Impact of Renin-Angiotensin-Aldosterone System Inhibition on Mortality in Critically Ill COVID-19 Patients with Pre-Existing Hypertension: A Prospective Cohort Study

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Abstract

Background

The influence of renin-angiotensin-aldosterone system (RAAS) inhibitors on the critically ill COVID-19 patients with pre-existing hypertension remains uncertain. This study examined the impact of previous use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) on the critically ill COVID-19 patients.

Methods

Data from an international, prospective, observational cohort study involving 354 hospitals spanning 54 countries were included. A cohort of 746 COVID-19 patients with pre-existing hypertension admitted to intensive care units (ICUs) in 2020 were targeted. Multi-state survival analysis was performed to evaluate in-hospital mortality and hospital length of stay up to 90 days following ICU admission.

Results

A total of 746 patients were included - 543 (73%) with pre-existing hypertension had received ACEi/ARBs before ICU admission, while 203 (27%) had not. Cox proportional hazards model showed that previous ACEi/ARB use was associated with a decreased hazard of in-hospital death (HR, 0.73, 95% CI, 0.58 to 0.93). Sensitivity analysis adjusted for propensity scores showed similar results for hazards of death. The average length of hospital stay was longer in ACEi/ARB group with 21.4 days (95% CI: 19.9 to 23.0 days) in ICU and 6.7 days (5.9 to 7.6 days) in general ward compared to non-ACEi/ARB group with 16.2 days (14.1 to 18.5 days) and 6.3 days (5.0 to 7.7 days), respectively. When analysed separately, there was insufficient evidence of differential effects between ACEi and ARB use on the hazards of death and discharge.

Conclusions

In critically ill COVID-19 patients with comorbid hypertension, use of ACEi/ARBs prior to ICU admission was associated with a reduced risk of in-hospital mortality following adjustment for baseline characteristics although patients with ACEi/ARB showed longer length of hospital stay.

Background

The effect of renin-angiotensin-aldosterone system (RAAS) therapy on an individual's susceptibility to, and severity of, COVID–19 has been a source of debate throughout the COVID-19 pandemic(1–3). The biological rationale for this arises from the understanding that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the viral agent responsible for COVID-19, enters human target cells by binding to the membrane-bound mono-carboxypeptidase — angiotensin-converting enzyme 2 (ACE-2) — resulting in both internalization and degradation of the enzyme(4–6). ACE-2 expression is especially high in respiratory epithelium(7) – the main route of SARS-CoV-2 entry into the body.

Mechanistically, treatment with RAAS inhibitors — like angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) — is known to induce the upregulation of ACE-2 expression, and it is around this that speculation hinges and has resulted in conflicting hypotheses(1–3,8,9). On one hand, RAAS inhibitors could promote more severe COVID-19, with upregulated ACE-2 increasing the substrate for SARS-CoV-2 infectivity and severity(10,11). Conversely, ACE-2 upregulation may protect the lung via its downstream breakdown of angiotensin II and by increasing the expression of angiotensin-1-7 and 1-9, both of which have vasodilatory and anti-inflammatory effects. This controversy has resulted in the release of statements, from health regulatory authorities and scientific societies, recommending that patients should not discontinue ACEi/ARB therapy in the absence of conclusive evidence of harm(12).

The aim of this study was to examine the role of ACEi/ARB exposure on outcomes among COVID-19 patients with pre-existing hypertension admitted to intensive care units (ICUs). Outcomes included in-hospital mortality (primary outcome), length of ICU stay and general ward stay. We used prospectively-collected data from the international COVID-19 Critical Care Consortium incorporating ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease (COVID-19–CCC/ECMOCARD)(13).

Methods

Study design and subject participation

Study data were extracted for analysis from the COVID-19-CCC/ECMOCARD registry, the rationale and design of which have been detailed in **Document S1 (Additional file 1)** and previous publication(13). COVID-19-CCC/ECMOCARD is an international observational cohort study involving 354 hospitals spanning 54 countries across six continents. All participating sites obtained local ethics committee approval, and waivers of informed consent were granted for all patients. Recruiting sites and all contributors/collaborators are listed in **Document S2 (Additional file 1)**. The COVID-19-CCC collaborates through the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and their Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI). De-identified data were collected prospectively (but not necessarily consecutively) for enrolled patients and stored via the REDCap (Vanderbilt/NIH/NCATS UL1 TRooo445 v.10.0.23) electronic data capture tool hosted at the University of Oxford in the United Kingdom and the University of Queensland in Australia.

Inclusion criteria were: (1) age ≧18 years, (2) clinically suspected or laboratory confirmed SARS-CoV-2 infection, (3) admission to an ICU, (4) hypertension recorded as a comorbidity at the time of admission, and (5) knowledge of whether they had previously received (taken within 14 days of admission) any antihypertensive therapy. Patients who met all the criteria from (1) to (5) were enrolled. Hypertension were defined as someone having elevated arterial blood pressure diagnosed clinically, >140mmHg systolic or >90mmHg diastolic.

Patients with pre-existing hypertension (regardless of the blood pressure on admission or during hospital stay) then were divided into two groups; 1) ACEi/ARB group, and 2) non-ACEi/ARB group, based upon

reported prior use of an ACEi and/or ARB. ACEi/ARB group patients were those with hypertension who had taken ACEi and/or ARB within two weeks of admission to the ICU. Non-ACEi/ARB group patients were those with hypertension who had taken antihypertensive therapy except for ACEi and/or ARB within two weeks of admission.

Data collection and outcome measures:

For all enrolled patients, the following information was collected using an electronic case report form **(Additional file 1: Document S3**): demographics, comorbidities, medications, laboratory values, complications, and outcomes. Additional case report forms **(Additional file 1: Document S4**) were completed for patients who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Analyses were performed on all eligible patients included in the database from December 1st, 2019 through December 30th, 2020. Outcomes included in-hospital mortality (primary outcome), length of ICU stay and length of general ward stay assessed up to 90 days following ICU admission.

Statistical analysis

Baseline characteristics were summarized by descriptive statistics stratified by patient group. Characteristics covered patient demographics, comorbidities, admission signs and symptoms and laboratory results within the first day of ICU admission. Complications during hospitalization, the use of different management strategies in the first 28 days of ICU admission, and final outcomes at the end of the study were also summarized. Continuous variables were reported as medians with interquartile ranges (IQR). Categorial variables were reported as frequencies with percentages. The number of available observations were reported for all variables to show levels of data completeness. Hypothesis testing of between group differences in baseline characteristics was deemed inappropriate following recommendations for statistical reporting of observational studies(14).

Length of stay and in-hospital mortality were analysed as time-to-event outcomes using multi-state survival analysis. Modelling as time-to-event outcomes allowed us to include data on all patients regardless of outcome and accounted for death and discharged alive as competing risks. Outcomes were modelled up to 90 days following admission. Independent right censoring was applied to patients who were still in hospital at 90 days, at their last known follow-up time or at date of transfer to another facility.

Expected length of stay was examined separately for each patient group using a multistate model, unadjusted for baseline characteristics. The model was defined by four states: ICU, General ward, Discharged alive, Died **(Additional file 2: Figure S1**). Patients entered the model through the general ward state or ICU state if admitted to ICU on the same day as hospital admission. Whilst in ICU, patients either died or returned to the general ward after being discharged from ICU. Following ICU discharge, patients either died or were discharged alive from hospital. Length of stay was estimated from expected times spent in the general ward and ICU states. Cumulative morality risks at 30, 60 and 90 days from ICU admission were estimated from cumulative incidence functions starting in the ICU state, accounting for hospital discharge as a competing risk.

Follow-up analysis examined the influence of ACEi/ARB use on the hazards of death and discharged alive, accounting for baseline characteristics. Outcomes were analysed using a multi-state Cox proportional hazard model. Baseline characteristics included as model covariates were patient group, age, sex, body mass index (BMI), week of ICU admission, geographic region and major ethnicities (Black, Latin American, South Asian, White/Caucasian, Other including minority groups) and selected comorbidities (diabetes, smoking, chronic cardiac disease, chronic kidney disease). Missing data in covariates (BMI 7%, Chronic cardiac disease <1%, Chronic kidney diseases < 1%, Diabetes < 1% and Smoking 23%) was assumed missing at random and imputed by multiple imputation using chained equations (MICE). Tests for proportionality based on Schoenfeld residuals were applied to all covariates(14). Model results were reported separately for death and discharged alive as pooled hazard ratios with 95% confidence intervals (CI).

We further considered adjusting for the influence of baseline characteristics on reported use of ACEi/ARB versus non-ACEi/ARB treatment(s) before admission. Analysis followed recommendations for inverse probability weighting applied for time-to-event outcomes(15). Inverse probability weights were defined using propensity scores that estimated the probability of belonging to the ACEi/ARB group. Propensity scores considered the same baseline characteristics applied in the Cox proportional hazards model. Resulting propensity scores were then used to weight observations in a multi-state Cox model with patient group as the only covariate.

To evaluate differential effects between ACEi and ARB use, sensitivity analysis considered patient stratification into ACEi, ARB and non-ACEi/ARB groups; associations with the hazards of death and discharge were explored.

All analyses were completed in R 4.0.3. Code for multistate analysis of length of stay was adapted from a published study on COVID-19 patients(16).

Results

Patient characteristics:

During the period of study, a total of 1,202 patients with COVID-19 and pre-existing hypertension were admitted to COVID-19-CCC participating ICUs. Of these, 456 patients with missing data of antihypertensive therapy were excluded according to the inclusion criteria. The final cohort for statistical analysis comprised of 746 participants with pre-existing hypertension on antihypertensive therapy **(Additional file 2: Figure S2**). The median age of patients was 65 years [IQR, 57 to 73] and 489 were male (66%). The median Sepsis-related Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score was 6 [IQR, 4 to 9] and 18 [IQR, 12 to 24], respectively.

Baseline characteristics:

A total of 543 patients (73%) reported use of ACEi/ARB therapy (median age 65 years [IQR, 57-73], 67% men) within the two weeks prior to ICU admission, while 203 (27%) had not (median age 66 years [IQR, 55-73], 63% men). Admission characteristics of the ACEi/ARB and non-ACEi/ARB groups are compared in **Tables 1 and 2**. Both groups included similar percentage of diabetes and chronic cardiac disease {ACEi/ARB group vs. non-ACEi/ARB group: Diabetes, 253 (47%) vs. 91 (45%); chronic cardiac disease, 136 (25%) vs. 59 (29%)}. Chronic kidney disease was reported less in the ACEi/ARB group {80(15%) vs. 53 (26%)}. The usage of calcium channel blocker (CCB) and β-blocker was less frequent in ACEi/ARB groups than non-ACEi/ARB groups {114 (25%) vs. 115 (57%), and 112 (25%) vs. 111 (55%), respectively}.

Details of patient management while in the ICU are summarised in **Table 3**. Corticosteroids and management of patients in the prone position were more often observed in ACEi/ARB group than non-ACEi/ARB group {248 (56%) vs. 78 (46%), and 292 (55%) of 469 vs. 93 (46%), respectively}.

Descriptive statistics for complications recorded at any time during hospitalization are summarised in **Table S1 (Additional file 2)** and **Figure 1**. Across selected complications, cardiac arrythmias were more frequent in the ACEi/ARB group {ACEi/ARB group vs. non-ACEi/ARB group: 154 (33%) vs. 45 (25%), p=0.055}.

Final outcomes at the end of the study are summarised in **Table 4**. Death in hospital was observed in 260 (48%) of 543 in ACEi/ARB group and in 112 (55%) of 203 in non-ACEi/ARB group. Although the main cause of death was similar in the two groups, death due to septic shock was less observed in ACEi/ARB group than non-ACEi/ARB group {14 (5%) of 258 vs. 16 (11%) of 111, respectively}.

Length of ICU and hospital stay

Results for expected ICU and general ward stay are summarised in **Figure 2** and **Table S2 (Additional file 2).** Expected lengths of stay were longer in the ACEi/ARB group than non-ACEi/ARB group, with an average time of 21.4 days (95% CI, 19.9 to 23.0) vs. 16.2 days (95% CI, 14.1 to 18.5) for ICU, and 6.7 days (95% CI, 5.9 to 7.6) vs. 6.3 days (95% CI, 5.0 to 7.7) in general ward, respectively.

In-hospital mortality

Cumulative incidence of mortality between patient groups indicated differences in mortality up to 30 days from ICU admission (43.5%, SE = 2.2% for ACEi/ARB, and 51.3%, SE = 3.6% for non-ACEi/ARB). By 90 days, expected mortality estimated from the multistate model was 50.9% (SE = 2.2%) and 59.3% (SE = 3.5%) for ACEi/ARB and non-ACEi/ARB groups, respectively **(Additional file 2: Table S2**). Cumulative probabilities of death and discharged alive from ICU admission between ACEi/ARB and non-ACEi/ARB groups are shown in **Figure 3**. Hypothesis testing of cumulative incidence functions from time of ICU admission showed a statistically significant difference in the risk of death (test statistic=7.48, df=1, p=0.006), but not discharged alive (test statistic=1.18, df=1, p=0.277).

Results from multistate Cox regression are presented in **Figure 4** and **Table S3 (Additional file 2)**. Modelling indicated ACEi/ARB use was associated with a lower hazard of in-hospital mortality (HR, 0.73,

95% CI, 0.58-0.93, p = 0.011), but shared no association with the discharge hazard (HR, 0.83, 95% CI, 0.62-1.11, p=0.20). Adjustment by propensity scores showed that ACEi/ARB use was significantly associated with a lower hazard of death (HR,0.73, 95% CI, 0.58-0.91, p=0.006). **(Additional file 2: Table S4).**
When ACEi use or ARB use was modelled separately, both ACEi use and ARB returned similar, statistically significant fixed effects for the hazard of death; HR 0.70 (95% CI, 0.53-0.93, p = 0.014) and HR 0.74 (95% CI, 0.56-0.97, p = 0.028), for ACEi and ARB respectively (**Additional file 2: Table S5**). Similar outcomes were observed following adjustment by propensity score **(Additional file 2: Table S6),** suggesting there was limited evidence of differential effects between ACEi and ARB group on chosen outcomes.

Discussion

In this large, international, observational study of prospectively recruited patients with COVID-19 and comorbid hypertension requiring admission to an ICU, the previous use of ACEi/ARB prior to ICU admission was common. In this cohort, we made two important clinical observations. First, the previous use of ACEi/ARB was associated with a reduced risk of in-hospital mortality, compared with not being on either drug class, with the greatest separation between these two groups evident within the first 30 days after admission. Second, despite the improved in-hospital mortality, patients with ACEi/ARB showed longer length of ICU and general ward stay.

Previous use of ACEi/ARB was associated with a reduced risk of in-hospital mortality, compared with not being on either drug class. This is a study to examine mortality of ACEi/ARB vs. non-ACEi/ARB users among critically ill COVID-19 patients specifically managed in the ICU settings. Compared with previous research, our analysis accounted for potential confounders as baseline characteristics, including cardiac comorbidities. In a previous study of a cohort of 187 patients with COVID-19, Guo et al reported that the mortality of RAAS inhibitor users (36.8%; 6 of 19) was higher than that of non-users of RAAS inhibitors (25.6%; 43 of 168)[10]. However, it was uncertain if the higher mortality was related to RAAS inhibitors or a different background, where the RAAS inhibitor group might have a higher rate of comorbidities of cardiovascular disease. A recent meta-analysis involving 28,872 of COVID-19 patients, which showed a significant association between RAAS inhibition and reduced risk of death in the sub-cohort of hypertension(17), provides similar evidence to that reported in our results. Although cardiac arrhythmias were more common in the ACEi/ARB group in a current study corresponding with previous reports(18,19), it did not impact rates of mortality. Furthermore, the frequency of other cardiac complications during admission (e.g. heart failure, cardiac ischemia and cardiac arrest) was similar between the two groups. As such, the benefit of RAAS inhibitors could be distinct from the well-established prognostic benefit that ACEi/ARB therapy has on cardiovascular diseases(20). This is potentially related to the anti-inflammatory actions of angiotensin-1-7 and 1-9, both of which are increased by ACEi/ARB through upregulation of ACE-2(21,22). Both have vasodilatory and anti-inflammatory effects through Mas receptors and angiotensin II type 2 receptors, respectively(21,23). Some researchers, like Gurwitz et al, even proposed RAAS inhibitors as a tentative treatment for COVID-19 aiming to increase ACE-2(24) expecting anti-inflammatory effects. In addition, the lower rate of death due to septic shock in ACEi/ARB group in our

study, corresponding with another study(9), may be due to the anti-inflammatory effect of ACEi/ARB. In 2020, Hsu et al conducted a retrospective, propensity score-matched study targeting 3,168 sepsis patients with prior use of RAAS inhibitors, but unrelated to COVID-19 infection. They reported that the short-term (up to 90 days) mortality after sepsis was substantially lower among those who were already established on RAAS inhibitor treatment when sepsis occurred(25). Evidence is limited, but some experimental studies suggested that angiotensin II has a pro-inflammatory effect and causes endothelial and microvascular dysfunctions(26,27). RAAS inhibitors may also reduce inflammatory cytokines thus preventing sepsis-related adverse effects by reducing angiotensin II through ACE-2 upregulation.

Despite the improved in-hospital mortality, patients with ACEi/ARB showed a longer length of ICU and general ward stay. In the retrospective study, targeting from non-severe to severe hospitalized COVID-19 patients, Li et al reported that ACEi/ARB group (n=115) and non-ACEi/ARB group (n=247) did not have a significant difference in hospital stay {median 19 days [IQR 13-27] and median 19 days [IQR 11-27], respectively} in contrast to this study. However, when they compared the length of hospital stay of COVID-19 patients with hypertension (n=362) between survivors (n=285) and non-survivors (n=77), the data showed that survivors had a trend to stay longer {median 19 days [IQR 13-26]} than non-survivors {median 15 days [IQR 6-30], p=0.73}(28). This may potentially be because the non-survivors could have had more severe disease and died earlier than the survivors. This interpretation is similar to that by Rees et al in a systematic review showing that patients who were discharged alive tended to stay longer than those who died during admission(29).

This is an international report investigating any association between ACEi/ARB use and outcomes in a large group of critically ill COVID-19 patients specifically managed in the ICU settings. The inferences are, therefore, not limited by clinical practices specific to single-country studies. Except for differences such as the rates of corticosteroid administration and prone positioning, the two treatment groups were well matched, in terms of baseline characteristics and the clinical management they received.

Some of the limitations exist in this study. First, our data lacks the information on the latest timing of medications taken in the two weeks prior to admission and whether they were continued post-hospitalization. Similarly, we lack data on dose and specific ACEi/ARB agents. Therefore, our results are based on the estimation that the enough effect of medications with an appropriate dosage continued at least up to hospitalization. Second, limited data availability on SOFA score and APACHE-II score meant that adjustment for disease severity at time of ICU admission was not possible. However, considering that over 95% of patients in both ACEi/ARB group and non-ACEi/ARB group required mechanical ventilation, it is certain that patients enrolled were critically ill patients requiring ICU management. Finally, the voluntary nature of site participation means that our data could be skewed favouring centres with sufficient resources to enter data.

Abbreviations

ACE-2: Angiotensin-converting enzyme 2

ACEi: Angiotensin-converting enzyme inhibitor

APACHE-II: Acute Physiology and Chronic Health Evaluation II

ARB: Angiotensin receptor blockers

ARDS: Acute respiratory distress syndrome

BMI: Body mass index

CCB: Calcium channel blocker

CCC: Critical care consortium

CI: Confidence interval

COVID-19: Coronavirus disease-19

ECMO: Extracorporeal membrane oxygenation

ECMOCARD: ExtraCorporeal Membrane Oxygenation for 2019 novel Coronavirus Acute Respiratory Disease

HR: Hazard ratio

ICU: Intensive care unit

IQR: Interquartile ranges

ISARIC: the International Severe Acute Respiratory and Emerging Infection Consortium

MICE: Multiple imputation using chained equations

RAAS: Renin-angiotensin-aldosterone system

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SE: Standard error

SOFA: Sepsis-related Organ Failure Assessment

SPRINT-SARI: Short PeRiod IncideNce sTudy of Severe Acute Respiratory Infection

Declarations

Ethics approval and consent to participate

This Study was conducted as a cardiac sub-study of the COVID-19-CCC/ECMOCARD registry(13). As this study was a multicentre international study, each participating site obtained local ethics committee approval, and waivers of informed consent were granted for all patients as all data are collected routinely. A complete summary of ethics and regulatory approvals is included in the main COVID-19-CCC protocol(13). De-identified data were collected for enrolled patients.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the COVID-19-CCC/ECMOCARD research group but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the COVID-19-CCC/ECMOCARD research group.

Competing interests

GLB and JFF received research funds, through their affiliated institution, from Fisher & Paykel for studies related to high-flow oxygen therapy. The remaining authors have nothing to disclose.

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Authors' contributions

KS, NW, NO, JYS, GLB, JFF and RCA were responsible for the study concept and design. KS, NW, JPF, JYS, GLB and JFF were responsible for the acquisition and analysis of data. All authors contributed to the interpretation of the data. KS, NH, NO and JPF drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version. RCA is a guarantor. The corresponding author attests that all listed authors meet authorship criteria.

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Tables

Table 1. Baseline characteristics

Characteristic	ACEi/ARB	Available number	non-ACEi/ARB	Available number
	Demographics			
Age (years), median (IQR)	65(57 to 73)	543	66(55 to 73)	203
Male, n (%)	362 (67)	543	127 (63)	203
BMI (kg/m2), median (IQR)	29.4(26.1 to 34.0)	494	29.2(24.8 to 33.9)	194
Ethnicity, n (%)				
Aboriginal	7 (1)	506	1 (1)	195
Arab	11 (2)	506	4 (2)	195
Black	58 (11)	506	48 (25)	195
East Asian	21 (4)	506	10 (5)	195
South Asian	21 (4)	506	13 (7)	195
West Asian	3 (1)	506	1 (1)	195
Latin American	102 (20)	506	17 (9)	195
Other	28 (6)	506	17 (9)	195
White	255 (50)	506	84 (43)	195
Geographic region, n (%)				
Africa	55 (10)	543	39 (19)	203
Asia	6 (1)	543	1 (0)	203
Australia and New Zealand	165 (30)	543	57 (28)	203
Europe	102 (19)	543	8 (4)	203
Latin America and the Caribbean	196 (36)	543	98 (48)	203
Northern America	55 (10)	543	39 (19)	203
	Admission signs and symptoms			
Heart rate (beats/minute), median (IQR)	92(80 to 105)	515	92(78 to 106)	186
Systolic BP (mmHg), median (IQR)	130(114 to 148)	513	128(110 to 150)	188
Diastolic BP (mmHg),	72(61 to 82)	513	70(61 to 83)	188

median (IQR)				
Respiratory rate (breaths/minute), median (IQR)	25(20 to 30)	490	24(20 to 30)	181
Oxygen saturation (%), median (IQR)	91(84 to 95)	516	94(89 to 97)	191
Cough, n (%)	379 (75)	507	129 (70)	184
Fever, n (%)	412 (80)	518	142 (75)	190
Malaise, n (%)	277 (58)	481	79 (44)	178
Dyspnoea, n (%)	437 (82)	530	159 (82)	530
	Reported comorbidities			
Smoking, n (%)	167 (40)	416	69 (45)	153
Diabetes, n (%)	253 (47)	539	91 (45)	201
Chronic cardiac disease, n (%)	136 (25)	539	59 (29)	202
Chronic pulmonary disease, n (%)	72 (13)	541	43 (21)	201
Chronic kidney disease, n (%)	80 (15)	540	53 (26)	201
Chronic neurological disorder, n (%)	36 (7)	539	18 (9)	201
Severe liver disease, n (%)	27 (5)	541	21 (10)	202
Malignant neoplasm, n (%)	32 (6)	540	13 (6)	201
	Reported use of anti-hypertensive drugs on admission			
Diuretic, n (%)	94 (20)	462	46 (23)	203
Calcium channel blocker, n (%)	114 (25)	462	115 (57)	203
β-blocker, n (%)	112 (24)	462	111 (55)	203
α-blocker, n (%)	6 (1)	462	4 (2)	203

ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, BMI: body mass index

Table 2. Laboratory examinations within first 24hrs of ICU admission.

Characteristic	ACEi/ARB median (IQR)	Available number	non-ACEi/ARB median (IQR)}	Available number
Haemoglobin (g/L)	12.7(11.0 to 13.8)	417	11.4(9.6 to 13.5)	169
Neutrophil (10^9/L)	8.6(5.7 to 11.9)	310	7.2(4.2 to 11.0)	102
Lymphocyte (10^9/L)	0.8(0.5 to 1.2)	322	0.7(0.4 to 1.1)	113
Platelets (10^9/L)	220(167 to 280)	398	196(136 to 270)	166
C-reactive protein (mg/L)	130(48 to 257)	126	121(37 to 249)	60
Procalcitonin (ng/mL)	0.30(0.17 to 0.94)	141	0.75(0.26 to 1.80)	52
Bilirubin (μmol/L)	0.58(0.35 to 0.90)	305	0.60(0.40 to 1.00)	125
AST (U/L)	0.80(0.57 to 1.25)	256	0.80(0.55 to 1.17)	109
ALT (U/L)	0.60(0.38 to 1.14)	259	0.52(0.33 to 0.87)	113
Blood urea nitrogen (mmol/L)	2.1(1.2 to 3.6)	362	2.1(1.2 to 4.0)	156
Creatinine (μmol/L)	1.1(0.8 to 1.6)	415	1.2(0.9 to 2.2)	169
Sodium (mmol/L)	137(134 to 140)	333	138(135 to 142)	134
Potassium (mmol/L)	4.1(3.7 to 4.6)	334	4.2(3.7 to 4.6)	133

ACEi: angiotensin-converting enzyme inhibitor, ALT: alanine aminotransferase, ARB: angiotensin II receptor blocker, AST: aspartate aminotransferase

Table 3. ICU management within the first 28 days following ICU admission.

Characteristic	ACEi/ARB n (%)	Available number	non-ACEi/ARB n (%)	Available number
Antivirals	225 (53)	427	92 (57)	162
Antibiotics	506 (96)	527	189 (94)	200
Corticosteroids	248 (56)	440	78 (46)	170
Heparin	356 (87)	411	128 (84)	152
Prone position	292 (55)	532	93 (46)	202
Mechanical ventilation	511 (96)	533	193 (96)	202
ECMO	81 (15)	532	26 (13)	202
Inhaled nitric oxide	56 (11)	532	23 (11)	202
CRRT	91 (18)	499	39 (21)	188
Vasoactive drugs	308 (63)	492	117 (63)	187
Cardiac assist devices	34 (7)	501	12 (6)	192
Transfused RBC	112 (24)	461	48 (26)	183
Transfused Platelets	18 (4)	461	5 (3)	183
Transfused Plasma	23 (5)	461	11 (6)	183

ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CRRT: continuous renal replacement therapies, ECMO: extracorporeal membrane oxygenation

Table 4. Final outcomes at the end of study.

Outcome	ACEi/ARB n (%)	Available number	non-ACEi/ARB n (%)	Available number
Died in hospital	260 (48)	543	112 (55)	203
Discharged alive from hospital	227 (42)	543	69 (34)	203
Transferred to another facility	7543 (1)	543	1 (0)	203
Outcome not finalised	49 (9)	543	21 (10)	203
Recorded cause of death				
Cardiac Failure	17 (7)	258	4 (4)	111
Cerebrovascular accident	3 (1)	258	3 (3)	111
Haemorrhagic shock	3 (1)	258	0 (0)	111
Multi-organ failure	86 (33)	258	30 (27)	111
Respiratory failure	100 (39)	258	48 (43)	111
Septic shock	14 (5)	258	16 (14)	111
Other	19 (7)	258	7 (6)	111
Missing	16 (6)	258	3 (3)	111

Cause of death information is provided for patients known to have died in hospital. ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker

Figures

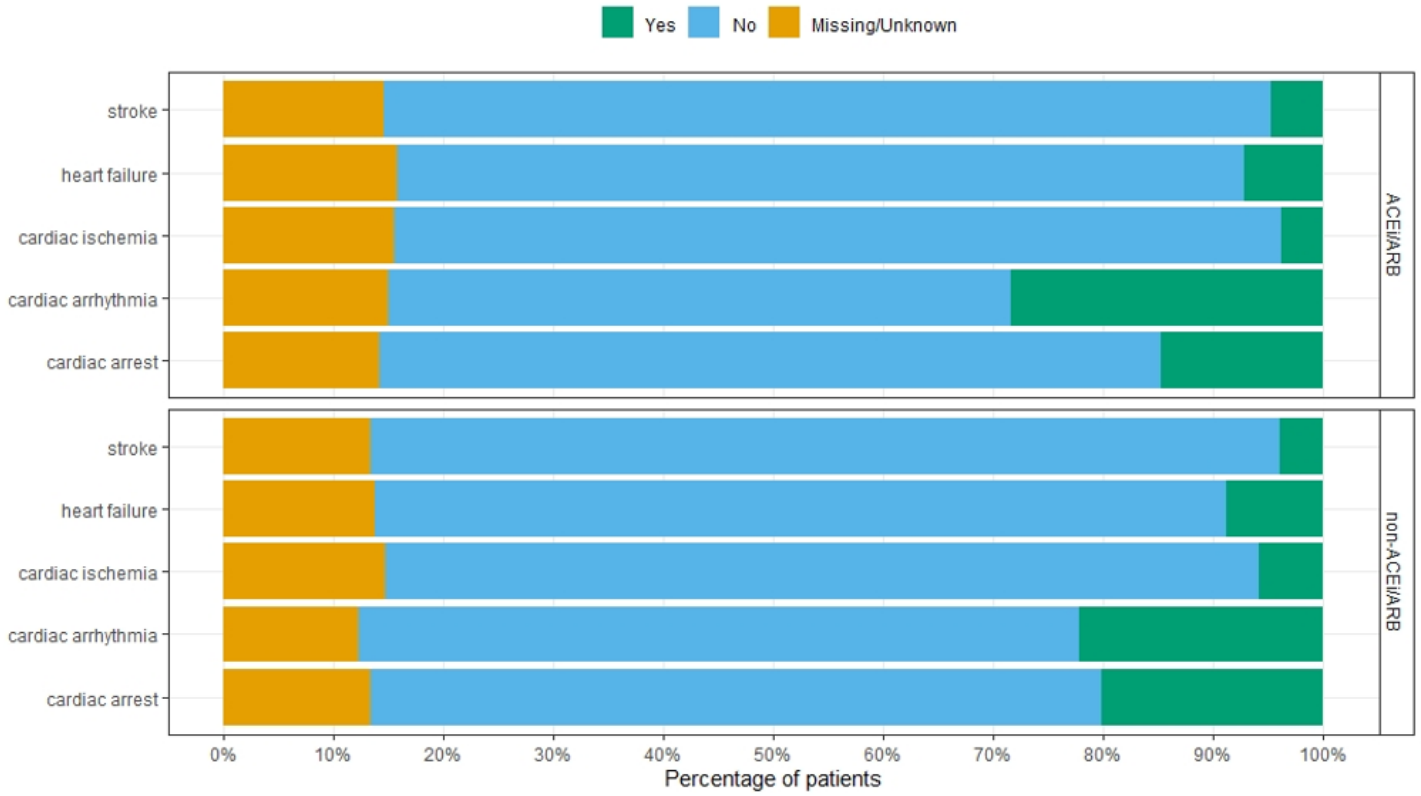

Figure 1

Descriptive statistics for complications recorded at any time during hospitalization, by patient group. ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker

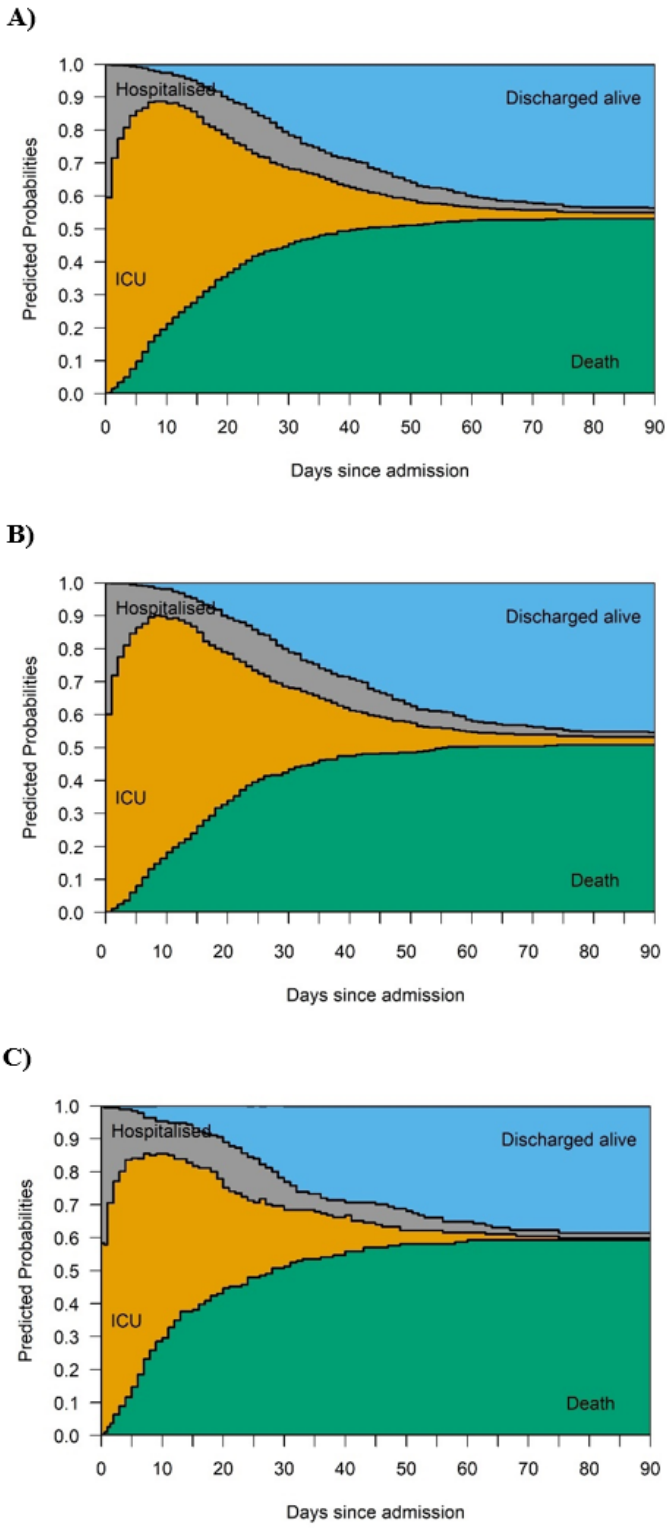

Figure 2

Multistate model results for expected ICU stay and hospital stay up to 90 days from hospital admission. (A) all included patients (n=663); (B) ACEi/ARB group; and (C) Non-ACEi/ARB group. ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CI: confidence intervals, ICU: intensive care unit

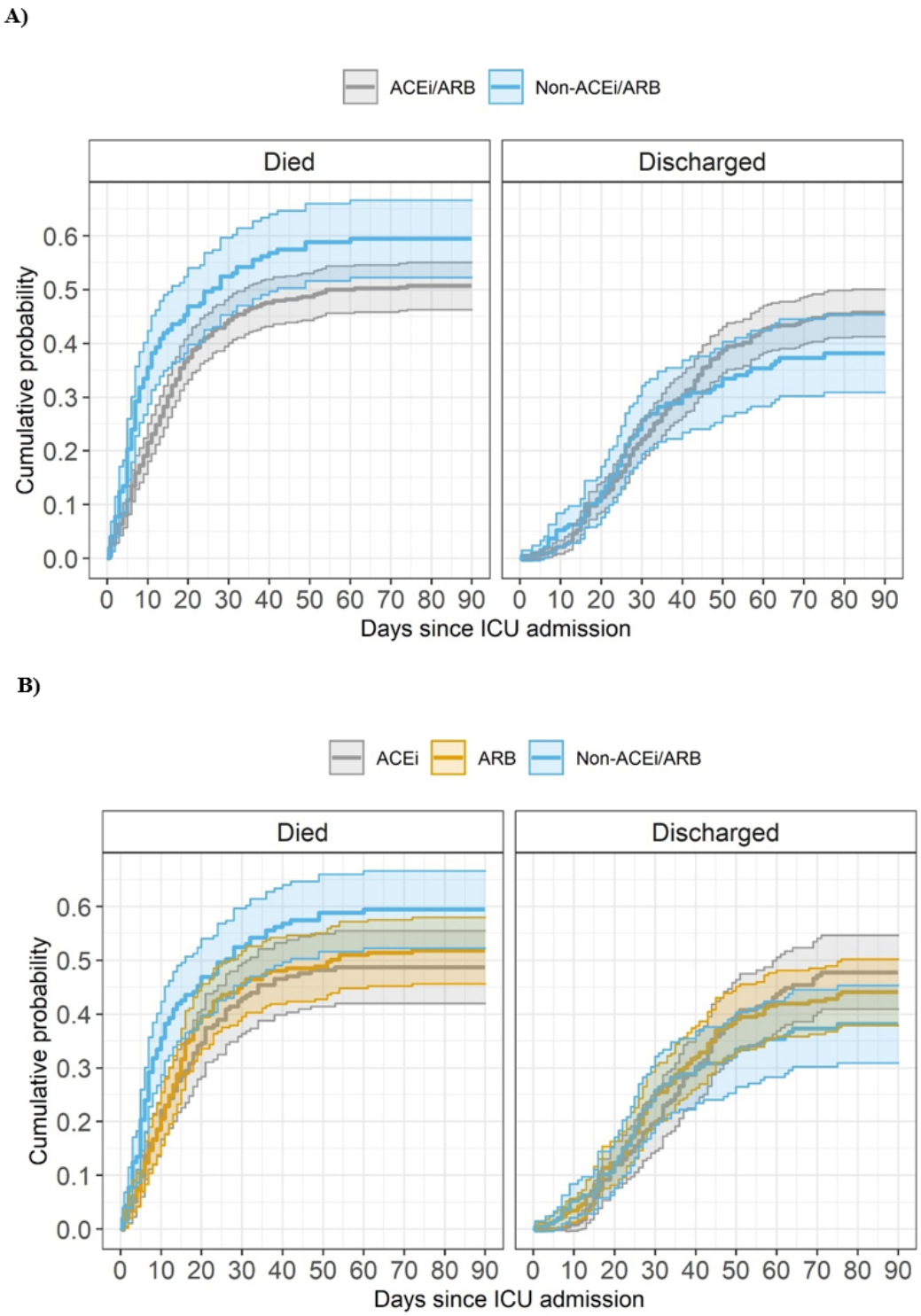

Figure 3

Cumulative probabilities of death and discharge from ICU admission. A) between ACEi/ARB and non-ACEi/ARB groups; B) between ACEI, ARB and non-ACEI/ARB groups. Results are not adjusted for baseline characteristics. ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, ICU: intensive care unit

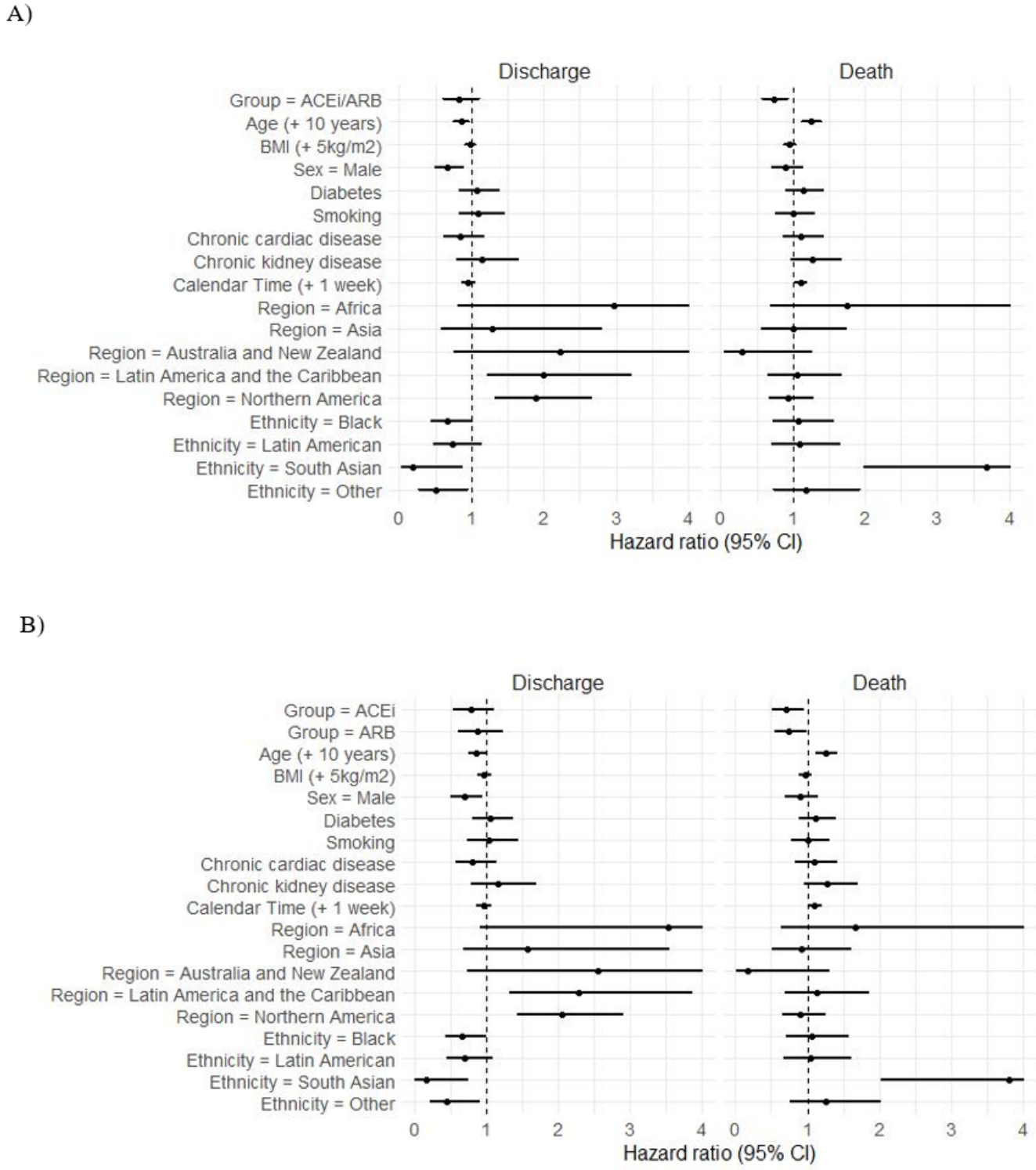

Figure 4

Forest plot derived from multistate Cox regression. A) Primary analysis with ACEi/ARB versus non-ACEi/ARB groups as a fixed effect; B) Sensitivity analysis where ACEi/ARB is split into ACEi and ARB groups (n = 41 excluded due to insufficient data to determine stratification). This accounts for competing risks of in-hospital death and hospital discharge up to 90 days from ICU admission. Week of ICU admission indicates calendar time. ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin II

receptor blocker, BMI: body mass index, CI: confidence intervals, ICU: intensive care unit. Terms with an upper confidence limit greater than 4 have been truncated for presentation.

Supplementary Files

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