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Metformin is associated with reduced COVID-19 severity in patients with prediabetes

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ABSTRACT

Aims: Studies suggest that metformin is associated with reduced COVID-19 severity in individuals with diabetes compared to other antihyperglycemics. We assessed if metformin is associated with reduced incidence of severe COVID-19 for patients with prediabetes or polycystic ovary syndrome (PCOS), common diseases that increase the risk of severe COVID-19.

Methods: This observational, retrospective study utilized EHR data from 52 hospitals for COVID-19 patients with PCOS or prediabetes treated with metformin or levothyroxine/ondansetron (controls). After balancing via inverse probability score weighting, associations with COVID-19 severity were assessed by logistic regression.

Results: In the prediabetes cohort, when compared to levothyroxine, metformin was associated with a significantly lower incidence of COVID-19 with "mild-ED" or worse (OR [95% CI]: 0.636, [0.455–0.888]) and "moderate" or worse severity (0.493 [0.339–0.718]). Compared to ondansetron, metformin was associated with lower incidence of "mild-ED" or worse severity (0.039 [0.026–0.057]), "moderate" or worse (0.045 [0.03–0.069]), "severe" or worse (0.183 [0.077–0.431]), and "mortality/hospice" (0.223 [0.071–0.694]). For PCOS, metformin showed no significant differences in severity compared to levothyroxine, but was associated with a significantly lower incidence of "mild-ED" or worse (0.101 [0.061–0.166]), and "moderate" or worse (0.094 [0.049–0.18]) COVID-19 outcome compared to ondansetron.

Conclusions: Metformin use is associated with less severe COVID-19 in patients with prediabetes or PCOS.

1. Introduction

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome (SARS)-associated coronavirus-2 (SARS-CoV-2), clinicians and researchers have sought new therapeutic options for COVID-19 patients. Current treatments, consisting of antiviral and immune-based interventions, have reduced but not eliminated COVID-19-related morbidity and mortality [1–2]. One strategy for identifying new agents is drug repurposing: identifying previously approved medications that may be effective for treatment of COVID-19. This process reduces the time and cost required to identify new therapeutic options compared to novel

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drug discovery [3–4].

Several studies have proposed that metformin, a routinely prescribed antihyperglycemic agent, reduces COVID-19 severity, the incidence of acute respiratory distress syndrome (ARDS), and intensive care admission in patients with diabetes taking the medication prior to onset of infection [5–9]. It has been suggested that metformin use may also reduce susceptibility to SARS-CoV-2 infection by increasing AMP-activated protein kinase (AMPK) cell signaling, inhibiting binding of the viral spike protein, and preventing viral entry into the cell [10–11]. Metformin may attenuate immune inflammatory responses and release of proinflammatory cytokines [10]. As COVID-19 can cause cytokine storm, immune modulatory activity is desirable to avoid excessive inflammation and impaired organ function [12].

Metformin is primarily prescribed for individuals with Type 2 Diabetes Mellitus (T2DM), but it is also recommended for off-label use in other groups. Two sizable populations who may benefit from off-label metformin usage are individuals who have prediabetes and those with polycystic ovary syndrome (PCOS). Notably, these two populations overlap substantially [13].

Prediabetes is a state of intermediate hyperglycemia due to insulin resistance that poses a high risk for progression to diabetes. Individuals with prediabetes usually have a higher than normal variability of blood glucose concentration, but less than the threshold for diagnosing diabetes [14]. The American Diabetes Association (ADA) 2021 guidelines define prediabetes as the presence of any the following: a fasting plasma glucose of 100 mg/dl to 125 mg/dl (5.6–6.9 mmol/L), a 2-hour plasma glucose during a 75-gram oral glucose tolerance test between 140 mg/dl to 199 mg/dl (7.8–11 mmol/L), or a hemoglobin A1c of 5.7 % to 6.4 % (39–47 mmol/mol) [15]. Without proper management, between 25 % and 50 % of people with prediabetes progress to diabetes [16]. Management for prediabetes involves intensive lifestyle changes, including weight loss, to reduce the risk of progression to diabetes. In addition, metformin can reduce or delay the incidence of diabetes in individuals with prediabetes [17].

PCOS occurs in up to 12 % of reproductive-aged women worldwide and is a diagnosis of exclusion made by the presence of 2 of the 3 Rotterdam Criteria (oligomenorrhea/amenorrhea, clinical or biochemical evidence of hyperandrogenism, and polycystic morphology of ovaries on ultrasound [18–19] in absence of thyroid disorders, states of prolactin excess, and congenital adrenal hyperplasia [20]. Although insulin resistance is not a defining feature of PCOS, it is present in approximately 75 % of patients with PCOS independent of their BMI [21–22]. However, the presence of obesity has been shown to reduce insulin sensitivity twofold, which in turn is thought to worsen the hyperandrogenism characteristic of PCOS [22–24]. Despite extensive study, the mechanisms of impaired glucose utilization in PCOS remain unknown. There are no medications approved by the Food and Drug Administration (FDA) for treating PCOS; available therapies are largely used to manage symptoms [25]. One of these therapies is metformin, which is commonly used off-label in patients with PCOS to increase insulin sensitization, induce ovulation, regulate menstrual cycles, and aid weight loss [21].

For individuals at high risk for severe COVID-19, approaches to prevent poor COVID-19 outcomes are highly desirable. Given that many patients with prediabetes and/or PCOS are at high risk for severe COVID-19 and already take metformin, they are ideal populations for evaluating the impact of metformin usage prior to COVID-19 infection. We hypothesize that documented usage of metformin prior to COVID-19 infection will be associated with decreased severity of COVID-19 infection outcomes. Metformin use prior to infection may be a simple and affordable way to improve COVID-19 outcomes for patients with prediabetes or PCOS.

2. Methods

2.1. Data source

This retrospective observational study utilized clinical patient data aggregated in the National COVID Cohort Collaborative (N3C) (covid.cd2h.org). The N3C Data Enclave harmonizes electronic health record (EHR) data from over 13 million patients in the United States from a total of 74 institutions. This investigation leveraged data from 53 institutions that provided cases who met the inclusion criteria.

Source data within the N3C enclave is harmonized into Observational Medical Outcomes Partnership (OMOP) [26] version 5.3.1 format. The OMOP model includes standardized definitions of conditions, lab tests, procedures, and other relevant clinical data including positive COVID-19 laboratory tests [27–28].

2.2. Study population and eligibility criteria

Our study included patients who were identified as being COVID-19 positive by positive SARS-CoV-2 laboratory test (polymerase chain reaction or antigen) after January 1, 2020. Positive patients were assigned to one or both of the prediabetes and PCOS cohorts as follows. Patients were identified as having prediabetes if they had either a documented history of the condition of prediabetes (included concepts in Table 1) or hemoglobin A1C (HbA1C) between 5.7 % and 6.4 % (ADA-recognized range for prediabetes) prior to COVID-19 diagnosis [29]. Patients were identified as having PCOS if they had a documented history of the condition (included concepts in Table 1).

We removed patients from both cohorts who had either 1) a documented history of the condition of diabetes mellitus type 1, diabetes mellitus type 2, gestational diabetes, or another diagnosed condition that is characterized by abnormal blood glucose (Supplemental File 1); or 2) a documented HbA1C $\geq$ 6.5 % (ADA-recognized range for diabetes) [29].

We defined metformin users as those patients who had recorded use [30] of metformin beginning on or before the start date of the visit

Table 1
Cohort definition concept sets for polycystic ovary syndrome (PCOS) and prediabetes.

Cohort	OMOP Concept ID	Concept Name
PCOS	3654296	Polycystic ovary syndrome of bilateral ovaries
PCOS	3654294	Polycystic ovary syndrome of right ovary
PCOS	40443308	Polycystic ovary syndrome
PCOS	3654295	Polycystic ovary syndrome of left ovary
Prediabetes	4029951	Impaired glucose tolerance in MODY
Prediabetes	4229140	Impaired glucose tolerance associated with insulin receptor abnormality
Prediabetes	40316773	Prediabetes
Prediabetes	4007106	[D]Glucose tolerance test abnormal
Prediabetes	4251180	Impaired glucose tolerance associated with hormonal etiology
Prediabetes	4311629	Impaired glucose tolerance
Prediabetes	37201113	Prediabetes
Prediabetes	3176858	Prediabetes
Prediabetes	4045297	Impaired glucose tolerance in obese
Prediabetes	4136531	Impaired glucose tolerance in nonobese
Prediabetes	4111906	Impaired glucose tolerance associated with pancreatic disease
Prediabetes	37018196	Prediabetes
Prediabetes	3107926	Prediabetes
Prediabetes	4027550	Impaired glucose tolerance with hyperinsulinism
Prediabetes	44808385	Pre-diabetes
Prediabetes	4047260	Impaired glucose tolerance associated with genetic syndrome
Prediabetes	4263688	Impaired glucose tolerance associated with drugs
Prediabetes	44826981	Impaired fasting glucose
Prediabetes	45597199	Impaired fasting glucose

during which the patient was diagnosed with COVID-19 and overlapping for at least one day with the COVID-19 visit.

As there were no other anti-hyperglycemic medications used frequently in patients without diabetes, we considered other medications unrelated to prediabetes or PCOS as controls. We chose levothyroxine and ondansetron within our study population as comparator drugs for the creation of our control sub-cohorts. Levothyroxine is a synthetic thyroid hormone medication that is used to treat hypothyroidism and other thyroid-related conditions [31]. Similar to metformin, levothyroxine is a prescription-only medication in the United States, is taken orally, and requires daily usage and adherence for maximal therapeutic benefit. Levothyroxine has substantial usage in our study population, and is not known to be a successful therapeutic intervention for COVID-19. Ondansetron is an antiemetic medication, often used in patients undergoing chemotherapy or radiotherapy [32]. Ondansetron is a prescription medication and can be administered orally or intravenously. Most of those prescribed ondansetron use it daily, and usage is adequate in our study population to use it as a comparator drug. Some recent studies found a decrease in all-cause mortality in COVID-19 patients when ondansetron is given after COVID onset [33–34]. This suggests that ondansetron may be a conservative choice of comparator medication.

As with metformin, individuals were defined as using levothyroxine or ondansetron if they had a drug era for either medication beginning on or before the date of COVID-19 diagnosis and continuing for at least one day. Any patients using metformin in combination with levothyroxine and/or ondansetron were excluded from the study population ($n < 20$ for PCOS, $n = 41$ for prediabetes).

OMOP concept ID codes for all conditions and medications used in this analysis are listed in Supplemental File 1. Codesets containing the relevant concept IDs for each construct were formulated using ATLAS (https://atlas-covid19.ohdsi.org/), the graphical user interface for the OMOP common data model [35].

2.3. Study design

We explored the potential association between treatment with metformin and severity of COVID-19 within the prediabetes and PCOS cohorts. We assessed covariates for collinearity, imputed missing values, and conducted inverse probability weighting, followed by logistic regression analysis.

2.4. Missingness imputation

Missing values were imputed for BMI, race (white versus non-white), and ethnicity. We compared various imputation models including missRanger [36–37] and different MICE imputers [38] on a (limited) complete dataset. All the models resulted in comparable estimates and we therefore chose the missForest implementation provided by missRanger (with a number of trees in the random forest equal to 101) because our experiments on a larger patient cohort showed its higher validity when compared to the MICE models [39].

2.5. Propensity score weighting

Inverse probability weighting was performed using the "Weightthem"method implemented in the R MatchThem package [40] using "propensity score" weights, the Average Treatment Effect on the Treated (ATT) estimand, and the "within" approach. Propensity score weighting was performed within each imputed dataset, all the weighted datasets were input to individual logistic regression models and the obtained estimates were then pooled via Rubin's rule (Supplemental Figs. S1-S2) [41]. As such, for each imputed dataset, patients within a cohort (e.g. prediabetes, PCOS) with recorded metformin use were weighted to improve the overall matching with respect to another patient cohort with recorded levothyroxine or ondansetron use, but not metformin use. The propensity score formula included age, race, ethnicity, sex (only included for prediabetes), smoking status or nicotine dependence, Charlson Comorbidity Index, BMI, and a set of comorbidities, including PCOS (only for prediabetes patients) and prediabetes (only for PCOS patients), with prevalence higher than 2 % (Table 2).

2.6. Outcome definition

The outcome of interest for this investigation was COVID-19 clinical severity. Clinical severity was classified using the Clinical Progression

Table 2A
Demographics of the prediabetes cohort with levothyroxine comparator * Native Hawaiian or Other Pacific Islander.

	All patients	On Levothyroxine	On Metformin	p-value
n	3136	2736	400	
DEMOGRAPHICS				
Age	59.27 (15.03)	61.18 (14.07)	46.52 (14.99)	0
BMI	33.74 (8.39)	32.98 (7.97)	38.20 (9.36)	0
Length of stay	8.14 (39.64)	7.88 (32.18)	9.93 (72.44)	0.336
INPATIENT/ OUTPATIENT				
Inpatient or ED	1250 (39.9%)	1161 (42.4%)	89 (22.2%)	0
GENDER				0.081
Male	766 (24.4%)	651 (23.8%)	115 (28.7%)	
Female	2367 (75.5%)	2082 (76.1%)	285 (71.2%)	0.041
RACE				0
White	2105 (79.3%)	1887 (81.1%)	218 (66.5%)	0
Black or African American	418 (13.3%)	325 (11.9%)	93 (23.2%)	
Asian	103 (3.3%)	>20	<20	
Other	23 (0.7%)	<20	<20	
NHOPI*	<20	<20	<20	
ETHNICITY				0
Hispanic or Latino	669 (22.9%)	555 (21.8%)	114 (31.1%)	
Not Hispanic or Latino	2247 (77.1%)	1994 (78.2%)	253 (68.9%)	
CCI	1045 (33.3%)	980 (35.8%)	65 (16.2%)	0
Current or former smoker	660 (21.0%)	571 (20.9%)	89 (22.2%)	0.571
HOSPITAL EVENTS				
Invasive ventilation	105 (3.3%)	>20	<20	0.019
ECMO	<20	<20	<20	1
COMORBIDITIES				
Hypertension	1656 (52.8%)	1489 (54.4%)	167 (41.8%)	0
Neoplasm	1206 (38.5%)	1115 (40.8%)	91 (22.8%)	0
Heart disease	985 (31.4%)	938 (34.3%)	47 (11.8%)	0
Chronic respiratory disease	817 (26.1%)	732 (26.8%)	85 (21.2%)	0.023
Liver disease	351 (11.2%)	322 (11.8%)	29 (7.2%)	0.01
Kidney disease	343 (10.9%)	>20	<20	0
Nicotine dependence	269 (8.6%)	245 (9.0%)	24 (6.0%)	0.061
Cerebral infarction	96 (3.1%)	>20	<20	0.036
Arthritis	90 (2.9%)	>20	<20	0.055
Dementia	88 (2.8%)	>20	<20	0.005
PCOS	81 (2.6%)	<20	>20	0
Psoriasis	63 (2.0%)	>20	<20	0.177

Table 2B
Demographics of the PCOS cohort with levothyroxine comparator * Native Hawaiian or Other Pacific Islander.

	All patients	On Levothyroxine	On Metformin	p-value
n	282	86	196	
DEMOGRAPHICS				
Age	33.18 (8.42)	35.81 (8.06)	32.03 (8.33)	0
BMI	37.90 (8.94)	36.73 (8.38)	38.43 (9.15)	0.173
Length of stay	7.04 (39.95)	12.51 (64.96)	4.63 (21.00)	0.128
INPATIENT/ OUTPATIENT				
Inpatient or ED	72 (25.5%)	28 (32.6%)	44 (22.4%)	0.1
RACE				0.379
White	190 (67.4%)	65 (75.6%)	125 (63.8%)	0.059
Black or African American	33 (11.7%)	< 20	> 20	
Asian	< 20	< 20	< 20	
Other	< 20	< 20	< 20	
NHOPI*	< 20	< 20	< 20	
ETHNICITY				0.85
Hispanic or Latino	63 (24.8%)	< 20	>20	
Not Hispanic or Latino	191 (75.2%)	59 (76.6%)	132 (74.6%)	
CCI	30 (10.6%)	< 20	< 20	0.008
Current or former smoker	59 (20.9%)	< 20	>20	0.267
HOSPITAL EVENTS				
AKI in hospital	<20	<20	<20	0.671
Invasive ventilation	<20	<20	<20	0.671
ECMO	0	0	0	–
COMORBIDITIES				
Prediabetes	84 (29.8%)	< 20	> 20	0.044
Neoplasm	57 (20.2%)	22 (25.6%)	35 (17.9%)	0.185
Hypertension	54 (19.1%)	< 20	>20	0.992
Chronic respiratory disease	49 (17.4%)	< 20	>20	1
Heart disease	21 (7.4%)	< 20	< 20	0.302
Liver disease	< 20	< 20	< 20	0.005
Nicotine dependence	< 20	< 20	< 20	0.966
Kidney disease	< 20	< 20	< 20	0.759

Scale (CPS) established by the World Health Organization (WHO) for COVID-19 clinical research [42] modified into the five following categories: "mild" (outpatient, WHO severity 1–3); "mild ED" (outpatient with ED visit, WHO severity 3); "moderate" (hospitalized without invasive ventilation, WHO severity 4–6); "severe" (hospitalized with invasive ventilation or ECMO, WHO severity 7–9); and "mortality/hospice" (hospital mortality or discharge to hospice, WHO Severity 10) [28]. To develop ordinal classifications for patient severity, patients were assigned to severity groups according to the maximum clinical severity during their index encounter [28], which was defined as the medical encounter during which a positive COVID-19 test was documented for the first time. These classes were used to create four derived outcome variables based on COVID-19 severity: "mild ED" or worse, "moderate" or worse, "severe" or worse, and "mortality/hospice".

The control-matched participants within the comparison were individuals with prediabetes or PCOS who used levothyroxine or ondansetron for conditions unrelated to prediabetes. The adjusted cohorts were then used to assess the association between metformin use and COVID-19 severity ("mild", "mild ED", "moderate", "severe", "mortality/hospice") when compared to levothyroxine or ondansetron use.

Table 2C
Demographics of the prediabetes cohort with ondansetron comparator * Native Hawaiian or Other Pacific Islander.

	All patients	On Ondansentron	On Metformin	p-value
n	8015	7618	397	
DEMOGRAPHICS				
age	57.82 (16.14)	58.41 (15.98)	46.80 (15.09)	0
BMI	33.22 (8.78)	32.85 (8.62)	37.88 (9.41)	0
length of stay	10.66 (49.07)	10.75 (47.57)	8.91 (72.00)	0.466
INPATIENT/ OUTPATIENT				
Inpatient or ED	6614 (82.5%)	6544 (85.9%)	70 (17.6%)	0
GENDER				0
Male	3346 (41.7%)	3235 (42.5%)	111 (28.0%)	
Female	4661 (58.2%)	4375 (57.4%)	286 (72.0%)	
RACE				0.07
White	4738 (59.1%)	4515 (59.3%)	223 (56.2%)	
Black or African American	1873 (23.4%)	1781 (23.4%)	92 (23.2%)	
Asian	228 (2.8%)	> 20	< 20	
Other	> 20	> 20	< 20	
NHOPI*	20 (0.2%)	< 20	< 20	
ETHNICITY				0
Hispanic or Latino	1275 (17.3%)	1163 (16.6%)	112 (30.4%)	
Not Hispanic or Latino	6088 (82.7%)	5831 (83.4%)	257 (69.6%)	
CCI > 1	2583 (32.2%)	2520 (33.1%)	63 (15.9%)	0
Current or former smoker	1456 (18.2%)	1368 (18.0%)	88 (22.2%)	0.04
HOSPITAL EVENTS				
AKI in hospital	973 (12.1%)	> 20	< 20	0
Invasive ventilation	40 (0.5%)	> 20	< 20	0.725
ECMO	552 (6.9%)	> 20	< 20	0
COMORBIDITIES				
hypertension	3884 (48.5%)	3720 (48.8%)	164 (41.3%)	0.004
heart disease	2659 (33.2%)	2614 (34.3%)	45 (11.3%)	0
neoplasm	2492 (31.1%)	2400 (31.5%)	92 (23.2%)	0.001
chronic respiratory disease	1787 (22.3%)	1704 (22.4%)	83 (20.9%)	0.535
kidney disease	935 (11.7%)	> 20	< 20	0
liver disease	849 (10.6%)	822 (10.8%)	27 (6.8%)	0.015
nicotine dependence	759 (9.5%)	734 (9.6%)	25 (6.3%)	0.033
cerebral infarction	327 (4.1%)	> 20	< 20	0
dementia	213 (2.7%)	> 20	< 20	0.01
arthritis	193 (2.4%)	> 20	< 20	0.304

2.7. Covariates

We evaluated COVID-19 severity and its association with metformin and other covariates: age, race, ethnicity, sex (only included for prediabetes), smoking status, Charlson Comorbidity Index, BMI, prediabetes (only included for PCOS), PCOS (only included for prediabetes) and other comorbidities (kidney disease, liver disease, hypertension, dementia, neoplasm, arthritis, heart disease, chronic respiratory disease,

Table 2D
Demographics of the PCOS cohort with ondansetron comparator * Native Hawaiian or Other Pacific Islander.

	All patients	On Ondansentron	On Metformin	p-value
n	501	309	192	
DEMOGRAPHICS				
age	32.54 (8.95)	32.63 (9.21)	32.39 (8.52)	0.762
BMI	37.94 (9.39)	37.87 (9.60)	38.04 (9.13)	0.862
length of stay	5.45 (53.44)	6.94 (67.02)	3.04 (15.00)	0.427
INPATIENT/ OUTPATIENT				
Inpatient or ED	229 (45.7%)	195 (63.1%)	34 (17.7%)	0
RACE				0.561
White	331 (66.1%)	210 (68.0%)	121 (63.0%)	
Black or African American	76 (15.2%)	49 (15.9%)	27 (14.1%)	
Asian	< 20	< 20	< 20	
Other	< 20	< 20	< 20	
NHOPI*	< 20	< 20	< 20	
ETHNICITY				0.224
Hispanic or Latino	100 (22.6%)	55 (20.4%)	45 (25.9%)	
Not Hispanic or Latino	401 (87.4%)	214 (79.6%)	129 (74.1%)	
CCI > 1	75 (15.0%)	> 20	< 20	0.001
Current or former smoker	96 (19.2%)	50 (16.2%)	46 (24.0%)	0.042
HOSPITAL EVENTS				
AKI in hospital	< 20	< 20	0	0.286
Invasive ventilation	0	0	0	–
ECMO	< 20	< 20	0	0.698
COMORBIDITIES				
prediabetes	121 (24.2%)	56 (18.1%)	65 (33.9%)	0
neoplasm	118 (23.6%)	85 (27.5%)	33 (17.2%)	0.011
hypertension	117 (23.4%)	85 (27.5%)	32 (16.7%)	0.007
chronic respiratory disease	101 (20.2%)	71 (23.0%)	30 (15.6%)	0.06
heart disease	60 (12.0%)	> 20	< 20	0
liver disease	45 (9.0%)	> 20	< 20	0.001
nicotine dependence	41 (8.2%)	> 20	< 20	0.037

psoriasis, lupus, Alzheimer's disease, cerebral infarction, immunosuppression, PCOS, nicotine dependence) that occurred in>2 % of the cohort.

2.8. Statistical analysis

To investigate the association of metformin and other covariates with COVID-19 severity, we applied the glm function of the stats R package [43] to perform logistic regression on each imputed and matched dataset.

For each outcome, we independently performed a logistic regression (LR) to evaluate COVID-19 severity and its association with metformin and other covariates. Since in the PCOS cohort, the number of patients with COVID-19 severity of "severe" or "mortality/hospice" was very small, we omitted LR for these two outcome variables. For "on metformin" status, we pooled the LR estimates across all the imputed datasets by Rubin's rule and we recorded the corresponding p-values, the pooled odds ratios and their 95 % confidence intervals. The p-values obtained for the "on metformin" status on the prediabetes and PCOS cohorts were adjusted by Bonferroni correction to account for family-wise False Discovery Rate (FDR).

Covariates were combined or removed when significant collinearity was detected to avoid biased regression coefficients. Collinearity between covariates was assessed by calculating the generalized variance inflation factor (GVIF) [44–45]. For all cohorts, we observed high GVIF (>5) for race and Charlson Comorbidity Index (CCI) [46] (data not shown), likely due to low representation in a variety of race categories and CCI values. To alleviate that collinearity, while still including race and CCI within the regression, the race category was modified into a binary "white"/"non-white" variable, and the CCI variable was converted to a binary variable "CCI $\leq$ 1"/"CCI > 1". No other included variables showed a GVIF>5.

We used the *EValue* R package (version 4.1.2) to determine the minimum strength of an unmeasured confounder in the logistic regression that would be required to change the conclusion that metformin was associated with reduced severity of COVID-19 [47]. We treated the outcome of decreased COVID-19 severity as a non-rare outcome (as it occurred more frequently than 15 %). For a more conservative estimate, we report the E-value estimate for the confidence interval of the odds ratio that is closest to the null, as recommended by VanderWeele et al. [47].

3. Results

In the current study, two cohorts of COVID-19 positive individuals were identified for assessing the association between metformin usage and COVID-19 severity outcomes. The two cohorts developed were prediabetes and PCOS (Fig. 1). Data for this project were derived from 53 total sites, among which only 26 provided PCOS case data. For this study, data was included up to May 12, 2022. The predictors with missing data were age, BMI, race, and ethnicity (see Supplemental Table 1), with an overall percentage of cases with any missing values equal to 30 % and 35 % in PCOS (for levothyroxine and ondansetron comparators respectively) and 38 % and 53 % in prediabetes patients (for levothyroxine and ondansetron comparators respectively,). Little's test supported the assumption of Missing At Random over Missing Completely at Random data, p-value < 0.05 [48].

For the PCOS cohort, we evaluated 282 patients (metformin versus levothyroxine) and 501 patients (metformin versus ondansetron). For the prediabetes cohort, we evaluated 3136 patients (metformin versus levothyroxine) and 8015 patients (metformin versus ondansetron) (Fig. 1). Table 2 shows the demographics of both cohorts, including the CCI score. Distribution of reported COVID-19 severity scores are in Table 3.

For the PCOS cohort, no significant association between metformin usage and decreased COVID-19 severity was observed as compared to the levothyroxine control group (Fig. 2). Within the metformin-levothyroxine assessment, white race was significantly associated with COVID-19 severity in both of the logistic regressions, but no other significant associations were observed (Supplementary Figs. S3a-b). However, in the metformin-ondansetron comparison for patients with PCOS (Fig. 2, Supplementary Figs. S3c-d), metformin use was significantly associated with a decreased incidence of COVID severity of "mild ED" or worse (OR: 0.101, 95 % CI 0.061–0.166, Bonferroni adj. p = 0), and "moderate" or worse (OR: 0.094, 95 % CI 0.049–0.18, adj. p = 0). In the "mild ED" or worse regression, the comorbidity of prediabetes indicated a potential increase in incidence of more severe COVID infection.

Assessment of the prediabetes cohort indicated a significant association of metformin usage with decreased incidence of COVID-19 severity of "mild ED" or worse (OR: 0.636, 95 % CI 0.455–0.888, adj. p = 0.0315) and "moderate" or worse (OR: 0.493, 95 % CI 0.339–0.718, adj. p = 0.0009) versus levothyroxine (Fig. 2). Additionally, lower incidence of "mild ED" or worse severity (OR: 0.039, 95 % CI 0.026–0.057, adj. p = 0), "moderate" or worse (OR: 0.045, 95 % CI 0.03–0.069, adj. p = 0), "severe" or worse (OR: 0.183, 95 % CI 0.077–0.431, adj. p = 0.0004), and "hospice or death from COVID" (OR: 0.223, 95 % CI 0.071–0.694, adj. p = 0.0385) were seen in metformin

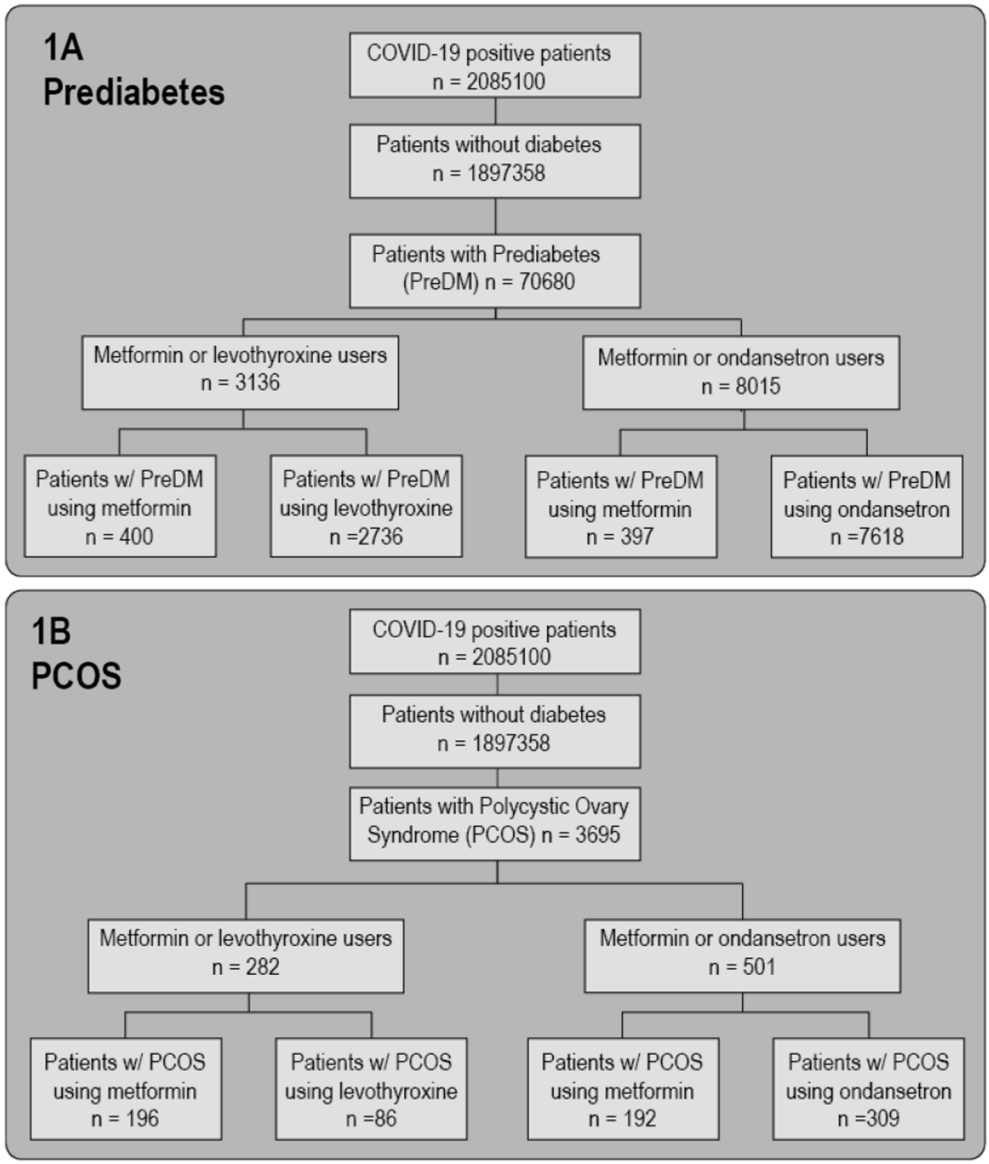

Fig. 1. Definition of prediabetes and PCOS cohorts. COVID-19 positive patients were filtered to remove any individuals with diabetes and then separated into prediabetes (PreDM) (1A) and Polycystic Ovary Syndrome (PCOS) (1B) cohorts. For both cohorts, we selected patients that had a recorded usage of either metformin or levothyroxine (left) and metformin or ondansetron (right). Patients who used both metformin and the control medication (levothyroxine or ondansetron) were excluded from the analyses.

versus ondansetron analyses (Fig. 2).

In agreement with other prior investigations, we observed a significant association of COVID-19 severity "moderate" or worse with age for patients with prediabetes (Supplementary Figs. S4a-h) in several evaluations. Unexpectedly, for patients with prediabetes we saw significantly decreased incidence of more severe COVID-19 in patients with chronic respiratory disease (Supplementary Figs. S4a-h) or hypertension (Supplementary Figs. S4a-h and Supplementary Figs. S6), and for those with Hispanic or Latino ethnicity (Figs. S4a-h) in some evaluations, possibly due to the non-collapsibility of odds ratios [49–50] and/or confounding factors such as behavior. A secondary analysis using logistic regression confirmed that metformin, as well as Hispanic or Latino ethnicity, are associated with decreased incidence of more severe COVID-19; on the other hand, chronic respiratory disease and hypertension do not show any significant association with COVID-19 severity (Supplementary Fig. S6). Heart disease (Figs. S4a-b) and history of neoplasm (Supplementary Fig. S3a) were variably associated with a higher incidence of severe disease outcomes.

To assess the sensitivity of our findings to uncorrected confounders, we calculated the E-value for the observed values of the odds ratio with significant p-values in Fig. 2 [47]. To explain the association of metformin use with decreased COVID-19 severity in the prediabetes cohort compared to levothyroxine, an unmeasured confounder would need to be associated with both the treatment and the outcome with an odds ratio of 0.79 (upper bound 0.93) ("mild ED" or worse) and 0.70 (upper bound 0.84) ("moderate" or worse) above and beyond the confounders included in the regression. To explain the association of metformin use with decreased COVID-19 severity in the PCOS cohort compared to ondansetron, an unmeasured confounder would need to be associated with both the treatment and the outcome with an odds ratio of 0.32 (upper bound 0.41) ("mild ED" or worse), 0.31 (upper bound 0.42) ("moderate" or worse), and in the prediabetes cohort, an odds ratio of 0.20 (upper bound 0.24) ("mild ED" or worse), 0.21 (upper bound 0.26) ("moderate" or worse), 0.43 (upper bound 0.66) ("severe" or worse), and 0.47 (upper bound 0.83) ("mortality/hospice").

Since gastrointestinal symptoms, including nausea and vomiting, may be associated with more severe COVID-19 infection [51–52], we also performed sensitivity analyses in which patients who initiated ondansetron (a medication frequently prescribed for nausea and vomiting) the day of their COVID-19 index diagnosis, possibly for nausea or vomiting related to COVID-19 infection, were excluded (Supplementary Fig. S7 and S8). Results of these sensitivity analyses were consistent with our main analyses. In individuals with prediabetes, protective effects of metformin were confirmed for the "mild ED" or worse, "moderate" or

Table 3
COVID-19 severity outcome of patients in prediabetes and PCOS cohorts for metformin or levothyroxine (3A) and metformin or ondansetron (3B). Cohen's D is also reported as an estimate of the effect-size; large effect sizes (absolute value of Cohen's D > 0.8) are indicated by an asterisk. Values<20 patients are obscured to reduce the risk of patient reidentification.

(A)

	PCOS				Prediabetes			
	All	Metformin	Levothyroxine	Cohen's D	All	Metformin	Levothyroxine	Cohen's D
n	282	196	86		3136	400	2736	
Mild	210 (74.5%)	152 (77.6%)	58 (67.4%)	−0.233	1875 (59.8%)	310 (77.5%)	1565 (57.2%)	−0.418
Mild ED	34 (12.1%)	>20	<20	0.084	191 (6.1%)	31 (7.8%)	160 (5.8%)	0.080
Moderate	36 (12.8%)	>20	<20	0.203	849 (27.1%)	51 (12.8%)	798 (29.2%)	0.374
Severe	< 20	<20	<20	0.079	57 (1.8%)	< 20	> 20	0.070
Mortality / hospice	< 20	< 20	<20		164 (5.2%)	< 20	> 20	

(B)

	PCOS				Prediabetes			
	All	Metformin	Ondansentron	Cohen's D	All	Metformin	Ondansentron	Cohen's D
n	501	192	309		8015	397	7618	
Mild	270 (53.9%)	158 (82.3%)	112 (36.2%)	−1.040*	1383 (17.3%)	326 (82.1%)	1057 (13.9%)	−1.963*
Mild ED	93 (18.6%)	21 (10.9%)	72 (23.3%)	0.324	889 (11.1%)	30 (7.6%)	859 (11.3%)	0.119
Moderate	132 (26.3%)	< 20	> 20	0.827*	4711 (58.8%)	34 (8.6%)	4677 (61.4%)	1.108*
Severe	< 20	< 20	< 20	0.131	328 (4.1%)	< 20	> 20	0.179
Mortality/ hospice	< 20	< 20	< 20		704 (8.8%)	< 20	> 20	

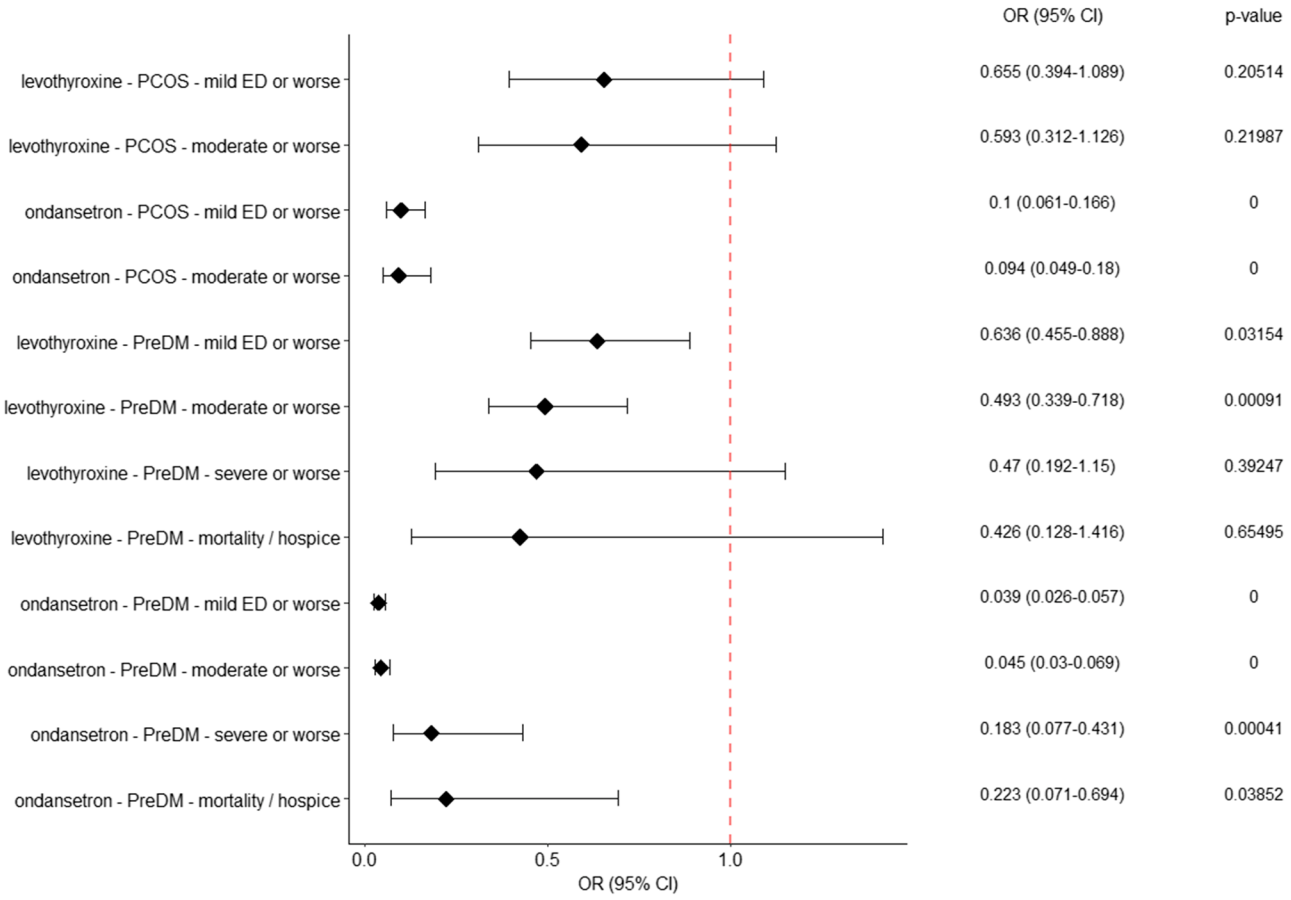

Fig. 2. Association between metformin usage and COVID-19 severity in PCOS and prediabetes cohorts. Odds ratios (x-axis) and adjusted p-values are shown for the given combination of drug, cohort and outcome. For the PCOS cohort, there were insufficient patients with severe or worse disease or mortality/hospice for a logistic regression to be performed. All p-values are Bonferonni corrected. A comparison of the estimates obtained before and after cohort weighting provides an estimate of the effect size (Supplementary Fig. S5). Note that estimates are comparable, even for groups that show large effect sizes according to Cohen's D (Table 2).

worse, and "severe" or worse analyses. Significance was not seen in the "mortality/hospice" analysis, potentially due to insufficient cohort size. The corresponding sensitivity analyses in the PCOS evaluation were largely unchanged compared with our main analyses.

4. Discussion

We observed a significant association between metformin use and less severe COVID-19 in the prediabetes cohort compared with levothyroxine or ondansetron use, and within the PCOS cohort compared to ondansetron use. While multiple studies have been conducted to assess metformin impact on COVID-19 in the type 2 diabetes population, this is the largest study to date investigating off-label usage including individuals with prediabetes or PCOS. These findings are consistent with prior investigations in type 2 diabetes patients, in which metformin users were reported to have lower COVID-19 severity [6,10,53].

The proposed mechanisms for metformin as a potential mediator of severe COVID-19 infection include its effect on blood glucose regulation via AMPK stimulation and glucose-6-phosphate (G6P) inhibition, which reduce hepatic gluconeogenesis [54–55], as well as decreased reactive oxygen species production at the respiratory-chain complex 1 [56–57]. Given the increased inflammation seen in both hyperglycemia and COVID-19, metformin's capacity to attenuate immune inflammatory responses via reduced proinflammatory cytokines offers multiple potential benefits to individuals with altered glycemic control, including those with prediabetes or PCOS [10]. Reduced inflammation may be beneficial during the hyperinflammatory state of COVID-19 infection [2], and can also delay progression to diabetes or onset of cardiovascular disease in individuals with prediabetes [58].

Considering the impact of COVID-19 on populations investigated in this study, additional potential interventions to prevent or mitigate COVID-19 severity are greatly desired. While PCOS is a common endocrine disorder, its etiology and pathophysiology are not fully elucidated and clinical care for patients with PCOS can be inconsistent even during non-pandemic times [59]. Additionally, a wide swath of risk factors for severe COVID-19 are commonly observed in patients with PCOS, including obesity, hypertension, and metabolic syndrome [59]. As these cardio-metabolic risk factors are more frequently seen in patients with PCOS compared to the general population, patient risk for acquiring COVID-19 with severe presentation is increased [60]. One report indicated that individuals with PCOS have a 28 % increased risk of COVID-19 infection [61].

The current study's association of metformin with reduced incidence of severe COVID-19 outcomes (compared to ondansetron) in the PCOS cohort supports a potential use case for metformin use in PCOS patients who are at elevated risk for severe COVID-19 infections. While no significant findings were observed in the metformin versus levothyroxine comparison for PCOS patients, it is possible that analyses were not sufficiently powered to detect the improvement mediated by metformin. Of some note, although not statistically significant, point estimates of the odds ratio (metformin versus levothyroxine) were directionally consistent in both populations. Given the potential impact an alternative COVID-19 therapy may pose for patients with PCOS, further investigation into this population with metformin and other drug repurposing candidates seems warranted.

Individuals with prediabetes also face increased COVID-19 risk compared to the general population. Although not meeting the threshold for type 2 diabetes diagnosis, individuals with prediabetes experience reduced insulin sensitivity and glycemic dysregulation [62]. The consistent moderate hyperglycemia experienced by individuals with prediabetes can be accompanied by chronic vascular complications including blood pressure changes and cognitive dysfunction [63]. Additionally, prediabetes may be an important risk factor for COVID-19 [62]. From our investigation, metformin usage in individuals with prediabetes was associated with a significant decrease in COVID severity when compared to levothyroxine or ondansetron users. The association of metformin use with reduced COVID severity may indicate metformin's potential as a mitigator of severe COVID outcome.

Personalized clinical assessment should continue to be the standard of care for determining if metformin usage is appropriate. However, given these outcomes, clinicians may consider recommending metformin for high COVID-19 risk patients with prediabetes as it may support a reduced incidence of severe COVID. Future investigations using prospective trials and potentially randomized controlled trials are needed to further elucidate the relationship between metformin and COVID-19 outcome.

5. Limitations

This analysis is retrospective and is subject to confounding. Our study utilizes electronic health record data, which may contain some inaccuracies such as incomplete recording of patient data or incomplete/incorrect translation of source EHR data to the OMOP format used by N3C, despite efforts to harmonize and quality-check these data centrally. Further, while metformin and comparator drug usage were assumed to be consistent with prescriptions, medication compliance levels are not reported in our data set.

We were unable to identify a similar oral antihyperglycemic medication (e.g. sulfonylureas, thiazolidinediones) for comparison with metformin due to limited usage of those medications within our study cohorts in the populations of interest. We chose levothyroxine as an inactive comparator drug because of its similarity to metformin with respect to typical daily usage requirement, prescription requirement, and primarily oral administration modality [64], and because levothyroxine is not known to affect COVID-19 severity. However, it is possible that excessive or deficient levels of thyroid hormone in patients with thyroid disease may be associated with increased risk for poor COVID severity outcomes [65–66], which may introduce a bias toward more severe COVID-19 outcome in patients using levothyroxine. This is contradicted in other investigations, particularly with thyroid diseases that are being actively managed [67–68].

We chose a second comparator drug, ondansetron, to ensure the robustness of our finding using levothyroxine as a comparator. One of the indications for ondansetron is chemotherapy/radiotherapy induced nausea, which theoretically selects for a population with more cancer patients, who may be at risk for more severe COVID-19 outcome. However, we applied propensity weighting to balance our cohort with respect to neoplasm. Nonetheless, residual confounding by indication may still exist. Some reports have identified an association between ondansetron and a reduction in all cause mortality for patients who started taking ondansetron following admission to the hospital for COVID-19 [33–34]. We believe ondansetron therefore represents a conservative choice of comparator drug, as our current knowledge of this drug indicates that it is likely neutral or associated with a slight benefit to COVID-19 outcome, and its use a comparator drug will therefore tend to underestimate any beneficial association of metformin with COVID-19 outcome. Sensitivity analysis performed by excluding patients prescribed ondansetron on the day of COVID-19 presentation confirmed the main results of our original analysis, indicating that ondansetron newly prescribed during COVID-19 presentation is not biasing our result.

We observed a limited number of patients (<20) in the severe and mortality/hospice categories in both the PCOS and prediabetes cohorts, which may have limited the statistical power to detect an association between metformin use and COVID-19 severity. This also made us unable to investigate the extent to which metformin lowers the risk of mechanical ventilation or death in patients with prediabetes. Future studies with greater cohort sizes may address this limitation.

6. Conclusion

In summary, this retrospective analysis of electronic health record data supports and extends the previously described association between lower COVID-19 disease severity and metformin usage. However, the inherent limitations of observational analyses leave opportunities for future work in this area. The generalizability of our findings should be evaluated and future research utilizing a larger sample and/or a

prospective design, including relevant immunologic biomarkers, may help elucidate the mechanisms that underlie metformin's association with less severe COVID-19 outcome. Prediabetes and PCOS are common conditions and metformin is a safe, inexpensive and widely used drug, so our findings suggest its potential for improving COVID outcomes for many people at low cost.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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