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ORIGINAL ARTICLE

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A UK nationwide study of adults admitted to hospital with diabetic ketoacidosis or hyperosmolar hyperglycaemic state and COVID-19

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Abstract

Aims: To investigate characteristics of people hospitalized with coronavirus-disease-2019 (COVID-19) and diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS), and to identify risk factors for mortality and intensive care admission.

Names and affiliations for the Association of British Clinical Diabetologists (ABCD) COVID-19 audit group are provided in the online appendix.

Materials and methods: Retrospective cohort study with anonymized data from the Association of British Clinical Diabetologists nationwide audit of hospital admissions with COVID-19 and diabetes, from start of pandemic to November 2021. The primary outcome was inpatient mortality. DKA and HHS were adjudicated against national criteria. Age-adjusted odds ratios were calculated using logistic regression.

Results: In total, 85 confirmed DKA cases, and 20 HHS, occurred among 4073 people (211 type 1 diabetes, 3748 type 2 diabetes, 114 unknown type) hospitalized with COVID-19. Mean (SD) age was 60 (18.2) years in DKA and 74 (11.8) years in HHS ($p < .001$). A higher proportion of patients with HHS than with DKA were of non-White ethnicity (71.4% vs 39.0% $p = .038$). Mortality in DKA was 36.8% (n = 57) and 3.8% (n = 26) in type 2 and type 1 diabetes respectively. Among people with type 2 diabetes and DKA, mortality was lower in insulin users compared with non-users [21.4% vs. 52.2%; age-adjusted odds ratio 0.13 (95% CI 0.03-0.60)]. Crude mortality was lower in DKA than HHS (25.9% vs. 65.0%, $p = .001$) and in statin users versus non-users (36.4% vs. 100%; $p = .035$) but these were not statistically significant after age adjustment.

Conclusions: Hospitalization with COVID-19 and adjudicated DKA is four times more common than HHS but both associate with substantial mortality. There is a strong association of previous insulin therapy with survival in type 2 diabetes-associated DKA.

KEYWORDS
insulin therapy, pharmacoepidemiology, real-world evidence, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus is an independent risk factor for in-hospital mortality in patients admitted with COVID-19.[1] Exploring and understanding the effect of COVID-19 infection on the manifestation, natural history and outcomes of those with diabetes is therefore important, particularly for those presenting with diabetes-related emergencies. This is particularly true because the COVID-19 pandemic appears to have precipitated an increase in hyperglycaemic emergencies in those without a previously recognized diagnosis of diabetes.[2]

Reports to date describe patients admitted with hyperglycaemia and COVID-19 as older, with a higher body mass index (BMI) and more diabetes-related complications than those admitted with hyperglycaemia but without COVID-19.[3] COVID-19-associated hyperglycaemic crises have also been described as requiring higher insulin doses, taking longer to treat and being associated with greater mortality than hyperglycaemic crises in the absence of COVID-19.[4-6] People from ethnic minorities and with a previous clinical diagnosis of type 2 diabetes[7,8] appear to be over-represented among patients with COVID-19 and diabetic ketoacidosis (DKA).

Despite these findings, there are significant gaps in our understanding of COVID-19-associated hyperglycaemic emergencies. Notably, there have been surprisingly few studies exploring the effects of COVID-19 on hyperosmolar hyperglycaemic state (HHS) and only case reports have been published to date.[9] Many of the studies in this area have been small and the classification of DKA and HHS has been unclear.[10] The relative contribution of these two hyperglycaemic emergencies during the COVID-19 pandemic has not been described and the effect of different diabetes therapies on outcomes remains to be explored. The extent to which established prognostic factors for patients admitted with DKA and HHS are valid in the context of COVID-19 is also not clear. Furthermore, some previous studies have originated from single centres or from health care systems where access to health care may be restricted and associated with sampling error.[8]

Our aim was to provide further clarity on the demographics, natural history and outcomes of confirmed DKA and HHS hyperglycaemic emergencies in people admitted to hospital with COVID-19 infection across the UK.

2 | MATERIALS AND METHODS

2.1 | Patients and settings

A detailed description of the method of data collection for the ABCD nationwide audit of individuals admitted to hospital with COVID-19 and diabetes has been published elsewhere.[11] In brief, diabetes specialist teams in National Health Service (NHS) hospitals throughout the UK contribute pseudonymized data on patients with diabetes who have been admitted to hospital with COVID-19, confirmed by a positive SARS-CoV-2 test, since the beginning of the pandemic. In most centres, patients are identified through the systematic assessment of the clinical records of all people admitted with a positive SARS-CoV-2 test. In other centres, data have been reported only for patients with diabetes and COVID-19 who have

required clinical input from the diabetes specialist team. For the current study, audit data were included up to a cut-off date of 8 November 2021.

Using a standard proforma, contributors to the ABCD audit are asked to provide demographic data for each patient, including sex, age, ethnicity and Index of Multiple Deprivation quintile, which is a composite measure of local neighbourhood deprivation, derived from UK constituent nations' census data.[12-14] Contributors are also asked to provide clinical data for each patient, including type and duration of diabetes, BMI, pre-COVID-19 diabetes treatments, complications and comorbidities, the results of biochemistry assays performed on admission to hospital with COVID-19, and whether a diagnosis of DKA and/or HHS was made.[15]

To maximize validity, we limited our definition of DKA to cases that met each diagnostic criterion of the Joint British Diabetes Societies (JBDS) DKA guidance,[16] based on admission biochemistry. Adjudication was performed independently by two clinicians. Confirmed DKA was ascertained by evidence of:

1. blood glucose >11.0 mmol/L (equivalent to ≥200 mg/dl) or known to have diabetes mellitus, and
2. blood β-hydroxybutyrate ≥3.0 mmol/L and/or urinalysis ketones >2+, and
3. venous pH <7.3 and/or serum bicarbonate <15.0 mmol/L.

HHS is a clinical diagnosis, with biochemical criteria intended to define hyperglycaemia and hyperosmolality, and to exclude significant acidosis.[17,18] The data collection proforma did not include variables for mental status, clinical hypovolaemia or serum osmolality. To maximize validity, our analysis of HHS was therefore confined to adjudicated cases meeting the following criteria, based on the UK JBDS guideline for management of HHS[18]:

1. identified by contributor as HHS, and
2. blood glucose ≥30.0 mmol/L (equivalent to ≥540 mg/dl), and
3. venous blood pH ≥7.3 and/or serum bicarbonate ≥15.0 mmol/L, and
4. capillary blood β-hydroxybutyrate <3.0 mmol/L or no value provided.

2.2 | Outcomes

The primary outcome in this analysis of the ABCD audit was inpatient case fatality, and the secondary outcome was admission to an intensive care unit (ICU).

2.3 | Statistical analysis

Clinical characteristics are reported as n (%) for categorical variables. Continuous variables are reported as mean (SD). Differences between groups in normally distributed continuous variables were assessed with Student's t-tests, and in non-normally distributed continuous variables with Mann-Whitney U-tests. Proportions were compared with either Pearson's χ^2 test or Fisher's exact test and the Freeman-Halton extension for tables exceeding 2 × 2. Logistic regression models were used to calculate odds ratios (ORs) for mortality and for ICU admission adjusting for age. In all cases, two-tailed $p < .05$ was considered statistically significant. Statistical analysis was performed using SPSS 28 (IBM Software) and Prism 8.4.3 (GraphPad Software).

3 | RESULTS

3.1 | Diabetic ketoacidosis demographic and clinical characteristics

Of 4073 cases of COVID-19 and diabetes included in the audit, 211 were reported to have type 1 diabetes, and 3748 to have type 2 diabetes, with the remainder of type not stated or unknown. In total, 173 individuals were identified by contributors as having developed DKA, among whom 85 had admission biochemistry results fulfilling the criteria for classification as confirmed DKA (Figure 1). Among the remaining 88 cases, 40 were missing one or more essential admission biochemistry results, and the other 48 were reported with β-hydroxybutyrate and/or pH and/or bicarbonate values on admission that were inconsistent with JBDS diagnostic criteria for ketoacidosis.[16] There were no significant demographic differences between these cases and the confirmed DKA cohort (Supporting information, Table S1), and sensitivity analyses revealed similar case-fatality and ORs for mortality by year-increment in age (data not shown). Nevertheless, further analysis is confined to individuals in whom the diagnosis of DKA was confirmed by adjudication of admission biochemistry (Supporting information, Table S2).

The confirmed DKA cohort (Table 1) comprised 15 men and 11 women with type 1 diabetes, 39 men and 18 women with type 2 diabetes, and one man and one woman with diabetes of unknown type. The mean (SD) age of those admitted with DKA complicating type 1 diabetes was 48 (20.7) years, and with type 2 diabetes was 66 (13.7) years. Diabetes was newly diagnosed in six people, all of whom were classified as having type 1 diabetes.

BMI data were available in the confirmed DKA cohort for eight people with type 1 diabetes [mean (SD) BMI 28.4 (4.3) kg/m^2] and for 29 people with type 2 diabetes [27.1 [6.0] kg/m^2]. glycated haemoglobin (HbA1c) data before or during the admission were available for 24 people with type 1 diabetes [mean (SD) HbA1c 11.9 (4.5)%, 107 (26.0) mmol/mol] and for 50 people with type 2 diabetes [mean (SD) HbA1c 10.3 (5.0)%, 89 (31.6) mmol/mol].

Pre-admission antidiabetic medications (Table 2) included insulin for 28 of 57 individuals with type 2 diabetes. Sodium-glucose cotransporter 2 inhibitors were used by eight individuals with confirmed DKA in total, comprising six with type 2 diabetes, one with diabetes of unknown type, and one (as an adjunct to insulin) with pre-existing type 1 diabetes.

3.2 | Diabetic ketoacidosis outcomes

In the entire confirmed DKA cohort, the mean (SD) age of people who died was 71.6 (12.5) years, and of people who survived was 55.5

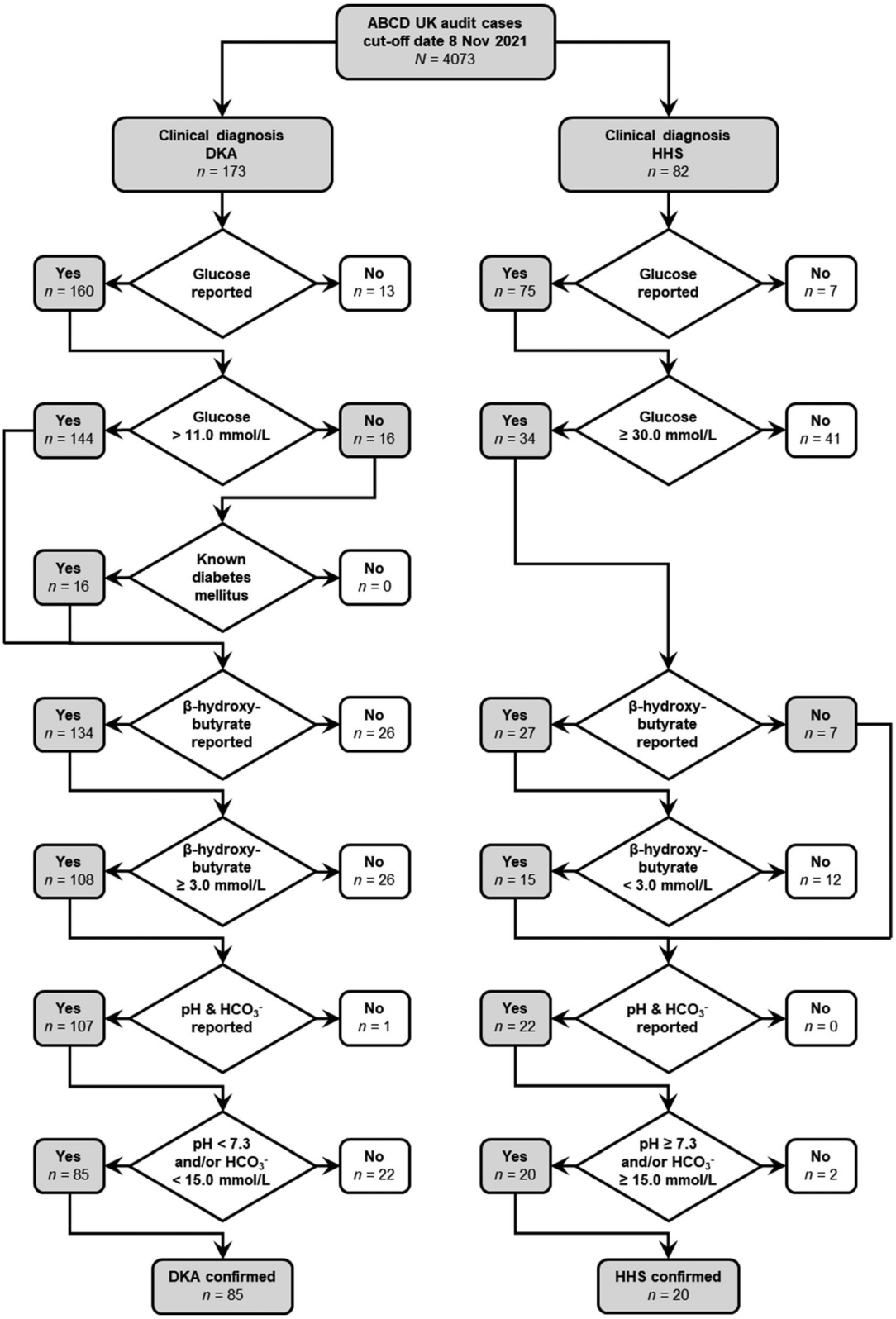

FIGURE 1 Flowchart showing case ascertainment of clinical diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) diagnoses, based on admission biochemistry assay results.

(18.1) years ($p < .001$). The mean (SD) age of men who died was 69.1 (13.3) years, versus 75.2 (9.3) years for women (difference 6.1 years; 95% CI −5.1 to 17.4; $p = .268$). There were 13 deaths in men and nine in women, corresponding to case fatality 23.6% and 30.0% respectively ($p = .61$). In a logistic regression model adjusted for sex, the OR for death with each year-increment in age was 1.065 (95% CI

TABLE 1 Demographic and clinical characteristics of the confirmed DKA and confirmed HHS cohorts

Parameter	Confirmed DKA (n)	Confirmed HHS (n)
Age (years)		
0–19	2	-
20–39	9	-
40–59	29	2
60–79	30	8
80–99	15	10
Sex		
Female	30	8
Male	55	12
Diabetes type		
Type 1 diabetes	26	-
Type 2 diabetes	57	20
Other or unknown	2	-
Duration of diabetes		
New onset	6	-
<5 years	5	1
5–14 years	12	4
≥15 years	17	5
Unknown	45	10
Ethnicity		
Asian	6	1
Black	15	8
White	36	4
Other	2	1
Unknown	26	6
IMD quintile		
1 (most deprived)	11	3
2	12	3
3	7	2
4	5	2
5 (least deprived)	6	-
Unknown	44	10
BMI (kg/m^2)		
<25	15	3
25–29.99	13	5
30–39.99	8	2
≥40	1	1
Unknown	48	9
Smoking status		
Never smoked	25	2
Current or ex-smoker	7	3
Unknown	53	15

Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycaemic state; IMD, Index of Multiple Deprivation.

1.026-1.105; $p < .001$). A higher proportion of people with type 2 diabetes than with type 1 diabetes died (case fatality 36.8%, vs. 3.8% for type 1 diabetes; $p = .0011$).

Mortality was not significantly associated with diabetes duration, BMI, ethnicity, index of multiple deprivation (Figure 2), admission biochemistry (pH, bicarbonate, glucose, β-hydroxybutyrate, lactate, creatinine; Supporting information, Table S2), HbA1c (Supporting information, Table S3), or diabetic complications (nephropathy, neuropathy, retinopathy, peripheral vascular disease, ischaemic heart disease, foot ulcer; Supporting information, Table S4). Among other comorbidities, a difference in crude mortality was apparent for dementia (case fatality 80% for those with dementia, vs. 26% for those without; $p = .028$) but this was not statistically significant after age adjustment.

The distribution of baseline medications by type of diabetes and case fatality are shown in Table 2. Insulin therapy data were submitted for 77 individuals, with a case-fatality of 11.1% for those on insulin before admission, and 52.2% for those not on insulin ($p < .001$). To investigate whether this difference could be explained solely by greater survival in patients with type 1 diabetes, a regression model was constructed with data limited to those with type 2 diabetes; after adjustment for age, sex and baseline HbA1c, before insulin treatment in people with type 2 diabetes and confirmed DKA was associated with OR for death of 0.131 (95% CI 0.022-0.777; $p = .025$) versus those not on insulin before admission (Figure 3).

In the 78 individuals with confirmed DKA for whom ICU data were available, proportions admitted to ICU were 35%, 47.6%, 33.3% and 5.3% in the youngest, second, third and oldest quartiles, respectively ($p = .020$). No significant difference was apparent between admission to ICU by type of diabetes (type 1 diabetes 20.8%; type 2 diabetes 34.6%; unknown 50%; $p = .353$), nor between ethnicity groups (White 27.6%; non-White 52.2%; $p = .090$). There was no significant difference between case fatality for people with confirmed DKA who were admitted to ICU (29.2%) and those not admitted to ICU (22.2%; $p = .572$). For further comparison, the case fatality in people for whom ICU admission data were missing was 42.9%.

The JBDS-IP treatment guideline-recommended biochemical criteria for critical care involvement in management of DKA include venous pH <7.1 and ketones >6.0 mmol/L.[16] After adjustment for age and sex, the OR for ICU admission with pH <7.1, compared with pH ≥7.1, was 4.163 (95% CI 1.440-12.037; $p = .008$), whereas no significant associations were apparent for either β-hydroxybutyrate (ketones) or glucose concentrations, whether treated as continuous variables or as binary categories [β-hydroxybutyrate >6.0 mmol/L vs. ≤6.0 mmol/L; glucose >20.0 mmol/L (360 mg/dl) vs. ≤20.0 mmol/L].

3.3 | Hyperosmolar hyperglycaemic state demographic and clinical characteristics

Of 4073 cases of COVID-19 and diabetes, 82 were reported to have developed HHS, of whom 20 were assessed as fulfilling all the

TABLE 2 Usual medication before admission of confirmed DKA and confirmed HHS cohorts, stratified by type of diabetes and mortality

Cohort	Parameter		All	Type 1 diabetes		Type 2 diabetes	
			n	All n	Deceased n (%)	All n	Deceased n (%)
Confirmed DKA		All patients with type 1 or type 2 diabetes	83	26	1 (3.8)	57	21 (36.8)
	Insulin	Prescribed	52	24	-	28	6 (21.4)
		Not prescribed	23	-	-	23	12 (52.2)
	Number of OHAs[a]	0	15	10	-	5	3 (60.0)
		1	20	3	-	17	5 (29.4)
		2	15	-	-	15	6 (40.0)
		3	10	-	-	10	4 (40.0)
	GLP-1RA	Prescribed	3	-	-	3	-
		Not prescribed	52	12	-	40	17 (42.5)
	ACEi/ARB	Prescribed	20	4	-	16	6 (37.5)
		Not prescribed	38	9	-	29	12 (41.4)
	Statins	Prescribed	26	4	-	22	8 (36.4)
		Not prescribed	33	9	-	24	9 (37.5)
	Antiplatelets	Prescribed	12	2	-	10	5 (50.0)
		Not prescribed	40	11	-	29	9 (31.0)
	Anticoagulants	Prescribed	15	5	-	10	2 (20.0)
		Not prescribed	33	6	-	27	10 (37.0)
Confirmed HHS		Entire cohort	20	-	-	20	13 (65.0)
	Insulin	Prescribed	10	-	-	10	5 (50.0)
		Not prescribed	8	-	-	8	6 (75.0)
	Number of OHAs	0	4	-	-	4	3 (75.0)
		1	7	-	-	7	5 (71.4)
		2	4	-	-	4	1 (25.0)
		3	3	-	-	3	2 (66.7)
	GLP-1RA	Prescribed	2	-	-	2	-
		Not prescribed	15	-	-	15	11 (73.3)
	ACEi/ARB	Prescribed	10	-	-	10	5 (50.0)
		Not prescribed	7	-	-	7	5 (71.4)
	Statins	Prescribed	11	-	-	11	4 (36.4)
		Not prescribed	6	-	-	6	6 (100)
	Antiplatelets	Prescribed	4	-	-	4	1 (25.0)
		Not prescribed	7	-	-	7	6 (85.7)
	Anticoagulants	Prescribed	2	-	-	2	1 (50.0)
		Not prescribed	10	-	-	10	7 (70.0)

Note: Missing data are omitted, as are the two individuals with diabetes of unknown type, both of whom survived.

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DKA, diabetic ketoacidosis; GLP-1RA, glucagon-like peptide-1 receptor agonists; HHS, hyperosmolar hyperglycaemic state; OHAs, oral hyperglycaemic agents.

[a]Among those in the confirmed DKA cohort taking sodium-glucose cotransporter 2 inhibitors, one had type 1 diabetes and survived, six had type 2 diabetes, of whom four survived, and one had unknown type of diabetes, and survived.

biochemical criteria for adjudicated classification as confirmed HHS (Figure 1). Among the remaining 62 cases, 48 were either missing admission glucose data or had glucose concentrations below the JBDS-IP guideline diagnostic threshold (≥30 mmol/L or 540 mg/dl), and the remaining 14 had β-hydroxybutyrate and/or pH and/or bicarbonate values that were inconsistent with JBDS diagnostic criteria for significant HHS.[18] There were no significant demographic differences between these cases and the confirmed HHS cohort (Supporting Information, Table S5). Sensitivity analyses revealed that there was no significant difference in case fatality, and that ORs for

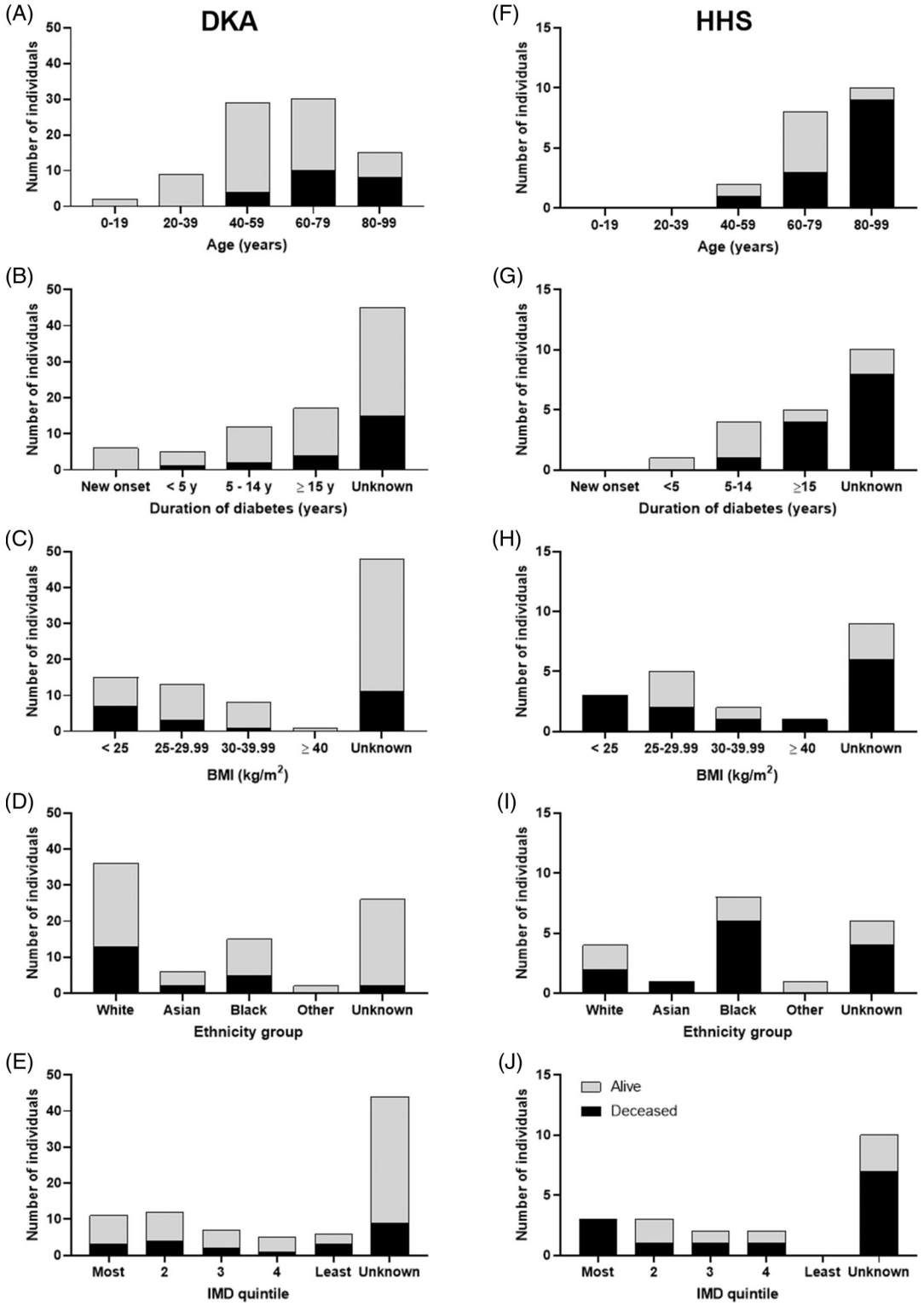

FIGURE 2 (A-E) Distribution of demographic characteristics of confirmed diabetic ketoacidosis (DKA) and (F-J) of confirmed hyperosmolar hyperglycaemic state (HHS) cohorts, (A,F) by age, (B,G) duration of diabetes, (C,H) body mass index (BMI), (D,I) ethnicity group and (E,J) Index of Multiple Deprivation (IMD) quintile. Grey shading: discharged from hospital alive. Black shading: deceased. Age and duration of diabetes were reported in whole years. Ethnicity groups combined several national census categories ("White" combined White English, Welsh, Scottish, Northern Irish or British, White Irish, White Gypsy or Irish Traveller, and any other White background; "Asian" combined Asian or Asian British Indian, Asian or Asian British Pakistani, Asian or Asian British Bangladeshi, Asian or Asian British Chinese, and any other Asian or Asian British background; "Black" combined Black or Black British African, Black or Black British Caribbean, and any other Black or Black British background; "Other" combined Arab and any other ethnic background; no individuals were recorded with a mixed ethnic background). IMD quintiles were ranked from first (most deprived), to fifth (least deprived).

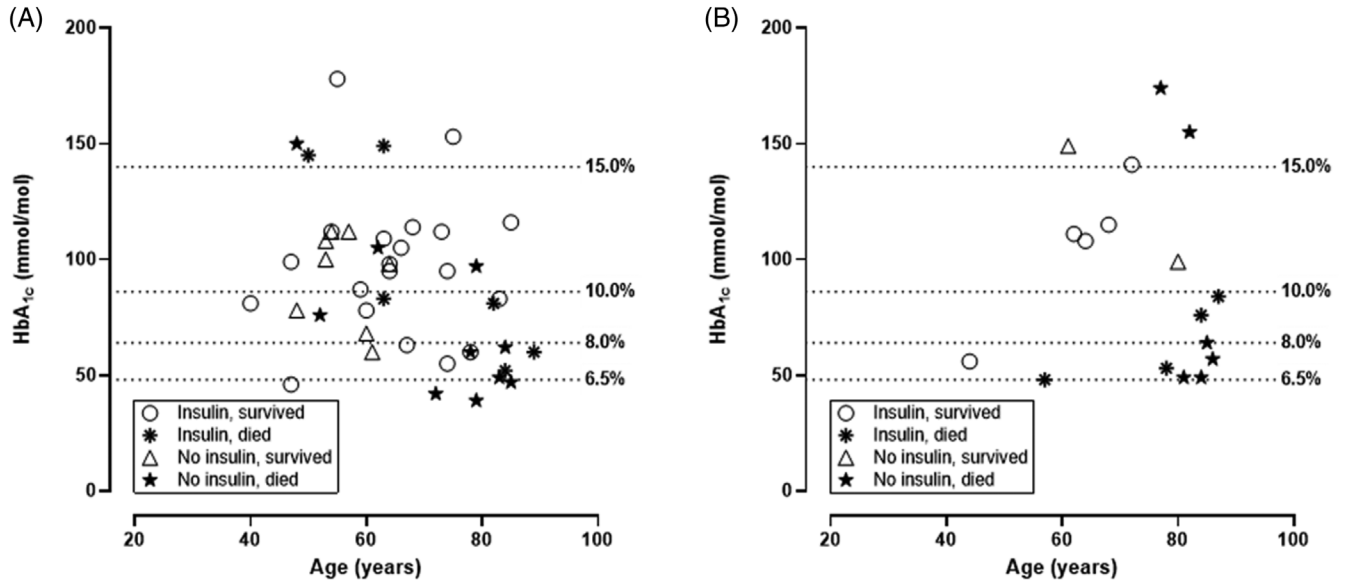

FIGURE 3 Scatter plot of glycated haemoglobin (HbA1c) and age, describing mortality by previous insulin use, in people with type 2 diabetes in the (A) confirmed hyperosmolar hyperglycaemic state cohort, and (B) entire confirmed diabetic ketoacidosis cohort.

mortality by year increment in age were similar (data not shown). Nevertheless, for consistency, further analysis is confined to individuals in whom the diagnosis of HHS was confirmed by adjudication of admission biochemistry (Supporting Information, Table S6).

The confirmed HHS cohort (Table 1) comprised 12 (60%) men and eight (40%) women, all with type 2 diabetes. They were significantly older than the confirmed DKA cohort, with mean (SD) age 74 (11.8) years, versus 60 (18.2) years; $p < .001$. Their mean (SD) HbA1c was 89 (42.2) mmol/mol, measured a mean (SD) of 200 (204) days before admission to hospital. 40% of the cohort was of Black ethnicity; the proportion of people of non-White ethnicity was significantly greater in the confirmed HHS cohort than in the confirmed DKA cohort (71.4% vs. 39.0% respectively; $p = .038$). Pre-admission prescriptions are summarized in Table 2, and further detail on medication classes, diabetic complications, and co-morbidities is available in Supporting Information (Table S7).

3.4 | Hyperosmolar hyperglycaemic state outcomes

Mortality was significantly greater among people with COVID-19 and confirmed HHS, compared with those with COVID-19 and confirmed DKA (case fatality 65.0% vs. 29.9%; $p < .001$). This remains the case when the comparison is limited, in the COVID-19 and confirmed DKA cohort, to those with type 2 diabetes ($p = .029$). The mean (SD) age of those who died with confirmed HHS was 79 (8.6) years versus 64 (11.2) years for those who survived ($p = .004$) but sex was not significantly associated with outcome (case fatality 50% for women vs. 75% for men; $p = .356$). Among prescriptions before admission, a difference in crude mortality was apparent only for statins (case fatality 36.4% for those taking statins before admission, vs. 100% for those not taking statins; $p = .035$) but this was not statistically significant after adjustment for age. Regarding previous insulin therapy (Figure 3), there was no significant difference in case fatality (75% for those not on insulin, vs. 50% for those using insulin before admission; $p = .367$).

No significant associations with mortality were identified for other variables, including diabetes duration, BMI, index of multiple deprivation (Figure 2), admission biochemistry (pH, bicarbonate, glucose, β-hydroxybutyrate, lactate, creatinine; Supporting Information, Table S6), HbA1c (Supporting Information, Table S8), or diabetic complications (nephropathy, neuropathy, retinopathy, peripheral vascular disease, ischaemic heart disease, foot ulcer; Supporting Information, Table S7).

Data on ICU admission were available for every member of the confirmed HHS cohort. While there was a significant difference in age [mean (SD) 60 (2.6) years for those admitted to ICU, $n = 3$, vs. 77 (11.0) years for those not admitted to ICU; $p = .02$], the difference in mortality was not statistically significant (case fatality 33.3% for those admitted to ICU, vs. 70.6% for those not admitted; $p = .270$).

4 | DISCUSSION

To our knowledge, this is one of the largest studies of COVID-19-associated hyperglycaemic emergencies and one that provides granular data on the characteristics of clearly defined DKA and HHS. We show for the first time that DKA is four times more common than HHS as a hyperglycaemic emergency and that case fatality for patients admitted in HHS is more than two-fold greater than for DKA. We show also that not being on insulin therapy before admission is associated with poor prognosis in those presenting with COVID-

19-associated DKA. Our data support previous reports that people with type 2 diabetes, compared with those with type 1 diabetes, account for a greater proportion of COVID-19-associated DKA than non-COVID-19-associated DKA.[7] They also support previous reports that age and type 2 diabetes are associated with poor prognosis.[3,4] We also show for the first time that significant acidosis, although not ketonaemia or hyperglycaemia, is associated with increased likelihood of ICU admission in COVID-19-associated DKA, while supporting previous reports that BMI and non-White ethnicity are also associated with ICU admission.[19]

This study provides the first clear description of the effect of COVID-19 on the presentation and outcomes of patients admitted in HHS. To our knowledge, the only publications of clinical experience with COVID-19 and HHS to date are case reports[9,20-22] and small case series,[10,23,24] in which most cases were classified as mixed DKA/HHS; excluding mixed DKA/HHS, the total number of published COVID-19-associated HHS cases to date is just five. There have thus been too few publications available to provide a clear picture of the effect of COVID-19 on patients presenting with HHS. Here, using our national dataset, we show that patients presenting with COVID-19 and HHS tend to be older, and are more likely to be of non-White ethnicity, than those with COVID-19 and DKA. We also show that crude mortality in COVID-19 and HHS is greater in people who are not taking statins before admission, compared with those who are on statins. As mortality is also associated with advancing age, we speculate that absence of a statin from pre-admission prescriptions in this cohort may be a surrogate marker for advancing frailty and consequent deprescribing.

Our data on COVID-19-associated hyperglycaemic emergencies should be interpreted in the context of pre-pandemic literature showing that comorbid pneumonia is a poor prognostic factor in DKA and HHS, responsible for a two-fold increase in 28-day case fatality in one case series.[25] Furthermore, an extensive review of case series found that infection and reduced adherence to therapy are, internationally, the two most common causes of DKA.[26] While the relative importance of these factors varies between countries, the commonest cause in the UK is infection.[27,28] Nevertheless, a UK population-level study found that, compared with pre-pandemic frequencies, DKA occurred less commonly in people with type 1 diabetes during the first and second waves of the COVID-19 pandemic, while being more common in people with newly diagnosed diabetes and those with pre-existing type 2 diabetes.[29]

The strengths of this study are the availability of a large, multicentre dataset from the NHS, which provides almost all emergency hospital care in the UK; the ethnically diverse population; the adjudication by two senior clinicians of detailed biochemistry results that, unlike most studies performed with routine health care data, allowed careful characterization of each clinical case, and the widespread sampling of all hospital admissions presenting with COVID-19 and diabetes, including those with HHS. We also chose to adjudicate DKA and HHS diagnoses using national guideline-based biochemical criteria that are mutually exclusive, thus providing a clear picture of each condition separately. The limitations include incompleteness of some variables; reliance on clinical classification of diabetes type without moderation by autoantibody status, C-peptide secretion or genetic risk scores; the potential for hospital-to-hospital variation in criteria for escalation of care to ICU, which could affect assessment of risk factors for ICU admission; the fact that we did not seek data on non-metabolic markers of COVID-19 severity reflecting, for instance, respiratory failure or thrombotic disease; the small number of people with confirmed HHS, meaning that the power of the study to detect associations with risk factors was limited; the risk at contributing centres of data entry errors during transcription from medical records and of variation in attribution of audit categories, and the scope for confounding.

There are several findings worth highlighting. The data suggest that the current criteria for prioritization of care in patients admitted with either DKA or HHS appear valid when these hyperglycaemic states are precipitated by COVID-19. This is reassuring and suggests that the current national guidelines[16,18] are equally useful for COVID-19-associated DKA and HHS as for other underlying causes of severe metabolic derangement among people with diabetes. It is also worth noting that approximately two-thirds of DKA admissions in this carefully characterized cohort were from patients with a previous diagnosis of type 2 diabetes. While this supports previously published studies of COVID-19-associated DKA in the UK,[7] the ratio is in stark contrast to non-COVID-19-associated DKA, where only a quarter of DKA cases have a previous diagnosis of type 2 diabetes.[30] The increase in DKA presentations in type 2 diabetes might be explained by several reasons, including misclassification at diagnosis. We did not ask contributors to provide data on markers of islet autoimmunity, nor on C-peptide secretion, but these would have been illuminating and might have led to reclassification in some cases. People of Black ethnicity appear to be over-represented, which may reflect greater prevalence of ketosis-prone type 2 diabetes, leading to DKA in states of high insulin resistance.[31] There is also evidence that SARS-CoV-2 can induce severe insulin deficiency, both through indirect deleterious effects on beta-cell function of COVID-19-associated cytokine storm, and through direct viral infection of pancreatic islet beta-cells causing apoptosis and lymphocytic islet infiltration.[32,33] One may speculate that these mechanisms could be relevant to type 2 diabetes-associated DKA particularly in people with significant insulin deficiency, manifested by high HbA1c as in our cohort.

In the context of COVID-19-associated DKA in patients with type 2 diabetes, there was a strong association between previous insulin therapy and survival, which could not be explained by age or HbA1c. It is interesting that the protective association of previous insulin therapy was not found in non-COVID-19 associated DKA in patients with type 2 diabetes (subanalysis of data from Ooi et al.,[30] data not shown). While a pre-pandemic multinational ICU case series found that DKA mortality was lower in people with diabetes who had been on insulin treatment before admission, compared with those not on insulin, the authors reported having insufficient data to differentiate between type 1 and type 2 diabetes.[34] On the other hand, a recent review has found evidence of increased mortality in COVID-19 and DKA with new-onset diabetes, probably in the absence of previous insulin therapy.[35] In the current study, our finding could be explained by

deprescribing of insulin in those who were frail and nearer the end of life, although this would not account for the absence of a protective association in non-COVID-19-associated DKA. Data on the cause of death of each participant could help inform a discussion on potential mechanisms underlying these findings. Larger studies are also needed to investigate the association between previous glucagon-like peptide-1 receptor agonist and anticoagulant therapy with survival in patients with type 2 diabetes admitted with DKA given that these associations did not reach statistical significance in this study.

In summary, in this large study of well-characterized COVID-19-associated hyperglycaemic emergencies admitted to UK hospitals, we show a preponderance of DKA over HHS, with the former dominated by patients with a previous diagnosis of type 2 diabetes. In patients with type 2 diabetes, we showed strong associations between survival and previous insulin therapy in those admitted in DKA, after adjustment for age, sex and HbA1c, and between crude mortality and previous statin therapy in those admitted in HHS. These associations are worth further investigation. Finally, we showed that the current guidelines for the escalation of care in DKA and HHS are fit for purpose in the context of COVID-19.

AUTHOR CONTRIBUTIONS

BCTF and PN co-designed and performed the analysis and drafted the manuscript. All authors contributed to the conception and design of the study, interpretation of the data, critical review of the paper, and gave final approval of the submitted version. BCTF and PN had full access to all the data in the study, are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

BCTF has acted as a consultant, speaker or received grants from Abbott Diabetes, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Medtronic, MSD, Napp, Novo Nordisk and Sanofi. YR is an employee of Abbott Diabetes Care. REJR has received speaker fees and/or consultancy fees and/or educational sponsorships from AstraZeneca, BioQuest, GI Dynamics, Janssen, Novo Nordisk, Sanofi-Aventis and Takeda. SH has received educational funding support from Sanofi-Aventis and consulting fees from Eli Lilly and Oviva. DP has acted as a consultant, speaker or received grants from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Napp and Novo Nordisk. PK has received personal fees from Napp and attends Health Education West Midlands Specialist training days that receive support from Novo Nordisk. SHW attends meetings of the Scottish Study Group for Care of Diabetes in the Young that receive support from Novo Nordisk. EGW has received personal fees from Abbott Diabetes Care, Dexcom, Glooko/Diasend, Eli Lilly, Embecta, Insulet, Medtronic, Novo Nordisk and Sanofi-Aventis. KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG/Menarini Group, Janssen and Napp. RR has acted as a consultant, speaker or received grants from Novo Nordisk, Eli Lilly and Boehringer Ingelheim. PN has acted as a consultant or speaker for Abbott Diabetes, Eli Lilly, Sanofi. All the other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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