Pharmacological Predictors of Morbidity and Mortality in COVID-19

Christopher Oddy, MBBS, James McCaul, MBBS, Polly Keeling, MBChB, Jonathan Allington, MBBS, Dhanuja Senn, MBBS, Neesa Soni, MBBS, Hannah Morrison, MBChB, Ruwani Mawella, MBBS, Thomas Samuel, MBBS, and John Dixon, PhD

Abstract

The interaction of coronavirus disease (COVID-19) with the majority of common prescriptions is broadly unknown. The purpose of this study is to identify medications associated with altered disease outcomes in COVID-19. A retrospective cohort composed of all adult inpatient admissions to our center with COVID-19 was analyzed. Data concerning all antecedent prescriptions were collected and agents brought forward for analysis if prescribed to at least 20 patients in our cohort. Forty-two medications and 22 classes of medication were examined. Groups were propensity score matched and analyzed by logistic and linear regression. The majority of medications did not show a statistically significant relationship with altered disease outcomes. Lower mortality was associated with use of pregabalin (hazard ratio [HR], 0.10; 95% confidence interval [CI], 0.01-0.92; \( P = .049 \)) and inhalers of any type (HR, 0.33; 95%CI, 0.14-0.80; \( P = .015 \)), specifically beclomethasone (HR, 0.10; 95%CI, 0.01-0.82; \( P = .032 \)), tiotropium (HR, 0.07; 95%CI, 0.01-0.83; \( P = .035 \)), and steroid-containing inhalers (HR, 0.35; 95%CI, 0.15-0.79; \( P = .013 \)). Gliclazide (HR, 4.37; 95%CI, 1.26-15.18; \( P = .032 \)) and proton pump inhibitor (HR, 1.72; 95%CI, 1.06-2.79; \( P = .028 \)) use was associated with greater mortality. Diuretic (HR, 0.07; 95%CI, 0.01-0.37; \( P = .002 \)) and statin (HR, 0.35; 95%CI, 0.17-0.73; \( P = .006 \)) use was associated with lower rates of critical care admission. Our data lends confidence to observing usual practice in patients with COVID-19 by continuing antecedent prescriptions in the absence of an alternative acute contraindication. We highlight potential benefits in investigation of diuretics, inhalers, pregabalin, and statins as therapeutic agents for COVID-19 and support further assessment of the safety of gliclazide and proton pump inhibitors in the acute illness.

Keywords

COVID-19, medications, prescriptions, propensity score matched, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represented an unprecedented challenge for clinicians in 2020. Uncertainty in day-to-day decision making is familiar to clinicians working with patients admitted with coronavirus disease 2019 (COVID-19). The absence of clear, evidence-based guidelines make clinical judgments surrounding these patients complex.

Polypharmacy in the United Kingdom is common in hospitalized patients. It is well understood that prescription medications can cause iatrogenic harm and that acute illness may render medications that are otherwise well tolerated harmful to their recipients. The interaction of COVID-19 with the multitude of agents prescribed to many individuals is broadly unknown.

A limited number of studies have examined certain classes of medication in the context of SARS-CoV-2 infection, revealing several robust associations. Some point to the clear opportunity for adjusting prescriptions to the benefit of patients admitted with COVID-19 with greater understanding of how the disease interacts with commonly used agents. Evidently, there is much still to be understood about how outcomes in COVID-19 are affected by individuals’ prior prescriptions and benefits to exploring this.

Identifying medications associated with worsened outcomes in COVID-19 may be of additional benefit in risk stratification. The prescription of certain agents is reserved for only severe or uncontrolled disease, and their prescription therefore may inform clinicians about the severity of an individual’s prior conditions. Current risk prediction models rely on demographic characteristics and comorbidities alone. Identifying agents that are associated with morbidity and mortality in COVID-19 might therefore be valuable, alongside these matrices, in signposting highly comorbid patients that are vulnerable to severe disease. This may be especially
The purpose of the present study is to identify medications associated with altered disease outcomes in COVID-19 by examining all antecedent prescriptions held by participants in our cohort.

Methods

Study Design and Participants

The study received sponsorship from Epsom and St Helier University Hospitals National Health Service (NHS) Trust. The requirement for ethical review was waived by the Office for Research Ethics Committees Northern Ireland (IRAS ID: 283834).

A retrospective cohort composed of all adults admitted to our center with confirmed SARS-CoV-2 infection between January 10 and June 1, 2020, was analyzed. Infection was confirmed in all cases by detection of SARS-CoV-2 RNA on nasal/oropharyngeal swab. Patients were included if their admissions data listed COVID-19 as the primary or secondary reason for admission, or if COVID-19 was documented as the primary (1a) or secondary (1b) cause of death on their medical certificate of cause of death. Patients meeting these criteria were excluded if their admission was ongoing or uncoded by August 1, 2020. Admissions with a primary or secondary diagnosis of COVID-19 were selected to prevent morbidity associated with unrelated clinical sequelae being reflected in analyses. The order of diagnosis codes is assigned according to their clinical significance, related morbidity, and implications for management. Numerous patients were excluded by this criterion and most likely represent mild or incidental cases.

Data Collection

Patients meeting our inclusion criteria were collated by our search engine, alongside admission data and coding comprising their demographic characteristics and past medical history. Antecedent prescriptions and outcomes data were extracted manually from electronic hospital records. Prescriptions were recorded according to their recommended international nonproprietary names. Mixed formulations were recorded as each of the components’ recommended international nonproprietary names separated by a forward slash. Once collected, patients’ prescriptions were systematically screened and categorized for analysis if \( \geq 20 \) patients received a particular agent. Where possible during data extraction, guided by the wider literature, commonly prescribed classes of medication were identified and collated for analysis.

Definitions

**Antecedent Prescriptions.** Antecedent prescriptions were defined as active physician-ordered prescriptions prescribed to patients at the point of attendance at our center for their COVID-19–related admission. Over-the-counter prescriptions were not considered. These were identified from emergency department notes for their COVID-19–related admission and general practice records. Additional medications were identified from inpatient pharmacist “medicine reconciliations” derived from individuals’ NHS Summary Care Record.

**Outcome Measures.** Our primary outcome measures were inpatient mortality and intensive care unit (ICU) admission. Secondary outcomes considered were maximum oxygen requirement (liters per minute), maximum National Early Warning Score 2 (NEWS-2), maximum C-reactive protein (CRP) concentration (milligrams per liter), and maximum acute kidney injury (AKI) stage. AKI was defined according to Kidney Disease: Improving Global Outcomes creatinine criteria. NEWS-2 score was calculated according to standards set by the Royal College of Physicians (United Kingdom).

**Maximum Oxygen Requirement.** Maximum oxygen requirement for each patient was defined as the highest flow rate of oxygen delivered to a patient in liters per minute for more than 2 sets of observations. This was to account for titration to saturations. Venturi device percentages were converted to liters per minute by the following conversion: \( 24\% = 3 \text{ L/min}, 28\% = 5 \text{ L/min}, 35\% = 9 \text{ L/min}, 40\% = 11 \text{ L/min}, \text{ and } 60\% = 13.5 \text{ L/min} \). Patients requiring invasive or noninvasive positive pressure ventilation were given a maximal score of 15 L/min allowing for comparison with the remainder of the cohort.

** Statistical Analysis

Continuous variables were reported as mean values ± standard deviation. Categorical variables were reported as counts and percentages. Each group of participants that were prescribed a particular agent or class of medication underwent propensity score matching to balance baseline characteristics. Propensity scores were calculated using logistic regression, adjusting for factors relevant to the prescription of each agent, which are presented in Table 1. Members of each group were matched with 2 control subjects using a “greedy nearest-neighbor” algorithm with replacement and a caliper of 0.0 to achieve optimal balance. Cases without an appropriate match were discarded from analysis cohorts. Matching adequacy for each selected covariate was assessed by calculating standardized mean differences for each factor. A summary of
Table 1. Subgroup Details

| Medication                  | N   | Mean Age (±SD) | Factors Considered in Propensity Score Matching | Matched Cases | Matched Controls | Higher in Cases | Higher in Controls |
|-----------------------------|-----|---------------|------------------------------------------------|---------------|-----------------|-----------------|-------------------|
| Entire cohort               | 612 | 69.6 (±17.8)  | ...                                             | ...           | ...             | ...             | ...               |
| Individual agents           |     |               |                                                 |               |                 |                 |                   |
| Alfacalcidol                | 27  | 69.2 (±13.7)  | *Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, vitamin D deficiency, osteoporosis* | 24            | 23              | Age, diabetes mellitus | ...               |
| Allopurinol                 | 28  | 70.5 (±15.5)  | *Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, hematological cancer* | 27            | 46              | ...             | ...               |
| Amlodipine                  | 108 | 72.5 (±13.3)  | *Age, sex, race/ethnicity (white [any]/other), hypertension, heart failure, ischemic heart disease* | 107           | 134             | ...             | ...               |
| Apixaban                    | 28  | 83.5 (±8.4)   | *Age, sex, race/ethnicity (White[any]/other), ischemic heart disease, valve disease, rhythm disorders, peripheral vascular disease, history of venous thromboembolism, history of cerebrovascular accident* | 28            | 41              | ...             | ...               |
| Aspirin                     | 83  | 77.2 (±12.6)  | *Age, sex, race/ethnicity (White[any]/other), diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident* | 83            | 107             | ...             | ...               |
| Atorvastatin                | 129 | 74.1 (±13.2)  | *Age, sex, race/ethnicity (White[any]/other), heart failure, ischemic heart disease, hyperlipidemia, peripheral vascular disease, history of cerebrovascular accident* | 127           | 159             | ...             | ...               |
| Beclometasone inhaler       | 29  | 68.6 (±16.4)  | *Age, sex, race/ethnicity (White[any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis)* | 27            | 42              | Male, White race/ethnicity | ...               |
| Bisoprolol                  | 113 | 75.8 (±13.5)  | *Age, sex, race/ethnicity (White[any]/other), hypertension, heart failure, ischemic heart disease, valve disease, rhythm disorders* | 112           | 138             | ...             | ...               |
| Budesonide/ Formoterol inhaler | 21 | 61.4 (±14.2)  | *Age, sex, race/ethnicity (White [any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis)* | 21            | 34              | White race/ethnicity, other pulmonary disorders | ...               |
| Bumetanide                  | 21  | 77.1 (±16.1)  | *Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, hypertension, heart failure* | 21            | 37              | ...             | ...               |
| Carbocisteine               | 29  | 78.6 (±10.0)  | *Age, sex, race/ethnicity (White [any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis)* | 28            | 43              | ...             | ...               |

(Continued)
| Medication      | N   | Mean Age (±SD) | Factors Considered in Propensity Score Matching                                                                 | Matched Cases | Matched Controls | Higher in Cases | Higher in Controls |
|-----------------|-----|----------------|-----------------------------------------------------------------------------------------------------------------|---------------|------------------|-----------------|-------------------|
| Cholecalciferol | 123 | 78.5 (±13.8)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, vitamin D deficiency, osteoporosis | 114           | 152              | ...             | ...               |
| Citalopram      | 24  | 72.5 (±17.7)   | Age, sex, race/ethnicity (White [any]/other), mental health diagnosis                                           | 24            | 45               | ...             | ...               |
| Clopidogrel     | 50  | 77.9 (±12.9)   | Age, sex, race/ethnicity (White [any]/other), diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 49            | 80               | ...             | ...               |
| Codeine phosphate | 30 | 74.2 (±16.0)   | Age, sex, race/ethnicity (White [any]/other)                                                                 | 30            | 53               | ...             | ...               |
| Donepezil       | 20  | 82.1 (±9.4)    | Age, sex, race/ethnicity (White [any]/other), dementia                                                         | 20            | 33               | ...             | ...               |
| Doxazosin       | 36  | 69.9 (±15.8)   | Age, sex, race/ethnicity (White [any]/other), hypertension                                                    | 35            | 64               | ...             | ...               |
| Epoetin beta    | 27  | 71.2 (±14.1)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, hematological cancer, anemia | 26            | 20               | ...             | ...               |
| Finasteride     | 21  | 83.4 (±5.2)    | Age, sex, race/ethnicity (White [any]/other), benign prostatic hyperplasia                                     | 20            | 34               | ...             | ...               |
| Folic acid      | 42  | 71.6 (±16.7)   | Age, sex, race/ethnicity (White [any]/other), anemia                                                           | 41            | 73               | ...             | ...               |
| Furosemide      | 55  | 78.2 (±12.3)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, hypertension, heart failure | 54            | 89               | ...             | ...               |
| Gliclazide      | 28  | 68.9 (±13.2)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 28            | 56               | ...             | ...               |
| Levotyroxine    | 57  | 74 (±15.0)     | Age, sex, race/ethnicity (White [any]/other), hypothyroid                                                      | 27            | 23               | ...             | White race/ethnicity |
| Linagliptin     | 21  | 73.8 (±13.1)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 21            | 27               | ...             | ...               |
| Losartan        | 25  | 76.2 (±12.9)   | Age, sex, race/ethnicity (White [any]/other), diabetes mellitus, hypertension, heart failure, ischemic heart disease | 25            | 43               | ...             | ...               |
| Macrogol        | 42  | 82.2 (±11.9)   | Age, sex, race/ethnicity (White [any]/other), dementia                                                          | 42            | 69               | ...             | White race/ethnicity |

(Continued)
| Medication       | N  | Mean Age (±SD) | Factors Considered in Propensity Score Matching                                                                 | Matched Cases | Matched Controls | Higher in Cases | Higher in Controls |
|-----------------|----|---------------|---------------------------------------------------------------------------------------------------------------|---------------|------------------|-----------------|--------------------|
| Metformin       | 79 | 69.2 (±14.5)  | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 67            | 51               |                 |                    |
| Mirtazapine     | 27 | 78.7 (±12.1)  | Age, sex, race/ethnicity (White [any]/other), mental health diagnosis                                        | 27            | 47               |                 |                    |
| No medications | 81 | 53.1 (±18.6)  | Age, sex, race/ethnicity (White [any]/other)                                                                 | 81            | 112              |                 |                    |
| Omeprazole      | 114| 73.3 (±14.3)  | Age, sex, race/ethnicity (White [any]/other), ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident, history of venous thromboembolism, personal use of aspirin, personal use of steroids, gastroesophageal reflux and gastritis | 114           | 153              |                 |                    |
| Paracetamol     | 70 | 76 (±14.9)    | Age, sex, race/ethnicity (White [any]/other)                                                                 | 68            | 107              |                 |                    |
| Prednisolone    | 48 | 71.1 (±14.4)  | Age, sex, race/ethnicity (White [any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis), organ transplant, autoimmune disorders | 47            | 68               | Asthma           |                    |
| Pregabalin      | 21 | 70.2 (±15.6)  | Age, sex, race/ethnicity (White [any]/other), anxiety, epilepsy, chronic pain syndromes (neuropathic pain, fibromyalgia) | 21            | 40               |                 |                    |
| Ramipril        | 75 | 72.4 (±13.5)  | Age, sex, race/ethnicity (White [any]/other), diabetes mellitus, hypertension, heart failure, ischemic heart disease | 72            | 105              |                 |                    |
| Salbutamol inhaler | 81 | 71.3 (±14.8)  | Age, sex, race/ethnicity (White [any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis) | 80            | 83               |                 |                    |
| Senna           | 40 | 80.3 (±13.3)  | Age, sex, race/ethnicity (White [any]/other), dementia                                                                 | 40            | 68               |                 |                    |
| Sertraline      | 25 | 74.5 (±14.6)  | Age, sex, race/ethnicity (White [any]/other), mental health diagnosis                                        | 24            | 44               |                 |                    |
| Simvastatin     | 77 | 77.8 (±10.4)  | Age, sex, race/ethnicity (White [any]/other), heart failure, ischemic heart disease, hyperlipidemia, peripheral vascular disease, history of cerebrovascular accident | 75            | 112              |                 |                    |

(Continued)
| Medication       | N     | Mean Age (±SD) | Factors Considered in Propensity Score Matching                                                                 | Matched Cases | Matched Controls | Higher in Cases | Higher in Controls |
|------------------|-------|----------------|-----------------------------------------------------------------------------------------------------------------|---------------|------------------|-----------------|-------------------|
| Sitagliptin      | 22    | 69.9 (±12.3)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 22            | 30               | ...             | ...               |
| Tamsulosin       | 40    | 79.9 (±8.5)    | Age, sex, race/ethnicity (White [any]/other), benign prostatic hyperplasia                                      | 40            | 55               | ...             | ...               |
| Tiotropium inhaler| 23    | 79.9 (±7.7)    | Age, sex, race/ethnicity (White [any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis) | 22            | 30               | ...             | ...               |
| Warfarin         | 32    | 75.1 (±14.5)   | Age, sex, race/ethnicity (White [any]/other), ischemic heart disease, valvular disease, rhythm disorders, peripheral vascular disease, history of venous thromboembolism, history of cerebrovascular accident | 31            | 62               | ...             | ...               |
| Classes of medication       |       |                |                                                                                                                 |               |                  |                 |                   |
| ACEIs            | 98    | 74.2 (±13.9)   | Age, sex, race/ethnicity (White [any]/other), diabetes mellitus, hypertension, heart failure, ischemic heart disease | 98            | 132              | ...             | ...               |
| ACEIs/ARBs       | 151   | 74.5 (±13.0)   | Age, sex, race/ethnicity (White [any]/other), diabetes mellitus, hypertension, heart failure, ischemic heart disease | 151           | 161              | ...             | ...               |
| ARBs             | 54    | 75.2 (±11.2)   | Age, sex, race/ethnicity (White [any]/other), diabetes mellitus, hypertension, heart failure, ischemic heart disease | 53            | 89               | ...             | ...               |
| Anticoagulants   | 88    | 79.9 (±11.4)   | Age, sex, race/ethnicity (White [any]/other), hypertension, heart failure, ischemic heart disease                | 87            | 91               | ...             | ...               |
| Antiepileptics   | 63    | 67.4 (±17.5)   | Age, sex, race/ethnicity (White [any]/other), epilepsy                                                       | 63            | 83               | ...             | ...               |
| Antidepressants  | 76    | 71.9 (±15.9)   | Age, sex, race/ethnicity (White [any]/other), mental health diagnosis                                        | 74            | 114              | ...             | ...               |
| Antiplatelets    | 126   | 78.1 (±12.3)   | Age, sex, race/ethnicity (White [any]/other), diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 126           | 149              | ...             | Age               |
| Antipsychotics   | 31    | 72.8 (±15.9)   | Age, sex, race/ethnicity (White [any]/other), mental health diagnosis                                        | 31            | 49               | ...             | ...               |

(Continued)
| Medication                  | N  | Mean Age (±SD) | Factors Considered in Propensity Score Matching                                                                 | Matched Cases | Matched Controls | Higher in Cases | Higher in Controls |
|----------------------------|----|----------------|----------------------------------------------------------------------------------------------------------------|---------------|------------------|-----------------|-------------------|
| Antithrombotics            | 200| 79 (±11.7)     | Age, sex, race/ethnicity (White [any]/other), ischemic heart disease, valve disease, rhythm disorders, peripheral vascular disease, history of venous thromboembolism, history of cerebrovascular accident | 194           | 134              | …               | …                 |
| Benzodiazepines            | 24 | 75.8 (±17.6)   | Age, sex, race/ethnicity (White [any]/other), mental health diagnosis                                           | 24            | 47               | …               | …                 |
| Beta blockers              | 127| 75.4 (±14.6)   | Age, sex, race/ethnicity (White [any]/other), hypertension, heart failure, ischemic heart disease, valve disease, rhythm disorders | 126           | 162              | …               | …                 |
| Calcium channel blockers   | 128| 73.6 (±13.5)   | Age, sex, race/ethnicity (White [any]/other), hypertension, heart failure, ischemic heart disease               | 128           | 151              | …               | …                 |
| Direct oral anticoagulants | 51 | 83.2 (±8.1)    | Age, sex, race/ethnicity (White [any]/other), ischemic heart disease, valve disease, rhythm disorders, peripheral vascular disease, history of venous thromboembolism, history of cerebrovascular accident | 50            | 67               | …               | …                 |
| Diuretics                  | 106| 76.7 (±13.0)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, hypertension, heart failure | 105           | 185              | …               | …                 |
| Immunosuppressants         | 74 | 72.8 (±13.8)   | Age, sex, race/ethnicity (White [any]/other), organ transplant, autoimmune disorders                            | 74            | 89               | …               | …                 |
| Inhalers (all)             | 141| 71.1 (±14.9)   | Age, sex, race/ethnicity (White [any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis) | 112           | 61               | …               | …                 |
| Inhalers (steroid)         | 109| 70.1 (±14.7)   | Age, sex, race/ethnicity (White [any]/other), chronic obstructive pulmonary disease, asthma, other pulmonary disorders (bronchiectasis, pulmonary fibrosis) | 103           | 64               | …               | …                 |
| Insulin (all)              | 45 | 66.1 (±15)     | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 37            | 50               | …               | …                 |
| Iron supplementation       | 45 | 76.5 (±15.8)   | Age, sex, race/ethnicity (White [any]/other), anemia                                                          | 44            | 78               | …               | …                 |
| Oral antihyperglycemics    | 106| 69.8 (±14.2)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 105           | 82               | …               | …                 |

(Continued)
Table 1. Continued

| Medication                        | N   | Mean Age (±SD) | Factors Considered in Propensity Score Matching                                                                 | Matched Cases | Matched Controls | Higher in Cases | Higher in Controls |
|-----------------------------------|-----|----------------|----------------------------------------------------------------------------------------------------------------|---------------|------------------|-----------------|-------------------|
| Oral antihyperglycemics (second line) | 68  | 69.5 (±14.0)   | Age, sex, race/ethnicity (White [any]/other), chronic kidney disease (stage), organ transplant, diabetes mellitus, hypertension, ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident | 67            | 71               | ...             | ...               |
| Proton pump inhibitors            | 133 | 73.8 (±14.0)   | Age, sex, race/ethnicity (White [any]/other), ischemic heart disease, peripheral vascular disease, history of cerebrovascular accident, history of venous thromboembolism, personal use of aspirin, personal use of steroids, gastroesophageal reflux and gastritis | 130           | 260              | ...             | ...               |
| Statins                           | 222 | 75.7 (±12.3)   | Age, sex, race/ethnicity (White [any]/other), heart failure, ischemic heart disease, hyperlipidemia, peripheral vascular disease, history of cerebrovascular accident | 222           | 197              | ...             | ...               |
| Vitamin D supplementation         | 144 | 76.6 (±14.6)   | Age, sex, race/ethnicity (White [any]/other), organ transplant, chronic kidney disease (stage), diabetes mellitus, vitamin D deficiency, osteoporosis | 138           | 165              | ...             | ...               |

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; SD, standard deviation. Medications brought forward for analysis are listed alphabetically. The number of participants receiving each agent and the average age of each group before matching is listed in columns 2 and 3. Variables entered into propensity score matching algorithms for each medication are displayed in column four. Columns 5 and 6 display the numbers of cases and controls in each cohort after matching—both cases and controls were discarded during matching if an appropriate match could not be found. Columns 7 and 8 display unbalanced covariates after matching, with column 7 displaying covariates that were higher or more frequent in the treated group, and column 8 the untreated group. Individual agents are listed first followed by classes of medication. Medications are displayed according to their recommended international nonproprietary names. Mixed formulations are recorded as each of the components’ recommended international nonproprietary names separated by a forward slash.

Unbalanced covariates for each matched sample in both cases and controls is presented in Table 1.

We performed propensity score matching 100 times for each group, as a bootstrapping process, sampling from the untreated remainder of the cohort.28 Participants selected from the untreated remainder varied with each matching analysis provided they fulfilled all of the criteria specified in the algorithm. This was due to relatively small subgroup sizes and thus a large pool of potential untreated matches. Hence, postmatching analysis was conducted on each matched cohort separately and an average of each of the 100 analyses calculated. Discarded treated cases and unbalanced factors in each matched cohort for a particular medication were the same due to strict specified criteria, samples of which were checked manually throughout.

Postmatching analysis was conducted using logistic and linear regression models. Logistic models were employed where the dependent variable was binary—our primary outcome measures—whereas linear models were used when analyzing continuous dependent variables. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs), and P values, each of which represent a bootstrapped average of the results from each of the 100 matched cohorts for each medication.

Variables considered for postmatching adjustment were drawn from established risk prediction models and population analyses.20–22 The “Enter” method was employed entering variables with a univariate logistic association with our primary outcome measure, mortality, with a P value of <.2 into our models. Variables adjusted for were age, sex, race/ethnicity (White [any]/other), diabetes mellitus, chronic kidney disease (stage), hypertension, ischemic heart disease, heart failure, heart rhythm disorders, valve disease, hyperlipidemia, peripheral vascular disease, chronic obstructive pulmonary disease, asthma, other pulmonary...
disorders (bronchiectasis, pulmonary fibrosis), history of venous thromboembolism, history of cerebrovascular accident, dementia, osteoporosis, vitamin D deficiency, hematological cancer, and organ transplant.

No sample size calculation was performed because we were unable to find appropriate published data from which to calculate this before data collection. A 2-sided \( \alpha \) of \( 1<0.05 \) was considered statistically significant. All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL).

Results

Population Characteristics

Six hundred twelve admissions met our inclusion criteria, of which 354 (57.8%) were male. The average age of our cohort was 69.6 (±17.8) years. Four hundred thirty-two (70.6%) of participants were of White race/ethnicity, the remaining 180 (29.4%) were Black-Asian minority ethnicities. Eighty-six patients (14.1%) were admitted to the ICU, and 281 (45.9%) patients died. The rate of mortality in this cohort was escalated significantly associated with higher rates of critical care admission.

When examined through this lens, we observe that the majority of medications examined did not alter risk of morbidity and critical care admission.

Significantly lower mortality was associated with use of pregabalin (HR, 0.10; 95%CI, 0.01-0.92; \( P = .049 \)), inhalers of any type (HR, 0.33; 95%CI, 0.14-0.80; \( P = .015 \)), and specifically beclometasone (HR, 0.10; 95%CI, 0.01-0.82; \( P = .032 \)), tiotropium (HR, 0.07; 95%CI, 0.01-0.83; \( P = .035 \)), and steroid-containing inhalers (HR, 0.35; 95%CI, 0.15-0.79; \( P = .013 \)). Increased mortality was associated with use of gliclazide (HR, 4.37; 95%CI, 1.26-15.18; \( P = .020 \)) and proton pump inhibitors (PPIs; HR, 1.72; 95%CI, 1.06-2.79; \( P = .028 \)) (Figure 1; Figure S2).

Lower rates of ICU admission were observed in participants taking furosemide (HR, 0.05; 95%CI, 0.01-0.48; \( P = .011 \)), diuretics of any type (HR, 0.07; 95%CI, 0.01-0.37; \( P = .002 \)), and statins (HR, 0.35; 95%CI, 0.17-0.73; \( P = .006 \)), whereas higher rates were seen with angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) use (HR, 2.19; 95%CI, 1.02-4.70; \( P = .047 \)) (Figure 1; Figure S3).

Adjusted associations of each medication class with our secondary outcome measures—oxygen requirements (Figure S4), NEWS-2 score (Figure S5), CRP concentration (Figure S6), and AKI stage (Figure S7)—are described (Table 2). Similar to the primary outcomes, the majority of medications were not significantly associated with altered secondary outcomes. Our main findings are summarized in Figure 1, with HRs for all measured outcomes plotted together.

Discussion

The purpose of this study was to identify medications associated with altered disease outcomes in COVID-19, primarily with a view to assessing the safety of common agents. We demonstrate that the majority of medications were not significantly associated with altered disease outcomes. While our subgroup sizes preclude drawing any strong conclusions regarding particular agents, it is clear that of the medications examined, few are strongly associated with clinically significant morbidity. Given that our data set affirms well-established associations with similar subgroup sizes, for example, the relationships of certain comorbidities with clinical outcomes, these findings can be contextualized.

When examined through this lens, we observe that the majority of medications examined did not alter risk of morbidity and mortality in COVID-19 as much as prior health conditions, for which we saw more marked effects. It is also worth noting that the majority of agents that had an association with outcomes conferred a diminished risk of adverse events. In practice, our data imply that, in the absence of an alternative acute contraindication, there is no basis for suspending most antecedent prescriptions when patients are admitted to the hospital with COVID-19.

Comparison With the Literature

ACEIs and ARBs. ACEIs/ARBs in our cohort were significantly associated with higher rates of critical care admission and a greater rise in CRP but not mortality. The proportionally large body of evidence on this topic favors ACEIs/ARBs as generally protective against mortality and severe disease outcomes in COVID-19.8,9
| Drug Name                        | HR (95%CI) | P Value | Intensive Care Admission | CRP Concentration | AKI Stage | NEVIS-2 Score | Mortality | Oxygen Requirements | NEWS-2 Score |
|---------------------------------|------------|---------|--------------------------|-------------------|-----------|---------------|-----------|---------------------|--------------|
| Individual agents               |            |         |                          |                   |           |               |           |                     |              |
| Alfacalcidol                    | 0.32 (0.02-4.98) | .415 |                          |                   |           |               |           |                     |              |
| Allopurinol                     | 0.93 (0.46-1.86) | .721 |                          |                   |           |               |           |                     |              |
| Amlodipine                      | 0.88 (0.62-1.10) | .322 |                          |                   |           |               |           |                     |              |
| Apixaban                        | 0.90 (0.49-1.63) | .639 |                          |                   |           |               |           |                     |              |
| Aspirin                         | 0.92 (0.49-1.50) | .562 |                          |                   |           |               |           |                     |              |
| Atorvastatin                    | 0.88 (0.52-1.50) | .322 |                          |                   |           |               |           |                     |              |
| Beclometasone inhaler           | 0.10 (0.01-0.82) | .250 |                          |                   |           |               |           |                     |              |
| Bisoprolol                      | 0.94 (0.94-1.94) | .808 |                          |                   |           |               |           |                     |              |
| Budesonide/Formoterol inhaler   | 7.87 (0.33-192.21) | .175 |                          |                   |           |               |           |                     |              |
| Bumetanide                      | 0.89 (0.52-1.50) | .322 |                          |                   |           |               |           |                     |              |
| Carbocisteine                   | 0.88 (0.52-1.50) | .562 |                          |                   |           |               |           |                     |              |
| Cholecalciferol                 | 1.05 (0.60-1.84) | .861 |                          |                   |           |               |           |                     |              |
| Citalopram                      | 1.58 (0.19-14.38) | .534 |                          |                   |           |               |           |                     |              |
| Clopidogrel                     | 0.57 (0.22-1.52) | .266 |                          |                   |           |               |           |                     |              |
| Codeine phosphate               | 2.33 (0.61-9.10) | .306 |                          |                   |           |               |           |                     |              |
| Donepezil                       | 1.10 (0.14-11.29) | .748 |                          |                   |           |               |           |                     |              |
| Doxazosin                       | 1.38 (0.32-12.9) | .299 |                          |                   |           |               |           |                     |              |
| Epoetin beta                    | 0.27 (0.02-3.25) | .299 |                          |                   |           |               |           |                     |              |
| Finasteride                     | 4.01 (0.43-42.96) | .592 |                          |                   |           |               |           |                     |              |
| Folic acid                      | 1.38 (0.34-3.50) | .564 |                          |                   |           |               |           |                     |              |
| Furosemide                      | 1.38 (0.34-3.50) | .564 |                          |                   |           |               |           |                     |              |
| Gabapentin                      | 1.38 (0.34-3.50) | .564 |                          |                   |           |               |           |                     |              |
| Gliclazide                      | 4.37 (1.26-15.18) | .020 |                          |                   |           |               |           |                     |              |
| Levothyroxine                   | 5.15 (0.23-182.33) | .198 |                          |                   |           |               |           |                     |              |
| Linagliptin                     | 0.24 (0.01-6.20) | .260 |                          |                   |           |               |           |                     |              |
| Lopinavir                       | 1.10 (0.14-11.29) | .748 |                          |                   |           |               |           |                     |              |
| Losartan                        | 1.02 (0.43-2.29) | .322 |                          |                   |           |               |           |                     |              |
| Macrogol                        | 2.18 (0.84-5.46) | .137 |                          |                   |           |               |           |                     |              |
| Metformin                       | 1.01 (0.43-2.39) | .974 |                          |                   |           |               |           |                     |              |
| Mirtazapine                     | 1.01 (0.27-3.77) | .771 |                          |                   |           |               |           |                     |              |
| No medications                  | 0.74 (0.25-2.20) | .578 |                          |                   |           |               |           |                     |              |
| Omeprazole                      | 1.53 (0.87-2.71) | .145 |                          |                   |           |               |           |                     |              |
| Paracetamol                     | 0.73 (0.35-1.51) | .422 |                          |                   |           |               |           |                     |              |
| Prednisolone                    | 0.64 (0.23-1.96) | .435 |                          |                   |           |               |           |                     |              |
| Pregabalin                      | 1.00 (0.20-5.00) | .980 |                          |                   |           |               |           |                     |              |
| Raloxifene                      | 1.14 (0.57-2.26) | .499 |                          |                   |           |               |           |                     |              |
| Sibutramine Inh.                | 1.28 (0.61-2.67) | .511 |                          |                   |           |               |           |                     |              |
| Senna                           | 0.80 (0.29-2.23) | .620 |                          |                   |           |               |           |                     |              |
| Sertraline                       | 1.82 (0.39-8.67) | .031 |                          |                   |           |               |           |                     |              |

(Continued)
| Drug Name                | Mortality (HR (95%CI)) | P Value | Intensive Care Admission (HR (95%CI)) | P Value | Oxygen Requirements (HR (95%CI)) | P Value | NEWS-2 Score (HR (95%CI)) | P Value | CRP Concentration (HR (95%CI)) | P Value | AKI Stage (HR (95%CI)) | P Value |
|-------------------------|------------------------|---------|--------------------------------------|---------|----------------------------------|---------|--------------------------|---------|-------------------------------|---------|--------------------------|---------|
| Simvastatin             | 0.84 (0.41-1.72)       | .024    | 0.47 (0.12-1.88)                     | .007    | 0.96 (0.63-1.46)                 | .002    | 0.81 (0.86-1.36)          | .000    | 0.52 (0.89-1.32)              | .000    | 0.88 (0.59-1.32)            | .047    |
| Sitagliptin             | 4.01 (0.46-35.95)      | .000    | 1.47 (0.20-10.73)                    | .000    | 1.09 (0.47-2.55)                 | .000    | 0.86 (0.69-1.32)          | .000    | 0.76 (1.04-2.84)              | .000    | 0.95 (0.39-2.29)            | .000    |
| Tamsulosin              | 1.25 (0.43-3.63)       | .000    | 4.74 (0.18-109.66)                   | .000    | 0.10 (0.11-17.26)                | .000    | 0.73 (0.47-1.15)          | .000    | 0.32 (1.19-6.20)              | .000    | 0.54 (0.27-1.04)            | .000    |
| Tiotropium inhaler      | 0.07 (0.01-0.82)       | .000    | ...                                  | .000    | 0.35 (0.12-10.23)                | .000    | 0.06 (0.02-0.28)          | .000    | 0.36 (0.20-1.23)              | .000    | 0.15 (0.69-2.98)            | .000    |
| Warfarin                | 2.65 (0.68-10.36)      | .000    | 1.74 (0.27-11.38)                    | .000    | 0.56 (0.64-2.29)                 | .000    | 1.25 (0.90-1.75)          | .000    | 1.55 (0.85-2.82)              | .000    | 1.49 (1.54-3.81)            | <.001   |

**Classes of medication**

**ACEIs, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; NEWS-2, National Early Warning Score 2; SD, standard deviation.**

Medications brought forward for analysis are listed alphabetically alongside adjusted HRs (HR ± 95%CI) for their associations with our outcome measures and P values for each relationship. HRs are expressed as the likelihood of a 5 L/min increase for oxygen requirements, 5-point increase for NEWS-2 score, and 100 mg/L for CRP concentration. Statistically significant relationships are displayed in bold.

Individual agents are listed first, followed by classes of medication. Medications are displayed according to their recommended international nonproprietary names. Mixed formulations are recorded as each of the components’ recommended international nonproprietary names separated by a forward slash.
Figure 1. Summary of main findings. Adjusted hazard ratios (HR ± 95%CI) for primary and secondary outcomes imparted by each medication listed. Hazard ratios are expressed as the likelihood of a 5 L/min increase for oxygen requirements, 5-point increase for NEWS-2 score, and 100 mg/L for CRP concentration. Significant associations are colorized with hazard ratios displayed in bold. The $P$ value for each relationship is plotted adjacent. The selected agents are listed alphabetically. Pregabalin was taken exclusively by participants who did not require ICU admission, and hence a HR could not be calculated; the association of pregabalin with ICU admission is left blank. Medications are displayed according to their recommended international nonproprietary names.

While our findings are incongruous with the wider literature, examination of this subgroup reveals that the majority of these patients did not receive their ACEIs/ARBs in the hospital—an intervention that we found to be strongly associated with poorer outcomes after adjustment for common reasons for ACEI/ARB suspension.29 These observations may explicate the findings of the present study.

### Diuretics

Diuretics were associated with decreased rates of ICU admission, reduced oxygen requirements, and lower CRP. Hippisley-Cox et al.17 observed a similar association of diuretics with reduced critical care admission in a cohort of 8.3 million participants; however, the relationship was nonsignificant (HR, 0.60; 95%CI, 0.32-1.11; $P = .102$). The relationship between diuretic use and mortality demonstrated here was

| Medication | Mortality | ICU Admission | Oxygen Requirements | NEWS-2 Score | CRP Concentration | AKI Stage |
|------------|-----------|---------------|---------------------|--------------|------------------|-----------|
| ACEIs/ARBs | Mortality | 0.98 (0.91-1.06) | 1.21 (1.02-1.42) | 1.12 (0.97-1.29) | 1.43 (1.07-1.90) | 1.01 (0.79-1.29) |
| Diuretics  | Mortality | 0.86 (0.49-1.51) | 0.10 (0.03-0.43) | 0.73 (0.51-0.99) | 1.06 (0.90-1.25) | 0.68 (0.51-0.91) | 0.89 (0.69-1.13) |
| Gliclazide | Mortality | 4.37 (1.26-15.18) | 2.82 (0.85-12.60) | 2.12 (1.15-3.80) | 1.26 (0.93-1.70) | 2.05 (1.03-4.07) | 1.27 (0.98-1.67) |
| Inhalers   | Mortality | 0.33 (0.14-0.80) | 1.39 (0.28-6.96) | 0.90 (0.57-1.44) | 0.80 (0.63-1.03) | 0.98 (0.65-1.53) | 1.04 (0.74-1.47) |
| Steroid Inhalers | Mortality | 0.35 (0.15-0.79) | 0.89 (0.20-3.89) | 0.79 (0.49-1.28) | 0.79 (0.61-1.02) | 0.91 (0.58-1.42) | 0.93 (0.69-1.26) |
| PPIs       | Mortality | 1.72 (1.06-2.79) | 1.29 (0.38-2.87) | 1.16 (0.89-1.52) | 1.08 (0.94-1.25) | 1.16 (0.96-1.40) | 0.98 (0.78-1.22) |
| Pregabalin | Mortality | 0.10 (0.01-0.92) | 0.64 (0.27-1.49) | 0.72 (0.40-1.13) | 0.38 (0.16-0.99) | 0.76 (0.40-1.45) |
| Statins    | Mortality | 0.73 (0.46-1.15) | 0.35 (0.17-0.73) | 1.01 (0.76-1.31) | 1.09 (0.95-1.25) | 0.95 (0.74-1.23) | 0.82 (0.65-1.02) |
Our analysis, using a considerably smaller sample size of 133, produced a similar effect size (HR, 1.72; 95%CI, 1.06-2.79). Ramachandran et al observed a similar phenomenon. Almario et al showed that PPI use is associated with a higher likelihood of testing positive for SARS-CoV-2 infection. The basis for these findings is presently purely speculative and is explored in detail in the aforementioned publications. Importantly, PPIs represent a medication that could be safely suspended during acute COVID-19 illness given their indication is commonly for symptomatic relief. Suspension of PPIs might, therefore, be a suitable subject for future randomized control trials. Our findings corroborate previously observed associations of PPI use and worsened outcomes in COVID-19 and thus support further inquiry into this matter.

**Gliclazide.** Gliclazide was shown to be significantly associated with increased mortality, greater oxygen requirements, and rise in CRP, with all other outcome measures worsened. Gliclazide is an oral antihyperglycemic (OAHG) that is prescribed as a second-line adjunctive therapy in the management of type II diabetes if lifestyle changes and metformin alone do not achieve satisfactory control. It is plausible to speculate, then, that the effect observed here is due to participants in the sample having poorer diabetic control, rendering them susceptible to adverse outcomes. This effect, however, was not observed in patients prescribed any second-line OAHG, bolstering the assertion that these effects are not simply related to worse premorbid condition. One study has examined the impact of sulfonyleureas, a class of OAHGs of which gliclazide is a member, on critical care admission, concluding that their use is positively associated. Further study of gliclazide, or more broadly sulfonyleureas, in COVID-19 is clearly necessary to evaluate the safety of this agent in the acute setting.

**Inhalers.** Use of inhalers of any formulation, and specifically steroid-containing inhalers, was associated with lower mortality in our cohort. There are several plausible mechanisms by which inhalers might curtail harm caused by SARS-CoV-2 pneumonia. The available evidence surrounding inhaler use in COVID-19 is limited. One review compared outcomes in patients prescribed inhaled steroids with those taking other forms of inhaler, concluding that there was no indication that either conferred a greater risk of mortality than the other. Presently, there are no other studies comparing the outcomes of patients prescribed inhalers with appropriately matched controls, or interventional trials. A number of registered clinical trials are currently under way and represent the next stage in examining these as therapeutic agents.

**Proton Pump Inhibitors.** We show that PPI use is associated with greater mortality in a propensity-matched analysis. Presently, there are 3 peer-reviewed publications that have examined the role of PPIs in COVID-19. Lee demonstrated that, in a nationwide propensity-matched cohort including 14 163 PPI users, PPI use was associated with a higher mortality (HR, 1.63; 95%CI, 1.03-2.53). Our analysis, using a considerably smaller sample size of 133, produced a similar effect size (HR, 1.72; 95%CI, 1.06-2.79). Ramachandran et al observed a similar phenomenon. Almario et al showed that PPI use is associated with a higher likelihood of testing positive for SARS-CoV-2 infection. The basis for these findings is presently purely speculative and is explored in detail in the aforementioned publications. Importantly, PPIs represent a medication that could be safely suspended during acute COVID-19 illness given their indication is commonly for symptomatic relief. Suspension of PPIs might, therefore, be a suitable subject for future randomized control trials. Our findings corroborate previously observed associations of PPI use and worsened outcomes in COVID-19 and thus support further inquiry into this matter.

**Pregabalin.** Pregabalin was associated with reduced mortality, lower CRP, and showed nonsignificant improvement in all other outcome measures. No patients who were prescribed pregabalin were admitted to ICU, although the small sample size renders this likely to be a chance phenomenon. The association of pregabalin with mortality may relate to downregulation of angiotensin-converting enzyme 2, the SARS-CoV-2 functional receptor, associated with its use. Further retrospective data with larger sample sizes would be required to examine this association further before justifying unlicensed use as a therapy for COVID-19.

**Statins.** The impact of statin use in patients with COVID-19 has been an active matter of debate. Statins have been shown to be associated with reduced rates of ICU admission, diminished symptom severity, and lower mortality. We observed a significantly reduced risk of critical care admission associated with statin use and a nonsignificant reduction in mortality, the latter of which may have been in relation to our subgroup size.

**Vitamin D Supplementation.** Vitamin D deficiency has been consistently observed to be associated with poorer disease outcomes in COVID-19. We did not observe any significant associations of vitamin D supplementation with outcomes in our cohort, although nonsignificant improvement in all of our outcome measures was shown. This may be due to a combination of a small sample size, a modest effect size of vitamin D supplementation, and a lack of adjustment for serum vitamin D concentration.

**Limitations**

There are several inherent limitations to delineating causality from purely retrospective observational data that our study shares with all publications of this nature. Specifically, our study is limited by our sample size. While subgroup sizes were adequate for several classes of medication, the majority of subgroups for...
individual agents were fairly small, making our findings prone to both type I and type II errors. We examined all antecedent prescriptions and set an arbitrary minimum of 20 participants receiving a particular medication, or class of medication, as an entrance criterion for analysis. No strong conclusions can be made about many of the agents we examined, although it is worth nothing that this was not the aim of our study.

Our primary aim was to identify medications associated with morbidity and mortality in patients admitted to the hospital with COVID-19. While we collected data on all medications, a large number of agents and classes of agent were not brought forward for analysis and thus remain unexamined. Additionally, the absence of certain medical specialties at our center prevented gathering data on medications common to the conditions managed under them.

While we extracted data from several sources to identify antecedent prescriptions, it is possible that these data were incomplete. Data was not collected on the duration of use of each prescription, nor on their inpatient use. Subgroup analysis of patients who had only recently received prescriptions or who had had their prescriptions suspended in the hospital may have strengthened or revealed some associations.

Finally, the use of propensity score matching to balance baseline characteristics is prone to bias. Unmeasured factors, such as premorbid disease severity, were not incorporated into the matching analysis and may have been unbalanced between groups. Additionally, while subjects might be matched appropriately, due to our small subgroup sizes, it is possible that matched controls were not representative of the population at large. There are also numerous methods of propensity score matching, with use of one over another having the potential to alter results.

Conclusions
We demonstrate that numerous common prescriptions do not associate with altered disease outcomes in patients hospitalized with COVID-19. Our data lend confidence to observing usual practice in patients admitted with SARS-CoV-2 infection by continuing antecedent prescriptions in the absence of an alternative acute contraindication. Our data corroborates several previously demonstrated associations and exhibit some novel interactions. We highlight potential benefits in investigation of diuretics, inhalers, pregabalin, and statins as therapeutic agents for COVID-19 and support further assessment of the safety of gliclazide and PPIs in the acute illness. Our findings provide valuable pilot data for future studies to draw from, and from which power calculations can be performed. The associations demonstrated here offer a basis for further examination of particular agents in the context of COVID-19 in studies appropriately powered to examine an effect.

Acknowledgments
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Search engine design was conducted by Rob McBarron, Business Intelligence Manager at Epsom & St Helier University Hospitals NHS Trust. Assistance with Python scripting to facilitate statistical analysis was provided by Jon Peck, SPSS technical advisor with IBM. No aid in writing this publication was sought from either a medical writer or medical editor. We disclose no personal communications instrumental in the completion of this manuscript that are not otherwise recognized by authorship.

Conflicts of Interest
All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work, and no other relationships or activities that could appear to have influenced the submitted work. All authors had full access to the full data. The corresponding author accepts responsibility to submit for publication.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. No funding was sought at any point during the completion of this work. No external source has pecuniary interest in the publication of this manuscript nor aided in data collection, analysis, interpretation, or trial design. No pharmaceutical company or other agency has provided funds to any authors as recompense for writing this article.

Author Contributions
Data collection was conducted by C.O., J.A., J.M., P.K., D.S., N.S., H.M., R.W., and T.S. C.O. was responsible for the conception, planning, conduct, and reporting of this project. Oversight on all aspects of the project was conducted by C.O. and J.D., who will act as guarantors. Statistical analysis was performed by C.O. and both checked and ratified by Dr. David Young, lecturer in the Department of Mathematics and Statistics at Strathclyde University. Image processing and figure production was performed by author C.O. Article writing was conducted by C.O. and was proofread by J.M., P.K., and J.D.

Data Accessibility Statement
Deidentified individual participant data will be available including data dictionaries. Specifically, a case may be
submitted for provision of individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices). Study documentation including the study protocol and statistical analysis plan may also be requested. Data will be available following publication ending 5 years after this date as per data handling measures specified in the study protocol. Access will be granted to requestors submitting a methodologically sound proposal to the corresponding author C.O. (christopher.oddy1@nhs.net) and granted only to achieve the aims proposed in the submitted proposal. Requestors must sign a data access agreement that is approved by the confidentiality advisory board at Epsom & St Helier University Hospitals NHS Trust.

References

1. Payne RA. The epidemiology of polypharmacy. Clin Med (Lond). 2016;16(3):465-469.
2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259.
3. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health. 2020;13(10):1373-1380.
4. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis [published online ahead of print 2020]. Crit Rev Food Sci Nutr. 2020;1-9.
5. Almario CV, Chey WD, Spiegel BMR. Increased risk of COVID-19 among users of proton pump inhibitors. Am J Gastroenterol. 2020;115(10):1707-1715.
6. Lee SW, Ha EK, Yeniya A, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. Gut. 2020;70(1):76-84.
7. Ramachandran P, Perisetti A, Gajendran M, et al. Pre-hospitalization proton pump inhibitor use and clinical outcomes in COVID-19 [published online ahead of print 2020]. Eur J Gastroenterol Hepatol. 2020.
8. Yokoyama Y, Aikawa T, Takagi H, Brässoulos A, Kuno T. Association of renin-angiotensin-aldosterone system inhibitors with mortality and testing positive of COVID-19: Meta-analysis. J Med Virol. 2020;92(4):2084-2089.
9. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: a systematic review and meta-analysis. Pharmacol Res. 2020;158:104927.
10. Daniels LB, Sitapati AM, Zhang J, et al. Relation of statin use prior to admission to severity and recovery among COVID-19 inpatients. Am J Cardiol. 2020;136:149-155.
11. Zhang XJ, Qin JJ, Cheng X, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metab. 2020;32(2):176-187.e174.
12. De Spiegeleer A, Bronselaer A, Teo JT, et al. The effects of ARBs, ACEis, and statins on clinical outcomes of COVID-19 infection among nursing home residents. J Am Med Dir Assoc. 2020;21(7):909-914.e902.
13. Kow CS, Hasan SS. Meta-analysis of effect of statins in patients with COVID-19. Am J Cardiol. 2020;134:153-155.
14. Russo V, Di Maio M, Attena E, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. Pharmacol Res. 2020;159:104965.
15. Maldonado E, Tao D, Mackey K. Antithrombotic therapies in COVID-19 disease: a systematic review. J Gen Intern Med. 2020;35(9):2698-2706.
16. Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol. 2020;190(4):e192-e195.
17. Hippisley-Cox J, Young D, Coupland C, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. Heart. 2020;106(19):1503-1511.
18. Yahiya A, Hemmati N, Derakhshan P, et al. Angiotensin enzyme inhibitors and angiotensin receptor blockers as protective factors in COVID-19 mortality: a retrospective cohort study [published online ahead of print 2020]. Intern Emerg Med. 2020:1-11.
19. Singh D, Halpin DMG. Inhaled corticosteroids and COVID-19-related mortality: confounding or clarifying? Lancet Respir Med. 2020;8(11):1065-1066.
20. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ. 2020;371:m3731.
21. Knight SR, Ho A, Pius R, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 2020;370:m3339.
22. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-436.
23. Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev. 2016;37(2):85-98.
24. Royal College of Physicians. National Early Warning Score (NEWS) 2. https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2. Published December 19, 2017. Accessed November 9, 2020.
25. O’Driscoll BR, Howard LS, Earis J, Mak V. British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings. BMJ Open Respiratory Research. 2017;4(1):e000170.
26. Austin PC. A comparison of 12 algorithms for matching on the propensity score. Stat Med. 2014;33(6):1057-1069.
27. Ming K, Rosenbaum PR. Substantial gains in bias reduction from matching with a variable number of controls. Biometries. 2000;56(1):118-124.
28. Geldof T, Popovic D, Van Damme N, Huys I, Van Dyck W. Nearest neighbour propensity score matching and bootstrapping for estimating binary patient response in oncology: A Monte Carlo simulation. Sci Rep. 2020;10(1):964.
29. Oddy CJ, Allington J, McCaul JA, et al. Inpatient omission of ACEi and ARBs is associated with morbidity and mortality in COVID-19. In-press. 2021.
30. Awad ZM, El-Ganainy SO, ElMallah AI, Khedr SM, Khattab MM, El-Khatib AS. Assessment of pregabalin-induced cardiotoxicity in rats: Mechanistic role of angiotensin 1–7. Cardiovasc Toxicol. 2020;20(3):301-311.

Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.