Risk Factors for Severe COVID-19 Among In-Centre Haemodialysis Patients.

Statistical Analysis Plan

Study Title: Risk factors for severe COVID-19 among in-centre haemodialysis patients.

Short Title: Severe COVID in ICHD patients.

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1. INTRODUCTION

1.1. STUDY BACKGROUND

Coronavirus disease 2019 (COVID-19) presents on a clinical spectrum, with severe disease requiring supplemental oxygenation, escalating to mechanical ventilation and even extra-corporeal membrane oxygenation (ECMO) in extreme cases. Factors influencing the severity of presentation has been rigorously interrogated in the general population, and include cardiovascular disease, diabetes mellitus, chronic lung disease, obesity, malignancy, immunosuppression and chronic kidney disease. The elucidation of these factors has directly informed public health advice, by defining at-risk patient groups who are advised to strictly social distance or shield, and is likely to guide rationing of the recently approved vaccinations.

Although those who require in-centre haemodialysis (ICHD) fall into the high risk category, not all develop severe disease. Understanding risk factors for severity of COVID19 among ICHD patients is of the utmost priority; traditional public health measures cannot apply to this group due to their obligation to travel to and from their units, and the need to interact with health care professionals at least three times a week. In this study, we report the incidence of COVID19 among HD patients in the midlands, a strongly multi-ethnic region in the United Kingdom, and explore risk factors for severity of infection, defining a cohort for whom added protective measures may need to be considered in the context of global easing of ‘lockdowns’, and perhaps who should be prioritised for vaccinations when they become available.

1.2. STUDY OBJECTIVES

This study aims to provide insights into unresolved questions regarding risk factors that may predispose to severe COVID19 among in-centre haemodialysis (ICHD) patients.

Hypothesis:

1. Obesity, diabetes, ethnicity are risk factors for severe COVID19 among ICHD patients

2. The Charlson Co-morbidity Score and Socioeconomic Deprivation are risk factors for severe COVID19 among ICHD patients

1.3. STUDY DESIGN

The study design is a multi-centre, retrospective cross-sectional observational study.
1.4. **SAMPLE SIZE**

Estimated sample size based on UK renal registry data is 350. This is the total number of patients with COVID19 in dialysis units based in the midlands between February 2020 to August 2020, and is therefore all the data available to us at present. Based on our pilot data of 69 patients, this sample should be adequate enough to detect the effect of BMI, Diabetes and Socioeconomic deprivation (as measured by the index of multiple deprivation (IMD)), however it may not be adequate enough to detect the effect of ethnicity or the Charlson Co-morbidity index. Sample size calculations were performed assuming an alpha of 0.5 and a power of 80% (https://clincalc.com/stats/samplesize.aspx):

<table>
<thead>
<tr>
<th>Condition</th>
<th>Severe COVID in BMI &gt;/=25</th>
<th>Severe COVID in BMI &lt;25</th>
<th>Severe COVID in Diabetes</th>
<th>Severe COVID in non-diabetics</th>
<th>Severe COVID in White British</th>
<th>Severe COVID in other ethnicities</th>
<th>Severe COVID in lowest IMD deciles</th>
<th>Severe COVID in highest IMD deciles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>Total n = 206 (103 in each group)</td>
<td>Total n = 206 (103 in each group)</td>
<td>Total n = 76 (38 in each group)</td>
<td>Total n = 76 (38 in each group)</td>
<td>Total n = 3100 (1550 in each group)</td>
<td>Total n = 3100 (1550 in each group)</td>
<td>Total n = 80 (40 in each group)</td>
<td>Total n = 80 (40 in each group)</td>
</tr>
</tbody>
</table>

1.5. **STUDY POPULATIONS**

All ICHD patients who tested positive for COVID19, on a hospital based real time reverse transcription quantitative polymerase chain reaction tests, were included in this study.

1.6. **STATISTICAL ANALYSIS PLAN (SAP)**

1.6.1. **SAP OBJECTIVES**

The objective of this SAP is to describe the statistical analyses to be carried out for the final analysis of this study.
1.8.2. **General Principles**

An alpha level of 0.05, and confidence intervals be set at 95% will be used for all statistical tests. Power of 0.8 was assumed when calculating sample sizes.

1.8.3. **Software**

Analyses will be carried out using SPSS, R, or Prism.

2. **Analysis**

2.1. **Study Populations**

All ICHD patients who tested positive for COVID19, on a hospital based real time reverse transcription quantitative polymerase chain reaction tests, will be included in this study.

These patients will be divided into those who had severe COVID19 (defined as respiratory support with supplemental oxygen or more, and/or a CRP of >75) and those who were able to oxygenate effectively on room air (no supplemental oxygen, or further interventions required).

2.2. **Outcomes**

2.2.1. **Primary Outcome**

The primary outcome of this study is COVID severity, as defined above in section 2.1. The effect of exposures on this outcome will be assessed in this study and has been detailed in section 2.3.
2.3. EXPOSURES

2.3.1 Primary Exposures

The primary exposures of interest are:

1) Diabetes status (collected as a yes/no categorical variable), inclusive of all variants.

2) BMI collected as a continuous variable

3) Ethnicity, defined as a categorical variable based on office of national statistics categories.

4) The Charlson Comorbidity index

5) Social deprivation will be collected using the English Index of Multiple Deprivation rank and deciles, as an ordinal variable.

2.3.2 Exploratory Exposures

Exploratory exposures of interest will include association age, sex, dialysis vintage, dialysis access, renin-angiotensin inhibition, transplant status, immunosuppression status, haemoglobin, vitamin D supplementation and blood pressure.

2.4 ANALYSIS PLAN

2.4.1 Baseline data

Incidence of COVID-19 and Severe COVID-19 will be calculated against the total dialysis population belonging to each participating haemodialysis unit, during the time frame of data collection.

Continuous variables will be summarised by mean and standard deviation, minimum and maximum. Categorical variables will be summarised by N (%).
2.4.2 Exposure effect exploration

The incidence of severe COVID between exposed and non exposed groups, as defined in sections 2.3.1 and 2.3.2 will be compared. Continuous variables will be summarised by mean and standard deviation, minimum and maximum. Categorical variables will be summarised by N (%).

2.4.3 Modelling – adjusted and unadjusted

Risk factor effects on primary outcomes (severe COVID19) will be analysed using logistic regression models. Adjustments will be made for sex, age and ethnicity.

3. DOCUMENT HISTORY

This is version 1.3 of the SAP for this study, dated 19th of December 2020, the fourth iteration of this document.