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Pharmacological Predictors of Morbidity and Mortality in COVID-19

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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; $P = .020$) 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.[1] 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.[2] 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.[3–19] 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.[6] 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.[20–22] 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

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pertinent when the severity of a patient's prior conditions is unknown.

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.[23] NEWS-2 score was calculated according to standards set by the Royal College of Physicians (United Kingdom).[24]

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 L/min, 28% = 5 L/min, 35% = 9 L/min, 40% = 11 L/min, and 60% = 13.5 L/min.[25] 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 $\pm$ 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.[26,27] 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*)

Table 1. 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	…	…
Levothyroxine	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*)

Table 1. 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, chromic 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*)

Table 1. 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, valve 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), ischemic heart disease, valve disease, rhythm disorders, peripheral vascular disease, history of venous thromboembolism, history of cerebrovascular accident	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*)

Table 1. 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 α of 1<.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 by our inclusion criteria excluding mild cases. Data was complete for each participant.

Forty-two medications were prescribed to at least 20 study participants and were brought forward for analysis. A further 24 groups of medication were collated, and analysis was conducted on the resulting 66 categories. The distribution of prescriptions in our cohort, including agents that were not brought forward for analysis, is displayed in Figure S1. The number of participants prescribed each medication, or class of medication, before admission is presented in Table 1 alongside the mean age of each group, factors considered in each propensity matching algorithm, case and control numbers in each matched cohort, and a summary of unbalanced covariates after matching. Fifty-nine of the 66 matched cohorts had no unbalanced covariates (Table 1).

Medications Associated With Morbidity and Mortality

The relationships between each medication, or class of medication, and our primary outcome measures were explored, adjusting for age, sex, race/ethnicity, and relevant comorbidities (Table 2). The majority of medications showed nonsignificant associations with mortality 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 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; $P = .013$). 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]

Table 2. Medications and Outcome Measures

	Mortality		Intensive Care Admission		Oxygen Requirements		NEWS-2 Score		CRP Concentration		AKI Stage	
Drug Name	HR (95%CI)	*P* Value	HR	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Individual agents												
Alfacalcidol	0.32 (0.02-4.98)	.415	…	…	0.71 (0.25-2.00)	.501	0.79 (0.49-1.28)	.324	1.48 (0.48-4.60)	.481	1.35 (0.66-2.75)	.398
Allopurinol	1.10 (0.28-4.34)	.824	4.54 (0.21-97.49)	.344	1.23 (0.59-2.58)	.580	1.12 (0.75-1.68)	.573	1.07 (0.53-2.17)	.851	0.84 (0.46-1.55)	.575
Amlodipine	0.90 (0.49-1.63)	.721	0.62 (0.24-1.59)	.322	1.01 (0.72-1.41)	.848	0.97 (0.81-1.15)	.684	0.86 (0.62-1.21)	.401	1.16 (0.86-1.55)	.334
Apixaban	3.86 (0.87-17.10)	.079	…	…	1.07 (0.54-2.11)	.854	1.25 (0.91-1.73)	.171	0.90 (0.50-1.61)	.707	1.22 (0.78-1.91)	.378
Aspirin	0.93 (0.46-1.86)	.808	0.70 (0.16-3.02)	.625	0.96 (0.65-1.41)	.807	0.94 (0.77-1.14)	.526	1.16 (0.81-1.67)	.414	1.08 (0.77-1.50)	.668
Atorvastatin	0.88 (0.52-1.50)	.639	0.53 (0.21-1.33)	.178	1.02 (0.76-1.39)	.869	1.07 (0.91-1.24)	.422	0.91 (0.67-1.22)	.527	1.07 (0.82-1.40)	.597
Beclometasone inhaler	0.10 (0.01-0.82)	**.032**	4.54 (0.13-150.75)	.250	0.72 (0.33-1.58)	.410	0.76 (0.52-1.12)	.159	0.66 (0.33-1.32)	.237	1.68 (0.96-2.92)	.067
Bisoprolol	1.14 (0.63-2.07)	.674	0.38 (0.13-1.12)	.081	0.94 (0.67-1.31)	.697	1.06 (0.89-1.27)	.490	0.83 (0.61-1.13)	.232	0.98 (0.73-1.30)	.871
Budesonide/Formoterol inhaler	7.87 (0.33-192.21)	.175	3.17 (0.19-53.05)	.422	1.64 (0.72-3.73)	.234	1.29 (0.75-2.21)	.351	1.72 (0.82-3.61)	.149	0.90 (0.57-1.40)	.620
Bumetanide	0.34 (0.05-2.31)	.271	…	…	0.60 (0.28-1.31)	.194	0.99 (0.67-1.46)	.966	0.91 (0.44-1.87)	.793	1.36 (0.76-2.46)	.295
Carbocisteine	0.25 (0.06-1.17)	.087	…	…	0.59 (0.32-1.10)	.105	0.74 (0.53-1.03)	.104	0.72 (0.42-1.25)	.279	0.77 (0.44-1.35)	.362
Cholecalciferol	1.05 (0.60-1.84)	.861	0.59 (0.20-1.73)	.339	1.00 (0.74-1.36)	.905	1.01 (0.86-1.20)	.885	0.93 (0.69-1.24)	.611	0.78 (0.61-0.99)	**.047**
Citalopram	1.59 (0.19-14.38)	.534	2.12 (0.06-86.71)	.686	1.23 (0.61-2.47)	.559	1.09 (0.77-1.53)	.583	1.94 (1.08-3.48)	**.033**	0.90 (0.50-1.62)	.668
Clopidogrel	0.57 (0.22-1.52)	.266	0.18 (0.01-8.20)	.342	0.97 (0.60-1.56)	.854	1.01 (0.78-1.31)	.876	0.59 (0.37-0.95)	**.031**	0.58 (0.37-0.91)	**.022**
Codeine phosphate	2.33 (0.61-9.10)	.306	-	-	0.91 (0.48-1.70)	.691	1.27 (0.91-1.77)	.201	0.96 (0.53-1.76)	.803	1.14 (0.69-1.90)	.595
Donepezil	1.10 (0.14-11.29)	.748	…	…	0.73 (0.35-1.56)	.443	0.90 (0.56-1.46)	.664	1.37 (0.76-2.47)	.289	0.94 (0.55-1.61)	.795
Doxazosin	1.38 (0.32-5.90)	.713	0.21 (0.01-7.40)	.244	0.86 (0.43-1.72)	.649	1.08 (0.76-1.52)	.682	0.41 (0.21-0.79)	.018	0.61 (0.33-1.12)	.119
Epoetin beta	0.27 (0.02-3.25)	.299	…	…	0.37 (0.12-1.15)	.086	0.68 (0.40-1.14)	.134	0.49 (0.16-1.55)	.218	0.74 (0.29-1.84)	.497
Finasteride	4.01 (0.43-42.96)	.592	…	…	0.74 (0.33-1.65)	.467	1.02 (0.69-1.50)	.664	1.20 (0.66-2.18)	.563	1.07 (0.64-1.81)	.740
Folic acid	1.13 (0.36-3.50)	.664	0.94 (0.03-52.66)	.475	0.85 (0.50-1.45)	.566	1.03 (0.76-1.41)	.752	0.84 (0.49-1.46)	.555	1.13 (0.73-1.74)	.596
Furosemide	1.85 (0.80-4.29)	.157	0.05 (0.01-0.48)	**.011**	0.86 (0.54-1.35)	.504	1.02 (0.79-1.31)	.879	0.80 (0.52-1.22)	.296	0.90 (0.62-1.29)	.566
Gliclazide	4.37 (1.26-15.18)	**.020**	2.82 (0.63-12.60)	.174	2.12 (1.15-3.90)	**.017**	1.26 (0.93-1.70)	.130	2.05 (1.03-4.07)	**.041**	1.27 (0.68-2.37)	.449
Levothyroxine	5.15 (0.23-182.33)	.198	…	…	2.79 (0.92-8.41)	.098	1.66 (0.95-2.92)	.146	1.99 (0.63-6.22)	.281	1.42 (0.53-3.76)	.491
Linagliptin	0.24 (0.01-6.20)	.260	…	…	0.80 (0.31-2.08)	.638	1.02 (0.57-1.82)	.871	0.59 (0.20-1.78)	.344	0.80 (0.32-2.03)	.638
Losartan	0.55 (0.13-2.40)	.430	…	…	0.87 (0.39-1.94)	.722	0.86 (0.58-1.27)	.448	1.11 (0.46-2.65)	.805	1.19 (0.67-2.10)	.560
Macrogol	2.18 (0.84-5.68)	.135	…	…	1.19 (0.72-1.95)	.511	1.12 (0.85-1.49)	.421	0.98 (0.64-1.50)	.852	1.00 (0.70-1.42)	.804
Metformin	1.01 (0.43-2.39)	.974	0.95 (0.25-3.68)	.944	1.11 (0.66-1.86)	.690	1.12 (0.86-1.48)	.394	0.94 (0.55-1.60)	.807	0.90 (0.59-1.37)	.612
Mirtazapine	1.01 (0.27-3.77)	.771	…	…	0.55 (0.28-1.08)	.107	1.01 (0.70-1.46)	.656	0.74 (0.40-1.35)	.329	0.84 (0.52-1.37)	.532
No medications	0.74 (0.25-2.20)	.578	1.19 (0.47-3.03)	.719	0.91 (0.61-1.36)	.661	0.91 (0.73-1.13)	.475	0.89 (0.55-1.42)	.626	1.13 (0.80-1.59)	.476
Omeprazole	1.53 (0.87-2.71)	.145	1.82 (0.64-5.13)	.270	1.05 (0.77-1.43)	.768	1.02 (0.86-1.21)	.791	1.03 (0.77-1.37)	.830	0.98 (0.76-1.25)	.850
Paracetamol	0.73 (0.35-1.51)	.422	0.44 (0.07-3.08)	.366	0.87 (0.59-1.29)	.510	0.84 (0.68-1.04)	.128	0.66 (0.45-0.97)	**.045**	0.99 (0.72-1.36)	.796
Prednisolone	0.64 (0.21-1.96)	.435	1.11 (0.23-5.42)	.900	1.09 (0.67-1.79)	.724	0.96 (0.74-1.22)	.716	0.76 (0.46-1.24)	.274	0.80 (0.51-1.24)	.314
Pregabalin	0.10 (0.01-0.92)	**.049**	…	…	0.63 (0.27-1.49)	.345	0.71 (0.45-1.13)	.218	0.38 (0.16-0.90)	**.042**	0.76 (0.40-1.45)	.432
Ramipril	1.14 (0.57-2.26)	.722	1.06 (0.39-2.86)	.835	1.23 (0.83-1.81)	.311	1.12 (0.92-1.35)	.272	1.06 (0.71-1.58)	.795	0.99 (0.71-1.38)	.894
Salbutamol inhaler	0.77 (0.36-1.66)	.503	0.40 (0.08-2.13)	.283	0.89 (0.58-1.36)	.579	0.89 (0.70-1.11)	.293	0.79 (0.53-1.17)	.240	0.94 (0.70-1.26)	.664
Senna	0.80 (0.29-2.23)	.620	…	…	0.74 (0.44-1.25)	.288	0.91 (0.66-1.24)	.560	0.56 (0.35-0.90)	**.021**	1.03 (0.69-1.54)	.789
Sertraline	1.82 (0.39-8.67)	.514	2.38 (0.06-95.97)	.647	1.21 (0.59-2.51)	.616	1.07 (0.71-1.63)	.706	0.80 (0.41-1.58)	.522	1.03 (0.64-1.67)	.753

(*Continued*)

Table 2. (Continued)

	Mortality		Intensive Care Admission		Oxygen Requirements		NEWS-2 Score		CRP Concentration		AKI Stage	
Drug Name	HR (95%CI)	*P* Value	HR	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Simvastatin	0.84 (0.41-1.72)	.638	0.47 (0.12-1.88)	.287	0.96 (0.63-1.46)	.815	1.08 (0.86-1.36)	.523	0.88 (0.59-1.32)	.547	0.67 (0.48-0.94)	**.024**
Sitagliptin	4.01 (0.46-35.95)	.251	1.47 (0.20-10.73)	.706	1.09 (0.47-2.55)	.836	0.95 (0.69-1.32)	.764	1.12 (0.44-2.84)	.805	0.95 (0.39-2.29)	.888
Tamsulosin	1.25 (0.43-3.63)	.690	4.74 (0.10-189.66)	.619	1.10 (0.61-1.96)	.737	1.17 (0.86-1.58)	.332	1.19 (0.69-2.06)	.545	1.24 (0.77-1.99)	.382
Tiotropium inhaler	0.07 (0.01-0.82)	**.035**	…	…	0.35 (0.12-1.03)	.058	0.54 (0.29-1.00)	.064	0.58 (0.28-1.22)	.153	1.62 (0.91-2.85)	.098
Warfarin	2.65 (0.68-10.36)	.161	1.74 (0.27-11.38)	.562	1.22 (0.64-2.29)	.543	1.25 (0.90-1.75)	.182	1.55 (0.85-2.82)	.149	2.42 (1.54-3.81)	**<.001**
Classes of medication												
ACEIs	1.70 (0.92-3.17)	.095	1.44 (0.55-3.79)	.495	1.38 (0.98-1.94)	.072	1.20 (1.02-1.43)	**.034**	1.51 (1.05-2.16)	**.028**	1.16 (0.88-1.53)	.295
ACEIs/ARBs	0.98 (0.59-1.62)	.909	2.19 (1.02-4.70)	**.047**	1.20 (0.91-1.59)	.206	1.12 (0.97-1.28)	.131	1.43 (1.07-1.90)	**.016**	1.00 (0.79-1.28)	.936
ARBs	0.66 (0.28-1.54)	.337	3.68 (0.58-25.83)	.235	0.93 (0.59-1.46)	.759	1.01 (0.81-1.26)	.867	0.90 (0.57-1.42)	.652	1.01 (0.68-1.50)	.846
Anticoagulants	1.73 (0.85-3.49)	.133	0.58 (0.11-3.11)	.525	1.02 (0.68-1.51)	.922	1.21 (0.99-1.48)	.069	1.10 (0.76-1.60)	.618	1.08 (0.79-1.49)	.620
Antiepileptics	0.84 (0.39-1.84)	.672	0.26 (0.06-1.06)	.061	0.83 (0.53-1.28)	.397	0.91 (0.71-1.17)	.498	0.74 (0.48-1.15)	.211	0.96 (0.64-1.43)	.796
Antidepressants	1.81 (0.87-3.79)	.140	3.43 (0.84-14.25)	.132	1.35 (0.92-1.98)	.161	1.12 (0.91-1.37)	.293	1.12 (0.78-1.60)	.567	1.06 (0.78-1.44)	.717
Antiplatelets	0.64 (0.36-1.14)	.135	0.52 (0.15-1.73)	.285	0.85 (0.63-1.16)	.321	0.87 (0.74-1.03)	.102	0.91 (0.67-1.23)	.553	0.89 (0.68-1.16)	.386
Antipsychotics	1.37 (0.36-5.19)	.605	0.27 (0.01-11.10)	.469	0.59 (0.31-1.12)	.145	0.93 (0.64-1.35)	.592	0.73 (0.40-1.33)	.323	0.95 (0.54-1.67)	.773
Antithrombotics	0.92 (0.55-1.52)	.738	0.56 (0.18-1.68)	.301	0.95 (0.71-1.28)	.758	1.03 (0.88-1.20)	.722	1.09 (0.82-1.44)	.577	1.03 (0.81-1.31)	.799
Benzodiazepines	2.52 (0.52-12.53)	.302	…	…	0.85 (0.40-1.78)	.635	1.22 (0.80-1.87)	.407	0.87 (0.49-1.57)	.591	1.51 (0.87-2.62)	.175
Beta blockers	0.86 (0.49-1.49)	.591	0.38 (0.13-1.06)	.065	0.89 (0.65-1.22)	.478	1.05 (0.89-1.23)	.585	0.79 (0.58-1.08)	.141	1.00 (0.77-1.30)	.920
Calcium channel blockers	0.68 (0.40-1.17)	.167	1.18 (0.52-2.65)	.708	1.03 (0.77-1.39)	.825	0.90 (0.77-1.05)	.193	0.76 (0.56-1.04)	.093	1.17 (0.91-1.52)	.220
Direct oral anticoagulants	1.19 (0.47-3.01)	.715	…	…	0.95 (0.56-1.61)	.798	1.07 (0.82-1.41)	.614	0.83 (0.51-1.34)	.442	0.75 (0.52-1.09)	.137
Diuretics	0.86 (0.49-1.51)	.597	0.10 (0.03-0.43)	**.002**	0.72 (0.53-0.99)	**.042**	1.06 (0.90-1.25)	.501	0.68 (0.51-0.91)	**.010**	0.89 (0.69-1.13)	.327
Immunosuppressants	1.29 (0.56-2.99)	.541	0.42 (0.08-2.35)	.327	1.15 (0.75-1.76)	.540	1.02 (0.80-1.30)	.813	1.07 (0.72-1.60)	.745	0.88 (0.61-1.28)	.518
Inhalers (all)	0.33 (0.14-0.80)	**.015**	1.39 (0.28-6.95)	.692	0.90 (0.56-1.44)	.661	0.80 (0.63-1.03)	.084	0.98 (0.63-1.53)	.908	1.04 (0.74-1.47)	.779
Inhalers (steroid)	0.35 (0.15-0.79)	**.013**	0.89 (0.20-3.89)	.878	0.79 (0.49-1.25)	.313	0.79 (0.61-1.02)	.068	0.91 (0.58-1.42)	.677	0.93 (0.66-1.32)	.697
Insulin (all)	1.04 (0.35-3.08)	.949	0.46 (0.07-2.93)	.406	0.86 (0.46-1.60)	.637	0.96 (0.70-1.33)	.816	1.18 (0.63-2.21)	.606	1.17 (0.69-1.99)	.555
Iron supplementation	0.91 (0.35-2.37)	.750	…	…	0.91 (0.56-1.48)	.676	0.83 (0.64-1.09)	.203	0.73 (0.47-1.11)	.155	0.81 (0.54-1.22)	.335
Oral antihyperglycemics	1.46 (0.65-3.27)	.360	1.46 (0.38-5.60)	.577	1.03 (0.64-1.67)	.889	1.12 (0.87-1.43)	.375	1.27 (0.77-2.10)	.354	1.06 (0.69-1.62)	.790
Oral anti-hyperglycemics (second line)	1.92 (0.84-4.42)	.129	0.66 (0.21-2.12)	.488	1.04 (0.66-1.66)	.850	1.19 (0.93-1.51)	.166	0.99 (0.61-1.61)	.889	0.87 (0.58-1.32)	.517
Proton pump inhibitors	1.72 (1.06-2.79)	**.028**	1.29 (0.58-2.87)	.533	1.16 (0.89-1.52)	.272	1.08 (0.94-1.25)	.272	1.16 (0.90-1.50)	.245	0.98 (0.79-1.22)	.875
Statins	0.73 (0.46-1.15)	.188	0.35 (0.17-0.73)	**.006**	1.01 (0.78-1.31)	.891	1.09 (0.95-1.25)	.226	0.95 (0.74-1.23)	.702	0.82 (0.65-1.02)	.077
Vitamin D supplementation	0.78 (0.46-1.31)	.347	0.63 (0.22-1.85)	.405	0.91 (0.69-1.21)	.525	0.97 (0.82-1.14)	.730	0.92 (0.69-1.21)	.554	0.84 (0.66-1.07)	.169

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.

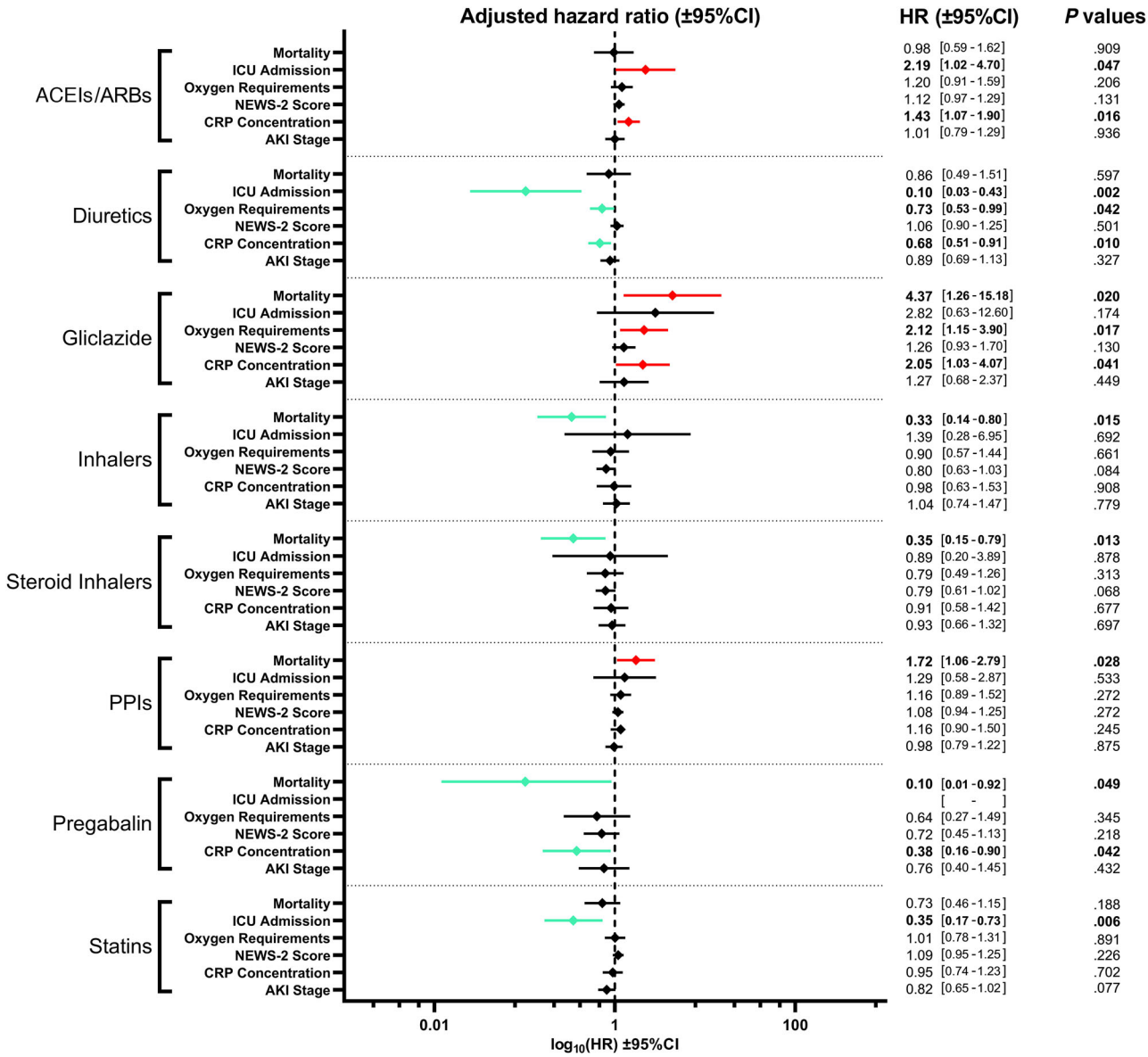

Figure 1. Summary of main findings. Adjusted hazard ratios (HR ± 95%CI) for primary and secondary outcomes imparted by each medication listed. Hazard ratios are expressed as the likelihood of a 5 L/min increase for oxygen requirements, 5-point increase for NEWS-2 score, and 100 mg/L for CRP concentration. 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.

ACEIs, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; ICU, intensive care unit; NEWS-2, National Early Warning Score 2; PPIs, proton pump inhibitors.

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

nonsignificant, which has been observed previously.[18] The implication of these findings is that these agents may confer some protection against adverse outcomes in COVID-19 and are likely safe, but that the effect is modest in size.

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 sulfonylureas, a class of OAHGs of which gliclazide is a member, on critical care admission, concluding that their use is positively associated.[17] Further study of gliclazide, or more broadly sulfonylureas, 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.[19] 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).[6] 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[7] observed a similar phenomenon. Almario et al[5] 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.[5–7] 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.[30] 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.[10–13] 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.[3,4] 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.

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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.

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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.

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