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RESEARCH LETTER

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The benefit of dexamethasone in patients with COVID-19 infection is preserved in patients with diabetes

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KEYWORDS: COVID-19, dexamethasone, diabetes, mortality

1 | INTRODUCTION

Dexamethasone significantly reduces mortality[1] and is now standard treatment for patients with COVID-19 who require supplemental oxygen and/or mechanical ventilation. However, supraphysiological doses of glucocorticoids may exacerbate dysglycaemia and precipitate hyperglycaemic complications, particularly in those with or at risk of type 2 diabetes.[2] The RECOVERY trial[1] reported a low incidence of hyperglycaemic complications (2/1996, 0.1%), although the real-world incidence is likely to be much higher.[3] Type 2 diabetes itself increases the risk of severe COVID-19,[4] and hyperglycaemia independently predicts poor outcomes.[5] We investigated the possibility that patients with diabetes may derive less survival benefit from steroid therapy in the setting of severe COVID-19 infection.

Chioma Izzi-Engbeaya and Victoria Salem are joint senior authors.

2 | METHODS

We performed a retrospective analysis of the characteristics of all nonpregnant adults hospitalized with COVID-19 infection between 9 March 2020 and 22 April 2020 (UK COVID-19 Wave 1)[6] and between 1 November 2020 and 31 January 2021 (UK COVID-19 Wave 2) in three hospitals within Imperial College Healthcare NHS Trust (ICHNT), London. Clinical factors associated with a composite outcome of death and/or intensive care unit (ICU) admission, or mortality alone, within 30 days of COVID-19 diagnosis were assessed in all patients in Wave 1 and Wave 2 combined.

In Wave 1, dexamethasone was not used as a treatment for COVID-19 infection in ICHNT. By Wave 2, ICHNT inpatient COVID-19 treatment guidelines included 6 mg/d dexamethasone as standard of care for all patients admitted with COVID-19 infection that required supplemental oxygen, regardless of their diabetes status.

We also recorded dexamethasone-induced hyperglycaemic complications in Wave 2, as well as length of stay in hospital in Wave 1 and Wave 2.

GraphPad Prism 9.0 statistical software was used to perform Mann-Whitney tests on nonparametric data, and Fisher's exact tests were used for univariate analyses. Matlab code and STATA software were used to perform unbiased multivariate logistic regression analysis to determine factors associated with death and/or ICU admission or 30-day mortality alone. The multivariate analysis was performed on all 2261 patients studied (Wave 1[6] plus Wave 2) and we report both the logit coefficients and associated odds ratios. In brief, this analysis aims to identify and quantify the contribution of both preexisting conditions and presenting clinical features that are independently (eg, all other measured features being equal) associated with death from COVID-19.

One of the measures that were chosen a priori was FiO_2, that is, the maximum oxygen requirement during admission—a direct measure of disease severity. Rather than arbitrarily remove this factor from this analysis, we elected to control for the potential endogeneity[7] of FiO_2 (which would otherwise invalidate the statistical analysis), we ran a first stage regression of FiO_2 on a set of exogenous regressors (clinical frailty score, admission temperature, respiratory rate, heart rate and systolic blood pressure), which showed a good fit (R^2 of 30%). Thereafter the logit specifications were run in STATA, adding the residuals from the first stage regressions. Both regressions displayed a good fit, with adjusted R^2 equal to 36% for the composite primary endpoint of death and/or ICU admission and 31% for 30-day mortality alone. This increased our confidence that our findings were unbiased.

3 | RESULTS

During Wave 2, 1372 adults were admitted to ICHNT hospitals with COVID-19 compared with 889 admissions in Wave 1.[6] There was no improvement in the composite endpoint of death/ICU admission between Wave 1 and Wave 2 (Wave 1: 34.7% vs. Wave 2: 33.6%; $P = 0.60$). However, there was a significant reduction in 30-day mortality alone in Wave 2, both for the entire cohort (Wave 1: 27.5%

TABLE 1 Multivariate analysis of clinical factors independently associated with the primary outcome of death or intensive care unit admission in patients hospitalized due to COVID-19

Variable	Death or ICU admission within 30 days			
	Logit coefficient	SE	OR	SE
Wave 1	−0.484	0.281	0.616	0.18
Age	**0.183****	0.00063	**1.018****	0.00662
Weight (kg)	**−0.00937***	0.00419	**0.991***	0.00427
Female	**−0.335***	0.155	**0.715***	0.114
White	0.194	0.157	1.02	0.171
Diabetes	−0.289	0.229	0.749	0.174
Stroke	−0.0506	0.224	0.951	0.216
Heart disease (IHD +/− CCF)	**0.413***	0.178	**1.511***	0.289
Hypertension	−0.0461	0.163	0.955	0.159
Admission eGFR	**−0.0157****	0.00303	**0.984****	0.0031
FiO_2 (maximum during admission)	**0.0711****	0.00927	**1.074****	0.0104
Dexamethasone usage—patients without diabetes	**−0.854***	0.349	**0.426***	0.149
Dexamethasone usage—patients with diabetes	**−0.786***	0.357	**0.456***	0.174
Remdesivir	−0.0995	0.201	0.905	0.186
Tociluzimab	−0.12	0.453	0.887	0.39
Residual FiO_2	−0.00951	0.00942		
Constant	−3.254**	0.723		

Note: Unselected multivariate logistic (Logit) analysis of clinical variables that were collected for patients admitted with swab positive COVID-19 in Wave 1 and Wave 2 combined, as applied to the composite outcome of death and/or ICU admission within 30 days. Regressors were included if accurate data was available for >80% of the combined pool of 2261 patients. For categorical variables, a positive "estimate" indicates an increased risk of the composite outcome (death or ICU admission) with that variable present, and a negative estimate indicates a reduced risk of the composite outcome if that variable is present. For continuous variables, a positive "estimate" indicates an increased risk of the composite outcome with that variable increasing, and a negative estimate indicates a reduced risk of the composite outcome if that variable is decreasing. The *P* value is a measure of the confidence of that variable being an independent predictor of the composite outcome corrected for all of the other regressors listed. Bold values are used to highlight variables with significant *P*-values.

Abbreviations: CCF, congestive cardiac failure; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; IHD, ischaemic heart disease; ICU, intensive care unit; OR, odds ratio.

*P <0.05;

**P <0.01 for the independent logit coefficient or OR.

vs. Wave 2: 17.2%; $P < 0.001$, odds ratio [OR] 0.55 [95%CI 0.45-0.67]) and for patients with diabetes (Wave 1: 36.1% vs. Wave 2: 22.3%; $P < 0.001$, OR 0.51 [95%CI 0.37-0.70]).

Demographic and clinical characteristics of those admitted across both waves were similar. Duration of hospital admission was longer in Wave 2 (median [interquartile range] Wave 2: 11 [6-20] days vs. Wave 1: 8 [4-16] days; $P < 0.0001$). Diabetes was a recorded comorbidity for 337/889 patients (38%) in Wave 1[6] and for 456/1372 patients (33%) in Wave 2, with the majority having type 2 diabetes (Wave 1: 96% vs. Wave 2: 98%). The 2020/2021 prevalence of diabetes amongst adults in our local area was 3.5%.[8] Supporting Information Table S1 details the univariate analysis of clinical and demographic features of patients with diabetes associated with ICU admission/death within 30 days of COVID-19 diagnosis for Wave 2, which are very similar to our previously published findings for patients with diabetes in Wave 1.[6]

Similar to Wave 1,[6] univariate analysis of all patients in Wave 2 demonstrated that male gender (OR 1.56 [95%CI 1.29-1.90]; $P < 0.001$), hypertension (OR 1.54 [95%CI 1.28-1.87]; $P < 0.001$), heart failure (OR 2.65 [95%CI 1.83-3.87]; $P < 0.001$), increased frailty (Clinical Frailty Score ≥7: OR 2.43 [95%CI 1.72-3.44]; $P < 0.001$), impaired renal function (admission estimated glomerular filtration rate [eGFR] <60 mL/kg/min: OR 2.39 [95%CI 1.95-2.91]; $P < 0.001$) and hyperglycaemia (admission capillary blood glucose ≥10 nmol/L [180 mg/dL]: OR 1.50 [95%CI 1.07-2.07]; $P = 0.02$) were associated with an increased risk of death/ICU admission. Unlike in Wave 1,[6] in Wave 2, Black patients had a higher risk of ICU admission/death compared with White patients (OR 1.52 [95%CI 1.06-2.17]; $P = 0.03$).

Multivariate analysis of clinical factors associated with the composite risk of death/ICU admission for all 2261 patients are shown in Table 1. Ischaemic heart disease and renal failure were independent predictors of poor outcome, over and above a diagnosis of diabetes per se, suggesting that multimorbidity rather than any one risk factor alone is the major driver for COVID-19 mortality.[9] For the composite outcome of ICU admission/death (Table 1) as well as the single outcome of mortality alone (Table 2), the contributions of the major clinical risk factors to the odds of severe disease were similar to those which have been reported. We present the logit coefficient for the independent effect of dexamethasone usage for patients with and without diabetes, which allows us to conclude that the beneficial effect is not different

TABLE 2 Multivariate analysis of clinical factors independently associated with the death in patients hospitalized due to COVID-19

Variable	Death within 30 days			
	Logit coefficient	SE	OR	SE
Wave 1	0.372	0.305	1.451	0.416
Age	**0.0601****	0.00802	**1.062****	0.00825
Weight (kg)	−0.000987	0.00463	0.999	0.00451
Female	−0.325	0.167	0.723	0.124
White	0.104	0.169	1.11	0.19
Diabetes	−0.0793	0.231	0.924	0.191
Stroke	0.00737	0.223	1.007	0.2
Heart disease (IHD +/− CCF)	**0.486****	0.185	**1.625****	0.284
Hypertension	0.149	0.179	1.161	0.213
Admission eGFR	**−0.0176****	0.00326	**0.983****	0.00316
FiO_2 (maximum during admission)	**0.0329****	0.0107	**1.033****	0.0115
Dexamethasone usage—patients without diabetes	−0.184	0.378	0.832	0.311
Dexamethasone usage—patients with diabetes	0.0323	0.419	1.033	0.405
Remdesivir	−0.397	0.254	0.673	0.164
Tociluzimab	**−1.22***	0.609	**0.295***	0.173
Residual FiO_2	0.0147	0.0113		
Constant	−6.46**	0.932		

Note: Unselected multivariate logistic (Logit) analysis of clinical variables that were collected for patients admitted with swab positive COVID-19 in Wave 1 and Wave 2 combined, as applied to the outcome of death within 30 days. Regressors were included if accurate data was available for >80% of the combined pool of 2261 patients. For categorical variables, a positive "estimate" indicates an increased risk of the outcome (death) with that variable present, and a negative estimate indicates a reduced risk of the outcome (death) if that variable is present. For continuous variables, a positive "estimate" indicates an increased risk of the outcome (death) with that variable increasing, and a negative estimate indicates a reduced risk of the outcome (death) if that variable is decreasing. The *P* value is a measure of the confidence of that variable being an independent predictor of the primary outcome corrected for all of the other regressors listed. Bold values are used to highlight variables with significant *P*-values.

Abbreviations: CCF, congestive cardiac failure; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; IHD, ischaemic heart disease; OR, odds ratio.

*P <0.05;

**P <0.01 for the independent logit coefficient or OR.

between these two groups (all other cofactors being equal). Dexamethasone use was associated with a lower probability of ICU admission/death (Table 1), and its effect was very similar in patients with and without diabetes ($P = 0.82$ using an F-test for equality of the logit coefficients). However, dexamethasone use was not associated with a reduction in mortality in patients with diabetes and in patients without diabetes (Table 2).

Dexamethasone was not used as a treatment for COVID-19 during Wave 1. In Wave 2, dexamethasone was used in 68.2% of patients (n = 935), 35% of whom had diabetes (indicating no bias against patients with diabetes for the use of dexamethasone). Only 21 patients who were eligible for dexamethasone treatment (ie, required supplemental oxygen) did not receive dexamethasone: four received alternative corticosteroid therapy (prednisolone and/or methylprednisolone), five had a transient oxygen requirement, one self-discharged and 11 rapidly deteriorated and received palliative care. Amongst patients who received dexamethasone, there was no difference in median length of stay between patients with diabetes and patients without diabetes (with diabetes 11 [interquartile range 6-19] vs. without diabetes 10 [interquartile range 6-18]; $P = 0.18$).

The doses of dexamethasone used are shown in Supporting Information Table S2. A total of 90% of patients (841/935) received 6 mg/d dexamethasone (ie, the dose used in the RECOVERY trial[1]). Unsurprisingly, the average capillary blood glucose levels in the 72-hour period following COVID-19 diagnosis were higher in patients with diabetes treated with dexamethasone compared to patients with diabetes who were not treated with dexamethasone (12.3 ± 4.4 vs. 10.0 ± 4.3 mmol/L; $P < 0.0001$).

Hyperglycaemia meeting the threshold for additional pharmacotherapy (ie, ≥12 mmol/L) occurred in 19% of patients (178/935) who received dexamethasone (21 patients were treated with oral antihyperglycaemic agents, 122 were treated with insulin alone, 33 were treated with both insulin and oral antihyperglycaemic agents and two patients did not receive antihyperglycaemic therapy). Of all patients admitted in Wave 2, 19 (ie, 1.4% [19/1372], 11% [19/178] of all patients with dexamethasone-induced hyperglycaemia) were classified as having dexamethasone-induced diabetes, based on no prior diagnosis of diabetes at admission and the requirement for new antihyperglycaemic medication at discharge. Furthermore, in dexamethasone-treated patients, 1.4% (13/935) developed diabetic ketoacidosis and 2.7% (25/935) developed hyperglycaemic hyperosmolar syndrome. Of the patients who developed dexamethasone-induced hyperglycaemia, neither pre-existing diabetes nor type of glucose-lowering treatment received were associated with increased risk of ICU admission/death on univariate analysis (Supporting Information Table S3).

4 | DISCUSSION

Mortality within 30 days of COVID-19 diagnosis was significantly lower in Wave 2, with dexamethasone usage (but not remdesivir) independently associated with a reduced risk of ICU admission and/or death. By 10 January 2021 (in London), vaccine coverage was low (1st dose received: 29.5% of people aged ≥80 years and 1.1% of people aged <80 years; 2nd dose received: 9.1% of people aged ≥80 years and 0.1% of people aged <80 years[10]); thus, it is unlikely that vaccination would have had a major effect on the reduced mortality seen in Wave 2 in this study.

Multivariate analysis revealed that the independent effect size of dexamethasone on reducing COVID-19 severity was similar for patients with and without diabetes. This suggests that the benefits of dexamethasone in people with diabetes remain substantial despite the occurrence of dexamethasone-related hyperglycaemic complications in a fifth of patients. Dexamethasone should continue to be used with confidence in patients with diabetes and severe COVID-19, but treatment guidelines should incorporate strategies for identification and management of steroid-induced hyperglycaemia.[2] Service providers must also be aware of the extra resource required to manage glycaemic complications whilst treating inpatients and also post discharge.[3]

CONFLICT OF INTEREST

All authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Victoria Salem and Tricia M. Tan. Investigation: all authors. Analysis: Walter Distaso, Pei Chia Eng, Chioma Izzi-Engbeaya and Victoria Salem Data curation: Pei Chia Eng, Chioma Izzi-Engbeaya. and Victoria Salem. Writing – original draft: Pei Chia Eng, Chioma Izzi-Engbeaya and Victoria Salem. Writing – review and editing: all authors. Victoria Salem is the guarantor of this work, had full access to the data, and accepts full responsibility for integrity of the data and the accuracy of the data analysis.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Full access to primary data and statistical analyses are available upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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