Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Metformin in SARS-CoV-2 infection: A hidden path – from altered inflammation to reduced mortality. A review from the literature

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ABSTRACT

SARS-CoV-2 infection has been a major threat to human health and a huge challenge to Medicine. In only two years, COVID-19 affected >350 million people, causing >5.6 million deaths. Chronic inflammatory states, such as diabetes or obesity, are known risk factors for COVID-19 poorest outcomes, with higher risk for disease severity and greater mortality. Metformin remains on the first line of the management of hyperglycemia in type 2 diabetes. Through its anti-inflammatory and immunomodulatory mechanisms, metformin appears as an opportunity to control the dysregulated cytokine storm secondary to SARS-CoV-2 infection. Recent studies point towards a potential protective role of metformin in the course of COVID-19, showing that current or previous treatment with metformin associates with better outcomes.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was a novel coronavirus strain unknown to mankind until December 2019. Then, Wuhan (Hubei province, China) became the center of an outbreak of pneumonia of unknown cause which raised intense attention not only within China but worldwide.[1,2] On March 11th 2020, the global spread of the coronavirus disease 2019 (COVID-19) was finally declared a pandemic by the World Health Organization (WHO).[3] Several physical conditions, such as older age, diabetes mellitus, hypertension, and obesity increase the odds of SARS-CoV-2 infection, leading to a higher risk of complications and death from COVID-19.[3] SARS-CoV-2, through a mechanism that remains largely speculative, triggers a cytokine storm, inducing the development of various complications.[4,6] Considering patients with COVID-19, those with diabetes have much higher levels of inflammatory markers, suggesting that this proinflammatory state can lead to a rapid clinical deterioration and poor COVID-19 outcomes.[5] SARS-CoV-2 infects human epithelial cells by binding to angiotensin-converting enzyme 2 (ACE-2),[6] a membrane bound protein expressed in type I and type II alveolar epithelial cells in the lungs and upper respiratory tract and in several other human tissues.[7,8]

Metformin arose from herbal ancestry in medieval Europe and can be traced from the use of *Galega officinalis*. In the 1920s its glucose-lowering properties were discovered, and later in 1957, Jean Sterne introduced it for the treatment of adult-onset diabetes.[9] Following the improvement in morbidity and mortality in type 2 diabetes (T2D), metformin has been recommended as the first line options of oral treatment for T2D by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) since 2006.[10,11]

Metformin appears to have a protective role in the disease course of COVID-19 and several mechanisms have been proposed to explain this result. Metformin inhibits adenosine triphosphate (ATP) synthesis which increases adenosine monophosphate (AMP) and adenosine diphosphate (ADP) levels that indirectly induce the activation of AMP-activated protein kinase (AMPK) in hepatocytes, which leads to ACE-2 conformational and functional changes, resulting in decreased binding with SARS-CoV-2 and subsequently to a reduction in its infectivity.[12] Furthermore, the activation of AMPK inhibits the inflammatory response that potentially contributes to mortality through the cytokine storm or vascular damage.[13] Lastly, AMPK activation inhibits the mammalian target of rapamycin (mTOR),[14] which plays a major role in Middle East respiratory syndrome coronavirus (MERS-CoV) infection.[15]

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Given the multiple similarities between the two viruses, it is plausible to assume that mTOR inhibition by metformin may result in a reduction of SARS-CoV-2 infectivity and mortality.[16]

2. Materials and methods

Research data for the present analysis was primarily retrieved by a keyword-base PUBMED search, using relevant keywords (Metformin) AND (COVID-19 OR SARS-CoV-2). The search was last updated on the 5th of January of 2022 and included publications from the 1st of January of 2020 to the 31st of December of 2021. Only human studies published in English were analyzed. Our online search yielded 166 articles. After reviewing all titles and abstracts, meta-analysis, systematic-reviews, other reviews, opinions, commentaries or letters and case reports were removed, leading to the exclusion of 127 titles. Sixty one papers went for full-text-review, and finally 37 publications were included.[17–54]

3. Results

3.1. Metformin and COVID-19 mortality

A total of 31 studies assessed the relationship between metformin use and the risk of mortality among COVID-19 patients. In 26 studies, metformin use was associated with a 13 to 90 % reduction in mortality in COVID-19 patients (22 of them with statistical significance). In one study, metformin was associated with a reduction in mortality of 21.5 % in women ($p = 0.03$).[17] Two studies found no association between the glucose lowering drug and COVID-19 mortality.[18,19] Another 2 studies revealed an increased risk for COVID-19 mortality (26–98 %).[20,21]

Crouse et al.[22] showed that metformin treatment prior to the diagnosis of COVID-19 was independently associated with a significant decrease in mortality in patients with diabetes and COVID-19 (OR 0.33; 95 % CI 0.13–0.84; $p = 0.0210$). If patients had more severe metabolic disease (higher body mass index [BMI] and glycated hemoglobin [HbA1c]), leading to an increased risk for death in SARS-CoV-2 infection, metformin use drastically reduces this risk. In a small sized study, Blanc et al.[23] demonstrated that the previous use of metformin in COVID-19 patients was associated with a reduced probability of death ($p = 0.0237$). In 89 COVID-19 patients, only 1 patient on glucose lowering treatment died — however, it was not clearly specified if this was one of the 13 metformin users. Al-Salameh et al.[24] reported that the benefit of metformin use in COVID-19 disease course is seen with its continuation during the hospital stay, rather than previous exposure (OR 0.31; 95 % CI 0.10–0.90; $p = 0.04$ vs. OR 3.64; 95 % CI 1.24–11.45; $p = 0.02$ [death or ICU admission]), also confirming that patients that discontinued metformin at hospital admission had worse clinical status (higher leukocytosis, C reactive protein [CRP] and blood glucose). Dave et al.[25] verified that metformin use was related with a reduced risk of mortality (OR 0.77; 95 % CI 0.64–0.92) and hospitalization (OR 0.62; 95 % CI 0.55–0.77) in people living with diabetes (PLWD). Wander et al.[26] examined 64,892 veterans with COVID-19 and concluded that metformin use was related to a decreased risk of death at 30 days (OR 0.84; 95 % CI 0.78–0.91) and in follow-up (4.4 to 13.1 months) (HR 0.84; 95 % CI 0.79–0.89). In France, Wargny et al.[27] showed that routine metformin therapy is independently associated with a favorable outcome, leading to higher odds of discharge (OR 1.40; 95 % CI 0.82–1.81) and lower risk of death at 28 days (OR 0.65; 95 % CI 0.45–0.93). In a nationwide observational cohort study, Khunti et al.[28] found a lower risk of death in COVID-19 patients treated with metformin (HR 0.77; 95 % CI 0.73–0.81). Although it was a nationwide study, with a large study population, it failed to provide information regarding COVID-19 disease severity or even in metformin adherence during the follow-up. Nafakhi et al.[29] reported a decreased risk of in-hospital death among patients treated with metformin (OR 0.1; 95 % CI 0.1–0.6; $p = 0.025$). Saygili et al.[30] evaluated the effect of preadmission metformin treatment on the mortality of COVID-19, and verified that it was related with a significatively lower risk in overall mortality (HR 0.585; 95 % CI 0.371–0.920; $p = 0.020$) and a trend with in-hospital mortality (HR 0.568; 95 % CI 0.306–1.052; $p = 0.072$).

In one study, Bramante et al.[31] analyzed the outpatient previous use of metformin in COVID-19 patients and verified a significant reduction in mortality from COVID-19 (OR 0.32; 95 % CI 0.15–0.66; $p = 0.002$). On a simultaneous study, Bramante et al.[17] showed that metformin use was significantly associated with decreased mortality in women with obesity or T2D admitted for COVID-19 (HR 0.79; 95 % CI 0.64–0.98; $p = 0.03$), but there was not a significant decrease in mortality among men (HR 0.957; 95 % CI 0.82–1.14; $p = 0.689$), neither in overall mortality (HR 0.884; 95 % CI 0.778–1.003; $p = 0.056$). In Brazil, Tamura et al.[32] verified that continuous use of metformin during hospitalization was related with lower death rates from COVID-19 (2.1 % vs. 21.1 %; $p = 0.001$) and that its use leaded to a reduction on in-hospital death risk (HR 0.248; 95 % CI 0.089–0.685). Pérez-Belmonte et al.[33] showed that even though patients treated with metformin had higher rates of in-hospital complications (66.4 %; $p = 0.030$), they presented a significantly reduction of in-hospital death rate (OR 0.73; 95 % CI 0.58–0.90; $p = 0.004$). In a nationwide observational study, Lalau et al.[34] assessed the impact of prior metformin use in patients with T2D hospitalized for COVID-19. These patients showed significantly lower odds of 28-day mortality (OR 0.710; 95 % CI 0.537–0.938; $p < 0.0001$), but not a significative reduction in 7-day mortality (OR 0.688; 95 % CI 0.470–1.007); however, it is unclear if metformin use was stopped or continued after hospital admission. Li et al.[35] verified that metformin was an independent predictor of survival in COVID-19 patients with T2D (5.4 % vs. 22.3 %; $p = 0.0222$). On another study, Li et al.[36] found that in-hospital metformin use was significantly associated with a lower risk of death (2.0 % vs. 21.0 % [with another glucose lowering drug] vs. 42.6 % [without glucose lowering medication]; p = 0.0222). Luo et al.[37] compared metformin users vs. nonusers hospitalized for COVID-19 and verified a significant reduction of in-hospital mortality in the metformin group (2.9 % vs. 12.3 %; $p = 0.01$). Lally et al.[38] evaluated the mortality benefit among older COVID-19 patients and concluded that metformin use is associated with a lower risk of death at 30 days (HR 0.48; 95 % CI 0.28–0.84). Ghany et al.[39] assessed the metformin effect on a minority of insurance patients who developed COVID-19 and founded a lower death risk associated with this glucose lowering agent (HR 0.34, 95 % CI 0.14–0.59; $p < 0.01$); moreover, they presented lower odds for death when using higher doses of metformin (OR 0.23; 95 % CI 0.06–0.78; $p = 0.01$ [1000 mg vs. lower dosages]). In Lombardy, Ojeda-Fernández et al.[40] analyzed 31,966 patients with diabetes and COVID-19 and found a lower risk in overall mortality (OR 0.86; 95 % CI 0.81–0.91) and in-hospital mortality (OR 0.79; 95 % CI 0.74–0.86) associated with metformin use. Tignanelli et al.[41] evaluated the potential mitigating effect of metabolic treatments in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in 26,896 COVID-19 patients, and concluded that the treatment with metformin for the metabolic syndrome was independently associated with all-cause in- and out-of-hospital mortality in COVID-19 (OR 0.52; 95 % CI 0.35–0.77; $p = 0.001$). In Hong Kong, Luk et al.,[42] in a territory-wide retrospective cohort of 1220 COVID-19 patients, showed that preadmission metformin use was linked to a reduced risk of serious outcomes and to a significant reduction of in-hospital death (HR 0.51; 95 % CI 0.27–0.97; $p = 0.039$). Jiang et al.[43] conducted a multicenter retrospective analysis of patients with T2D hospitalized for COVID-19 and verified a non-significant lower death risk at 30 days in those treated with metformin (HR 0.48; 95 % CI 0.13–1.74; $p = 0.2635$). Wang et al.[44] analyzed 39,829 T2D patients treated with metformin or another glucose lowering drug and verified that the prescription of metformin in primary care does not influence susceptibility to COVID-19, neither COVID-19 related mortality (HR 0.89; 95 % CI 0.74–1.07). On the analysis of 9532 United States (US) Veterans with COVID-19, Wallace et al.[45] found a reduced risk of mortality with the maintenance of metformin during

hospitalization (OR 0.35; 95 % CI 0.28–0.45) and with its initiation at admission (OR 0.19; 95 % CI 0.07–0.47) and an increased risk of mortality with its withdrawal (OR 1.54; 95 % CI 1.30–1.82). Orioli et al.[46] analyzed diabetic patients with confirmed COVID-19 and compared survivors to non-survivors, and confirmed that the latter were less often treated with metformin ($p = 0.036$). Finally, Ong et al.[47] showed a significant reduction in odds of death from COVID-19 in patients with T2D treated in-hospital with metformin (OR 0.103; $p = 0.002$) and with home/in-hospital metformin (OR 0.173; $p = 0.005$). Although the lower risk was dose independent (p = 0.002), this study indicated that the greatest benefit was achieved with 1 to 2 g per day (OR 0.252; $p \leq 0.001$) (Fig. 1).

No association between metformin use and the probability of death from COVID-19 in individuals with T2D was found by Oh et al.,[18] nor by Cheng et al..[19] The former showed that even though the odds of developing COVID-19 were lower in patients under metformin (OR 0.70; $p < 0.001$), its use was not related with an in-hospital mortality reduction (OR 1.26; $p = 0.301$). The latter reported that metformin use was significantly related with higher incidence of acidosis (OR 2.45; 95 % CI 1.08–5.54; $p = 0.032$) and lactic acidosis (OR 4.66; 95 % CI 1.45–14.99; $p = 0.010$) particularly in severe COVID-19 presentations, but not with 28-day mortality (HR 0.87; 95 % CI 0.36–2.12; $p = 0.757$).

On the other hand, two different studies revealed an apparent increase of death risk associated with glucose lowering drug use in COVID-19 patients. In South Korea, Do et al.[20] showed that metformin can have a protective effect in the development of COVID-19, but reported higher mortality rates in patients treated with glucose lowering agents (6.4 % [no-treatment] vs. 10.9 % [metformin] vs. 16.8 % [other than metformin]; $p < 0.001$). In the Netherlands, Singh et al.[21] analyzed COVID-19 patients from 30 countries and concluded that metformin use was related to a higher first 3-week death rate (OR 0.02; 95 % CI 0.002–0.04; $p = 0.02$).

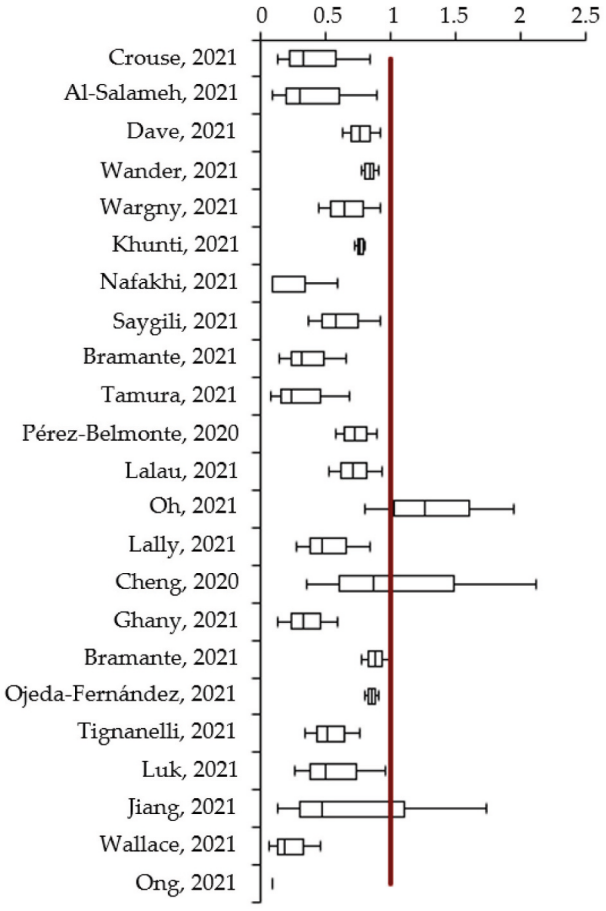

Fig. 1. Association between metformin use and COVID-19 related mortality.

3.2. Metformin and hospital admission for COVID-19

Seven studies assessed the effect of metformin use in hospital admission for COVID-19 and five of them confirmed a significant reduction.

Dave et al.[25] showed that PLWD were significantly more likely to be admitted to hospital by SARS-CoV-2 infection (OR 3.73; 95 % CI 3.53–3.94; $p < 0.0001$), but the use of metformin was linked with a lower risk of hospitalization (OR 0.62; 95 % CI 0.55–0.71; $p < 0.0001$). Nonetheless, no data about metabolic control differences was given, and the authors only admitted that metformin use may reflect less advanced diabetes and fewer complications. Boye et al.[48] analyzed 36,364 insured patients admitted for COVID-19 and concluded that metformin was associated with lower odds of hospitalization (OR 0.78; 95 % CI 0.71–0.86). In another study of ensured patients, Ghany et al.[39] verified that metformin use was linked to a lower hospital admission (HR 0.71; 95 % CI 0.52–0.86; $p = 0.01$), but found no significant effect on the duration of hospitalization (median length of stay for metformin users was 11 days [IQR 5–46] and 14 days [IQR 6–30] for non-users; $p = 0.5$). Ando et al.[49] showed that metformin use was related to a reduction in hospitalization risk (HR 0.61; 95 % CI 0.377–0.987; $p = 0.044$). Tignanelli et al.[41] evaluated the effect of metabolic treatments in NAFLD/NASH patients with SARS-CoV-2 infection and confirmed a reduced risk for hospital admission in patients under metformin (OR 0.81; 95 % CI 0.67–0.98; $p = 0.03$) and statin in ambulatory; other treatments with cardiovascular benefits, such as GLP1-RA and SGLT2, were not associated with decreased odds of admission.

Though describing a reduction in hospital admission, this decrease did not reach statistically significance on the two other studies: Bramante et al.[31] (OR 0.78; 95 % CI 0.58–1.04; $p = 0.087$) and Ojeda-Fernández et al.[40] (OR 0.97; 95 % CI 0.94–1.00) (Fig. 2).

3.3. Metformin and Intensive Care Unit (ICU) admission for COVID-19

Regarding ICU admission, six studies described a lower tendency in patients treated with metformin, although all but one were statistically significant.

Pérez-Belmonte et al.[33] reported that metformin use was related to a reduction on ICU admission of COVID-19 patients (OR 0.78; 95 % CI 0.63–0.96; $p = 0.020$), but only in univariate models. Ojeda-Fernández

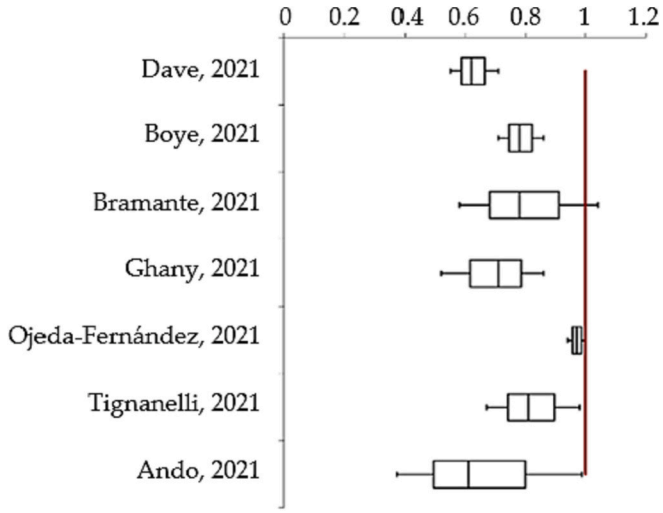

Fig. 2. Association between metformin use and hospital admission for COVID-19.

et al.[40] also found that biguanide use led to a reduction in ICU need (OR 0.78; 95 % CI 0.64–0.95). Luk et al.[42] evaluated the ICU requirement for COVID-19 and verified that preadmission use of metformin was linked to reduced risks of serious outcomes, including lower risk of ICU admission (HR 0.53; 95 % CI 0.33–0.86; $p = 0.010$). In the analysis of 16,504 individuals with T2D and COVID-19, Wang et al.[50] showed that metformin use was related to a reduction in ICU risk of admission (HR 0.88; 95 % CI 0.81–0.97; p = 0.01). In a relatively small multicenter retrospective study, Cheng et al.[51] verified a lower probability of ICU admission in patients treated with metformin in ambulatory (OR 0.04; 95 % CI 0.00–0.99; $p = 0.049$). Lastly, Bramante et al.[31] showed that previous exposure to metformin was related to a non-significant reduction in ICU need of admission (OR 0.68; 95 % CI 0.45–1.02; $p = 0.060$) (Fig. 3).

3.4. Metformin and the need of Invasive Mechanical Ventilation (IMV) in COVID-19 patients

Three studies analyzed the effect of metformin use in the need for IMV. Similarly to the previous findings, Pérez-Belmonte et al.[33] found, in univariate models, a reduction in the need for IMV with metformin preadmission use (OR 0.78; 95 % CI 0.63–0.96; $p = 0.020$). Lalau et al.[34] reported a non-significant reduction for IMV need on day 7 (OR 0.838; 95 % CI 0.649–1.082), but significant on day 28 (OR 0.783; 95 % CI 0.537–0.938; $p = 0.0001$). Luk et al.[42] suggested a possible protective rule of metformin against severe respiratory infection and showed a reduction in risk for IMV need in COVID-19 patients treated with metformin (HR 0.51; 95 % CI 0.27–0.97; $p = 0.041$) (Fig. 4).

3.5. Metformin and Acute Respiratory Distress Syndrome (ARDS) incidence in COVID-19 patients

Metformin use can have a protective role in ARDS incidence in COVID-19 patients. Ghany et al.[39] showed a reduction in ARDS incidence in COVID-19 elderly patients (HR 0.72; 95 % CI 0.52–0.86; $p <$ 0.01). In another study, Jiang et al.[43] concluded that the metformin benefit differs significantly by gender, revealing a lower probability of ARDS in women with SARS-CoV-2 infection (OR 0.13; 95 % CI 0.02–0.80; $p = 0.0276$), but not in men (OR 0.21; 95 % CI 0.03–1.47; $p = 0.1150$). In the analysis of patients from 16 hospitals, Cheng et al.[19] also found a significant reduction in ARDS incidence related to metformin use (0.66; 95 % CI 0.46–0.96; $p = 0.028$) (Fig. 5).

3.6. Metformin and other outcomes in COVID-19

Several studies described other different benefits of metformin use in COVID-19 course and only two identified a potential risk associated with biguanide exposure.

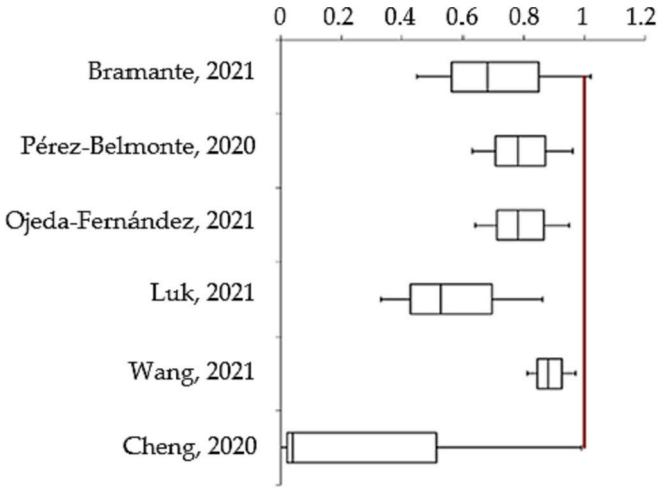

Fig. 3. Association between metformin use and ICU admission for COVID-19.

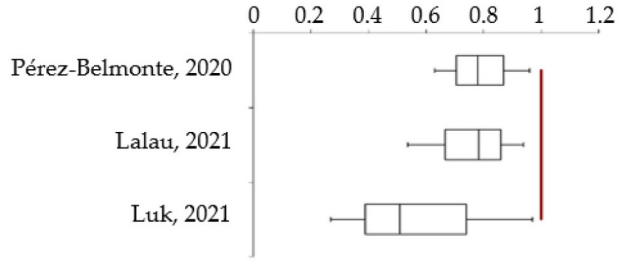

Fig. 4. Association between metformin use and IMV need in COVID-19 patients.

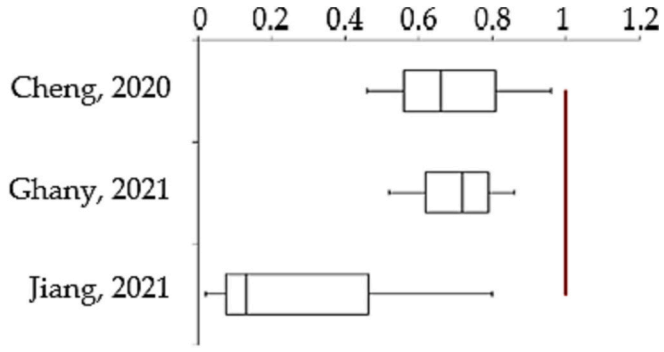

Fig. 5. Association between metformin use and ARDS incidence in COVID-19 patients.

Oh et al.[18] showed that previous metformin use (at least 90 days) was related to a lower COVID-19 incidence among T2D patients (OR 0.70; 95 % CI 0.61–0.80; $p < 0.001$). Wang et al.[44] reported that T2D women taking metformin presented lower susceptibility to SARS-CoV-2 infection (HR 0.68; 95 % CI 0.48–0.96). Tamura et al.[32] verified that previous metformin use was related to a reduced clinical severity at hospital admission ($p = 0.001$). In a small retrospective cohort study, Al-kuraishy et al.[52] analyzed 42 COVID-19 patients and concluded that metformin use was associated with a lower acute lung injury (ALI) and computerized tomography (CT) scan score for COVID-19 ($p = 0.03$). Wargny et al.,[27] in a nationwide multicenter study of patients with diabetes admitted in hospital for COVID-19, found that metformin was independently associated with a favorable outcome, being related to a higher chance of survival (OR 1.40; 95 % CI 1.08–1.81).

Opposite to the previous findings, Yitao et al.[53] concluded that metformin was associated with greater clinical deterioration (OR 3.961; 95 % CI 1.020–15.368; $p = 0.047$). Similarly, Gao et al.[54] concluded that metformin use was related to increasing probability of severe disease during hospitalization and to a higher risk of disease progression (OR 3.964; 95 % CI 1.034–15.194; $p = 0.045$).

4. Discussion

Our review intended to clarify the potential association between metformin use and COVID-19 evolution. This review indicates that there may be a protective effect of metformin on COVID-19 patients, from decreasing incidence or susceptibility to SARS-CoV-2 infection (Oh et al.[18] and Wang et al.[44]), to the need for hospital or ICU admission or even lowering mortality risk.[16,21–44] Nevertheless, we cannot ignore the studies that point out an eventual risk association with higher clinical deterioration (Yitao et al.[53]), increased risk of disease progression (Gao et al.[54]), no-association with mortality (Oh et al.[18] and Cheng et al.[19]), or

even greater chance of death (Singh et al.[21] and Do et al.[20]). Moreover, it is important to acknowledge that the vaccination status was not evaluated.

All articles reviewed were retrospective studies, leading to an intrinsic limitation – being subject to recall or misclassification bias, confounding factors and could not determine the precise cause-effect relationship, but only the existence of an eventual association. With respect to sample size, only one study had <50 participants,[52] 22 > 1000, 11 > 10,000 and one without any reference to the number of patients.[21] When it comes to the number of COVID-19 patients with a history of metformin use, 9 studies presented <50 patients, 16 > 500, 12 > 1000.

Concerning mortality related to COVID-19, metformin use is consistently related to a reduction, except in two studies: Singh et al.[21] revealed an increasing risk with the biguanide, but there is no data about number of participants, only that the results comprise the analysis of participants from 30 countries; and Do et al.[20] showed, in the analysis of 1865 COVID-19 patients and 469 with history of metformin exposure, that the use of glucose lowering drugs was related to a higher risk of death, but no difference between antidiabetic groups was specified.

It is also important to consider that the hospital admission reflects disease severity that could be translated in renal or hepatic impairment witch are contraindications for metformin use, leading to its withdrawal; thus, it is plausible to assume that SARS-CoV-2 severity led to increased mortality and not the metformin withdrawal.

On the other hand, metformin use was also related with better outcomes in COVID-19 patients, apart from two studies: Gao et al.[54] admitted a higher risk of disease progression associated with metformin use in a small analysis of 110 COVID-19 patients, 46 of them exposed to metformin; and Yitao et al.[53] reported a greater clinical deterioration, but only 9 of the 257 COVID-19 patients analyzed were treated with metformin.

Taking on consideration those findings, it is plausible to assume that metformin might have a beneficial role in COVID-19 course, suggesting a possible role of this biguanide against severe respiratory tract infections; yet it is not possible to ignore the eventual risks presented by some studies, though with less robust design. Regarding this potential benefit, it is crucial to consider that it is possible that metformin use may reflect less advanced diabetes and subsequently lower risk of complications.

Moreover, it is of high importance to highlight the potential sex dependent benefits exhibited by metformin use.[17,43] This significant gender difference may be explained by a higher up-regulation of the protein expression of interleukin-10 (IL-10) and decreased tumor necrosis factor alpha (TNF-α) by metformin in females than in males.

Lastly, one of the major considerations expected from our review was related to metformin dosage: to investigate whether there is any dose-dependent effect in COVID-19 disease course. Only two studies approached this question: Ghany et al.[39] showed more expressive reduction with 1000 mg daily compared with lower doses of metformin; and Ong et al.[47] verified the greatest benefit with 1000 to 2000 mg of metformin per day, but the analysis of metformin users showed no association between metformin dose and COVID-19 mortality. Unfortunately, none of the reports have surfaced recommendations nor suggestions on what it concerns to an optimal protective dose of metformin. It is also important to highlight that none of the studies showed data about neither therapeutic adherence, nor to explicit duration of metformin use, nor about continuation or discontinuation at hospital admission.

The molecular mechanism responsible for the potential protective role of metformin in COVID-19 remains unclear. It is known that SARS-CoV-2 enters the human epithelial cells by binding to ACE-2, but what triggers the cytokine storm that leads to severe COVID-19 presentation and outcomes remains unknown. Theoretically, metformin could decrease SARS-CoV-2 binding to ACE-2 by altering the conformation and function of the latter through AMPK activation or even that this activation could inhibit the unadjusted inflammatory response. Furthermore, metformin may decrease TNF-α by up-regulation of IL-10. This reduction appears to be potentially higher in women than in men, leading to a gender-dependent protective mechanism. Finally, the inhibition of mTOR by metformin activation of AMPK could lead to a reduction in SARS-CoV-2 infectivity and subsequently mortality.

In the future, randomized controlled trials should be conducted to confirm or refute the protective role of metformin against COVID-19 and to clearly assess dosage, posology, minimal exposure/treatment duration and potential in-hospital use.

5. Conclusions

Metformin use seems to be associated with reduced risk for mortality in COVID-19 patients. Being linked to a diminished need for hospital and ICU admission and to a lower incidence of ARDS or IMV need, metformin also appears to lead to a potential reduction in SARS-CoV-2 infection incidence and disease progression. However, the contradictory results cannot be ignored, nor can potential confounding factors be excluded. The use and management of metformin in COVID-19 patients need to be individually assessed and physicians have to carefully evaluate the risks and benefits of its use in COVID-19 patients. Prospective randomized control trials are mandatory to appraise the effect of metformin treatment in COVID-19 patients, with special focus on time of exposure, duration of treatment, dosage and potential mechanisms of action.

CRediT authorship contribution statement

Conceptualization, A.R.P. and D.C.M.; methodology, A.R.P.; software, A.R.P.; validation, A.R.P.; formal analysis, A.R.P.; investigation, A.R.P.; resources, A.R.P.; data curation, A.R.P.; writing—original draft preparation, A.R.P.; writing—review and editing, D.C.M., M.R. and J.S.N.; visualization, A.R.P.; supervision, D.C.M. and J.S.N.; project administration, D.C.M. and J.S.N. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

Not applicable.

Informed consent statement

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability statement

Not applicable.

Appendix A

Table 1
Characteristics of included studies. Comparison of metformin effect on COVID-19 mortality in the included studies.

Author	Country	Design	Data Collection	Participants	COVID-19 Patients	Metformin Users	Mortality in COVID-19	HR/OR
Crouse, 2021	USA	Retrospective	25/02 - 22/06/2020	25 326	604	76	Lower	OR 0.33; 95% CI 0.13-0.84; p = 0.0210
Blanc, 2020	France	Retrospective	02/03 - 08/04/2020	179	89	13 (COVID-19)	Lower	OR unknown; p = 0.0237
Al-Salameh, 2021	France	Retrospective	24/01 - 23/05/2020	145	145	90	Lower	OR 0.31; 95% CI 0.10-0.90; p = 0.04
Dave, 2021	South Africa	Retrospective	04/03 - 15/07/2020	64 476	64 476	Unknown	Lower	OR 0.77; 95% CI 0.64-0.92; p < 0.0001
Wander, 2021	USA	Retrospective	01/03/2020 - 10/03/2021	64 892	64 892	29 685	Lower (30 days) Lower (in follow-up)	OR 0.84; 95% CI 0.78-0.91 HR 0.84; 95% CI 0.79-0.89
Wargny, 2021	France	Retrospective	10/03 - 10/04/2020	2 796	2 796	1 553	Lower (28-day)	OR 0.65; 95% CI 0.45-0.93
Khunti, 2021	UK	Retrospective	16/02 - 31/08/2020	2 851 465	13 479 (deaths)	1 800 005	Lower	HR 0.77; 95% CI 0.73-0.81
Nafakhi, 2021	France	Retrospective	20/08 - 05/10/2020	192	192	35	Lower (in-hospital)	OR 0.1; 95% CI 0.1-0.6; p = 0.025
Saygili, 2021	Ireland	Retrospective	12/03 - 22/12/2020	586	586	432	Lower (in-hospital) Lower (post-discharge) Lower (overall)	HR 0.568; 95% CI 0.306-1.052; p = 0.072 HR 0.652; 95% CI 0.324-1.310; p= 0.23 HR 0.585; 95% CI 0.371-0.920; p = 0.020
Bramante, 2021	USA	Retrospective	04/03 - 04/12/2020	9 555	9 555	676	Lower	OR 0.32; 95% CI 0.15-0.66; p = 0.002
Tamura, 2021	Brazil	Retrospective	10/03 - 13/11/2020	1 083	1 083	231	Lower (in-hospital)	HR 0.248; 95% CI 0.089-0.685
Pérez-Belmonte, 2020	Spain	Retrospective	01/03 - 19/07/2020	2 666	2 666	1 618	Lower (in-hospital)	OR 0.73; 95% CI 0.58-0.90; p = 0.004
Lalau, 2021	France	Retrospective	10/03 - 10/04/2020	2 449	2 449	1 496	Lower (7-day) Lower (28-day)	OR 0.688; 95 CI 0.470-1.007; p < 0.0001 OR 0.710; 95% CI 0.537-0.938; p < 0.0001
Li, 2020	China	Retrospective	23/01 - 19/03/2020	131	131	37	Lower	5.4 *vs.* 22.3 %; p = 0.0222
Luo, 2020	China	Retrospective	27/01 - 24/03/2020	283	283	104	Lower	2.9 vs. 12.3 %; p = 0.01
Oh, 2021	South Korea	Retrospective	01/01 - 04/06/2020	27 493	2 047	7 204	Not associated	OR 1.26; 95% CI 0.81-1.95; p = 0.301
Lally, 2021	USA	Retrospective	01/03 - 13/05/2020	775	775	39	Lower (30 days)	HR 0.48; 95% CI 0.28-0.84
Cheng, 2020	China	Retrospective	30/12/2019 - 13/04/2020	1 213	1 213	535	Not associated (28-day)	HR 0.87; 95% CI 0.36-2.12; p = 0.757
Ghany, 2021	USA	Retrospective	01/01 - 14/08/2020	1 139	1 139	392	Lower Lower (1000 mg *id vs.* lower doses)	HR 0.34; 95% CI 0.14-0.59; p < 0.01 OR 0.23; 95% CI 0.06-0.78; p = 0.01
Bramante, 2021	USA	Retrospective	01/01 - 01/07/2020	6 256	6 256	3 923	Lower in women Not associated	HR 0.79; 95% CI 0.64-0.98; p = 0.03 HR 0.884; 95% CI 0.778-1.003; p = 0.056

Author	Country	Design	Data Collection	Participants	COVID-19 Patients	Metformin Users	Mortality in COVID-19	HR/OR
Ojeda-Fernández, 2021	Italy	Retrospective	15/02 – 15/03/2021	31 966	31 966	23 327	Lower (all-mortality) Lower (in-hospital)	OR 0.86; CI95 0.81-0.91 OR 0.79; 95% CI 0.74-0.86
Tignanelli, 2021	USA	Retrospective	01/03/2020 - 26/01/2021	26 896	26 896	1 057	Lower	OR 0.52; 95% CI 0.35-0.77; p = 0.001
Do, 2021	South Korea	Retrospective	01/02 - 15/05/2020	1 865	1 865	469	Higher with glucose lowering medication	6.4 *vs.* 10.9 (Metformin) *vs.* 16.8 % (other than Metformin); p < 0.001
Li, 2021	China	Retrospective	23/01 - 19/03/2020	131	131	37	Lower	2 (Metformin) *vs.* 21 (another glucose lowering drug) *vs.* 42.6% (w/o treatment); p = 0.0222
Luk, 2021	China	Retrospective	23/01/2020 - 28/02/2021	1 220	1 220	737	Lower (in-hospital)	HR 0.51; 95% CI 0.27-0.97; p = 0.039
Jiang, 2021	China	Retrospective	31/12/2019 – 31/03/2020	328	328	100	Lower (30 days)	HR 0.48; 95% CI 0.13-1.74; p = 0.2635
Wang, 2021	UK	Retrospective	30/01 - 13/10/2020	39 829	603	29 558	Lower	HR 0.89; 95% CI 0.74-1.07
Wallace, 2021	USA	Retrospective	10/12/2020 (unclear)	9 532	9 532	Not specified	Lower (starting Metformin) Lower (maintaining Metformin) Higher (withdrawal of Metformin)	OR 0.19; 95% CI 0.07-0.47 OR 0.35; 95% CI 0.28-0.45 OR 1.54; 95% CI 1.30-1.82
Orioli, 2021	Belgium	Retrospective	01/03 - 06/05/2020	73	73	48	Non-survivors - less often treated with Metformin	p = 0.036
Ong, 2021	Philippines	Retrospective	01/03 - 30/09/2020	355	355	186	Lower (in-hospital Metformin) Lower (at home and in-hospital Metformin)	OR 0.103; p = 0.002 OR 0.173; p = 0.005
Singh, 2020	The Netherlands	Retrospective	Unknown	Unknown	Unknown	Unknown	Higher (first 3 weeks)	OR 0.02; 95% CI 0.002-0.04; p = 0.02

95 % CI, 95 % confidence interval; HR, hazard ratio; OR, odds ratio.

Table 2
Characteristics of included studies. Comparison of metformin effect in other disease outcomes: incidence, progression, hospital and ICU admission, IMV need, ARDS and ALI, in the included studies.

Author	Country	Design	Data Collection	Participants	COVID-19 Patients	Metformin Users	Outcome	HR/OR
Gao, 2020	China	Retrospective	31/01 - 20/03/2020	110	110	56	Higher risk of disease progression	OR 3.964, 95% CI 1.034-15.194; p= 0.045
Dave, 2021	South Africa	Retrospective	04/03 - 15/07/2020	64 476	64 476	Unknown	Lower hospital admission	OR 0.62; 95% CI 0.55-0.71; p < 0.0001
Boye, 2021	USA	Retrospective	01/01/2019 - 15/07/2020	36 364	36 364	4 250	Lower hospital admission	OR 0.78; 95% CI 0.71-0.86
Wargny, 2021	France	Retrospective	10/03 - 10/04/2020	2 796	2 796	1 553	Higher chance of discharge	OR 1.40; 95% CI 1.08-1.81
Bramante, 2021	USA	Retrospective	04/03 - 04/12/2020	9 555	9 555	676	Lower hospital admission Lower ICU admission	OR 0.78; 95% CI 0.58-1.04; p = 0.087 OR 0.68; 95% CI 0.45-1.02; p = 0.060
Tamura, 2021	Brazil	Retrospective	10/03 - 13/11/2020	1 083	1 083	231	Reduced clinical severity	P = 0.001
Pérez-Belmonte, 2020	Spain	Retrospective	01/03 - 19/07/2020	2 666	2 666	1 618	Lower ICU admission or IMV need Lower in-hospital complications	OR 0.78; 95% CI 0.63-0.96; p = 0.020 OR 0.76; 95% CI 0.62-0.94; p = 0.011
Lalau, 2021	France	Retrospective	10/03 - 10/04/2020	2 449	2 449	1 496	Lower IMV need (7-day) Lower IMV need (28-day)	OR 0.838; 95% CI 0.649-1.082; p = 0.0001 OR 0.783; 95% CI 0.537-0.938; p = 0.0001
Oh, 2021	South Korea	Retrospective	01/01 - 04/06/2020	27 493	2 047	7 204	Lower incidence of COVID-19	OR 0.70; 95% CI 0.61-0.80; p < 0.001
Cheng, 2020	China	Retrospective	30/12/2019 - 13/04/2020	1 213	1 213	535	Lower incidence of ARDS Higher acidosis Higher lactic acidosis	HR 0.66; 95% CI 0.46-0.96; p= 0.028 HR 2.45; 95% CI 1.08-5.54; p= 0.032 HR 4.66; 95% CI 1.45-14.99; p = 0.010
Ghany, 2021	USA	Retrospective	01/01 - 14/08/2020	1 139	1 139	392	Lower incidence of ARDS Lower hospital admission Lower duration of admission 11 *vs.* 14 days	HR 0.72; 95% CI 0.52-0.86; p < 0.01 HR 0.71; 95% CI 0.52-0.86; p = 0.01 p = 0.5
Ojeda-Fernández, 2021	Italy	Retrospective	15/02 – 15/03/2021	31 966	31 966	23 327	Lower hospital admission Lower ICU admission	OR 0.97; 95% CI 0.94-1.00 OR 0.78; 95% CI 0.64-0.95
Tignanelli, 2021	USA	Retrospective	01/03/2020 - 26/01/2021	25 962	25 962	1 057	Lower hospital admission (w/o alcohol abuse)	OR 0.81; 95% CI 0.67-0.98; p = 0.03
Ando, 2021	Japan	Retrospective	01/01 - 30/11/2020	28 095	28 095	668	Lower hospital admission	HR 0.61; 95% CI 0.377-0.987; p = 0.044
Luk, 2021	China	Retrospective	23/01/2020 - 28/02/2021	1 220	1 220	737	Lower ICU admission Lower IMV need	HR 0.53; 95% CI 0.33-0.86; p = 0.010 HR 0.51; 95% CI 0.27-0.97; p = 0.041
Wang, 2021	USA	Retrospective	01/01/2017 - 11/06/2020	16 504	16 504	6 504	Lower ICU admission	HR 0.88; 95% CI 0.81-0.97; p = 0.01
Cheng, 2021	China	Retrospective	19/01 - 09/04/2020	407	407	40	Lower ICU admission	OR 0.04; 95% CI 0.00-0.99; p = 0.049
Al-kuraishy, 2021	Iraq	Retrospective	Unknown	42	42	22 (850 mg *tid*)	Lower ALI and CT scan score percentage for COVID-19	30.62 ± 10.64 *vs.* 36.31 ± 5.03; p = 0.03
Jiang, 2021	China	Retrospective	31/12/2019 – 31/03/2020	328	328	100	Lower ARDS in women	OR 0.13; 95% CI 0.02-0.80; p = 0.0276
Wang, 2021	UK	Retrospective	30/01 - 13/10/2020	39 829	603	29 558	Lower susceptibility to COVID-19 in women taking Metformin	HR 0.68; 95% CI 0.48-0.96
Yitao, 2021	China	Retrospective	23/01 - 21/03/2020	257	257	9	Higher clinical deterioration	OR 3.961; 95% CI 1.020-15.368; p = 0.047

95 % CI, 95 % confidence interval; ALI, acute lung injury; ARDS, Acute Respiratory Distress Syndrome; CT, computarized tomography; HR, hazard ratio; ICU, Intensive Care Unit; IMV, Invasive Mechanical Ventilation; OR, odds ratio; w/o, without.

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