

# Role of Ecologic ACE I/D Polymorphism Data Towards Prediction of COVID-19 Epidemiology

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## Research Article

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# Abstract

COVID-19 displays marked variability in the clinical course as well as regional epidemiology. Abnormalities in RAAS system especially stemming from genetic variability in ACE and ACE2 expression (including ACE I/D polymorphism) have been proposed to explain underlying pathogenesis and variability in SARS-CoV-2 infection. In a meta-regression data set of 30 countries, we found significant associations of ACE I/D ratio and COVID-19 prevalence, deaths and recovery rate but not when adjusted for possible confounders. This ecological study suggests potential of ACE I/D data as predictive biomarker COVID-19 risk and severity in a population specific manner, subject to validation in large genetic epidemiological and functional studies.

## Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a global pandemic with concerning figures for total cases (>26.5 millions), deaths (>0.9 million), and serious/critical (>58 thousands) (<https://www.worldometers.info/coronavirus/> as of September 01, 2020) with serious global effects on healthcare, economy and life style. COVID-19 epidemiological data displays regional tropism where Europe seems to have suffered from a higher incidence and death rates than China and other East Asian countries [1]. In addition, significant heterogeneity in clinical course of COVID-19 disease has also been observed ranging from asymptomatic carriers and mild flu-like symptoms to severe respiratory distress with increased risk of multi-organ failure and subsequent death [2]. This data suggests that viral and host genetic modulators in addition to the classical systemic risk factors and socio-behavioral differences could differentially facilitate COVID-19 infection and outcome. As a result, global efforts such as COVID-19 host genetics initiative (<https://www.covid19hg.org/>), and vaccine development are in progress with special focus on host genetic determinants to better understand its pathophysiology and ways to combat it.

The renin-angiotensin-aldosterone system (RAAS) is involved in regulation of blood pressure and extracellular volume and is regulated by reciprocal interaction of two key angiotensin converting enzyme (ACE) analogs *i.e.* ACE1 (converts angiotension I to angiotension II) and ACE2 (metabolizes angiotension II) [3]. COVID-19 represents a condition where the delicate RAAS hemostatic balance is disturbed resulting in vasoconstrictive, pro-inflammatory, pro-fibrotic and pro-apoptotic effects of unopposed angiotension II which may explain acute lung injury and other pathologies observed as a result of SARS-CoV-2 infection [reviewed in [4]]. Several observations support the evident association between RAAS imbalance and COVID-19 disease including; (1) the ACE2 is the main cellular receptor for the SARS-CoV-2 and this interaction results in exhaustion and reduced expression of ACE2 [5,6], (2) animal models of SARS-CoV and disrupted ACE2 demonstrating ACE2 downregulation mediated severe lung and cardiovascular injuries [7,8], (3) recombinant ACE2 offers protection against lung injury in mice and SARS-CoV-2 infection in human organoids [9], and functional genetic variations in ACE2 and its analog ACE, especially the 287bp insertion/deletion (Ins/Del) polymorphism (rs4646994), may reflect variability in ACE and ACE2 levels in general population (e.g. D allele of ACE I/D polymorphism mediates higher ACE

expression) [10] and have been associated with acute respiratory distress syndrome (ARDS), hypertension, obesity/metabolic syndrome, cardiovascular risk, and abnormal blood clotting tendency; all of which represent clinical hallmarks of severe COVID-19 disease [reviewed in [4,11]]. In contrast, no clinical advantage was observed in COVID-19 patients treated with ACE inhibitors or angiotension receptor blockers (mediating high ACE2 and low angiotension II) [12], suggesting that further efforts are needed to fully comprehend the role of RAAS in COVID-19. Therefore, the present study employed an ecological meta-regression design to evaluate the ACE1 I/D genotypic data in relation to the observed differences in COVID-19 epidemiological parameters in different ethnicities especially in European and Asian countries.

The ACE I/D polymorphism frequency data for each country was retrieved from previously published studies following the Systematic Studies and Meta-Analysis Reporting System (PRISMA) guidelines. The main inclusion criteria for studies was reporting of ACE I/D variant genotypic data in healthy population. I and D allele frequencies for ACE polymorphism in healthy controls of each study were retrieved and used for estimations of cumulative I/D ratio for each country.

COVID-19 data pertaining to prevalence, serious or critical patients, deaths and recovery rate for each country (per 10<sup>6</sup> population for all variables) were extracted as available from [www.worldometers.info/coronavirus/countries](http://www.worldometers.info/coronavirus/countries) website. Since different indicators of economy, health services and prevalence of relevant chronic health conditions may modulate country specific COVID-19 data, different confounding variables including COVID-19 diagnostic tests performed (number per 10<sup>6</sup> inhabitants), GDP/capita (PPP), current health expenditure/capita (PPP), healthy life expectancy at birth, DALY diabetes mellitus, DALY hypertensive heart disease and DALY respiratory infections as retrieved from the World Health Organization website [www.who.int/countries/en/](http://www.who.int/countries/en/).

Comprehensive Meta-Analysis version 3 was used to generate the forest plot where points of estimation (I/D ratios) were calculated by dividing frequency of I-allele with that of D-allele among all the studies of each country along with standard error of each ratio (for countries having more than one study). Normal distribution of variables was checked using Shapiro-Wilk test and non-normally distributed variables were log-transformed using log<sub>10</sub> function. The estimated value of association, p-value and meta-analytic scatterplots were generated using Metafor R package. Multivariable linear regression models were constructed where COVID-19 epidemiological measures (prevalence, serious or critical patients, deaths and recovery rate) were taken as outcome variables while considering ACE I/D ratio and above mentioned confounding variables as explanatory factors. All the statistics were performed on R version 4.0.2. A two tailed *p*-value less than 0.05 was considered as significant.

We first performed a crude overall analysis including all countries (n=47), where the univariate regression analysis suggested no significant associations between ACE I/D ratio and COVID-19 epidemiological parameters (**Online Resource Supplementary Table S1**). Similar trends with no significant associations were observed in multivariate regression analysis after adjusting the data for possible confounders (**Online Resource Supplementary Table S2**). However, when data was subdivided into two major groups

(Asian and European countries), it was observed that a decrease in ACE I/D ratio was significantly associated with an increase in COVID-19 mediated deaths/million only in Asians (point estimate = -3.21,  $p = 0.01$ ). However, univariate and multivariate regression results showed non-significant associations of the COVID-19 log-transformed prevalence, deaths, serious or critical and recovery rate with ACE I/D polymorphism in the Europeans (**Online Resource Supplementary Tables S1 and S2**).

We further performed quality control of our cumulative dataset by including only countries (a) with more than one studies for ACE I/D ratio, and (b) with ACE I/D polymorphism frequencies conforming to HWE, thus, resulting in a total of 30 countries in this refined dataset. The meta-analysis results for cumulative ACE I/D ratio of included studies are presented in **Figure 1**. The overall point estimate was 0.625 (95% CI 0.60-0.65) with no apparent publication bias as shown in **Online Resource Supplementary Figure S1**. Asian countries displayed relatively higher ACE I/D allele frequency ratios (all  $\geq 0.85$  with an average of 1.01) compared to European countries (average ACE I/D ratio of 0.60).

Meta-regression results for this refined dataset indicated a significant association of ACE I/D ratio with the COVID-19 prevalence (point estimate = -0.059,  $p = 0.001$ ), deaths/million (point estimate = -0.039,  $p = 0.01$ ), and recovery rate (point estimate = -0.037,  $p = 0.02$ ) (**Figure 2**) but not with severity of the disease (point estimate = -0.030,  $p = 0.18$ ). However, none of these associations persisted when data was adjusted for possible confounding variables in multivariate regression analyses (**Table 1**).

The COVID-19 related data and knowledge is rapidly evolving. Our meta-regression results indicate a possible correlation of ACE I/D polymorphism with COVID-19 prevalence, deaths and recovery rate. It means that the countries with lower ACE I/D ratios (i.e. high frequency of D allele) showed higher prevalence and deaths due to COVID-19 infection especially in the context of European versus Asian countries. However, this correlation could not be established when adjusted for possible confounders, although multivariate regression analysis was not performed in Asian sub-group due to low sample size. Overall, the ACE I/D variant presents specific genotypic frequency in Caucasian and Asian populations. Most European (especially North European) and East Asian (as some South European) countries demonstration high and low distribution of the D/D genotype, respectively. These population specific genotypic distributions may have resulted from the long-term human migration patterns eastward and westward across the vast Eurasian continent. The present findings based on ACE I/D data offer explanation, at least partially, for the observed differences in COVID-19 prevalence and mortality between the East Asian and European countries. However, it is noteworthy that differential socio-economical, healthcare and societal/behavioral factors among different ethnicities may significantly modulate these apparent associations between ACE I/D polymorphism and COVID-19 epidemiological measures.

Previously various studies reported association of ACE I/D polymorphism either with COVID-19 prevalence [13-16], or mortality (affected by COVID-19 testing intensity) or deaths/million (independent of COVID-19 testing intensity) [15,16,11,17] or with recovery rate [18]. The variability in the results of the previous meta-regression reports may have originated from differences in; (1) measure of ACE I/D polymorphism and COVID-19 parameters used and source/method of data retrieval, (2) relative

distribution of ethnicities/countries included, and (3) the data analysis approaches (*e.g.* adjustment for possible confounders and sensitivity analyses).

Functionally, COVID-19 patients with low I/D ratios may have an unopposed abundance of angiotensin II protein in their blood resulting from more D-allele mediated excessive ACE expression on one hand and downregulation of ACE2 receptor because of SARS-Cov-2 engagement on the other, thus triggering downstream deleterious effects most notably of which is acute lung injury [4]. This RAAS imbalance due to ACE abundance may also explain why elders are more susceptible to COVID-19 infection [19]. In addition, preliminary evidence was also provided by a recent study reporting hypertension dependent association of ACE DD genotype and severe COVID-19 using a sample set of 204 Spanish SARS-CoV-2 infected patients [20]. Thus, excessive serum ACE levels and/or presence of ACE Del/Del genotype may still predict a more severe clinical course in SARS-CoV-2 infection.

Nevertheless, the present study has some limitations. Due to the ecologic study design, the results of the present study should be considered as a mean to develop hypothesis rather than definitive casual associations and should not be subjected to individual level interpretations. In addition, several additional confounders of genetic, epigenetic, social/behavioral and environmental in origin may contribute towards observed COVID-19 epidemiology data and thus should be accounted for in the future studies.

In conclusion, the results of present study should be interpreted with caution and further studies following genetic epidemiological, cohort and experimental study designs with functional validations and based on samples from COVID-19 patients should be conducted to delineate definitive causal relationship between the genetic variants in RAAS, especially ACE I/D polymorphism, and outcome of the COVID-19.

## **Declarations**

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### **Conflicts of interest/Competing interests**

The authors have no relevant financial or non-financial interests to disclose.

### **Availability of data and material**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Code availability**

Not applicable.

## Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ali Amar, Abdul Rafay and Madiha Shakoor. The first draft of the manuscript was written by Ali Amar and Shagufta Khaliq while manuscript review and editing were performed by Ali Amar, Aiysha Abid and Shagufta Khaliq. All authors read and approved the final manuscript.

## Ethics approval

Not applicable.

## Consent to participate

Not applicable.

## Consent for publication

Not applicable.

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## Tables

**Table 1: Multivariate meta-regression analysis for association of ACE I/D polymorphism and COVID-19 epidemiological parameters in refined dataset (n=30)**

Parameters	Confounders included	Confounders remained	Presence of the ACE I/D ratio
Covid-19 prevalence/10 <sup>6</sup> population	ACE I/D ratio, x1,x2,x3,x4,x5,x6 and x7	-	No
Covid-19 deaths/10 <sup>6</sup> population	ACE I/D ratio, x1,x2,x3,x4,x5,x6 and x7	-	No
Covid-19 serious or critical/10 <sup>6</sup> population	ACE I/D ratio, x1,x2,x3,x4,x5,x6 and x7	-	No
Covid-19 recovery rate/10 <sup>6</sup> population	ACE I/D ratio, x1,x2,x3,x4,x5,x6 and x7	-	No

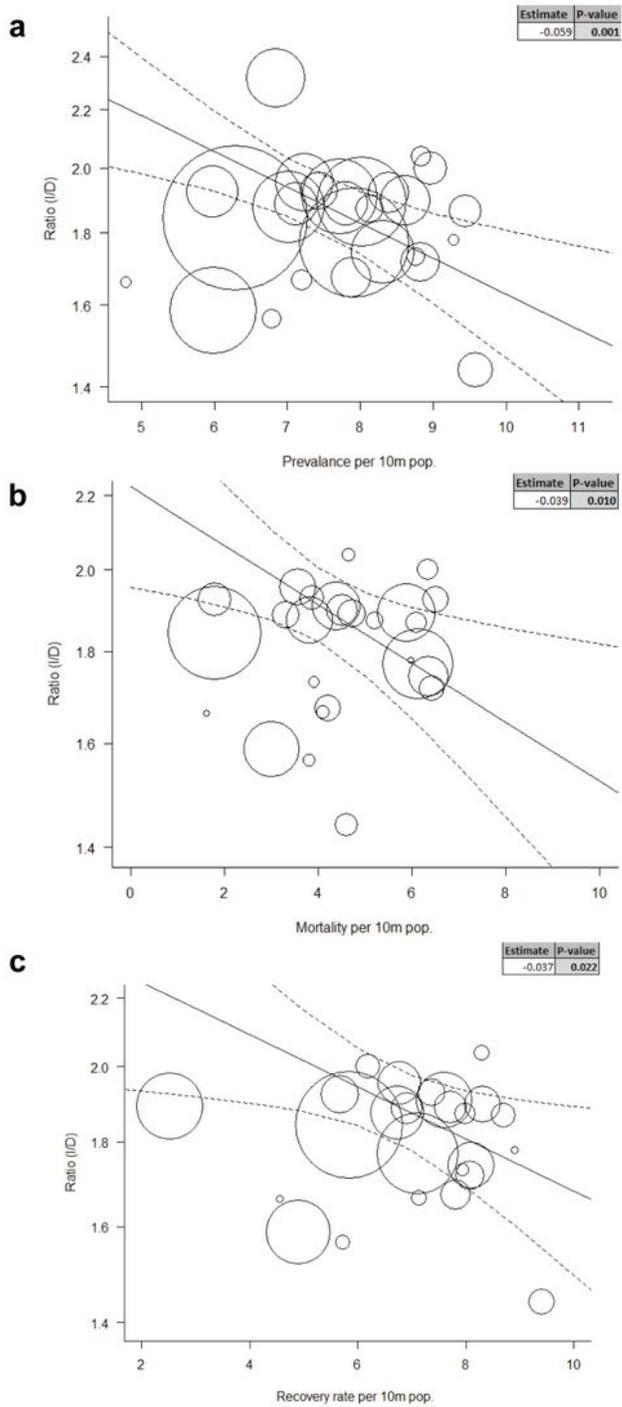
x1 = number of COVID-19 diagnostic tests performed per 10<sup>6</sup> population), x2 = GDP/capita 2017 (PPP), x3 = Current health expenditure/capita 2017 (PPP), x4 = Healthy life expectancy at birth 2016, both sexes (Years), x5 = DALY 2016 diabetes mellitus, x6 = DALY 2016 hypertensive heart disease, and x7 = DALY 2016 respiratory infections.

## Figures

Model	Study name	Statistics for each study							Point estimate and 95% CI					
		Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	-1.00	-0.50	0.00	0.50	1.00	
	Australia	0.612	0.027	0.001	0.559	0.666	22.431	0.000						+
	Austria	0.647	0.053	0.003	0.544	0.750	12.302	0.000						+
	Brazil	0.576	0.345	0.119	-0.099	1.251	1.671	0.095						+
	China	0.908	0.097	0.009	0.717	1.098	9.337	0.000						+
	Czech Republic	0.671	0.068	0.005	0.537	0.804	9.837	0.000						+
	Finland	0.511	0.187	0.035	0.144	0.877	2.733	0.006						+
	France	0.572	0.036	0.001	0.501	0.643	15.799	0.000						+
	Germany	0.636	0.091	0.008	0.459	0.814	7.020	0.000						+
	Greece	0.463	0.046	0.002	0.373	0.552	10.119	0.000						+
	Hong Kong	1.146	0.250	0.063	0.656	1.636	4.581	0.000						+
	India	0.841	0.067	0.005	0.709	0.973	12.466	0.000						+
	Iran	0.627	0.142	0.020	0.350	0.905	4.430	0.000						+
	Israel	0.549	0.220	0.048	0.118	0.980	2.495	0.013						+
	Italy	0.556	0.063	0.004	0.433	0.680	8.842	0.000						+
	Japan	0.981	0.097	0.009	0.792	1.171	10.155	0.000						+
	Kuwait	0.365	0.112	0.013	0.145	0.585	3.252	0.001						+
	Netherland	0.638	0.044	0.002	0.552	0.724	14.477	0.000						+
	Norway	0.657	0.105	0.011	0.451	0.863	6.250	0.000						+
	Pakistan	0.635	0.092	0.008	0.455	0.815	6.913	0.000						+
	Poland	0.629	0.055	0.003	0.521	0.737	11.429	0.000						+
	Russia	0.641	0.080	0.006	0.485	0.797	8.056	0.000						+
	Slovakia	0.655	0.077	0.006	0.505	0.806	8.531	0.000						+
	South Africa	0.712	0.193	0.037	0.335	1.090	3.698	0.000						+
	South Korea	0.850	0.130	0.017	0.595	1.104	6.552	0.000						+
	Spain	0.541	0.101	0.010	0.343	0.739	5.354	0.000						+
	Sweden	0.693	0.120	0.015	0.457	0.929	5.756	0.000						+
	Taiwan	1.180	0.203	0.041	0.782	1.578	5.817	0.000						+
	Turkey	0.515	0.097	0.009	0.324	0.705	5.291	0.000						+
	UK	0.655	0.096	0.009	0.467	0.842	6.832	0.000						+
	USA	0.625	0.122	0.015	0.387	0.863	5.141	0.000						+
Fixed		0.625	0.013	0.000	0.600	0.650	48.880	0.000						+
Random		0.650	0.024	0.001	0.604	0.697	27.448	0.000						+

**Figure 1**

Forest plot depicting pooled analysis of ACE I/D ratios in the refined dataset of 30 countries



**Figure 2**

Meta-regression of the ACE I/D ratios with COVID-19 (a) log-prevalence/106 population, (b) log-deaths/106 population, and (c) log-recovery rate/106 population

## Supplementary Files

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