LESS ORGAN DYSFUNCTION AND LOWER MORTALITY IN WAVE 3 THAN IN WAVES 1 AND 2 OF HOSPITALIZED COVID-19 PATIENTS IN CANADA

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For ARBs CORONA I

Conception and design: TL, JS, KCT, PKM, KD, GH, JAR.

Analysis: TL

Interpretation: TL, MPC, DCV, TCL, KCT, BBW, DS, JHB, KRW, GH, AM, FL, RF, NF, DM, JS, DMP, JCM, KDB, SM, PKM, GH, KD, GR, JAR.

Drafting the manuscript for important intellectual content: TL, MPC, DCV, TCL, KCT, BBW, DS, JHB, KRW, GH, AM, FL, RF, NF, DM, JS, DMP, JCM, KDB, SM, PKM, GH, KD, GR, JAR.

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Key Words: coronavirus, COVID-19, wave, mortality, ventilation, vasopressors, renal replacement therapy,

Word count: 2492

Abstract word count: 289

Figures: 2

Tables: 3

Funding Statement:

This study is funded by a grant from the Canadian Institutes of Health Research (CIHR #439993) to James A. Russell and St. Paul's Hospital Foundation to James A. Russell.

John Boyd is a recipient of a Providence Health Care Research Scholarship.

Keith Walley is supported by Canadian Institutes of Health Research (CIHR) Foundation Grant FDN 154311.

Donald Vinh is supported by the Fonds de recherche du Québec – Santé Clinician-Scientist scholar program.

Srinivas Murthy is supported by the Health Research Foundation and Innovative Medicines Canada Chair in Pandemic Preparedness Research

Declaration of competing interests:

See page 27.

ABSTRACT

Background: The COVID-19 epidemic grows and there have now been multiple waves in many countries. However, it is unknown whether mortality and organ dysfunction differ between waves.

Methods This is a sub-study of ARBs CORONA I, a multicentre Canadian pragmatic observational cohort study of adults hospitalized with acute COVID-19. The onset and end of waves 1, 2 and 3 were determined for the provinces of British Columbia, Ontario and Quebec in Canada using provincial health data. Unadjusted and adjusted generalized linear regression were used to compare 28-day and in-hospital mortality and use of invasive mechanical ventilation, vasopressors and renal replacement therapy between waves.

Results 520, 572 and 245 patients in waves 1, 2 and 3 respectively from nine sites were included. Patients in wave 3 were generally younger and had fewer co-morbidities. Unadjusted 28-day mortality rate was significantly lower in wave 3 (7.8%) compared to waves 2 (16.3%) and 1 (18.3%), and the difference remained significant in the adjusted analyses (OR (95% CI): wave 3 vs.1: 0.46 (0.26, 0.81), wave 3 vs 2: 0.52 (0.29, 1.91), wave 2 vs. 1: 0.89 (0.61, 1.29)). Compared to wave 1, after adjusting for difference in baseline characteristics, use of ventilation or vasopressors were less common in waves 2 and 3, while use of renal replacement therapy was less in wave 3. Possible mechanisms are unknown but include patient selection and residual differences in patient demographics and characteristics, differential use of effective therapies (e.g. dexamethasone), changes in SARS-CoV-2 (variants of concern) or roll out of the vaccination program.

Interpretation: There was progressively decreasing severity with waves among hospitalized adult patients with COVID-19, evidenced by lower mortality and use of organ-supportive

therapy. Changes in at-risk group and management strategies may explain these improved outcomes.

Word count: 289

Registration: ClinicalTrials.gov Identifier is: NCT04510623

INTRODUCTION

The COVID-19 pandemic now has three waves in Canada. Epidemics generally spread through a succession of waves that reflect factors on multiple timescales.

Differences in outcomes among waves could be due to differences in patient demographics and characteristics (e.g. age, co-morbidities), viral characteristics (e.g. viral load, infectivity, toxicity and variants of concern), host characteristics (e.g. immunity, genetics(1)), resources (hospital and ICU beds), and treatments (medications and ventilation therapies). Studies in different countries reveal differences in case numbers across various waves but to date, there are no reports of how hospitalized patients with acute COVID-19 differ in organ dysfunction and use of organ-supporting care such as ventilation, vasopressors and renal replacement therapy (RRT) across waves. Furthermore, differences in baseline characteristics of patients across waves would necessitate adjusted analyses but not all studies have done such analyses. Thus, it is unknown whether organ dysfunction and mortality – adjusted for baseline risk such as age and co-morbidities - differ between waves.

Our hypothesis was that there are differences in patient characteristics, mortality and use of ventilation, vasopressors and RRT among adults hospitalized with acute COVID-19 across waves 1, 2 and 3 in Canada.

METHODS

Ethics

This study was approved by Providence Health Care and the University of British Columbia Human Research Committee and by each of the contributing clinical sites. Anonymized clinical data and use of discarded plasma from clinical blood tests were deemed low risk and informed consent was deemed not necessary for this research.

Patient Selection Criteria

This is a sub-study of ARBs CORONA I(2), a multicentre Canadian pragmatic observational cohort study to examine association of pre-existing use of angiotensin receptor blockers and patient outcomes. Inclusion criteria were individuals over 18 years of age who had confirmed COVID-19 infection (according to local hospital or provincial laboratories clinically approved laboratory testing for SARS-CoV-2) who were admitted to hospital for acute COVID-19. We excluded acute COVID-19 readmissions, Emergency Room admissions without hospitalization and those admitted to hospital with positive SARS-CoV-2 test but their acute illness was not due to acute COVID-19. The Alberta site in ARBs CORONA I was different from other participating sites in that it only enrolled patients who were admitted to ICU. As such, comparisons between waves would be confounded by the percentage of patients coming from the Alberta site in each wave. We thus excluded patients from the Alberta site in the current analysis (**Appendix S1**).

Definitions of waves 1, 2 and 3 in the provinces of British Columbia (BC), Ontario and Quebec were derived from Canadian national reports (https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html) by visual examination of daily case count for

each province (**Figure 1**). Two authors (TL and JAR) independently reviewed the national report to determine the timing of each wave. Differences were resolved by consensus.

Baseline Characteristics

Age, sex, presence of co-morbidities, heart rate, respiratory rate, temperature, blood pressure, arterial oxygen saturation (SaO_2), serum creatinine, and use of oxygen were recorded at baseline (study enrollment).

COVID-19 Therapies

We recorded use of COVID-19 vaccines, corticosteroids and anti-viral agents during the hospital course. Use of hydroxychloroquine, interleukin 6 inhibitors and therapeutic anticoagulation were not systematically captured.

Outcomes

28-day and in-hospital mortality were recorded. For patients discharged alive prior to day 28 and subsequently lost to follow up, they were assumed to be survivors at day 28.

Organ dysfunction was scored as the use of invasive mechanical ventilation, vasopressors and RRT and as days alive and free (DAF) of invasive mechanical ventilation, vasopressors and RRT. Mortality is a competing risk for the calculation of DAF of vasopressors, ventilation and RRT because mortality rates over the observation period are high. To increase the penalty for non-survival, DAF of ventilation, vasopressors, and RRT (over 14 days) were summed and all non-survivors over the observation period were assigned zero vasopressor, ventilation and RRT-free

days(6). DAF of vasopressors, ventilation and RRT for survivors was calculated by subtracting number of days with use for vasopressors, ventilation and RRT from 14. A high DAF score indicates less organ dysfunction.

Statistical Analyses

Baseline characteristics were compared between waves using Chi-square test, Fisher's exact test, ANOVA or Kruskal–Wallis test as appropriate. Unadjusted and adjusted regression analyses (adjusting for pre-defined adjustment factors in ARBs CORONA I, including age, sex, co-morbidities (chronic heart disease, hypertension, chronic kidney disease and diabetes; the commonest co-morbidities of COVID-19 (3-5) associated with increased risk of ICU admission and death(5)) and baseline systolic blood pressure, plus potential confounders of organ dysfunction that were different across waves: baseline heart rate, SaO_2 and creatinine) were done to compare outcomes across waves. Logistic regression was used to compare 28-day and in-hospital mortality, and ever-ventilated, ever-used vasopressors or ever-received RRT during hospitalization or during the first 14 days between the three waves. Results were expressed as odds ratio (OR). DAF between waves was compared using 0-1 inflated beta regression as the observed data has a U-shape distribution. DAF was expressed as proportion of days (i.e., divided by 14) in the regression model and then back transformed for interpretation. Results were expressed as mean difference (MD) in DAF. Adjusted analysis for DAF RRT was not feasible numerically as too few patients used RRT during the first 14 days. Within each regression model, the outcome was compared between pair of waves (2 vs. 1, 3 vs. 1 and 3 vs. 2) by testing the appropriate contrast. We accounted for site effect in all regression analyses (unadjusted and adjusted) as the regional distribution of patients was different across waves due

to varying level of site participation over time. For logistic regression, site was considered as a random effect. For 0-1 inflated beta regression, site effect was considered as fixed instead of random due to numerical issues and computational limitations.

Missing data was minimal for the outcomes considered and thus patients with missing data were simply excluded from the corresponding analysis. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) and R 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). P <0.05 was considered statistically significant.

Results

A total of 1337 evaluable patients admitted from March 2, 2020 to April 14, 2021 were included in the current analysis. There were 520 (38.9%), 572 (42.8%) and 245 (18.3%) patients in waves 1, 2 and 3 respectively (**Figure 1**). The regional distribution of enrolled patients varied across waves due to varying level of site participation, with Ontario contributing few patients in wave 1 and Quebec contributing almost no patients after wave 1.

There were many significant differences in baseline characteristics among patients in waves 1, 2 and 3 at baseline. Patients in wave 3 were younger (mean: 63.3, 65.8 and 70.2 years in waves 3, 2 and 1 respectively, p<0.001), were more likely to be healthy with fewer co-morbidities (60.7%, 67.0% and 71.4% in waves 3, 2 and 1 respectively for any of chronic cardiac disease, hypertension, chronic kidney disease, and diabetes, p=0.011), especially chronic cardiac disease (19%, 25% and 32.1% in waves 3, 2 and 1 respectively, p<0.001) (**Table 1**). There were

significantly more patients with dementia in the first wave, likely due to outbreaks in long term care facility during the first wave.

Treatments differed across waves. Lopinavir/ritonavir was used in 2.5% of patients in wave 1 and none in waves 2 and 3, while use of remdesivir increased from 1.6% to 16.9% from wave 1 to 2, but then dropped to 9.8% in wave 3.

Use of corticosteroid increased over time, with 30.8%, 87.2% and 91% from wave 1 to 3. Importantly, use of dexamethasone increased from 10.8% of patients in wave 1 to 84.3% and 89% of patients in waves 2 and 3 respectively (**Table 2**). Initiation of dexamethasone was also sooner in latter waves. Among patients ever on dexamethasone during hospitalization, 42.6%, 63.8% and 67.5% initiated treatment on hospital admission day (p=0.003) and 72.2%, 89.1% and 93.3% initiated by day 1 (p<0.001) in waves 1, 2 and 3 respectively.

28-day mortality rate was 18.3%, 16.3% and 7.8% in wave 1, 2 and 3 respectively. The rate was significantly lower in wave 3 than waves 1 and 2 in both unadjusted and adjusted analysis (adjusted OR (95% CI): 0.46 (0.26, 0.81), p=0.007 for wave 3 vs 1 and 0.52 (0.29, 0.91), p=0.022 for wave 3 vs 2; **Figure 2 and Table E1**). The findings for in-hospital mortality were similar.

Use of ventilation, vasopressors or RRT decreased over waves (**Table 3**). There was significantly less use of ventilation during hospitalization in wave 3 compared to waves 1 and 2 (adjusted OR (95% CI): wave 3 vs. 1: 0.34 (0.22, 0.54), p<0.001; wave 3 vs 2: 0.59 (0.38, 0.92),

p=0.021) and in wave 2 compared to 1 (adjusted OR (95% CI): 0.58 (0.42, 0.80), p<0.001). Use of vasopressors were less common in waves 2 and 3 compared to wave 1, but there was no significant difference between waves 2 and 3 (**Figure 2 and Table E2**). The results regarding differences between waves were similar for use of ventilation or vasopressors within the first 14 days (**Figure 2 and Table E3**). Use of RRT during hospitalization was significantly less in wave 3 compared to wave 1 (**Figure 2 and Tables E2**).

Significantly more DAF ventilation was observed in latter waves (adjusted MD (95% CI): wave 2 vs 1: 1.39 (0.29, 2.41), p<0.001; wave 3 vs. 1: 2.32 (1.28, 3.33), p<0.001; wave 3 vs. 2: 0.94 (0.14, 1.62), p=0.017) and also for DAF vasopressors (adjusted MD (95% CI): wave 3 vs. 1: 1.30 (0.20, 2.19), p<0.001; wave 3 vs. 2: 0.81 (0.05, 1.60), p=0.026). In contrast, DAF RRT was not significantly different across waves (**Figure 2 and Tables E4**).

Vaccines could mitigate severity of COVID-19; 24 (1.8%) patients (n=3 (0.5%) and 21 (8.6%) in waves 2 and 3 respectively) had vaccines in our cohort before admission for acute COVID-19, with 11 patients had the vaccine for more than 14 days prior to admission. However, these numbers were too small to do analyses of the association of vaccines on outcomes between waves 2 and 3.

Interpretation

There were large differences in acute care outcomes between waves one, two and three in patients hospitalized with acute COVID-19 in Canada. Mortality and use of ventilation, vasopressors and RRT were significantly lower in wave three than wave one in unadjusted

analyses and in analyses adjusted for potential confounders. We identified dramatically increased use of dexamethasone as a potential reason for better outcomes in later waves even in adjusted analyses.

Lower mortality and less need for ventilation, vasopressors and RRT in wave 3 vs. waves 1 and 2 could be due to differences in SARS-CoV-2 (viral load and frequency of variants of concern), differences in patient severity of illness (e.g. due to better population immunity), differences in treatment that could alter outcomes (e.g. vaccines, dexamethasone, tocilizumab), differences in risk according to ethnicity or differences in ICU bed availability.

Dexamethasone decreased mortality(7) and increased days alive and free of ventilation(8) in COVID-19 trials. Dexamethasone could have decreased need for ventilation and perhaps vasopressors in our study because use of dexamethasone increased dramatically from 10.8% of patients in wave 1 to 84.3% and 89% of patients in waves 2 and 3 respectively when there was less need for ventilation, vasopressors and renal replacement therapy. It is remarkable that use of dexamethasone increased so rapidly and so dramatically in practice in Canada. We suspect that the strikingly positive results of the pivotal trial of dexamethasone (decreased mortality and use of ventilation) and the tremendous public and clinical awareness of the COVID-19 pandemic drove this very rapid change in practice.

Some studies also found decreased mortality in waves following the first wave of COVID-19(9, 10). In a 43-country study(10), there was lower mortality in the second wave than in the first wave. Domingo and colleagues(11) found differences in mortality (double in wave 1 vs. wave 2)

accounted for by differences in ICU admission and use of ventilation. In a multi-country study of waves 1 and 2, ages were similar between waves but the proportion of deaths of nursing home residents decreased in most countries in the second wave(12). More anticoagulation and corticosteroids in wave two might have reduced mortality in hospitalized COVID-19 patients in Milan Italy(13). Similarly, in a region of Spain, patients from the second wave were more often treated with non-invasive mechanical ventilation and corticosteroids, and less often with invasive mechanical ventilation, usual oxygen therapy and anticoagulants(14). In contrast, other studies found increased mortality in later COVID-19 waves in Africa(15) and South Korea(16).

In our study, we do not know if variants of concern in our patients played a role in decreasing need for ventilation and vasopressors in wave 3 compared to waves 1 and 2 because we did not measure SARS-CoV-2 genotype for variants of concern. Variants of concern increased in frequency in later waves in Italy (yet mortality was lower compared to the first wave(17)) and Japan(18, 19).

We did not assess immunity in our patients so cannot determine whether immunity played a role in decreasing need for ventilation and vasopressors in wave 3 compared to waves 1 and 2. Barallat and colleagues(20) found that seroprevalence of anti-SARS-CoV-2 IgG in the healthcare workers of Barcelona was higher than the general population in the same geographical area in wave one. Utrero-Rico and colleagues(21) showed that IL-6 levels predicted mortality in both the first and second waves of COVID-19 in Europe.

Vaccines could also mitigate severity of COVID-19, but mass vaccination program in Canada did not roll out until later part of wave 2. The number of vaccinated patients in our cohort was too small to formally assess whether vaccines contributed to the difference in patient outcomes between waves.

Starting in wave 2, and prominently in wave 3, health care providers became partially and sometimes fully vaccinated. We note anecdotally that health care providers attended patients at the bedside more frequently when the health care providers perceived that they were safer due to vaccination and availability of adequate PPE. This may have impacted patient outcomes.

There are limitations of our study. In this association study we cannot determine causation, but we do add further evidence regarding differences in characteristics, treatments and outcomes of patients in waves 1, 2 and 3. The regional distribution of enrolled patients also changed significantly across waves which could have confounded our results. Another potential limitation is inadequate sample size, particularly in wave 3, which limited our statistical power for the analysis. In addition, site selectivity is a limitation because our study was based mainly in tertiary centers participating in research. Our study did not require consent and research coordinators used SARS-CoV-2 positive tests in the hospital laboratory to find patients, but some patients may have been missed.

In conclusion, patients in wave 3 were younger and had fewer co-morbidities than patients in earlier waves and had lower mortality and needed less organ supporting care even after

accounting for these differences on age and co-morbidities. Changes in at-risk group and management strategies (such as corticosteroids) may explain these improved outcomes.

Table 1. Baseline characteristics of patients admitted with acute COVID-19 overall and in waves 1, 2 and 3.

Variable	All (n=1337)	Wave 1st (n=520)	Wave 2nd (n=572)	Wave 3rd (n=245)	P
Admission date, n (%)					-
Mar 2020 - May 2020	429 (32.1)	429 (82.5)	0 (0.0)	0 (0.0)	
Jun 2020 - Aug 2020	34 (2.5)	34 (6.5)	0 (0.0)	0 (0.0)	
Sep 2020 - Nov 2020	276 (20.6)	57 (11.0)	219 (38.3)	0 (0.0)	
Dec 2020 - Feb 2021	386 (28.9)	0 (0.0)	353 (61.7)	33 (13.5)	
Mar 2021 - Apr 2021	212 (15.9)	0 (0.0)	0 (0.0)	212 (86.5)	
COVID-19 confirmed status, n (%)					<0.001
Positive - screening test	82 (6.1)	67 (12.9)	13 (2.3)	2 (0.8)	
Positive - definitive test	1255 (93.9)	453 (87.1)	559 (97.7)	243 (99.2)	
Positive for other pathogen, n (%)	11 (0.8)	9 (1.7)	2 (0.3)	0 (0.0)	0.016
Sex, n (%)					0.263
Unknown	1	1	0	0	
Male	791 (59.2)	293 (56.5)	348 (60.8)	150 (61.2)	
Female	545 (40.8)	226 (43.5)	224 (39.2)	95 (38.8)	
Age					<0.001
Mean (SD)	67.0 (17.1)	70.2 (16.3)	65.8 (17.3)	63.3 (17.1)	
Range	(20.0, 103.0)	(23.0, 103.0)	(20.0, 100.0)	(23.0, 101.0)	
Co-morbidities, n (%) ^					
Any of the four below	899/1331 (67.5)	370/518 (71.4)	381/569 (67.0)	148/244 (60.7)	0.011
Chronic cardiac disease	353/1324 (26.7)	166/517 (32.1)	141/565 (25.0)	46/242 (19.0)	<0.001
Chronic kidney disease	199/1332 (14.9)	82/519 (15.8)	94/570 (16.5)	23/243 (9.5)	0.029
Hypertension	709/1330 (53.3)	295/519 (56.8)	299/569 (52.5)	115/242 (47.5)	0.050
Diabetes	424/1330 (31.9)	170/518 (32.8)	183/568 (32.2)	71/244 (29.1)	0.574
Chronic pulmonary disease	214/1327 (16.1)	102/519 (19.7)	81/567 (14.3)	31/241 (12.9)	0.018
Liver disease	56/1331 (4.2)	21/517 (4.1)	21/570 (3.7)	14/244 (5.7)	0.400
Chronic neurological disorder	147/1330 (11.1)	68/519 (13.1)	56/569 (9.8)	23/242 (9.5)	0.161
Malignant neoplasm	101/1324 (7.6)	43/517 (8.3)	36/564 (6.4)	22/243 (9.1)	0.318
Chronic hematologic disease	60/1330 (4.5)	30/518 (5.8)	25/569 (4.4)	5/243 (2.1)	0.068
AIDS / HIV	10/1305 (0.8)	4/491 (0.8)	2/570 (0.4)	4/244 (1.6)	0.154
Rheumatologic disorder	150/1330 (11.3)	41/517 (7.9)	76/570 (13.3)	33/243 (13.6)	0.009
Dementia	154/1328 (11.6)	100/516 (19.4)	42/569 (7.4)	12/243 (4.9)	<0.001
Malnutrition	11/1331 (0.8)	8/517 (1.5)	3/570 (0.5)	0/244 (0.0)	0.062
Admitted to ICU on hospital admission day, n (%)	218 (16.3)	104 (20.0)	83 (14.5)	31 (12.8)	0.012
Organ support on admission day					
Invasive mechanical ventilation, n (%)	102/1337 (7.6)	55/520 (10.6)	34/572 (5.9)	13/245 (5.3)	0.005
RRT or dialysis, n (%)	18/1320 (1.4)	8/511 (1.6)	7/567 (1.2)	3/242 (1.2)	0.881
Vasopressors, n (%)	81/1337 (6.1)	35/520 (6.7)	33/572 (5.8)	13/245 (5.3)	0.690
Temperature (°C) - mean (SD)	37.5 (0.9)	37.5 (0.9)	37.4 (0.9)	37.4 (0.8)	0.118
Missing, n	31	19	9	3	
Heart rate (beats per minute) - mean (SD)	94.2 (20.3)	91.4 (20.6)	95.5 (20.3)	97.4 (19.1)	<0.001
Missing, n	12	6	3	3	
Respiratory rate (breaths per minute) - mean (SD)	24.0 (7.3)	22.9 (6.4)	24.9 (7.9)	24.2 (7.5)	<0.001
Missing, n	24	15	5	4	
sBP - mean (SD)	129.4 (22.7)	128.8 (22.9)	130.6 (23.4)	128.0 (20.5)	0.238
Missing, n	9	2	5	2	
dBP - mean (SD)	73.8 (12.6)	73.7 (11.9)	74.4 (13.2)	72.5 (12.5)	0.165
Missing, n	25	3	14	8	

Variable	All (n=1337)	Wave 1st (n=520)	2nd (n=572)	3rd (n=245)	P
Oxygen saturation (SaO2; %) - mean (SD)	91.9 (7.2)	93.5 (4.2)	90.8 (8.6)	91.1 (7.9)	<0.001
Missing, n	17	13	2	2	
Required oxygen therapy, n (%)	436/1290 (33.8)	186/516 (36.0)	174/541 (32.2)	76/233 (32.6)	0.376
WBC count (x10³/µL) - Median (IQR)	6.6 (4.9, 9.0)	6.5 (4.9, 8.6)	7.0 (5.1, 9.2)	6.4 (4.7, 9.1)	0.090
Missing, n	27	17	6	4	
Haemoglobin (g/L) - Median (IQR)	132.0 (117.0, 145.0)	130.0 (118.0, 145.0)	132.0 (117.0, 145.0)	134.0 (119.0, 145.0)	0.470
Missing, n	26	15	7	4	
Creatinine (µmol/L) - Median (IQR)	85.0 (69.0, 115.0)	84.0 (68.0, 114.0)	87.0 (70.0, 121.0)	82.0 (66.0, 107.0)	0.036
Missing, n	28	10	11	7	

Table 2. COVID-19 therapies during the hospital course.

Variable, n (%)	All (n=1337)	Wave			P
		1st (n=520)	2nd (n=572)	3rd (n=245)	
Antiviral agent	211/1330 (15.9)	72/516 (14.0)	106/569 (18.6)	33/245 (13.5)	0.057
Lopinavir/Ritonavir	13/1330 (1.0)	13/516 (2.5)	0/569 (0.0)	0/245 (0.0)	<0.001
Remdesivir	128/1330 (9.6)	8/516 (1.6)	96/569 (16.9)	24/245 (9.8)	<0.001
Antibiotic	1119 (83.7)	434 (83.5)	486 (85.0)	199 (81.2)	0.408
Corticosteroid	882 (66.0)	160 (30.8)	499 (87.2)	223 (91.0)	<0.001
Dexamethasone	756 (56.5)	56 (10.8)	482 (84.3)	218 (89.0)	<0.001
Antifungal agent	73 (5.5)	34 (6.5)	23 (4.0)	16 (6.5)	0.135

P value was based on Chi-square test or Fisher's exact test as appropriate.

Table 3. Outcomes of patients admitted to hospital with acute COVID-19 overall, and according to waves 1, 2 and 3.

Variable	All (n=1337)	Wave 1st (n=520)	Wave 2nd (n=572)	Wave 3rd (n=245)
28-day mortality, n (%)	207 (15.5)	95 (18.3)	93 (16.3)	19 (7.8)
In-hospital death, n (%)	238 (17.8)	111 (21.3)	103 (18.0)	24 (9.8)
Admitted to ICU, n (%)	495/1336 (37.1)	201/520 (38.7)	215/572 (37.6)	79/244 (32.4)
Organ support while hospitalized, n (%)				
Invasive mechanical ventilation	281/1337 (21.0)	130/520 (25.0)	116/572 (20.3)	35/245 (14.3)
RRT or dialysis	68/1320 (5.2)	33/511 (6.5)	30/567 (5.3)	5/242 (2.1)
Vasopressors	285/1337 (21.3)	120/520 (23.1)	123/572 (21.5)	42/245 (17.1)
Organ support during first 14 days, n (%)				
Invasive mechanical ventilation	275/1337 (20.6)	127/520 (24.4)	115/572 (20.1)	33/245 (13.5)
RRT or dialysis	55/1315 (4.2)	26/508 (5.1)	24/565 (4.2)	5/242 (2.1)
Vasopressors	278/1335 (20.8)	116/520 (22.3)	121/571 (21.2)	41/244 (16.8)
DAF invasive mechanical ventilation - first 14 days				
Mean (SD)	10.8 (5.4)	10.0 (5.9)	11.0 (5.3)	12.2 (4.3)
Unknown, n	7	2	2	3
DAF RRT- first 14 days				
Mean (SD)	12.2 (4.6)	11.8 (5.0)	12.3 (4.5)	13.1 (3.4)
Unknown, n	18	11	5	2
DAF Vasopressors - first 14 days				
Mean (SD)	11.3 (5.1)	10.7 (5.5)	11.3 (5.0)	12.4 (3.9)
Unknown, n	6	2	2	2
Hospital length of stay*				
Median (IQR)	9.0 (5.0, 19.0)	13.0 (7.0, 25.0)	8.0 (5.0, 15.0)	9.0 (5.0, 15.0)
Range	(2.0, 135.0)	(2.0, 135.0)	(2.0, 77.0)	(2.0, 66.0)

* Among those who discharged alive.

Figure 1. Definition of waves 1, 2 and 3 and number of patients enrolled in each wave by province.

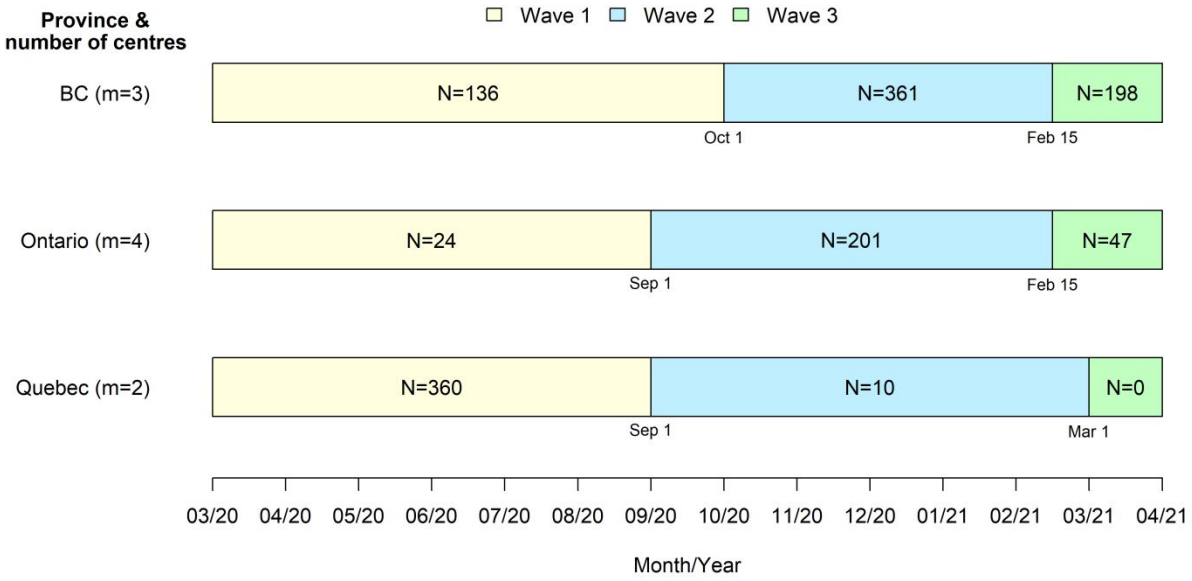
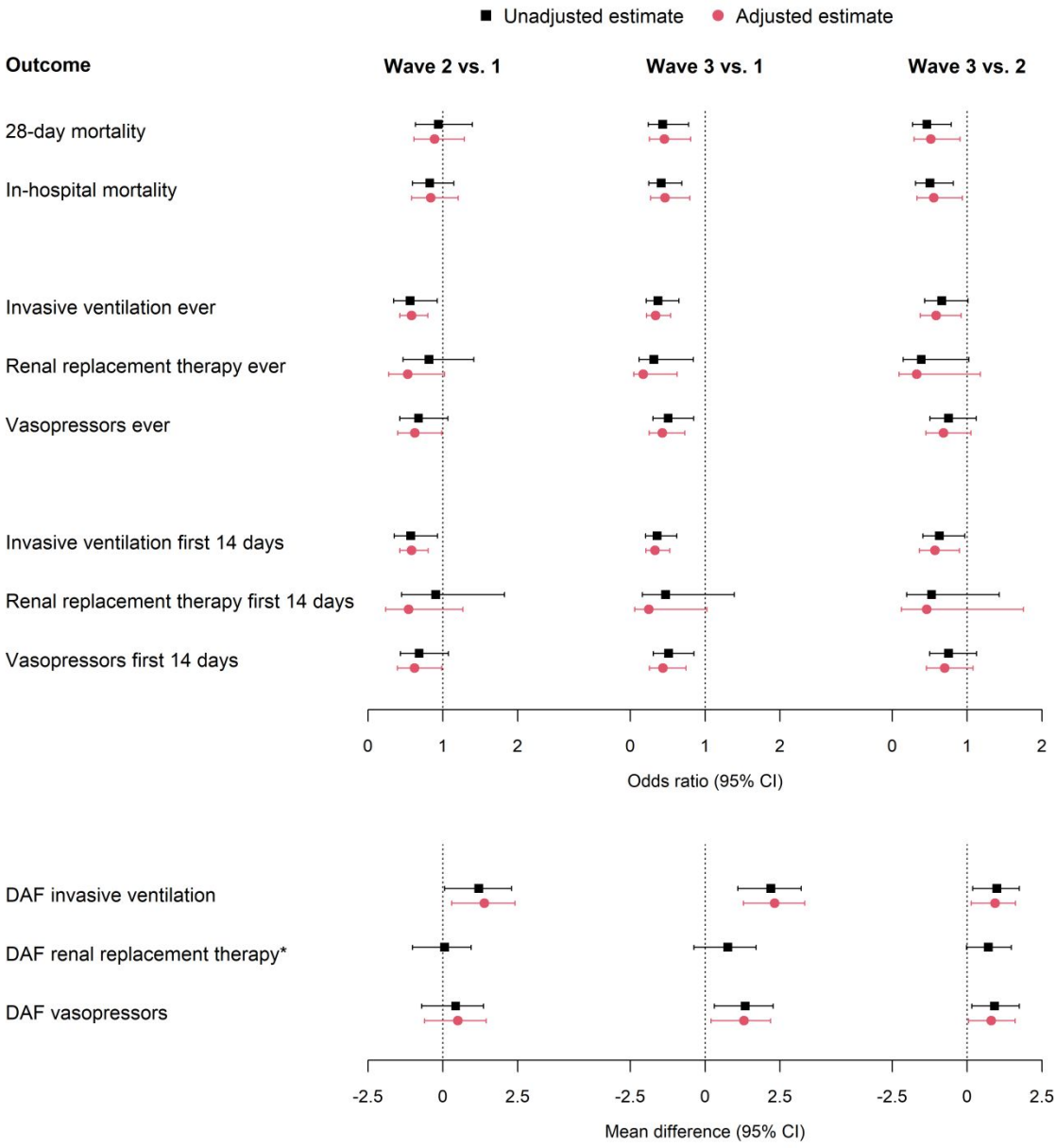


Figure 2. Comparison of outcomes between waves by regression analysis



* Adjusted regression analysis was not feasible numerically as too few patients used RRT during the first 14 days.

ACKNOWLEDGEMENTS

We thank the patients and families who participated in the ARBs CORONA I study which has increased our understanding of COVID-19. We also thank the many dedicated clinicians (doctors, nurses, therapists and others) who cared for these patients and comforted their families. We also thank the investigators in the ARBs CORONA I study for their ongoing support and tireless collaboration (Appendix S2).

Authors' Contributions

TL performed the analysis, drafted the manuscript and contributed to the CIHR grant that led to this manuscript. MPC, DCV, TCL, KCT, BWW, DS, JHB, KRW, FL, RF, DM, JS, DMP, JCM, KDB and SM contributed to the manuscript and to the CIHR grant that led to this manuscript. GH, AM, NF, PKM, GH, KD and GR contributed to the manuscript. JAR wrote the CIHR grant that led to this manuscript, the first draft and the final drafts of this manuscript.

Competing Interests Statement

Dr. Russell reports patents owned by the University of British Columbia (UBC) that are related to the use of PCSK9 inhibitor(s) in sepsis, and related to the use of vasopressin in septic shock and a patent owned by Ferring for use of selepressin in septic shock. Dr. Russell is an inventor on these patents. Dr. Russell was a founder, Director and shareholder in Cyon Therapeutics Inc. and is a shareholder in Molecular You Corp.

Dr. Russell reports receiving consulting fees in the last 3 years from:

1. Asahi Kesai Pharmaceuticals of America (AKPA)(was developing recombinant thrombomodulin in sepsis).
2. SIB Therapeutics LLC (developing a sepsis drug).
3. Ferring Pharmaceuticals (manufactures vasopressin and developing selepressin).

Dr. Russell is no longer actively consulting for the following:

4. La Jolla Pharmaceuticals (developing angiotensin II; Dr. Russell chaired the DSMB of a trial of angiotensin II from 2015 - 2017).
5. PAR Pharma (sells prepared bags of vasopressin).

Dr. Russell reports having received an investigator-initiated grant from Grifols (entitled "Is HBP a mechanism of albumin's efficacy in human septic shock?") that was provided to and administered by UBC.

All other authors state that they have no competing interests.

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Supplement

Appendix S1

We enrolled 2088 patients in ARBs CORONA I. The following patients were excluded from the current analysis.

- Acute COVID-19 readmissions (n=37)
- Emergency Room admissions without hospitalization (n=125)
- Patients admitted to hospital but not due to acute COVID-19 (n=220)
- Patients with unknown discharge outcome or currently still hospitalized (n=19)
- Patients from the Alberta site (n=350)

Alberta site was different from the other participating sites in that it only enrolled patients who were admitted to ICU. Because the percentage of data from Alberta in ARBs CORONA I varied across waves (13%, 28% and 17% in waves 1, 2 and 3 respectively), the inclusion of Alberta site would thus confound and skew the results (for example, with the inclusion of Alberta data, ICU admission rate became 47%, 55% and 44% in waves 1, 2 and 3 respectively).

Appendix S2

British Columbia:

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Province of Quebec (PQ):

CHUS, Sherbrooke, PQ, Can.: Dr. Francois Lamontagne. McGill University Health Centre, Montreal, PQ, Can.: Dr. Matthew P. Cheng, Dr. Todd C. Lee.

Ontario:

Sunnybrook Hospital, Toronto, Ont. Can.: Dr. Robert Fowler. Mount Sinai Hospital, Toronto, Ont. Can.: Dr. Allison McGeer. St Michael's Hospital, Toronto, Ont., Can.: Drs. John Marshall, Art Slutsky. Kingston General Hospital, Kingston, Ont., Can.: Drs. David Maslove, Santiago Perez Patrigeon. University of Ottawa, Ottawa, Ont., Can.: Dr. Kevin Burns.

Manitoba:

Winnipeg Health Sciences Centre, Winnipeg, Man., Can.: Dr. Anand Kumar.

Alberta:

Foothills Hospital, Calgary, Alberta, Can.: Dr. Brent Winston.

University of Alberta, Edmonton, Alta., Can.: Dr. Oleksa Rewa.

USA:

University of Pennsylvania, Philadelphia, Pa., USA: Dr. Michael Harhay.

The following persons and institutions participated in the ARBs CORONA I Study: **Steering Committee** – J.A. Russell (chair), Genevieve Rocheleau (former project manager), Puneet Mann (project manager), D. Sweet, G. Haljan, M. Cheng, D. C. Vinh, T. Lee, F. Lamontagne, B. Winston, O. Rewa, J. Marshall, A. McGeer, R. Fowler, David Maslove, Santiago Perez Patrigeon. **Management Committee** - J.A. Russell (chair), Genevieve Rocheleau (project manager), Puneet Mann (project manager), Karen Tran, Joel Singer. **Data Management** – J. Singer, T. Lee.

CLINICAL CENTERS AND ARBS CORONA I INVESTIGATORS:

Canada. British Columbia: *St. Paul's Hospital* (Coordinating Centre) - J.A. Russell, K.R. Walley, J. Boyd, T. Lee, J. Singer. *Vancouver General Hospital* - D. Sweet, K. Tran. *Royal Columbian Hospital* – S. Reynolds. *Surrey Memorial Hospital* - G. Haljan. **Quebec***: McGill University Centre Hospital* – M.P. Cheng, D.C. Vinh, TC Lee. *Sherbrooke* – F. Lamontagne. **Alberta:** *Calgary General Hospital* – B. Winston, *University of Alberta* - O. Rewa. **Ontario**: *St. Michael's Hospital* – J. Marshall, A. Slutsky. *Mount Sinai Hospital* – A. McGeer, V. Sivanantham. *Sunnybrook and Women's College Health Science Centre* – R. Fowler. *Kingston General Hospital* - David Maslove, Santiago Perez Patrigeon.

Table E1 – Mortality in patients hospitalized with acute COVID-19 in unadjusted and adjusted analyses.

	28-day mortality				In-hospital death			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis	
Variable	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**
Wave								
2 vs 1	0.94 (0.63, 1.39)	0.750	0.89 (0.61, 1.29)	0.528	0.82 (0.59, 1.14)	0.246	0.84 (0.58, 1.20)	0.333
3 vs 1	0.43 (0.24, 0.78)	0.005	0.46 (0.26, 0.81)	0.007	0.41 (0.25, 0.69)	<0.001	0.46 (0.27, 0.80)	0.005
3 vs 2	0.46 (0.27, 0.79)	0.004	0.52 (0.29, 0.91)	0.022	0.50 (0.31, 0.81)	0.005	0.56 (0.33, 0.94)	0.028
Male			1.06 (0.74, 1.52)	0.733			1.29 (0.92, 1.82)	0.139
Age (per 10 years increase)			2.23 (1.91, 2.61)	<0.001			1.99 (1.73, 2.30)	<0.001
SBP (per 10mm Hg increase)			0.93 (0.86, 1.00)	0.058			0.93 (0.87, 1.00)	0.051
Chronic kidney disease			0.94 (0.56, 1.59)	0.823			0.88 (0.53, 1.45)	0.609
Chronic cardiac disease			0.92 (0.63, 1.33)	0.642			0.97 (0.68, 1.39)	0.882
Diabetes			1.57 (1.10, 2.25)	0.013			1.43 (1.02, 2.00)	0.037
Hypertension			0.85 (0.58, 1.25)	0.403			0.93 (0.65, 1.33)	0.683
Heart rate (per 10 beats/minute increase)			1.18 (1.08, 1.29)	<0.001			1.11 (1.02, 1.21)	0.014
Creatinine (per log µmol/L increase)			1.86 (1.25, 2.75)	0.002			1.91 (1.32, 2.76)	<0.001
Oxygen saturation - SaO2 (per 5 % increase)			0.79 (0.71, 0.88)	<0.001			0.80 (0.72, 0.89)	<0.001

Odds ratio of **<1** implied **less likely** to experience the outcome.

Table E2. Use of mechanical ventilation, renal replacement therapy (RRT) and vasopressors in patients hospitalized with acute COVID-19 in unadjusted and adjusted analyses.

	Mechanical ventilation - while hospitalized				RRT - while hospitalized				Use of vasopressors - while hospitalized			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis	
Variable	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Diff (95% CI)**	**P**	**Diff (95% CI)**	**P**
Wave												
2 vs 1	0.56 (0.34, 0.93)	0.023	0.58 (0.42, 0.80)	<0.001	0.81 (0.47, 1.41)	0.463	0.53 (0.28, 1.02)	0.058	0.67 (0.43, 1.07)	0.092	0.63 (0.40, 0.98)	0.042
3 vs 1	0.37 (0.21, 0.65)	<0.001	0.34 (0.22, 0.54)	<0.001	0.32 (0.12, 0.84)	0.022	0.17 (0.05, 0.63)	0.008	0.51 (0.30, 0.85)	0.009	0.43 (0.25, 0.73)	0.002
3 vs 2	0.66 (0.43, 1.01)	0.056	0.59 (0.38, 0.92)	0.021	0.39 (0.15, 1.03)	0.056	0.33 (0.09, 1.18)	0.087	0.75 (0.51, 1.12)	0.165	0.69 (0.45, 1.05)	0.084
Male			1.44 (1.05, 1.96)	0.022			1.11 (0.57, 2.17)	0.764			1.61 (1.18, 2.21)	0.003
Age (per 10 years increase)			0.83 (0.75, 0.92)	<0.001			0.73 (0.57, 0.92)	0.008			0.91 (0.82, 1.01)	0.071
SBP (per 10mm Hg increase)			1.01 (0.94, 1.07)	0.855			1.14 (1.01, 1.30)	0.038			0.94 (0.88, 1.00)	0.063
Chronic kidney disease			0.55 (0.31, 0.97)	0.039			0.41 (0.16, 1.09)	0.073			0.49 (0.28, 0.87)	0.014
Chronic cardiac disease			0.86 (0.60, 1.24)	0.425			1.82 (0.91, 3.65)	0.091			0.97 (0.67, 1.39)	0.858
Diabetes			1.49 (1.09, 2.04)	0.013			1.23 (0.65, 2.33)	0.533			1.31 (0.96, 1.80)	0.091
Hypertension			1.20 (0.86, 1.69)	0.290			2.69 (1.15, 6.27)	0.022			1.14 (0.81, 1.59)	0.460
Heart rate (per 10 beats/minute increase)			1.05 (0.98, 1.13)	0.174			1.01 (0.87, 1.18)	0.879			1.08 (1.00, 1.16)	0.041
Creatinine (per log µmol/L increase)			1.52 (1.07, 2.16)	0.019			8.97 (4.88, 16.49)	<0.001			1.71 (1.21, 2.43)	0.003
Oxygen saturation - SaO2 (per 5 % increase)			0.75 (0.68, 0.82)	<0.001			0.88 (0.73, 1.04)	0.141			0.75 (0.68, 0.83)	<0.001

Odds ratio of **<1** implied **less likely** to experience the outcome.

Table E3. Use of mechanical ventilation, renal replacement therapy (RRT) and vasopressors over 14 days in patients hospitalized with acute COVID-19 in unadjusted and adjusted analyses.

	Mechanical ventilation - first 14 days				RRT- first 14 days				Use of vasopressors - first 14 days			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis	
Variable	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Diff (95% CI)**	**P**	**Diff (95% CI)**	**P**
Wave												
2 vs 1	0.57 (0.35, 0.93)	0.024	0.58 (0.42, 0.80)	<0.001	0.90 (0.45, 1.82)	0.778	0.54 (0.23, 1.27)	0.157	0.68 (0.43, 1.07)	0.097	0.62 (0.39, 0.98)	0.042
3 vs 1	0.36 (0.21, 0.62)	<0.001	0.33 (0.21, 0.53)	<0.001	0.48 (0.16, 1.39)	0.175	0.25 (0.06, 1.02)	0.054	0.51 (0.31, 0.85)	0.010	0.44 (0.26, 0.74)	0.002
3 vs 2	0.63 (0.41, 0.97)	0.036	0.57 (0.36, 0.90)	0.016	0.53 (0.19, 1.43)	0.207	0.46 (0.12, 1.75)	0.255	0.75 (0.50, 1.13)	0.166	0.70 (0.46, 1.08)	0.108
Male			1.42 (1.04, 1.94)	0.028			0.97 (0.46, 2.02)	0.927			1.59 (1.16, 2.17)	0.004
Age (per 10 years increase)			0.83 (0.75, 0.93)	<0.001			0.66 (0.51, 0.86)	0.002			0.92 (0.83, 1.02)	0.109
SBP (per 10mm Hg increase)			1.00 (0.94, 1.07)	0.897			1.14 (0.99, 1.31)	0.072			0.94 (0.88, 1.00)	0.051
Chronic kidney disease			0.52 (0.29, 0.93)	0.028			0.58 (0.21, 1.65)	0.308			0.47 (0.26, 0.84)	0.011
Chronic cardiac disease			0.84 (0.58, 1.21)	0.348			2.22 (1.03, 4.80)	0.042			0.95 (0.66, 1.37)	0.785
Diabetes			1.48 (1.08, 2.03)	0.015			1.00 (0.49, 2.06)	0.992			1.32 (0.96, 1.81)	0.090
Hypertension			1.18 (0.84, 1.66)	0.340			3.36 (1.25, 8.98)	0.016			1.09 (0.77, 1.53)	0.626
Heart rate (per 10 beats/minute increase)			1.05 (0.98, 1.14)	0.160			0.98 (0.83, 1.16)	0.823			1.08 (1.01, 1.17)	0.034
Creatinine (per log µmol/L increase)			1.57 (1.11, 2.24)	0.011			7.54 (4.00, 14.19)	<0.001			1.77 (1.25, 2.52)	0.001
Oxygen saturation - SaO2 (per 5 % increase)			0.74 (0.68, 0.82)	<0.001			0.88 (0.72, 1.08)	0.221			0.75 (0.68, 0.82)	<0.001

Odds ratio of **<1** implied **less likely** to experience the outcome.

Table E4. Days alive and free of organ support by zero-one inflated beta regression in patients hospitalized with acute COVID-19.

	DAF mechanical ventilation - first 14 days				DAF RRT - first 14 days				DAF vasopressors - first 14 days			
	Unadjusted analysis		Adjusted analysis		Unadjusted analysis		Adjusted analysis*		Unadjusted analysis		Adjusted analysis	
Variable	**Mean diff (95% CI)**	**P**	**Mean diff (95% CI)**	**P**	**Mean diff (95% CI)**	**P**	**Mean diff (95% CI)**	**P**	**Mean diff (95% CI)**	**P**	**Mean diff (95% CI)**	**P**
Wave												
2 vs 1	1.20 (0.06, 2.29)	<0.001	1.39 (0.29, 2.41)	<0.001	0.06 (-1.01, 0.94)	0.910	-		0.43 (-0.71, 1.35)	0.177	0.49 (-0.61, 1.44)	0.111
3 vs 1	2.20 (1.09, 3.21)	<0.001	2.32 (1.28, 3.33)	<0.001	0.76 (-0.37, 1.70)	0.141	-		1.34 (0.31, 2.27)	<0.001	1.30 (0.20, 2.19)	<0.001
3 vs 2	1.00 (0.19, 1.74)	0.013	0.94 (0.14, 1.62)	0.017	0.71 (-0.02, 1.47)	0.063	-		0.91 (0.16, 1.74)	0.014	0.81 (0.05, 1.60)	0.026
Male			-0.38 (-0.93, 0.22)	0.185			-				-0.25 (-0.79, 0.31)	0.365
Age (per 10 years increase)			-0.57 (-0.80, -0.35)	<0.001			-				-0.73 (-0.95, -0.54)	<0.001
SBP (per 10mm Hg increase)			0.12 (-0.01, 0.24)	0.066			-				0.12 (-0.00, 0.24)	0.043
Chronic kidney disease			0.30 (-0.78, 1.16)	0.469			-				0.22 (-0.76, 1.11)	0.552
Chronic cardiac disease			0.13 (-0.62, 0.81)	0.689			-				0.02 (-0.67, 0.64)	0.944
Diabetes			-0.89 (-1.56, -0.23)	0.004			-				-0.66 (-1.30, -0.08)	0.023
Hypertension			0.27 (-0.39, 0.95)	0.344			-				0.33 (-0.27, 0.94)	0.213
Heart rate (per 10 beats/minute increase)			-0.28 (-0.45, -0.13)	<0.001			-				-0.28 (-0.44, -0.13)	<0.001
Creatinine (per log µmol/L increase)			-0.98 (-1.60, -0.40)	0.001			-				-0.96 (-1.53, -0.35)	0.001
Oxygen saturation - SaO2 (per 5 % increase)			0.55 (0.39, 0.73)	<0.001			-				0.45 (0.30, 0.60)	0.001

* Adjusted regression analysis was not feasible numerically as too few patients used RRT during the first 14 days and so most DAF values were 0 or 14.

Estimated difference of **>0** implied **more** days alive free of organ support (i.e., better outcome).