Aim: To know whether metformin use has different influence on cardiovascular risks in patients with type 2 diabetes mellitus (T2DM) and chronic obstructive pulmonary disease (COPD) as compared with metformin no-use.

Methods: This study employed a retrospective cohort study design. Using propensity score matching, we recruited 55,224 pairs of metformin users and nonusers from Taiwan’s National Health Insurance Research Database between 1 January 2000, and 31 December 2017. Cox proportional-hazards models with robust standard error estimates were used to compare the risks of cardiovascular outcomes.

Results: The mean study period of metformin users and nonusers was 11.04 (5.46) and 12.30 (4.85) years, respectively. Compared with the nonuse of metformin, the adjusted hazard ratios (95% CI) of metformin use for composited cardiovascular events, stroke, coronary artery disease, and heart failure were 0.51 (0.48–0.53), 0.62 (0.59–0.64), 0.48 (0.46–0.50), and 0.61 (0.57–0.65), respectively. The longer cumulative duration of metformin use had even lower adjusted hazard ratios compared with metformin nonuse.

Conclusion: In patients with coexisting T2DM and COPD, metformin use was associated with significantly lower risks of CVD; moreover, longer duration of metformin use was associated with a lower risk of CVD. A well-designed prospective study is required to verify the results.

KEYWORDS
coronary artery disease, heart failure, metformin, stroke, cardiovascular events
Introduction

Chronic obstructive pulmonary disease (COPD) is caused by smoking or air pollution and progressively limits the airflow. Furthermore, it can cause chronic inflammation of the respiratory tract and whole body and may exacerbate intermittently (Bhatt and Dransfield, 2013). Approximately 5%-10% of the population of the United States has COPD (Bhatt and Dransfield, 2013). Currently, COPD affects approximately 380 million individuals worldwide (Lopez et al., 2006). It is sixth among diseases in terms of global mortality and caused approximately 3.3 million deaths in 2019 (GBD 2019 Diseases and Injuries Collaborators, 2020). Type 2 diabetes mellitus (T2DM) is a hyperglycemic disease caused by insulin resistance and insufficient insulin secretion, which may be caused by obesity and reduced physical activity (International Diabetes Federation (IDF), 2019). The global prevalence rate of T2DM is approximately 9.3%. Currently, there are approximately 463 million patients with diabetes worldwide, and this figure is expected to increase to 578 million by 2030 (International Diabetes Federation (IDF), 2019). In 2019, it ranked eighth among diseases in terms of mortality (GBD 2019 Diseases and Injuries Collaborators, 2020).

T2DM, possibly through hyperglycemia-induced oxidative stress and inflammation, can cause pulmonary microvascular complications, diminish lung function, exacerbate COPD, and increase mortality (Gläser et al., 2015). Approximately 10% of people with T2DM also have COPD. Moreover, T2DM aggravates the progression and mortality risk of patients with COPD (Gläser et al., 2015). COPD, possibly through chronic inflammation and high-dose corticosteroid use, can lead to the development or deterioration of T2DM (Gläser et al., 2015). Therefore, COPD coexisting with T2DM is not uncommon, and it represents a relatively serious chronic disease that requires careful management (Gläser et al., 2015). Cardiovascular disease (CVD) shares many of the same causes with T2DM and COPD, such as old age, smoking, metabolic syndrome, and systemic inflammation (Bhatt and Dransfield, 2013). Therefore, CVD often occurs in patients with T2DM and COPD and is the leading cause of death among them (Bhatt and Dransfield, 2013; Low Wang et al., 2016). When using medications to treat patients with T2DM and COPD, it may be crucial to consider whether those medications have any effect on CVD risk.

Metformin has long been the world’s first-line medication for managing T2DM (American Diabetes Association, 2021). In the UK Prospective Diabetes Study (UKPDS), metformin use in overweight patients with T2DM was demonstrated to reduce the risk of myocardial infarction (UK Prospective Diabetes Study (UKPDS) Group, 1998). Its use in patients with COPD can cause lactic acidosis because they are prone to hypoxia; however, a later study confirmed that the incidence is very low (approximately 0.03 cases per 1000 person-years) (Bailey and Turner, 1996). Our previous study disclosed that metformin use in patients with COPD was associated with a reduced risk of mortality compared with metformin nonuse (Yen et al., 2018). Metformin exhibits antioxidant, anti-inflammatory, and possibly cardioprotective actions despite its glucose-lowering effect (Nesti and Natali, 2017). Therefore, we conducted this retrospective cohort study to investigate the influence of metformin use on CVD in patients with comorbid T2DM and COPD are different compared with metformin nonuse.

Materials and methods

Study population

Taiwan established its National Health Insurance (NHI) program in 1995. People are only required to pay a small premium, while their employers and the government pay the largest proportion (Cheng, 2003). By 2000, approximately 99% of Taiwan’s people had joined the NHI program. The NHI Research Database (NHIRD) contains data on the insured’s age, sex, place of residence, salary, medications, clinical procedures, and diagnosis according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM. The NIH Bureau regularly evaluates the diagnostic codes and medical management of clinical units to ensure correct diagnoses as well as the proper disposal of the NHI system. Additionally, to govern the usage of the NHIRD, Taiwan’s Ministry of Health and Welfare constructed the Health and Welfare Data Center (HWDC) in 2016 to standardize data management for all available health care data. All methods employed by this study were performed in accordance with the Declaration of Helsinki. The identifiable information of patients and caregivers was deidentified before release; therefore, the need for informed consent was waived. This study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH109-109-REC2-031).

Study design

We consecutively selected patients who had received the diagnoses of T2DM and COPD between 1 January 2000, and 31 December 2017; they were followed up to 31 December 2018. The diagnosis of T2DM and COPD was considered using the ICD-9-CM code or ICD-10-CM code (Supplementary Table S1) for at least two outpatient visits or one hospitalization record. Validation using ICD codes to define T2DM, COPD, and CVD has been performed by previous studies in Taiwan (Lin et al., 2005; Cheng et al., 2014; Lin et al., 2017; Su et al., 2019). We have further evaluated the severity of COPD. Mild-to-moderate COPD exacerbation was defined by the medication of antibiotics or systemic corticosteroids within 1 year, and...
which was managed in the outpatient setting. Severe COPD exacerbation was considered in the event of an emergency room (ER) visit or hospitalization within 1 year (Rodriguez-Roisin, 2000). Patients were excluded (Figure 1) if they (1) were <40 or >100 years old; (2) did not use antidiabetic drugs; (3) had missing data of age or sex; (4) were diagnosed as having type 1 DM, hepatic failure, or were undergoing dialysis; (5) were followed up for less than 180 days after the index date to exclude latent diseases; or (6) had been diagnosed as having COPD or T2DM before January 1, 2000, to exclude prevalent diseases.

Procedures

Comorbidity date was defined as the date of concurrent diagnosis of COPD and T2DM (Figure 2). Within 90 days following said date, patients who received metformin for at least 30 days were defined as metformin users, whereas those who never received metformin during the study period were defined as metformin nonusers. We defined the first date of metformin use after the comorbidity date as the index date. The index date of the control group was defined as the same period from the comorbidity date to the index date of the study group. Some related variables were assessed and matched between the metformin user and nonuser, including age, sex, comorbidity, Diabetes Complication Severity Index (DCSI) score and medication. Preexisting comorbidities including overweight; obesity; severe obesity; smoking status; the comorbidities of hypertension, dyslipidemia, chronic kidney disease (CKD), coronary artery disease (CAD), stroke, heart failure, peripheral arterial occlusive disease (PAOD), and atrial fibrillation diagnosed within 1 year before the index date; and medications use including respiratory drugs, antidiabetic drugs, antihypertensive drugs, statins, and aspirin during the study period. Glucagon-like peptide one receptor agonists were marketed in Taiwan since 2011, sodium-glucose cotransporter-2 inhibitors were marketed in Taiwan since 2015. Because the number of patients receiving these two antidiabetic medications

FIGURE 1
Flow diagram of the recruitment process.

FIGURE 2
The concurrent diagnosis of T2DM and COPD was defined as the comorbidity date. The first date of metformin use after the comorbidity date was defined as the index date.
TABLE 1 Characteristics and medication use between metformin users and nonusers among patients with T2DM and COPD.

| Characteristics | Before PSM | Metformin users | SMD | Metformin users | After PSM | Metformin users | SMD |
|-----------------|------------|-----------------|-----|----------------|-----------|-----------------|-----|
|                 | N = 1,37,479 | N = 3,98,011 | N = 55,224 | N = 55,224 |
| **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
|**Age, y** | | | | | | | |
|<55 | 28,030 | 20.39 | 131,642 | 33.07 | 0.28 | 14,252 | 29.91 | 12,833 | 26.93 | 0.04 |
|55–65 | 35,742 | 26.00 | 132,119 | 33.19 | 0.15 | 15,566 | 32.66 | 16,929 | 35.52 | 0.04 |
|>65 | 73,707 | 53.61 | 134,250 | 37.73 | 0.4 | 17,838 | 37.43 | 17,894 | 37.55 | 0.02 |
|Mean ± SD | 65.88 ± 12.02 | 60.46 ± 10.93 | 0.47 | 61.47 ± 11.02 | 61.78 ± 10.42 | 0.01 |
|**Sex** | | | | | | | |
|Female | 66,328 | 48.25 | 172,661 | 43.38 | 0.1 | 24,970 | 52.40 | 24,628 | 51.68 | 0.009 |
|Male | 71,151 | 51.75 | 2,25,350 | 56.62 | 0.1 | 22,686 | 47.60 | 23,028 | 48.32 | 0.009 |
|**Comorbidity** | | | | | | | |
|**Obesity** | | | | | | | |
|Overweight | 147 | 0.11 | 147 | 0.11 | 0.009 | 70 | 0.15 | 64 | 0.13 | 0.003 |
|Obesity | 384 | 0.28 | 20,48 | 0.51 | 0.03 | 225 | 0.47 | 200 | 0.42 | 0.007 |
|Severe obesity | 58 | 0.04 | 249 | 0.06 | 0.008 | 32 | 0.07 | 30 | 0.06 | 0.001 |
|Smoking | 1698 | 1.24 | 6491 | 1.63 | 0.03 | 8821 | 1.72 | 777 | 1.63 | 0.007 |
|**Chronic kidney disease** | | | | | | | |
|Severe obesity | 19,146 | 13.93 | 28,733 | 7.22 | 0.21 | 5107 | 10.72 | 5226 | 10.97 | 0.008 |
|**PAOD** | | | | | | | |
|Severe obesity | 58 | 0.04 | 249 | 0.06 | 0.008 | 32 | 0.07 | 30 | 0.06 | 0.001 |
|Severe obesity | 4,600 | 3.03 | 8033 | 2.02 | 0.06 | 1313 | 2.76 | 1341 | 2.81 | 0.003 |
|Severe obesity | 45,317 | 3.03 | 8033 | 2.02 | 0.06 | 1313 | 2.76 | 1341 | 2.81 | 0.003 |
|Severe obesity | 6854 | 4.99 | 11,599 | 2.91 | 0.11 | 1719 | 3.61 | 1804 | 3.79 | 0.01 |
|Exacerbation of COPD | | | | | | | |
|Severe obesity | 51,230 | 37.26 | 1,59,713 | 40.13 | 0.06 | 18,508 | 38.83 | 18,554 | 38.93 | 0.004 |
|Moderate | 74,310 | 54.05 | 2,20,326 | 55.36 | 0.03 | 26,758 | 56.15 | 26,654 | 55.93 | 0.002 |
|Severe | 11,939 | 8.68 | 17,972 | 4.52 | 0.17 | 2390 | 5.02 | 2448 | 5.14 | 0.006 |
|DCSI score | | | | | | | |
|0 | 37,518 | 27.29 | 144,371 | 36.27 | 0.19 | 15,851 | 33.26 | 15,865 | 33.29 | 0.001 |
|1 | 17,762 | 12.92 | 55,773 | 14.01 | 0.03 | 7421 | 15.57 | 7253 | 15.22 | 0.009 |
|2 | 82,199 | 59.79 | 197,867 | 49.71 | 0.2 | 24,384 | 51.17 | 24,538 | 51.49 | 0.006 |
|**Medication** | | | | | | | |
|Respiratory drugs | | | | | | | |
|β2 bronchodilator inhalants | 59,154 | 43.03 | 149,300 | 37.51 | 0.11 | 14,227 | 29.85 | 14,439 | 30.30 | 0.01 |
|Anticholinergic inhalants | 41,564 | 30.23 | 97,761 | 24.56 | 0.13 | 9007 | 18.90 | 9078 | 19.05 | 0.004 |
|Corticosteroid inhalants | 91,110 | 66.27 | 251,303 | 63.14 | 0.07 | 30,674 | 64.37 | 30,701 | 64.42 | 0.001 |
|Oral systemic corticosteroid | 6954 | 5.07 | 16,320 | 4.10 | 0.05 | 1593 | 3.34 | 1561 | 3.28 | 0.003 |
|Methylxanthine | 42,011 | 30.56 | 1,00,381 | 25.22 | 0.11 | 9317 | 19.55 | 9456 | 19.84 | 0.007 |
|Antidiabetic drugs | | | | | | | |
|Sulphonylurea | 24,443 | 17.78 | 183,854 | 46.19 | 0.95 | 17,821 | 32.7 | 17,881 | 32.38 | 0.002 |
|TZD | 16,153 | 11.75 | 1,00,740 | 25.31 | 0.73 | 12,928 | 23.41 | 13,170 | 23.85 | 0.02 |
|DPP4 inhibitor | 21,460 | 15.61 | 148,219 | 37.24 | 1.07 | 11,128 | 21.99 | 11,641 | 21.08 | 0.003 |
|AGI | 21,779 | 15.84 | 1,25,181 | 31.45 | 0.69 | 16,225 | 30.15 | 15,381 | 20.61 | 0.01 |
|Insulin | 59,734 | 43.45 | 59,246 | 14.89 | 0.44 | 14,000 | 29.38 | 15,644 | 28.33 | 0.02 |

(Continued on following page)
was so small that they didn’t be contained in the baseline co-medications. To accurately reflect the characteristics of our patients with COPD and T2DM, we used the DCSI score (Young et al., 2008) to evaluate T2DM severity and the number of moderate or severe exacerbations of COPD to investigate the stability of COPD.

**Main outcomes**

Hospitalized stroke, CAD, heart failure, and composite cardiovascular events were the main outcomes of this study. We calculated the events and incidence rates of composite cardiovascular events, stroke, CAD, and heart failure during the study period. The cumulative incidences of stroke, CAD, and heart failure were also compared between metformin users and nonusers.

**Statistical analyses**

Propensity-score matching was used to match the related covariates between metformin users and nonusers (D’Agostino, 1998). The propensity score was estimated for each patient using nonparsimonious multivariable logistic regression, with metformin use as the dependent variable. We included 32 clinically relevant covariates as independent variables (Table 1). The nearest-neighbor algorithm was used to construct matched pairs, assuming the standardized mean difference of ≤ 0.05 to be a negligible difference between the case and comparison cohorts.

Crude and multivariable-adjusted Cox proportional-hazards models were utilized to compare outcomes between metformin users and nonusers. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) of metformin users compared with nonusers. To calculate the investigated CVD risks, we censored patients until the date of death, date of respective outcomes, or at the end of the follow-up on 31 December 2018, whichever occurred first. The Kaplan-Meier method and log-rank tests were used to compare the cumulative incidence of stroke, CAD, and heart failure during the follow-up period between metformin users and nonusers. We also assessed the cumulative duration of metformin use for the risk of stroke, CAD, and heart failure compared with metformin nonuse.

SAS (version 9.4; SAS Institute, Cary, NC, United States) was used for the statistical analyses; a 2-tailed p value < 0.05 was considered significant.

**Results**

**Participants**

From 1 January 2000, to 31 December 2017, 1,192,677 patients were diagnosed as having COPD and T2DM. After certain ineligible cases were excluded, we identified 398,011 metformin users and 137,479 nonusers during the study period. Figure 1 presents a flow diagram of the recruitment process.
Before propensity-score matching, we observed that the distribution of demographics, comorbidities and medications were significantly different between metformin users and nonusers (Table 1). After matching, 55,224 paired patients with COPD and T2DM were selected. In the matched cohorts, the mean (SD) age was 61.63 (10.72) years, and the mean T2DM duration was 2.02 (3.35) years. The mean study period of metformin users and nonusers was 11.04 (5.46) and 12.30 (4.85) years, respectively.

**Main outcomes**

In the matched cohorts (Table 2), 9236 (16.72%) metformin users and 14,806 (26.81%) nonusers developed composite cardiovascular events during the follow-up period (incidence rate: 15.75 vs. 28.12 per 1000 person-years). In multivariable model, the metformin user had a significantly lower incidence of composite cardiovascular events compared with nonusers (aHR = 0.51, 95%CI = 0.48–0.53).

As presented in Table 2, compared with nonusers, metformin users were associated with significantly lower risks of hospitalized stroke (aHR 0.62, 95% CI 0.59–0.64), hospitalized CAD (aHR 0.48, 95% CI 0.46–0.50), and heart failure (aHR 0.61, 95% CI 0.57–0.65), respectively. The Kaplan–Meier analysis illustrated that the cumulative incidences of stroke, CAD, and heart failure were significantly lower in metformin users than in nonusers (Figure 3).

**Cumulative duration of metformin use**

The association between the cumulative duration of metformin use and the risk of stroke, CAD and heart failure were further analyzed and presented in Table 3. We found that longer cumulative durations of metformin use were associated with lower risks of stroke, CAD, and heart failure; the p values for the trend of cumulative duration of metformin use in stroke, CAD and heart failure risk were less than 0.0001.

**Discussion**

This study demonstrated that metformin use in patients with T2DM and COPD was associated with significantly lower risks of composite cardiovascular events, CAD, stroke, and heart failure. In addition, a longer cumulative duration of metformin use was associated with an even lower risk of cardiovascular events.

Cardiovascular disease is the most critical complication of T2DM (Low Wang et al., 2016), and patients with T2DM for a longer duration are at higher risk of CVD (Sattar, 2013). Patients with COPD, possibly through the common pathogenic factors of aging, smoking, and chronic inflammation, are also prone to complications from CVD (Bhatt and Dransfield, 2013; Rabe et al., 2018). CVDs are the most common and lethal comorbidities in patients with T2DM and COPD (Bhatt and Dransfield, 2013; Rabe et al., 2018). Metformin has been reported to reduce the mortality risk in patients with COPD or chronic lower respiratory diseases (Yen et al., 2018; Ho et al., 2019; Mendy et al., 2019). The classic UKPDS also demonstrated that metformin use in overweight patients with T2DM had a significantly lower risk of mortality and myocardial infarction (MI), and this result persisted in the posttrial observational data (Holman et al., 2008). A randomized trial of insulin-treated patients with T2DM revealed that metformin use was associated with a lower risk of a composite cardiovascular endpoint compared with a placebo (Kooy et al., 2009). A meta-analysis of observational studies confirmed that metformin use was related to reduced MI risk compared with sulphonylureas use (Pladevall et al., 2016). Furthermore, metformin use in patients with T2DM was reported to be associated with a lower risk of hospitalization for heart failure in Taiwan (Tseng, 2019). However, a meta-analysis of randomized clinical trials of metformin use in patients with T2DM disclosed a neutral effect in reducing CVD risk (Griffin et al., 2017). This may be because of the small size of some studies as well as their short follow-up periods with low event rates. In brief, these studies have suggested that metformin may have beneficial cardiovascular effects, especially in certain populations such as overweight or

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**TABLE 2 Hazard ratios and 95% confidence intervals of hospitalization cardiovascular outcomes associated with metformin use.**

| Outcomes                          | Metformin nonusers (n = 55 224) | Metformin users (n = 55 224) | Crude HR (95% CI) | p value | Adjusted HR (95% CI) | p value |
|-----------------------------------|---------------------------------|-----------------------------|-------------------|---------|----------------------|---------|
|                                   | Events PY IR                    | Events PY IR                |                   |         |                      |         |
| Composited cardiovascular outcomes| 14,806 [526,554] 28.12          | 9236 [586,432] 15.75        | 0.55 (0.54–0.56)  | <0.0001 | 0.51 (0.48–0.53)     | <0.0001 |
| Stroke                            | 6702 [579,875] 11.56            | 4614 [603,619] 7.62         | 0.66 (0.63–0.69)  | <0.0001 | 0.62 (0.59–0.64)     | <0.0001 |
| CAD                               | 9728 [559,808] 17.38            | 5251 [603,868] 8.70         | 0.50 (0.48–0.52)  | <0.0001 | 0.48 (0.46–0.50)     | <0.0001 |
| Heart failure                     | 2220 [612,224] 3.63             | 1368 [620,659] 2.20         | 0.60 (0.57–0.64)  | <0.0001 | 0.61 (0.57–0.65)     | <0.0001 |
FIGURE 3
Cumulative risks of cardiovascular events between metformin users and nonusers. (A) stroke, (B) coronary artery disease (CAD), and (C) heart failure.
Our study also disclosed that metformin use in patients with T2DM and COPD was associated with a prominently lower risk of CVD compared with metformin nonuse; furthermore, a longer duration of metformin use was associated with a lower risk of CVD. Metformin, through inhibiting mitochondrial respiratory-chain complex 1, can activate the liver kinase B1 (LKB1)/adenosine 5′-monophosphate-activated protein kinase (AMPK) pathway, inhibit hepatic gluconeogenesis, reduce advanced glycation end products (AGEs), diminish oxidative stress and chronic systemic inflammation (Nesti and Natali, 2017). Metformin can also improve insulin resistance by activating tyrosine kinase, which can attenuate the sympathetic tone, decrease vasoconstriction, and reduce blood pressure (Nesti and Natali, 2017). Clinical and animal studies have demonstrated that metformin could reduce cardiac endothelial dysfunction (Sardu et al., 2019), attenuate cardiac ischemia reperfusion injury, and positively affect cardiac performance during acute heart stress (Bhatt and Dransfield, 2013; Nesti and Natali, 2017). Moreover, metformin can attenuate remodeling of the heart after cardiac injury as well as reduce cardiac hypertrophy (Bhatt and Dransfield, 2013).

Table 3: Hazard ratios of cardiovascular outcomes associated with the cumulative duration of metformin use.

| Event | PY | IR | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------|----|----|-------------------|---------------------|
| a) Stroke (n = 11,516) Nonuse | 6702 | 579,875 | 11.56 | 1 (Reference) |
| <180 days | 1962 | 186,538 | 10.52 | 0.91 (0.87-0.96)** | 0.81 (0.77-0.86)*** |
| 180–360 days | 761 | 97,788 | 7.78 | 0.67 (0.63-0.73)*** | 0.64 (0.60-0.69)*** |
| 361–720 days | 846 | 129,633 | 6.53 | 0.56 (0.52-0.61)*** | 0.57 (0.53-0.61)*** |
| >720 days | 1045 | 191,659 | 5.45 | 0.46 (0.43-0.49)*** | 0.42 (0.40-0.45)*** |
| P for trend | | | | <0.0001 |
| b) CAD (n = 14,979) Nonuse | 9728 | 559,808 | 17.38 | 1 (Reference) |
| <180 days | 2194 | 187,484 | 11.70 | 0.67 (0.64-0.71)*** | 0.64 (0.61-0.67)*** |
| 180–360 days | 918 | 97,787 | 9.39 | 0.54 (0.51-0.58)*** | 0.53 (0.50-0.57)*** |
| 361–720 days | 986 | 129,600 | 7.61 | 0.44 (0.41-0.46)*** | 0.43 (0.40-0.46)*** |
| >720 days | 1153 | 188,996 | 6.10 | 0.34 (0.32-0.36)*** | 0.31 (0.30-0.32)*** |
| P for trend | | | | <0.0001 |
| c) Heart failure (n = 3588) Nonuse | 2220 | 612,224 | 3.63 | 1 (Reference) |
| <180 days | 516 | 184,674 | 2.79 | 0.78 (0.71-0.86)*** | 0.76 (0.69-0.84)*** |
| 180–360 days | 216 | 98,218 | 2.20 | 0.61 (0.53-0.70)*** | 0.64 (0.56-0.74)*** |
| 361–720 days | 276 | 133,018 | 2.07 | 0.57 (0.51-0.65)*** | 0.63 (0.56-0.71)*** |
| >720 days | 360 | 204,748 | 1.76 | 0.48 (0.43-0.53)*** | 0.44 (0.40-0.50)*** |
| P for trend | | | | <0.0001 |

***p < 0.001. Abbreviations: CI, confidence interval; HR, hazard ratio; IR, Incidence rate = per 1000 person-years; PY, Person-years. aHR, adjusted for age, sex, comorbidities, DSCI, score, and medication listed in Table 1.
calculation of diabetes and COPD severity scores. Instead, we used clinical records of the number of moderate and severe exacerbations to evaluate COPD severity, and the DCSI to evaluate the severity of T2DM. Second, the NHIRD is lack of complete information on dietary patterns, family history, and physical activity; accurate population data for alcohol consumption and smoking status are also difficult to obtain. The lack of such data may have influenced the results of metformin use and outcome assessment. Furthermore, we cannot completely rule out the possibility of confounding by indication; that is, metformin users may have a lower disease burden than nonusers who take insulin or other oral antidiabetic drugs. However, we performed propensity-score matching to optimally balance many relevant variables between the study and control groups to minimize bias from possible confounding factors. Third, we are never sure about the effective intake of metformin, because the blood metformin levels are not available. Fourth, this study was Chinese population–based research, and therefore, its result may not be applicable to other ethnicities. Finally, cohort studies inevitably face some unknown confounding factors, and thus, randomized controlled studies are required to verify our results.

COPD and T2DM are both common chronic diseases with a usually indolent evolution and systemic complications. CVDs are critical complications of T2DM and COPD, and usually underdiagnosed and under-treated in these patients (Holman et al., 2008). CVD can also worsen the prognosis of patients with T2DM and COPD. Our study demonstrated that metformin use was associated with a significantly lower risk of CVD compared with metformin nonuse. If metformin can truly reduce the risk of CVD in this high risk group of patients, it shall have the potential to modify the natural history of these diseases. A well-designed prospective study is warranted to confirm our results.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Data of this study are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance (NHI) Administration. The data utilized in this study cannot be made available in the paper, the supplemental files, or in a public repository due to the “Personal Information Protection Act” executed by Taiwan government starting from 2012. Requests for data can be sent as a formal proposal to the NHIRD Office (https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html) or by email to stsung@mohw.gov.ty.

Ethics statement

The studies involving human participants were reviewed and approved by this study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH109-109-REC2-031). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, F-SY, C-CH, and C-MH. Methodology, F-SY and C-CH. Software, C-MH. Validation, L-TC and C-CH. Formal analysis, L-TC. Investigation, L-TC. Resources, JC-CW. Data curation, C.M.H. Writing—original draft preparation, F-SY. Writing—review and editing, JC-CW and C-CH. Visualization, C-MH. Supervision, C-CH and C-MH. Project administration, JC-CW and L-TC. Funding acquisition, C-MH. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.919881/full#supplementary-material

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