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Metformin therapy, severity and mortality of SARS-CoV-2 infection: a meta-analysis

ABSTRACT

Background. It has been postulated that metformin could have anti-SARS-CoV-2 action. This raises the hypothesis that people who take metformin may have lower SARS-CoV-2 severity and/or mortality.

Objectives. To conduct a meta-analysis of the association between the use of Metformin and risk of severity and mortality in SARS-CoV-2 infection.

Methods. We searched PubMed, EMBASE, Google scholar, the Cochrane Database of Systematic Reviews and preprint servers (medRxiv and Research Square) for studies published between December 2019 and January 2021. Data was extracted on study location, year of publication, design, number of participants, sex, age at baseline, body mass index, and exposure and outcome definition. Effect statistics were pooled using random effects models with 95% confidence intervals (CI). The quality of included studies was assessed with the Newcastle-Ottawa Scale (NOS).

Results. Thirty-two observational studies were included, combining to a total sample of 44306 participants. The mean NOS score of included studies was 7.9. Results suggested that metformin use was associated with a reduced risk of SARS-CoV-2 mortality (OR = 0.56, 95% CI: 0.46–0.68, P < 0.001; 22 studies) but not with disease severity (OR = 0.85, 95% CI: 0.71–1.02, P = 0.077; 15 studies). In the subgroup analysis, metformin reduces the risk of mortality (OR = 0.69, 95% CI: 0.55–0.88; P = 0.002) and severity (OR = 0.83, 95% CI: 0.70–0.97, P = 0.023) in patients aged 70 and above.

Conclusions. The use of metformin was associated to lower risk of mortality from SARS-CoV-2 infection. This association does not imply causation and further research is required to clarify potential mechanisms. (Clin Diabetol 2021; 10; 4: 317–329)

Key words: SARS-CoV-2 infection, COVID-19, metformin, mortality, type 2 diabetes

Introduction

Metformin (dimethyl biguanide) roots from the medieval European herbal medicine (*Galega officinalis*, *French lilac),* rich in guanidine and was used in patients with influenza [1–3]. Metformin is a guanidine derivative synthesized in the 1920s and approved by the FDA in 1994 and since 2009 is the first-line oral treatment for type 2 diabetes mellitus (T2DM) according to the ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) [4].

At the liver level, metformin inhibits the mitochondrial respiratory chain, activating AMP protein kinase (AMPK) and improving insulin sensitivity through effects on fat metabolism; additionally, it decreases cAMP, thus reducing the expression of gluconeogenic enzymes. Furthermore, metformin inhibits fructose-1,6-bisphosphatase by a hepatic AMPK-independent mechanism [2].

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SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor to enter the human cell, through the interaction of its spike proteins (S1) with the N-terminal region of ACE2. As part of the process, the RBD-PD complex is formed, made up of the receptor binding domain (RBD) of the virus bound to the PD (the protease domain) of the human ACE2 receptor [5]. It has been postulated that in the pathophysiology of the acute lung injury (ALI) caused by SARS-CoV-2, ACE2 is involved through autophagy linked to the AMPK/mTOR pathway [6]. In animal studies, AMPK has been shown to increase ACE2 expression and stability by phosphorylation of ACE2 [6].

It has been hypothesized that by acting on AMPK, metformin may reduce the inflow of SARS-CoV-2 to the cell and avoid downregulation of ACE2 receptors caused by the virus [7]. Previous studies in animal models have shown that metformin may have immunomodulatory, antiviral and preventive activity against acute lung injury [8, 9]. In the context of the current COVID-19 pandemic, it is not known if humans with type 2 diabetes who use metformin may have protection against adverse outcomes from SARS-CoV-2 infection. Hence, the present systematic review investigated the association between previous use of Metformin in diabetic patients and mortality and severity from SARS-CoV-2 infection.

Methods

This study was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [10].

Search strategy

Two independent investigators performed a systematic review in PubMed, EMBASE, Google scholar, the Cochrane Database of Systematic Reviews and preprint servers (medRxiv and Research Square) for studies published between December 2019 and January 2021. The full search strategy can be seen in Appendix 1.

Eligibility criteria

The inclusion criteria for the studies were: randomized controlled trials (RCTs) or observational studies reporting data on Metformin and risk of SARS-CoV-2 infection mortality and/or severity. We included studies in English (all ages) that presented data on hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs) with confidence intervals (CIs) or offered enough data to allow those to be calculated.

Quality assessment

The quality of observational studies (cohort and case control studies) and RCTs were appraised according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [11] and the Cochrane Risk of Bias Assessment Tool [12] respectively. Two investigators evaluated the quality of the studies independently. Conflicting results were resolved by discussion and involvement of a third reviewer if necessary.

Data extraction

The following data were extracted from each study: authors, study location, year of publication, study design, number of participants, sex, age at baseline, outcome definition, exposure definition, body mass index (BMI) and effect estimates and 95% CIs.

Statistical analyses

Statistical analyses

Primary analyses evaluated the association (hazard ratios, relative risks or odds ratios) between metformin and risk of mortality in SARS-CoV-2 infection. We used the random effects model with an inverse variance method to calculate the pooled RRs and 95% CIs according to the heterogeneity between studies [13]. In order to calculate the effect size of metformin and risk of severity of in SARS-CoV-2 infection, the relative risk or odds ratio published by the authors of the included studies were used. The overall estimates in the pooled analysis were obtained using Stata 13 software (Stata Corp LP, College Station, TX). Subgroups analyses were performed according to mean age and BMI.

Results

Characteristics of included studies

The flowchart of included studies is detailed in Figure 1. Out of 946 potentially relevant articles, and following application of inclusion criteria, 32 studies were retained including a total of 44306 participants. The included studies were conducted in Austria [14], Belgium [15], China [16–24], France [25–27], Hong Kong [28], Iraq [29], Italy [30, 31], Russia [32]which determines the high relevance of risk factor analysis for outcomes in DM patients to substantiate the strategy for this category of patients. AIM: To assess the effect of clinical and demographic parameters (age, gender, body mass index (BMI, South Korea [33, 34], Spain [35, 36], UK [37–41] and USA [42–45].

In terms of study design, 18 were case-control, 12 cohort, and 2 cross-sectional studies. Across studies, mean age was 66.7 + 5.3 years and 54.8% were men. The mean BMI was 27.5 + 2.8 (13 studies). The mean NOS score of included studies was 7.9 (range: 7–9). The full characteristics of included studies are detailed in Table 1.

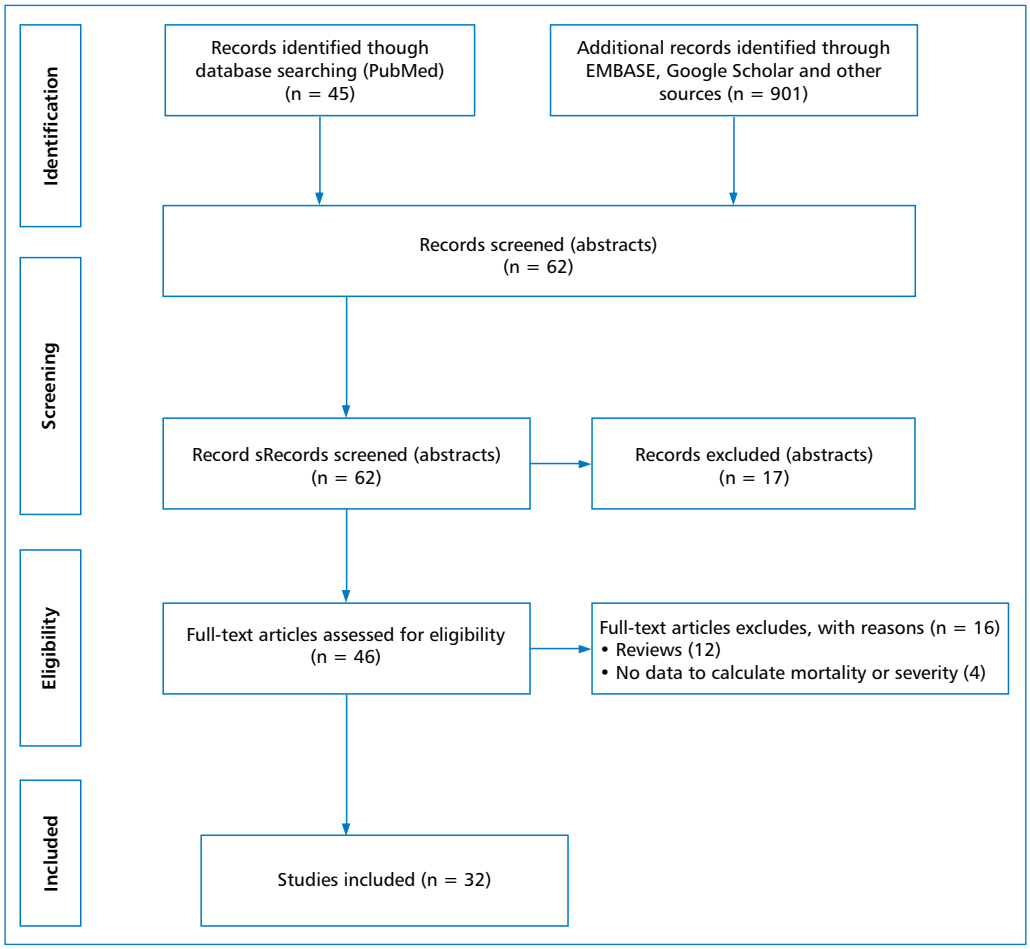

Figure 1. Study screening flowchart

Metformin and risk of mortality in SARS-CoV-2 infection

As shown in Figure 2, Metformin use was associated with reduced risk of mortality (OR = 0.56, 95% CI: 0.46–0.68, P < 0.001; 22 studies)

Metformin and risk of severe SARS-CoV-2 infection

The severity criteria of the included studies (15) were intensive care unit (ICU) admission (7 studies), acute respiratory distress syndrome (2), mechanical ventilation (3), and CT image / ICU admission / mechanical ventilation (3) (Table 1). And as shown in Figure 3, metformin was not significantly associated with disease severity (OR = 0.85, 95% CI: 0.71–1.02, P = 0.077; 15 studies).

Metformin and risk of mortality and severe (composite endpoint) SARS-CoV-2 infection

Three studies analyzed composite endpoint (mortality and severity) [27, 28, 40] and metformin was not significantly associated with disease severity and mortality (OR = 0.82, 95% CI: 0.44–1.53, P = 0.025).

Age and BMI subanalyses

In the subgroup analysis, metformin reduces the risk of mortality (OR = 0.69, 95% CI: 0.55–0.88; P = 0.002) and severity (OR = 0.83, 95% CI: 0.70–0.97, P = 0.023) in patients aged 70 and above. In studies with a predominance of male, metformin reduces the risk of mortality (OR = 0.62, 95% CI: 0.50–0.77; P < 0.001) and severity (OR = 0.84, 95% CI: 0.73–0.97; P = 0.016). In the studies that reported BMI, apparently the decrease in mortality was greater in those with BMI > 30 compared to those with BMI < 30 (OR = 0.49, 95% CI: 0.41–0.58 vs. OR = 0.30, 95% CI: 0.17–0.54); there were no severity studies with BMI > 30. The sub-analysis by sex was not done, because the studies did not report their results separately, except for one study [44].

Table 1. Characteristics of the 32 studies included in the meta-analysis

Author	Country	Preprint	Study design	Sample	Meanage	Sex male [%]	BMI	Outcome	CKD	HbA_{1C}	Comorbidities	NOS
Bramante et al. (2020)	USA	No	C	6256	75	47.2	Missing	Mortality	Met = 147(6.3%) vs. No Met = 729 (18.6%)	NR	Hypertension (56.3%), coronary artery disease (19.5%), heart failure(21%), cancer (12%), COPD (13%), CKD (15.7%)	8
Cariou et al. (2020)	France	No	C	1317	69.8	64.9	28.4	Mortality and severity (tracheal intubation for mechanical ventilation)	355/1066 (33.3%)	8.1 ± 1.9	Heart failure (11.6%), liver cirrhosis (10.7%), cancer (15.%), COPD (10.4%), end stage renal failure (7.2%)	8
Chen et al. (2020)	China	No	CC	120	66	53.43	NR	Mortality and severity (critical illness)	16/120 (3.3%)	Met = 7.70 (6.90–9.13) vs. 8.40 (7.35–10.65)	Diabetes (15.%), hypertension (30%), cardiovascular disease (10%), chronic kidney disease (5%), chronic lung disease (2%), tumor (2%)	9
Luo et al. (2020)	China	No	CC	283	63	53	NR	Mortality and severity (CT imagen, ICU admission, mechanical ventilation)	1/104 (1%)	NR	Diabetes (100%), hypertension (60%), coronary heart disease (11%),	9
Mirani et al. (2020)	Italy	No	CC	90	69	72.5	NR	Mortality and severity (Invasive ventilation)	Met (8/69,12%) no Met (9/21, 43%)	NR	NR	8
Crouse A. et al. (2020)	USA	Yes	CC	220	NR	45	NR	Mortality	NR	7.3 ± 1.3	Diabetes (39.6%), hypertension (48%),	8
Kim M et al. (2020)	South Korea	No	CC	1082	68.3	41.5	24.2	Severity (ICU admission)	32/1082 (2.6%)	7.70 ±1.79	Missing	8
Jiang et al. 2020	China	No	C	148	65	44.6	NR	Mortality and severity (acute respiratory distress syndrome)	NR	Met = 8.1 [7.0,10.0] vs. 7.6 [6.9, 9.2]	Coronary heart disease(10%), asthma (8%)	8
Cheng X. et al. (2020)	China	No	CC	1213	63	52.1	NR	Mortality and severity (acute respiratory distress syndrome;)	30/1213 (2.5%)	8.1, (IQR, 7.0%–9.9%)	COPD (1%), coronary heart disease, (15%), heart failure (0.2%), cerebrovascular diseases (4%), chronic liver disease (2%)	8

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Table 1 (cont.). Characteristics of the 32 studies included in the meta-analysis

Author	Country	Preprint	Study design	Sample	Meanage	Sex male [%]	BMI	Outcome	CKD	HbA_{1C}	Comorbidities	NOS
Philipose et al. (2020)	UK	Yes	CC	466	72	59	NR g	Mortality	NR	NR	Type 2 diabetes mellitus (34%), hypertension (50%), cardiac history (34%), stroke History (12%), respiratory history (28%)	8
Gao et al. 2020	China	No	CC	110	65	41.8	NR	Severity (ICU admission)	NR	NR	Hypertension (31%), hyperlipidemia (14%)	8
Lally et al. 2020	USA	No	CC	755	75.6	97.3	27.6	Mortality	195/755 (25.2%)	7.49 ± 1.44	Diabetes (40%), dementia (69%), pulmonary disease (34%), hypothyroid (12%), tumor (17%), psychoses (42%)	8
Pérez-Belmonte et al. 2020	Spain	No	CC	1488	74.9	61.9	NR	Mortality and severity (ICU admission)	Moderate-severe: Metf (39/825), No Met (192/663)	NR	Hypertension (76%), dyslipidemia (65%), chronic kidney disease (13%), coronary artery disease (16%), heart failure (13%), COPD (13%)	8
Wang et al. 2020	USA	No	C	58	67	52	27.6	Mortality	14/58 (24%) or eGFR < 60 (24%)	NR	Hypertension (64%), hyperlipidemia (62%), diabetes (28%), congestive heart failure (12%), lung disease (COPD, emphysema, asthma, bronchiectasis) (21%)	8
Yan et al. 2020	China	No	C	58	49.18	51.7	24.01	Severity (ICU admission)	1/58 (1.7%)	NR	Hypertension (22%), cardio or cerebrovascular (3%), tumour (2%)	8
Hippisley-Cox et al. 2020	UK	No	C	19486	62.18	48.12	NR	Severity (ICU admission)	3442/19 486 (18%)	NR	NR	8
Shestakova et al.	Russia	No	CC	309	68	32.36	32.1	Mortality	15/309 (5%)	Death (7.7%), alive (7.4)	Cardiovascular disease (29%), chronic kidney disease (28%), hypertension (59%)	7
Sourij et al. 2020	Austria	No	C	238	71.1	63.6	NR	Mortality	14/238 (5.9%)	6.4 ± 1.4	Hypertension, (71%), cardica heart diseasea (27%), heart failure, (13%), chronic kidney disease (23%), cancer (16%), stroke (8%)	8

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Table 1 (cont.). Characteristics of the 32 studies included in the meta-analysis

Author	Country	Preprint	Study design	Sample	Meanage	Sex male [%]	BMI	Outcome	CKD	HbA_{1C}	Comorbidities	NOS
Li et al. 2020	China	No	CC	131	66.8	56.49	24.23	Mortality and severity (Invasive and Noninvasive ventilation)	NR	7.89 ± 1.85	coronary artery disease (21%), hypertension (60%), hyperlipidemia (11%)	8
Do et al. 2020	Korea	No	CC	564	64.8	51.8	NR	Mortality and severity (Mechanical ventilation)	138/469 (29.4%)	NR	Hypertension (74%), peptic ulcer disease (48%), myocardial infarction (7%), congestive heart failure (18%), cerebrovascular disease (31%)	8
Abu-Jamous et al. 2020	UK	No	CS	191	NR	NR	NR	Mortality	NR	NR	NR	7
Lasbleiz et al. 2020	France	No	CC	344	62.1	59.3	29.5	Severity (Inpatients vs outpatients)	49/344 (13.8%)	13.4 ± 1.8	Hypertension (64%), dyslipidemia (41%), ischemic heart disease (17%), cerebrovascular disease (6%), peripheral artery disease (4%), COPD (5%)	8
Zhang et al. 2020	China	No	C	58	62	60	23.6	Severity (admission to ICU, or mechanical ventilation, or death)	4/58 (7%)	NR	Hypertension (50%), coronary heart disease (15%), chronic lung disease (4%), cerebrovascular disease (10%), cancer (2%)	8
Liu et al. 2020	China	No	C	64	66	54.7	NR	Severity (ICU admission)	0/64 (0%)	8.1 (6.6–9.7)	Missing	8
Nafakhi et al. 2020	Iraq	No	CC	50	60	43	29.8	Mortality	NR	NR	Hypertension (66%), coronary artery disease (15%)	8
Goodall et al. 2020	UK	No	C	981	69	64.3	NR	Mortality	NR	NR	Hypertension (50%), heart failure (10%), ischaemic heart disease (15%), active malignancy (5%), asthma (8%), COPD (5%)	8
Xiang et al. 2020	Hong Kong	Yes	C	3858	68.1	44.74	27.38	Severity (hospitalized or fatal infection)	NR	NR	Missing	7

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Table 1 (cont.). Characteristics of the 32 studies included in the meta-analysis

Author	Country	Preprint	Study design	Sample	Meanage	Sex male [%]	BMI	Outcome	CKD	HbA_{1C}	Comorbidities	NOS
Lalau et al 2020	France	No	CC	2449	70.9	64	28.7	Mortality and severity (mechanical ventilation)	668/1990 (33.6%)	8.1 ± 1.8	Hypertension (80%), dyslipidaemia (49%), ischemic heart disease (27%), cerebrovascular disease (13%), heart failure (12%), cancer (9.7%)	9
Orioli et al. 2020	Belgium	No	CC	68	69	48	30.5	Mortality	34.2 (25/73)	7.1 [6.6-8.3]	cardiovascular disease; (44%), hypertension (81%), obstructive sleep apnea; (19%), cognitive impairment (21%), chronic liver disease (14%)	8
Izzi-Engbeaya et al. 2020	UK	Yes	C	889	65.8	60	NR	Mortality and seveity (ICU admission) (composite)	371/880 (42%) (eGFR < 60 mL/kg/min	8%	Hypertension (47%), hyperlipidaemia (33),i schaemic hear(16%), stroke (13%), heart failure (10%), COPD (9%), Active cancer (9%)	8
Cernigliaro et al.	Italy	No	CS	172	71	54	NR	Mortality and Severity (ICU admission)	NR	NR	NR	7
Ramos-Rincón et. al. 2020	Spain	Yes	CC	790	85.8	56.8	NR	Mortality	17.2% (136/790)	NR	Hypertension (84%), dementia (34%), obesity (> 30k g/m^2) (18%), coronary artery disease (19%), peripheral vascular disease (12%)	8

CKD: chronic kidney disease; NOS: Newcastle-Ottawa Quality Assessment Scale; BMI: body mass index; Met: Metformin; IQR: interquartile range; NR: not reported; CC: case control study; C: Cohort study; CS: cross-sectional study

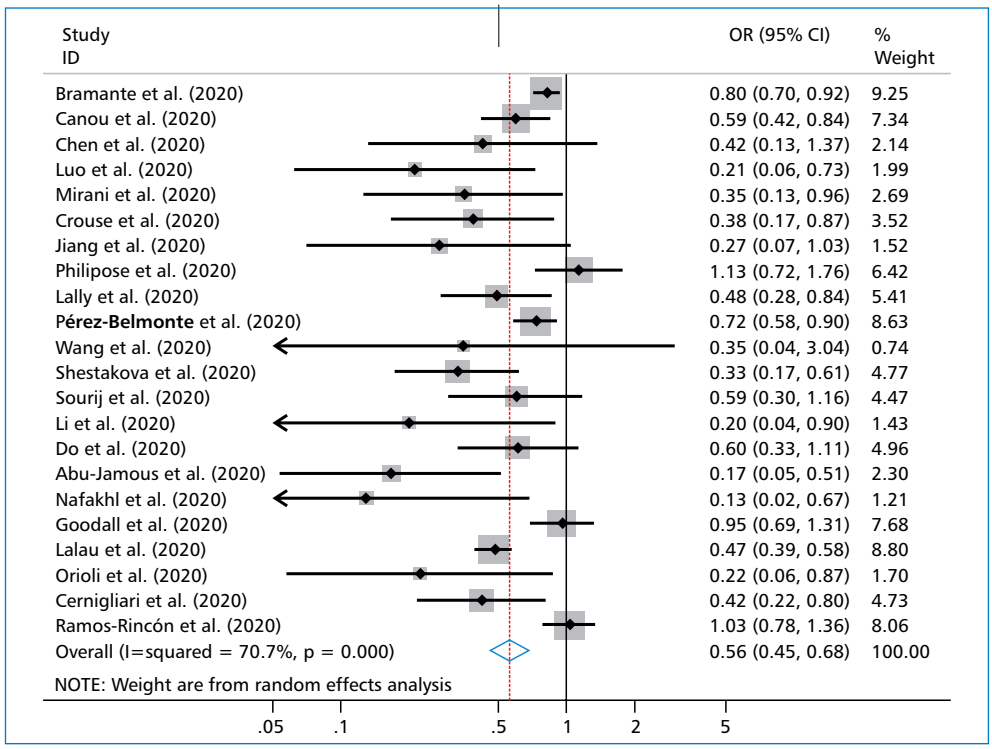

Figure 2. Forest plot of the Metformin and risk of mortality in SARS-CoV-2 infection. Analysis model: random effect. OR: odds ratio; CI: confidence interval

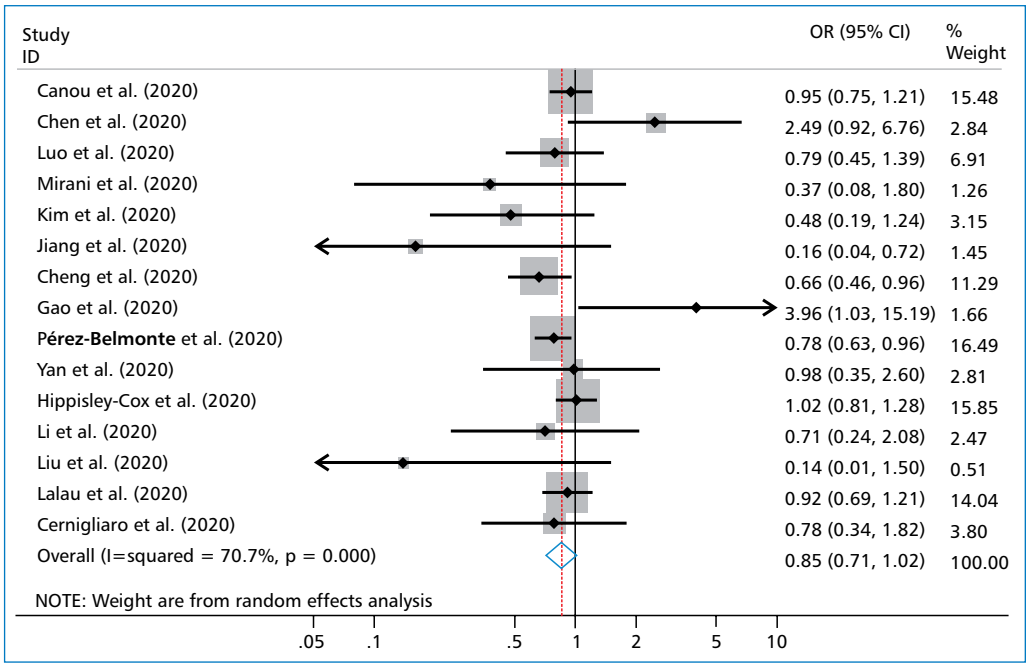

Figure 3. Forest plot of the Metformin and risk of severity in SARS-CoV-2 infection. Analysis model: random effect. OR: odds ratio; CI: confidence interval

Interleukin-6 (IL-6) levels

Only 2 studies measured the serum concentration of IL-2 in patients with or without metformin [16, 30], and both reported significantly lower IL-6 levels in the group on metformin.

Table 2. Association between use of Metformin and mortality and severity of SARS-CoV-2 infection — summary of subgroup analyses

Subgroup	Studies (n)	Adjusted OR (95% CI)	P
Age			
Mortality*			
< 70	12	0.43 (0.30–0.61)	< 0.001
≥ 70	8	0.69 (0.55–0.88)	0.002
Severity			
< 70	12	0.84 (0.64–1.11)	0.221
≥70	3	0.83 (0.70–0.97)	0.023
BMI			
Mortality			
< 30	6	0.49 (0.41–0.58)	< 0.001
≥ 30	2	0.30 (0.17–0.54)	< 0.001
Severity			
< 30	5	0.91 (0.77–1.08)	0.291
≥ 30	0		

Discussion

The present study found that the previous use of metformin in patients with type 2 diabetes is associated with lower risk of mortality from SARS-CoV-2 infection but not with disease severity. However, it should be noted that this association does not imply causality. In the subgroup analysis, we found a decrease in the risk of mortality and severity in those over 70 years of age. Additionally, some studies found that previous use of metformin in diabetic patients could be related to lower levels of IL-6 during COVID-19 infection.

Prior to this study, four meta-analytic studies were published with similar findings, although with fewer studies and without severity data [46–49]. On the other hand, before the COVID-19 pandemic, Liang *et al*. [50] published a meta-analytical study that found that the use of metformin prior to hospitalization for septic shock may reduce mortality in diabetic patients.

Using data from the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study, Lalau *et al*. [27] found that metformin was associated with a reduction in a composite endpoint (tracheal intubation for mechanical ventilation and/or death), and death by day 28, but linked to increased severity on admission regarding clinical, radiological, and biological features, compared with metformin non-users. The most likely explanation for this apparently discordant finding is that hospitalized patients who use metformin tend to be more multimorbid at baseline, rather than develop a more severe illness due to taking metformin. However, a hypothesis was proposed that the time lag between the onset of COVID-19 symptoms and hospital admission was significantly longer in metformin users, and the rate of dyspnoea, a major severity criterion, was not more frequent in metformin users [27].

In the subgroup analysis, we found that metformin users had decreased risk of mortality and severity in patients with an age equal to or older than 70 years; this finding could be interesting because according to a recent meta-analyzes on 59 studies showed that patients aged 70 and above have a higher risk for COVID-19 infection, severe disease, ICU admission and death [51]. The probable mechanism by which metformin reduces mortality and severity in patients older than 70 years would be through its action at the level of mitochondrial function. It is known that decline in mitochondrial function occurs with aging and may increase mortality; on the other hand, in the pathophysiology of SARS-CoV-2 infection there is the hypothesis that mitochondrial function is compromised, specifically the complex interaction of innate immune function, viral replication, hyperinflammatory state, and HIF-α / sirtuin pathways (hypoxia-inducible transcription factors, HIF) [52]. Currently there is enormous interest in drugs called "inflammaging or geroprotectors", so called because they are molecules which can target chronic inflammation associated with aging, obesity, and metabolic syndrome [53]. One of these inflammaging drugs, or geroprotectors, is metformin, because it activates 5'AMP-activated protein kinase (AMPK) and inhibits the mTOR pathway, may improve metabolic derangements, improve mitochondrial function, and decrease cytokine production [54]. Recently Bharath *et al*. [55] demonstrated *in vitro* that metformin improves autophagy and mitochondria in parallel to decrease inflammaging. The findings of the present study regarding a probable protective effect in the male sex require more studies, because the included studies did not report the respective analysis separately by gender, and the division between studies with a male or female predominance may be debatable. However, these results are published to be taken into account in the design of future studies.

At the biological level, there could be possible mechanisms associated with metformin-associated antiviral, immunomodulatory and preventive activity for acute lung injury. In this regard, the relationship between glucose metabolism and viral replication have, in the past few years, started to be the object of thorough investigation, starting from HIV-1 [56, 57]. The antiviral activity of metformin has been demonstrated in dengue virus infection, by restoring AMPK activity in early stages of infection [58], in animal models with Coxsackievirus B3 (CVB3) infection [59], and Kaposi sarcoma herpesvirus [60]. It has been postulated that

the anti-COVID-19 activity of metformin may be due to interference in the interaction of the ACE2 receptor and SARS-CoV-2, through its action on AMPK [7, 61]. At the level of human endothelial cells, AMPK phosphorylates ACE2 Ser680 and increases ACE2 expression by enhancing its stability. Metformin also enhances the phosphorylation and expression of ACE2 [28]. Phosphorylation produces a conformational and functional ACE2 receptor and decreases the binding of SARS-CoV-2, thus interfering with the entry of the virus into the human cell [7, 61]. There is the hypothesis that Metformin could negatively alter endocytosis, maturation of endosomes, and transport of virions to the replication site [62], producing an endosomal alkaline environment, due to its direct action on the eNHEs (Na+/H+ exchangers) and/or the V-ATPase, two membrane compartments for the maintenance and regulation of endosomal acidic pH [63–65]. This mechanism would thus be similar to that of a widely studied investigational anti-SARS-CoV-2 agent, i.e. hydroxychloroquine, which however gave controversial results *in vivo* [66, 67].

Metformin may have immunomodulatory activity because it reduces the production of pro-inflammatory cytokines using macrophages, causes the formation of neutrophil extracellular traps (NETs) and inhibits the production of cytokines from pathogenic Th1 and Th17 cells; therefore, it could potentially suppress the cytokine storm produced by severe COVID-19 [68]. Experimental studies in animal models have shown that metformin has an action against lung injury [69–72]. A recent study using bovine pulmonary artery endothelial cells (BPAEC), showed that metformin enhanced the vascular barrier integrity, since it produces an increase in the transendothelial resistance of endothelial monolayers [73]. Additionally, metformin may attenuate lung injury caused by the high pressure of mechanical ventilation [74].

Two studies included in this meta-analysis found significantly lower levels of IL-6 in diabetic patients with COVID-19 taking metformin compared to those who did not use it [16, 30]. In this regard, before the COVID-19 pandemic, it was known that multiple myeloma patients treated with metformin had significantly lower levels of IL-6R expression and promoted apoptosis of myeloma cells [75]. The use of metformin in patients with polycystic ovary syndrome reduces serum levels of IL-6 and improves chronic inflammation [76]. Metformin can also reduce IL-6 secretion by alveolar macrophages and reduce pulmonary thrombosis in mice [77]. Additionally, metformin can inhibit the IL-6 signaling pathway, thus overcoming the acquired resistance of lung cancer to epidermal growth factor receptor tyrosine kinase inhibitors [78]. There is, therefore, increasing interest in metformin as a potential therapeutic agent in COVID-19 infection [79].

Discontinuation of metformin has been recommended in patients with severe COVID-19 infection due to the potential risk of lactic acidosis [80]. However, in a study that included 1212 hospitalized patients with COVID-19 and pre-existing diabetes, Cheng *et al*. [18] found that metformin was associated with the incidence of acidosis, but not with an increase in mortality associated with COVID-19. On the contrary, metformin was associated with a significant decrease in heart failure and inflammation, but acidosis and kidney function should be carefully monitored in individuals with severe COVID-19 [18]. One study reported that 29% of patients hospitalized for COVID-19 continued to take metformin and lactic acidosis was not reported[81]. In clinical practice, metformin is generally suspended immediately after the patient is admitted in a severe state, to avoid lactic acidosis. It is possible that metformin has an effect after having been suspended, in this regard it is known that it appears to accumulate in erythrocytes, and after its suspension it remains detectable in erythrocytes up to 48 hours [82], so it takes nearly one week for total elimination of metformin from the body [83].

The present study has limitations derived from the design of the included studies, which are observational and some were preprints (4/32) and not clinical trials. Most of the included observational studies were retrospective cohorts and potential selection bias of patients is an indisputable concern. On the other hand, in the interpretation of the analysis of their groups, caution should be taken because few studies reported data on BMI.

In conclusion the present study found that the previous use of metformin in patients with type 2 diabetes is associated with a lower risk of mortality from SARS-CoV-2 infection, but not severity. This association does not imply causation and further research is required to clarify potential mechanisms.

Conflict of interest

None.

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Appendix 1

MEDLINE search strategy

We searched the NCBI and Medline databases for potentially eligible records.

The search terms were as follows:

#1: SARS-CoV-2 OR COVID-19

#2: metformin OR biguanides

#3: mortality OR severity

#4: #2 OR #3

#5: #1 AND #4