

Observational Study of Metformin and Risk of Mortality in Persons Hospitalized with Covid-19

Carolyn T. Bramante, MD, MPH;^{*1} Nicholas E. Ingraham, MD;^{*2} Thomas A. Murray, PhD;³ Schelomo Marmor, PhD, MPH;⁴ Shane Hovertsen;⁵ Jessica Gronski, PhD;⁵ Chace McNeil;⁵ Ruoying Feng, MD;² Gabriel Guzman, MD;² Nermine Abdelwahab, MD;² Samantha King, BS;⁴ Thomas Meehan, MD;² Bradley Benson, MD;¹ Deneen Vojta, MD;⁵ Kathryn M. Pendleton, MD;^{*2} Christopher J. Tignanelli, MD^{*4,6}

*Authors contributed equally to this manuscript

Author Affiliations:

¹ Department of Medicine, University of Minnesota, Division of General Internal Medicine, Minneapolis, MN

² Department of Medicine, University of Minnesota, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Minneapolis, MN

³ School of Public Health, University of Minnesota, Division of Biostatistics, Minneapolis, MN

⁴ Department of Surgery, University of Minnesota Division of Acute Care Surgery, Minneapolis, MN

⁵ Research and Development, UnitedHealth Group

⁶ Institute for Health Informatics, University of Minnesota, Minneapolis, MN

Correspondence:

Carolyn T. Bramante MD, MPH
420 Delaware St SE, MMC 276
Minneapolis, MN 55455
Office: (612) 626-1968
Fax: (612) 626-0439
Email: bramante@umn.edu

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Abstract

Background

Type 2 diabetes (T2DM) and obesity are significant risks for mortality in Covid19. Metformin has been hypothesized as a treatment for COVID19. Metformin has sex specific immunomodulatory effects which may elucidate treatment mechanisms in COVID-19. In this study we sought to identify whether metformin reduced mortality from Covid19 and if sex specific interactions exist.

Methods

De-identified claims data from UnitedHealth were used to identify persons with at least 6 months continuous coverage who were hospitalized with Covid-19. Persons in the metformin group had at least 90 days of metformin claims in the 12 months before hospitalization. Unadjusted and multivariate models were conducted to assess risk of mortality based on metformin as a home medication in individuals with T2DM and obesity, controlling for pre-morbid conditions, medications, demographics, and state. Heterogeneity of effect was assessed by sex.

Results

6,256 persons were included; 52.8% female; mean age 75 years. Metformin was associated with decreased mortality in women by logistic regression, OR 0.792 (0.640, 0.979); mixed effects OR 0.780 (0.631, 0.965); Cox proportional-hazards: HR 0.785 (0.650, 0.951); and propensity matching, OR of 0.759 (0.601, 0.960). TNF α inhibitors were associated with decreased mortality in the 38 persons taking them, by propensity matching, OR 0.19 (0.0378, 0.983).

Conclusions

Metformin was significantly associated with reduced mortality in women with obesity or T2DM in observational analyses of claims data from individuals hospitalized with Covid-19. This sex-specific finding is consistent with metformin's reduction of TNF α in females over males, and suggests that metformin conveys protection in Covid-19 through TNF α effects. Prospective studies are needed to understand mechanism and causality.

Introduction

The coronavirus disease 2019 (Covid-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has spread throughout the world.¹ Despite exponential growth in Covid-19 related research, better understanding of this highly contagious and lethal virus is needed. An overall mortality rate over 5% for all patients hospitalized with Covid-19 highlights the urgent need for treatments while vaccines are developed.²

Observational studies have sought to better identify risk factors correlated with mortality from Covid-19. An early retrospective study from China identified male sex and increased age as leading risk factors.³ Subsequent studies have identified hypertension, diabetes, coronary artery disease, tobacco use, and obesity as important risk factors for Covid-19.^{2,4-10} In persons hospitalized with Covid-19 with overweight and obesity (body mass index, $BMI \geq 25 \text{ kg/m}^2$), men have a higher risk of needing mechanical ventilation over women, after controlling for diabetes, hypertension, and cardiovascular disease, especially in men.¹⁰ Additionally, among individuals with Covid-19 and a $BMI \geq 25 \text{ kg/m}^2$, men have a higher risk of developing severe pneumonia than women.¹¹ This sex difference may be explained by the accumulation of visceral adiposity at lower BMI levels in men.¹²

Adipocytes, specifically visceral adipocytes, release inflammatory and coagulopathic mediators implicated in Covid-19 morbidity, including interleukin-6 (IL-6), tumor-necrosis-factor α (TNF α), d-dimer, and others.¹³⁻¹⁶ TNF α has been particularly important, with high levels of TNF α found in lung tissue of persons with Covid-19.¹⁷ TNF α contributes to insulin resistance,¹⁸ and levels of TNF α are higher in individuals with T2DM. Both T2DM and obesity are associated with lower levels of the anti-inflammatory cytokine, IL-10.¹⁹ Metformin has sex-specific benefits,²⁰ and decreases levels of TNF α and IL-6, and boosts levels of IL-10, significantly more in females more than males.²¹⁻²⁵ Metformin also increases activation of AMP-activated protein kinase (AMPK), which has important downstream effects in Covid-19.²⁶⁻²⁸

Given these favorable effects of metformin on TNF α and other inflammatory cytokines that contribute to Covid-19, our primary objective was to understand whether home metformin use was associated with decreased mortality in persons hospitalized with Covid-19. We hypothesized that metformin would be associated with decreased mortality from Covid-19 in persons with T2DM and obesity, and that this benefit would be higher in women compared to men given metformin's sex-specific anti-inflammatory effects. We also hypothesized that TNF α inhibitors would be associated with decreased mortality from Covid-19. We conducted a retrospective cohort analysis of de-identified claims data from UnitedHealth Group's Clinical Discovery Database of 6,256 persons hospitalized in the US with Covid-19 in 2020.

Methods

Design and Data

Retrospective analysis of claims from UnitedHealth Group (UHG)'s Clinical Discovery Database between January 1, 2020 – June 7, 2020. This database includes de-identified individual-level and state-level data for individuals with Covid-19 admissions in all 50 U.S. states, covering a diverse range of ages, ethnicities, and geographical regions. The claims data includes medical and pharmacy claims, laboratory results, and enrollment records. This study was approved by the University of Minnesota institutional review board (STUDY00001489) which provided a waiver of consent for this study.

Population

Individuals 18 years or older with T2DM or obesity, at least 6 months of continuous enrollment in 2019, and a hospitalization for Covid-19 confirmed by polymerase chain reaction (PCR), manual chart review by UHG, or reported from the hospital to UHG. Individuals with both commercial and Medicare Advantage insurance were included. Eighteen persons (0.12%) were missing age and were excluded. An assumption was made that there was no missingness among the other variables. Individuals with T2DM or obesity were included in the analysis (definition in Supplemental Materials 1).

Outcomes

Our primary outcome was in-hospital mortality defined using the hospital disposition indicator. The individuals who remained hospitalized on June 7, 2020 without a hospital disposition were censored in Cox proportional hazards model analyses and excluded from mixed model and propensity-matched analyses. The database did not include data related to in-hospital complications, ICU, or ventilator utilization and thus an analysis on these endpoints was not possible.

Independent Variable and confounding variables

The independent variable was a filled pharmacy prescription (visible through prescription claims, matching the generic drug ingredient with the string “metformin”) indicating use of metformin, and limited to patients with at least 90 days of metformin prescription from 12 months prior to Covid-19 diagnosis. Potential confounding medications hypothesized to be protective or harmful for patients with Covid-19 determined by a large evidence-based consortium were assessed, as were possible confounding co-morbidities (Supplemental Materials 1).²⁹

Statistical analysis

Cohort age was expressed by median and interquartile range (IQR), and compared by exposure group via Mann-Whitney U test. Categorical variables were expressed by percentages, and compared via Chi-squared tests.

To determine whether metformin use was independently associated with reduced mortality for patients hospitalized for Covid-19, multivariable models for mortality were developed with the use of the Least absolute shrinkage and selection operator (LASSO) method,³⁰ with the tuning parameter determined by the Akaike information criterion (AIC). We also considered clinically relevant pairwise interactions to determine whether their association with mortality differed according to metformin status. The non-linear effect of age was modeled in two manners, using restricted cubic splines or categorized as (0-55, 56-65, 66-75, 76-85, 86+). Given the low mortality for patients 0-55 (5.1%) compared with other age groupings,

this group was not further categorized. Univariate analysis was used to compare mortality for patients without vs with home metformin use. Subgroup analyses of multivariate models were performed by sex.

Multivariate models:

(1) Logistic regression, controlling for LASSO variables and state, with and without specific disease-medication interaction terms. (Table S1).

(2) Mixed-effects logistic regression with state-level random effects, controlling for LASSO variables, with and without specific disease-medication interaction terms. Only patients with known hospital disposition were included in this analysis (Table S2).

(3) Cox proportional-hazards regression by strata-specific and shared-frailty effects, with and without specific disease-medication interaction terms; censoring determined based on claims made after hospitalization up to June 7, 2020. Using a ‘best’ outcome approach, patients discharged not to hospice were assigned a censoring time equal to the longest observed hospital stay (169 days).^{31,32} Scaled Schoenfeld residual graphs and log-log plots were analyzed to confirm adequacy of the proportional hazards assumption for home metformin use (Table S3, Figure S1).

(4) Propensity matched mixed effects logistic regression was performed, stratified by metformin use. Propensity scores were estimated with logistic regression with variables selected by the aforementioned LASSO logistic model and two evenly matched groups were formed with the common caliper set at 0.2 (Figure S2), and a model with exact matching.^{33,34} Even distribution of propensity scores was confirmed between matched groups, with standardized differences less than 0.1 for all confounding variables (Figure S3). Univariate logistic regression was then used to compare mortality for persons who were receiving (vs not receiving) home metformin among the matched cohort. Kaplan-Meier survival curves were also estimated and compared using a log-rank test (Figure 2).

Sensitivity analyses were conducted in individuals with Covid-19 confirmed by PCR (n=4,105). Statistical analyses were performed using Stata MP, version 16 (StataCorp, College Station, TX). Statistical significance was defined as a two-tailed p -value < 0.05 .

Results

Characteristics of Cohort

Between Jan 1, 2020 – June 7, 2020, 15,380 individuals with pharmacy claims data and at least 6 months of enrollment were diagnosed and hospitalized with Covid-19 in UHG's Clinical Discovery Database (Figure 1). Overall 52.8% were female, median age 70 years (IQR 58- 80). Of these, 6,256 (40.7%) had a diagnosis of obesity or T2DM, of whom 1,185 (18.9%) died; and 2,333 (37.3%) had a metformin prescription. Individuals taking metformin were younger (73 vs 76 years), more often male (51.6% versus 44.6%), and fewer died during their hospitalization for Covid-19 (17.8% vs 21.3%). Most persons taking metformin had T2DM (99.3%) and hypertension (56.3%). About 4% of persons taking metformin had asthma, 6% had chronic kidney disease, 19.5% had coronary artery disease, and 4% had liver disease. Individuals on metformin were less likely to have a history of venous thromboembolism (2.7% vs 4.1%), (Table 1). In unadjusted analyses, metformin was associated with decreased mortality, OR 0.802 (0.701, 0.917) (Table 2).

Multivariate analyses of mortality by metformin use, in men and women with T2DM or obesity

Results of multivariate analyses are presented in Table 2. Mortality associated with all the variables in the multi-variate analyses are shown in Tables S1-S3. The log-log plot assessing the proportionality assumption is presented in Figure S1; the distribution of the estimated propensity-score is in Figure S2; the standardized difference in propensity-matched covariates is in Figure S3. Metformin use not associated with statistically significantly decreased mortality in the overall sample (Table 2).

Assessment for heterogeneity of effect by sex, in subgroups of women with T2DM or obesity

A Kaplan-Meier curve of survival by metformin use in men and women is shown in Figure 2. Metformin use was significantly associated with decreased mortality in women in logistic regression, OR 0.792 (0.640, 0.979); mixed effects model, OR 0.780 (0.631, 0.965); Cox proportional-hazards model, HR 0.785 (0.650, 0.951); and propensity-matched model, OR 0.759 (0.601, 0.960), (Table 2, Figure 3).

Sensitivity analyses in patients with confirmed Covid-19 disease by polymerase chain reaction

In unadjusted analyses men and women with T2DM or obesity, metformin was not significantly associated with decreased mortality, OR 0.859 (0.737, 1.002), nor by the Cox proportional hazards shared frailty model in women, HR 0.808 (0.651, 1.003). Metformin was significantly associated with decreased mortality in women with type-2 diabetes or obesity in the minimally adjusted Cox shared frailty model, OR 0.790 (0.637, 0.978), and the propensity matched model, 0.744 (0.565, 0.980).

Multivariate analysis of anti-TNF α inhibitors

Of the 15,362 persons included in the main analyses, 38 (0.25%) had claims for a TNF α inhibitor. In Cox proportional-hazards model, TNF α inhibitors were non-significantly associated with decreased mortality, HR 0.350 (0.0866, 1.415). In a propensity matched model, matched for the same variables as the metformin analyses, TNF α inhibitors were non-significantly associated with decreased mortality, 0.483 (0.0821, 2.845). In a propensity model matched only on age, sex, Charlson co-morbidity index, inflammatory bowel disease, rheumatoid arthritis and systemic lupus erythematosus, TNF α inhibitors were significantly associated with decreased mortality, OR 0.19 (0.0378, 0.983), (Figures S4, Table S4). A number of other variables were associated with increased or decreased risk of death from Covid-19, notably inflammatory bowel disease and asthma treated with beta2-agonists (Tables S1-S3).

Discussion

This is the first study to report decreased mortality with outpatient metformin use in women with T2DM or obesity in a large cohort of patients hospitalized in the US for Covid-19, and to describe a sex difference in this response to metformin. These findings could have wide-reaching effects, as over 42% of women in the US have obesity.³⁵ We found that metformin use was associated with significantly lower mortality among women across all multivariate analyses: logistic regression, mixed-effects analysis, Cox proportional-hazards, and propensity-matched models. The significant protective benefit in women compared to men may shed light on the mechanism by which metformin decreases mortality from Covid-19, as metformin has been shown to reduce TNF α in females more than males.^{20,24,25}

We also found reduced mortality in persons with outpatient use of TNF α inhibitors who were hospitalized for Covid-19. TNF α inhibitor use was associated with large decreases in odds of mortality, but these findings were not statistically significant, likely because of the small sample size of 38. Reduced mortality in persons who use TNF α inhibitors would support previous research that TNF α plays a large role in the pathology of Covid-19.³⁶ TNF α leads to macrophage activation and increased cytokine release, likely contributing to Covid-19 pathology.³⁷

We considered other (overlapping) mechanisms by which metformin could reduce the severity of SARS-CoV-2 infection: ACE2 receptor modulation (via AMPK), decreased cytokine release (IL6, TNF α , increased IL-10), improved neutrophil to lymphocyte ratio, decreased glycemia (via AMPK), mast cell stabilization, decreased thrombosis, and improved endothelial function.^{21,23-25,38-49} In patients with and without diabetes, metformin has been shown to decrease inflammatory mediators IL-6 and TNF α .²¹⁻²³ These effects are notable, as IL-6 and TNF α are thought to contribute to Covid-19 pathology.¹⁷ Metformin's effects on these cytokines have been shown to differ by sex, with favorable effects in female over male mice, particularly for TNF α .²⁵ Our findings of a strong sex-specific response to metformin in Covid-19 suggests that TNF α reduction may be the primary way by which metformin reduced mortality from Covid-19.

Our sex-specific findings are consistent with prior literature showing increased benefit of metformin use in women compared to men in other disease processes.²⁰ Possible reasons for sex-specific effects of metformin include the influence of sex hormones and epigenetic changes on the Y chromosome.⁵⁰ There are 2 other potential ways in which metformin might cause sex-specific responses in Covid-19: Metformin inhibits IgE- and aryl hydrocarbon- mediated mast cell activation,⁵¹ and mast cell activation has been implicated as an early indicator of inflammatory response to SARS-CoV2 and possibly cytokine storm.⁵² Mast cells from female rats cause a greater increase in TNF α than mast cells in male rats, which could be one reason for greater benefit from metformin in women than men.⁵³ Lastly, activation of AMPK by metformin can lead to increased expression of ACE2 and conformational changes

to ACE2, and possibly decreasing SARS-CoV-2 binding to the ACE2 receptor.^{41-43,54} Recent work by Li et al found that expression of ACE2 receptor was equal in male and female human lungs, but that cytokine responses differed between men and women.⁴⁴ This difference in subsequent inflammatory response and our sex-specific findings may support metformin's anti-inflammatory effects as the primary means of benefit in Covid-19.

Additionally, in our multivariate analyses, beta2-agonist use was associated with decreased mortality in patients with asthma across all analyses (Tables S1-S3). This benefit may come from beta2-agonists' effect on boosting IL-10, which is a predominantly anti-inflammatory cytokine that can reduce levels of TNF α .⁵⁵ Metformin has also been shown to boost levels of IL-10, in females more than males.^{21,22} The mortality benefit in persons with asthma on beta2-agonists, combined with our finding of mortality benefit from metformin use, suggest that IL-10 may also be important in Covid-19.

In summary, we found that metformin was associated with a significant decrease in mortality for women with T2DM or obesity who were hospitalized for Covid-19, in an observational analysis of de-identified claims. We found no significant mortality benefit in men with T2DM or obesity who were hospitalized with Covid-19. The sex-specific effects of metformin on TNF α , IL-6, and IL-10, and our findings of benefit in women, might indicate that metformin's protective effect in Covid-19 is primarily through effects on TNF α , IL-6, and IL-10. The importance of TNF α in Covid-19 is supported by our finding that TNF α inhibitor use was associated with decreased mortality from Covid-19. The fact that these outpatient medications convey benefit in patients hospitalized for Covid-19 is interesting because metformin is universally stopped at hospital admission, suggesting its protective effects begin prior to hospitalization.

Given metformin's good safety profile and availability, it should be prospectively assessed for protective benefit from Covid-19. Gastrointestinal side effects from metformin can be eliminated for over 85% of patients with use of the newer extended-release formulations, and further with administration at the end of a meal.⁵⁶ With the median time to hospitalization for Covid-19 being about 1 week, it is

necessary to understand the duration of metformin use that conveys benefit. With increased inflammation from adiposity, and obesity's association with increased risk of poor outcomes from Covid-19, metformin should also be assessed in patients of all BMI categories.

Limitations

Our study has several limitations. First, while claims data shows metformin prescribed as a home medication for at least 90 days within the last 12 months, it does not give information about adherence. Metformin is sometimes purchased without insurance claims in this population because of its low cost, thus some individuals in our control group may have the treatment, which would reduce the observed effect size. Prescriptions for outpatient use of metformin cannot be extrapolated to starting metformin at Covid-19 diagnosis or inpatient use. Retrospective analyses are subject to biases and unmeasured confounding.

Conclusion

In a large de-identified claims database of adults with T2DM or obesity, metformin was associated with significantly decreased mortality in women hospitalized with Covid-19, with no significant mortality reduction in men. Mechanistic reasons that support a sex-specific reason for metformin to be protective in Covid-19 include anti-inflammatory effects on IL-10, IL-6 and TNF α . We also found that TNF α inhibitors were associated with insignificantly reduced mortality, likely due to the small sample size. Metformin has a good safety profile and availability and needs to be prospectively assessed to understand mechanism, duration, timing of treatment necessary for benefit. Given obesity's pro-inflammatory effects that contribute to Covid-19 pathology, and the potential anti-inflammatory benefit of metformin in Covid-19, metformin should also be assessed in all BMI categories.

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Table 1: Demographic and clinical characteristics of patients hospitalized for Covid-19 with 6 months of continuous insurance coverage in 2019, comparing those on home metformin to those not on metformin.

Demographic characteristics	Metformin		P value*
	No (n=3,923)	Yes (n=2,333)	
Age, median (inter-quartile range)	76.0 (67.0, 84.0)	73.0 (66.0, 80.0)	<0.001
Age under 56 years, n (%)	266 (6.8%)	186 (8.0%)	
Age 56-65 years	535 (13.6%)	387 (16.6%)	
Age 66-75 years	1112 (28.3%)	808 (34.6%)	<0.001
Age 76-85 years	1234 (31.5%)	694 (29.7%)	
Age > 85 years	776 (19.8%)	258 (11.1%)	
Female sex, n (%)	2,173 (55.4%)	1,129 (48.4%)	
Transfer†, n (%)	705 (18.0%)	418 (17.9%)	0.96
Pre-existing Conditions, n (%)			
Type 2 Diabetes	3719 (94.8%)	2316 (99.3%)	<0.001
Type 1 Diabetes	278 (7.1%)	108 (4.6%)	<0.001
Essential hypertension	2370 (60.4%)	1314 (56.3%)	0.001
Tobacco	8 (0.2%)	5 (0.2%)	0.93
Coronary artery disease	864 (22.0%)	456 (19.5%)	0.020
Heart failure with preserved ejection fraction	346 (8.8%)	121 (5.2%)	<0.001
Heart failure with reduced ejection fraction	344 (8.8%)	133 (5.7%)	<0.001
Heart failure, unspecified	659 (16.8%)	239 (10.2%)	<0.001
Liver disease	160 (4.1%)	102 (4.4%)	0.58
Venous thromboembolism	161 (4.1%)	62 (2.7%)	0.003
Neutropenia	9 (0.2%)	5 (0.2%)	0.90
Cancer	441 (11.2%)	281 (12.0%)	0.34
Coagulation defect	54 (1.4%)	14 (0.6%)	0.004
Valve Repair	33 (0.8%)	17 (0.7%)	0.63
Chronic obstructive pulmonary disease	688 (17.5%)	305 (13.1%)	<0.001
Interstitial lung disease	70 (1.8%)	33 (1.4%)	0.27
Chronic kidney disease, stage 3, 4	729 (18.6%)	147 (6.3%)	<0.001
Chronic kidney disease, unspecified	527 (13.4%)	219 (9.4%)	<0.001
End stage renal disease	297 (7.6%)	14 (0.6%)	<0.001
Atrial fibrillation	630 (16.1%)	290 (12.4%)	<0.001

Cerebrovascular accident/transient ischemic attack	432 (11.0%)	207 (8.9%)	0.007
Alcohol abuse	43 (1.1%)	17 (0.7%)	0.15
Human immune deficiency virus (HIV)	18 (0.5%)	18 (0.8%)	0.11
Asthma	166 (4.2%)	96 (4.1%)	0.82
General influenza	65 (1.7%)	35 (1.5%)	0.63
Swine, avian influenza	17 (0.4%)	12 (0.5%)	0.65
Inflammatory bowel disease	28 (0.7%)	11 (0.5%)	0.24
Systemic lupus erythematosus, rheumatoid arthritis	73 (1.9%)	27 (1.2%)	0.032
Dementia	663 (16.9%)	273 (11.7%)	<0.001
Charlson comorbidity index, median score (IQR)	5.0 (3.0, 7.0)	4.0 (3.0, 6.0)	<0.001
Diabetes complications severity index, median (IQR)	2.0 (1.0, 4.0)	2.0 (0.0, 3.0)	<0.001
Death	791 (21.3%)	394 (17.8%)	0.001
Body Mass Index Category			
Absence of any weight-related code	3548 (90.4%)	2215 (94.9%)	
Overweight (BMI 25-30)	21 (0.5%)	7 (0.3%)	
Class I obesity (BMI 31-35)	35 (0.9%)	10 (0.4%)	<0.001
Class II obesity (BMI 36-40)	20 (0.5%)	6 (0.3%)	
Class III obesity (BMI 40+)	190 (4.8%)	62 (2.7%)	
Obesity unspecified	109 (2.8%)	33 (1.4%)	
Medications			
Bile Acid	8 (0.2%)	2 (0.1%)	0.26
Angiotensin-converting enzyme inhibitors	1069 (27.2%)	912 (39.1%)	<0.001
Angiotensin II receptor blocker	1003 (25.6%)	731 (31.3%)	<0.001
Statin	2591 (66.0%)	1860 (79.7%)	<0.001
Antiplatelet	618 (15.8%)	342 (14.7%)	0.25
Anticoagulation	808 (20.6%)	407 (17.4%)	0.002
Tenofovir	5 (0.1%)	5 (0.2%)	0.41
Highly Active Antiretroviral Therapy (HAART)	16 (0.4%)	14 (0.6%)	0.29
Azithromycin	541 (13.8%)	321 (13.8%)	0.97
Second line diabetes medications	27 (0.7%)	35 (1.5%)	0.002
Insulin	1564 (39.9%)	783 (33.6%)	<0.001
Steroids	1010 (25.7%)	546 (23.4%)	0.038
Hydroxychloroquine	47 (1.2%)	14 (0.6%)	0.020

Janus Kinase Inhibitors	3 (0.1%)	1 (<1%)	0.61
Calcineurin Inhibitors	85 (2.2%)	31 (1.3%)	0.018
mTor Inhibitor	1 (<1%)	0 (0.0%)	0.44
Beta Blocker	2136 (54.4%)	1213 (52.0%)	0.060
Ivermectin	35 (0.9%)	13 (0.6%)	0.14
Beta2 Agonist	1233 (31.4%)	608 (26.1%)	<0.001
Allopurinol	400 (10.2%)	189 (8.1%)	0.006
Azathioprine & Mycophenolate mofetil	42 (1.1%)	13 (0.6%)	0.035
Montelukast	289 (7.4%)	181 (7.8%)	0.57
Nonsteroidal anti-inflammatory drugs	362 (9.2%)	316 (13.5%)	<0.001
Diuretics	1604 (40.9%)	670 (28.7%)	<0.001
Mast cell stabilizer	65 (1.7%)	41 (1.8%)	0.77
Valacyclovir, acyclovir, valgancyclovir	129 (3.3%)	72 (3.1%)	0.66

* P value derived by chi-square or T-test as appropriate.

† Transfer represents inter-hospital transfer during the hospitalization for COVID-19.

Table 2. Association between home metformin use and mortality in unadjusted and adjusted analyses in patients with type 2 diabetes or obesity, hospitalized for Covid-19 (confirmed or presumed).*

Primary analyses, overall population	Odds Ratio (95% CI)	P value
Unadjusted	0.802 (0.701, 0.917)	0.001
Logistic regression with full covariate list	0.911 (0.784, 1.060)	0.227
Logistic regression with Lasso selection variables §	0.904 (0.782, 1.045)	0.173
Mixed Effects Model §	0.898 (0.777, 1.038)	0.144
Cox proportional-hazards, HR, stratified model §	0.887 (0.782, 1.008)	0.065
Cox proportional-hazards, HR, shared frailty model §	0.884 (0.778, 1.003)	0.056
Propensity Matched Model, † exact matching	0.912 (0.777, 1.071)	0.261
Log-rank test		0.146
Propensity Matched Model, caliper 0.2 †	0.898 (0.768, 1.051)	0.180
Log-rank test		0.096
Subgroup analysis in females		
Logistic regression §	0.792 (0.640, 0.979)	0.031
With disease-medication interaction terms**	0.788 (0.637, 0.975)	0.029
Mixed Effects Model §	0.780 (0.631, 0.965)	0.022
With disease-medication interaction terms**	0.780 (0.631, 0.965)	0.022
Cox proportional-hazards, HR, shared frailty model §	0.785 (0.650, 0.951)	0.013
With disease-medication interaction terms**	0.782 (0.646, 0.947)	0.012
Propensity Matched Model †, caliper 0.2	0.759 (0.601, 0.960)	0.021
Log-rank test		0.015
Sensitivity analyses in females with confirmed Covid-19 disease by polymerase chain reaction		
Cox proportional-hazards, HR, shared frailty model §, female	0.808 (0.651, 1.003)	0.053
Cox proportional-hazards, HR, shared frailty model ‡, female	0.790 (0.637, 0.978)	0.031
Propensity Matched Model, † female	0.744 (0.565, 0.980)	0.035
Log-rank test		0.019

*In patients with at least 6 months of continuous coverage in 2019 and 90 days of metformin use.

§Adjusted for variables selected by Lasso: age, sex (in overall, not in subgroups by sex), comorbidities (hypertension, tobacco use, venous thromboembolism, neutropenia, chronic obstructive pulmonary disease, chronic kidney disease, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, charlson comorbidity index, and the diabetes complications and severity index); and medications (bile acids, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), steroids, ivermectin, beta2agonists, mast cell stabilizers, allopurinol, azathioprine, mycophenolate mofetil), and state. **Hypertension with ACEi, ARB use; Asthma with beta2-agonist use

†Matched on the same variables as the Logistic, Mixed effects, and Cox models.

‡ Adjusted only for age and co-morbidity indices.

demographic and clinical characteristics by logistic regression model.*

Demographic characteristics	Odds Ratio (95% CI)	P value
Age under 56	Reference group	
Age 56-65 years	1.241 (0.829, 1.867)	0.295
Age 66-75 years	1.980 (1.370, 2.866)	<0.001
Age 76-85 years	2.567 (1.775, 3.711)	<0.001
Age > 85 years	3.042 (2.070, 4.470)	<0.001
Male sex (female as reference group)	1.428 (1.210, 1.686)	<0.001
Pre-existing Conditions		
Charlson comorbidity index	1.023 (0.990, 1.057)	0.170
DCSI	0.981 (0.938, 1.0249)	0.341
Venous Thromboembolism	0.647 (0.435, 0.964)	0.032
Essential HTN (no HTN, no ACE/ARB is ref)	1.108 (0.905, 1.356)	0.320

Supplementary Tables: Table S1. Association between mortality and

With ACEi	1.004 (0.807, 1.248)	0.972
With ARB	1.293 (1.040, 1.607)	0.021
With ACEi and ARB	0.722 (0.386, 1.370)	0.319
ACEi use, with no HTN	0.878 (0.671, 1.150)	0.345
ARB use, with no HTN	1.145 (0.873, 1.502)	0.329
Asthma (no asthma, no beta2agonist is ref)	1.242 (0.565, 2.730)	0.589
With beta2agonist	0.582 (0.373, 0.908)	0.017
Beta2agonist, no asthma	1.117 (0.942, 1.325)	0.203
Asthma (dichotomous variable)	0.620 (0.421, 0.912)	0.015
Neutropenia	2.061 (0.643, 6.605)	0.224
Chronic obstructive pulmonary disease	1.136 (0.926, 1.393)	0.221
Chronic kidney disease	1.143 (0.935, 1.408)	0.193
Alcohol abuse	0.632 (0.292, 1.371)	0.245
HIV	1.511 (0.618, 3.707)	0.365
Inflammatory bowel disease	0.318 (0.094, 1.325)	0.066
Dementia	1.195 (0.996, 1.434)	0.056
Home Medications		
Bile acid	2.032 (0.543, 7.614)	0.293
Steroids	1.120 (0.952, 1.318)	0.172
Ivermectin	1.415 (0.697, 2.870)	0.337
Mast cell stabilizer	0.661 (0.344, 1.272)	0.216
Allopurinol	1.513 (1.224, 1.870)	<0.001
Azathioprine & Mycophenolate mofetil	3.307 (1.764, 6.201)	<0.001

* Adjusted for variables in the table and state in which the hospitalization occurred

Abbreviations: DCSI=diabetes complications severity index; HTN=hypertension;

ACEi= Angiotensin-converting enzyme inhibitors; ARB=angiotensin 2 receptor blocker

Table S2. Associations between mortality and demographic and clinical characteristics by mixed-effects analysis.*

Demographic characteristics	Odds Ratio (95% CI)	P value
Age under 56	Reference group	
Age 56-65 years	1.276 (0.857, 1.900)	0.230
Age 66-75 years	2.050 (1.426, 2.947)	<0.001
Age 76-85 years	2.667 (1.856, 3.832)	<0.001
Age > 85 years	3.190 (2.183, 4.661)	<0.001
Male sex (female as reference group)	1.428 (1.210, 1.686)	<0.001
Pre-existing Conditions		
Charlson comorbidity index	1.021 (0.988, 1.055)	0.207
DCSI	0.979 (0.937, 1.0230)	0.341
Venous Thromboembolism	0.656 (0.441, 0.975)	0.037
Essential HTN (no HTN, no ACE/ARB is ref)	1.113 (0.910, 1.360)	0.297

With ACEi	0.995 (0.802, 1.236)	0.966
With ARB	1.307 (1.054, 1.622)	0.015
With ACEi and ARB	0.718 (0.379, 1.360)	0.310
ACEi use, with no HTN	0.864 (0.661, 1.129)	0.283
ARB use, with no HTN	1.135 (0.867, 1.486)	0.357
Asthma (no asthma, no beta2agonist is ref)	1.250 (0.571, 2.737)	0.576
With Beta2agonist	0.586 (0.377, 0.913)	0.018
Beta2agonist, no asthma	1.116 (0.942, 1.321)	0.204
Asthma (dichotomous variable)	0.624 (0.424, 0.916)	0.016
Neutropenia	2.121 (0.665, 6.773)	0.204
Chronic obstructive pulmonary disease	1.116 (0.912, 1.367)	0.287
Chronic kidney disease	1.136 (0.930, 1.3870)	0.212
Alcohol abuse	0.638 (0.295, 1.380)	0.254
HIV	1.499 (0.621, 3.622)	0.368
Inflammatory bowel disease	0.315 (0.093, 1.322)	0.204
Dementia	1.198 (0.999, 1.436)	0.051
Home Medications		
Bile acid	2.039 (0.546, 7.613)	0.289
Steroids	1.122 (0.955, 1.320)	0.161
Ivermectin	1.448 (0.720, 2.13)	0.299
Mast cell stabilizer	0.685 (0.357, 1.313)	0.254
Allopurinol	1.516 (1.229, 1.872)	<0.001
Azathioprine & Mycophenolate mofetil	3.267 (1.753, 6.087)	<0.001

* Adjusted for variables in the table and state in which the hospitalization occurred

Abbreviations: DCSI=diabetes complications severity index; HTN=hypertension;

ACEi= Angiotensin-converting enzyme inhibitors; ARB=angiotensin 2 receptor blocker

Table S3. Associations between mortality and demographic and clinical characteristics by Cox proportional-hazards, shared frailty model.*

Demographic characteristics	Hazard Ratio (95% CI)	P value
Age < 56 years	Reference group	
Age 56-65 years	1.259 (0.868, 1.827)	0.225
Age 66-75 years	1.895 (1.351, 2.659)	<0.001
Age 76-85 years	2.426 (1.731, 3.399)	<0.001
Age > 85 years	2.850 (2.009, 4.043)	<0.001
Male sex (female as reference group)	1.464 (1.301, 1.648)	<0.001
Pre-existing Conditions		
Charlson comorbidity index	1.022 (0.993, 1.051)	0.132
DCSI	0.937 (0.937, 1.011)	0.163
Venous Thromboembolism	0.699 (0.490, 0.996)	0.047
Essential HTN (no HTN is reference group)	1.087 (0.913, 1.293)	0.349

With ACEi	0.984 (0.814, 1.190)	0.869
With ARB	1.218 (1.011, 1.466)	0.038
With ACEi and ARB	0.769 (0.429, 1.379)	0.379
ACEi use, with no HTN	0.847 (0.667, 1.076)	0.174
ARB use, with no HTN	1.110 (0.877, 1.404)	0.386
Asthma (no asthma, no beta2agonist is ref)	1.146 (0.591, 2.22)	0.686
Asthma with beta2agonist	0.612 (0.408, 0.918)	0.018
Beta2agonist, no asthma	1.085 (0.937, 1.257)	0.275
Asthma, dichotomous variable	0.652 (0.461, 0.924)	0.016
Tobacco use	1.11e ¹³ (0, 0)	1.000
Chronic obstructive pulmonary disease	1.119 (0.938, 1.336)	0.211
Chronic kidney disease	1.113 (0.938, 1.320)	0.219
Alcohol abuse	0.724 (0.360, 1.457)	0.366
HIV	1.173 (0.571, 2.417)	0.661
Inflammatory bowel disease	0.335 (0.108, 1.057)	0.060
Dementia	1.172 (1.005, 1.368)	0.044
Home Medications		
Bile acid	1.921 (0.708, 5.211)	0.200
Angiotensin-converting enzyme inhibitors	0.869 (0.757, 0.997)	0.046
Angiotensin 2 receptor blockers	1.091 (0.952, 1.249)	0.210
Steroids	1.094 (0.951, 1.259)	0.209
Ivermectin	1.444 (0.809, 2.576)	0.213
Beta 2 agonist	1.066 (0.921, 1.233)	0.391
Mast cell stabilizer	0.674 (0.370, 1.227)	0.197
Allopurinol	1.384 (1.161, 1.649)	<0.001
Azathioprine & Mycophenolate mofetil	2.485 (1.542, 4.004)	<0.001

*Adjusted for the variables in this table and state in which the hospitalization occurred.

Abbreviations: DCSI=diabetes complications severity index. HTN=hypertension; ACEi=

Angiotensin-converting enzyme inhibitors; ARB=angiotensin 2 receptor blocker

Table S4. Association between home TNF-alpha use and mortality in persons hospitalized for Covid-19 (confirmed or presumed).*

Cox proportional-hazards, HR, stratified model §	0.361 (0.0894, 1.414)	0.153
Cox proportional-hazards, HR, shared frailty model §	0.350 (0.087, 1.415)	0.141
Propensity Matched Model†, caliper 0.2	0.483 (0.082, 2.844)	0.421
Log-rank test		0.307
Propensity Matched Model‡, caliper 0.2	0.193 (0.038, 0.983)	0.048
Log-rank test		0.032

*In patients with at least 6 months of continuous coverage in 2019 and 90 days of metformin use.

§Adjusted for variables selected by Lasso: age, sex (in overall, not in subgroups by sex), comorbidities (hypertension, tobacco use, venous thromboembolism, neutropenia, chronic obstructive pulmonary disease, chronic kidney disease, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, charlson comorbidity index, and the diabetes complications and severity index); and medications (bile acids, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), steroids, ivermectin, beta2agonists, mast cell stabilizers, allopurinol, azathioprine, mycophenolate mofetil), and state. **Hypertension with ACEi, ARB use; Asthma with beta2-agonist use

†Matched on the same variables as the Logistic, Mixed effects, and Cox models.

‡ Matched on only for age, sex, charlson co-morbidity index, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease.

Figure 1: Study diagram detailing selection of patients in United Healthcare Covid-19 Database

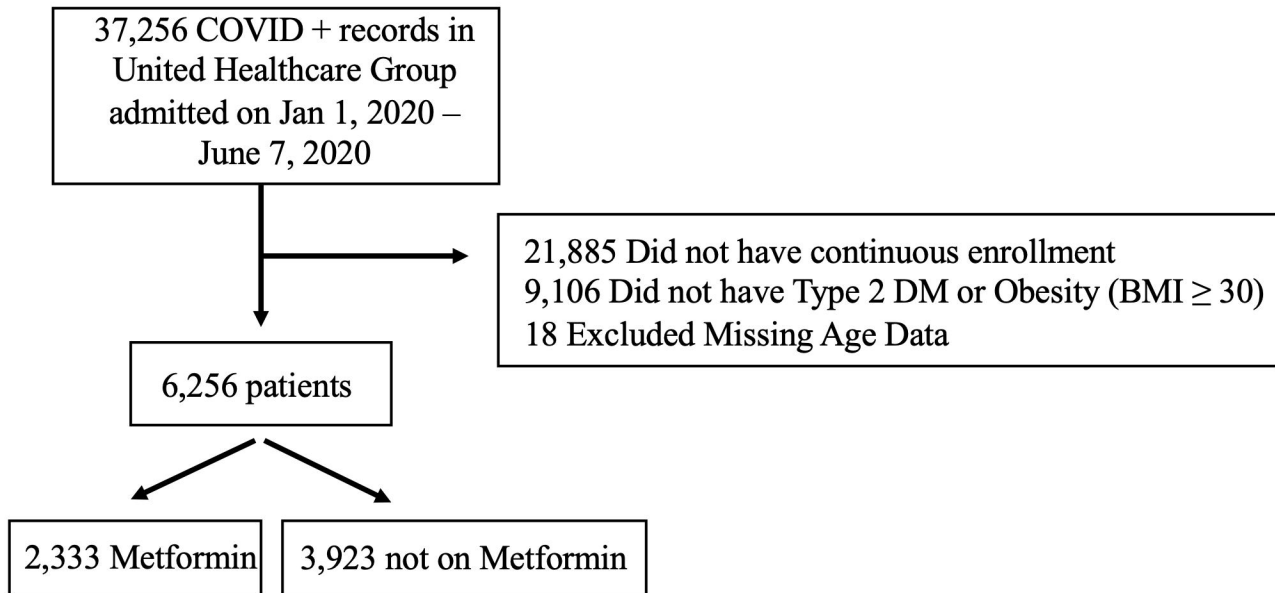
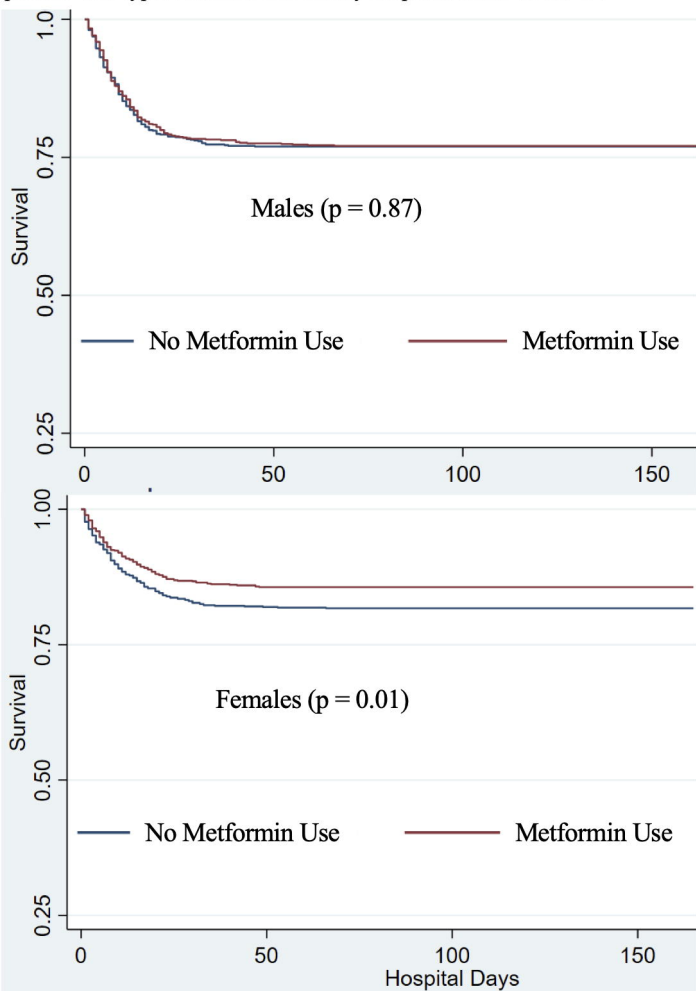


Figure 2. Kaplan Meier curve by metformin use, with propensity matching in persons with type 2 diabetes and obesity hospitalized for Covid-19.*



*With variables selected by LASSO with AIC, matching caliper 0.2

Figure 3. Subgroup analysis of mortality associated with metformin use vs no metformin use in hospitalizations for Covid-19, among women and men with type 2 diabetes or obesity. Bars represent 95% CI's.

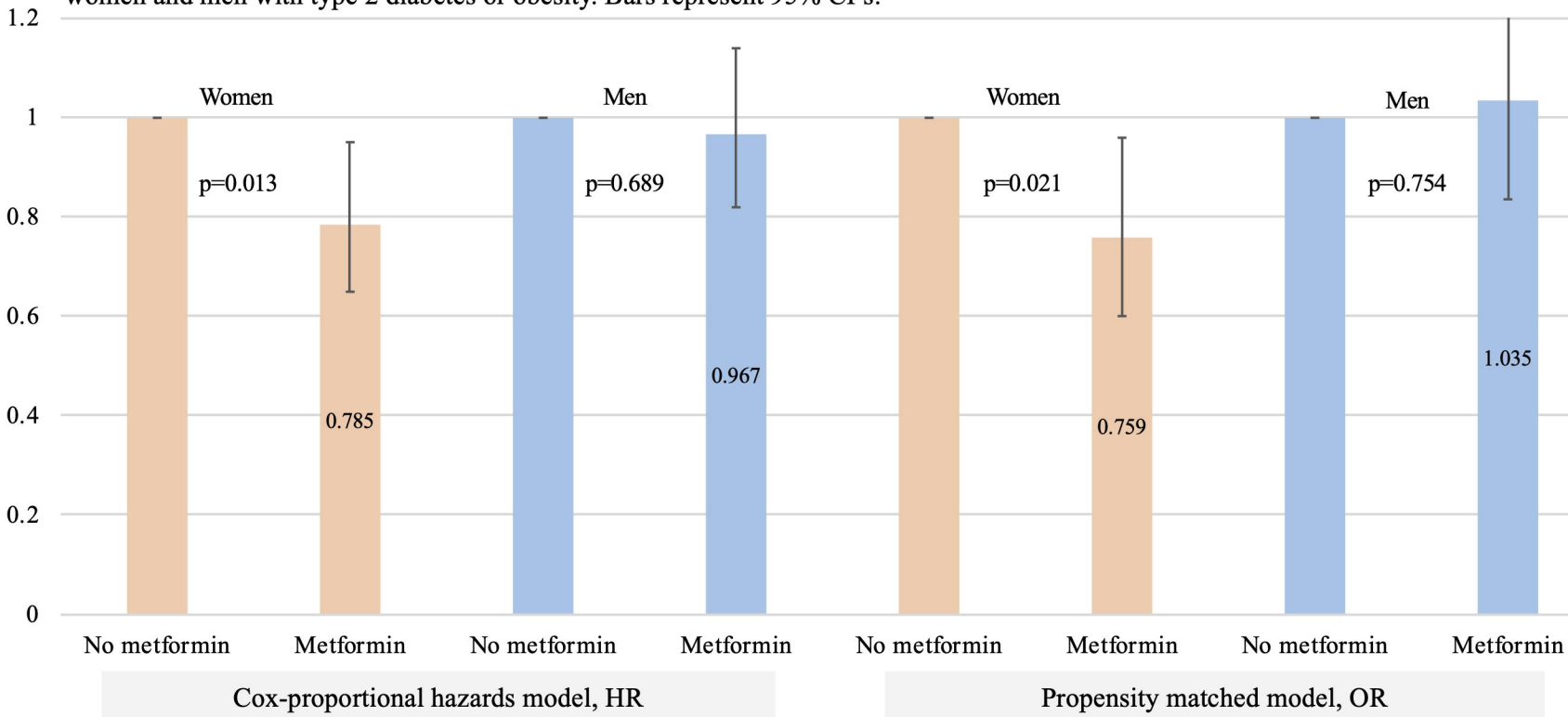


Figure S1. Log log plot assessing the proportionality assumption

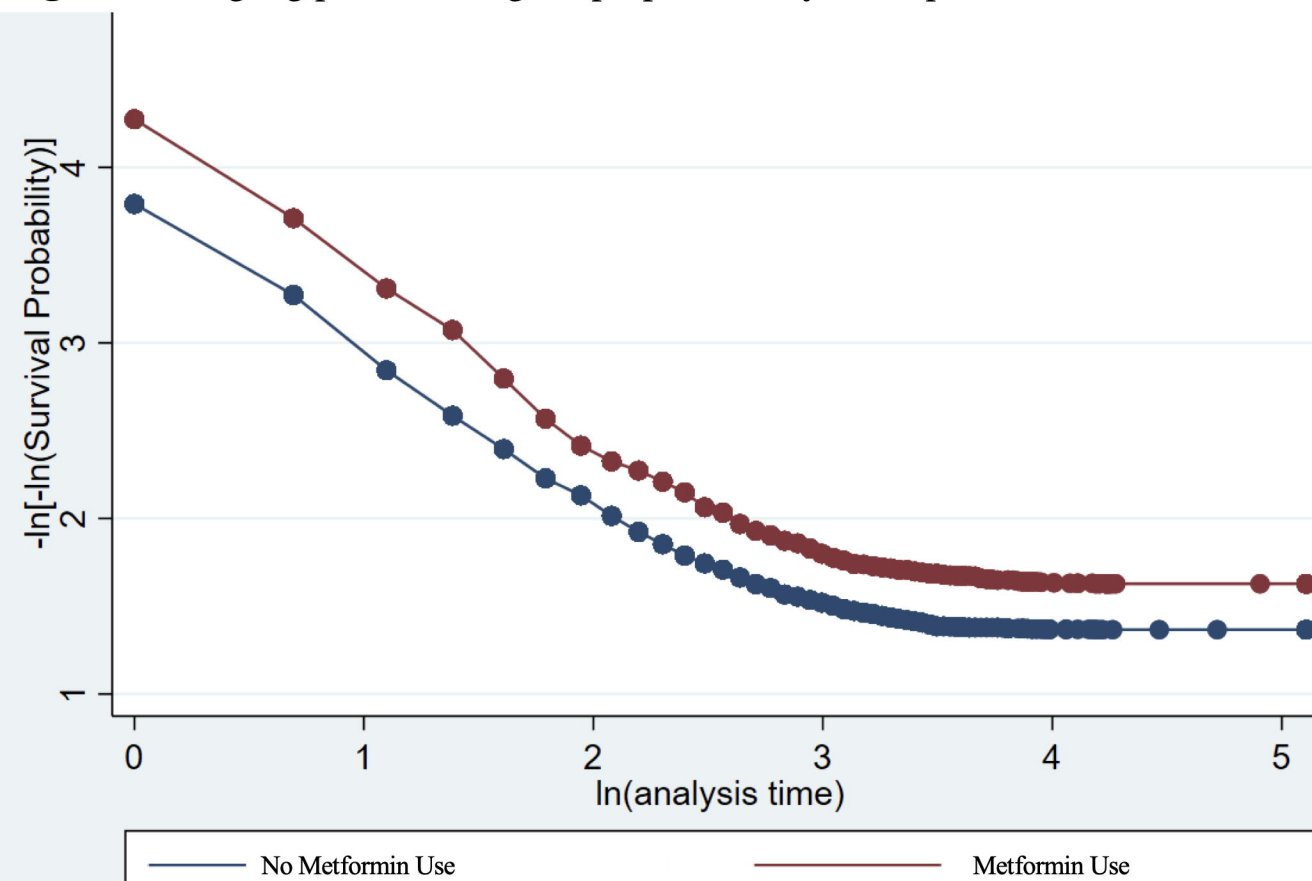
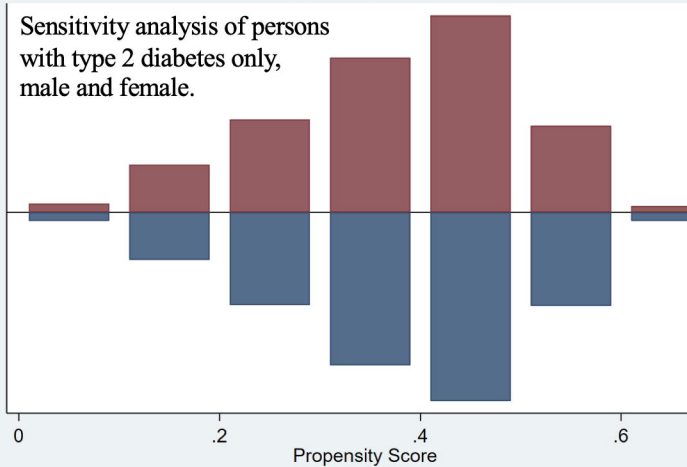
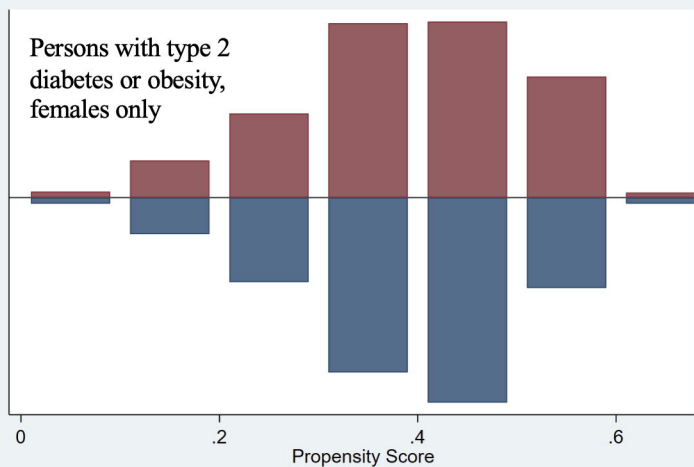
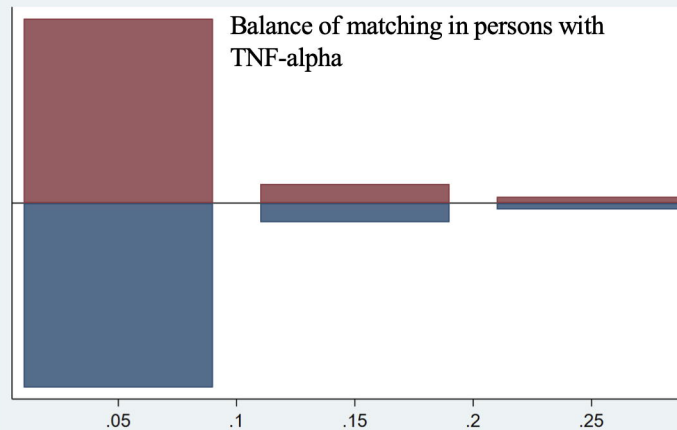
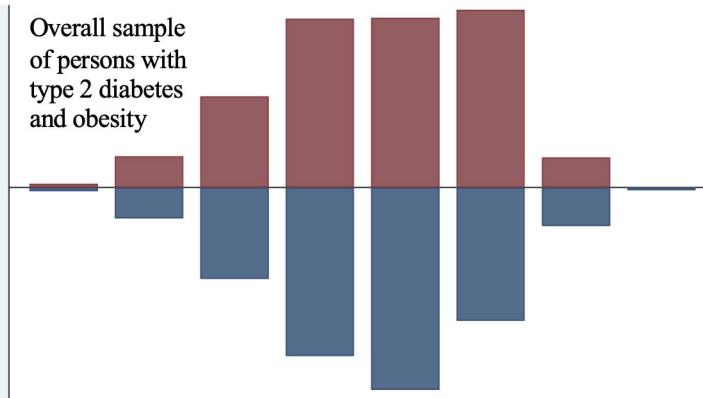


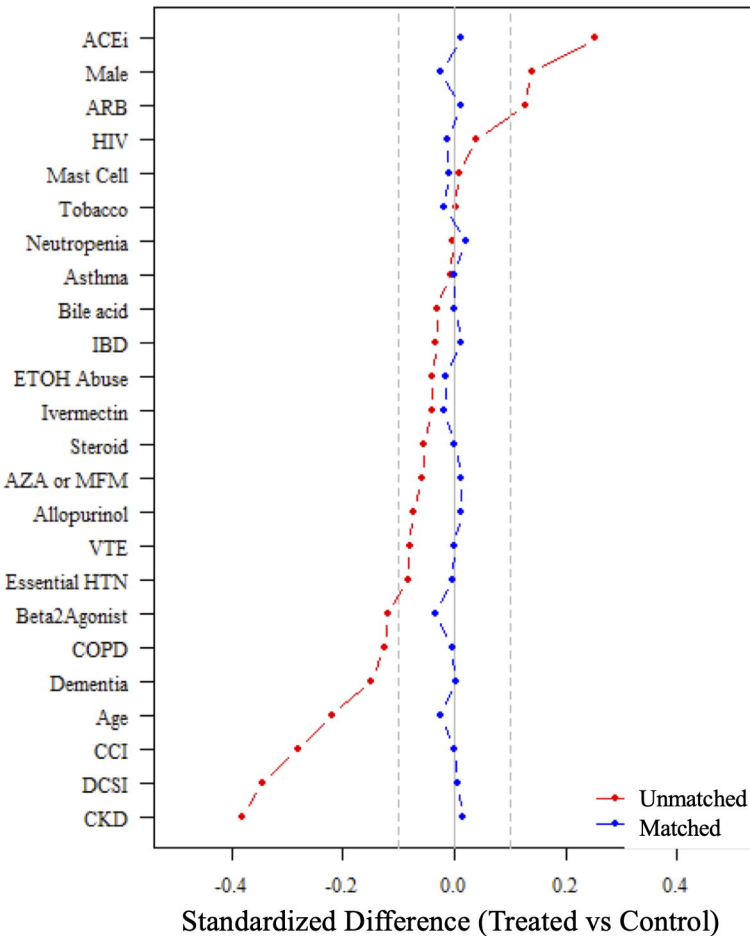
Figure S2. Balance of matching with caliper 0.2



No metformin Metformin

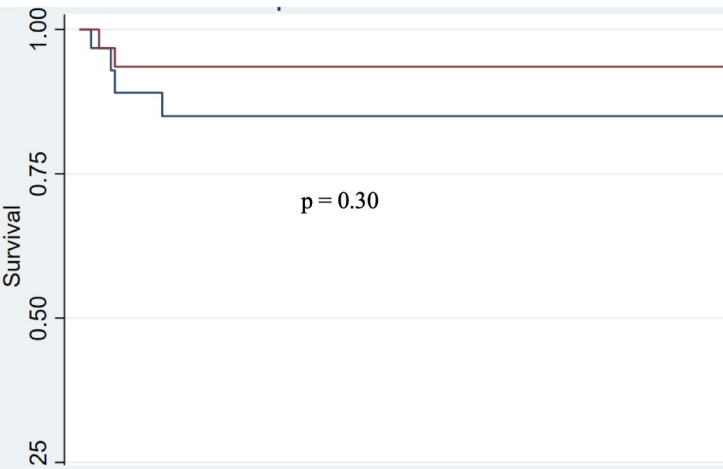
No metformin Metformin

Figure S3. Propensity matched covariate balance

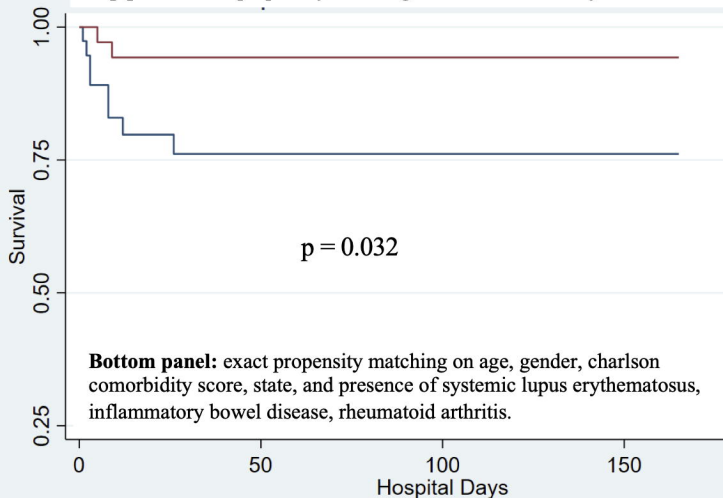


Abbreviations: ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin 2 receptor blocker; IBD=inflammatory bowel disease; ETOH=alcohol; AZA=azathioprine; MFM=mycophenolate mofetil; VTE=venous thromboembolism; HTN=hypertension; COPD=chronic obstructive pulmonary disease; CCI=charlson comorbidity index; DCSI=diabetes complications and severity index; CKD=chronic kidney disease.

Figure S4. Kaplan Meier curve by TNF-alpha inhibitor use, with propensity matching in persons hospitalized for Covid-19.



Top panel: exact propensity matching on all 32 variables by LASSO



Bottom panel: exact propensity matching on age, gender, charlson comorbidity score, state, and presence of systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis.

— No TNF-alpha inhibitor use — TNF-alpha inhibitor use