Systematic Review and Meta-Analysis

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Biologic DMARDs and targeted synthetic DMARDs and the risk of all-cause mortality in rheumatoid arthritis

A systematic review and meta-analysis

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Abstract

Background: The aim of this study was to perform a meta-analysis to compare the risk of all-cause mortality between biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) and non-b/tsDMARDs involving patients with rheumatoid arthritis (RA).

Methods: We performed a systematic review of articles published up to August 2021 using electronic databases. We included studies that reported all-cause mortality in RA patients and compared b/tsDMARDs and non-b/tsDMARDs.

Results: We included a total of 77 studies involving 64,428 patients. These comprised 44,227 patients treated with b/tsDMARDs and 20,201 treated with non-b/tsDMARDs. The occurrence of all-cause mortality was the primary outcome. The risk of all-cause mortality between the 2 treatments was not significantly different (relative risk = 1.08; 95% confidence interval = 0.98–1.19). However, subgroup analyses showed significant increase in risks of mortality in anti-TNFs users with RA compared with non-b/tsDMARDs (relative risk = 1.47, 95% confidence interval = 1.02–2.12). No significant differences were found after subgroup analyses based on other molecules involved and study duration.

Conclusion: In comparison with non-b/tsDMARDs, our results suggest that antitumor necrosis factor therapy is associated with observed increased risks of mortality and further investigation is needed.

Abbreviations: ACR = American College of Rheumatology, anti-CD20 = anti-cluster of differentiation 20, b/tsDMARDs = biological/targeted synthetic disease-modifying antirheumatic drugs, CI = confidence interval, CTLA4Ig = cytotoxic T lymphocyte antigen-4 Ig, EULAR = European League Against Rheumatism, iIL-6 = interleukin-6 inhibitor, iJAK = janus kinase inhibitor, RA = rheumatoid arthritis, RR = relative risk.

Keywords: DMARDs, mortality, rheumatoid arthritis

1. Introduction

During the past 2 decades, biological disease-modifying antirheumatic drugs (bDMARDs)[1] and targeted synthetic (ts) DMARDs[2] have been demonstrated to be effective in the treatment of rheumatoid arthritis (RA). These drugs have played a significant role in improving the clinical symptoms and enhancing the quality of life of patients[3,4] and were recommended by the European League Against Rheumatism (EULAR).[5] At present, bDMARDs and tsDMARDs are widely used.

However, it is still unclear whether bDMARDs or tsDMARDs[6] can improve the mortality rate in patients with RA. Since inflammatory factors play a significant role in antitumor and anti-infection responses, much has been written about the concern that these new drugs may increase the risks of infections,[7,8] malignancy,[9,10] heart disease,[11] and other serious adverse events. Data from the British Society for Rheumatology Biologics Register showed that the proportion of deaths attributable to RA-interstitial lung disease is higher in patients treated with anti-tumor necrosis factor (TNF) therapy.[12] On the other hand, RA can be well controlled using b/tsDMARDs. Owing to chronic inflammation could be well controlled and the rate of glucocorticoid use was reduced, these therapeutics appear superior to conventional synthetic (cs) DMARDs in reducing mortality.[13–15] But no difference was also found in the risk of mortality between b/tsDMARDs and csDMARDs, as mentioned in some other research works.[16,17]

In order to reveal the association between the use of b/tsDMARDs and the risks of mortality events in RA patients further, we designed and performed a meta-analysis with the aim to evaluate whether treatments with b/tsDMARDs would reduce the risk of mortality events in patients with RA.

The authors have no funding and conflicts of interest to disclose.

All data relevant to the study are included in the article. No more additional data are available.

The authors have no competing interest.

Supplemental Digital Content is available for this article.

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2. Methods

2.1. Literature search

According to the recommendations from the Cochrane Handbook for Systematic Reviews for meta-analysis, we conducted systematic searches in PubMed, the Cochrane databases, Embase, and manual searches of reference lists from systematic reviews and original publications. Studies published in English from January 1, 2000, to August 20, 2021, were selected. The search terms included the following keywords: adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, tofacitinib, baricitinib, upadacitinib, rituximab, tocilizumab, sarilumab, abatacept, rheumatoid arthritis, randomized controlled trial, observational study, cohort study, mortality, and all adults. We limited our search to articles published in the English language and human clinical trials. As the basis of the strategies applied for other electronic databases, we used the PubMed search strategy.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were as follows: the target population was adults with RA diagnosed according to the 1987 American College of Rheumatology criteria or the 2010 American College of Rheumatology/

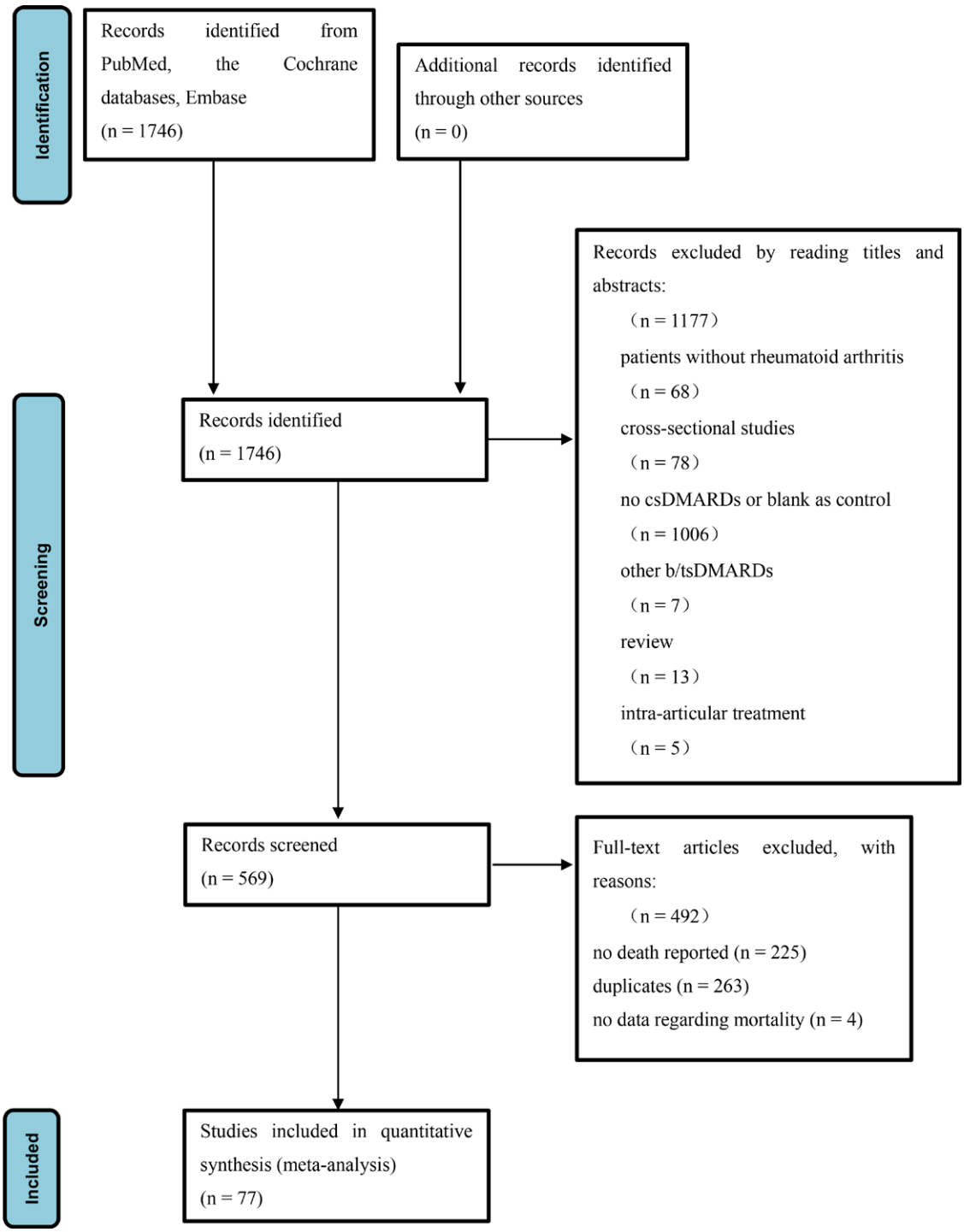

Figure 1. Flow diagram of articles evaluated for inclusion and exclusion. b/tsDMARD = biological/ targeted synthetic disease-modifying antirheumatic drug, csDMARD = conventional synthetic disease-modifying antirheumatic drug.

EULAR criteria; randomized controlled trial (RCT, observational study and cohort study; interventions that included the bDMARDs or tsDMARDs listed above according to the 2019 EULAR recommendations.[5] The exclusion criteria were as follows: studies in which no death reported, studies in which no csDMARDs or blank as control group, and studies in which interventions were delivered through intra-articular treatment.

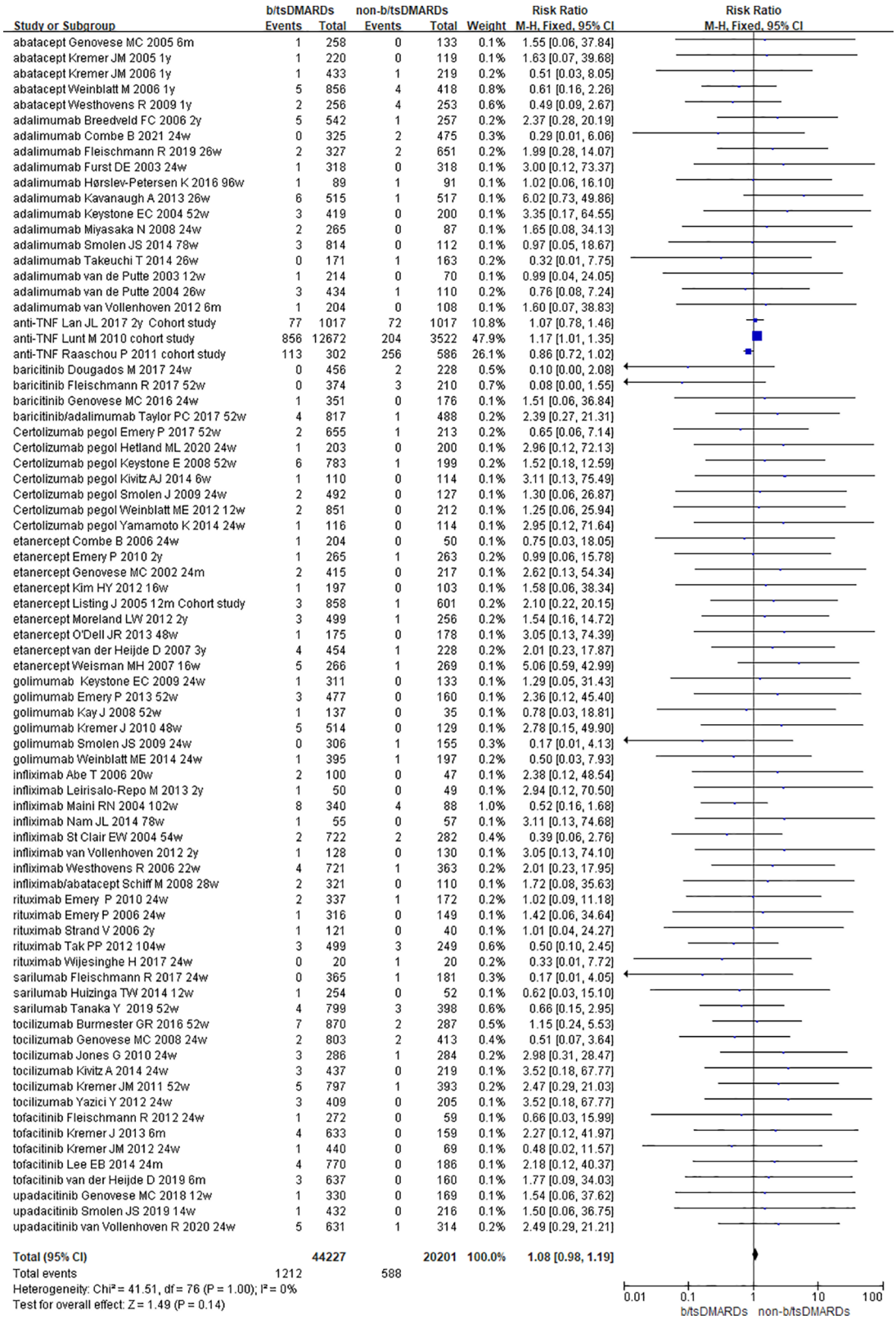

Figure 2. Forest plot of trials comparing b/tsDMARDs with non-b/tsDMARDs for the risk of all-cause mortality in patients with rheumatoid arthritis. b/tsDMARD = biological/ targeted synthetic disease-modifying antirheumatic drug, CI = confidence interval.

Two investigators (M.D.P. and Z.S.) independently extracted data from articles using a customized form available upon request from the authors. Disagreements were resolved by consensus. This is a systematic review, and ethical approval was not required.

2.3. Data analysis

The Review Manager statistical software package (version 5.3, The Cochrane Collaboration, London, United Kingdom) was used to perform statistical analyses. We conducted this meta-analysis according to the Preferred Reporting Items for

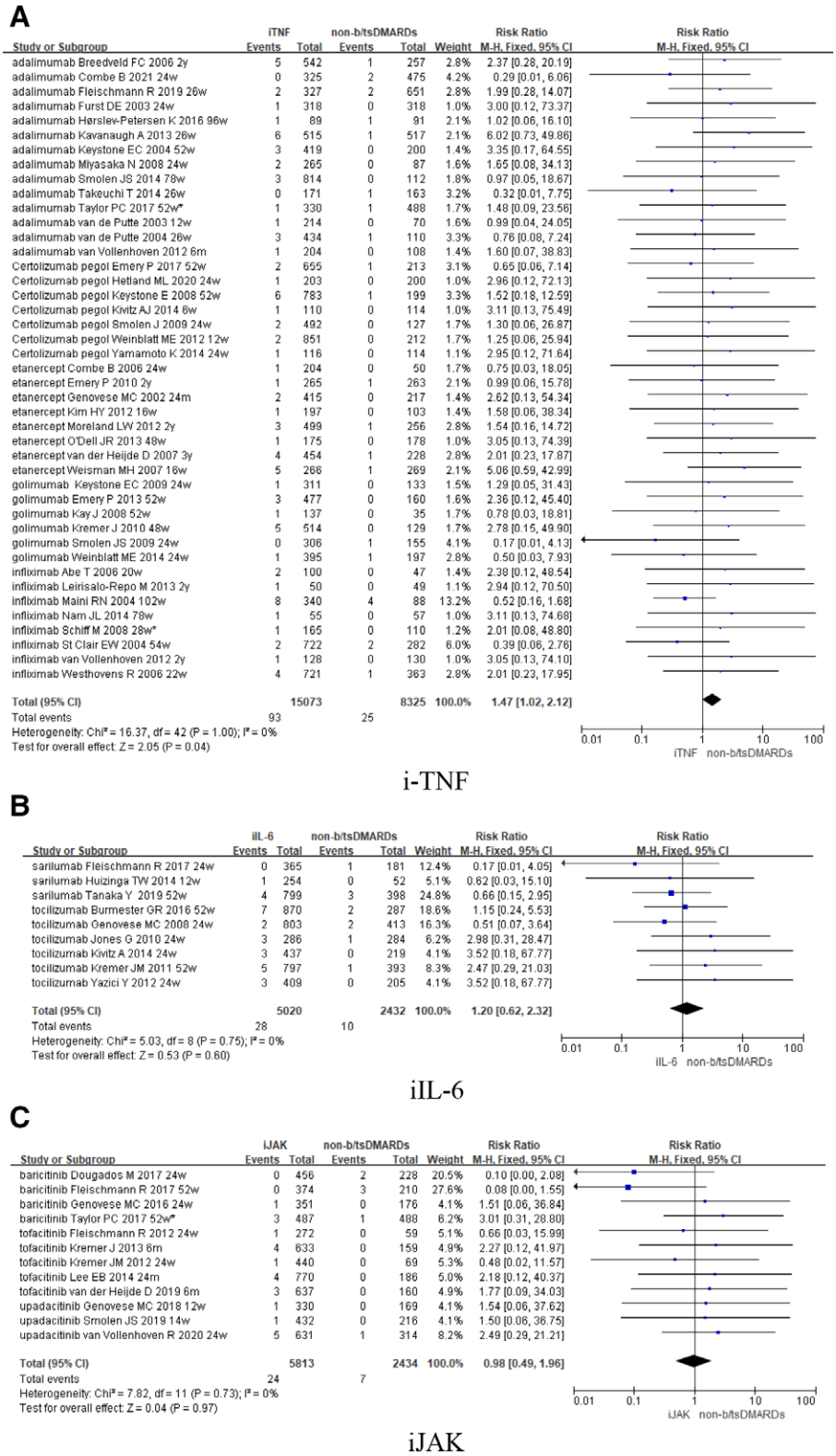

Figure 3. The associations between the use of different b/tsDMARDs molecules involved and mortality endpoint. anti-CD20 = anti-cluster of differentiation 20, b/tsDMARD = biological/ targeted synthetic disease-modifying antirheumatic drug, CI = confidence interval, CTLA4Ig = cytotoxic T lymphocyte antigen-4 Ig, iIL-6 = interleukin-6 inhibitor, iJAK = janus kinase inhibitor, iTNF = tumor necrosis factor inhibitor.

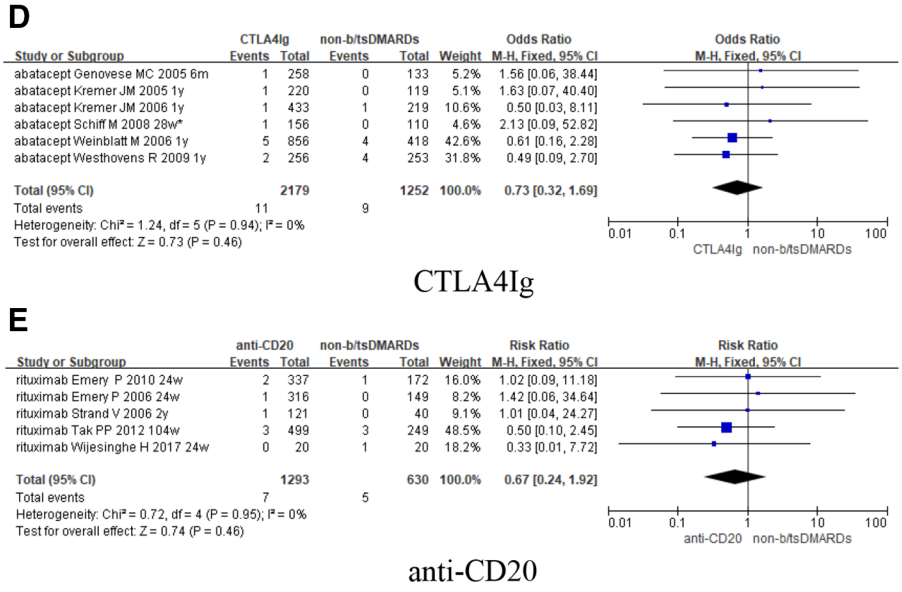

Figure 3. Continued

Systematic Reviews and Meta-Analyses guidelines for conducting and reporting meta-analyses.[18]

Statistical heterogeneity was tested with an I^2 statistic calculation.[19] In the statistical analysis, a high level of heterogeneity was defined as an $I^2 > 50\%$, whereas a low level of heterogeneity was defined as an $I^2 \leq 50\%$. For analysis, we used a fixed-effects model. Qualities of the observational studies were evaluated using the Newcastle-Ottawa Scale, and qualities of RCTs were evaluated using the Cochrane risk of bias tool. A third investigator (H.F.Z.) confirmed the accuracy of the abstractions and study quality evaluation.

We performed additional subgroup analyses to determine whether the findings would change substantially. For the subgroup analyses, we divided the studies according to the following: different types of studies (RCTs or cohort studies), rate of clinical application of different molecules (TNF inhibitors, Janus kinase [JAK] inhibitors, interleukin [IL]-6 inhibitors, cytotoxic T lymphocyte antigen-4 [CTLA4] Ig, and anti-CD20 monoclonal antibodies), and study duration (excluding studies <6 months, 1 year, or 2 years). Specific causes of mortality such as infections, malignancy, heart disease, respiratory disease, digestive system disease, cerebral disease, suicide, unknown, and others were analyzed in subgroups.

3. Results

3.1. Summaries of included studies

The flowchart for the study selection process is summarized in Figure 1. Among the initially analyzed 1746 studies, 77 studies fulfilled our inclusion criteria with 73 RCTs and 4 cohort studies, respectively. The RCTs consisted of 4 baricitinib studies[20–23] (one of which included adalimumab[22]), 5 tofacitinib studies,[24–28] 3 upadacitinib studies,[29–31] 13 adalimumab studies,[32–44] 7 certolizumab pegol studies,[45–51] 8 etanercept studies,[52–59] 6 golimumab studies,[60–65] 8 infliximab studies[66–73] (one of which included abatacept[69]), 3 sarilumab studies,[74–76] 6 tocilizumab studies,[77–82] 5 abatacept studies,[83–87] and 5 rituximab studies.[88–92] The cohort studies consisted of 4 anti-TNF studies[93–96] (see Table S1A, B, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates baseline characteristics of included studies).

The risk of bias for RCT was systematically evaluated by the Cochrane tool. Most of our comparison analyses indicated the RCTs had a high quality of evidence, and only 5 studies were assessed as high or unclear risk (see Fig. S1A, B, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates evaluation for risk of bias in included RCTs). Funnel plots indicated an even distribution for the mean values of the parameters evaluated (see Fig. S2, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates the funnel plot of included RCTs). The included cohort studies were of relatively high quality as Newcastle-Ottawa Scale suggested (see Table S2, Supplemental Digital Content, http://links.lww.com/MD/G845, which illustrates evaluation for risk of bias in included cohort studies).

The range of study duration was from 6 weeks to 3 years, and 64,428 patients were included in the analysis. Among these patients, 44,227 were treated with b/tsDMARDs, and 20,201 were treated with non-b/tsDMARDs.

3.2. Primary outcome

3.2.1. Mortality of any cause upon b/tsDMARD compared with non-b/tsDMARDs. During the study duration, 1212 (2.74%) deaths were observed in patients treated with b/tsDMARDs compared to 588 (2.91%) deaths in those treated with non-b/tsDMARDs. Compared with non-b/tsDMARDs users, the risks of mortality were not significantly increased in b/tsDMARDs users (relative risk [RR] = 1.08; 95% confidence interval [CI] = 0.98–1.19; Fig. 2).

3.3. Secondary analyses

3.3.1. Subgroup analyses with respect to molecules involved (TNF inhibitors, JAK inhibitors, IL-6 inhibitors, CTLA4Ig and anti-CD20 Ag) in RCTs. When stratified by the molecules involved, subgroup analyses showed significant increase in risks of mortality in anti-TNFs users with RA compared with non-b/tsDMARDs (RR = 1.47, 95% CI = 1.02–2.12). But no significant difference was found between other molecules subgroups. We observed the following: in the iIL-6 subgroup: RR = 1.20, 95% CI = 0.62–2.32; in the JAK inhibitor subgroup: RR = 0.98, 95% CI = 0.49–1.96; in the CTLA4Ig subgroup: RR = 0.73, 95% CI = 0.32–1.69; and in the anti-CD20 subgroup: RR = 0.67, 95% CI = 0.24–1.92 (Fig. 3).

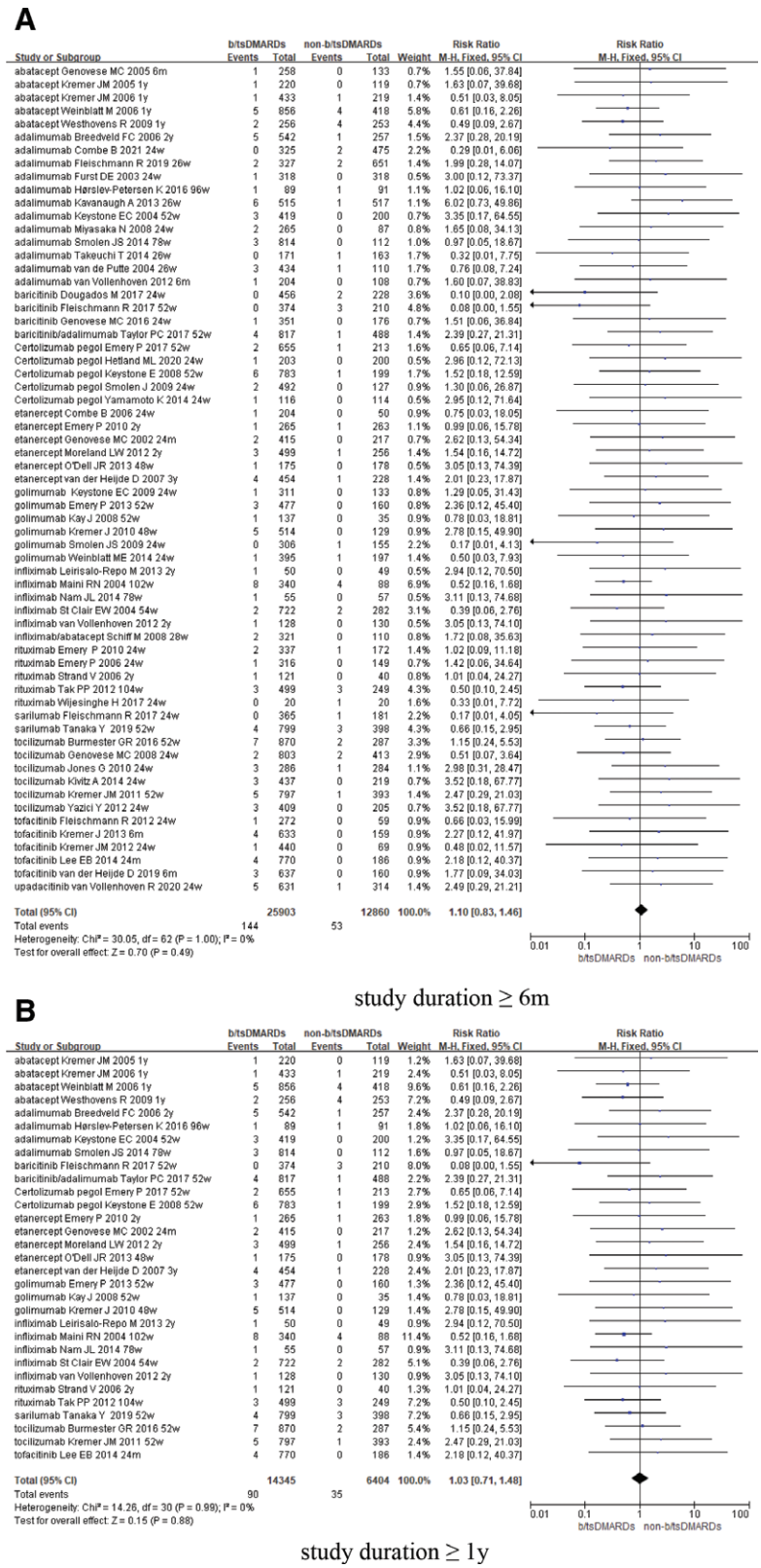

Figure 4. The associations between the different study duration and mortality endpoint. b/tsDMARD = biological/ targeted synthetic disease-modifying anti-rheumatic drug, CI = confidence interval.

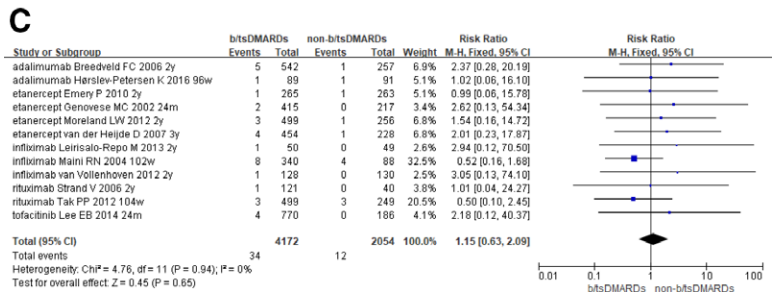

Figure 4. Continued

3.3.2. Subgroup analyses with respect to the study duration (studies <6 months, 1 year, or 2 years were excluded) in RCTs. For this subgroup analysis, the results suggested no significant difference in the mortality rate between b/tsDMARDs and non-b/tsDMARDs according to different study duration. We observed the following: in the study duration ≥6-month subgroup: RR = 1.10; 95% CI = 0.83–1.46; in the study duration ≥1-year subgroup: RR = 1.03; 95% CI = 0.71–1.48; in the study duration ≥2-year subgroup: RR = 1.15; 95% CI = 0.63–2.09 (Fig. 4).

3.3.3. Subgroup analyses for mortality of any cause upon b/tsDMARD compared with non-b/tsDMARDs in cohort studies. For this subgroup analysis, the results suggested no significant difference in the mortality rate between b/tsDMARDs and non-b/tsDMARDs in cohort studies. (RR = 1.06; 95% CI = 0.95–1.18; Fig. 5).

3.3.4. Proportion of different causes of death for b/tsDMARDs and non-b/tsDMARDs in RCTs. In this subgroup analysis, specific causes of mortality (infections, malignancy, heart disease, pulmonary disease, digestive system disease, cerebral disease, suicide, unknown, and others) were evaluated. In both subgroups, the most common cause of mortality was infections and heart disease (Fig. 6).

4. Discussion

In our meta-analysis, we included RCTs and cohort studies covering all the bDMARDs and tsDMARDs recommended by the EULAR.[5] To our knowledge, this was the largest review of mortality associated with b/tsDMARD therapy in RA. In the meta-analysis, we compared the risk of mortality between b/tsDMARDs and non-b/tsDMARDs. By analyzing the existing data, the use of b/tsDMARDs might not be associated with increased risks of mortality, consistent with previous views.[16]

However, the risks of mortality increased in the anti-TNFs treatment group in the subgroup analysis as the data showed. Different from our results, an earlier meta-analysis, including RCTs, found no difference between the 2 therapies.[17] Another meta-analysis reported that anti-TNFs could even decrease mortality in RA patients.[14] It is worth noting that the inclusion criteria in these meta-analyses were different from ours. Interventions were limited strictly to anti-TNFs alone and comparators included placebo and csDMARDs in the previous meta-analysis.[17] While only cohort studies from worldwide biologic registers were included in the another meta-analysis,[14] patients from the anti-TNFs group and the csDMARD group were not matched mostly. Different from the meta-analysis studies mentioned above, the aim of our study was to compare the risk of all-cause mortality between b/tsDMARDs and non-b/tsDMARDs; all RCTs and cohort studies were included and all the patients involved in b/tsDMARDs treatment were calculated.

In our study, the leading causes of death in the anti-TNFs or b/tsDMARDs groups were heart disease, followed by infections and malignancy. In terms of the causes of death in RA patients, heart disease seems to be the most important, and the rates in b/tsDMARDs and anti-TNFs were slightly higher than non-b/tsDMARDs as the histograms showed. Consistent with our findings, possible worsening of cardiovascular function has been reported in anti-TNFs formerly.[11] However, a meta-analysis published recently indicated that the use of bDMARDs might be associated with the reduced risks of cardiovascular death in RA.[97] Different retrieval methods and calculation methods may lead to different results. More investigations are needed to validate conclusions.

In both treatment groups, infections was an important causes of death, and the rates in b/tsDMARDs and anti-TNFs were both lower than the control groups to a small degree. As previous data showed, an increase in serious infections might be associated with the anti-TNFs treatment in patients with RA compared to csDMARDs.[98–100] In terms of mortality, our data indicated that infections were slightly more serious in the non-b/tsDMARDs treatment.

Comparing with the non-b/tsDMARDs, the risk of malignancy in b/tsDMARDs was significantly elevated, especially in anti-TNFs treatment. As reported previously, Published data showed an increase in overall cancer risk in patients on anti-TNFs,[101] consistent with our results. A 2- to 3-fold increase in risk with a potential dose-dependent relation between treatment and malignancy was observed.[102,103] Due to the short study duration of the RCTs possibly, the proportion of malignancy was <20%. It is worth noting that a recent meta-analysis, in which only a case–control or cohort study was considered,

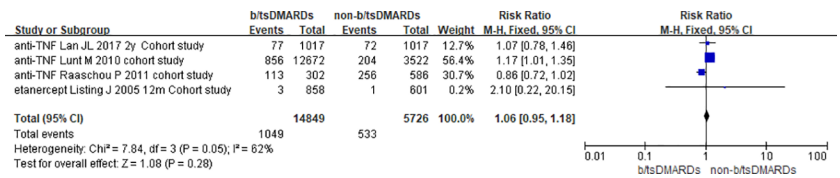

Figure 5. Forest plot of trials comparing b/tsDMARDs with non-b/tsDMARDs for the risk of all-cause mortality in cohort studies. anti-TNF = antitumor necrosis factor, b/tsDMARD = biological/ targeted synthetic disease-modifying antirheumatic drug, CI = confidence interval.

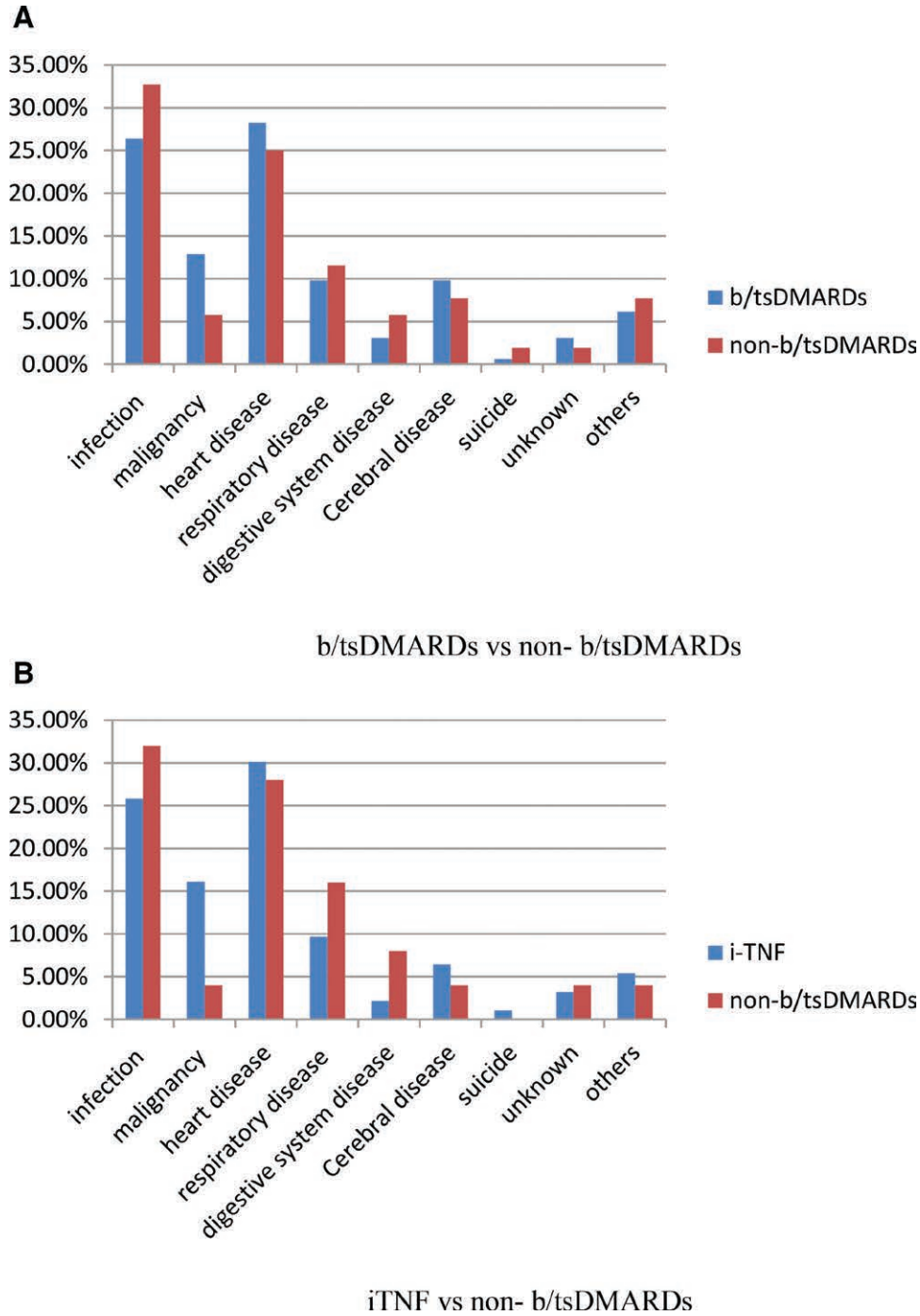

Figure 6. Proportion of different causes of death in b/tsDMARDs and non-b/tsDMARDs in RCTs. b/tsDMARD = biological/targeted synthetic disease-modifying antirheumatic drug, iTNF = tumor necrosis factor inhibitor, RCT = randomized controlled trial.

showed no increased risk of developing cancer overall or some specific subtypes in RA patients with prior cancer receiving biologics.[104] More investigations are warranted to explore the risk of cancer.

We also performed subgroup analyses based on other molecules (JAK inhibitors, IL-6 inhibitors, CTLA4Ig, and anti-CD20 Ag) and the study duration (>6 months, 1 year, or 2 years). No influence on the risk of mortality in RA patients was found for the 2 treatments in any of these subgroups. Compared with anti-TNFs, studies related to other molecules were lesser relatively. More data regarding these molecules are needed to confirm the influence on mortality.

Our study findings should be interpreted with several limitations taken into consideration. First, the studies included in the meta-analysis had a short duration (<3 years) and are therefore not suitable for evaluating delayed-onset events such as long-term mortality. Moreover, results from RCTs may not be transposable to "real life" because patients eligible for RCTs have fewer comorbidities than those encountered in our daily practice. Second, the comparability between the 2 treatment groups decreased in the cohort studies from worldwide biologic registers owing to significant limitations relating to bias and confounding factors. High-quality and long-term controlled clinical trials are needed for further confirmation. Third, the

included studies spanned >20 years, and early studies were different from more recent studies in terms of the patients enrolled and the study design, although no effects from publication date bias were found.

5. Conclusion

Our meta-analysis shows that b/tsDMARDs is not associated with a higher risk of mortality due to any cause during RCTs or the cohort studies in patients with RA compared to non-b/tsDMARDs. While the anti-TNFs treatment increased, the risks of mortality maybe. Further studies are required to assess the long-term effects of b/tsDMARDs on mortality.

Author contributions

HFZ conceptualized this study and designed the systematic review protocol; MDP and ZS performed the study selection and data extraction; ZS performed the statistical analyses; MDP prepared the outlines and wrote the manuscript. All authors contributed to the critical revision of manuscript drafts. Mengduan Pang and Zhe Sun contributed equally to the manuscript.

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