Association between angiotensin blockade and COVID-19 severity in Hong Kong: a territory-wide study

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Specific author contributions: Ka Shing Cheung was involved with study concept and design; analysis and interpretation of data, drafting of manuscript, and approval of the final version of the manuscript. IFN Hung and Wai K Leung were involved with the study concept and design, critical revision of the manuscript for important intellectual content, study supervision, and approval of the final version of the manuscript.

Financial support: Nil

Potential competing interests: Nil

Word count: 501

Number of tables: 1

Number of figures: 0

We read this commentary[1] with interest on the role of angiotensin converting enzymes inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are in COVID-19 incidence and severity. Recent observational studies did not show increased risk of disease severity with ACEI/ARB use,[2,3] and an observational study[4] even reported a lower mortality risk with ACEIs (adjusted odds ratio [aOR]:0.33). However, all these studies did not adjust for laboratory parameters, which may confound the observed association.

We conducted a territory-wide retrospective cohort study by retrieving data from territory-wide electronic healthcare database ing Hong Kong Hospital Authority. We identified all patients aged ≥18 years diagnosed with COVID-19 between 1 January 2020 and 27 April 2020. The primary outcome was severe disease including (1)severe pneumonia, (2)critical complication (respiratory failure, septic shock and/or multiple organ dysfunction), (3)ventilatory support (invasive or non-invasive), (4)intensive care unit admission or (5)death. Drug exposure including ACEIs and ARBs was defined as ever exposure within 5 years before admission. Multivariable logistic regression model was performed by adjusting for other covariates including age, sex, comorbidities (diabetes mellitus, hypertension, ischemic heart disease, stroke and atrial fibrillation), other medications (aspirin, statins, proton pump inhibitors), and laboratory parameters (leukocyte, platelet, C-reactive protein [CRP], creatinine, sodium, potassium, alkaline phosphatase, alanine aminotransferase, albumin, globulin, and lactate dehydrogenase [LDH]).

Of 734 COVID-19 patients, 73 (9.9%) had severe disease as defined. There were 13 and 18 ACEI and ARB users. ACEI use was associated with a lower risk of severe disease (aOR:0.14, 95 % CI:0.02–0.87), but there was no significant association between ARB use and severe disease (aOR:1.86, 95% CI:0.31–9.97). Other independent risk factors for severe disease were leukocyte count >$11x10^9$/L (aOR:5.98, 95% CI:1.55–2.19), C-reactive protein >1mg/dL (aOR:3.42, 95% CI,:1.76–6.68), and lactate dehydrogenase >280U/L (aOR:5.91, 95% CI:2.89–12.13).

Our findings corroborate the results of Mehra et al,[4] which showed a lower mortality with ACEI use. While ACEI/ARBs should not be discontinued in COVID-19 patients, further multi-center studies including patients of different ethnicities are needed to clarify the potential beneficial effects of ACEIs.

References

Table 1. Baseline characteristics of the whole cohort and according to ACEI use

	Whole cohort (n=734)	ACEI users (n=13)	Non-ACEI users (n=721)	p-value
Age > 65 years (n, %)	70 (9.5%)	7 (53.8%)	63 (8.7%)	< 0.001
Male (n, %)	388 (52.9%)	9 (69.2%)	379 (52.6%)	0.273
Diabetes mellitus* (n, %)	25 (3.4%)	5 (38.5%)	20 (2.8%)	< 0.001
Hypertension and cardiovascular diseases* (n, %)	71 (9.7%)	10 (76.9%)	61 (8.5%)	< 0.001
Aspirin (n, %)	19 (2.6%)	5 (38.5%)	14 (1.9%)	< 0.001
Statins (n, %)	36 (4.9%)	7 (53.8%)	29 (4.0%)	< 0.001
PPIs (n, %)	48 (6.5%)	4 (30.8%)	44 (6.1%)	0.007
ARBs (n, %)	18 (2.5%)	4 (30.8%)	14 (1.9%)	< 0.001
Leucocyte count > 11 ($x10^9$/L) (n, %)	19 (2.6%)	3 (23.1%)	16 (2.2%)	0.004
Platelet count >150 (x 10^9/L) (n, %)	70 (9.5%)	2 (15.4%)	68 (9.4%)	0.356
CRP >1mg/dL (n, %)	181 (24.7%)	8 (61.5%)	173 (24.0%)	0.005
LDH >280U/L (n, %)	96 (13.1%)	9 (69.2%)	87 (12.1%)	< 0.001
Albumin <34 (g/L) (n, %)	47 (6.4%)	2 (15.4%)	45 (6.2%)	0.200
Globulin >35 (g/L) (n, %)	255 (34.7%)	8 (61.5%)	247 (34.4%)	0.073
ALP > 110 (U/L) (n, %)	23 (3.1%)	3 (23.1%)	20 (2.8%)	0.006
ALT > 40 (U/L) (n, %)	147 (20.0%)	4 (30.8%)	133 (18.4%)	0.278
Creatinine (umol/L)	73 (62–86)	94 (76–100)	73 (62–86)	0.004
Sodium (mmol/L)	140 (138–141)	136 (134–139)	140 (138–141)	0.001
Potassium (mmol/L)	3.9 (3.7–4.2)	4.5 (3.9–4.5)	3.9 (3.7–4.2)	0.019

*Diabetes mellitus was identified by the ICD-9 code and the use of anti-diabetics medications (including insulin, metformin, sulphonylureas, glitazones, dipeptydyl peptidase-4 inhibitors, sodium glucose co-transporter inhibitors, glucaogon-like peptide-1 agonists).

Hypertension was identified by the ICD-9 code and the use of other anti-hypertensive agents (including alpha blockers, beta blockers, calcium channel blockers, diuretics, hydralazine and methyldopa). Cardiovascular diseases included ischemic heart disease, atrial fibrillation, and stroke.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; PPIs, proton pump inhibitors; ARBs, angiotensin receptor blockers; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; ALT, alanine aminotransferase