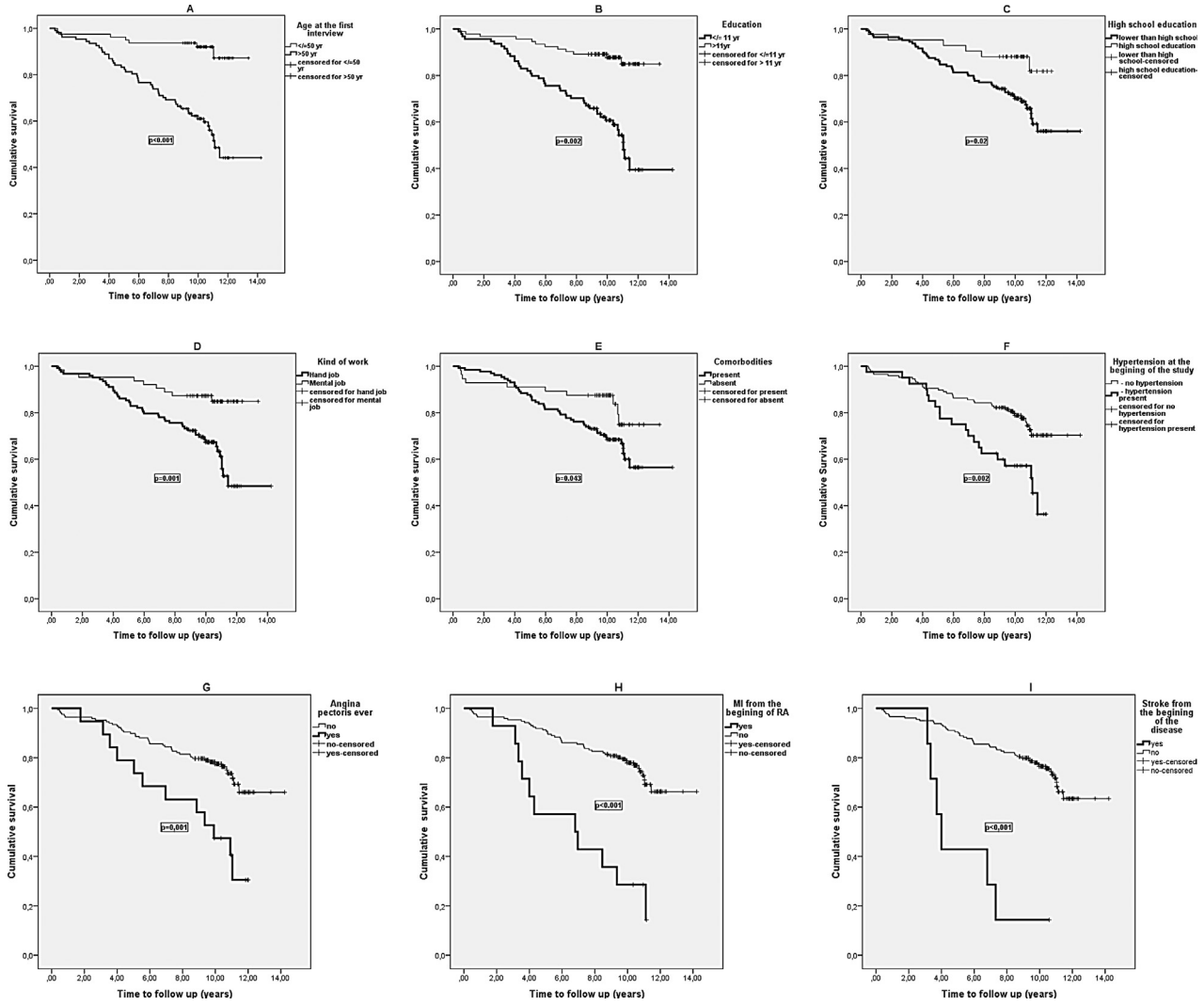


**Fig. 1 – Kaplan–Meier curves of survival according to the following factors: age at first interview (graphic A); education in years (graphic B); high school education (graphic C); mental job performed (graphic D); comorbidities present (graphic E); hypertension (graphic F); angina pectoris ever (graphic G); myocardial infarction (graphic H); and stroke (graphic I).**

between the studies exist, cardiovascular causes are considered as major predictors of death in the RA population. Systemic analysis by Avin-Zubieta et al. included 24 studies comprising 111 758 patients with 22 927 cardiovascular events.

**Table 3 – The effect of predictors associated with the fatal outcome in rheumatoid arthritis cohort.[a]**

| Predictor | HR | 95% CI | P |
|---|---|---|---|
| Age >50 years | 4.59 | 2.04–10.30 | <0.001 |
| Education in years ≤11 | 3.30 | 1.72–6.33 | <0.001 |
| Angina pectoris ever | 1.98 | 1.03–3.80 | 0.04 |
| Stroke | 5.33 | 2.13–13.32 | <0.001 |

[a] Variables excluded from the final model were: high school education (yes/no), mental/hand job performed, comorbidities present (yes/no), hypertension (yes/no), myocardial infarction (yes/no). The variables were adjusted using multivariate COX regression model, using Forward Stepwise data entering method.

Overall, there was a 50% increased risk of cardiovascular death in patients with RA [15]. Mortality risks for ischemic heart disease and cerebrovascular accidents were increased by 59% and 52%, respectively. Unfortunately, RA patients are less likely to report symptoms of angina and more likely to experience unrecognized myocardial infarction (HR = 2.13, 95% CI 1.13, 4.03) and succumb from sudden cardiac death (HR = 1.94, 95% CI 1.06, 3.55) according to the population-based cohort study conducted by Maradit-Kremers et al. in Minnesota [16]. Although traditional cardiovascular disease risk factors were found to contribute to the increased risk of mortality in RA patients, they did not fully explain the increased cardiovascular mortality observed in RA. Instead, increased inflammation associated with RA appears to contribute substantially to the increased cardiovascular mortality [17,18]. The role of humoral autoimmunity, namely autoantibodies against heat shock proteins, cardiolipin and beta2-glycoprotein I, and its link with atherosclerosis in RA have been raised in a review by Pereira and Borba [19].

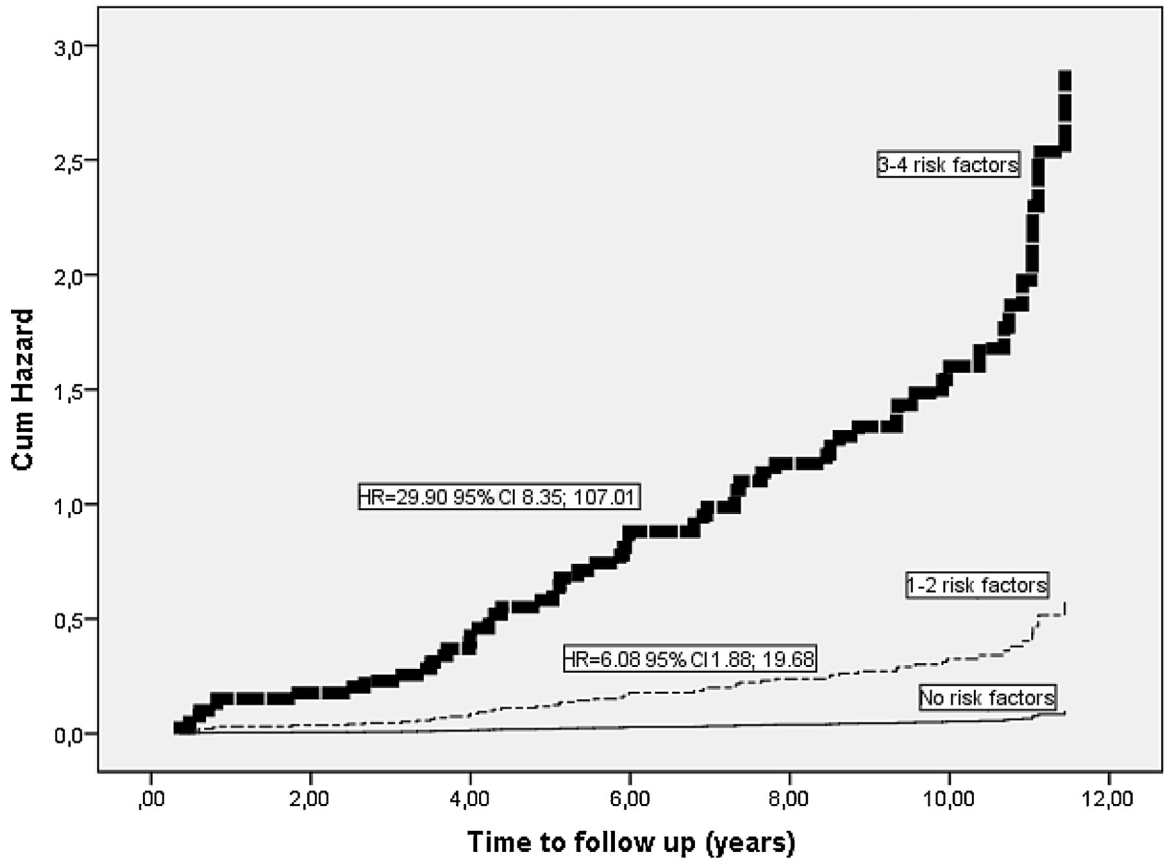


**Fig. 2 – Hazard risk for increasing number of risk factors for fatal event (no risk factors; 1–2 risk factors and 3–4 risk factors) in a cohort of 186 rheumatoid arthritis patients.**

Other determinants of excess mortality in RA are related to sociodemographic factors showing that lower formal education and socioeconomic class may contribute to the worth outcome of the disease. In parallel, people with higher education possess greater willingness to acknowledge their disease and report the illness or side effects of the treatment [20,21]. The extent, to which age and gender add to the risk for increased mortality in RA, is still not clear. The results of the review conducted by Anderson [22] failed to show a clear association between gender, age and mortality, except for the increased mortality among elderly women [23]. Nevertheless, according to the review by Goronzy et al. by several immune aging biomarkers, the immune system in patients with RA is prematurely aged by more than 20 years [24]. According to this publication one major pathogenetic mechanism is a defect in telomere maintenance and DNA repair that causes accelerated death.

Our data are consistent with the data aggregated in the systemic reviews and review articles and we found the stroke being the strongest predictor of the fatal outcome. To note, we did not find important any directly disease-related factor predicting the fatal outcome. Our data to some extent contradict with the findings by Radovits et al. [4]. In the quoted study the significant baseline predictors of survival were sex, age, rheumatoid factor, disability, disease activity scores and comorbidity. To oppose, the disease-related characteristics were not important in our study. We believe it greatly depends on a sample size of the study and the way it was assembled. The study by Radovits et al. likewise other quoted systematic review studies analyzed the data of thousand patients while the sample size of this study was considerably smaller and was limited to the tertiary clinical center [4]. We do not consider the geo-environmental factors could affect our results, because the prevalence and clinical characteristics of RA in this cohort are consistent with the epidemiological data as reported in Northern Europe and North America [10,25,26].

Our study could not omit the limitations, and the major limitation is the lack of causes of death that could be sought only by reviewing the death certificates. The authors made attempts to review the death certificates but found the death causes not suitable for scientific evaluation. Few death certificates indicated clearly the primary cause of the disease, the majority of them stated the cause of death as general atherosclerosis and it was mostly the case when the person died at home. Since we did not analyze the causes of the death, our conclusions are related to predictors of the fatal outcome only, and could not be related to the death causes. Second, the predictors included into the study were evaluated only once at the enrolment period and were not re-evaluated periodically. The study period was relatively long, this why some of the factors absent in the beginning may appear in the course of disease.

We conclude that our findings support literature data that cardiovascular diseases in RA patients should be monitored

carefully and assessed annually for cardiovascular risk stratification as it is recommended by the European League Against Rheumatism [27]. In addition, those who meet several predictors of the fatal outcome should be referred to the specialists even more frequently and addressed aggressively because their risk to die increases dramatically.

## 5. Conclusions

In this prospective cohort study we identified four factors related to the mortality of RA patients. None of them is directly disease related. The Cox regression model identified four major factors having an impact on survival. Stroke and age over 50 years at the onset of RA were identified as major factors with a fivefold risk increase. Less important but still significant factors increasing risk of death were education less than 11 years and angina pectoris with a threefold and twofold risk increase, respectively. While sociodemographic factors could barely be improved, the cardiovascular factors could be potentially addressed by therapeutic strategies and aggressive approach of comorbidities treatment in RA patients.

## Conflict of interest

The authors state no conflict of interest.

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