Decreased comorbidities in rheumatoid arthritis patients treated with a biologic agent

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Abstract

Objective. Biologics have been linked to both anti-autoimmune and anti-inflammatory mechanisms. We examine the long-term effects of biologics on rheumatoid arthritis (RA) patients in a real-world analytic cohort study using a nationwide database. Design. We designed a cohort study using the National Health Insurance Research Database in Taiwan between 1997 and 2010. Methods. Based on biologics and other anti-rheumatic agent prescriptions, we divided all patients into either the biologics group or the non-biologics group. The outcomes were the incidence rate of each comorbidity and the hazard ratio of each comorbidity between those using biologics and those not. We followed patients from the index date to the date on which the database ended. Results. In total, 19,681 patients were eligible for analysis in this study. During an average follow-up of 15 years, the event rates of each comorbidity differed significantly between the users and non-users of biologics with regard to cardiovascular comorbidity, metabolic comorbidity, rheumatologic comorbidity, and the miscellaneous comorbidity (all $p<0.05$). The usage of biologic agents in RA patients reduced the HR of cardiovascular comorbidities by 18%, metabolic comorbidities by 17%, rheumatology comorbidities by 36%, and miscellaneous comorbidities by 15% compared to those patients who did not use biologics. Oncology comorbidities and infection comorbidities were not affected by treatment with biologics ($p>0.05$). Conclusions. Biologics may have benefits beyond arthritis control with regard to reducing real-world comorbidities.

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In total, 19,681 patients were eligible for analysis in this study. During an average follow-up of 15 years, the event rates of each comorbidity differed significantly between the users and non-users of biologics with regard to cardiovascular comorbidity, metabolic comorbidity, rheumatologic comorbidity, and the miscellaneous comorbidity (all $p<0.05$). The usage of biologic agents in RA patients reduced the HR of cardiovascular

comorbidities by 18%, metabolic comorbidities by 17%, rheumatology comorbidities by 36%, and miscellaneous comorbidities by 15% compared to those patients who did not use biologics. Oncology comorbidities and infection comorbidities were not affected by treatment with biologics ($p>0.05$).

Conclusions.

Biologics may have benefits beyond arthritis control with regard to reducing real-world comorbidities.

Keywords: rheumatoid arthritis, biologics, comorbidity, real-world data.

Introduction

In this study, we aimed to identify whether biologics treatment in rheumatoid arthritis (RA) patients was capable of preventing comorbidities in this population [1]. Biologics have been used for more than 15 years in Taiwan, and their efficacy has been discussed elsewhere and confirmed to be protective against joint structure damage in RA patients. Whether biologics' beneficial effect influences comorbidities throughout the body is still under evaluation.

Among RA patients, the first comorbidities that need to be considered are cardiovascular events, followed by metabolic problems like diabetes and dyslipidemia. Diabetes mellitus, together with a number of risk factors of metabolic origin, can result in an increased risk for early mortality [2]. Considerable evidence has demonstrated that chronic low-grade inflammation caused by activating the innate immune system is vital in the pathogenesis of diabetes and other major complications. Diabetes is also a risk factor for cardiovascular comorbidities itself. In addition to these common comorbidities, RA is an autoimmune disease that can overlap other rheumatic or orthopedic-related comorbidities, such as gout, osteoporotic fractures, inflammatory bowel disease, psoriasis, etc. In the long run, the malignancy could be devastating due to chronic inflammation and tissue damage in RA patients.

Several other comorbidities that need to be considered include infectious diseases caused by the immune deviation of RA patients or the hepatic or nephrotic damage caused by medication side effects. Such pulmonary diseases as interstitial lung disease, asthmatic bronchitis, or chronic obstructive pulmonary disease are all listed in our analysis (Table 1).

The purpose of this study was to determine the long-term effect of biologic agents on RA patients in a real-world setting by using a nationwide database. Therefore, we designed a simulated analytic cohort study with strict selection and matching to determine whether long-term biologic agent use could affect the overall mortality rate of RA patients. In the current retrospective study, we compared the mortality rate between biologics users and non-biologics users in RA patients in Taiwan.

Materials and Methods

The single-payer compulsory National Health Insurance (NHI) program was initiated in Taiwan in 1995. The program provides universal coverage to most residents in Taiwan. The NHI Research Database (NHIRD) provided data about complete outpatient visits, hospital admissions, prescriptions, catastrophic illness information, and vital status of 99% of Taiwan's 23 million people. The bureau of the NHI released the NHIRD for research purposes. In this study, we adopted the data obtained through the Longitudinal Health Insurance Database 2005 (LHID 2005) from the NHIRD. This LHID 2005 database included registration and medical claims for 1,000,000 randomly sampled patients from the total number of NHRI enrollees. The LHID2005 data set allows researchers to follow up on all the medical services utilized by these 1,000,000 individuals since the initiation of the NHI in 1995. To protect individual privacy, the original identification numbers of the beneficiaries' data were encrypted for privacy. Encryption procedures were consistent with other datasets and ensured that all claims data could be linked in order to obtain additional medically relevant data. All data that could be used to identify patients or care providers, including the names of medical institutions and physicians, were encrypted. Our study protocol was approved by the institute review board of Chang Gung Memorial Hospital, Kaohsiung, Taiwan without the need of any informed consent.

Data source

We derived the real-world data of this prospective cohort study from Taiwan's National Health Insurance Research Database (NHIRD). NHIRD is an administrative database from Taiwan's National Health Insurance (NHI) program, the country's compulsory and single-payer national health insurance system. The NHI program covers almost all outpatient visits, emergency room services, admission services, medical care services, and medications. Services include physician diagnosis, blood tests like biochemistry and complete blood count, imaging studies like chest X-rays and computed tomography, medication, and surgery. The bureau of the NHI released the NHIRD for research purposes. In this study, we adopted the data obtained through the Longitudinal Health Insurance Database 2005 (LHID 2005) from the NHIRD. This LHID 2005 database included registration and medical claims for 1,000,000 randomly sampled patients from the total number of NHRI enrollees. The LHID2005 data set allows researchers to follow up on all the medical services utilized by these 1,000,000 individuals since the start of the NHI in 1995.

This study was approval by the Chang Gung Medical Foundation's Institutional Review Board (IRB No.: 201600763B1).

Study design

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Co-morbidities and outcomes

Since the LHID 2005 does not include laboratory exam result\souts (i.e., HbA1C, c-reactive protein), we selected several clinical indicators to represent disease comorbidities, including several major organ diseases such as cardiovascular comorbidities, endocrine comorbidities, rheumatic or orthopedics comorbidities, oncology comorbidities, infection comorbidities, and miscellaneous comorbidities. Such comorbidities as hypertension, dyslipidemia, gout, chronic kidney disease, coronary artery disease, interstitial lung disease, malignancy, stroke, and hepatitis B/C were recorded.

Statistical analysis

We carried out *chi-square analysis* in order to compare the biologics and non-biologics groups. We compared the characteristics of the biologics patients and non-biologics patients, adopting the t-test for continuous variables and the chi-square test for categorical variables. The incidence of mortality was reported as the event rate (proportion of events) and incidence density (number of events per 100 person-years). We adopted Cox proportional hazard model to compare the risk of mortality between the two groups. Furthermore, we used the Poisson regression model to compare the annual number of admissions for autoimmune disease between the study groups, treating the log-transformed follow-up year as an offset variable. Finally, the hazard ratio of the patients of the two groups was calculated with survival analysis. We considered a p -value < 0.05 to be statistically significant. All data analysis was conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

- Ethics approval and consent to participate

This retrospective database analysis study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and

its later amendments or comparable ethical standards. The Longitudinal Health Insurance Database 2005 provides only de-identified samples, which Ethical approval was waived by the local Ethics Committee.

Results

Eligible patients

We found a total of 19,681 patients with RA in the Longitudinal Health Insurance Database 2005 (LHID 2005). Of those, 15,097 patients had cardiovascular diagnostic coding. Patients who did not have associated cardiovascular coding were not listed in Table 2 for analysis. Among these patients, 4,810 patients were diagnosed with RA, nine of which were treated with biologic agents. Similarly, 13,384 patients had metabolic diagnostic coding. Patients that did not have associated metabolic coding were not listed in Table 2 for analysis. Among these patients, 5,680 patients were diagnosed with RA, nine of which were treated with biologic agents.

In the LHID 2005 database, 18,114 patients had rheumatologic or orthopedic diagnostic coding. Patients who did not have associated rheumatologic or orthopedic coding were not listed in Table 2 for analysis. Among these patients, 2,269 patients were diagnosed with RA, seven of which were treated with biologic agents. Again, in the LHID 2005 database, 19,681 patients had oncologic diagnostic coding. Patients that did not have associated oncologic coding were not listed in Table 2 for analysis. Among these patients, 3,148 patients were diagnosed with RA, 23 of which were treated with biologic agents. Of the 18,944 patients with infectious related diagnostic coding, 1,092 patients were diagnosed with RA, and seven of those were treated with biologic agents. Finally, 13,047 had miscellaneous diagnostic coding related to RA. Among these patients, 4,996 patients were diagnosed with RA, seven of which were treated with biologic agents.

Baseline characteristics for study participants

Table 2 lists patient characteristics with rheumatoid arthritis, their comorbidities, and their treatment status with or without biologic agents. We found a total of 19,681 patients with RA in the Longitudinal Health Insurance Database 2005 (LHID 2005). Of those, 19,323 patients were older than sixteen years old, while the remaining 358 patients were sixteen years old or younger. In total, the sample included 12,720 female patients and 6,961 male patients. Basically, the biologics users accounted for only a few patients compared to non-biologics users. Only 156 patients among the LHID 2005 cohort used biologics. We observed no statistical significance regarding using biologics between those older and younger than sixteen years old ($p=0.61$). On the other hand, we observed significant differences between male and female patients using biologics ($p<0.0001$).

Biologics are beneficial regarding cardiovascular comorbidity, metabolic comorbidity, rheumatologic comorbidity, and miscellaneous comorbidity in the current study

With an average 15-year follow-up duration, the event rate of different medical comorbidities in the biologics group and in the non-biologics group are shown in Table 2, which compares the incidence of each comorbidity with the usage of biologic agents. This result indicates that the incidence rates of cardiovascular comorbidity, metabolic comorbidity, rheumatologic comorbidity, and miscellaneous comorbidity were all significantly lower in the biologics group (all $p<0.05$). However, the usage of biologic agents does not change the incidence of oncology or infectious comorbidities (both $p>0.05$, Table 2).

Outcomes of multivariate-adjusted hazard ratio (HR) of each comorbidity

Both the detailed incidence rate and the hazard ratio (HR) of each comorbidity in RA patients are demonstrated in Table 3. The effects of gender, age, and biologics to each comorbidity were demonstrated separately. The occurrence of cardiovascular comorbidities was 9% higher in male RA patients than in female RA patients (crude HR), or 10% higher with multivariate-adjusted HR. The occurrence of cardiovascular comorbidities was 27.63 times higher in RA patients over the age of 16 years than in RA patients 16 years old and younger (crude HR), or 28.11 times higher with multivariate-adjusted HR. The use of biologic agents in RA

patients could reduce both the crude HR and the multivariate-adjusted HR of cardiovascular comorbidities by 18% compared to those patients who did not (Table 3).

The metabolic comorbidities occur 11% more in female RA patients than in male RA patients (crude HR), or 10% more with multivariate-adjusted HR in female RA patients. Metabolic comorbidities are 5.79 times more likely in RA patients over the age of 16 years old than in RA patients 16 years old or younger (crude HR), or 5.72 times higher with multivariate-adjusted HR. The use of biologic agents in RA patients could reduce both the crude HR and the multivariate-adjusted HR of metabolic comorbidities by 17% compared to those patients who did not (Table 3).

Rheumatology comorbidities were 3% higher in female RA patients than in male RA patients (crude HR), or 3% higher with multivariate-adjusted HR. They were 1.25 times higher in RA patients over the age of 16 years old than in RA patients 16 years old or younger (crude HR), or 1.25 times higher with multivariate-adjusted HR. The usage of biologic agents in RA patients could reduce the HR of rheumatology comorbidities by 36% compared to those patients who did not with crude HR and by 35% compared to those patients who did not with the multivariate-adjusted HR. (Table 3).

Oncology comorbidities occurred 25% more in male RA patients than in female RA patients (crude HR), or 26% more with multivariate-adjusted HR. Regarding age, the oncology comorbidities were 3.37 times higher in RA patients over the age of 16 years old than in RA patients 16 years old or younger (crude HR), or 3.5 times higher with multivariate-adjusted HR. The use of biologic agents in RA patients could reduce both the crude HR and the multivariate-adjusted HR of oncology comorbidities by 65% compared to those patients who did not, but we observed no significant statistical differences between users and non-users of biologics ($p>0.05$) (Tables 2 and 3).

Infection comorbidities were 25% more likely in male RA patients than in female RA patients (crude HR), or 26% more likely with multivariate-adjusted HR. The occurrence of infection comorbidities was 3.37 times higher in RA patients over the age of 16 years old than in RA patients 16 years old or younger (crude HR), or 3.5 times higher with multivariate-adjusted HR. The usage of biologic agents in RA patients could reduce the HR of infection comorbidities by 77% compared to those patients who did not with crude HR and by 81% of those patients who did not with the multivariate-adjusted HR. However, no statistically significant differences were found between users and non-users of biologics ($p>0.05$) (Tables 2 and 3).

Miscellaneous comorbidities were 6% higher in male RA patients than in female RA patients (crude HR), or 7% higher with multivariate-adjusted HR. The miscellaneous comorbidities were 1.52 times higher in RA patients over the age of 16 years old than in RA patients 16 years old or younger (crude HR), or 1.55 times higher with multivariate-adjusted HR. The usage of biologic agents in RA patients could reduce both the crude HR and the multivariate-adjusted HR of miscellaneous comorbidities to 15% of those patients who did not (Table 3).

Discussion

This large RA cohort study demonstrates that patients that have been prescribed biologics have a significantly decreased rate of cardiovascular comorbidity, metabolic comorbidity, rheumatologic comorbidity, and miscellaneous comorbidity (all $p<0.05$), but with a similar rate of oncology and infectious comorbidity incidence (both $p>0.05$) (Table 2). The **extra-joint benefit**from being treated with the biologics has been documented by previous studies, including improved cardiovascular outcome [5], improved insulin resistance [6], improved trabecular bone mass, and decreased bone loss [7, 8], but with a stable malignancy rate [9]. Furthermore, a recent article mentioned that patients with RA appeared to be at a higher risk of lung cancer and lymphoma, but a lower risk of colorectal and breast cancer [10], which contribute equally to the malignancy rate. Also, that the biologic agents did not induce malignancy was demonstrated in another meta-analysis research [11]. On the other hand, the infection comorbidities, which should be increased in patients treated with biologics [12, 13], was not seen in our current study. This finding may have been because the risk management program arose before all the biologic agents could be issued by physicians, thus making the incidence rate of infections too low to be detected in this cohort.

The prescription of biologic agents to RA patients was not affected by**age discrimination** (p=0.61), but it was affected by**gender,** with female being predominant (p<0.0001) (Table 2). One possible explanation for this phenomenon is that the female RA patients may have higher pain scores [14], which could be a surrogate marker for higher disease activity, implying a much higher chance to get access to biologics treatment. Regarding the age effect of comorbidities (Table 3), a selection bias may arise in treating juvenile RA or adult RA patients [15, 16], but age itself is still a risk factor for all the comorbidities in treating RA patients [17].

In the current study, the infection outcome comparison between biologics users and non-biologics users seems to be neutral, which differs from previous studies on the deteriorated effect of biologics with regard to tuberculosis infection [11], bacterial infection [18], and other opportunistic infections [19-21]. The different results of infection rate could be a bias related to a mixture of different mechanisms of biologics [22, 23] or different components of the biologics [23].

Regarding miscellaneous comorbidities, whether exposure to biologics has a deteriorating [24] or neutral [25] effect on kidney function is still debated, but biologics may have benefits related to reducing chronic obstructive pulmonary disease in RA patients [26]. Furthermore, other studies have been performed on biologics in cardiovascular events [5, 27], hepatoma [28], cancers [5], and atherothrombosis [29]. To the best of our knowledge, no specific research dealing with the biologics effect on miscellaneous comorbidities has yet been published.

Likewise, respiratory failure is mostly caused by inflammation [30] and increased oxidative stress [31]. Biologics may be significantly associated with lung disease in RA patients [32-34]. Another review article mentioned that MTX, LEF, TNFi, RTX, and TCZ may cause pneumonitis [35], which was not demonstrated in our current study and warrants further investigation.

Our study has certain limitations that should be mentioned at this point. This study is designed to evaluate an organ system-oriented comorbidity in RA, which limits the individual causative etiology of comorbidity results. Furthermore, this retrospective observation cohort study only reflects a particular interval of time, which certain types of biologic agents available in Taiwan. Different time inveral and a different mixture of patients could have different results. In general, we found that biologics may be associated with decreasing several comorbidities in RA patients in this particular cohort study.

- Table 1. Comorbidities of rheumatoid arthritis, categorized by system

Cardiovascular:

- Atrial fibrillation (ICD-9: 427.31)
- Hypertension (ICD-9: 401-405)
- Acute myocardial infarction: Any hospitalization with a diagnosis of ICD-9: 410.x
- Coronary heart disease (ICD-9: 410–414)
- Heart failure (ICD-9: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, or 428)
- Cerebral vascular incident (CVA) (ICD-9: 430–438)
- Deep vein thrombosis (DVT) and pulmonary thromboembolism (PE): PE (ICD-9: 415.1), iatrogenic PE (ICD-9: 415.11), and DVT (ICD-9: 453.8)

Endocrine:

- Hyperlipidemias (ICD-9: 272)
- Diabetes mellitus (ICD-9: 250)
- Thyroid disorders: thyroid cancer (ICD-9: 193), hypothyroidism (ICD-9: 244), hyperthyroidism (ICD-9: 242), and thyroiditis (ICD-9: 245)

Rheumatic or orthopedics:

- Gout (ICD-9: 274)
- Hip fracture (ICD-9: 820) and operation codes 7855, 7925, 7935, 7995, or 8152
- Inflammatory bowel disease: ulcerative colitis (ICD-9: 556) and Crohn's disease (ICD-9: 555)
- Psoriasis (ICD-9: 696, 696.1 or 696.8)

Oncology:

- Malignancy (ICD-9: 140–208)
- Lymphoma (ICD-9: 200, 201, 202, or 203)

Infection:

Tuberculosis (ICD-9: 010.x–018.x)

Viral hepatitis: HBV (ICD-9: 070.2, 0.70.3, or V02.61) and HCV (ICD-9: 070.41, 070.44, 070.51, 070.54, or V02.62)

Miscellaneous:

- Chronic obstructive pulmonary disease (ICD-9: 491, 492, or 496)
- Asthma (ICD-9: 493)
- Chronic kidney disease (ICD-9: 582, 583, 585, 586, or 588)
- Chronic liver diseases (ICD-9: 456.0–456.2, 571.2, 571.4–571.6, or 572)

- Table 2. Demographic data of patients with rheumatoid arthritis, their incidence rates of comorbidities, and their treatment status with or without biologic agents.

	Rheumatoid Arthritis$^{\alpha}$	Rheumatoid Arthritis$^{\alpha}$		Biologic Agents	Biologic Agents		No Biologic Agents	No Biologic Agents	*p*-v
	N=19681	%		N^{1}=156	%		N^{2}=19525	%	
Age									
[?] 16	358	1.82		2	1.28		356	1.82	0.6
>16	19323	98.18		154	98.72		19169	98.18	
Gender									
Male	6961	35.37		23	14.74		6938	35.53	<.
Female	12720	64.63		133	85.26		12587	64.47	
Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Incidence rate of various medical disease categories	Inc rat var me cal dis cat
Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Cardiovascular$^{\beta}$ (n=15097)	Ca (n=
without	10287	68.14		112	92.56		10175	67.94	<.
with	4810	31.86		9	7.44		4801	32.06	
Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Metabolic$^{\gamma}$ (n=13384)	Me (n=
without	7704	57.56		80	89.89		7628	57.35	<.
with	5680	42.44		9	10.11		5672	42.65	
Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rheumatology$^{\delta}$ (n=18114)	Rh (n=
without	15845	87.47		131	94.93		15714	87.42	<.

	Rheumatoid Arthritis$^{\alpha}$	Rheumatoid Arthritis$^{\alpha}$		Biologic Agents	Biologic Agents		No Biologic Agents	No Biologic Agents	p-v
with Oncology$^{\varepsilon}$ (n=19681)	2269 Oncology$^{\varepsilon}$ (n=19681)	12.53 Oncology$^{\varepsilon}$ (n=19681)	Oncology$^{\varepsilon}$ (n=19681)	7 Oncology$^{\varepsilon}$ (n=19681)	5.07 Oncology$^{\varepsilon}$ (n=19681)	Oncology$^{\varepsilon}$ (n=19681)	2262 Oncology$^{\varepsilon}$ (n=19681)	12.58 Oncology$^{\varepsilon}$ (n=19681)	On (n=
without	16533	84.00		133	85.26		16400	83.99	0.6
with Infection$^{\zeta}$ (n=18944)	3148 Infection$^{\zeta}$ (n=18944)	16.00 Infection$^{\zeta}$ (n=18944)	Infection$^{\zeta}$ (n=18944)	23 Infection$^{\zeta}$ (n=18944)	14.74 Infection$^{\zeta}$ (n=18944)	Infection$^{\zeta}$ (n=18944)	3125 Infection$^{\zeta}$ (n=18944)	16.01 Infection$^{\zeta}$ (n=18944)	Inf (n=
without	17852	94.24		140	95.24		17712	94.23	0.6
with Miscellaneous (n=13047)	1092 Miscellaneous (n=13047)	5.76 Miscellaneous (n=13047)	Miscellaneous (n=13047)	7 Miscellaneous (n=13047)	4.76 Miscellaneous (n=13047)	Miscellaneous (n=13047)	1085 Miscellaneous (n=13047)	5.77 Miscellaneous (n=13047)	Mi (n=
without	8051	61.71		86	92.47		7965	61.49	<.
with	4996	38.29		7	7.53		4989	38.51	

$^{\alpha}$ indicates ICD9: 714.0

juvenile inflammatory arthritis in patients 16 years old or younger, and those diagnosed as rheumatoid arthritis in patients over 16 years old.

$^{\beta}$ indicates atrial fibrillation (ICD-9: 427.31), hypertension (ICD-9: 401-405), and acute myocardial infarction: Any hospitalization with a diagnosis of ICD-9: 410.x, coronary heart disease (ICD-9: 410–414), heart failure (ICD-9: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, or 428), cerebral vascular accident (CVA) (ICD-9: 430–438), deep vein thrombosis (DVT), and pulmonary thromboembolism (PE): PE (ICD-9: 415.1), iatrogenic PE (ICD-9: 415.11) and DVT (ICD-9: 453.8)

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$^{\delta}$indicates gout (ICD-9: 274), hip fracture (ICD-9: 820), operation codes 7855, 7925, 7935, 7995, or 8152, and inflammatory bowel disease: ulcerative colitis (ICD-9: 556), Crohn's disease (ICD-9: 555), and psoriasis (ICD-9: 696, 696.1, and 696.8)

$^{\varepsilon}$ indicates malignancy (ICD-9: 140–208) and lymphoma (ICD-9: 200, 201, 202, or 203)

$^{\zeta}$ indicates tuberculosis (ICD-9: 010.x–018.x) and viral hepatitis: HBV (ICD-9: 070.2, 0.70.3, and V02.61) and HCV (ICD-9: 070.41, 070.44, 070.51, 070.54, V02.62)

$^{\eta}$ indicates chronic obstructive pulmonary disease (ICD-9: 491, 492, and 496), asthma (ICD-9: 493), chronic kidney disease (ICD-9: 582, 583, 585, 586, and 588), and chronic liver diseases (ICD-9: 456.0–456.2, 571.2, 571.4–571.6, and 572)

p-value demonstrates the chi-square analysis between each comorbidity and the usage of biologic agents.

* indicates $p<0.05$

N^1 indicates biologics users

N^2 indicates non-biologics users

Table 3. Outcomes of crude and multivariate-adjusted hazard ratio (HR) of each comorbidity in rheumatoid arthritis patients.

	Number of patients	Number of person-years	Number of patients with each comorbidity	Incident rate (per 100,000 person-years)	Crude HR (95%CI)	Multivariate-adjusted HR* (95% CI)
Cardiovascular comorbidities	Cardiovascular comorbidities	Cardiovascular comorbidities	Cardiovascular comorbidities	Cardiovascular comorbidities	Cardiovascular comorbidities	Cardiovascular comorbidities
Gender						
Female	9874	67453.32	3044	4512.75	1.00	1.00
Male	5223	35926.71	1766	4915.56	1.09 (1.03˜1.16)	1.10 (1.04˜1.17)
Age						
[?] 16	356	3055.91	5	163.62	1.00	1.00
>16	14741	100324.12	4805	4789.48	28.63 (11.91˜68.01)	29.11 (12.11˜69.98)
Biologic agents						
No	14976	102282.55	4801	4693.86	1.00	1.00
Yes	121	1097.49	9	820.05	0.18 (0.09˜0.35)	0.18 (0.09˜0.35)
Metabolic comorbidities	Metabolic comorbidities	Metabolic comorbidities	Metabolic comorbidities	Metabolic comorbidities	Metabolic comorbidities	Metabolic comorbidities
Gender						
Female	8405	53287.36	3663	43581.20	1.00	1.00
Male	4979	33172.56	2017	40510.14	0.89 (0.85˜0.94)	0.90 (0.85˜0.95)
Age						
[?] 16	350	2906.98	28	8000.00	1.00	1.00
>16	13034	83552.95	5652	43363.51	6.79 (4.69˜9.84)	6.72 (4.64˜9.75)
Biologic agents						
No	13295	85638.11	5671	42655.13	1.00	1.00
Yes	89	821.82	9	10112.36	0.17 (0.09˜0.33)	0.17 (0.09˜0.32)
Rheumatology comorbidities	Rheumatology comorbidities	Rheumatology comorbidities	Rheumatology comorbidities	Rheumatology comorbidities	Rheumatology comorbidities	Rheumatology comorbidities
Gender						
Female	11742	91810.66	1472	12536.19	1.00	1.00
Male	6372	51469.19	797	12507.85	0.97 (0.89˜1.06)	0.97 (0.89˜1.06)
Age						
[?] 16	339	2838.61	20	5899.71	1.00	1.00
>16	17775	140441.23	2249	12652.60	2.25 (1.45˜3.50)	2.25 (1.45˜3.49)
Biologic agents						
No	17976	142017.51	2262	12583.44	1.00	1.00
Yes	138	1262.33	7	5072.46	0.36 (0.17˜0.75)	0.35 (0.17˜0.74)
Oncology comorbidities	Oncology comorbidities	Oncology comorbidities	Oncology comorbidities	Oncology comorbidities	Oncology comorbidities	Oncology comorbidities

	Number of patients	Number of person-years	Number of patients with each comorbidity	Incident rate (per 100,000 person-years)	Crude HR (95%CI)	Multivariate-adjusted HR* (95% CI)
Gender						
Female	1974	106819.39	12720	644376.90	1.00	1.00
Male	1174	60389.63	6961	592930.15	1.04 (0.97˜1.12)	1.04 (0.97˜1.12)
Age						
[?] 16	10	3121.68	358	3580000.00	1.00	1.00
>16	3138	164087.34	19323	615774.38	6.23 (3.35˜11.58)	6.26 (3.37˜11.64)
Biologic agents						
No	3125	165753.94	19525	624800.00	1.00	1.00
Yes	23	1455.08	156	678260.87	0.65 (0.43˜0.98)	0.65 (0.43˜0.98)
Infection comorbidities	Infection comorbidities	Infection comorbidities	Infection comorbidities	Infection comorbidities	Infection comorbidities	Infection comorbidities
Gender						
Female	12278	100003.67	646	5261.44	1.00	1.00
Male	6666	55516.31	446	6690.67	1.25 (1.11˜1.41)	1.26 (1.11˜1.42)
Age						
[?] 16	357	3095.73	5	1400.56	1.00	1.00
>16	18587	152424.25	1087	5848.17	4.37 (1.81˜10.51)	4.50 (1.87˜10.83)
Biologic agents						
No	18797	154185.62	1085	5772.20	1.00	1.00
Yes	147	1334.37	7	4761.90	0.77 (0.36˜1.61)	0.81 (0.38˜1.70)
Miscellaneous comorbidities	Miscellaneous comorbidities	Miscellaneous comorbidities	Miscellaneous comorbidities	Miscellaneous comorbidities	Miscellaneous comorbidities	Miscellaneous comorbidities
Gender						
Female	8545	53604.52	3206	5980.84	1.00	1.00
Male	4502	28281.48	1790	6329.23	1.06 (1.01˜1.13)	1.07 (1.01˜1.13)
Age						
[?] 16	273	2094.36	49	2339.62	1.00	1.00
>16	12774	79791.65	4947	6199.90	2.52 (1.90˜3.34)	2.55 (1.92˜3.38)
Biologic agents						
No	8601	53954.71	3220	5967.97	1.00	1.00
Yes	93	826.53	7	846.92	0.15 (0.07˜0.31)	0.15 (0.07˜0.31)

- Consent to publish

The authors read and approved the final manuscript and agree to publish.

- Availability of data and materials

No further underlying research material is associated with this article.

- Competing interests

The author declares no competing interests.

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- Authors' Contributions

YJS participated in draft the manuscript. HCK participated in its design and coordination.

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