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

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

Short running title: UK nationwide study of DKA, HHS & COVID-19

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ABSTRACT

AIMS

To investigate characteristics of people hospitalised 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.

MATERIALS AND METHODS

Retrospective cohort study with anonymised 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. Primary outcome was inpatient mortality. DKA and HHS were adjudicated against national criteria. Age-adjusted odds ratios (ORs) were calculated using logistic regression.

RESULTS

85 confirmed DKA cases, and 20 HHS, occurred among 4073 people (211 type 1 diabetes, 3748 type 2 diabetes, 114 unknown type) hospitalised with COVID-19. Mean(SD) age was 60(18.2)y in DKA and 74(11.8)y in HHS (P<0.001). A higher proportion of patients with HHS than with DKA were of non-White ethnicity (71.4% vs 39.0% P=0.038). 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 to non-users (21.4% vs. 52.2%; age-adjusted OR 0.13 [95%CI 0.03–0.60]).

Crude mortality was lower in DKA than HHS (25.9% vs. 65.0%, *P*=0.001) and in statin users vs non-users (36.4% vs. 100%; *P*=0.035) but these were not statistically significant after age adjustment.

CONCLUSIONS

Hospitalisation 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 prior insulin therapy with survival in type 2 diabetes-associated DKA.

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, especially 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 recognised diagnosis of diabetes.[2]

Reports to date describe patients admitted with hyperglycaemia and COVID-19 as older, with a higher 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 syndrome (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 healthcare systems where access to healthcare 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.

MATERIALS AND METHODS

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 pseudonymised data on patients with diabetes who have been admitted to hospital with COVID-19, confirmed by positive SARS-CoV-2 test, since the beginning of the pandemic. In most centres, patients are identified through 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 8th 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 co-morbidities, 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 maximise 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:

a) Blood glucose > 11.0 mmol/L (equivalent to ≥ 200 mg/dl) or known to have diabetes mellitus, and
b) Blood β-hydroxybutyrate ≥ 3.0 mmol/L and/or urinalysis ketones > 2+, and
c) 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, also, to exclude significant acidosis.[17,18] The data collection proforma did not include variables for mental status, clinical hypovolaemia or serum osmolality. To maximise 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]

a) Identified by contributor as HHS, and

b) Blood glucose ≥ 30.0 mmol/L (equivalent to ≥ 540 mg/dl), and

c) Venous blood pH ≥ 7.3 and/or serum bicarbonate ≥ 15.0 mmol/L, and

d) Capillary blood β-hydroxybutyrate <3.0 mmol/L or no value provided.

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).

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 with Fisher's exact test and the Freeman-Halton extension for tables exceeding 2 x 2. Logistic regression models were used to calculate odds ratios for mortality and for ICU admission adjusting for age. In all cases, a two-tailed P value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 28 (IBM Software, Armonk, NY) and Prism 8.4.3 (GraphPad Software, San Diego, CA).

RESULTS

DKA 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. 173 individuals were identified by contributors as having developed DKA, amongst whom 85 had admission biochemistry results fulfilling the criteria for classification as *Confirmed DKA* (Figure 1). Amongst 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 (Supplementary Table S1), and sensitivity analyses revealed similar case-fatality and odds ratios 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 (Supplementary 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 6 people, all of whom were classified as having type 1 diabetes.

BMI data were available in the *Confirmed DKA* cohort for 8 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) $kg.m^{-2}$). HbA_{1c} data before or during the admission were available for 24 people with type 1 diabetes (mean(SD) HbA_{1c} 11.9 (4.5)% (107 (26.0) mmol/mol)) and for 50 people with type 2 diabetes (mean(SD) HbA_{1c} 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. SGLT2 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.

DKA 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 (18.1) years (P<0.001). The mean (SD) age of men who died was 69.1 (13.3) years, vs. 75.2 (9.3) years for women (difference 6.1 years; 95% CI -5.1 to 17.4; *P*=0.268). There were 13 deaths in men and 9 in women, corresponding to case-fatality 23.6% and 30.0% respectively (*P*=0.61). In a logistic regression model adjusted for sex, the odds ratio for death with each year-increment in age was 1.065 (95% CI 1.026 to 1.105; *P*<0.001). 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*=0.0011).

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; Supplementary Table S2), HbA_{1c} (Supplementary Table S3), or diabetic complications (nephropathy, neuropathy, retinopathy, peripheral vascular disease, ischaemic heart disease, foot ulcer; Supplementary Table S4). Amongst other co-morbidities, a difference in crude mortality was apparent for dementia (case-fatality 80% for those with dementia, vs. 26% for those without; P=0.028) but this was not statistically significant after age adjustment.

Distribution of baseline medications by type of diabetes and case fatality are shown in Table 2. Insulin therapy data were contributed for 77 individuals, with case-fatality of 11.1% for those on insulin prior to admission, and 52.2% for those not on insulin (P<0.001). 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 HbA_{1c}, prior 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=0.025) vs. those not on insulin prior to 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=0.020). 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=0.353), nor between ethnicity groups (White 27.6%; non-White 52.2%; P=0.090). 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=0.572). 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 to pH ≥7.1, was 4.163 (95%CI 1.440–12.037; *P*=0.008), 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).

HHS 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 biochemical criteria for adjudicated classification as *Confirmed HHS* (Figure 1). Amongst 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 (Supplementary Table S5). Sensitivity analyses revealed that there was no significant difference in case-fatality, and that ORs for 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 (Supplementary Table S6).

The *Confirmed HHS* cohort (Table 1) comprised 12 (60%) men and 8 (40%) women, all with type 2 diabetes. They were significantly older than the *Confirmed DKA* cohort, with mean (SD) age 74

(11.8) years, vs. 60 (18.2) years; $P<0.001$. Their mean (SD) HbA_{1c} 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; $P=0.038$). Pre-admission prescriptions are summarised in Table 2, and further detail on medication classes, diabetic complications, and co-morbidities is available in Supplementary Table S7.

HHS Outcomes

Mortality was significantly greater amongst people with COVID-19 and *confirmed HHS*, compared to those with COVID-19 and *confirmed DKA* (case-fatality 65.0% vs. 29.9%; $P<0.001$). This remains the case when the comparison is limited, in the COVID-19 and *confirmed DKA* cohort, to those with type 2 diabetes ($P=0.029$). The mean (SD) age of those who died with *confirmed HHS* was 79 (8.6) years, vs. 64 (11.2) years for those who survived ($P=0.004$) but sex was not significantly associated with outcome (case-fatality 50% for women vs. 75% for men; $P=0.356$). Among prescriptions prior to admission, a difference in crude mortality was apparent only for statins (case-fatality 36.4% for those taking statins prior to admission, vs. 100% for those not taking statins; $P=0.035$) but this was not statistically significant after adjustment for age. Regarding prior insulin therapy (Figure 3), there was no significant difference in case-fatality (75% for those not on insulin, vs. 50% for those using insulin prior to admission; $P=0.367$).

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; Supplementary Table S6), HbA_{1c} (Supplementary Table S8), or diabetic complications (nephropathy, neuropathy, retinopathy, peripheral vascular disease, ischaemic heart disease, foot ulcer; Supplementary 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*=0.02), 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*=0.270).

DISCUSSION

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 prior to 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 to 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 prior to admission, compared to 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 co-morbid 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 to 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, multi-centre 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 healthcare data, allowed careful characterisation 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 prioritisation 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 characterised cohort were from patients with a prior diagnosis of type 2 diabetes. Whilst 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 HbA_{1c} as in our cohort.

In the context of COVID-19-associated DKA in patients with type 2 diabetes, there was a strong association between prior insulin therapy and survival which could not be explained by age or HbA_{1c}. It is interesting that the protective association of prior 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 multi-national ICU case series found that DKA mortality was lower in people with diabetes who had been on insulin treatment prior to admission, compared to 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, likely to be in the absence of prior insulin therapy.[35] In the current study, our finding could be explained by deprescribing of

insulin in those who were frail and nearer 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 prior 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-characterised COVID-19-associated hyperglycaemic emergencies admitted to UK hospitals, we demonstrate a preponderance of DKA over HHS, with the former dominated by patients with a prior diagnosis of type 2 diabetes. In patients with type 2 diabetes, we demonstrate strong associations between survival and prior insulin therapy in those admitted in DKA, after adjustment for age, sex and HbA_{1c}, and between crude mortality and prior statin therapy in those admitted in HHS. These associations are worth further investigation. Finally, we demonstrate that the current guidelines for escalation of care in DKA and HHS are fit for purpose in the context of COVID-19.

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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.

Conflicts of interest: 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

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FIGURE LEGENDS

Figure 1: Flowchart demonstrating case ascertainment of clinical DKA and HHS diagnoses, based on admission biochemistry assay results.

Figure 2: Distribution of demographic characteristics of *Confirmed DKA* (panels A to E) and of *Confirmed HHS* cohorts (panels F to J), by age (panels A & F), duration of diabetes (panels B & G), body mass index (panels C & H), ethnicity group (panels D & I) and index of multiple deprivation quintile (panels E & J). 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 HbA_{1c} and age, describing mortality by prior insulin use, in people with type 2 diabetes in the *Confirmed DKA* cohort (panel A), and in the entire *Confirmed HHS* cohort (panel B).

TABLES

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

Table 1: Demographic and clinical characteristics of the *Confirmed DKA* and *Confirmed HHS* cohorts. IMD: Index of Multiple Deprivation. BMI: Body Mass Index.

Cohort				Type 1 diabetes			Type 2 diabetes		
			All	All	Deceased		All	Deceased	
	Parameter		*n*	*n*	*n*	(%)	*n*	*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†	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)

Cohort			Type 1 diabetes			Type 2 diabetes		
		All	All	Deceased		All	Deceased	
Parameter		*n*	*n*	*n*	(%)	*n*	*n*	(%)
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)

Table 2: Usual medication prior to admission of *Confirmed DKA* and *Confirmed HHS* cohorts, stratified by type of diabetes & mortality. Missing data are omitted, as are the two individuals with diabetes of unknown type, both of whom survived. OHAs: oral hypoglycaemic agents. GLP-1RA: glucagon-like peptide-1 receptor agonists. ACEi: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. † Amongst those in the *Confirmed DKA* cohort taking SGLT2 inhibitors, one had type 1 diabetes and survived, 6 had type 2 diabetes, of whom 4 survived, and one had unknown type of diabetes, and survived.

FIGURE 1

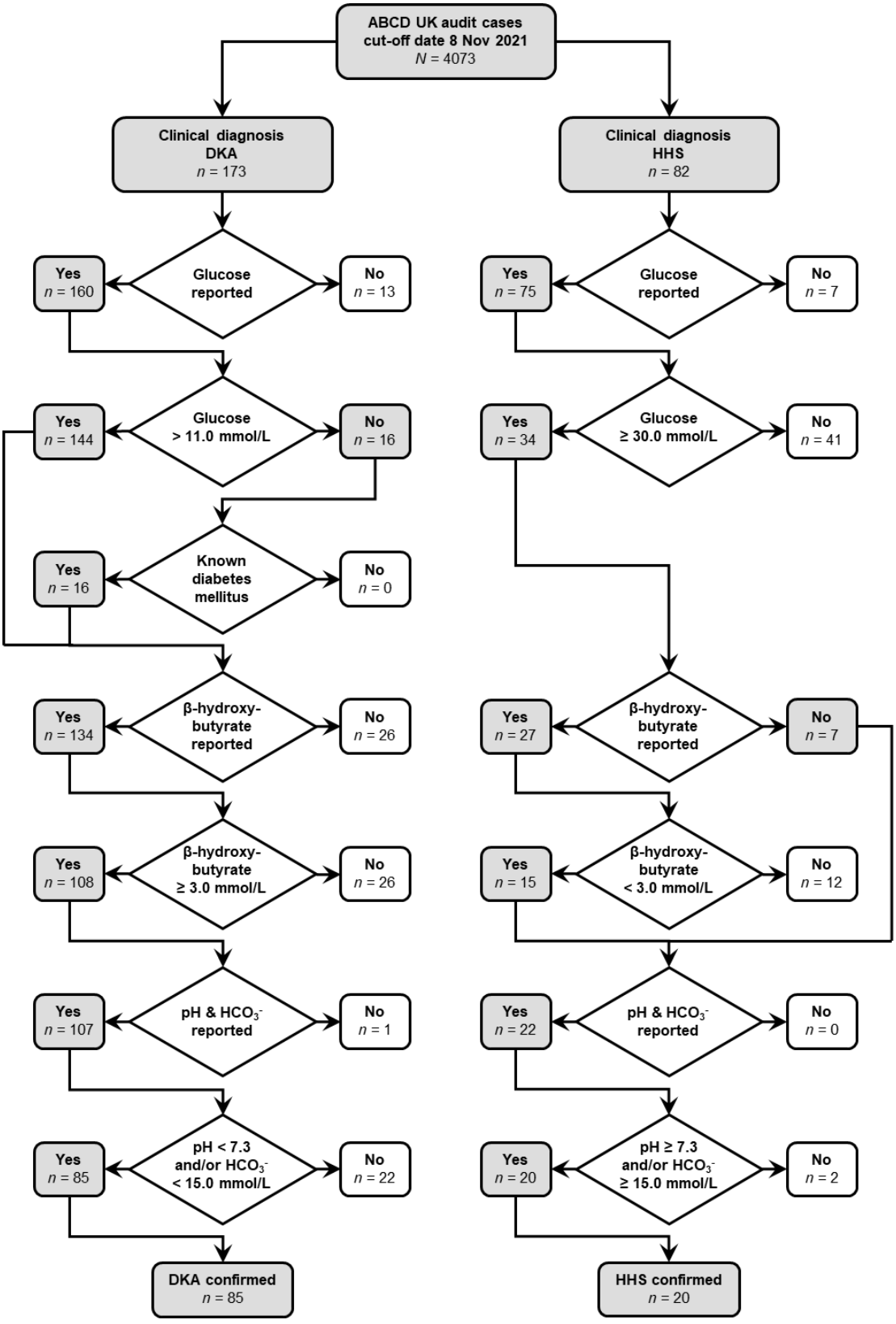

ABCD UK audit cases
cut-off date 8 Nov 2021
N = 4073
Clinical diagnosis
DKA
n = 173
Clinical diagnosis
HHS
n = 82
Glucose reported
Yes n = 160
No n = 13
Yes n = 75
No n = 7
Glucose > 11.0 mmol/L
Yes n = 144
No n = 16
Glucose ≥ 30.0 mmol/L
Yes n = 34
No n = 41
Known diabetes mellitus
Yes n = 16
No n = 0
β-hydroxy-butyrate reported
Yes n = 134
No n = 26
Yes n = 27
No n = 7
β-hydroxy-butyrate ≥ 3.0 mmol/L
Yes n = 108
No n = 26
β-hydroxy-butyrate < 3.0 mmol/L
Yes n = 15
No n = 12
pH & HCO3- reported
Yes n = 107
No n = 1
Yes n = 22
No n = 0
pH < 7.3 and/or HCO3- < 15.0 mmol/L
Yes n = 85
No n = 22
pH ≥ 7.3 and/or HCO3- ≥ 15.0 mmol/L
Yes n = 20
No n = 2
DKA confirmed
n = 85
HHS confirmed
n = 20

FIGURE 2

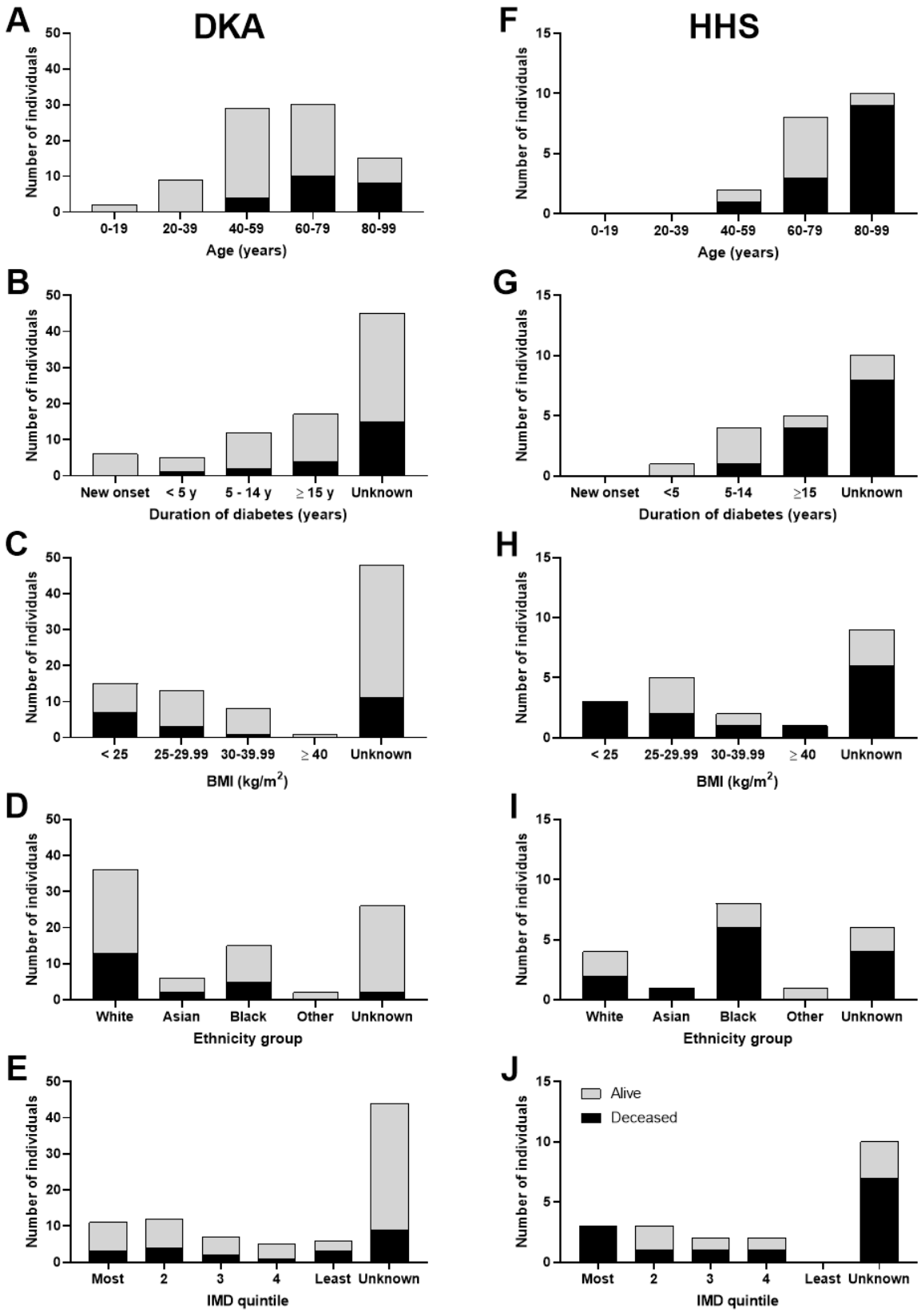
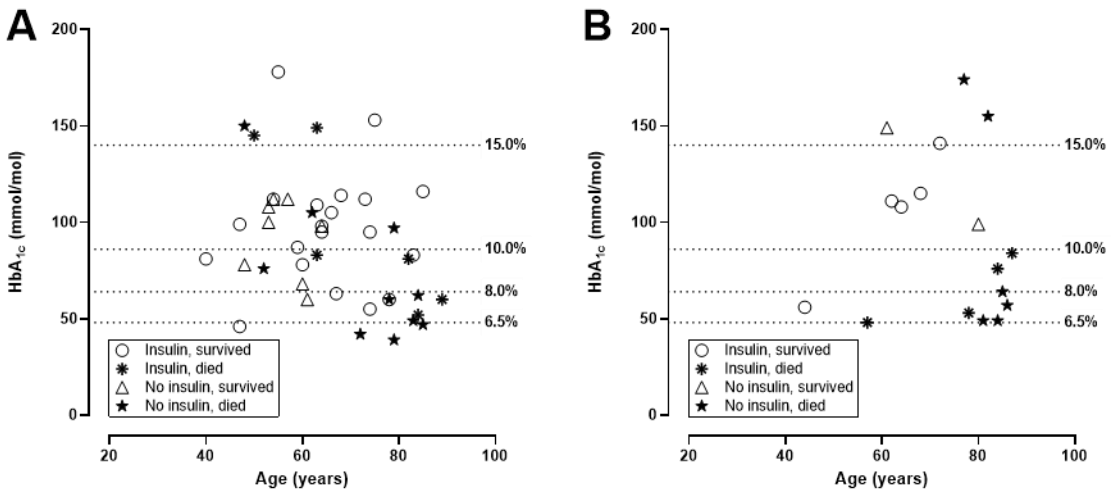

A
DKA
Number of individuals
Age (years)
0-19
20-39
40-59
60-79
80-99
B
Duration of diabetes (years)
New onset
< 5 y
5 - 14 y
≥ 15 y
Unknown
C
BMI (kg/m2)
< 25
25-29.99
30-39.99
≥ 40
Unknown
D
Ethnicity group
White
Asian
Black
Other
Unknown
E
IMD quintile
Most
2
3
4
Least
Unknown
F
HHS
G
<5
5-14
≥15
H
I
J
Alive
Deceased

FIGURE 3


A
B
HbA1c (mmol/mol)
200
150
100
50
0
15.0%
10.0%
8.0%
6.5%
Insulin, survived
Insulin, died
No insulin, survived
No insulin, died
20
40
60
80
100
Age (years)

Supplementary Material

Supplementary Material Table of Contents

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Variable	*Confirmed DKA*	*Unconfirmed DKA*	*P*-value
Sex (*n*) †			
Male	55	55	
Female	30	33	0.875
Ethnicity group (*n*) ‡			
White	36	39	
Asian	6	9	
Black	15	15	
Other	2	2	0.948
IMD quintile (*n*) ‡			
1 (most deprived)	11	16	
2	12	15	
3	7	9	
4	5	9	
5 (least deprived)	6	5	0.917
Type of diabetes (*n*) ‡			
Type 1 diabetes	26	27	
Type 2 diabetes	57	60	
Unknown type	2	1	0.950
Age (years) §			
n	85	88	
median	61	67	
IQR	47.5 – 74.5	52.25 – 76.00	0.183
BMI (kg.m^{-2}) §			
n	37	52	
median	25.83	24.62	
IQR	23.77 – 29.72	20.75 – 28.82	0.105

Table S1: Comparison of *Confirmed DKA* and *Unconfirmed DKA* cohort demographics. Tests indicated by † (Fisher's Exact), ‡ (Fisher-Freeman-Halton Exact), and § (independent-samples Mann-Whitney U).

	Total (*N* = 85)			Alive (*n* = 63)			Deceased (*n* = 22)			
	Mean	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	***P*-value**
pH										
Type 1 diabetes	7.10	0.16	26	7.10	0.16	25	7.26	-	1	
Type 2 diabetes	7.13	0.15	57	7.11	0.16	36	7.17	0.14	21	
Unknown type	7.10	0.17	2	7.10	0.17	2	-	-	-	
Combined types	7.12	0.16	85	7.10	0.16	63	7.17	0.14	22	0.0554
Bicarbonate (mmol/L)										
Type 1 diabetes	11.3	4.5	26	11.1	4.6	25	15.1	-	1	
Type 2 diabetes	10.7	4.5	55	9.8	4.8	34	12.3	3.3	21	
Unknown type	11.8	5.2	2	11.8	5.2	2	-	-	-	
Combined types	10.9	4.5	83	10.4	4.8	61	12.4	3.3	22	0.1473
Glucose (mmol/L)										
Type 1 diabetes	28.8	12.9	26	29.4	12.9	25	14.2	-	1	
Type 2 diabetes	26.3	14.0	†56	27.3	15.0	†35	24.5	11.9	21	
Unknown type	45.9	11.2	2	45.9	11.2	2	-	-	-	
Combined types	27.5	14.0	†84	28.8	14.5	†62	24.1	11.8	22	0.2229
β-hydroxybutyrate (mmol/L)										
Type 1 diabetes	5.1	1.3	†20	5.2	1.3	†19	4.1	-	1	
Type 2 diabetes	5.2	1.3	†54	5.3	1.2	†33	5.1	1.5	21	
Unknown type	4.5	0.5	2	4.5	0.5	2	-	-	-	
Combined types	5.2	1.3	†76	5.2	1.2	†54	5.1	1.5	22	0.6428
Lactate (mmol/L)										
Type 1 diabetes	3.2	2.0	21	3.2	2.0	21	-	-	-	
Type 2 diabetes	3.1	2.1	46	2.8	1.3	27	3.5	2.8	19	
Unknown type	5.0	2.6	2	5.0	2.6	2	-	-	-	
Combined types	3.2	2.1	69	3.0	1.7	50	3.5	2.8	19	0.6918
Creatinine (µmol/L)										
Type 1 diabetes	190	218	20	190	218	20	-	-	-	
Type 2 diabetes	151	98	51	143	89	32	163	110	19	
Unknown type	137	35	2	137	35	2	-	-	-	
Combined types	161	142	73	160	151	54	163	110	19	0.5143

Table S2: Admission biochemistry of *Confirmed DKA* cohort. Assays were conducted on a variety of main hospital laboratory analysers, and/or emergency department point-of-care bench-top machines, and/or hand-held point-of-care meters. Assay methods were not recorded in the audit. † Missing values for blood glucose and β-hydroxybutyrate were indicated by contributors to have been above the upper limit of the respective assay reportable ranges (URR). Missing values for other analytes were not recorded. *P*-values denote a comparison between Alive and Deceased groups by Mann-Whitney U-test for each analyte, combining results from all cases, irrespective of type of diabetes, without imputation for values above assay URR.

Parameter	Entire cohort	Alive	Deceased	*P*-value
HbA_{1c} (%)				
n	74	54	20	
mean (SD)	10.9 (5.0)	11.3 (4.7)	9.6 (5.4)	
median (IQR)	10.9 (8.7 – 12.4)	11.2 (9.7 – 12.4)	9.0 (7.1 – 11.6)	
HbA_{1c} (mmol/mol)				
n	74	54	20	
mean (SD)	95.2 (31.0)	100.2 (27.8)	81.8 (35.1)	
median (IQR)	95.0 (71.75 – 112.0)	98.5 (82.5 – 112.0)	75.0 (54.0 – 103.0)	0.301
Interval between most recent HbA_{1c} and admission (days)				
n	63	46	17	
mean (SD)	104.8 (192.4)	94.9 (35.1)	131.4 (176.2)	
median (IQR)	33.0 (2.0 – 133.5)	21.0 (1.0 – 97.25)	42.0 (18.5 – 197.0)	0.0574

Table S3: Latest available HbA_{1c} and interval between hospital admission and HbA_{1c} assay for *Confirmed DKA* cohort. *P*-value for difference in HbA_{1c} is derived from age-adjusted binomial logistic regression for mortality, treating age and HbA_{1c} as continuous variables. *P*-value for difference in interval between HbA1c and admission is derived from independent-samples Mann-Whitney U test.

Parameter	Entire cohort		Alive		Deceased		*P*-value
	n	%	*n*	%	*n*	%	
Sex †							
Female	30	35.3	21	24.7	9	10.6	
Male	55	64.7	42	49.4	13	15.3	
Total	85	100.0	63	74.1	22	25.9	0.6068
Chronic kidney disease stage ‡							
0, 1 or 2	37	43.5	32	37.6	5	5.9	
3	18	21.2	10	11.8	8	9.4	
4	10	11.8	7	8.2	3	3.5	
5	1	1.2	1	1.2	-	-	
RRT	2	2.4	2	2.4	-	-	0.4655
Active or previous diabetic foot ulcer †							
Yes	5	5.9	5	5.9	-	-	
No	50	58.8	41	48.2	9	10.6	0.5778
Diabetic nephropathy †							
Yes	8	9.4	7	8.2	1	1.2	
No	39	45.9	29	34.1	10	11.8	0.6593
Diabetic peripheral neuropathy †							
Yes	5	5.9	4	4.7	1	1.2	
No	38	44.7	28	32.9	10	11.8	>0.9999
Diabetic retinopathy †							
Yes	14	16.5	8	9.4	6	7.1	
No	31	36.5	24	28.2	7	8.2	0.2861
Peripheral vascular disease †							
Yes	3	3.5	2	2.4	1	1.2	
No	44	51.8	32	37.6	12	14.1	>0.9999
Ischaemic heart disease (including myocardial infarction) and/or heart failure †							
Yes	8	9.4	5	5.9	3	3.5	
No	36	42.4	29	34.1	7	8.2	0.3550
Stroke or Transient ischaemic attack †							
Yes	6	7.1	3	3.5	3	3.5	
No	50	58.8	38	44.7	12	14.1	0.3263
Hypertension †							
Yes	32	37.6	21	24.7	11	12.9	
No	27	31.8	21	24.7	6	7.1	0.3915
Dementia †							
Yes	5	5.9	1	1.2	4	4.7	
No	50	58.8	37	43.5	13	15.3	0.0278
Asthma †							
Yes	7	8.2	4	4.7	3	3.5	
No	44	51.8	33	38.8	11	12.9	0.3763
Chronic obstructive pulmonary disease †							
Yes	2	2.4	1	1.2	1	1.2	
No	46	54.1	33	38.8	13	15.3	0.5027
Malignant neoplasm †							
Yes	3	3.5	1	1.2	2	2.4	
No	48	56.5	36	42.4	12	14.1	0.1792
Smoker †							
Current or ex	7	8.2	5	5.9	2	2.4	
No	25	29.4	20	23.5	5	5.9	0.6317
Basal insulin †							
Yes	37	43.5	32	37.6	5	5.9	
No	30	35.3	17	20.0	13	15.3	0.0115

Parameter	Entire cohort		Alive		Deceased		*P*-value
	n	%	*n*	%	*n*	%	
Rapid insulin †							
Yes	35	41.2	31	36.5	4	4.7	
No	31	36.5	18	21.2	13	15.3	0.0099
Continuous subcutaneous insulin infusion †							
Yes	1	1.2	1	1.2	-	-	
No	42	49.4	33	38.8	9	10.6	>0.9999
Biphasic insulin †							
Yes	14	16.5	13	15.3	1	1.2	
No	49	57.6	33	38.8	16	18.8	0.0876
Any insulin (combined category) †							
Yes	54	63.5	48	56.5	6	7.1	
No	23	27.1	11	12.9	12	14.1	0.0002
Sulfonylurea †							
Yes	14	16.5	7	8.2	7	8.2	
No	44	51.8	33	38.8	11	12.9	0.1023
Metformin †							
Yes	38	44.7	26	30.6	12	14.1	
No	22	25.9	17	20.0	5	5.9	0.5599
Dipeptidyl Peptidase-4 inhibitor †							
Yes	19	22.4	12	14.1	7	8.2	
No	40	47.1	30	35.3	10	11.8	0.3718
Sodium glucose co-transporter-2 inhibitor †							
Yes	8	9.4	6	7.1	2	2.4	
No	50	58.8	36	42.4	14	16.5	>0.9999
Pioglitazone †							
Yes	3	3.5	2	2.4	1	1.2	
No	49	57.6	36	42.4	13	15.3	>0.9999
Glucagon-like peptide-1 receptor agonist †							
Yes	4	4.7	4	4.7	-	-	
No	53	62.4	36	42.4	17	20.0	0.3062
Meglitinide							
Yes	-	-	-	-	-	-	
No	52	61.2	38	44.7	14	16.5	-
Acarbose							
Yes	-	-	-	-	-	-	
No	52	61.2	38	44.7	14	16.5	-
Number of oral hypoglycaemic agents ‡							
0	16	18.8	13	15.3	3	3.5	
1	20	23.5	15	17.6	5	5.9	
2	16	18.8	10	11.8	6	7.1	
3	10	11.8	6	7.1	4	4.7	0.1576
Angiotension-2 converting enzyme inhibitor / angiotensin receptor blocker †							
Yes	20	23.5	14	16.5	6	7.1	
No	40	47.1	28	32.9	12	14.1	>0.9999
Oral corticosteroid †							
Yes	1	1.2	-	-	1	1.2	
No	51	60.0	38	44.7	13	15.3	0.2692
Statin †							
Yes	26	30.6	18	21.2	8	9.4	
No	35	41.2	26	30.6	9	10.6	0.7751
Antiplatelet †							
Yes	12	14.1	7	8.2	5	5.9	
No	42	49.4	33	38.8	9	10.6	0.2605

Parameter		Entire cohort		Alive		Deceased		*P*-value
		n	**%**	***n***	**%**	***n***	**%**	
Anticoagulant †								
	Yes	17	20.0	15	17.6	2	2.4	
	No	33	38.8	23	27.1	10	11.8	0.1811
Non-steroidal anti-inflammatory drug †								
	Yes	1	1.2	1	1.2	-	-	
	No	50	58.8	36	42.4	14	16.5	>0.9999

Table S4: Comparison of *Confirmed DKA* cohort clinical characteristics by mortality. RRT: renal replacement therapy. No corrections have been applied for multiple tests of statistical significance, and missing data are ignored. Tests indicated by † (Fisher's Exact test) and ‡ (χ^2 test for trend).

Variable	*Confirmed HHS*	*Unconfirmed HHS*	*P*-value
Sex (*n*) †			
Male	12	40	
Female	8	22	0.792
Ethnicity group (*n*) ‡			
White	4	14	
Asian	1	5	
Black	8	18	
Other	1	6	0.821
IMD quintile (*n*) ‡			
1 (most deprived)	3	8	
2	3	9	
3	2	3	
4	2	10	
5 (least deprived)	-	5	0.666
Age (years) §			
n	20	62	
median	79	73.5	
IQR	64.5 – 83.75	60 – 81	0.210
BMI (kg.m^{-2}) §			
n	11	34	
median	28.2	26.0	
IQR	23.66 – 37.73	23.87 – 28.18	0.255

Table S5: Comparison of *Confirmed HHS* and *Unconfirmed HHS* cohort demographics. Tests indicated by † (Fisher's Exact), ‡ (Fisher-Freeman-Halton Exact), and § (independent-samples Mann-Whitney U).

	Total (*N* = 20)			Alive (*n* = 7)			Deceased (*n* = 13)			
	Mean	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	***P*-value**
pH	7.33	0.07	18	7.31	0.09	5	7.34	0.05	13	0.4872
Bicarbonate (mmol/L)	23.3	5.4	19	22.7	2.5	7	23.7	6.5	12	0.7732
Glucose (mmol/L)	38.2	6.8	†19	36.3	4.4	7	39.3	7.7	†12	0.4673
β-hydroxybutyrate (mmol/L)	1.1	0.6	14	1.1	0.7	5	1.0	0.6	9	0.7737
Lactate (mmol/L)	3.0	1.9	18	2.9	2.5	6	3.0	1.5	12	0.4521
Creatinine (µmol/L)	275	231	19	256	272	7	286	202	12	0.6358

Table S6: Admission biochemistry of *Confirmed HHS* cohort. Assays were conducted on a variety of main hospital laboratory analysers, and/or emergency department point-of-care bench-top machines, and/or hand-held point-of-care meters. Assay methods were not recorded in the audit. † The missing value for blood glucose was indicated by the contributor to have been above the upper limit of the assay reportable range (URR). Missing values for other analytes were not recorded. *P*-values denote a comparison between Alive and Deceased groups by Mann-Whitney U-test for each analyte, without imputation for the value above assay URR.

Parameter	Entire cohort		Alive		Deceased		*P*-value
	n	%	*n*	%	*n*	%	
Sex †							
Female	8	40	4	20	4	20	
Male	12	60	3	15	9	45	0.3563
Total	20	100	7	35	13	65	
Chronic Kidney Disease stage ‡							
0, 1 or 2	5	25	1	5	4	20	
3	3	15	-	-	3	15	
4	3	15	2	10	1	5	
5	2	10	1	5	1	5	
RRT	-	-	-	-	-	-	0.1921
Foot ulcer							
Yes	-	-	-	-	-	-	
No	11	55	4	20	7	35	-
Diabetic nephropathy †							
Yes	9	45	3	15	6	30	
No	7	35	3	15	4	20	0.9999
Diabetic peripheral neuropathy †							
Yes	1	5	1	5	-	-	
No	12	60	5	25	7	35	0.4615
Diabetic retinopathy †							
Yes	5	25	1	5	4	20	
No	8	40	3	15	5	25	>0.9999
Peripheral vascular disease							
Yes	-	-	-	-	-	-	
No	13	65	5	25	8	40	-
Ischaemic heart disease †							
Yes	4	20	2	10	2	10	
No	8	40	2	10	6	30	0.5475
Stroke or transient ischaemic attack †							
Yes	4	20	2	10	2	10	
No	13	65	4	20	9	45	0.5840
Hypertension †							
Yes	8	40	2	10	6	30	
No	4	20	2	10	2	10	0.5475
Dementia †							
Yes	2	10	-	-	2	10	
No	9	45	4	20	5	25	0.4909
Asthma							
Yes	-	-	-	-	-	-	
No	12	60	4	20	8	40	-
Chronic obstructive pulmonary disease							
Yes	-	-	-	-	-	-	
No	12	60	4	20	8	40	-
Malignant neoplasm †							
Yes	1	5	-	-	1	5	
No	10	50	4	20	6	30	>0.9999
Smoker †							
Current or ex	3	15	1	5	2	10	
No	2	10	1	5	1	5	>0.9999
Basal insulin †							
Yes	8	40	5	25	3	15	
No	10	50	2	10	8	40	0.1448

Parameter		Entire cohort		Alive		Deceased		*P*-value
		n	%	*n*	%	*n*	%	
Rapid insulin †								
	Yes	1	5	1	5	-	-	
	No	16	80	5	25	11	55	0.3529
Pump								
	Yes	-	-	-	-	-	-	
	No	12	60	4	20	8	40	-
Premixed insulin †								
	Yes	2	10	-	-	2	10	
	No	15	75	6	30	9	45	0.5147
Any insulin †								
	Yes	10	50	5	25	5	25	
	No	8	40	2	10	6	30	0.3665
Sulfonylurea †								
	Yes	5	25	3	15	2	10	
	No	12	60	3	15	9	45	0.2801
Metformin †								
	Yes	9	45	3	15	6	30	
	No	8	40	3	15	5	25	>0.9999
Dipeptidyl peptidase-4 inhibitor †								
	Yes	6	30	4	20	2	10	
	No	12	60	3	15	9	45	0.1414
Sodium glucose co-transporter-2 inhibitor †								
	Yes	1	5	1	5	-	-	
	No	13	65	5	25	8	40	0.4286
Pioglitazone †								
	Yes	2	10	-	-	2	10	
	No	10	50	4	20	6	30	0.5152
Glucagon-like peptide-1 receptor agonist †								
	Yes	2	10	2	10	-	-	
	No	15	75	4	20	11	55	0.1103
Meglitinide								
	Yes	-	-	-	-	-	-	
	No	12	60	4	20	8	40	-
Acarbose †								
	Yes	1	5	-	-	1	5	
	No	11	55	4	20	7	35	>0.9999
Number of oral hypoglycaemic agents ‡								
	0	4	20	1	5	3	15	
	1	7	35	2	10	5	25	
	2	4	20	3	15	1	5	
	3	3	15	1	5	2	10	0.4203
Angiotensin-2 converting enzyme inhibitor / angiotensin receptor blocker †								
	Yes	10	50	5	25	5	25	
	No	7	35	2	10	5	25	0.6221
Oral corticosteroid								
	Yes	-	-	-	-	-	-	
	No	11	55	4	20	7	35	-
Statin †								
	Yes	11	55	7	35	4	20	
	No	6	30	-	-	6	30	0.0345
Antiplatelet †								
	Yes	4	20	3	15	1	5	
	No	7	35	1	5	6	30	0.0879

Parameter	Entire cohort		Alive		Deceased		*P*-value
	n	**%**	***n***	**%**	***n***	**%**	
Anticoagulant †							
Yes	2	10	1	5	1	5	
No	10	50	3	15	7	35	>0.9999
Non-steroidal anti-inflammatory drug							
Yes	-	-	-	-	-	-	
No	11	55	4	20	7	35	-

Table S7: Comparison of *Confirmed HHS* cohort clinical characteristics by mortality. RRT: renal replacement therapy. No corrections have been applied for multiple tests of statistical significance, and missing data are ignored. Tests indicated by † (Fisher's Exact test) and ‡ (χ^2 test for trend).

Parameter	Entire cohort	Alive	Deceased	*P*-value
HbA_{1c} (%)				
n	19	7	12	
mean (SD)	10.3 (5.9)	12.3 (4.7)	9.0 (6.0)	
median (IQR)	9.1 (6.9 – 12.5)	12.3 (11.2 – 15.1)	7.2 (6.6 – 9.7)	
HbA_{1c} (mmol/mol)				
n	19	7	12	
mean (SD)	88.6 (41.0)	111.3 (28.1)	75.4 (41.6)	
median (IQR)	76 (52 – 113)	111 (99 – 141)	55 (49 – 82)	0.134
Interval between most recent HbA_{1c} and admission (days)				
n	18	7	11	
mean (SD)	200.3 (204.3)	95.3 (51.6)	267.1 (216.2)	
median (IQR)	205.5 (22.0 – 288.0)	11.0 (7.0 – 276.0)	218.0 (133.0 – 335.0)	0.0853

Table S8: Latest available HbA_{1c} and interval between hospital admission and HbA_{1c} assay for *Confirmed HHS* cohort. *P*-value for difference in HbA_{1c} is derived from age-adjusted binomial logistic regression for mortality, treating age and HbA_{1c} as continuous variables. *P*-value for difference in interval between HbA1c and admission is derived from independent-samples Mann-Whitney U test.