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Proceeding Paper

Mortality in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study and Systematic Review †

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Abstract: *Background and Objectives*: Mortality rates among patients with rheumatoid arthritis (RA) have been reported to be higher than in the general population. The long-term prognosis of RA has improved in recent years due to early diagnosis, as well as effective pharmacological treatment, and this may be able to diminish the excess mortality risk. This study was designed to investigate mortality (a) in patients with RA in a retrospectively defined national RA cohort in comparison with the general Lithuanian population, and (b) to conduct a systematic review of the literature from different countries and meta-analysis. *Materials and Methods*: In this national retrospective cohort study, patients with a first-time diagnosis of RA in 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 the Health Information Center at the Institute of Hygiene, for the vital status of these patients and date of death if documented. The standardized mortality ratios (SMRs) with 95% confidence intervals (CI) obtained for all-cause mortality in patients with RA adjusted for age, sex, and calendar year were calculated. The search for published studies using the combination of keywords "rheumatoid arthritis AND standardized mortality ratio" was performed in MEDLINE (via PubMed, OVID, and EBSCO), Science Direct, Taylor & Francis, and Springer databases. Studies were selected according to described inclusion and exclusion criteria listed in the paper, and a meta-analysis was conducted. A random-effect meta-analysis model was used to compute the pooled standardized mortality ratios (meta-SMRs). *Results*: Overall, 4623 patients with newly diagnosed RA during the 2013–2017 period were identified and enrolled in the Lithuanian population-based cohort. The mean age of patients at the time of RA diagnosis was 58.7 (standard deviation (SD) 15.1) years, and 77.1% of the patients were women. The estimated SMR for all-cause mortality was 1.15 (95% CI 1.02, 1.29). The SMR for men (SMR 1.14, 95% CI 0.94, 1.39) was higher than for women (SMR 1.03, 95% CI 0.89, 1.19). A systematic literature search revealed 12 studies meeting the inclusion criteria, starting from 2010 to 2020, representing 50,072 patients. The meta-SMR in patients with RA for all-cause mortality was 1.41 (95% CI 1.29, 1.55). All-cause mortality risk was higher for men (meta-SMR 1.53, 95% CI 1.31, 1.78) than for women (meta-SMR 1.46, 95% CI 1.2, 1.77). *Conclusions*: In a retrospectively defined population-based national RA cohort, a 15% excess risk of death was observed among patients with RA compared to the general Lithuanian population. Patients with RA have a higher mortality risk than the general population. Published data indicate that the risk of mortality is increased by 41% in patients with RA compared to the general population. Excessive all-cause mortality risk is higher in men than in women. National data showed lower standardized mortality compared to literature data.

Keywords: rheumatoid arthritis; mortality; standardized mortality ratio; retrospective cohort study; systematic review

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1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder that limits a person's performance of physical functions and has a negative impact on quality of life [1,2]. Higher mortality rates in patients with RA compared to the general population were first described in a longitudinal observational study over 65 years ago [3]. The long-term prognosis of RA has improved in recent years due to early diagnosis and effective pharmacological treatment [4], resulting in most RA patients achieving stable clinical remission or experiencing lower disease activity [5]. Nevertheless, most studies have found that RA is still associated with higher mortality risk than the general population [6–10]. The main causes of death identified among RA patients are increased incidence of circulatory system diseases, cancer, and respiratory conditions [11]. However, some studies reported that the mortality in patients with RA was similar to or even lower than that of the general population [12–14]. Reasons for the contradictory results could be explained by different types of cohorts, length of the follow-up, and the geographical location of the study [7]. Given these conflicting results, a better estimation of the mortality risk among RA patients over time is essential to understand the prognosis of this disease.

Hence, the objectives of this study were to investigate mortality (a) in patients with RA in a retrospectively defined national RA cohort in comparison with the general Lithuanian population; and (b) to conduct a systematic review of the literature from different countries and meta-analysis.

2. Materials and Methods

2.1. Data Sources

This national retrospective cohort study was performed using the data of Lithuanian Compulsory Health Insurance Information System database SVEIDRA. It is a population-based database that captures all physician visits, procedures, hospitalizations, diagnoses, and prescribed reimbursed medications to all residents of Lithuania since 1995. The main information sources of this database are healthcare institutions and medication prescriptions released by pharmacies.

We were allowed to use the information from SVEIDRA for all patients who had a first-time diagnosis of RA (diagnosis codes M05 and M06 according to International Classification of Diseases 10th version (ICD-10) during the period between 1 January 2013 and 31 December 2017. All participants were classified as cases if they had records of at least one prescription of the medications for RA reimbursed by the state, including glucocorticoids, conventional synthetic (methotrexate, azathioprine, leflunomide, sulfasalazine, and hydroxychloroquine), or biological disease-modifying drugs. Cases of children (<18 years old at the time of diagnosis) were excluded, as well as cases with an unidentifiable identification code. The final 4623 cases were cross-checked with the Health Information Center at the Institute of Hygiene for the vital status of these patients and date of death if documented.

2.2. Search Strategy, Study Selection, and Data Extraction

We conducted a systematic review and meta-analysis from 1 September 2020 to 15 December according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. The search for published studies using a combination of keywords "rheumatoid arthritis AND standardized mortality ratio" was performed in MEDLINE (via PubMed, OVID and EBSCO), Science Direct, Taylor & Francis, and Springer databases. Eligibility criteria were (1) study population with rheumatoid arthritis aged 15 and over; (2) retrospective or prospective cohort studies published in the period 2010–2020; and (3) mortality as the outcome of interest, reported as a standardized mortality ratio (SMR) or easily calculated from reported data for the entire study period. If data were duplicated in more than one article, only the most recent one was included. Studies on cancers, cardiovascular diseases, or infections related to the musculoskeletal system, as well as studies dealing solely with predictors of mortality but not reporting rates or reporting only hypothetical empirical data, were excluded from this review.

Two authors independently reviewed the title and abstract of studies identified in the electronic search to exclude studies that did not address the main research question of interest, considering the described inclusion and exclusion criteria (see above). The full texts of the remaining articles were examined to determine whether they contained relevant information; discrepancy in article selection was resolved by consensus.

Data collected were the general characteristics of each study and the outcomes measured: primary author, year of publication, geographic location of the population studied, study design, number of participants, age at baseline of the patients, time period of study, SMR and confidence intervals (CI), and observed and expected death.

Assessment of risk of bias relied on the Newcastle–Ottawa scale for cohorts and only moderate- to high-quality studies were included in the review [16]. According to the reported scale, studies were evaluated across three domains: selection (four questions) and comparability (two questions) of study groups and determination of the outcome of interest (three questions), with all questions having a score of 1, except for comparability of study groups, where separate points were awarded for controlling age and/or sex (maximum 2 points). Hence, a score with a range of 0–9 was allocated to each study, and those with a score of 8 or more were considered to be high-quality studies, whereas those with a score of 6 to 7 were categorized as moderate-quality studies.

2.3. Statistical Methods

The SMRs were identified in order to compare the mortality in the retrospectively defined national RA cohort with the general population. The SMRs were computed as the ratio of the number of observed deaths in a study population divided by the number of expected deaths if the study population had the same age-, sex-, and calendar year-specific rates as the general population, with 95% CI. Indirect standardization was used to calculate the expected number of deaths for the study population. Person-years were estimated from the date of RA diagnosis to the first of the death or end of the follow-up (31 December 2017). Expected numbers were computed as multiplication of the exact person-years under observation in the cohort by sex-, calendar year-, and 5 year age group-specific national death rates. National mortality data were obtained from Statistics Lithuania for the years 2013–2017 [17]. We calculated the SMR for all-cause mortality.

Only studies reporting SMR were included in the systematic review and meta-analysis. If an SMR or its 95% CI was not directly provided, then it was estimated from the reported observed (O) and expected (E) deaths as follows SMR = O/E; 95% CI = SMR $\pm$ 1.96$\sqrt{}$ O/E. A random-effect meta-analysis model described by DerSimonian and Laird was used to compute the pooled standardized mortality ratios (meta-SMRs) with 95% CI [18]. The meta-SMR shows a summary estimate of the increased risk of death in patients with RA compared with the general population, weighted by the inverse of the variance the log of the SMRs of each study. We assessed heterogeneity between study-specific estimates using the inconsistency index (I^2 statistic). All analyses were performed using WINPEPI [19].

3. Results

During the period between 2013 and 2017, we identified 4623 patients with RA. The mean age of these patients at the time of RA diagnosis was 58.7 (standard deviation (SD) 15.1) years. The cohort consisted mainly of women (77.1%), and the mean duration of follow-up was 2.78 years. A total of 278 patients died during the study period: 98 men and 180 women. The overall mean age at death was 74.8 (SD 10.6) years.

The estimated SMR for all-cause mortality was 1.15 (95% CI 1.02, 1.29) over the period between 2013 and 2017 (Table 1). This indicates a 15% higher risk of mortality compared with the general Lithuanian population. In men, SMR was 1.14 (95% CI 0.94, 1.39), and, in women, it was 1.03 (95% CI 0.89, 1.19).

Table 1. All-cause mortality in patients with rheumatoid arthritis during the entire study period.

	N	O	E	SMR (95% CI)
Overall	4623	278	241	1.15 (1.02, 1.29)
Men	1059	98	86	1.14 (0.94, 1.39)
Women	3564	180	175	1.03 (0.89, 1.19)

CI, confidence interval; E, expected number of deaths; *N*, number of participants; O, observed number of deaths; SMR, standardized mortality ratio.

The electronic search of MEDLINE (via PubMed, OVID, and EBSCO), Science Direct, Tylor and Francis, and Springer databases yielded 797 articles (Figure 1), being reduced to 394 after removal of duplicates, incomplete text, and articles older than 2010. The selection by title and abstract left 23 articles. Finally, only 12 studies met the complete set of selection criteria and were included in the review. Articles were excluded mainly because no SMR was provided or could not be calculated from the reported data for the entire study period (n = 5), unspecified age of participants or study sample consisted of patients under 15 years of age (n = 5), and hypothetical empirical data were reported (n = 1).

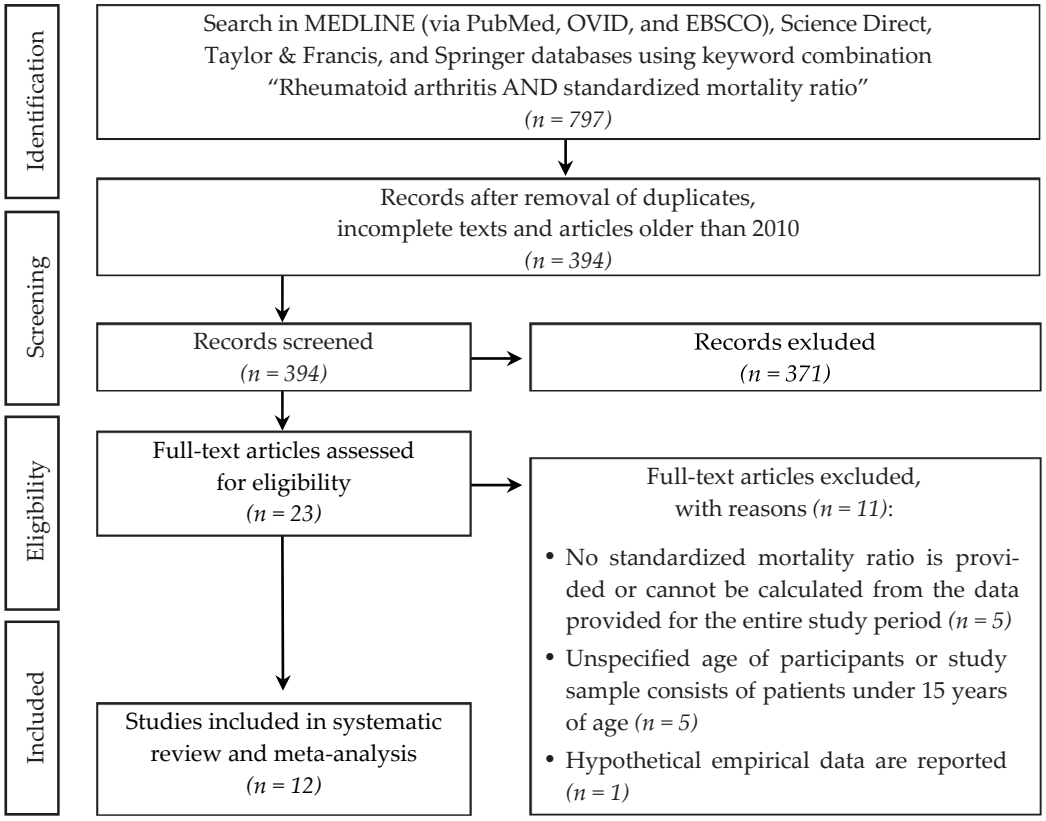

Figure 1. PRISMA flow diagram of the selection of studies.

The revealed 12 studies represented 50,072 patients, and 6060 deaths occurred during follow-up. Eight of the studies were performed in Europe and four in other parts of the world. Inclusion start-up ranged from 1985 to 2010, and RA diagnosis was mostly based on American College of Rheumatology or American Rheumatism Association classification criteria. Table 2 represents the main characteristics of all included studies, and Table 3 shows the results on mortality by study.

Table 2. Main characteristics of all included studies on mortality risk in patients with rheumatoid arthritis.

Reference	Location	Study Design	Time Period	Age at Baseline, Mean (SD) or Median (Range)	No. of Patients with RA
Abasolo et al., 2016 [20]	Spain	RCS	1994–2013	61 (48–72)	2271 (M: 573; W: 1698)
England et al., 2016 [21]	USA	PCS	2000–2012	64.6 (10.4)	1652 (M: 1652; W: 0)
van den Hoek et al., 2016 [22]	The Netherlands	PCS	1997–2012	60.4 (15.4)	1213 (M: 332; W: 881)
Humphreys et al., 2014 [23]	UK	RCS	1990–2011	57 (47–68)	1419 (M: 460; W: 959)
Kapetanovic et al., 2011 [24]	Sweden	PCS	1985–2008	52 (12)	183 (M: 68; W: 115)
Kuo et al., 2013 [25]	Taiwan	RCS	2002–2007	53.7 (14)	15,967 (M: 3562; W: 12,405)
Lassere et al., 2012 [8]	Australia	PCS	1990–2004	53.8 (13.8)	608 (M: 172; W: 436)
Listing et al., 2015 [9]	Germany	PCS	2001–2011	55.8 (12.4)	8908 (M: 2025; W: 6883)
Mikuls et al., 2011 [26]	USA	PCS	2002–2009	65 (11)	1015 (M: 1015; W: 0)
Ometto et al., 2018 [10]	Italy	PCS	2010–2015	(20–89)	16,098 (M: 3864; W: 12,234)
Pedersen et al., 2018 [27]	Denmark	RCS	1995–2013	63 (53–71)	509 (M: 165; W: 344)
Troelsen et al., 2010 [28]	Denmark	PCS	1995–1998	62 (20–87)	229 (M: 42; W: 187)

M, men; PCS, prospective cohort study; RA, rheumatoid arthritis; RCS, retrospective cohort study; SD, standard deviation; UK, United Kingdom; USA, United States of America; W, women.

Table 3. Standardized mortality ratio in patients with rheumatoid arthritis over time for each study.

Reference	Overall SMR (95% CI)	Men SMR (95% CI)	Women SMR (95% CI)
Abasolo et al., 2016 [20]	1.89 (1.72, 2.08)	1.49 (1.26, 1.74)	2.22 (1.97, 2.5)
England et al., 2016 [21]	NR	1.97 (1.77, 2.19)	NR
van den Hoek et al., 2016 [22]	1.54 (1.41, 1.67)	1.32 (1.13, 1.55)	1.62 (1.46, 1.8)
Humphreys et al., 2014 [23]	1.22 (1.07, 1.4)	NR	NR
Kapetanovic et al., 2011 [24]	1.23 (0.97, 1.55)	1.55 (1.06, 2.19)	1.04 (0.74, 1.44)
Kuo et al., 2013 [25]	1.25 (1.18, 1.33)	1.24 (1.12, 1.38)	1.26 (1.16, 1.36)
Lassere et al., 2012 [8]	1.65 (1.44, 1.85)	1.76 (1.41, 2.16)	1.82 (1.54, 2.09)
Listing et al., 2015 [9]	1.49 (1.36, 1.63)	1.41 (1.2, 1.65)	1.53 (1.37, 1.71)
Mikuls et al., 2011 [26]	NR	2.1 (1.8, 2.5)	NR
Ometto et al., 2018 [10]	1.42 (1.36, 1.48)	NR	NR
Pedersen et al., 2018 [27]	1.04 (0.9, 1.19) [1]	1.16 (0.95, 1.43)	0.96 (0.79, 1.15)
Troelsen et al., 2010 [28]	1.5 (1.2, 1.9)	NR	NR

[1] Not provided by authors; obtained from the reported observed (O) and expected (E) deaths as follows: SMR = O/E; 95% CI = SMR $\pm$ $1.96\sqrt{\text{O/E}}$. CI, confidence interval; NR, not reported; SMR, standardized mortality ratio.

The results of the meta-analysis are shown in Figure 2. The meta-SMR in patients with RA for all-cause mortality was 1.41 (95% CI 1.29, 1.55). Literature data indicate that the risk of mortality is increased by 41% in patients with RA compared to the general population. Excessive all-cause mortality risk was higher for men (meta-SMR 1.53, 95% CI 1.31, 1.78) than for women (meta-SMR 1.46, 95% CI 1.2, 1.77) (Table 4).

Table 4. Results of the meta-analysis of patients with rheumatoid arthritis 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

CI, confidence interval; I^2, inconsistency index; SMR, standardized mortality ratio.

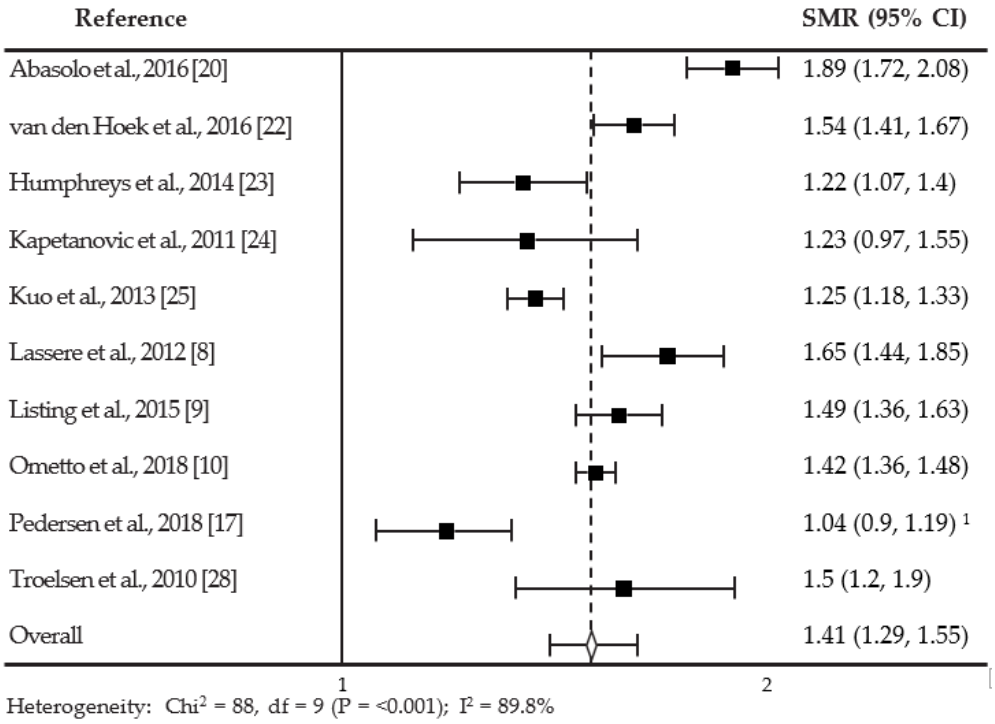

Figure 2. Forest plot of the standardized mortality ratio in patients with rheumatoid arthritis for all-cause mortality.

4. Discussion

Using data from national registries as official state-run sources, we assessed patients with RA in Lithuania and found a 15% excess risk of death in this cohort compared with the general population. However, identified national data showed lower standardized mortality if compared to literature data. In our performed systematic review and meta-analysis, patients with RA had a 41% higher risk of mortality compared with the general population. Our findings are in line with two previously published meta-analyses on the issue of mortality in RA. In both studies, the revealed meta-SMR was similar to that identified in our study; the reported meta-SMR in meta-analysis performed by Toledano et al. was 1.44 (95% CI 1.23, 1.69) [6], whereas that in the meta-analysis conducted by Dadoun et al. was 1.47 (95% CI 1.19, 1.83) [7]. These similarities to other study results reveal that excess mortality in RA still occurs and that the overall mortality rate is still as high as it was in previous decades [7]. According to the review of Sokka et al., the leading causes of death in RA patients are similar to the general population, with cardiovascular diseases being the most common cause of death, along with more infection, pulmonary, and renal disease in RA than in the general population [29]. Therefore, the reasons for the indicated lower mortality among RA patients in Lithuania might be the same reasons that could be applied 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 the mortality of patients with RA.

Additionally, mortality risk was slightly higher for men than for women in our retrospectively defined national RA cohort. Data supporting this finding were reported in studies of patients living in Sweden and Denmark [24,27]. Nonetheless, our observation is contrary to the studies performed in countries such as Germany and Spain [9,20]. Evidence suggests that the difference between the mortality in men and women with RA can be

due to innate and adaptive immune responses and environmental, dietary, and lifestyle factors [30,31]. Notably, our identified meta-SMR in the conducted meta-analysis was also higher among men than in women. However, this result is in contrast to the meta-analysis performed by Toledano et al., which reported higher mortality risk among women compared to men [6].

Some limitations of this study should be mentioned. One of the inclusion criteria in this national retrospective cohort study was information about at least one prescription of medication for RA reimbursed by the state; therefore, some cases of RA might have been omitted in cases where the patient was not treated with state-reimbursed medications. The major limitation of this study was the short follow-up period (on average, 2.78 years). 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.

According to our established results and the studies included in the meta-analysis, we can conclude that patients with RA have an increased risk of death compared to the general population. 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.

5. Conclusions

Our findings support the hypothesis that patients with RA have higher risk of mortality than the general population. In a retrospectively defined population-based national RA cohort, a 15% excess risk of death was observed among patients with RA compared to the general Lithuanian population. National data showed lower standardized mortality compared to literature data, revealing that the risk of mortality is increased by 41% in patients with RA compared with the general population. Excessive all-cause mortality risk was higher in men than in women.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Lithuanian Ethics Committee: approval number 158200-17-958-462, 7 November 2017. The document granting permission to conduct this study may be added upon request.

Informed Consent Statement: This study received a waiver for an informed consent form being signed by participants. The document granting permission to conduct the study without informed consent may be added upon request.

Data Availability Statement: The data presented in this study are not publicly available because they contain the identification code for each person included in this study. Data could not be put in any repository because of local ethical restrictions and new rules that came into force on personal data availability in 2017.

Conflicts of Interest: The authors declare no conflict of interest.

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