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MORTALITY IN PATIENTS WITH RHEUMATOID ARTHRITIS: A RETROSPECTIVE COHORT STUDY AND SYSTEMATIC REVIEW

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BACKGROUND

- **Mortality rates among patients with RA have been reported to be higher than in the general population (Toledano et al., 2012; Dadoun et al., 2013).**

- **The long-term prognosis of RA has improved in recent years due to early diagnosis as well as effective pharmacological treatment (Monti et al., 2015) and may be able to diminish the excess mortality risk.**

Abbreviations: CI, confidence intervals; RA, rheumatoid arthritis; SMR, standardized mortality ratio.

OBJECTIVES

- **To investigate mortality in patients with RA in a retrospectively defined national RA cohort in comparison with the general Lithuanian population;**

- **To conduct a systematic review with meta-analysis of the literature from different countries.**

Abbreviations: RA, rheumatoid arthritis.

MATERIALS AND METHODS (1)

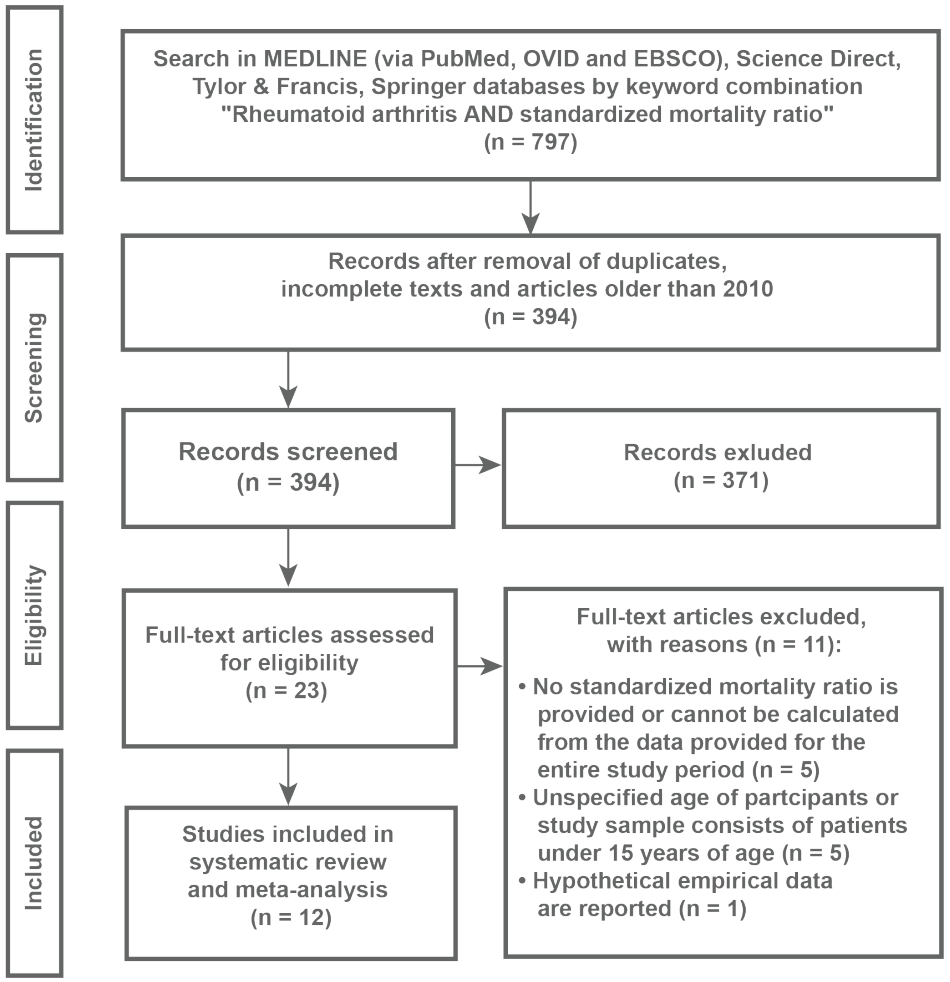
- Patients with the first-time diagnosis of RA during the period between 1 January 2013 and 31 December 2017 were identified from the Lithuanian Compulsory Health Insurance Information System database SVEIDRA.

- All cases were cross-checked with Health Information center at the Institute of Hygiene, for the vital status of these patients and date of death if the fact of death was documented.

- SMRs with 95% CI obtained for all-cause mortality in patients with RA adjusted for age, sex, and calendar year, were calculated.

Abbreviations: CI, confidence intervals; RA, rheumatoid arthritis; SMR, standardized mortality ratio.

MATERIALS AND METHODS (2)



- Assessment of risk of bias relied on the **New Castle-Ottawa scale for cohorts** and only moderate to high-quality studies were included in the review (Wells et al., n.d.).
- A **random-effect meta-analysis model** described by DerSimonian and Laird was used to compute the pooled standardized mortality ratios with 95% CI (DerSimonian et al., 1986).

Figure 1. PRISMA flow diagram of the selection of studies.

Abbreviations: CI, confidence intervals; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RESULTS (1)

- During the period between 2013 and 2017, we have identified **4 623** patients with RA.
- The mean age of these patients at the time of RA diagnosis was **58.7** (SD 15.1) years.
- The cohort consisted **mainly of women** (77.1%), and the mean duration of follow-up was **2.78 years**.

Table 1. All-cause mortality in patients with RA during the entire study period (2013–2017).

	N	O	E	SMR (95% CI)
Overall	4 623	278	241	1.15 (1.02, 1.29)
Men	1 059	98	86	1.14 (0.94, 1.39)
Women	3 564	180	175	1.03 (0.89, 1.19)

Abbreviations: CI, confidence intervals; E, expected number of deaths; N, number of participants; O, observed number of deaths; SD, standard deviation; SMR, standardized mortality ratio.

RESULTS (2)

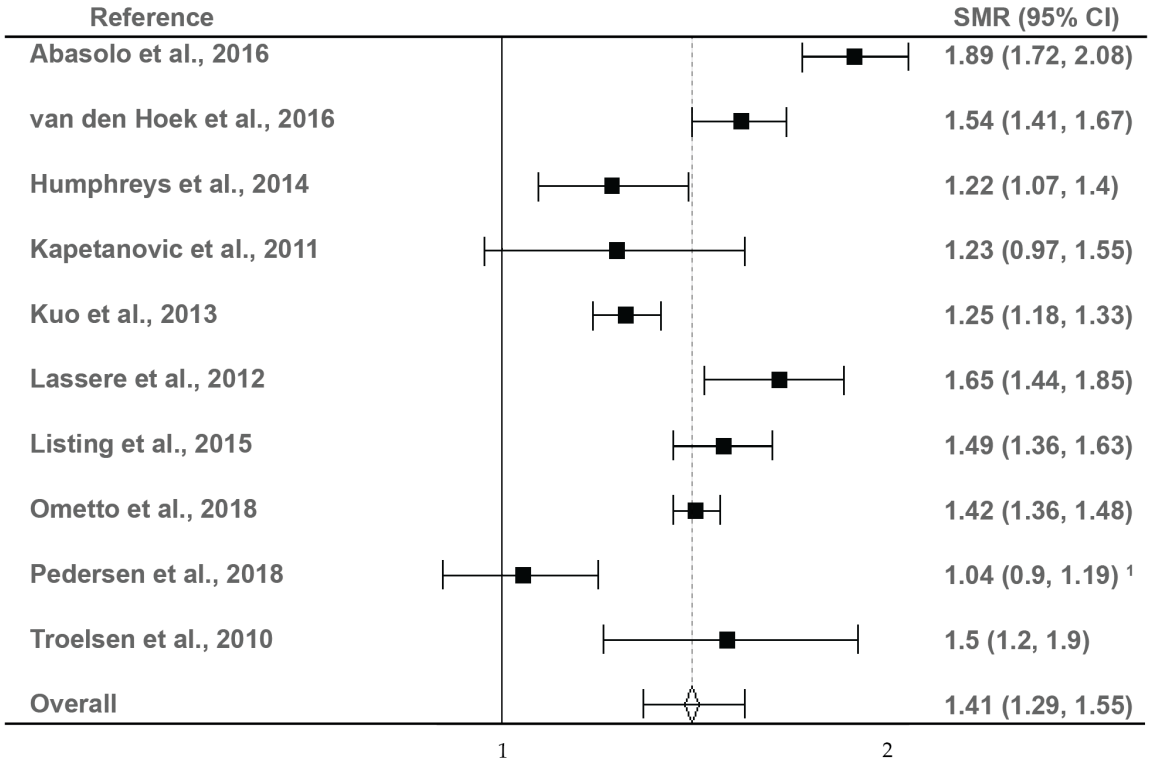
- Revealed 12 studies represented **50 072 patients**, and **6 060 deaths** occurred during follow-up.
- Inclusion start-up ranged **from 1985 to 2010**.
- RA diagnosis was mostly based on American College of Rheumatology or American Rheumatism Association classification criteria.

Table 2. Results of the meta-analysis of patients with RA for all-cause mortality overall and by sex.

	No. of studies	SMR (95% CI)	Heterogeneity, using I^2 (%)
Overall	10	1.41 (1.29, 1.55)	89.8
Men	9	1.53 (1.31, 1.78)	87.6
Women	7	1.46 (1.2, 1.77)	93.7

Abbreviations: CI, confidence intervals; I^2, inconsistency index; RA, rheumatoid arthritis; SMR, standardized mortality ratio.

RESULTS (3)



Heterogeneity: $Chi^2 = 88$, df = 9 (P = <0.001); $I^2 = 89.8\%$

[1] not provided by authors, obtained from the reported observed (O) and expected (E) deaths,
as SMR = O/E and its 95% CI = SMR ± 1.96√ O/E

Figure 2. Forest plot of the SMR in patients with RA for all-cause mortality.

Abbreviations: CI, confidence intervals; df, degree of freedom; I^2, inconsistency index; RA, rheumatoid arthritis; SMR, standardized mortality ratio.

DISCUSSION (1)

- **The reasons for the indicated lower mortality among RA patients in Lithuania (SMR 1.15 (1.02, 1.29)) might be the same that could apply to the general population, improvements in rheumatology care and new treatment strategies such as conventional synthetic and biological disease modifying drugs introduced since 2003 may have had an impact on mortality of patients with RA.**

Abbreviations: RA, rheumatoid arthritis; SMR, standardized mortality ratio.

DISCUSSION (2)

- Our findings in systemic literature review are in line with previously two published meta-analyses on the issue of mortality in RA. In both studies meta-SMR were similar to that identified in our study.

Table 3. Results of the meta-analyses of patients with RA for all-cause mortality.

Meta-analysis	SMR (95% CI)
Toledano et al., 2012	1.44 (1.23, 1.69)
Dadoun et al., 2013	1.47 (1.19, 1.83)
Conducted by us, 2021	1.41 (1.29, 1.55)

Abbreviations: CI, confidence intervals; RA, rheumatoid arthritis; SMR, standardized mortality ratio.

LIMITATIONS

- One of the inclusion criteria in this national retrospective cohort study was information about **at least one prescription** of the medications for RA reimbursed by the state, therefore, some cases of RA might be omitted in a case when patient is not treated with state-reimbursed medications.

- The major limitation of this retrospective cohort study was **a short follow-up** of the patients.

- Furthermore, some studies evaluating mortality in RA patients were excluded because **the data needed in order to calculate the SMR were not available** in the articles.

Abbreviations: RA, rheumatoid arthritis.

CONCLUSIONS

- **Using national registries data from official state-run sources, we have assessed patients with RA in Lithuania and found a 15% excess risk of death in this cohort compared with the general population.**

- **In our performed systematic review and meta-analysis patients with RA had a 41% higher risk of mortality compared with the general population.**

- **Excessive all-cause mortality risk was higher in males than in women.**

- **Despite new treatment strategies, RA remains a serious disease posing an increased risk of mortality and other studies are required to identify factors that may decrease this risk to patients with RA.**

Abbreviations: RA, rheumatoid arthritis.

REFERENCES

- Dadoun, S.; Zeboulon-Ktorza, N.; Combescure, C.; Elhai, M.; Rozenberg, S.; Gossec, L.; et al. Mortality in rheumatoid arthritis over the last fifty years: Systematic review and meta-analysis. *Joint Bone Spine* 2013, 80, 29–33.
- DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986, 7, 177–188.
- Monti, S.; Montecucco, C.; Bugatti, S.; Caporali, R. Rheumatoid arthritis treatment: the earlier the better to prevent joint dam-age. *RMD Open* 2015, 1, 1–5.
- Sokka, T.; Abelson, B.; Pincus, T. Mortality in rheumatoid arthritis: 2008 update. *Clinical and Experimental Rheumatology* 2008, 26, 35–61.
- Toledano, E.; Candelas, G.; Rosales, Z.; Martínez Prada, C.; León, L.; Abásolo, L.; et al. A meta-analysis of mortality in rheumatic diseases. *Reumatologia Clinica* 2012, 8, 334–341.
- Wells, G.A.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 20 December 2020).

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