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Comorbid disease and ethnicity in emergency hospital admissions in east London

Statistical Analysis Plan

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Short title	Comorbid disease and ethnicity in emergency hospital admissions in east London
Methodology	Observational cohort study of outcomes in Black, Asian and Minority Ethnic (BAME) and non-BAME patients admitted to hospital following an emergency presentation
Objectives / aims	• To assess whether there is a difference in outcomes (death/organ support) between comorbidity and different ethnic backgrounds of patients with an emergency admission to hospital • To analyse differences in age, sex, and measure of socio-economic deprivation in patients of Black, Asian and other ethnicities, compared to non-BAME ethnicity and to understand their association with adverse outcomes
Number of participants	Around 100,000
Inclusion and exclusion criteria	**Inclusion Criteria:** • Age 18 years or over • Emergency presentation to hospital • Admission to a Barts Health NHS Trust hospital between 01/01/2013 and 31/12/2018 **Exclusion Criteria:** • Unknown or undisclosed ethnicity • Obstetric admissions
Statistical methodology and analysis (if applicable)	• Prospectively defined observational study • Descriptive and comparative analyses of demographics, clinical characteristics and clinical outcomes between patients of different ethnicities using univariate and multivariable analysis
Study duration	6 months

1. Introduction

1.1. Background

The COVID-19 global pandemic has resulted in significant mortality and morbidity over a relatively short period of time (1). Greater impact of disease in severity and death on people from Black, Asian and Minority Ethnic (BAME) backgrounds has been reported (2-4). Using data from all acute hospitals within Barts Health NHS Trust, we observed that patients from Asian and Black backgrounds are more likely to die from COVID-19 infection despite controlling for age, other previously identified confounders and frailty (5). Furthermore, given their much younger age, COVID-19 patients of Asian and Black backgrounds suffered disproportionate rates of premature death. This association appeared to be underpinned by a combination of factors including socio-economic status (SES), pre-existing health conditions, biological risk factors such as D-dimers, environmental, and structural determinants of health. However, their relative contribution is unclear.

Although COVID-19 has highlighted the effects of ethnic inequalities on health outcomes, these inequalities are not new. Health inequalities within and between ethnic minority groups have been widely documented (6). Ethnic minorities tend to have poorer health than majority ethnic groups. This has been clearly demonstrated in a range of conditions such as cardiovascular disease, diabetes, stroke, and hypertension (7). The relationship between ethnicity and health is complex as risk factors are likely to interact and are inextricably linked with wider social determinants. The important ethnic disparities unmasked during the COVID-19 pandemic may represent features of poorer underlying health status within BAME patients.

Whilst there is a body of evidence describing differences in race and ethnicity in the use of healthcare services, quality of health care and health outcomes, relatively few have been carried out in critically ill patients and the majority of studies have been conducted in healthcare systems where access and resource allocation differ (8). Prior studies have also been limited by sample size, inadequate risk adjustment and assessment of linked factors such as SES. A previous US observation study reported that minority ethnic patients presented with presenting with greater severity of illness to intensive care and had fewer elective admissions, however, there was no differences in mortality after adjustment for severity of illness suggesting possible disparities preceding admission (9).

1.1. Rationale

Barts Health is the largest NHS Trust serving a majority (60%) BAME population within an area with some of the worst socio-economic deprivation and highest neighbourhood Index of Multiple Deprivation (IMD) scores. Understanding the ethnicity disparities unmasked by the COVID-19 pandemic is crucial in determining underlying causes and identifying population specific interventions.

This aim of this comparative study is to determine in a cohort of non-COVID emergency hospital admissions within the same representative population in east London, whether there is a difference in outcomes in patients of different ethnicities. It will test the hypothesis that

patients of Black, Asian and other ethnicities have poorer outcomes defined using mortality and length of stay. Data generated has the potential to influence and shape relevant policy and practice to improve health outcomes in BAME communities.

2. Study objectives

2.1. Primary objective

This study aims to assess whether there is an comorbidity, age and sex adjusted difference in outcomes in different ethnicities of patients admitted with an emergency presentation to hospitals within Barts Health NHS Trust.

The study will test the hypothesis that there is an association between health outcomes defined using mortality and length of stay; and ethnicity; with patients of Black, Asian and other ethnicities having poorer outcomes as compared to patients of White ethnicity.

2.2. Secondary objective

We will examine the strength and nature of relationship between ethnic background and outcome in multivariable age, sex, co-morbidity, and frailty adjusted multivariable survival analysis.

We hypothesise that BAME background patients may be disproportionately younger, have greater baseline co-morbidity and have greater socio-economic deprivation than non-BAME counterparts and we will document these differences and explore their effects on outcome in the analysis.

2.3. Primary endpoint

The primary endpoint will be 30-day mortality from time of first hospital admission with an emergency presentation.

2.4. Secondary endpoints

The secondary endpoints will be:

- 1-year mortality
- Discharged from hospital alive
    - Discharge destination
- Length of stay in hospital

3. Study population

3.1. Inclusion criteria

- Age 18 years or over
- Emergency presentation to hospital
- Admission to a Barts Health NHS Trust hospital between 01/01/2013 and 31/12/2018

3.2. Exclusion criteria

- Unknown or undisclosed ethnicity status
- Obstetric admission

4. Study design

This is a prospectively defined observational cohort study utilising data from the Barts Health Electronic Patient Record (EPR) system.

Data analysis will include, but not limited to:

- A comparison of clinical characteristics between patients of different ethnicities.
- A comparison of age at presentation and age-standardised mortality between patients of different ethnicities.
- An assessment of clinical outcomes following an acute hospital admission.
- An assessment of ethnicity as a predictor of outcome using univariate and multivariable analysis. This will include adjustment for potential confounders such as co-morbidity and postcode of residence/Index of Multiple Deprivation (IMD).

5. Study procedures

Consent
This study involves the aggregated analysis of an anonymised dataset collated by members of the direct care team and should not require REC review or consent.

Data collection
Hospital Cerner Millennium Data Warehouse records will then be used to obtain clinical, demographic and blood results by members of the clinical team participating in this study.

No patient notes will be required or examined. This data will be recorded in a Microsoft Excel Database maintained under password protection on the secure Trust internal network. After results for each patient have been collated by a member of the direct clinical care team. Once collation of the database is complete an anonymised database lacking all patient identifiable details will be analysed by the investigators. For analysis see statistical details below.

Permissions
Procedures for data collection and study protocols have been approved by HRA under IRAS ID 273546, an amendment has been made for this study as a secondary analysis.

6. Statistical considerations

The Chief Investigator takes responsibility for the statistics and statistical oversight for this study.

6.1. Sample size

The cohort to be analysed in this study comprises patients admitted critical care at the Royal London Hospital between 1st January 2013 and 31st December 2018.

This will be a retrospective review of routinely collected data and we anticipate that around 100,000 patients will meet our inclusion criteria, but the final sample size will be dictated by the data available.

6.2. Method of analysis

Software
Statistical analyses will be performed using R: A language and environment for statistical computing (R Core Team (2020). R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/).

Statistical Analysis

Definitions

Ethnicity
The ethnic categories to be used will be the 16+1 ethnic data categories defined in the 2001 census which form national mandatory standard for the collection and analysis of ethnicity in the NHS data dictionary.

These are:

White

- A British
- B Irish
- C Any other White background

Mixed

- D White and Black Caribbean
- E White and Black African
- F White and Asian
- G Any other mixed background

Asian or Asian British

- H Indian

J Pakistani

K Bangladeshi

L Any other Asian background

Black or Black British

M Caribbean

N African

P Any other Black background

Other Ethnic Groups

R Chinese

S Any other ethnic group

-

Z Not stated (excluded from this analysis)

In order to preserve statistical power to detect differences between groups primary analysis will be performed between ethnicity as defined by the 5-high level groups White, Mixed, Asian or Asian British, Black or Black British and Other.

Death will be defined by the presence of a date of death or discharge destination "patient died" in hospital electronic records (these are synchronised with NHS spine to capture out of hospital deaths).

Emergency admissions will be categorised by medical or surgical.

Smoking
History of tobacco use will be defined by presence of the WHO ICD-10 codes F17·1-F17·2, Z72·0, Z87·8, Z71·6 and T65·2.

Ischaemic heart disease
Ischaemic heart disease (IHD) will be defined by the presence of the ICD-10 codes I23·4-I23·5, I24, I24·8-I24·9, I25, I25·3-I25·6, I25·8-I25·9, I34·1, I46·1, I51·8-I51·9, and I52.

End stage Renal disease
End stage Renal disease (ESRD) will be defined by the presence of the ICD10 codes I77·0, N16·5, N18·5, T82·4, T86·1, Y60·2, Y61·2, and Y62·2, Y84·1, Z49·0-Z49·2, Z94·0, Z99·2.

Comorbidity
Diagnosis of co-morbidities and assignment of Charlson Comorbidity Index will be based on mapping from ICD-10 coding from previous admissions. Diagnosis of Hypertension will be based on mapping ICD-10 codes to the Elixhauser comorbidity index.

Hospital frailty risk score
Hospital frailty risk score will be calculated from mapping ICD-10 coding of hospital attendances.

Acute Kidney injury
Acute kidney injury (AKI) within first 7 days of admission will be defined using the KDIGO 2012 creatinine criteria either a 1·5-fold rise over baseline within 7 days or 26 μmol rise within 48 hours. Baseline creatinine will be the median value in the 7 to 365 days before hospitalisation. Absent baseline creatinine will be determined based on an eGFR of 75 ml/min/1·72m^2 using the CKDepi formula or the admission value whichever is lower.

Chronic kidney disease
History of chronic kidney disease (CKD) using baseline eGFR will be calculated using last creatinine value available from results earlier than 7 days before hospitalisation. CKD will defined as baseline eGFR below 60 ml/min/1·72m^2.

Index of Multiple Deprivation
Index of Multiple Deprivation will be defined from patient home address postcode using UK government statistics https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019. IMD will be presented as raw score and quintiles within the greater London area

Analysis
Clinical outcomes for the whole cohort will be analysed and also stratified by ethnicity. Univariate and multivariable analyses will subsequently be used to investigate predictors of outcome for each ethnicity.

All continuous data will be expressed as median and interquartile range (IQRs) and categorical data as proportion. For continuous data, we will compare the mean difference between groups by ANOVA or Kruskal-Wallis test. For dichotomous data, we will use Pearson Chi-square test or Fisher exact test (if expected number less than 5). The log-rank and Wilcoxon test will be used for survival time comparisons between groups.

Sample Table 1

	Black	**Asian**	**Mixed**	**Other**	**White**	P value
Age						
Sex						
IMD quintile						
Smoking						
BMI						
Comorbidity						
Obesity						
IHD						
DM						
HTN						
CKD						
Charlson co-morbidity index						
Frailty						
Rockwood frailty score						

Hospital frailty risk score						
AKI						
Length of stay						
Death						
In-hospital						
30 day						
90 day						
Discharge destination						
Care home or equivalent						
Health-related institution						
Usual place of residence						
Hospice or equivalent						
Temporary place of residence						

Primary and Secondary Endpoint Analysis

Primary endpoint will be 30-day mortality between ethnic groupings adjusted for patient age and sex. A restricted cubic spline model will be used to account for non-linear effects of age. Mortality comparison will be analysed using Cox-proportional Hazard analysis censored at 30 days or time of maximal follow-up or logistic regression analysis if non-proportionality between ethnic groups and risk of death over time is evident.

Age and sex adjusted incidence of secondary endpoints will be assessed using logistic regression on Cox hazard models as appropriate.

Hospital site will be included in all models as a fixed effect variable to account for potential differences in care.

Multi-variable analyses

If available, the following variables will be collected and considered in multi-variable analysis for primary and secondary endpoints using logistic regression on Cox hazard models as appropriate

- Age
- Sex
- BMI
- Smoking status
- Clinical frailty Scale at admission if recorded
- Co-morbidities based on ICD-10 coding for current and previous admission based on established mapped to Charlson co-morbidty index and Elixhauser Index
- Specific comorbidities for consideration
    - Hypertension
    - Diabetes
    - CKD
- Index of Multiple deprivation (IMD)

Interaction with IMD

We will investigate if there is potential interaction between ethnicity and IMD in models.

Age-specific effects

Focusing on patients with an address in the boroughs of Tower Hamlets, Waltham Forest, and Newham, we will compare distribution of admissions by age across ethnic groups with distribution of people by age across ethnic groups within these boroughs. In order to account for differences in age structure between ethnic groups, we will calculate comparative mortality rates suing age-standardised mortality rates based on the 2013 European standard Population figures.

Sensitivity analyses

To assess the effect of including patients living outside the Barts Health NHS Trust catchment area, the primary survival outcomes analysis will be repeated using a subset of patients residing within Tower Hamlets, Newham, and Waltham Forest only. Multivariable analysis will be repeated using aggregate measures of frailty in place of specific co-morbidities listed above. Comparisons will be made between specific indications for hospital admission.

7. References

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