THE LANCET
Diabetes & Endocrinology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplementary Appendix

Methods:

The aim of this retrospective study was to gain insights in the biochemical characteristics and clinical outcomes of patients with Covid-19 presenting with hyperglycemic emergencies and/or hyperglycaemic ketonemia of any degree and to assess fluid and insulin requirements vs. the National and Local guidance for the management of DKA and HHS. A total of 35 patients were included from three UK Hospitals: the Royal Free Hospital, London, NW3 2QG; the North Middlesex University Hospital, N18 1QX, and Hinchinbrook Hospital North West Anglia Foundation Trust, PE29 6NT. Inclusion criteria were (1) hospitalisation with COVID-19 diagnosis confirmed biologically (by SARS-CoV-2 PCR test) and/or clinically/radiologically (i.e. as ground-glass opacity and/or crazy paving on chest computed tomography [CT] scan); (2) DKA and / or HHS at presentation in accident and emergency department; (3) known or new diagnosis of diabetes and presence of ketonemia (beta-hydroxybutyrate >0.6mmol/L); (4) Glasgow – Coma – Scale of at least 12 at admission to the hospital.

The study was part of an audit, which aimed to assess the management of diabetes emergencies in patients with Covid-19 infection, against National and local guidance in hyperglycemic emergencies. The audit has been approved by the respective audit departments in all three sites.

Data collection was performed by clinical staff in participating centres who systematically reviewed the hand-written and electronic medical files of all COVID-19 inpatients. All patients fulfilling the inclusion criteria were selected, as eligible for this study. Patients with DKA and/or HHS were treated with intravenous insulin, starting dose of 0.05-0.1 Units per kg of body weight per hour, whereas those with hyperglycemic ketosis received intravenous insulin 1-4 units/hour, based on their blood glucose levels and local guidelines.

We collected clinical/biochemical and anthropometric parameters at the time of presentation, details on admission to the intensive care unit as well as the outcome of the admission at the time of the study. Moreover, details were retrieved related with the classification of diabetes, glycaemic control prior to admission (i.e. HbA1c on at least two occasions, within the last 6 months before admission), as well as medical treatment for control of diabetes, if any. For this purpose, relative general and / or specialist practitioner and/or regular pharmacist or biomedical laboratory were contacted. Data on comorbidities and overall medication history were also included.

Statistical analysis

Data were analyzed with GraphPad Prism 8 (GraphPad) and the Statistical Package for the Social Sciences (SPSS) version 25. Quantitative data were expressed as median and interquartile range (IQR). Due to the small sample size, the within group analysis for HHS patients (n=2) was performed by presenting median values and range. Categorical variables were given as number (percentage) of participants. Correlation was assessed using Pearson correlation coefficient. The following categorizations were used to describe the strenght of correlations, according to the absolute value of r-coefficient, as follows: <0.20 very weak, 0.20-0.39 weak, 0.40-0.59 moderate, 0.60-0.79 strong, 0.80+ very strong. Kaplan-Meier curves were used to estimate the median time until intensive care admission and the median time to discharge. For all statistical analyses, $P < 0.05$ was considered statistically significant.

Supplementary Table 1: Correlation analysis between serum levels of ketones and time to ketone resolution with blood gas parameters using Pearson's correlation coefficient. Statistical significance was set at the level of P < 0.05

| Variables	Correlation coefficient	P
Capillary ketones		
- Activated partial thromboplastin time	-0.384	0.095
- Prothrombin time	-0.247	0.256
- pH at first hour	-0.368	0.035
- Serum bicarbonate (mmol/L)	-0.671	<0.001
- Base excess (mmol/L)	-0.564	0.001
- Lactate (mmol/L)	0.332	0.073
- Alanine aminotransferase (U/L)	0.415	0.023
- Lymphocytes	-0.364	0.037
- Total fluid volume (24hrs)	0.386	0.304
- Total fluid volume (24-48hrs)	-0.088	0.868
- Glycated haemoglobin (%)	0.119	0.637
Time to ketones resolution		
- Activated partial thromboplastin time	0.725	0.001
- Prothrombin time	0.752	<0.001
- pH at first hour	-0.408	0.025
- Serum bicarbonate (mmol/L)	-0.441	0.015
- Base excess (mmol/L)	-0.481	0.007
- Lactate (mmol/L)	-0.008	0.970
- Alanine aminotransferase (U/L)	0.047	0.823
- Lymphocytes	-0.148	0.453
- Total fluid volume (24hrs)	0.673	0.047
- Total fluid volume (24-48 hrs)	-0.381	0.456
- Glycated Haemoglobin (%)	-0.458	0.075

Supplementary Figure 1. Median values of serum ketones according to ethnicity, at the time of presentation in the emergency department.
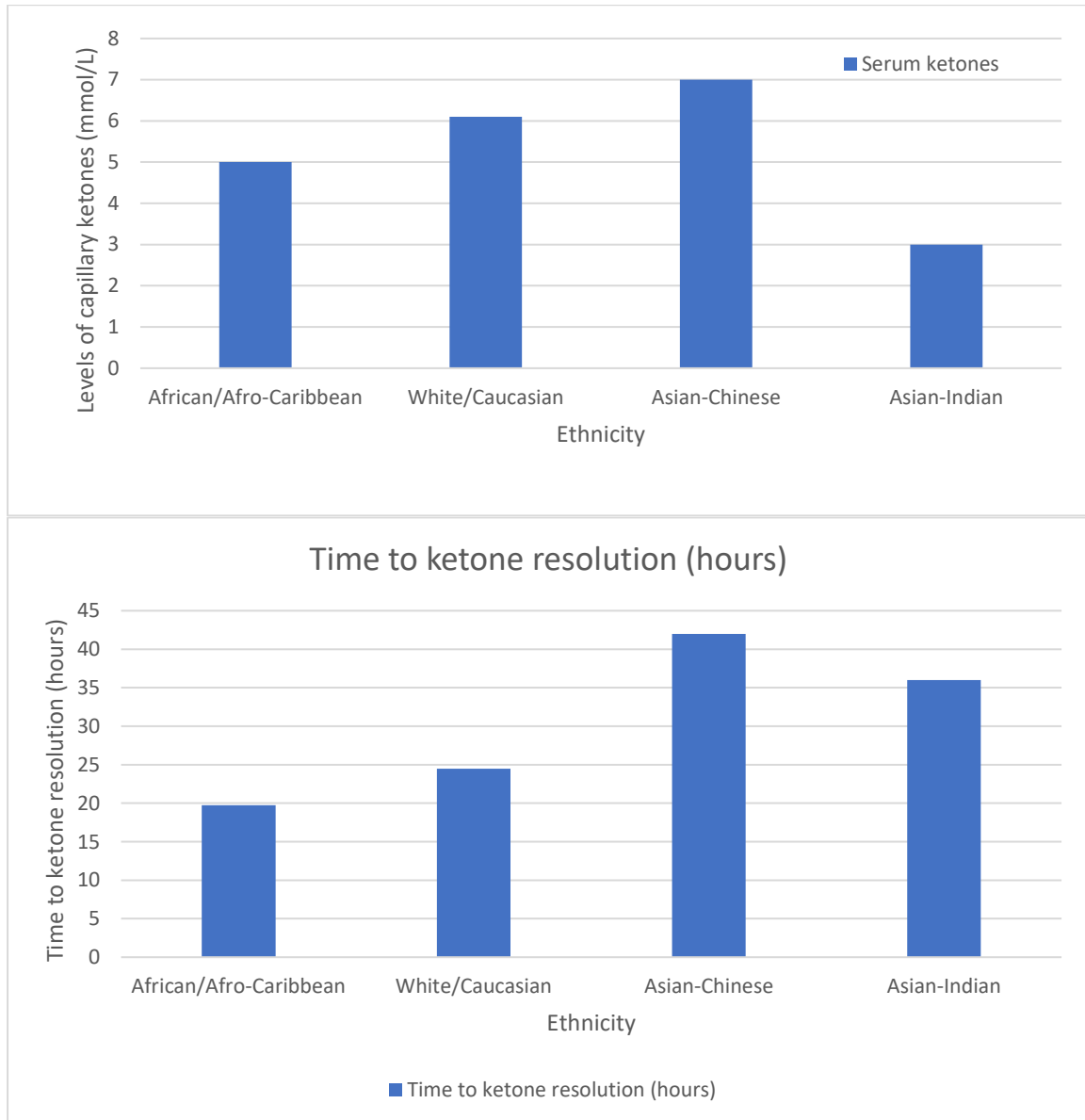
Supplementary Figure 2. Kaplan Meier curve presenting the median time from hospital admission until transfer to intensive care unit, for the total sample. Values are presented as median and 95% confidence interval.

Survival Function

Median, 3.00 days;
95% CI, 0.60 to 5.40

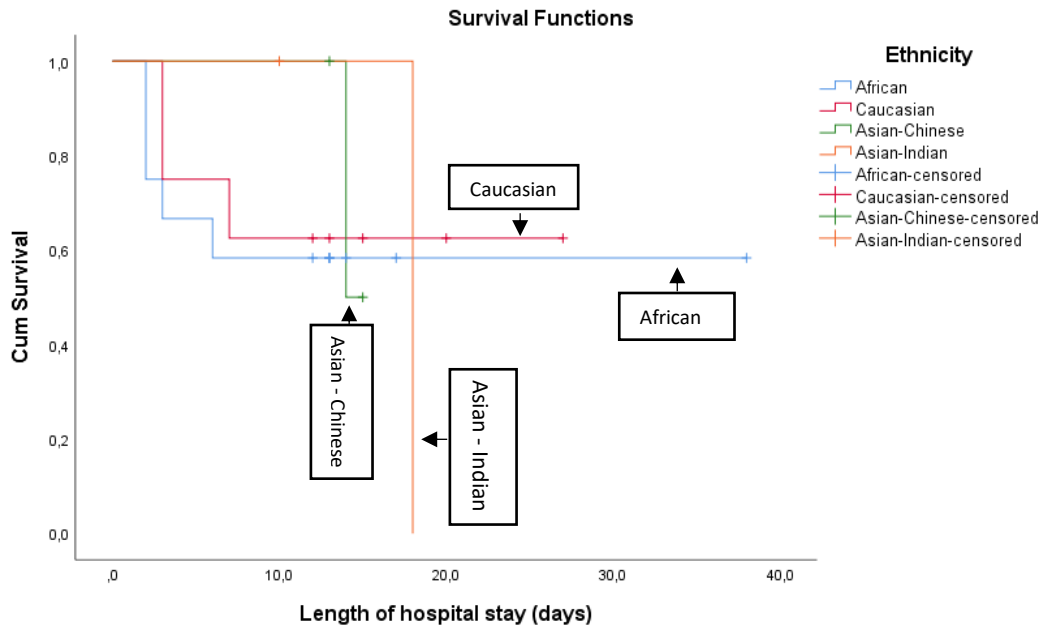| Number at risk						
6	5	4	3	2	1	0
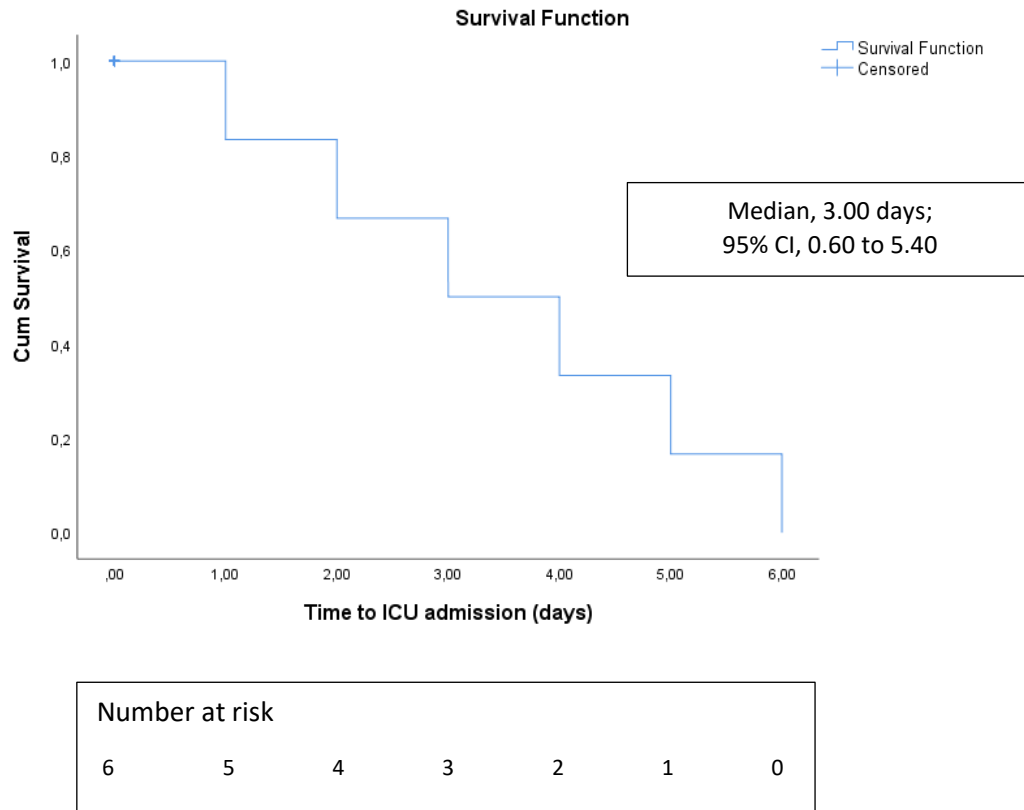
Supplementary Figure 3. Kaplan Meier curve presenting the median time until discharge for the total sample. Values are presented as median and 95% confidence interval.
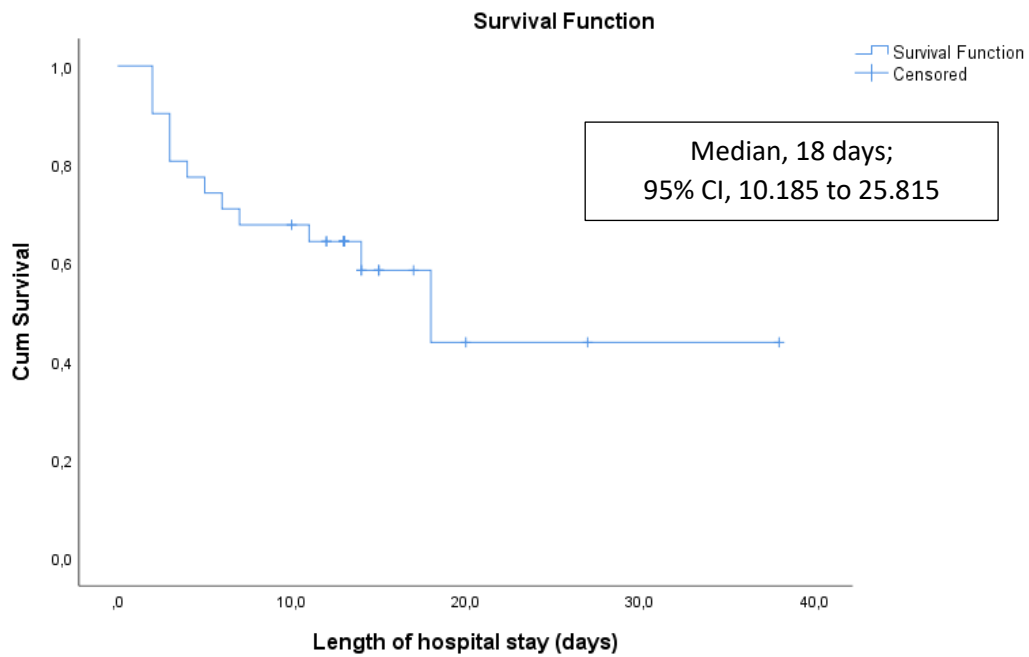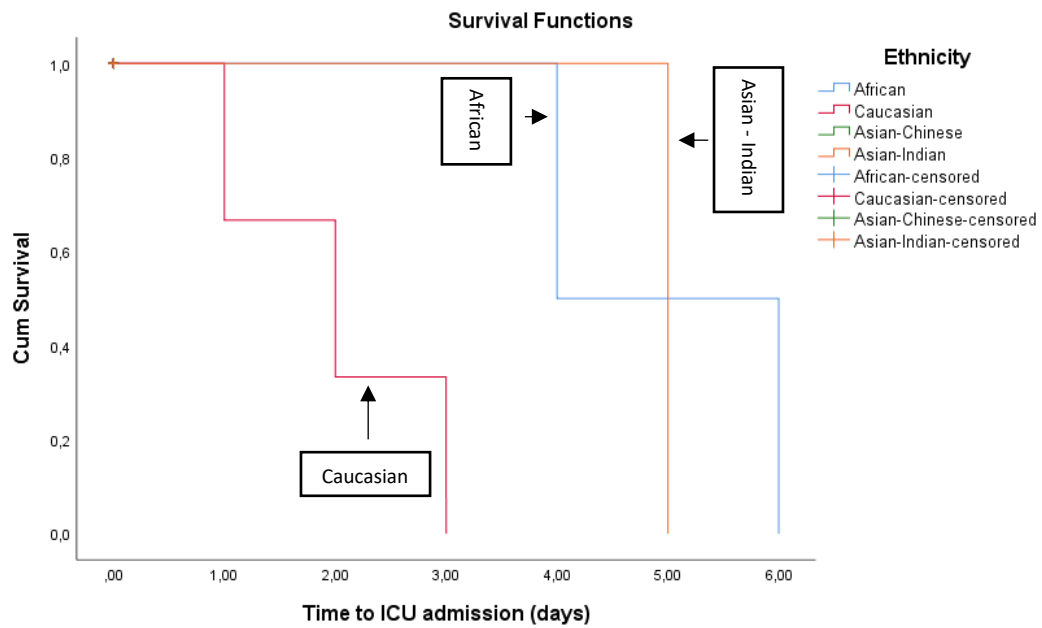

Number at risk

25	13	3	1	0

Supplementary Figure 4a. Kaplan Meier curve presenting the median time until discharge according to the ethnic background. Values are presented as median ± standard error (SE).

Number at risk				
Group African				
11	6	2	1	0
Group Caucasian				
6	4	1	0	0
Group Asian-Chinese				
2	2	0	0	0
Group Asian-Indian				
2	1	0	0	0

Supplementary Figure 4b. Kaplan Meier curve presenting the median time from admission to the hospital until transfer to the intensive care unit according to ethnicity. Results were compared using the log-rank test.

Number at risk

Group African

| 2 | 2 | 2 | 2 | 1 | 1 | 0 |

Group Caucasian

| 3 | 2 | 1 | 0 | 0 | 0 | 0 |

Group Asian-Chinese

| 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Group Asian-Indian

| 1 | 1 | 1 | 1 | 1 | 0 | 0 |

Contributors

EK and EA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: EK, AY and EA conceived the study. EK and EA established collaborative links. UA, HCB, RN, RM, MR were involved in study design aspects.

Acquisition, analysis, or interpretation of data: All authors

Patient recruitment: All authors

Statistical analysis: EA, EK

Drafting the manuscript: EK, EA.

Critical revision of the manuscript for important intellectual content: all co-authors.

All authors have approved the final version of the manuscript.