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Metformin and Covid-19: a systematic review of systematic reviews with meta-analysis

Fabio Petrelli[1], Iolanda Grappasonni[1], Cuc Thi Thu Nguyen[2], Marina Tesauro[3], Paola Pantanetti[4], Sonila Xhafa[5], Giovanni Cangelosi[4]

[1]School of Medicinal and Health Products Sciences, University of Camerino, Camerino, Italy; [2]Department of Pharmaceutical Administration and Economics, Hanoi University of Pharmacy, Hanoi, Vietnam; [3]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy; [4]Units of Diabetology, ASUR Marche, Fermo, Italy; [5]School of Science and Technology, University of Camerino, Camerino, Italy.

Abstract. *Introduction:* the COVID-19 infection, caused by severe Coronavirus 2 syndrome (Sars-Cov-2), immediately appeared to be the most tragic global pandemic event of the twentieth century. Right from the start of the pandemic, diabetic patients treated with metformin experienced a reduction in mortality and complications from COVID-19 compared to those with different treatments or no treatment. *Objective:* The main objective of the study was to observe the effects of metformin in diabetic hospitalized subjects infected with COVID-19. Specifically, the outcomes of hospitalization in Intensive Care Units or death were examined. *Materials and Methods:* A specific research PICOS was developed and the Pubmed, Embase and Scopus databases were consulted down to April 30, 2022. To estimate the extent of the metformin effect and risk of severity in SARS-CoV-2 infection, the Odd Ratio (OR) with 95% Confidence Interval (CI) published by the authors of the selected systematic reviews was used. *Results***:** from five systematic reviews 36 studies were selected. The final meta-analysis showed that thanks to treatment with metformin, Type II Diabetes (DM2) patients affected by COVID-19 had protection against risk of disease severity, complications (SE 0.80; CI 95%: 0.61 - 0.78; I^2: 70.5%) and mortality (SE 0.69; CI 95%: 0.65 - 0.98; I^2: 53,6%). *Conclusions:* More in-depth studies on the use of metformin, compared to other molecules, may be required to understand the real protective potential of the drug against negative outcomes caused by COVID-19 infection in DM2 patients. (www.actabiomedica.it)

Key words: Metformin, COVID-19, Type II diabetes (DM2), Systematic Review

Introduction

The COVID-19 infection, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov-2), immediately appeared to be the most tragic global pandemic event of the twentieth century (1). With almost half a billion infections (data from 5 April 2022) and over six million deaths, about two years after its worldwide spread it reached dimensions that were difficult to control (1,2). Type II diabetes mellitus (DM2) is one of the commonest chronic diseases in the world and one of those involving the greatest risk of permanent disability (3). From the first moments of the pandemic it immediately became clear that the presence of severe comorbidities such as arterial hypertension, chronic obstructive bronchitis, immunosuppression but above all DM2, were an unfavorable prognostic element for the evolution of COVID-19 (4,5). Patients with DM2 and COVID-19 are twice as likely to develop severe disease or die as the rest of the population (6). Metformin represents the first-choice molecule for diabetic subjects, also due to the ease of supply even in low-middle-income countries (7). Right from the start of the pandemic, diabetic patients on

metformin experienced a reduction in mortality and complications from Covid-19 compared to those with different treatments or no treatment (8).

Objective

The main objective of the study was to observe the effects of metformin in diabetic subjects infected with COVID-19. Specifically, the outcomes of hospitalization in Intensive Care Units or death were examined.

Materials and methods

The systematic review of systematic reviews was conducted with the preliminary development of a research protocol. In accordance with the Guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Prisma Method (9,10), the selected systematic reviews satisfied, prior to inclusion, the CASP Critical Appraisal Skills Program (11). The study involved the participation of two researchers for selection of studies to be included and a third expert to be involved in case of disputes (Flow Chart selection summarized in Figure 1). A specific research PICOS was developed:

- P: patients with DM2
- I: Metformin
- C: Metformin vs. other drugs vs. no drugs
- O: severity/mortality
- S: systematic review

The Pubmed, Embase and Scopus databases were consulted with a time limit of 30 April 2022 and the texts must have been published in English. The keywords used were the following:"COVID-19 stress syndrome", "COVID-19 post-intensive care syndrome", "COVID-19", "SARS-CoV-2", "adult multisystem inflammatory disease, COVID-19 related", "post-acute COVID-19 syndrome", "spike protein, SARS-CoV-2", "SARS-CoV-2 variants", "COVID-19 drug treatment", "Biguanides", "Metformin", "Review" and "Systematic Review". To estimate the extent of the effect of metformin and risk of severity in SARS-CoV-2 infection, the Odd Ratio (OR) with 95% Confidence Interval (CI) published by the authors of the selected systematic reviews was used. For study heterogeneity, the Q-test and the Higgins heterogeneity index (I^2) were used (12). We used random-effects weighted models to pool the specific effect sizes and their 95% CI if I^2 was >50%, while the fixed-effects weighted models were used if I^2 was ≤ 50%. The study included in final meta-analysis the study included after confront and analysis single systematic review included in the overview. The evaluation was supported of the CASP Critical Appraisal Skills Program (11). The meta-analysis was supported with free software ProMeta 3.0.

Results

Were included 5 Systematic Reviews, summarized in Table 1.

Lukito AA et al (13) performed a systematic review and meta-analysis of prospective and/or retrospective observational studies with a time limit of September 5, 2020. The main stated objective of the study was to analyze relevant mortality outcomes of

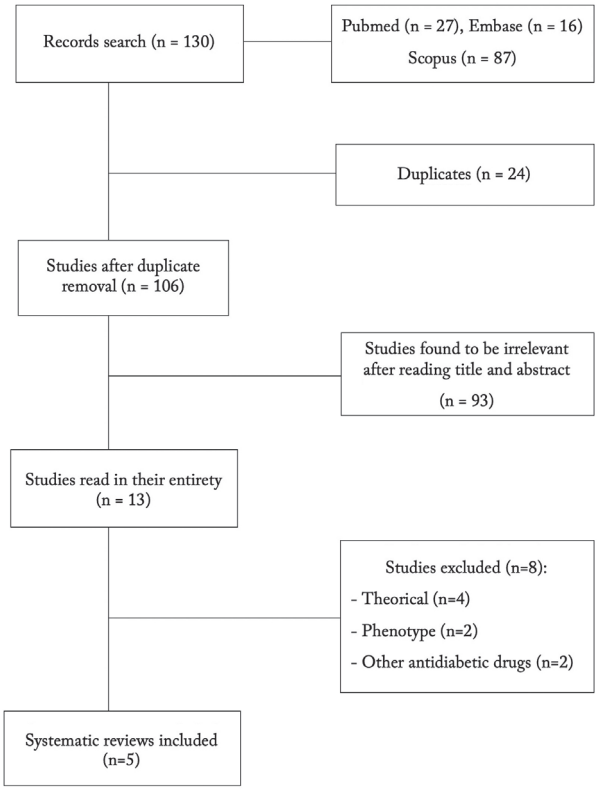

Figure 1. Selection Flow Chart

Table 1. Summary of systematic reviews included

Study	Materials and Methods	Results
Lukito AA et al (13) / 2020	Systematic review and meta-analysis of prospective and/or retrospective observational studies down to September 5, 2020	Nine studies with 10,233 subjects were included. Meta-analysis showed that metformin was associated with lower mortality in both the unadjusted model (OR 0.45 [0.25 - 0.81], p = 0.008; I^2: 63.9%, p = 0.026) and the adjusted one (OR 0.64 [0.43 - 0.97], p = 0.035; I^2: 52.1%, p = 0.064)
Oscanoa TJ et al (14) / 2021	Systematic review and meta-analysis of prospective and/or retrospective observational studies down to January 2021	Thirty-two studies with a total of 44,306 patients were included (18 controls, 12 cohorts, and 2 cross-sectional studies). In 22 studies, metformin was associated with a reduced risk of mortality (OR = 0.56, 95% CI: 0.46 - 0.68, p < 0.001) but in 15 studies, metformin was not significantly associated with disease severity (OR = 0.85, 95% CI: 0.71 - 1.02, p = 0.077)
Kan C et al (15) / 2021	Systematic review and meta-analysis prospective and/or retrospective observational studies down to February 2, 2021	Eighteen studies with 17,338 patients were included in the meta-analysis. Metformin (pooled OR, 0.69; p = 0.001) and sulfonylureas (pooled OR, 0.80; p = 0.016) were associated with lower mortality risk in patients with DM2 and COVID-19
Li Y et al (16) / 2021	Systematic review and meta-analysis of prospective and/or retrospective observational studies down to February 18, 2021	Twenty-eight studies with 2,910,462 participants were included. Meta-analysis of 19 studies showed that metformin was associated with a 34% lower COVID-19 mortality [OR 0.66; 95% CI, 0.56 - 0.78; I^2 = 67.9%] and 27% lower hospitalization rate (pooled OR, 0.73; 95% CI, 0.53 - 1.00; I^2 = 16.8%)
Yang W et al (17) / 2021	Systematic review and meta-analysis of prospective and/or retrospective observational studies down to June 6, 2021	Seventeen studies with 20,719 patients were included. The results showed that metformin is associated with reduced mortality and severity in patients with DM2: OR = 0.64, 95% CI = 0.51 - 0.79 for mortality and OR = 0.81, 95% CI = 0.66 - 0.99 for severity

diabetic patients with COVID-19 treated with metformin. In the reported qualitative/quantitative summary 9 studies with 10,233 subjects were included and the meta-analysis showed that metformin is associated with lower mortality both in the unadjusted model (OR 0.45 [0.25 - 0.81], p = 0.008; I^2: 63.9%, p = 0.026) and in the adjusted one (OR 0.64 [0.43 - 0.97], p = 0.035; I^2: 52.1%, p = 0.064). Oscanoa TJ et al (14) developed a systematic review and meta-analysis of prospective and/or retrospective observational studies down to January 2021. With this review, they aimed to observe outcomes of an association between the use of metformin in diabetic patients and mortality and severity from SARS-CoV-2 infection. Thirty-two studies with a total of 44,306 patients were included (18 controls, 12 cohorts, and 2 cross-sectional studies). In 22 studies, metformin was associated with a reduced risk of mortality (OR = 0.56, 95% CI: 0.46-0.68, p < 0.001) but in 15 there was no statistically significant finding regarding disease severity (OR = 0.85, 95% CI: 0.71-1.02, p = 0.077). In the systematic review and meta-analysis of prospective and/or retrospective observational studies performed by Kan C et al (15) down to February 2, 2021, the main objective declared by the authors was to analyze the results of the association of various antidiabetic drugs (including metformin) with mortality in patients with DM2 and COVID-19. In the meta-analysis, 18 studies with 17,338 patients were pooled. Metformin (pooled OR 0.69; p = 0.001) and sulfonylureas (pooled OR 0.80; p = 0.016) were associated with a lower risk of mortality in patients with DM2 and COVID-19. Li Y et al (16) performed a systematic review and meta-analysis of prospective and/or retrospective observational studies with a time limit of February 18, 2021. This study aimed to analyze outcomes on the benefits and risks of metformin in patients with COVID-19. Twenty-eight studies with 2,910,462 participants were entered. Meta-analysis of 19 studies showed that metformin is associated with a 34% lower COVID-19 mortality (OR 0.66; 95% CI, 0.56-0.78; I^2 = 67.9%) and that the hospitalization rate is 27% lower (pooled OR, 0.73; 95% CI, 0.53-1.00; I^2 = 16.8%). In the systematic review and meta-analysis of prospective and/

or retrospective observational studies by Yang W et al (17) relevant outcomes were sought regarding diabetic patients with COVID-19 treated with metformin. With a time limit of June 6, 2021, 17 studies with 20,719 COVID-19 patients with DM2 were included. The results showed that metformin is associated with reduced mortality and severity in patients with DM2 (OR = 0.64, 95% CI = 0.51-0.79 for mortality and OR = 0.81, 95% CI = 0.66 - 0.99 for severity).

Were included in the meta-analysis 36 studies screened from Systematic Review selected, summarized in Table 2.

Table 2. Summary of studies included in the meta-analysis

Study	Sample	OR Mortality (95% CI)	OR Severity (95% CI)
	411	0.19 (0.05 - 0.70)	
Cariou B et al (19) / Prospective / France	1317; 746 vs. 571	0.59 (0.42 - 0.84)	
Bramante BT et al (20) / Retrospective / USA	6256	0.802 (0.701 - 0.917)	
Bramante BT et al (21) Retrospective / USA	6256	0.80 (0.70 - 0.92)	
Bramante BT et al (22) Retrospective / USA	6256; 2333 vs. 3923	0.91 (0.78 -1.06)	
Chen Y et al (23) / Retrospective / USA	120; 43 vs. 77	0.42 (0.13 - 1.37)	2.49 (0.92 - 6.76)
Crouse A et al (24) / Retrospective / USA	239	0.38 (0.17 - 0.87)	
Kim MK et al (25) / Retrospective / South Corea	235	0.36 (0.10 - 1.23)	0.48 (0.19 -1.24)
Luo P et al (26) / Retrospective / China	283; 104 vs. 179	4.36 (1.22 - 15.59)	0.79 (0.45 - 1.39)
Philipose Z et al (27) / Retrospective / UK	159	1.39 (0.84 - 2.16)	
Cheng X et al (28) / Retrospective / China	1213; 687 vs. 535	1.65 (0.71 - 3.86)	0.66 (0.46 - 0.96)
Mirani M et al (29) / Case series / Italy	90; 69 vs. 21	0.35 (0.13 - 0.96)	0.37 (0.08 -1.80)
Jiang N et al (30) / Retrospective / China	328	0.48 (0.13 - 1.74)	0.18 (0.05 - 0.62)
Gao Y et al (31) / Case series / China	110		3.96 (1.03 - 15.19)
Lally MA et al (32) / Case series / USA	755	0.48 (0.28 - 0.84)	
Perez-Belmonte LM et al (33) / Case series / Spain	1488	0.72 (0.58 - 0.90)	0.78 (0.63 - 0.96)
Wang B et al (349 / Cohort Study / USA	58	0.35 (0.04 - 3.04)	
Wang J et al (35) / Cohort Study / UK	10183 vs.10183	0.87 (0.34 - 2.20)	
Yan H et al (36) / Cohort Study / China	58		0.98 (0.35 - 2.60)
Hippisley-Cox J et al (37) / Prospective / UK	19486		1.02 (0.81 - 1.28)
Shestakova SV et al (38) / Case series / Russia	309	0.33 (0.17 - 0.61)	
Sourij H et al (39) / Prospective / Austria	238	0.59 (0.30 - 1.16)	
Li J et al (40) / Case series / China	131	0.20 (0.04 - 0.90)	0.71 (0.24 - 2.08)
Do JY et al (41) / Case series / South Corea	564	0.60 (0.33 - 1.11)	
Liu Z et al (42) / Cohort Study / China	64		0.14 (0.01 - 1.50)
Nafakhi H et al (43) / Case series / Iraq	50	0.13 (0.02 - 0.67)	
Goodall JW et al (44) / Cohort Study / UK	981	0.95 (0.69 - 1.31)	
Lalau et al (45) / Case series / France	2449; 1496 vs. 953	0.47 (0.39 - 0.58)	0.92 (0.69 - 1.21)
Orioli L et al (46) / Case series / Belgium	68	0.22 (0.06 - 0.87)	
Cernigliaro A et al (47) / Cohort Study / Italy	172	0.42 (0.22 - 0.80)	0.78 (0.34 - 1.82)
Ramos-Rincon JM et al (48) / Prospective / Spain	790	1.03 (0.78 - 1.36)	
Wargny M et al (49) / Prospective / France	2794; 1553 vs. 1241	0.63 (0.52 - 0.77)	
Mirsoleymani S et al (50) / Retrospective / Iran	36 vs. 69	0.39 (0.12 - 1.22)	
Khunti K et al (51) / Cohort Study / UK	1800005 vs. 2851465	0.77 (0.73 - 0.81)	
Ghany R et al (52) / Retrospective / USA	1139	0.35 (0.17 - 0.71)	0.80 (0.66 - 1.25)
Oh TK et al (53) / Cohort Study / South Corea	2047	1.26 (0.81 - 1.95)	

Of the 36 studies included, 8 were conducted in the USA, 6 in the UK, 7 in China, 3 each in France and South Korea, 2 each in Spain and Italy, and 1 each in Belgium, Iran, Iraq, Austria and Russia. Twelve retrospective, 5 prospective, 10 control and 8 cohort studies were performed. The sample with the highest number of subjects included was that of the study by Khunti K et al51 with 1,800,005 cases and 2,851,465 controls, followed by Wang J et al (35) with 10,183 cases and controls and Hippisley-Cox J et al (37) with 19,486 overall subjects. Studies with smaller sample sizes (< 100) were the following: Orioli L et al (46) with 68 patients, Liu Z et al (42) with 64, Yan H et al (36), Wang B et al (34) with 58 and Nafakhy H et al (43) with 50 samples. The studies by Luo P et al (26) and Cheng X et al (28) gave the highest OR values for mortality, respectively 4.36 (1.22 - 15.59) and 1.65 (0.71 - 3.86), while the study by Nafakhy H et al (43) yielded the most protective values 0.13 (0.02 - 0.67), followed by Abu-Jamous B et al (18) with 0.19 (0.05 - 0.70), Li J et al (40) with 0.20 (0.04 - 0.90) and Orioli L et al (46) with 0.22 (0.06 - 0.87). As regards severity, the highest risk values were found in the study by Gao Y et al (31) with 3.96 (1.03 - 15.19) while the study by Liu Z et al (42) gave the highest protective ones with 0.14 (0.01 - 1.50).

However, the final meta-analysis (Figure 2 and 3) revealed that thanks to treatment with metformin, patients with DM2 affected by COVID-19 found protection regarding the risk of severity and complications (SE 0.80; CI 95%: 0.61 - 0.78; I^2: 70.5%) and mortality (SE 0.69; CI 95%: 0.65 - 0.98; I^2: 53,6%) compared to untreated or differently treated subjects.

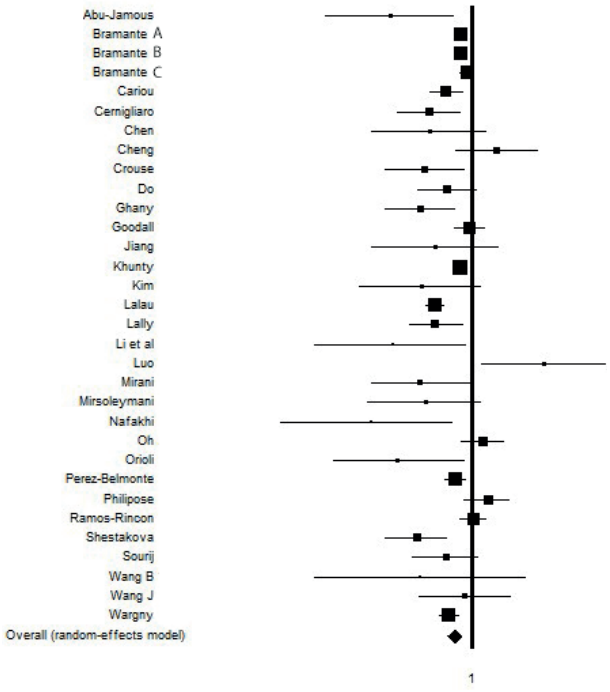

Figure 2. Forest Plot of metformin use and risk of mortality in SARS-CoV-2 infection.

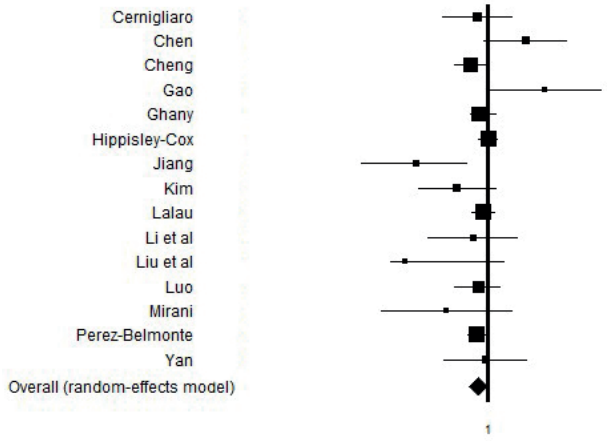

Figure 3. Forest Plot of metformin use and risk of severity in SARS-CoV-2 infection.

Conclusions

The most evident limitation our study is the insertion, in the systematic reviews included, studies carried out during the emergency period that had not always completed a rigorous peer-review process. This certainly influenced the result of the individual systematic reviews included in the study and probably the proposed Overview. Given the importance of the topics covered and the extremely high number of data collected, it was decided, in order to reach the best possible conclusions, to use all possible information present in the systematic reviews included. It highlights the fact that a widespread and easy-to-implement treatment such as Metformin, even in economically and socially disadvantaged contexts, can reduce the risk of severe complications or death in subjects with DM2

and COVID-19. From the first moments of the global spread of the pandemic, DM2 was one of the worst risk factors for outcomes from COVID-19 and admissions to Intensive Care Units (54,55), data that have been confirmed and consolidated over time (56). On DM2 management, the ability to actively involve the patient in a complex treatment process could be decisive in both the short and medium term of necessary post-COVID-19 health reorganization (57-64). More in-depth studies on the use of Metformin compared to other molecules could be decisive for understanding the real protective potential of the drug against negative outcomes caused by COVID-19 infection (65,66).

Conflict of Interest statement: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Consent for publication: All the authors have read the paper and agreed to submit the paper.

Availability of data and materials: The data that support the findings of this study are available on request from the corresponding author, IG upon reasonable request.

Competing interests: The authors declare no competing interests.

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Authors' contributions : FP and GC designed and conducted research, analyzed data and wrote the paper. All authors approved the final manuscript.

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Correspondence:
Received: 6 March 2023
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Prof Grappasonni Iolanda
School of Medicinal and Health Products Sciences
University of Camerino, Camerino, Italy
E-mail: iolanda.grappasonni@unicam.it