The Association of Premorbid Metformin Exposure With Mortality and Organ Dysfunction in Sepsis: A Systematic Review and Meta-Analysis

Kaiquan Tan, BSc[1]; Andrew Simpson, MBBS[2]; Stephen Huang , PhD[1,2];

Benjamin Tang, MBBS, PhD[1,3]; Anthony Mclean, MD, PhD[1,2]; Marek Nalos, MD, PhD[1,2,4]

Objectives: To examine the association between premorbid metformin exposure and mortality, hyperlactatemia, and organ dysfunction in sepsis.

Data Sources: PubMed and EMBASE (with Medline via Ovid) databases were searched for all studies of premorbid metformin exposure and sepsis published between January 1974 and August 2018.

Study Selection: Studies of at least 20 patients with sepsis that reported data on metformin use, mortality, and/or organ dysfunction were independently selected.

Data Extraction: Two reviewers abstracted data on study design, settings, study quality, participants, metformin exposure, mortality, initial lactate levels, and organ dysfunction. Risk of bias was independently assessed.

Data Synthesis: Eight observational studies fulfilled our criteria, comprising 4,144 patients with sepsis including 562 diabetics on metformin. Premorbid metformin exposure was associated with reduced mortality in sepsis (odds ratio, 0.57; 95% CI, 0.40–0.80). Between studies heterogeneity was low ($I^2 = 43\%$; $\tau^2 = 0.1$; $p = 0.09$). Premorbid metformin exposure was not significantly associated with initial lactate levels (mean difference, 0.39 [−0.50 to 1.28]; $I^2 = 72\%$; $p = 0.39$).

Conclusions: The meta-analysis suggests that premorbid metformin exposure is associated with decreased mortality in sepsis but not with hyperlactatemia. What are the potential mechanisms and whether there is any effect on organ dysfunction remain unclear.

Key Words: metformin; metformin-associated lactic acidosis; mortality; organ dysfunction; sepsis; systematic review

[1]Nepean Clinical School, Sydney Medical School, University of Sydney, Penrith, NSW, Australia.

[2]Department of Intensive Care Medicine, Nepean Hospital, Penrith, NSW, Australia.

[3]Centre for Immunology and Allergy Research, Westmead Millenium Institute, Westmead, NSW, Australia.

[4]Medical Intensive Care Unit, 1st Department of Medicine, University Hospital and Biomedicine Centre, Pilsen, Charles University Prague, Czech Republic.

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection is estimated to affect 30 million people worldwide every year with significant attributed morbidity and mortality (1, 2). Although advancements in treatment protocols have reduced in-hospital mortality (3, 4), therapies that improve sepsis survival by reducing organ dysfunction are scarce (5).

The global prevalence of diabetes has doubled from 4.7% in 1980 to 8.5% in 2014, with an estimated 422 million adults worldwide currently living with diabetes (6). Hyperglycemia predisposes the host to infection by altering host immune responses (7). There is, however, conflicting evidence as to whether diabetes increases or decreases morbidity and/or mortality from sepsis (8, 9).

Metformin is a commonly prescribed antidiabetic drug. Its use is associated with lower all-cause mortality when compared with other hypoglycemics (10). Metformin reduces glucose absorption, improves insulin sensitivity, and inhibits hepatic gluconeogenesis (11). On a cellular level, metformin inhibits mitochondrial

respiration at complex I, predominantly in the liver but also in the heart, kidneys, and muscles resulting in reduced fatty acid oxidation and increased lactate production (12–14). Although not contraindicated, metformin is usually stopped in patients with sepsis due to the risk of metformin accumulation and metformin-associated lactic acidosis (MALA) (14). A study by Christiansen et al (15), however, found that premorbid metformin use was associated with reduced mortality among intensive care patients with type 2 diabetes. Similarly, the outcome of patients with MALA is reported to be somewhat better than expected despite very low blood pH values (16, 17). Therefore, we set to systematically examine whether premorbid metformin exposure is associated with mortality, hyperlactatemia, and/or organ dysfunction in sepsis.

MATERIALS AND METHODS

This study was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology guidelines (18) and registered with the international prospective register of systematic reviews (PROSPERO, CRD42018094435).

Data Sources and Searches

We employed a high sensitivity strategy with the search last updated on September 26, 2018. Two databases, PubMed and EMBASE (with Medline via Ovid), were used. Timeframe of the search was from 1946 on PubMed, and from 1974 on EMBASE and Medline via Ovid. Search results were restricted to human adult articles only. No language limitations were applied. A detailed search strategy is appended (**Supplementary Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A23; **legend**, Supplemental Digital Content 15, http://links.lww.com/CCX/A37).

Study Selection

All studies must have included adult patients with sepsis cared for in the emergency department (ED) or ICU and exposure to metformin prior to an episode of sepsis or septic shock. Observational studies or clinical trials were eligible. Pediatric studies, case studies/small series (< 20 patients overall), reviews, conference abstracts, and secondary studies were not eligible. Inclusion criteria follow the Patient, Population, or Problem, Intervention, Comparison, Outcome, Study Design or Setting framework (19) (**Table 1**). Two investigators (K.T., M.N.) conducted an independent screening of all the abstracts according to the eligibility criteria. Any disagreements were resolved through discussion with a third investigator (A.S.).

Data Extraction and Quality Assessment

The full-text articles of all eligible studies were obtained and the data were extracted by two investigators (K.T., M.N.) in tandem. Authors were contacted directly to kindly provide missing research data or summary of events data as required.

The quality of studies and quality of evidence were formally and independently assessed by two investigators (K.T., M.N.) using the Risk Of Bias In Nonrandomized Studies - of Interventions instrument (20) and GRADE approach (21), respectively.

Data Synthesis and Analysis

Data from different studies were combined to obtain a pooled (summary) odds ratio (OR) using the Mantel-Haenszel method for random effects model (22). Between-study heterogeneity was measured by Higgin's and Thomson's I^2 (23). I^2 between 25% and 50% indicates low between-study heterogeneity, and between 50% and 75% and greater than 75% indicate moderate and high heterogeneity, respectively (24). Small study effects were examined by funnel plots in order to distinguish publication bias from other causes (25). Sensitivity analysis was carried out using the leave-one-out-at-a-time approach and subgroup analysis as described below.

Results were expressed as OR or mean difference (MD) and 95% CI. Where appropriate, the p values are also shown with statistical significance denoted as p values of less than 0.05, unless otherwise stated. Analyses were carried out using Review Manager Version 5.3 (The Cochrane Collaboration: Copenhagen, Denmark, 2014).

TABLE 1. "PICOS" Approach for Selecting Clinical Studies in the Systematic Search

PICOS	Study Characteristics
1) Participants	Adult patients with sepsis and/or septic shock
2) Intervention	Premorbid metformin exposure
3) Comparison	Primary: mortality between septic premorbid metformin users vs nonusers
	Secondary: organ dysfunction between septic metformin users and nonusers, initial lactate levels between septic metformin users and nonusers
	Sensitivity analysis: leave-one-out-at-a-time, excluding studies with high risk of bias, excluding studies with patient selection based on initial lactate levels > 5 mmol/L, excluding diabetic controls, excluding nondiabetic controls
4) Outcomes	Primary: mortality (at 28, 30 d, or hospital)
	Secondary: initial plasma lactate levels, initial glycemia, sepsis severity, vasopressor usage, mechanical ventilation, renal function
5) Study design	Prospective observational or retrospective cohort studies

PICOS = Patient, Population, or Problem, Intervention, Comparison, Outcome, Study Design or Setting.

Where data were reported as median values and interquartile range (IQR), we followed the recommendation by Greco et al (26) and equated medians to means, whereas SD was calculated as third quartile–first quartile (Q3–Q1); bias attributed to this assumption is generally conservative.

RESULTS

Study Selection

The initial search returned 310 abstract results. After removing 16 duplicates, 294 abstracts were manually screened. Twelve studies were selected for data analysis after meeting all inclusion criteria. Of the 12, seven studies did not report mortality data that clearly identified patients with sepsis from patients without sepsis or metformin users from nonusers. The corresponding authors were contacted to obtain the necessary data for analysis. Four authors replied and three of those were able to provide their unpublished data. The remaining authors could not be reached. The list of studies excluded is appended (**Supplementary Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCX/A24). Overall, a total of eight studies were found to be eligible, comprising 4144 patients with sepsis, including 562 diabetic patients on metformin prior to the episode of sepsis (**Fig. 1**). The authors declare no affiliation with any of the included studies.

Characteristics and Type of Studies

All studies were retrospective cohort studies except one prospective observational study by Van Vught et al (27). No controlled or randomized trials were identified. Each study was conducted in a different country with data collected between 2005 and 2014. Four studies (15, 27–29) were conducted in ICU, three (30–32) in ED, and one (33) in both ICU and ED.

The study populations described adult sepsis or septic shock patients with a wide range of illness severity as documented by the severity scoring systems and initial lactate levels. The definitions of sepsis, septic shock, and premorbid metformin exposure varied slightly across the studies, however, were reasonable and comparable to current definitions (34).

Two studies (29, 32) included only patients with septic shock, two (30, 31) included patients with severe sepsis and septic shock, whereas four studies (15, 27, 28, 33) did not specifically distinguish sepsis patients with and without shock. Six studies included mixed populations of surgical and medical patients and two studies (28, 32) included only medical patients. The smallest study included 25 patients (28) and the largest included 1947 patients (31). The characteristics of the studies are appended (**Supplementary Table 2**, Supplemental Digital Content 3, http://links.lww.com/CCX/A25; and **Supplementary Table 3**, Supplemental Digital Content 4, http://links.lww.com/CCX/A26).

Risk of Bias Assessment for Primary Outcome

Five studies (15, 27, 29–31) were judged to be of moderate risk of bias for the primary outcome of mortality. Three (28, 32, 33) studies were judged as having serious risk of bias in at least one of the domains, mainly due to selection bias, as patients were
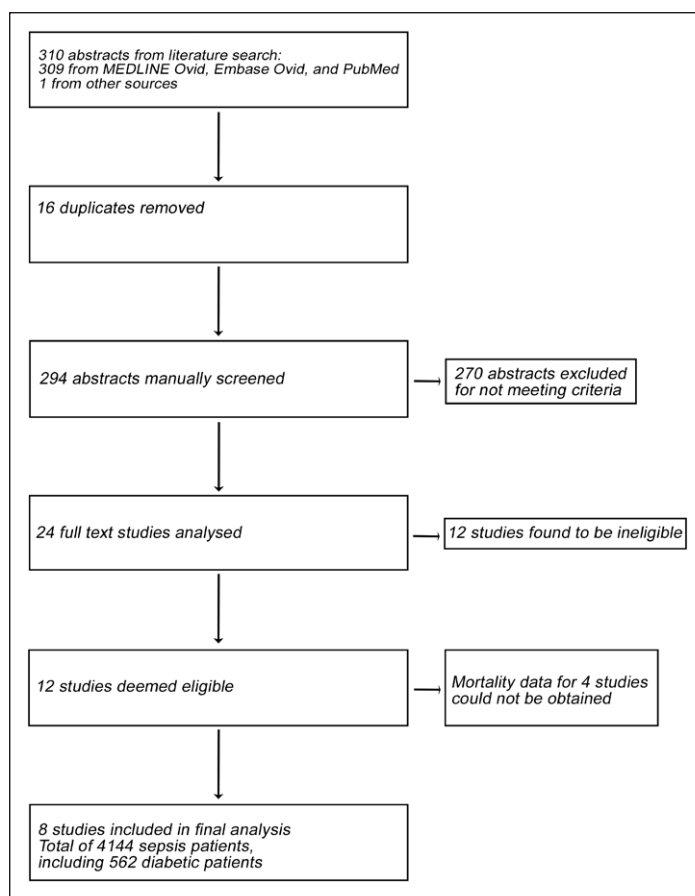

Figure 1. Flow diagram of study selection process.

included in the study based on plasma lactate levels greater than 5 mmol/L (28, 33) or greater than 10 mmol/L (32). The risk of bias assessment of each trial is appended (**Supplementary Fig. 2**, Supplemental Digital Content 5, http://links.lww.com/CCX/A27; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37) with reasonings (**Supplementary Table 4**, Supplemental Digital Content 6, http://links.lww.com/CCX/A28).

Primary Outcome

Mortality. The primary outcome analysis included mortality data of 4,144 patients from all eight included studies (28 d, 30 d, or hospital mortality). The absolute mortality rates were lower in patients on premorbid metformin in all eight studies. Accordingly, pooled meta-analysis revealed that premorbid metformin exposure was associated with improved survival in sepsis (OR, 0.57; 95% CI, 0.40–0.80; $p = 0.001$), with low heterogeneity ($i^2 = 43\%$; $\tau^2 = 0.10$; $p = 0.09$) (**Fig. 2**). Inspection of the funnel plot revealed that publication bias was unlikely (**Supplementary Fig. 3**, Supplemental Digital Content 7, http://links.lww.com/CCX/A29; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37). Due to the observational nature of the studies, GRADE quality of evidence for mortality outcome is judged to be low to moderate (**Supplementary Table 5**, Supplemental Digital Content 8, http://links.lww.com/CCX/A30).

Sensitivity Analysis. Using the leave-one-out-at-a-time approach did not significantly alter the results of the meta-analysis
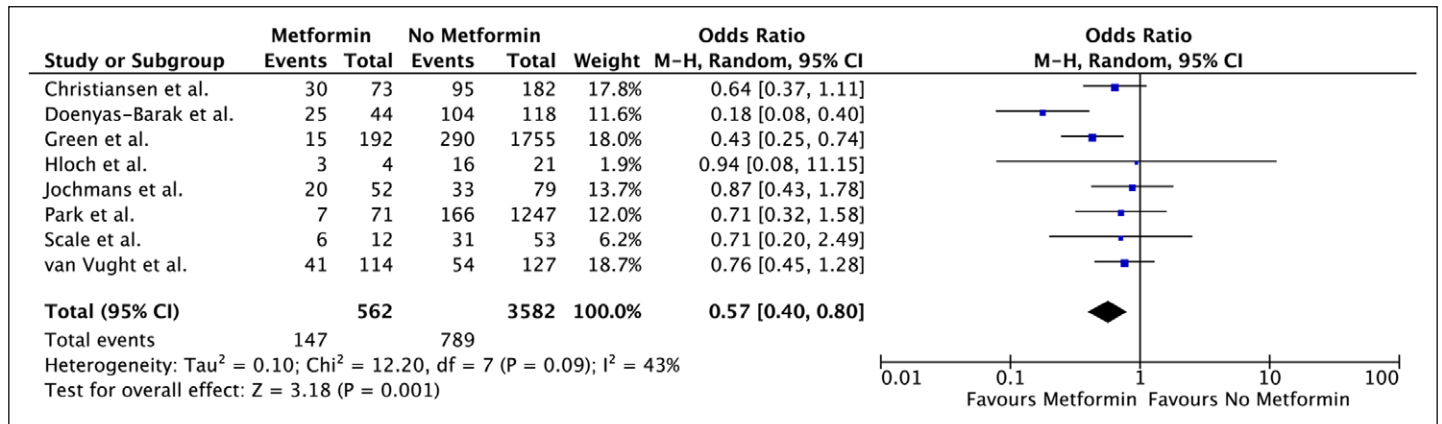
Figure 2. Global forest plot of sepsis mortality rates in studies comparing populations with premorbid metformin usage to populations without premorbid metformin usage. *Horizontal bars* represent 95% CIs. *df* = degrees of freedom, M-H = Mantel-Haenzel.

(**Supplementary Fig. 4a**, Supplemental Digital Content 9, http://links.lww.com/CCX/A31; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37). Excluding three studies (28, 32, 33) that had a serious risk of bias from selecting patients based on initial plasma lactate levels did not significantly affect the OR analysis (OR, 0.64; 95% CI, 0.49–0.84; p = 0.001; **Supplementary Fig. 4b**, Supplemental Digital Content 9, http://links.lww.com/CCX/A31; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37). Analysis of studies comparing diabetics to nondiabetics increased the strength of the association between premorbid metformin exposure and reduced mortality (OR, 0.42; 95% CI, 0.23–0.77; p = 0.005; **Supplementary Fig. 4c**, Supplemental Digital Content 9, http://links.lww.com/CCX/A31; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37). All studies comparing diabetics to nondiabetics were also conducted in ED. Interestingly, the association was blunted when comparing diabetic metformin users to diabetics not on metformin (OR, 0.74; 95% CI, 0.53–1.03; p = 0.07; **Supplementary Fig. 4d**, Supplemental Digital Content 9, http://links.lww.com/CCX/A31; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37). The findings may reflect the removal of confounding by the diagnosis of diabetes or may be related to the fact that these four studies were all done in ICU patients as discussed below.

The use of metformin is contraindicated in patients with advanced chronic renal failure (10). Consequently, the group of metformin users in three out of the eight included studies had significantly fewer patients with advanced chronic renal failure. Chronic renal failure may be an important source of confounding, as it is associated with poorer outcomes in patients with sepsis (35). Hence, we performed a sensitivity analysis including only studies without a significant difference in the presence of chronic renal failure between metformin users and nonusers. The result (OR, 0.44; 95% CI, 0.25–0.76; p = 0.003; **Supplementary Fig. 4e**, Supplemental Digital Content 10, http://links.lww.com/CCX/A32; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37) suggests that the association between metformin and decreased mortality in sepsis was not significantly influenced by fewer patients with advanced chronic renal failure among the metformin users. Inspection of the funnel plots revealed that publication bias was unlikely (**Supplementary Fig. 5a-c**, Supplemental
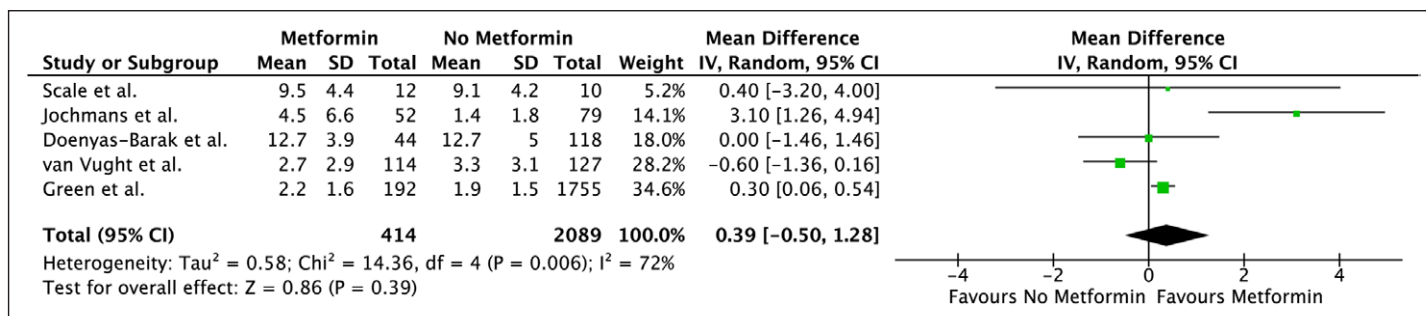
Digital Content 11, http://links.lww.com/CCX/A33—legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37; and **Supplementary Fig. 5d**, Supplemental Digital Content 12, http://links.lww.com/CCX/A34—legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37).

Secondary Outcomes

Initial Plasma Lactate Level. Four studies (27, 29, 31, 32) reported lactate levels as median and IQR. Scale and Harvey (33) provided raw data from which median and IQR were derived. Overall, only two studies (29, 30) reported significantly higher plasma lactate level in premorbid metformin users, but one (30) had missing SD data, precluding it from meta-analysis. Three studies (27, 28, 31) reported lactate levels that trended higher in metformin users but the increase was not significant. Two studies (32, 33) reported no significant differences in lactate levels between both populations and one study (15) did not provide a comparison of lactate levels. Overall, meta-analysis of five studies (27, 29, 31–33) indicates that plasma lactate levels are not significantly elevated due to premorbid metformin exposure (MD, 0.39 [–0.50 to 1.28]; i^2 = 0.72%; p = 0.39) (**Fig. 3**). Inspection of the funnel plot revealed that publication bias was unlikely (**Supplementary Fig. 6**, Supplemental Digital Content 13, http://links.lww.com/CCX/A35; legend, Supplemental Digital Content 15, http://links.lww.com/CCX/A37). The GRADE quality of evidence is low due to selection bias and inconsistency (Supplementary Table 5, Supplemental Digital Content 8, http://links.lww.com/CCX/A30).

Initial Glycemia. Three studies reported initial glucose levels. In one study (27) that included only diabetics, the initial glycemia was higher in the nonmetformin users. In two studies that included nondiabetics in the control group (30, 31), initial glycemia was higher in the metformin users as expected. The GRADE quality of evidence is very low (Supplementary Table 5, Supplemental Digital Content 8, http://links.lww.com/CCX/A30).

Organ Dysfunction. The data on organ dysfunction and sepsis severity were very heterogeneous, precluding meaningful meta-analysis. The following paragraphs summarize the most important findings and the data are presented in Supplementary Table 3 (Supplemental Digital Content 4, http://links.lww.com/CCX/A26). The GRADE quality of evidence for organ dysfunction data

Study or Subgroup	Metformin			No Metformin			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Scale et al.	9.5	4.4	12	9.1	4.2	10	5.2%	0.40 [−3.20, 4.00]
Jochmans et al.	4.5	6.6	52	1.4	1.8	79	14.1%	3.10 [1.26, 4.94]
Doenyas–Barak et al.	12.7	3.9	44	12.7	5	118	18.0%	0.00 [−1.46, 1.46]
van Vught et al.	2.7	2.9	114	3.3	3.1	127	28.2%	−0.60 [−1.36, 0.16]
Green et al.	2.2	1.6	192	1.9	1.5	1755	34.6%	0.30 [0.06, 0.54]
Total (95% CI)			**414**			**2089**	**100.0%**	**0.39 [−0.50, 1.28]**

Heterogeneity: Tau^2 = 0.58; Chi^2 = 14.36, df = 4 (P = 0.006); I^2 = 72%
Test for overall effect: Z = 0.86 (P = 0.39)

Figure 3. Forest plot of mean difference of initial plasma lactate levels comparing populations with premorbid metformin usage to populations without premorbid metformin usage. *df* = degrees of freedom.

is very low for all (Supplementary Table 5, Supplemental Digital Content 8, http://links.lww.com/CCX/A30).

Vasopressor Usage. Three studies (27, 29, 30) reported vasopressor usage comparing metformin users to nonusers. Two of those found significantly lower usage of vasopressors in premorbid metformin users (27, 30). Neither any significant differences in the maximum noradrenaline dose nor duration of noradrenaline administration were reported in the remaining study (29).

Mechanical Ventilation. Three studies (27, 29, 30) reported ventilation requirements of premorbid metformin users and metformin nonusers. No significant differences were found between the groups.

Renal Function. Renal function was measured across six studies (27–32) via four different variables (Table 3). Renal replacement therapy was more common in metformin users in two studies (28, 29). Two studies (27, 29) reported no significant difference in acute kidney injury (AKI) rates, whereas one study (32) reported a significant decrease in AKI rates with metformin usage.

Sepsis Severity. Five studies provided a comparison of sepsis severity scores between the groups, but each used a different score (Acute Physiology and Chronic Health Evaluation [APACHE] II, APACHE IV, Sequential Organ Failure Assessment, Predisposition, Infection [or Insult], Response and Organ dysfunction, and Simplified Acute Physiology Score II). Therefore, a meta-analysis linking sepsis severity and metformin exposure was impossible. Nonetheless, the five studies independently found that sepsis severity did not differ due to premorbid metformin exposure. The GRADE quality of evidence is low (Supplementary Table 5, Supplemental Digital Content 8, http://links.lww.com/CCX/A30).

DISCUSSION

To our knowledge, this is the first systematic review addressing the association between premorbid metformin exposure and mortality and organ dysfunction in sepsis. The main finding is that patients on premorbid metformin seem to have better odds of surviving sepsis. Our finding is relatively robust across a range of sensitivity analyses. Due to the observational nature of included studies, however, we cannot rule out potential confounding by various factors. Interestingly, secondary results suggest that in patients with sepsis, initial plasma lactate levels are not significantly associated with premorbid metformin exposure. Unfortunately, due to the variability in data reporting, we were unable to systematically analyze any association of premorbid metformin exposure with organ dysfunction in sepsis. Our results invite careful consideration regarding possible reasons for the association between decreased mortality in sepsis and prior metformin exposure.

First, hyperlactatemia or perceived risk of MALA could lead to an earlier and more aggressive treatment of sepsis, particularly, where Surviving Sepsis guidelines have been adopted. The guidelines use elevated lactate as one of the early triggers for the initiation of treatment protocols (36). However, the association between metformin exposure and increased lactate levels could not be confirmed by our systematic review.

Second, several pharmacodynamic effects of metformin could be protective in sepsis. The inhibition of mitochondrial enzymes of complex I of the respiratory chain and the mitochondrial isoform of glycerophosphate dehydrogenase at the time of increased inflammation may lead to reductions in mitochondrial electron transfer, oxygen consumption, generation of reactive oxygen species, and adenosine triphosphate (ATP) production and consumption. This is akin to hibernation, hence potentially affording mitochondrial protection (12, 37–40). Metformin also activates the cellular energy sensor adenosine monophosphate-activated protein kinase, which is otherwise induced by cellular stress (41, 42), switching off the ATP consuming pathways (38). This switch may improve cellular and organ function under the stressful conditions of initial sepsis, when the pharmacodynamic effect of premorbid metformin may still be present (43, 44).

Third, metformin has some antimicrobial properties that affect multiple bacterial and viral pathogens (45, 46). Metformin may facilitate bacterial eradication in sepsis by improving host neutrophil activation, chemotaxis, and phagocytosis and by inhibiting the differentiation of monocytes into macrophages, reducing their secretion of pro-inflammatory cytokines (49, 50). However, inhibition of cytokine secretion by metformin during protracted *Candida albicans* sepsis in mice led to reduced survival (47) and in mice with sepsis caused by *Escherichia coli*-induced peritonitis, metformin pretreatment had no effect on mortality (48).

The ability of metformin to improve insulin sensitivity, reduce hepatic gluconeogenesis, and improve blood sugar level control may also play a role during the initial stage of sepsis. Hyperglycemia, hypoglycemia, and large variability in blood sugar levels are associated with increased mortality, in particular, for nondiabetic patients with sepsis (49–52)..

The results of our meta-analysis are pertinent to critical care physicians, endocrinologists, and other practitioners. Metformin seems to confer overall survival benefit in the diabetic population and appears to be associated with reduced risk of developing sepsis and decreased mortality if sepsis develops (53–55). An association of metformin use with lower mortality in older patients with pneumonia was similarly reported in a preliminary study (56). Of interest, critically ill burned patients started on metformin instead of insulin displayed improved glycemic control and reduced inflammation (57). Our systematic review questions the often negatively perceived role of metformin use in patients with sepsis and in patients at risk of developing sepsis.

By nature of the subject, the eight included studies were all cohorts of patients with sepsis and did not include any randomized control trial. Thus, systematic confounding and risk of bias cannot be ruled out. In the sensitivity analysis, however, removing studies with a serious risk of bias did not affect our findings. The risk of bias can be minimized by adjusted analysis. Unfortunately, the six studies that provided adjusted analysis used different methods precluding direct comparison (15, 27, 29–32). An overview of adjusted risks is appended (**Supplementary Table 6**, Supplemental Digital Content 14, http://links.lww.com/CCX/A36). The relatively small number of included studies has reduced the power to detect any publication bias.

The sensitivity analysis also revealed that when only diabetic patients with sepsis are included in the control group, the certainty of the association between premorbid metformin exposure and decreased mortality is reduced. This may seem surprising as the higher prevalence of chronic renal failure in diabetics not exposed to metformin may have favored metformin users. The nonsignificant association in diabetics is likely explained by the relatively small number of patients in the four studies concerned; 700 diabetics, out of whom 243 patients were on metformin. Of note those studies were all conducted in the ICU. Other factors specific to diabetics, such as looser glycemia targets, less hypoglycemia, or the inclusion of type I diabetics in the control groups, could be responsible.

None of the studies were able to specify the duration or consistency of premorbid metformin exposure. The inconsistency could be a contributing factor to our finding regarding hyperlactatemia. A further reason could be the selection bias caused by the inclusion of patients with specific lactatemia threshold that may have obscured any differences in hyperlactatemia between the groups.

Another limitation of this review is the variability in the way sepsis severity and data on organ dysfunction variables were reported, which affected our ability to assess the influence of disease severity on patient outcome and to conduct meta-analysis on the prevalence and severity of specific organ dysfunctions. In the future, population-based studies or analysis of sepsis registries might be helpful to delineate whether premorbid metformin exposure is associated with specific organ protection in sepsis.

CONCLUSIONS

In conclusion, this systematic review and meta-analysis suggests that metformin exposure prior to an episode of sepsis may be associated with decreased mortality. We could not confirm that metformin significantly increases blood lactate levels in patients with sepsis. The association between premorbid metformin exposure and organ dysfunction in sepsis requires further investigation.

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