# VITAMIN D TREATMENT IS ASSOCIATED WITH REDUCED RISK OF MORTALITY IN PATIENTS WITH COVID-19: A CROSS-SECTIONAL MULTI-CENTRE OBSERVATIONAL STUDY

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ABSTRACT

Background: The 2019 novel coronavirus disease (Covid-19) worldwide pandemic has posed the most substantial and severe public health issue for several generations, and therapeutic options for it have not yet been optimised. Vitamin D has been proposed in the pharmacological management of Covid-19 by various sources. This study aimed to determine whether Covid-19 disease outcomes were affected by vitamin D status, and to elucidate any predictors of Covid-19 outcomes.

Methods: Patients hospitalised with Covid-19 were opportunistically recruited from three different UK hospitals and their data were collected. Logistic regression was used to determine any relationships between vitamin D status and various predictors, including mortality and ventilation, and to determine any relationships between mortality, ventilation, and various predictors.

Findings: Vitamin D status was not associated with any outcomes of Covid-19 investigated, following adjustment for age and sex. However, treatment with vitamin D was significantly associated with a reduced risk of death, following adjustment for age and sex ($OR_{adj}$ 0·48, 95% CI 0·32 – 0·70, p = $1{\cdot}79x10^{-4}$). This relationship remained significant when also adjusted for baseline vitamin D levels ($OR_{adj}$ 0·47, 95% CI 0·33 – 0·70, p = $1{\cdot}27x10^{-4}$).

Interpretation: Treatment with vitamin D, regardless of baseline serum vitamin D levels, appears to be associated with a reduced risk of mortality in acute in-patients admitted with Covid-19. Further work on large population studies needs to be carried out to determine adequate serum levels of vitamin D, as well as multi-dose clinical trials of vitamin D treatment to assess maximum efficacy.

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RESEARCH IN CONTEXT

Evidence before this study: We searched PubMed for articles published between 1st January 2020 and 4th September 2020, with the terms "Covid-19," "SARS-CoV2," "vitamin D," "cholecalciferol," and "25-hydroxyvitamin D." We did not restrict outr search by language or type of publication. Due to the rapid onset and clinical severity of Covid-19, large amounts of research have taken place to search for a viable therapeutic agent, either as treatment or adjunct to therapy. Several review and opinion articles postulated that vitamin D therapy might be effective in the management of Covid-19. There are few studies examining vitamin D levels and outcomes in patients with Covid-19, and none have investigated the role of concurrent treatment.

Added value of this study: We carried out a retrospective cross-sectional study of 986 participants recruited from three hospital sites in the UK. Participants had been hospitalised with Covid-19. We found that vitamin D status (replete/insufficient/deficient) had no effect on Covid-19 disease outcomes such as death and ventilation. However, we found that treatment with vitamin D (either maintenance or high-dose booster therapy) was associated with a reduced risk of mortality, regardless of baseline vitamin D status.

Implications of all the available evidence: Current definitions of "replete" vitamin D status may be too low for immune benefit in acute Covid-19 infection. Large-scale population studies must be carried out to ascertain what a replete level is in the setting of acute infection, and multi-dose trials must also be considered in order to determine the most efficacious dose of vitamin D.

## INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide pandemic has presented the largest global public health problem in several generations, and vast amounts of rapid research has taken place to find an effective therapeutic agent to manage the 2019 novel coronavirus disease (Covid-19) caused by SARS-CoV-2. A number of recent studies have raised the possibility of vitamin D (also known as cholecalciferol, and 25-hydroxyvitamin D) as an adjuvant to therapy for Covid-19[1-3], given its known antiviral effects[4]. Other reviews have suggested that replete vitamin D status may be important in preventing severe manifestations of Covid-19[5,6]. Other sources have proposed the interleukin (IL)-6 inhibitor tocilizumab as a potential treatment for Covid-19, and due to its modulator effect on IL-6, vitamin D has again been postulated as a potential therapeutic option[7].

A UK-based study by Panagiotou *et al* found that low serum vitamin D levels in Covid-19 in-patients were associated with a more severe disease course[8], but this small study of 134 patients only looked at serum levels and not concurrent vitamin D treatment. Furthermore, two meta-analyses have identified low vitamin D as a potential predictor of more severe Covid-19 disease outcomes[9,10], again without addressing any effect of treatment. To our knowledge, no study has addressed the effect of vitamin D treatment on outcomes on an individual-level basis, and very few studies exist regarding serum vitamin D levels and the outcomes of Covid-19 in-patient admissions.

Therefore, the primary research questions of this study were to determine whether vitamin D levels and status (i.e. replete/insufficient/deficient) affect outcomes in Covid-19 infection, whether vitamin D deficiency is associated with increased risk of Covid-19 infection, and whether treatment with vitamin D alters disease outcomes. Secondary objectives were to determine whether any patient characteristics were associated with Covid-19 outcomes, namely, mortality, and treatment with ventilation. To reach these objectives, we carried out a retrospective multi-centre cross-sectional observational study.

## METHODS

### *Participants*

Patients were opportunistically recruited from three acute hospital Trusts in the UK, namely, Tameside and Glossop NHS Foundation Trust, Lancashire Teaching Hospitals NHS Foundation Trust, and University Hospitals of Leicester NHS Trust. Ethical approval was granted by the Health and Care Research Wales Research Ethics Committee (IRAS number 285337). The study was also registered on Clinicaltrials.gov (reference number NCT04386044), prior to commencement.

Patients recruited were admitted between 27th January 2020 and 5th August 2020, and data were collected between 26th June 2020 and 7th August 2020. In-patients with a clinical diagnosis of Covid-19 identified by clinical coding (emergency use ICD code U07·1, Covid-19 confirmed by laboratory testing, and code U07·2, Covid-19 diagnosis where laboratory confirmation is inconclusive or not available[11]) were all included in the study. Patients were excluded if they were younger than 18 years of age and if the final clinical diagnosis was not Covid-19. Demographic and clinical data were obtained from the hospital admission associated with the diagnosis of Covid-19 using a combination of: electronic patient records (EPR), hard-copy patient records, and hospital laboratory data.

Outcome variables were defined as: vitamin D status (replete, >50 nmol/L; low, combining insufficient, 25-50 nmol/L, and deficient, <25 nmol/L; and deficient status alone), death, invasive ventilation via endotracheal intubation, and continuous positive airways pressure (CPAP) therapy. In the case of vitamin D status analysis, predictors also included death, ventilation, length of stay and discharge, which we defined as major adverse admission-related events (MAAREs). Deaths included deaths in hospital, and deaths following admission recorded during the data collection period e.g. following transfer or discharge. Additional predictors in all analysis included age, sex, non-Caucasian ethnicity, hospital-acquired Covid-19, low-flow and high-flow oxygen therapy, treatment with vitamin D (both supplementation dose and high-dose booster therapy), and common medical comorbidities of interest, as listed by clinicians in patient medical records. Hospital-acquired Covid-19 was defined as: (i) if a patient had been admitted with a different acute condition and had gone on to develop Covid-19 whilst an in-patient; or (ii) if a patient had been re-admitted within the 14-day incubation period and the second admission was for Covid-19. All laboratory measurements (including vitamin D levels) were carried out as part of routine clinical care of patients during their acute in-patient admissions. Vitamin D levels up to 12 weeks prior to admission with acute Covid-19 were included, if not measured during each participant's in-patient stay. A full list of variables measured and how they were obtained is listed in the Supplementary Material.

*Statistical methods*

Pearson's chi squared test was used to make between-group comparisons, where appropriate. Logistic regression was used to analyse predictor variables for potential associations with vitamin D status, with adjustment for age, and sex. Either the mean or median value, depending on each variable's distribution, was used to convert linear variables to binary high/low variables. Again, logistic regression (adjusted for age, and sex) was used to analyse predictor variables for potential associations with secondary Covid-19 outcomes. Variables with significant associations were placed into multivariate logistic models to adjust for any potential interactions between predictors. Missing values were treated as missing data and values were not imputed, because of the nature of the clinical data collected. All analysis was carried out in Stata (StataCorp LLC, College Station, Texas, USA), version 14.0.

RESULTS

A total of 986 participants were recruited from all three centres combined. The mean age of participants was 70·10 years (SD 17·39) and 451 participants were female (45·65%). Full summary statistics are detailed in Table 1.

*Associations with vitamin D status*

Replete vitamin D status was associated with reduced odds of intubation (OR 0·47, 95% CI 0·24 – 0·94, p = 0·032), but this relationship lost significance when adjusted for age and sex ($OR_{adj}$ 0·55, 95% CI 0·27 – 1·10, p = 0·090). Conversely, insufficient vitamin D status (≤50 nmol/L) was associated with proceeding to intubation (OR 2·12, 95% CI 1·07 – 4·22, p = 0·032), but again, this association lost significance when adjusted for age and sex ($OR_{adj}$ 1·83, 95% CI 0·91 – 3·69, p = 0·090). Deficient vitamin D status (<25 nmol/L) was associated with obesity, as documented in participants' clinical records (OR 2·24 (1·15 – 4·39, p = 0·018), and this remained significant following adjustment for age and sex ($OR_{adj}$ 2·21, 95% CI 1·12 – 4·37, p = 0·023). Solid organ transplant was also associated with vitamin D deficiency (OR 7·19, 95% CI 1·38 – 37·36, p = 0·019), and this remained significant following adjustment for age and sex ($OR_{adj}$ 7·04, 95% CI 1·35 – 36·72, p = 0·021). Vitamin D status was not associated with ethnicity, even following adjustment for whether patients were treated with vitamin D.

*Associations with death from Covid-19*

Several predictors were associated with death from Covid-19 in univariate analysis, and are detailed in Table 2. These predictors were then placed in a multivariate model, along with sex (Table 3, Figure 1). The following variables remained significantly associated with death from Covid-19: age >74 years ($OR_{adj}$ 3·69, 95% CI 2·41 – 5·64, p = $1{\cdot}57x10^{-9}$), high-flow $O_2$ treatment ($OR_{adj}$ 5·80 (3·71 – 9·08, p = $1{\cdot}3\ x10^{-14}$), ischaemic heart disease, IHD ($OR_{adj}$ 1·98, 95% CI 1·23 – 3·18, p = 0·005), creatinine >83 µmol/L ($OR_{adj}$ 1·56, 95% CI 1·05 – 2·31, p = 0·027), and female sex ($OR_{adj}$ 1.48, 95% CI 1·00 – 2·18, p = 0·048). There were significantly more female patients in the age category >74 years (p = 0·016) in the study population, but when analysis was stratified by age (older and younger than 74 years), female sex had no association with mortality (OR 0·88, 95% CI 0·56-1·39, p = 0·590, in patients aged ≤74 years; OR 0·82, 95% CI 0·57-1·18, 0·288, in patients aged >74 years). Two variables remained significantly protective of death from Covid-19: treatment with vitamin D ($OR_{adj}$ 0·48, 95% CI 0·32 – 0·70, p = $1{\cdot}79x10^{-4}$), and asthma ($OR_{adj}$ 0·29, 95% CI 0·13 – 0·63, p = 0·002). Furthermore, treatment with vitamin D also remained significant following adjustment for baseline vitamin D levels ($OR_{adj}$ 0·47, 95% CI 0·33 – 0·70, p = $1{\cdot}27x10^{-4}$). Patients with asthma were significantly younger, with fewer

patients in the age >74 years category ($p = 4{\cdot}29x10^{-8}$). When stratified by age, the protective effect of asthma was only preserved in patients ≤74 years ($OR_{adj}$0·16, 95% CI 0·06-0·44, $p = 4{\cdot}09x10^{-4}$; versus $OR_{adj}$ 0·80, 95% CI 0·37-1·72, p = 0·561, in patients aged >74 years). Mortality was not associated with the presence of diabetes mellitus (either type 1 or type 2), nor with baseline $Hb_A1c$, nor random glucose on admission.

*Associations with invasive ventilation and CPAP*

Again, several predictors were associated with participants receiving invasive ventilation via endotracheal tube (Table 4) or with CPAP (Table 6). Many patients receiving invasive ventilation had failed to respond to CPAP, hence the similarities in predictors associated with the two, and similarly, patients had failed to respond to both low-flow and high-flow oxygen delivery in order to require CPAP.

Following adjustment in a multivariate model including all significant associations with invasive ventilation from univariate analysis (Table 5), along with female sex, excluding oxygen treatment, intubation was associated with length of stay >10 days ($OR_{adj}$ 29·50, 95% CI 3·74 – 232·79, p = 0·001). Participants aged >74 years ($OR_{adj}$ 0·07, 95% CI 0·01 – 0·34, p = 0·001) or who had developed hospital-acquired Covid-19 ($OR_{adj}$ 0·09, 95% CI 0·01 – 0·75, p = 0·026) were less likely to receive invasive ventilation. Patients with hospital-acquired Covid-19 had a significantly higher proportion of patients in the age >74 years category (p = 0·005). Similarly, following adjustment in a multivariate model and excluding oxygen treatment (Table 7), age >74 was associated with less use of CPAP ($OR_{adj}$ 0·16, 95% CI 0·07 – 0·37, $p = 1{\cdot}16x10^{-5}$), and this was the only significantly associated predictor, excluding oxygen treatment.

## DISCUSSION

To our knowledge, this is the largest observational study of hospital in-patients with Covid-19 to examine any potential associations between the treatment of the acute infection and vitamin D status, and vitamin D treatment. We found that vitamin D status (replete/insufficient/deficient) was not associated with Covid-19 MAAREs, neither was it associated with ethnicity. However, treatment with vitamin D appeared to be protective against mortality, regardless of baseline vitamin D levels.

Our findings regarding vitamin D status appear to fit with a study utilising participants from the UK Biobank, which found no association between vitamin D levels and risk of Covid-19 infection[12]. The UK Biobank study looked at 348,598 participants, of whom, 449 had a confirmed diagnosis of Covid-19 as defined by a positive laboratory test for SARS-CoV-2 (only 0·13% of study population). However, it is likely that the Covid-19 cases from that study were managed in a mixture of hospitals and the community and vitamin D was measured between 2006 and 2010, and not contemporaneously with Covid-19 infection 10-14 years after recruitment to the UK Biobank. Our study adds extra

information regarding patients who, by their nature, have more severe disease, as they have been hospitalised. Additionally, our study provides information on vitamin D status as close to Covid-19 infection as possible, giving a more accurate picture of any interactions; we imposed a limit of 12 weeks on vitamin D levels prior to admission to mitigate for seasonal variation. Rhodes *et al* suggest that countries at a latitude above 35 degrees North have experienced increased mortality from Covid-19, suggesting a potential role for vitamin D in Covid-19 outcomes [13], but our findings do not implicate vitamin D in the role of increasing mortality rates in these countries. Two independent studies from Israel[14] and the USA[15] found that deficient vitamin D status was associated with increased risk of Covid-19, but did not address other outcome measures, apart from hospitalisation. Our findings appear to differ from those of other studies, but this could be due to power issues or a differing population. Given the emerging nature of this research, large meta-analyses will be required in the future when more data is available from multiple international sites.

Interestingly, treatment with vitamin D was associated with reduced odds of death, even following adjustment for baseline vitamin D levels. Treatment with vitamin D constituted either maintenance therapy (800-2,000IU daily) or high-dose booster therapy (up to 300,000IU total, split over multiple doses)[16]. This could be for a number of reasons. Firstly, it may be because it is not clear what an adequate amount of vitamin D is required to maintain immune health. UK guidance is that levels >25nmol/L are required to maintain musculoskeletal health[17], but this is within the range for deficiency[16] and does not take into account vitamin D's role outside of musculoskeletal health. It is possible that serum vitamin D levels might need to be higher than the recommended range in order to provide protection from more severe Covid-19 outcomes. An alternative hypothesis might be that not all patients had vitamin D measured during admission (755/986 participants), and the patients that had levels measured and acted on may have received overall more intensive treatment, resulting in better outcomes. From the level of data collected, it is not clear what the mechanisms are behind our findings. Nonetheless, vitamin D as a potential therapeutic option for Covid-19 is an attractive prospect, given its wide availability and low cost, particularly in developing nations, as well as its relatively safe side-effect profile in conjunction with regular monitoring of serum levels and serum adjusted calcium.

We found that obesity was significantly associated with deficient vitamin D status, and this is in keeping with a large meta-analysis of SNPs associated with body mass index (BMI) and with vitamin D in 42,024 patients, which found that increased BMI was associated with lower vitamin D levels[18]. A more recent meta-analysis of observational studies also found a dose-response association between vitamin D levels and reduced risk of abdominal obesity[19]. We also found an association between vitamin D deficiency and patients who had received a solid organ transplant. Again, these agree with other previous findings, which have demonstrated that low vitamin D levels are very common following solid organ transplantation, even in the long-term[20].

It is unsurprising that predictors such as age >74 years, IHD and baseline creatinine >83 μmol/L are associated with increased risk of death from Covid-19, as these are likely to represent patients with a poorer baseline of health with less physiological reserve to adequately cope with acute Covid-19 infection. The June 2020 report from the Office of National Statistics, ONS (covering England and Wales, where this study population was recruited from) shows an exponential rise in age-specific mortality rates as age increases[21], and this would fit with our data. Furthermore, a large multi-centre study in Italy found that older age, chronic kidney disease and coronary artery diseases were more common in patients who died[22], and our findings agree with this. We also found that the requirement for high-flow $O_2$ treatment was significantly associated with death; this is likely to represent more severe disease in patients who may then have gone on not to be deemed to be suitable for either invasive ventilation or CPAP, or who declined it. This would agree with our findings that patients aged >74 years were less likely to have received invasive ventilation and/or CPAP.

More interestingly, in our study population, females were more likely to die from Covid-19, although this could be explained by a significantly increased number of patients in the age >74 years category compared to those who were not in this category, although analysis was adjusted for age. This differs from a Spanish study that is still awaiting peer-review, which found an increased infection-related fatality risk of Covid-19 in males when compared to females, even when stratified by age[23]. Our study is much smaller with fewer centres, by comparison, so this may account for a difference in findings. However, the multi-centre nature of our study, based in varied geographical locations, means that it is likely to be representative of the UK.

Also of interest is the apparently protective characteristic of a patient having asthma. Asthma has long been thought of as a risk factor for a more severe Covid-19 disease course, but given that patients with asthma in our study population had significantly fewer patients in the age >74 years category, this is likely to be skewed in favour of younger patients. A US study had similar findings, where patients with asthma tended to be younger and did not have worse outcomes than patients without asthma[24]. In addition, Iaccarino *et al* found that chronic obstructive pulmonary disease (COPD), but not asthma, was associated with increased mortality from Covid-19[22].

We found that intubation was associated with increased length of stay, and logically, this would fit with a more severe disease course and often prolonged weaning of invasive ventilation, although we cannot say this conclusively from our data. Patients who had developed hospital-acquired Covid-19 were also significantly less likely to receive invasive ventilation, but this group had a higher proportion of older patients when compared with patients with community-acquired Covid-19. Therefore, patients with

hospital-acquired Covid-19 were likely to be older and frailer, particularly given that they were in hospital already with a different acute presenting illness.

This study's strengths lie in its recruitment of almost 1,000 acute Covid-19 hospital in-patients from three separate centres, with a high proportion of patients with available vitamin D levels. Our study population is generalisable to the rest of the UK, with similar demographics compared with the ONS figures. Patients were recruited from throughout the pandemic, so our population reflects changing treatment recommendations as the pandemic evolved and evidence increased. However, not all patients had vitamin D levels available, so power may have been improved with more vitamin D results. In addition, while results are potentially generalisable to the UK, results would need to be replicated in different populations to assess transferability of findings globally. Finally, due to the cross-sectional nature of this study, we are unable to ascertain cause and effect between associations, and we do not have a mechanistic understanding of our findings as yet. Longitudinal analysis of outcomes must be carried out in the future to determine any long-term sequelae of deficient vitamin D status during acute Covid-19 infection. There is also the potential for studies in whole blood and/or tissue to understand the mechanisms behind vitamin D status and Covid-19 severity.

In conclusion, treatment with vitamin D, regardless of baseline serum vitamin D levels, appears to be associated with a reduced risk of mortality in acute in-patients admitted with Covid-19. This suggests that further work should be carried out to determine what an adequate serum level of vitamin D might be from large-scale population studies, and paves the way for future clinical trials of vitamin D treatment, at multiple doses in order to assess maximum efficacy. This inexpensive and widely available treatment could have positive implications for the management of Covid-19 worldwide, particularly in developing nations.

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AUTHOR CONTRIBUTIONS
SFL and EBJ designed the study and obtained ethical approval. SL, EB, RM, JMP, M-FK and EBJ acquired the data. SL carried out the analysis. All authors were involved in the drafting of the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTERESTS

The authors have no conflicts of interest.

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TABLE 1. SUMMARY STATISTICS OF THE STUDY POPULATION.

| | | Number of participants with available data |
|---|---|---|
| Age (years), median [IQR] | 74 [60,84] | 981 |
| Female, n (%) | 451 (45·65%) | 984 |
| **Ethnicity, n (%)**<br>Caucasian<br>South Asian<br>East Asian<br>African Caribbean<br>Other<br>All non-Caucasian combined | <br>789 (79·70)<br>142 (14·34)<br>4 (0·40)<br>19 (1·92)<br>36 (3·64)<br>199 (20·18) | 986 |
| Vitamin D level, median [IQR] | 40 [24, 62] | |
| **Vitamin D status, n (%)**<br>Replete (>50 nmol/L)<br>Insufficient (≤50 nmol/L)<br>Deficient (<25 nmol/L) | <br>279 (36·95)<br>476 (63·05)<br>198 (26·23) | 755 |
| Received vitamin D treatment, n (%) | 342 (35·85) | 954 |
| Positive SARS-NCoV2 swab, n (%) | 928 (94·12) | 986 |
| Death, n (%) | 296 (31·49) | 940 |
| Hospital-acquired, n (%) | 229 (23·42) | 978 |
| PE during admission, n (%) | 32 (3·29) | 974 |
| Oxygen saturation ($SpO_2$) on admission, median [IQR] | 96 [94, 98] | 893 |
| C-reactive protein (CRP) on admission (mg/L), median [IQR] | 77·5 [27, 154] | 962 |
| D-dimer on admission (ng/mL), median [IQR] | 814 [3·34, 2149] | 236 |
| Creatinine on admission (μmol/L), median [IQR] | 83 [64, 116] | 979 |
| Adjusted calcium on admission (mmol/L), median [IQR] | 2·29 [2·19, 2·4] | 538 |
| Random glucose on admission (mmol/L), median [IQR] | 6·8 [5·8, 8·6] | 893 |
| Received low-flow oxygen (<10L/min), n (%) | 521 (53·44) | 975 |
| Received high-flow oxygen (≥10L/min), n (%) | 220 (22·54) | 976 |
| Received CPAP, n (%) | 94 (9·59) | 980 |
| Received invasive ventilation, n (%) | 53 (5·40) | 982 |
| Discharged, n (%) | 656 (68·48) | 958 |
| Length of stay (days), median [IQR] | 10 [5, 19] | 950 |
| Diabetes mellitus (both types I and II), n (%) | 282 (29·04) | 971 |
| Chronic obstructive pulmonary disease (COPD), n (%) | 165 (16·73) | 986 |
| Asthma, n (%) | 122 (12·37) | 986 |
| Ischaemic heart disease (IHD), n (%) | 157 (15·92) | 986 |
| Current or previous acute coronary syndrome, n (%) | 62 (6·29) | 986 |
| Heart failure, n (%) | 112 (11·36) | 986 |
| Hypertension, n (%) | 389 (39·45) | 986 |
| Current or previous transient ischaemic attack (TIA) or stroke, n (%) | 101 (10·24) | 986 |
| Dementia, n (%) | 140 (14·20) | 986 |
| Obesity, n (%) | 43 (4·36) | 986 |
| Malignancy of solid organ, n (%) | 131 (13·29) | 986 |

| | | |
|---|---|---|
| Malignancy of skin, n (%) | 14 (1·42) | 986 |
| Haematological malignancy, n (%) | 28 (2·84) | 986 |
| Solid organ transplant, n (%) | 9 (0·91) | 986 |
| Inflammatory arthritis, n (%) | 28 (2·84) | 986 |
| Inflammatory bowel disease, n (%) | 13 (1·32) | 986 |

TABLE 2. PREDICTORS ASSOCIATED WITH DEATH FROM COVID-19, UNIVARIATE ANALYSIS.

| | *OR (95% CI)* | *p-value (unadjusted)* | *$OR_{adj}$ (95% CI)* | *p-value (adjusted)* | *n* |
|---|---|---|---|---|---|
| Age >74 years | 2·84 (2·13-3·79) | $1{\cdot}51x10^{-12}$ | 2·88 (2·16-3·85) | $9{\cdot}43x10^{-13}$ | 935 |
| Treatment with vitamin D | 0·59 (0·43-0·80) | 0·001 | 0·48 (0·35-0·67) | $1{\cdot}36x10^{-5}$ | 904 |
| High-flow $O_2$ | 3·88 (2·82-5·34) | $9{\cdot}7x10^{-17}$ | 5·96 (4·10-8·66) | $7{\cdot}32x10^{-21}$ | 927 |
| Asthma | 0·29 (0·16-0·50) | 1·3E-05 | 0·41 (0·23-0·74) | 0·003 | 940 |
| IHD | 2·63 (1·85-3·74) | 8·28E-08 | 1·90 (1·31-2·75) | 0·001 | 940 |
| Vitamin D booster therapy | 0·49 (0·29-0·84) | 0·010 | 0·46 (0·26-0·81) | 0·006 | 338 |
| Vitamin D maintenance therapy | 2·02 (1·18-3·44) | 0·010 | 2·16 (1·24-3·77) | 0·006 | 338 |
| Admission $SpO_2$ <96% | 1·62 (1·21-2·18) | 0·001 | 1·52 (1·11-2·09) | 0·009 | 846 |
| CRP >77·5 mg/L | 1·67 (1·26-2·21) | $3{\cdot}84x10^{-4}$ | 1·72 (1·27-2·33) | $4x10^{-4}$ | 914 |
| Creatinine >83 µmol/L | 2·42 (1·82-3·22) | $1{\cdot}38x10^{-9}$ | 1·76 (1·28-2·41) | $4{\cdot}6x10^{-4}$ | 928 |
| Glucose >6·8 mmol/L | 1·36 (1·02-1·82) | 0·035 | 1·39 (1·02-1·89) | 0·035 | 848 |

TABLE 3. PREDICTORS ASSOCIATED WITH DEATH FROM COVID-19, MULTIVARIATE ANALYSIS, N = 716.

| | *$OR_{adj}$ (95% CI)* | *p-value* |
|---|---|---|
| Age >74 years | 3·69 (2·41-5·64) | $1{\cdot}57x10^{-9}$ |
| Treatment with vitamin D | 0·48 (0·32-0·70) | $1{\cdot}79x10^{-4}$ |
| High-flow $O_2$ | 5·80 (3·71-9·08) | $1{\cdot}3x10^{-14}$ |
| Asthma | 0·29 (0·13-0·63) | 0·002 |
| IHD | 1·98 (1·23-3·18) | 0·005 |
| Admission $SpO_2$ <96% | 1·23 (0·84-1·79) | 0·280 |
| CRP >77·5 mg/L | 1·31 (0·90-1·92) | 0·160 |
| Creatinine >83 µmol/L | 1·56 (1·05-2·31) | 0·027 |
| Glucose >6·8 mmol/L | 0·98 (0·68-1·43) | 0·932 |
| Female | 1·48 (1·00-2·18) | 0·048 |

TABLE 4. PREDICTORS ASSOCIATED WITH RECEIVING INVASIVE VENTILATION, UNIVARIATE ANALYSIS.

| | *OR (95% CI)* | *p-value (unadjusted)* | *$OR_{adj}$ (95% CI)* | *p-value (adjusted)* | *n* |
|---|---|---|---|---|---|
| Age >74 | 0·06 (0·02-0·18) | $1·65x10^{-6}$ | 0·06 (0·02-0·19) | $2·28x10^{-6}$ | 977 |
| Hospital-acquired | 0·25 (0·09-0·71) | 0·009 | 0·28 (0·10-0·78) | 0·015 | 970 |
| Treatment with vitamin D | 1·51 (0·86-2·63) | 0·150 | 1·82 (1·02-3·25) | 0·041 | 946 |
| PE | 4·58 (1·79-11·69) | 0·001 | 4·74 (1·77-12·73) | 0·002 | 966 |
| Low-flow $O_2$ | 2·51 (1·31-4·80) | 0·005 | 3·07 (1·58-5·98) | 0·001 | 967 |
| High-flow $O_2$ | 34·11 (14·35-81·07) | $1·34x10^{-15}$ | 39·04 (15·70-97·08) | $3·15x10^{-15}$ | 969 |
| CPAP | 19·26 (10·534-35·21) | $7·3x10^{-22}$ | 14·88 (8·02-27·60) | $1·07x10^{-17}$ | 972 |
| Obesity | 9·74 (4·72-20·08) | $7·11x10^{-10}$ | 6·67 (3·12-14·25) | $9·73x10^{-7}$ | 977 |
| Admission $SpO_2$ <96% | 2·45 (1·34-4·48) | 0·004 | 3·30 (1·73-6·28) | $2·78x10^{-4}$ | 886 |
| Admission CRP >77·5 mg/L | 3·30 (1·74-6·24) | $2·56x10^{-4}$ | 3·77 (1·94-7·35) | $9·37x10^{-5}$ | 953 |
| Length of stay >10 days | 17·22 (5·31-55·83) | $2·1x10^{-6}$ | 30·59 (9·06-103·25) | $3·57x10^{-8}$ | 942 |

TABLE 5. PREDICTORS ASSOCIATED WITH RECEIVING INVASIVE VENTILATION, MULTIVARIATE ANALYSIS, N = 770.

| | *$OR_{adj}$ (95% CI)* | *p-value* |
|---|---|---|
| Age >74 years | 0·07 (0·01-0·34) | 0·001 |
| Hospital-acquired Covid-19 | 0·09 (0·01-·75) | 0·026 |
| Treatment with vitamin D | 1·11 (0·45-2·73) | 0·828 |
| PE | 1·54 (0·40-5·95) | 0·532 |
| Low-flow $O_2$ | 1·05 (0·37-2·95) | 0·933 |
| High-flow $O_2$ | 23·27 (4·51-120·04) | $1·71x10^{-4}$ |
| CPAP | 1·40 (0·50-3·91) | 0·518 |
| Obesity | 0·92 (0·27-3·18) | 0·902 |
| Admission $SpO_2$ <96% | 1·14 (0·46-2·82) | 0·773 |
| Admission CRP >77·5 mg/L | 1·66 (0·55-5·02) | 0·373 |
| Length of stay >10 days | 29·50 (3·74-232·79) | 0·001 |
| Female | 0·90 (0·34-2·38) | 0·834 |

TABLE 6. PREDICTORS ASSOCIATED WITH RECEIVING CPAP, UNIVARIATE ANALYSIS.

| | *OR (95% CI)* | *p-value* | *$OR_{adj}$ (95% CI)* | *p-value (adjusted)* | *n* |
|---|---|---|---|---|---|
| Age >74 years | 0·22 (0·13-0·37) | $2{\cdot}17x10^{-8}$ | 0·23 (0·13-0·38) | $4{\cdot}06x10^{-8}$ | 975 |
| Treatment with vitamin D | 1·83 (1·19-2·82) | 0·006 | 2·17 (1·39-3·40) | 0·001 | 944 |
| PE | 5·53 (2·57-11·87) | $1{\cdot}1x10^{-5}$ | 5·92 (2·65-13·24) | $1{\cdot}47x10^{-5}$ | 964 |
| Low-flow $O_2$ | 4·96 (2·83-8·71) | $2{\cdot}41x10^{-8}$ | 4·96 (2·83-8·71) | $2{\cdot}41x10^{-8}$ | 965 |
| High-flow $O_2$ | 110·76 44·73-274·25) | $2{\cdot}54x10^{-24}$ | 110·76 44·73-274·25) | 2·54E-24 | 966 |
| Intubation | 14·26 (7·69-26·44) | $3{\cdot}4x10^{-17}$ | 14·26 (7·69-26·44) | $3{\cdot}4x10^{-17}$ | 972 |
| Obesity | 3·22 (1·58-6·60) | 0·001 | 3·22 (1·58-6·60) | 0·001 | 975 |
| Admission $SpO_2$ <96% | 2·92 (1·82-4·70) | $9{\cdot}9x10^{-6}$ | 2·92 (1·82-4·70) | $9{\cdot}9x10^{-6}$ | 883 |
| Admission CRP >77·5 mg/L | 2·94 (1·81-4·77) | $1{\cdot}36x10^{-5}$ | 2·94 (1·81-4·77) | $1{\cdot}36x10^{-5}$ | 951 |
| Length of stay >10 days | 4·86 (2·87-8·22) | $4{\cdot}15x10^{-9}$ | 4·86 (2·87-8·22) | $4{\cdot}15x10^{-9}$ | 940 |

TABLE 7. PREDICTORS ASSOCIATED WITH RECEIVING CPAP, MULTIVARIATE ANALYSIS, N = 775.

| | *$OR_{adj}$ (95% CI)* | *p-value* |
|---|---|---|
| Age >74 years | 0·16 (0·07-0·37) | $1{\cdot}16x10^{-5}$ |
| Treatment with vitamin D | 1·90 (0·95-3·82) | 0·071 |
| PE | 2·49 (0·72-8·68) | 0·151 |
| Low-flow $O_2$ | 2·16 (0·99-4·72) | 0·054 |
| High-flow $O_2$ | 52·91 (19·37-144·5127) | $9{\cdot}83x10^{-15}$ |
| Intubation | 1·74 (0·68-4·45) | 0·251 |
| Obesity | 0·88 (0·29-2·66) | 0·824 |
| Admission $SpO_2$ <96% | 1·46 (0·74-2·87) | 0·272 |
| Admission CRP >77·5 mg/L | 1·53 (0·71-3·28) | 0·276 |
| Length of stay >10 days | 1·34 (0·63-2·85) | 0·454 |
| Female | 1·11 (0·55-2·23) | 0·772 |

FIGURE 1. PREDICTORS ASSOCIATED WITH DEATH, MULTIVARIATE ANALYSIS.