Dear Editor,

We congratulate Ojeda-Fernández et al on their study of the association between metformin use and lower risks of hospitalization and mortality in COVID-19 patients with diabetes. The study, one of the largest yet published, emphasizes the consistency of the association between metformin use and improved COVID-19 outcomes after hospital admission and in the medium term. However, we believe the published data on this topic should be interpreted with caution. In Table 1, we present an up-to-date summary of studies on the relationship between metformin use and COVID-19 that (i) were published in peer-reviewed medical journals and (ii) included more than 100 patients overall and more than 50 metformin users in particular. Duplicate studies and studies published in languages other than English, French or Italian were excluded.

Our analysis of this large body of published data prompted several important remarks:

- All the studies had retrospective observational designs;
- The studies were very heterogeneous with regard to their settings (claims data and electronic health records, hospital stay data, COVID-19 databases, nursing home databases, and population databases), sample size (ranging from 172 COVID-19 patients with diabetes to more than 2 million people with diabetes and [in some cases] COVID-19), study population (people with diabetes, people with overweight and obesity, or more highly selected populations), and time frame (from the outbreak of COVID-19 in early 2020 to March 15, 2021);
- The variable used to describe metformin use differed markedly from one study to another: it ranged from prescription claims data (at some time before the COVID-19 but not necessarily in the immediate preceding period) to the treatment dispensed in hospital. Indeed, some publications did not specify how metformin use was ascertained;
- None of the studies examined the possibly protective roles of (i) long-term metformin treatment prior to COVID-19 onset and/or (ii) metformin maintenance during the hospital stay;
- The percentage of the study population exposed to metformin varied considerably (from approximately 7% to over 73%);
- Some critically important demographic characteristics and baseline variables were missing. This was particularly the case for body mass index (BMI; missing data in 15 of the 21 studies) and duration of diabetes (missing data in 19 studies). Consequently, these variables were not taken into account in the statistical analysis, which might have led to residual, unmeasured confounding effects;
- Most studies evaluated the mortality rate during the hospital stay or 28 to 30 days thereafter. However, some studies did not report this time interval, and only two studies reported on the medium-term mortality rate (respectively, 118 days and 4.4 months after hospital admission);
- With regard to statistical analyses, the most robust method (propensity-score matching/weighting that accounts for a large number of covariates) was used in barely half of the studies. Of course, the use of a propensity score necessarily results in a loss of statistical power, and the inclusion of a large number of covariates does not compensate for a lack of key variables (such as BMI and estimated glomerular filtration rate).

Overall, almost all the studies found that the short- and/or medium-term survival outcomes for metformin users were generally favourable. Ojeda-Fernández et al attributed the favourable association between metformin use and survival to a confounding effect of the indication; metformin is used early in the care trajectory for type 2 diabetes and is discontinued in long-term diabetes with cardiorenal comorbidities, whereas insulin is usually started later—typically when metformin is no longer indicated. Only few studies reported on the duration of diabetes in metformin users and non-users; this lack of data prevents meaningful conclusions from being drawn. However, 15 studies reported the proportion of participants who were being treated with insulin. Of these, 14 estimated the relative risk in the metformin group versus the non-metformin group. We performed a meta-regression analysis of the 14 datasets in order to determine whether or not the proportion of insulin-treated patients could account for the observed between-study heterogeneity. The analysis revealed a significant, inverse association between relative risk reduction and the proportion of insulin-treated patients (P = 0.0247). However, inclusion of the proportion of insulin-treated patients only reduced the I² value very slightly (from 69.3% to 68.83%)—meaning there was still a substantial amount of residual between-study variance.
### TABLE 1  Observational cohort studies evaluating the association between metformin use and survival in diabetic patients with COVID-19

| Author (country) | Design, setting and dates | Criterion for MET exposure | Number of patients with COVID-19 (exposed, %) | Main population characteristics | Proportion of insulin-treated patients | Endpoints | Main findings | Statistics | Interpretation | Major limitations/ sources of bias | Comments |
|------------------|---------------------------|-----------------------------|---------------------------------------------|-------------------------------|--------------------------------------|-----------|--------------|------------|---------------|----------------------------------|----------|
| Bramante (USA)   | Retrospective, claims data, Jan 1 to June 7, 2020 | >90 days within 12 months of COVID-19 diagnosis | 6256 (2333, 37.3%) | NR 2954, (47.2) | NR 37.5% | In-hospital mortality | OR 0.898 [95% CI 0.768-1.051] | Propensity-score matching | COVID-19 severity NA, BMI NA (>90%), imprecise definition of MET exposure, imprecise definition of the population (type 2 diabetes and obesity) | Lower mortality rate observed only in women |
| Bramante (USA)   | Retrospective, electronic health records, Mar 4 to Dec 4, 2020 | Home medication list for the 3 months before COVID-19 | 9555 (676, 7.1%) | 55 5036, (47.3) | 33.1 5.6% | Mortality | OR 0.38 [95% CI 0.16-0.91] | Propensity-score matching | COVID-19 severity NA, imprecise definition of the mortality outcome (in hospital and before hospital), imprecise definition of the population (overweight and obesity) | Selected population (BMI > 25 kg/m², age between 30 and 85 years), diabetes was not an inclusion criteria |
| Cernigliaro (Italy) | Retrospective, COVID-19 database, March 1 to June 26, 2020 | | 172 (82, 47.7%) | NR NR NR | 26.1% | Mortality | OR 0.44 [95% CI 0.22-0.87] | Logistic regression | BMI not accounted for, definition of MET exposure NA, imprecise definition of the mortality outcome | Adjustment for age and sex only |
| Cheng (China)    | Retrospective, hospital stay data, Dec 30, 2019 to April 13, 2020 | >3 days (in-hospital) | 1213 (678, 55.9%) | 63 632 (52.1) | 24.4 | 28-day mortality | HR 1.65 [95% CI 0.71-3.86] | Propensity-score matching | BMI not accounted for | MET use was associated with a higher incidence of lactic acidosis |

(Continues)
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|-----------------|---------------------------|-----------------------------|---------------------------------------------|---------------------------------|----------------------------------------|-----------|--------------|------------|----------------|
| Crouse (USA)    | Retrospective, COVID-19 testing, Feb 25 to Jun 22, 2020 | Prior to COVID-19 | 239 (76, 32%) | NR 121 (50.6) NR | 36.4% Mortality OR 0.33 [95% CI 0.13-0.84] | Logistic regression | COVID-19 severity NA, imprecise definition of MET exposure, no clear definition of the outcome (time range?) | Selected population (hospital staff and patients attending for elective procedures) |
| Dave (South Africa) | Retrospective, electronic health data, Mar 4 to Jul 15, 2020 | Prescribed metformin | 9305 (NR) 55 3657 (39.3) | NR | Mortality OR 0.77 [95% CI 0.64-0.92] | Logistic regression | COVID-19 severity NA, BMI NA, no clear definition of the outcome (time range?) | MET was associated with a reduced risk of hospital admission |
| Do (South Korea) | Retrospective, claims data, Feb 1 to May 15, 2020 | Adherence >80% in the year before COVID-19 | 1865 (469, 25.1%) 61 1096 (58.8) | NR | Mortality HR 0.77 [95% CI 0.44-1.35] | Cox regression | COVID-19 severity NA, missing BMI data, imprecise definition of MET exposure, no clear definition of the outcome (time range?) | The MET group was compared with patients with diabetes and not taking MET |
| Ghany (USA)     | Retrospective, electronic health records, Jan 1 to Aug 14, 2020 | ≥1 pharmacy claim in 2019-2020 (before COVID-19) | 1139 (392, 34.4%) 71.1 1019 (89.5) | 32.2 1.8% Mortality HR 0.34 [95% CI 0.19-0.59] | Cox regression | BMI not adjusted for, imprecise definition of MET exposure, no clear definition of the outcome (time range?) | Specific population: Elderly Medicare minority patients |
| Jiang (China)   | Retrospective, hospital stay data, Dec 31, 2019 to Mar 31, 2020 | MET prescription during hospitalization | 328 (100, 30.5%) | NR 174 (53) NR | 30-day mortality OR 0.54 [95% CI 0.13-2.26] | Propensity-score matching | BMI not adjusted for, small number of events (n = 28) |
| Khunti (UK)     | Retrospective, nationwide general practice database study, Feb 16 to Aug 31, 2020 | Prescription of MET by the general practitioner | NR, 2 851 465 people with diabetes (1 800 005, 63.1% on MET) | 67 1 593 730 (55.9) | 12.3% COVID-19 related mortality HR 0.77 [95% CI 0.73-0.81] | Cox regression | COVID-19 severity NA |

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|-----------------|---------------------------|----------------------------|---------------------------------------------|---------------------------------|--------------------------------------|-----------|--------------|------------|---------------|-------------------------------|----------|
| Lalau (France)  | Retrospective and prospective, hospital stay data, Mar 10 to Apr 10, 2020 | MET prescription on admission | 2449 (1496, 61.1%) | Mean/median age, years: 70.9, Men: 1568 (64), Median BMI, kg/m²: 28.7 | 36.8% | 28-day mortality | OR 0.71 [95% CI 0.54-0.94] | Propensity-score weighting | | | |
| Lally (USA)     | Retrospective, nursing homes, Mar 1 to May 13, 2020 | Bar-coded MET administration in the 14 days before COVID-19 | 775 (127, 16.4%) | Mean/median age, years: 75.6, Men: 754 (97.3), Median BMI, kg/m²: 27.3 | 13.3% | 30-day mortality | HR 0.48 [95% CI 0.28-0.84] | Cox regression | BMI and major comorbidities not accounted for | Specific population: Military veterans, the MET group was compared with patients without diabetes and not taking MET |
| Luk (Hong Kong) | Retrospective, electronic health records, Jan 23, 2020 to Feb 28, 2021 | Prescription record in the 12 months before COVID-19 | 1220 (737, 60.4%) | Mean/median age, years: 65.3, Men: 662 (54.3), Median BMI, kg/m²: 23.6 | 22.4% | In-hospital mortality | HR 0.51 [0.27-0.97] | Cox regression | BMI not accounted for, imprecise definition of MET exposure | |
| Luo (China)     | Retrospective, hospital stay data, Jan 27 to March 24, 2020 | >3 days (in-hospital) | 283 (104, 36.7%) | NR, Men: 156 (55.1), Median BMI, kg/m²: NR | 53.7% | In-hospital mortality | 2.9% vs 12.3%, P = 0.01 | Logistic regression | No adjustment for age and sex, BMI NA, small number of events (n = 25) | |
| Oh (South Korea)| Retrospective, population database, Jan 1 to Jun 26, 2020 | ≥90 days in 2019-2020 (prior to COVID-19) | 2047 (480, 23.4%) | NR, NR, NR, NR | NR | In-hospital mortality | OR 1.26 [95% CI 0.81-1.95] | Logistic regression | COVID-19 severity NA, imprecise definition of MET exposure, BMI NA | Lower rate of COVID-19 among MET users |
| Ojeda-Fernández (Italy) | Retrospective, COVID-19 database, Feb 15, 2020 to Mar 15, 2021 | ≥2 prescriptions of MET in 2019 | 31 966 (23 327, 73%) | Mean/median age, years: 71.9, Men: 19 118 (59.8), Median BMI, kg/m²: NR | 27.8% | In-hospital mortality | OR 0.74 [95% CI 0.67-0.81] | Propensity-score matching | BMI NA, imprecise definition of MET exposure | MET was associated with lower risk of total mortality during follow-up (OR 0.79 [95% CI 0.73-0.86]), mean follow-up was 118 days |

(Continues)
| Author (country)         | Design, setting and dates                      | Criterion for MET exposure                              | Number of patients with COVID-19 (exposed, %) | Main population characteristics | Propensity of insulin-treated patients | Endpoints | Main findings | Statistics                                                                 | Interpretation | Major limitations/sources of bias | Comments |
|--------------------------|-----------------------------------------------|--------------------------------------------------------|---------------------------------------------|---------------------------------------|---------------------------------------|-----------|----------------|-------------------------------------------------------------------------------|----------------|-------------------------------|----------|
| Ong (Philippines)        | Retrospective, hospital stay data, Mar 1 to Sep 30, 2020 | MET at home or in hospital                             | 355 (186, 52.4%)                           | Mean/median age, years Mean Men, N (%) | Mean/median BMI, kg/m² NR | 14.6%     | In-hospital mortality OR 0.43 [95% CI 0.23-0.82]                             | Logistic regression | BMI not accounted for            |          |
| Pérez-Belmonte (Spain)   | Retrospective, hospital stay data, Mar 1 to Jul 19, 2020 | MET at home                                            | 2666 (1618, 60.7%)                         | 64.9 1647 (61.9) NR                   | 27.6% In-hospital mortality OR 1.16 [95% CI 0.78-1.72] | Propensity-score matching | BMI not accounted for | These results concern MET monotherapy only |
| Saygili (Turkey)         | Retrospective, hospital stay data, Mar 12 to Dec 22, 2020 | MET used regularly in the 6 mo before COVID-19         | 586 (432, 73.7%)                           | 66 293 (50) NR                       | NR In-hospital mortality HR 0.57 [95% CI 0.31-1.05] | Propensity-score matching | BMI not accounted for | MET was associated with lower overall mortality |
| Tamura (Brazil)          | Retrospective, hospital stay data, Mar 10 to Nov 13, 2020 | MET at home or >24 h during hospitalization           | 188 (115, 61.2%)                           | 64.6 118 (62.8) 29.3                 | 32.4% In-hospital mortality HR 0.03 [95% CI 0.002-0.58] | Cox regression | BMI not accounted for, small number of events (19) |
| Wander (USA)             | Retrospective, electronic health records, Mar 1, 2020 to Mar 10, 2021 | Active prescription at the date of COVID-19 positivity | 64 892 (29 685, 45.7%)                  | 67.7 61 020 (94) NR                  | 28.5% 30-day mortality OR 0.84 [95% CI 0.78-0.91] | Logistic regression | |
| Wang (UK)                | Retrospective, population database, Jan 30 to Oct 13, 2020 | MET in the last 90 days before COVID-19               | 603 confirmed or suspected COVID-19 (415, 68.8%) | NR NR NR NR | 28-day mortality HR 0.87 [95% CI 0.34-2.20] | Propensity-score matching | |

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MET, metformin; NA, not available; NR, not reported; OR, odds ratio.
In conclusion, although the findings by Ojeda-Fernández et al reinforce the conclusion that metformin is associated with a lower rate of mortality in type 2 diabetes patients with COVID-19, the assessment of this association is still strewn with pitfalls. Therefore, more studies are needed.

**AUTHOR CONTRIBUTIONS**
Design and data collection: Abdallah Al-Salameh and Jean-Daniel Lalau. Analysis: Abdallah Al-Salameh, Nicolas Wiernsperger, Bertrand Cariou and Jean-Daniel Lalau. Writing manuscript: Abdallah Al-Salameh, Nicolas Wiernsperger, Bertrand Cariou and Jean-Daniel Lalau.

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**CONFLICT OF INTEREST**
Abdallah Al-Salameh reports personal fees from AstraZeneca, Lilly, and Novo Nordisk, none of which related to the subject discussed in this manuscript. Nicolas Wiernsperger declares no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported. Bertrand Cariou reports grants and personal fees from Amgen, personal fees from AstraZeneca, personal fees from Akcea, personal fees from Genfit, personal fees from Gilead, personal fees from Eli Lilly, personal fees from Novo Nordisk, personal fees from MSD, grants and personal fees from Sanofi, and grants and personal fees from Regeneron. Jean-Daniel Lalau reports personal fees from AstraZeneca, Brothier, Lilly, MSD, Novo Nordisk, Pfizer, and Sanofi.

**REFERENCES**
1. Ojeda-Fernández L, Foresta A, Macaluso G, et al. Metformin use is associated with a decrease in the risk of hospitalization and mortality in COVID-19 patients with diabetes: a population-based study in Lombardy. *Diabetes Obes Metab*. 2022;24(5):891-898. doi: 10.1111/dom.14648
2. Cernigliaro A, Allotta AV, Scondotto S. Can diabetes and its related hypoglycemic drug treatment be considered risk factors for health outcomes in COVID-19 patients? The results of a study in the population residing in Sicily region (southern Italy). *Epidemiol Prev*. 2020;44(5-6 Suppl 2):315-322. doi: 10.19191/EP20.5-6.S2.132
3. Khunti K, Knighton P, Zaccardi F, et al. Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. *Lancet Diabetes Endocrinol*. 2021;9(5):293-303. doi: 10.1016/S2213-8587(21)00050-4
4. Bramante CT, Buse J, Tamaritz L, et al. Outpatient metformin use is associated with reduced severity of COVID-19 disease in adults with overweight or obesity. *J Med Virol*. 2021;93(7):4273-4279. doi: 10.1002/jmv.26873
5. Ghany R, Palacio A, Dawkins E, et al. Metformin is associated with lower hospitalizations, mortality and severe coronavirus infection among elderly medicare minority patients in 8 states in USA. *Diabetes Metab Syndr*. 2021;15(2):513-518. doi: 10.1016/j.dsx.2021.02.022
6. Wunder PL, Lowy E, Beste LA, et al. Prior glucose-lowering medication use and 30-day outcomes among 64,892 veterans with diabetes and COVID-19. *Diabetes Care*. 2021;44(12):2708-2713. doi: 10.2337/dc21-1351