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Role of secondary sepsis in COVID-19 mortality: Observations on patients with preexisting diabetes mellitus and newly diagnosed hyperglycemia

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Abstract

Diabetics who develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are more likely to have severe disease, higher odds of intensive care requirement and mortality. Fifteen percent of patients have new onset hyperglycemia. We studied the comparative outcomes between prior DM, newly detected hyperglycemia and assessed role of secondary sepsis on mortality. RWe performed a r etrospective study of confirmed SARS-CoV-2 patients at a tertiary care hospital in Chennai, India. Patients were divided as 2 groups (Group 1: With preexisting diabetes mellitus, Group 2: With newly diagnosed hyperglycemia due to newly detected diabetes mellitus or non-diabetic hyperglycemia. Clinical and laboratory data was analysed. Two hundred and thirty eight patients had prior-diabetes mellitus (Group 1) and 40 had newly diagnosed hyperglycemia (Group 2). Thirty four of group 1 and 7 of group 2 patients required intensive care. Mean capillary blood glucose (MCBG) during hospital stay was 207 mg/dl (Group 1) and 192 mg/dl (Group 2). Twentysix patients (9.3%) had secondary sepsis of which sixteen died. Logistic regression identified secondary sepsis($p<0.0001$), elevated D-dimer >6 fold ($p= 0.0001$), elderly $p=0.0045$), male ($p=0.0006$), NLR >5 ($p=0.01$),serum creatinine ≥2 mg/dl ($p=0.0004$), FiO_2 requirement >0.6 in first 48 hours ($p=0.001$) as mortality predictors.Our study observed a 14.38 % prevalence of newly diagnosed DM or non-diabetic hyperglycemia. Secondary sepsis and >6 fold elevation in D-dimer were strong predictors of mortality. Steroid use possibly contributed to secondary sepsis. Early identification and aggressive management of secondary sepsis are necessary for diabetics.

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Introduction

Diabetes mellitus (DM) is the most common chronic illness worldwide with a global burden of 493 million as estimated (2019) by the International Diabetes Federation [1]. Synthesis of advanced glycosylation end products (AGE), pro-inflammatory cytokines, oxidative stress and increased adhesion molecules leading to inflammation are proposed mechanisms for poor outcomes of infection in DM [2]. Research from Asian and Western countries have shown that diabetics who develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are more likely to have severe disease, higher odds of intensive care requirement and greater risk of developing acute respiratory distress syndrome [3-5]. Initial reports from China suggested that presence of prior DM increased the hazard of mechanical ventilation and death [6]. Subsequent observations have identified new onset diabetes in SARS-CoV-2 infection with various explanations for this association [7]. The observation of new onset diabetes has been reported in SARS-CoV (2010) infection in a study wherein 20 of 39 participants developed diabetes [8]. This was attributed to virus induced damage to pancreatic islets. SARS-CoV-2, like its predecessor, binds to the angiotensin converting

enzyme 2 receptor, which is synthesized in many non-respiratory parts of the body which includes pancreatic islets, kidney and adipose tissues. Virus induced alterations to glucose metabolism is believed to result in new onset diabetes [9]. Higher stress conditions due to infection with SARS-CoV-2 may also trigger greater release of hyperglycemic hormones; such as glucocorticoids and catecholamines, leading to increased blood glucose levels [10]. However undiagnosed hyperglycemia with a prevalence as high as 12% has been reported among patients admitted to hospital for non-hyperglycemicreasons [11]. Published studies have assessed various associations between diabetes and SARS-CoV-2 including prevalence of DM, association between fasting blood sugar, HbA1c, pre and intra illness glycemic control and outcomes [3-7]. However comparative studies of outcomes between prior DM, newly diagnosed DM, and analysis of specific factors contributing to adverse outcomes are lacking. We aimed to compare the outcomes in the mentioned groups and assess the effect of steroids and the influence of secondary sepsis on in-hospital mortality.

Methods

Design and setting

This was a retrospective study at a tertiary care teaching hospital in Chennai, India. The study population were patients hospitalized in ward, high dependency unit and intensive care unit between May to August 2020 corresponding to the first wave of COVID in India. The subjects were aged >18 years, with confirmed SARS-CoV-2 by RT-PCR of naso-pharyngeal swab. Patients who were discharged <48 hours and those discharged against medical advice for whom outcomes were not known were excluded.

Classification of study population

Patients were divided into 2 groups. Group 1: patients with pre-existing diabetes mellitus based on history and/or documentation of blood sugar and HbA1c consistent with diabetes mellitus before the current illness. Group 2: patients with newly diagnosed hyperglycemia which includes a) those with newly detected diabetes mellitus as evidenced by fasting blood sugar ≥126 mg/dl, or post prandial blood sugar ≥200 mg/dl and a HbA1c ≥6.5 during current hospitalization; and b) those with non-diabetic hyperglycemia as evidenced by random blood sugar >140 mg/dl and HbA1c <6.5 as per the recent American Diabetes Association guidelines [12]. For all newly detected hyperglycemia blood sugars were rechecked at least twice to confirm hyperglycemia SARS-CoV-2 illness severity was classified based on need for oxygen support as i) mild (peripheral oxygen saturation >94% on room air); ii) moderate (saturation between 90-94%); and iii) severe (saturation <90%).

Data collection

Data collection was done by study investigators by manual perusal of inpatient case sheets, investigation in computerized patient data system and transcription database for discharge summaries. Details of basic demography, presence of symptoms (fever, throat pain, cough, dyspnea, diarrhea, anosmia, myalgia) hemodynamic parameters on admission and during course of stay, daily clinical assessment, initial and follow-up laboratory tests (complete blood count, venous blood sugar, capillary blood sugar, serum creatinine, serum electrolytes (Na, K, Cl, HCO_3) liver function tests (bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, albumin and globulin), C-reactive protein, serum ferritin, lactate dehydrogenase, D-dimer, cultures of body fluid as appropriate and additional tests requested by treating clinician), chest imaging, medications administered (steroids, heparin, remdesivir and antibiotics), oxygen support, organ dysfunction, secondary sepsis and final outcome were collected and analysed. Outcomes measured were death, discharge to home and complications during hospital stay.

Ethics

The study was approved by the Institutional Ethics Committee with waiver of informed consent of patients as permitted by the national regulatory body. Patient identification was deidentified reversibly for the purpose of analysis.

Statistical analysis

Variables were described as mean (standard deviation, interquartile range) and number (%). Difference between groups (means or proportions as appropriate) were assessed with Chi-square test, Fischer's exact test and *t*-test. Correlation was tested with Pearson correlation co-efficient followed by test of significance. Clinical and laboratory variables (age, gender, risk factors for COVID illness, glycated haemoglobin, mean capillary blood sugar during hospital stay, NLR, D-dimer, CRP, ferritin, LDH, serum bilirubin, transaminase, alkaline phosphatase, albumin, globulin, serum creatinine, secondary sepsis, requirement for oxygen) which had a sensitivity and specificity of >70% in predicting mortality were incorporated in the regression model and assessed .The model with the best goodness of fit was selected for analysing the factors associated with mortality. A p value of <0.05 was considered statistically significant. Comparison was not done if one or more of the comparing parameter was null. Statistical analysis was done by IBM.SPSS statistics software, 23.0 version.

Results

Presenting features

Two hundred and thirty eight patients had prior-diabetes mellites (Group 1) and 40 had newly diagnosed hyperglycemia (Group 2). The latter group had 12 non-diabetic hyperglycemia and 28 newly diagnosed diabetes mellitus as defined in the study methods. Patients in group 1 were significantly older compared to group 2 (p=0.0002). The interquartile range for age of entire study cohort was 54 to 67 years and three-fifths were men. The baseline characteristics of the study participants are described in Table 1. Group 2 had a higher frequency of symptoms compared to group 1 in terms of fever, cough, breathlessness, anosmia and dysgeusia. Proportion of severity of illness was not significantly different between groups. Presence of hypertension was more frequent in group 1 which was statistically significant (p=0.001). Mean glycated hemoglobin at admission was significantly lower in group 2 compared to group 1 (p=0.001). One hundred and eighty (75.6%) of group 1 patients were on oral hypoglycemic agents (OHA) and 58 were not on any diabetic medications at admission (had discontinued medication prior to current illness). Of the group of 12 with non-diabetic hyperglycemia, 7 had mild and 5 had moderate disease severity None had coexistent bacterial sepsis at hospitalization.

Course during hospital stay and mortality

Mean and median day of presentation to hospital after onset of symptoms was 4.62 and 5. Table 2 describes the lab parameters,

complications and medications administered in the study cohort. Thirty four of Group 1 and 7 of Group 2 patients required intensive care. Mean capillary blood glucose (MCBG) during hospital stay was 207 mg/dl (Group 1) and 192 mg/dl (Group 2). Participants who received steroids had a significantly higher MCBG (259±92.8 mg/dl) compared to those who did not receive steroids (171±60.5 mg/dl, p<0.001) .There was no significant difference (p=0.94) in the mean capillary blood glucose levels between patients who received methylprednisolone (256.6±92.87 mg/dl) and dexamethasone (258.2±77.7 mg/dl). Glycemic control among subjects who received steroid or no steroid is shown in Figures 1 and 2. Hundred and four received methylprednisolone (Group 1 = 94, Group 2 = 10) and 16 received dexamethasone (Group 1 = 10, Group 2 = 6). Figure 3 shows the positive correlation between

Table 1. Baseline characteristics of study participants.

Clinical variable	Group 1 Prior diabetes (n=238)	Group 2 Newly diagnosed hyperglycemia (n=40)	p-value
Age in years (mean±SD)	56.5±12	48.5±13.3	0.0002
Gender, n (%)			
Male	140 (58.8)	29(72.5)	0.10
Female	98 (41.2)	11(27.5)	
Presenting symptoms, n (%)			
Fever	214 (89.9)	40 (100)	0.03
Sore throat	58(24)	40 (100)	<0.001
Cough	100(42)	40 (100)	<0.001
Breathlessness	66 (27.7)	40 (100)	<0.001
Anosmia	21(8.8)	20(50)	<0.001
Dysgeusia	9(3.8)	8(20)	0.001
Myalgia	39(16.4)	39(97.5)	<0.001
Severity of illness, n (%)			
Mild	157 (66)	23 (57.5)	0.30
Moderate	51 (21.4)	10 (25)	0.61
Severe	30 (12.6)	7 (17.5)	0.39
Pre-existing illness, n (%)			
SHT	126 (52.9)	8 (20)	0.001
CAD	35 (14.7)	2 (5)	0.13
CKD	10 (4.2)	2 (5)	0.68
Prior glycemic control			
HbA1c	8.7±2.2	7.7±1.6	0.001

SHT, systemic hypertension; CAD, coronary artery disease; CKD, chronic kidney disease.

Table 2. Comparison of post hospitalization parameters.

Parameter	Group 1 Prior diabetes (n=238)	Group 2 Newly diagnosed hyperglycemia (n=40)	p-value
Mean, SD or n (%)			
NLR	5.8±18.3	4.01±4.6	0.56
Ferritin ng/mL	306.9±642.6	310±295.4	0.97
LDH IU/L	294.2±127.2	351.8±176.8	0.02
Blood sugar during hospital stay, mg/dl	207.2±88.8	192.4±70.5	0.45
D-Dimer, mg/L			
Normal	121 (54)	13 (37.1)	0.23
1 to 2 fold elevation	42 (18.8)	12 (34.3)	
2 to 6 fold elevation	29 (12.9)	4 (11.4)	
>6 fold elevation	32 (14.4)	6 (17.2)	
Chest X-ray, n (%)			
Normal	95 (39.9)	15(37.5)	0.94
Single lobar opacities	19(8)	3(7.5)	
Multi-lobar opacities	124(52.1)	22(55)	
Medications received, n (%)			
Steroids	104 (43.6)	17 (42.5)	0.89
Heparin	121 (50.8)	18 (45)	
Remdesivir	16 (6.7)	1 (2.5)	
Antibiotics	23 (9.7)	3 (7.5)	
Insulin	92 (38.7)	13 (32.5)	

NLR, neutrophil lymphocyte ratio; LDH, lactate dehydrogenase.

admission glycated hemoglobin and mean venous blood sugar during hospital stay (r=0.46, p<0.001).

Secondary bacterial infections: Twenty six patients (9.3%) received antibiotics for secondary bacterial infections of which sixteen died (Group 1 = 14, Group 2 = 2). The majority of the infections developed after a median of 6 days of hospital stay. Seven infections were polymicrobial (Group 1 = 6, Group 2 =1). The commonest foci of infection were lung or urinary tract. The blood stream pathogens were Acinetobacter (n=9), Klebsiella (n=3), Pseudomonas (n=2), Serratia (n=2) and Proteus (n=1). Nine patients in mild and moderate group had urinary tract infection, organisms included *Escherichia coli* (n=5), Enterococcus (n=3), Streptococci (n=1). The antibiotics administered were cefaperazone-sulbactum (n=3), piperacillin-tazobactum (n=6), meropenem (n=9), vancomycin (n=3), colistin (n=5). Four had candidemia and were treated with capsofungin. We did not observe any other fungal infections such as Mucormycosis during the hospital stay.

Eight patients had cardiac complications (Group 1 = 7, Group 2 = 1). This included one from group 2 who had posterior circulation stroke with atrial fibrillation (AF) and heart failure. Others from group 1 had AF (n=1), viral myocarditis (n=1), acute coronary syndrome (n=3), heart failure (n=2). Five of the patients who had cardiac complication also had secondary sepsis and all 8 died. Two had pneumothorax (one in each group). Overall, 24 (8.6%) patients died; 19 (8%) in Group 1 and 5 (12.5%) in Group 2. The difference in mortality between groups was not significant (p=0.34) Logistic regression (Table 3) identified secondary sepsis, elevated D-dimer

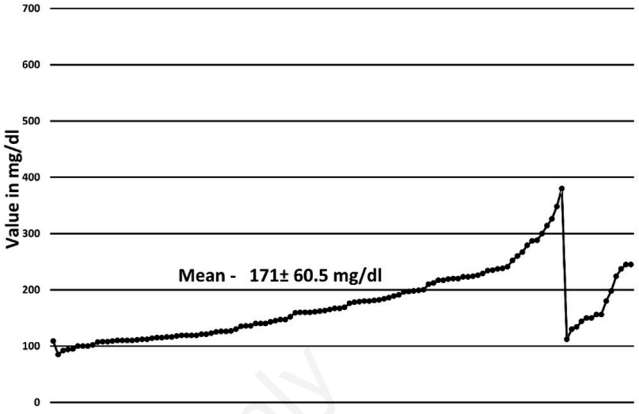

Figure 2. Mean capillary blood glucose values of patients not administered steroids therapy during hospital stay.

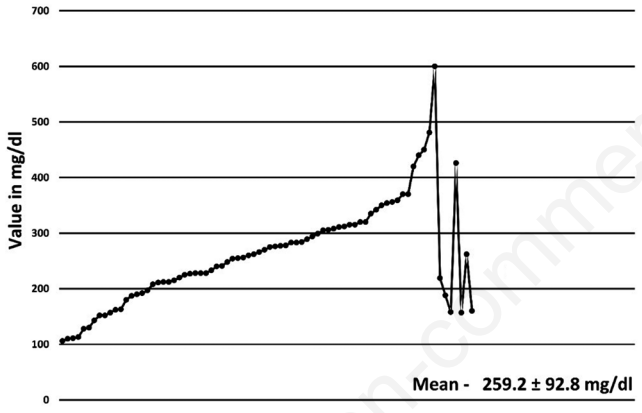

Figure 1. Mean capillary blood glucose values of patients administered steroids during hospital stay.

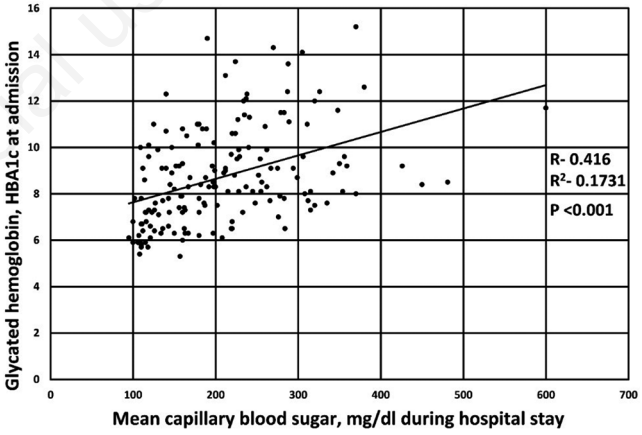

Figure 3. Relation between glycated hemoglobin and mean capillary blood glucose during hospital stay for all study subjects.

Table 3. Risk factors for mortality assessed using multiple logistic regression.

Variable	Odds ratio	Confidence interval Upper	Lower	p-value
Age ≥65 years	4.21	1.56	11.29	0.0045
Male gender	7.67	2.39	24.55	0.0006
Risk factors ≥3	1.79	0.68	4.72	0.23
MCBG >200 mg/dl	0.94	0.35	2.52	0.91
NLR >5	3.43	1.26	9.32	0.01
D-dimer >6 fold elevation	7.82	2.72	22.42	0.0001
CRP >10 fold elevation	1.55	0.57	4.17	0.38
Secondary sepsis	28.01	8.67	90.33	<0.0001
Serum creatinine ≥2 mg/dl	11.52	2.98	44.57	0.0004
FiO_2 >0.6 in the first 48 hour	4.18	1.78	9.82	0.001

MCBG, mean capillary blood glucose; NLR- neutrophil lymphocyte ratio; CRP, C-reactive protein; FiO2, fraction of inspired oxygen.

>6 fold, elderly age ≥65 years, male gender, elevated CRP >10 fold, NLR >5, serum creatinine ≥2 mg/dl, need for oxygen with FiO_2 requirement >0.6 in the first 48 h as predictors of mortality.

Discussion

Diabetes mellitus has been the second most common comorbidity after systemic hypertension in most of the large cohorts of SARS-CoV-2 infection [13]. Presence of diabetes mellitus poses an increased risk of severe bacterial, viral and fungal infections due to a variety of reasons including reduction in macrophage function with less polymorphonuclear mobilization, altered cytokine response and poor cell mediated immunity [14]. In SARS-CoV-2, the increase in thrombotic events is an added concern as diabetes mellitus causes endothelial dysfunction, enhanced platelet aggregation and activation and is associated with prothrombotic hypercoagulable state [15].

Meta-analysis on diabetic patients with SARS-CoV-2 infection has shown a mean age ranging between 47 to 60 years with a male preponderance which was consistent with finding seen in our study [16]. Data on new onset diabetes from 8 studies with a total patient population of 3711 has shown that a pooled proportion of 14.4% were newly diagnose [17]. This was similar to our study where 14.38% were newly diagnosed. Greater release of hyperglycemic hormones due to stress induced by the disease leading to increased blood glucose levels appears to play a significant role [10]. The effects of the virus on ACE-2 receptors and subsequent changes in the pancreatic islets such as direct beta cell damage and effect of unopposed angiotensin II which can impede secretion of insulin may explain the glycemic abnormality in SARS-CoV-2 infection [17] .

Presence of a high admission HbA1c of 7.7 in the newly diagnosed group possibly indicates a long duration of undiagnosed diabetes prior to hospitalization in our study. Hence, the observed new diabetes mellitus cannot be solely attributed to COVID-19 or its therapy and a significant proportion is probably undiagnosed diabetes mellitus that was diagnosed during hospitalization for COVID-19. In-hospital hyperglycemia is a common finding and represents an important marker of poor clinical outcome and mortality in patients with or without a history of DM [18]. While clinical symptoms were more common in Group 2, there were no differences between the two groups in terms of laboratory findings with the exception of LDH which was significantly higher in Group 2.

Worse outcomes and increased occurrence of diabetic ketoacidosis have been reported in SARS-CoV-2 infection in newly detected diabetic patients possibly due to infection related stress [19]. Steroids have been the only mortality lowering agent in the management of patients with severe SARS-CoV-2 infection. Evidence from the RECOVERY trial, which showed a one fifth to one third reduction in mortality in patients on oxygen and mechanical ventilation, led to steroid use as a standard of care [20]. The benefits of steroid appear to be due to reduction in systemic inflammation related organ injury. However it is well known that corticosteroids increase hepatic gluconeogenesis, augment glucose production and decrease its peripheral utilization, alter insulin secretion by reducing incretin effect all of which contribute to increase in blood sugars [21]. It is estimated that between 20-54% of patients treated with steroids develop diabetes [22]. This is linked to both the dose and duration of steroid therapy. One hundred and twenty (43%) of our patients were administered steroids which included all those who required either oxygen or ventilator support. There was a significant hyperglycemia in the group that received steroids compared to the rest. Steroids are also known to cause increased risk of infections. A meta-analysis showed high rates of associated secondary bacterial infection in patients treated with corticosteroids [23]. Use of steroids in diabetes irrespective of the indication has benefits and harms. Elderly patients with chronic obstructive pulmonary disease and diabetes on chronic use of corticosteroids had a 94% higher risk of being hospitalized [24]. Studies on postoperative infections showed diabetes, perioperative hyperglycemia and steroid use were associated with increased risk of infections [25,26].

However data on use of low dose short term steroids in sepsis in large studies such as ADRENAL did not show any difference in complications such as infections or wound dehiscence between the treated and untreated groups [27]. Steroids, while lowering mortality due to its beneficial effects on inflammation, may contribute to late mortality due to SARS-Cov-2 as evidenced by a high mortality among patients with secondary sepsis. A better reporting of sepsis and its outcome among steroid recipients would enable us to identify if steroid harms a sub-set of diabetic patients. A meta-analysis of 14 studies revealed an odds for mortality in diabetics ranging from 1.60 (America and Europe) to 2.12 (Asia) [28]. Our study had a mortality rate of 8.6%. Comparing the complications and mortality between the 2 groups, there was a trend towards higher mortality in newly detected hyperglycemia (12.5% *versus* 8%) despite the patients being younger, having less comorbidities and lower HbA1c than preexisting diabetes. Prior studies that focused specifically on mortality in COVID-19 with diabetes identified older age, male sex, altered body mass index, history of hypertension, cardiovascular disease, stroke, higher glucose, elevated creatinine, high NLR and C-reactive protein as predictors of mortality [29,30].

In addition, our study identified secondary bacterial or fungal sepsis, admission D-dimer >6 fold, oxygen requirement at admission with FiO_2>0.6 to be highly significant predictors of mortality.

It is possible that apart from poorly controlled diabetes, the administration of steroids also contributed partially to the occurrence of secondary infections. A meta-analysis of 24 studies that looked at bacterial coinfection and secondary infection in SARS-CoV-2 patients showed an overall rate of infection of 7.7% with Mycoplasma, Haemophilus and Pseudomonas being the commonest bacteria [31]. However this data was pre steroid use and mortality rates among those with secondary sepsis was not analysed. Data from China showed that gram negative bacteria were responsible for the majority of secondary infections that affected 6.8% of SARS-CoV-2 patients and was associated with a near 50% mortality [32].

Our study had no coinfections but 9.3% of secondary bacterial infections with gram negative organisms contributing to 100% of bacteremia and 55% of urinary tract infections. Four patients had candidemia(in all these cases, there was also gram negative sepsis) and all 4 succumbed to the disease. During the second wave of COVID infections in India, there have been reports of Mucormycosis, a diabetes defining illness, raising its ugly head with both rhinocerebral and pulmonary being the affected sites [33]. However, we did not see any Mucormycosis in hospital during the first wave.

Published studies have shown elevated D-dimer to be an important marker in assessment of poor outcomes possibly as a indicator of associated coagulopathy with a higher risk of developing arterial and venous thrombotic complications [34]. D-dimer is known to be higher in diabetics compared to non-diabetics, possibly due to an atherogenic state in the former [34]. Nevertheless very high values >6 fold compared to normal was predictive of adverse outcomes.

Hypoxia, especially room air saturation of <90% has consis-

tently been shown to have high risk of mortality, probably reflecting greater degree of lung involvement [35]. Presence of silent hypoxia, late hospital presentation are features that may be associated with hypoxia. No trial has looked at specific link to DM or need for particular FiO_2.We found that admission hypoxia with higher oxygen requirement was linked to outcomes.

Conclusions

Our study observed a higher prevalence of complications in newly detected hyperglycemia compared to preexisting diabetes mellitus though this was not statistically significant. Sepsis was a major cause for mortality and 16 patients who developed secondary sepsis died, raising the possibility of a detrimental effect of steroid use. Further studies focusing on identification and aggressive treatment of sepsis in diabetes especially among steroid recipients may help in lowering the mortality among diabetics with SARS-CoV-2 infection.

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