Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Angiotensin converting enzyme genotypes and mortality from COVID-19: An ecological study

Ar K Aung[a,b,*], Tess Aitken[a], Bing M Teh[c], Christiaan Yu[d], Richard Ofori-Asenso[a,e], Ken L Chin[a,f], Danny Liew[a,b,**]

[a] School of Public Health and Preventive Medicine, Monash University, Level 4, 553St Kilda Road, Melbourne, VIC 3004, Australia
[b] Department of General Medicine, Alfred Health, 55 Commercial Road, Melbourne, VIC 3004, Australia
[c] Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia
[d] Allergy, Immunology and Respiratory Medicine Department, Alfred Health, Melbourne, Australia
[e] Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[f] Melbourne Medical School, University of Melbourne, Melbourne, Australia

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SUMMARY

Background: Angiotensin converting enzyme (ACE) genotypes are known to be associated with development of acute respiratory distress syndrome (ARDS) and resultant mortality. In the present study, we examined the association between distribution frequency of ACE genotypes and COVID-19 mortality.
Methods: We undertook an ecological study to examine the association between ACE genotypes and COVID-19 mortality across 25 countries to represent different geographical regions of the world. The population frequencies of ACE genotypes were drawn from previously published reports and data on COVID-19-related mortality were extracted from 'Worldometer'. Multivariable analyses were also undertaken adjusting for age (median age), sex (percentage of females) and the number of COVID-19 tests undertaken. Associations between genotypes deletion/deletion (DD) and insertion/insertion (II) prevalence and COVID-19-related mortality (per million people per day since the first diagnosed case) were evaluated.
Results: The frequency of II genotype is highest in east Asian countries and lower among the European and African countries. An inverse geographical distribution frequency was noted for DD genotype. Increasing II genotype frequency was significantly associated with decreased COVID-19 mortality rates (adjusted incident rate ratio [IRR] 0.3, 95% confidence interval [CI]: 0.002–0.7, $p = 0.03$). However, no association was found between DD genotype frequency and COVID-19 mortality rates (adjusted IRR 4.3, 95% CI: 0.5–41.2, $p = 0.2$).
Conclusions: Distribution frequency of ACE insertion/insertion (II) genotype may have a significant influence on COVID-19 mortality. This information has potential utility for resource planning at a systemic level, as well as for clinical management.

Introduction

The coronavirus disease 2019 (COVID-19), caused by SARS-CoV2 virus, has evolved rapidly into a pandemic, with total confirmed cases of nearly 9 million, and more than 460,000 deaths worldwide as of 22 June 2020.[1] The COVID-19 fatality rates vary greatly across countries, and have been attributed to multiple factors including availability of healthcare resources and mitigation strategies, including border closures, social distancing, mass screening, contact tracing and quarantine.[2,3]

The clinical presentation of COVID-19 ranges from mild symptoms to potentially fatal respiratory failure due to development of adult respiratory distress syndrome (ARDS). The renin-angiotensin-aldosterone system (RAAS) has been implicated in the pathogenesis of COVID-19.[4] Moreover, the role of angiotensin converting enzymes 1 and 2 (ACE and ACE2) in the development of ARDS is well established.[5] The coronavirus utilises membrane bound ACE2 receptors for entry into alveolar epithelial cells. This disrupts counter regulatory mechanisms between ACE and ACE2, leading to endothelial dysfunction and activation of severe maladaptive immune responses, the hallmark of ARDS.[5,6]

* Corresponding author at: Department of General Medicine, Alfred Health, 55 Commercial Road, Melbourne, VIC 3004, Australia.
** Corresponding author at: School of Public Health and Preventive Medicine, Monash University, Level 4, 553St Kilda Road, Melbourne, VIC 3004, Australia.
E-mail addresses: A.Aung@alfred.org.au (A.K. Aung), Danny.Liew@monash.edu (D. Liew).

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The ACE gene is known to consist of two variant alleles; insertion (I) and deletion (D) polymorphisms.[7] The allelic distribution of the ACE gene within a population follows the Hardy-Weinberg equilibrium, with three distinct genotypes: II, ID, and DD.[8] Diseases such as stroke and diabetic nephropathy have been shown to be associated with the DD genotype.[9,10] Additionally, previous studies on patients with sepsis (not due to coronavirus) demonstrated an association between DD genotype and development of ARDS resulting in higher mortality risk[11] On the other hand, the II genotype is associated with decreased mortality from ARDS.[12] The ACE genotype distributions vary across geographical regions, with frequency of DD genotype being lowest among east Asian populations and highest among Caucasian and African populations.[8]

Recent studies demonstrate that infection with COVID-19 may be associated with I/D polymorphisms, with increasing D allele frequency correlating to a reduction in prevalence but increase in mortality from COVID-19 infection.[13,14] Currently, it remains unclear whether the observed variations in COVID-19 mortality among countries can be explained by variations in ACE polymorphisms, specifically in relation to the frequency of the II and DD genotypes. Hence, we undertook an ecological study to examine the association between the distribution frequency of ACE genotypes and COVID-19 mortality in selected countries representing different geographical regions of the world.

Methods

Genotype frequency data

Data on the distribution of ACE genotypes were collected for 25 countries representing a diverse cross-section of geographical regions of the world (Table 1). The data were drawn from systematic reviews and meta analyses published in the past 15 years (since 2005) examining ACE genotypes and risk of cardiovascular, respiratory, diabetes, renal and stroke diseases.[8,9,15–22] Published studies in English which contained the largest cohort of patients were selected to represent each country. For countries where ACE genotype data were not available from systematic reviews and meta-analyses, further searching was conducted through PubMed and Google Scholar, using search terms 'ACE polymorphisms + (country name)' or 'ACE genotype + (country name)'. The full list of citations for included studies can be found in Supplementary Materials. Selected studies for each country included genotype distribution data for healthy controls or general population and diseased populations, except for France, where data were not available for the general population. The combined data for healthy and diseased populations were taken as the overall genotype frequency of that particular country.

COVID-19 data

COVID-19 data as of 8 June 2020 were extracted from 'Worldometer', a website owned by Dadax providing daily updated coronavirus data since 15 February 2020.[23] For each of the selected countries, we extracted data pertaining to the number of confirmed COVID-19 cases, date of the first reported case, number of deaths and number of tests. COVID-19 related death was defined as per Worldometer's definition of cumulative number of deaths among detected cases (https://www.worldometers.info/coronavirus/about/). For countries in which the first case was reported prior to 15 February 2020, date of the first reported COVID-19 case was obtained from the 'Our World in Data' website, which presents updated figures provided by the European Centre for Disease Prevention and Control (ECDC).[24] The United Nations population database was used to collect information regarding population, median age and gender distribution.[25]

Table 1
Adjusted death rates from COVID-19 and II and DD genotype distribution of 25 included countries.

Region	Country	First case (date)	Tests/1million	Total Deaths	Death/1 million/day	II Genotype%	DD Genotype%	Genotype data source*
Asia	China	31-Dec-19	Not available	4634	0.14	40.6	19.0	Yan 2005
Asia	South Korea	20-Jan-20	19,860	273	0.17	36.9	15.5	Um 2003
Asia	Japan	24-Jan-20	2486	916	0.26	42.1	13.0	Mannami 2001
Asia	Singapore	24-Jan-20	69,824	25	0.12	47.9	8.4	Lau 2002
Asia	India	30-Jan-20	3381	7207	0.12	30.8	24.8	Pulla 2010
Central Asia	Iran	19-Feb-20	12,916	8281	14.08	26.1	20.4	Nikzamir 2008
Central Asia	Pakistan	26-Feb-20	3095	2002	0.48	23.0	22.3	Hussain 2018
Middle East	Saudi Arabia	2-Mar-20	27,525	712	1.7	30.4	22.5	Al-Saikhan 2017
Europe	UK	31-Jan-20	82,212	40,542	17.6	20.6	31.8	Steeds 2001
Europe	Italy	31-Jan-20	70,070	33,899	24.4	4.1	58.5	Santovito 2019
Europe	Spain	1-Feb-20	86,918	27,136	19.4	16.8	37.6	Alvarez 1999
Europe	France	24-Jan-20	21,213	29,155	12.4	17.6	35.6	Hadjadj 2008
Europe	Germany	27-Jan-20	51,906	8776	3.1	26.5	26.8	Pabst 2009
Europe	Sweden	1-Feb-20	27,279	4659	13.6	24.0	29.3	Zettergren 2017
Europe	Denmark	27-Feb-20	121,964	589	8.5	22.7	26.0	Bladbjerg 1999
Europe	Russia	1-Feb-20	87,173	5859	0.89	24.3	32.0	Fomicheva 2000
Europe	Turkey	10-Mar-20	27,728	4692	6.95	18.5	40.5	Serdaroglu 2005
Australasia	Australia (Non-indigenous)	25-Jan-20	63,510	102	0.09	19.8	32.2	Lester 1999
North America	US (All races)	23-Jan-20	64,325	112,469	8.7	21.2	27.6	Ned 2012
North America	Mexico	28-Feb-20	2609	13,699	5.3	37.7	15.6	Isordia-Salas 2019
South America	Brazil	25-Feb-20	4704	37,312	10.3	24.2	21.3	Pinheiro 2019
Africa	Nigeria	28-Feb-20	373	364	0.06	12.0	41.8	Kooffreh 2014
Africa	Tunisia	2-Mar-20	4684	49	0.19	11.8	64.7	Baroudi 2009
Africa	Egypt	15-Feb-20	1319	1237	0.43	4.8	40.0	Settin 2015
Africa	South Africa	5-Mar-20	15,513	989	1.29	10.5	45.4	Aung 2018

* Genotype frequency data reflect the overall prevalence (of both cases and controls) in each included study. Where cases or control groups data are missing, and no alternative source of genotype data exists, the available data is taken as the overall genotype data. Complete list of citations and details of included studies can be found in Supplementary Materials.

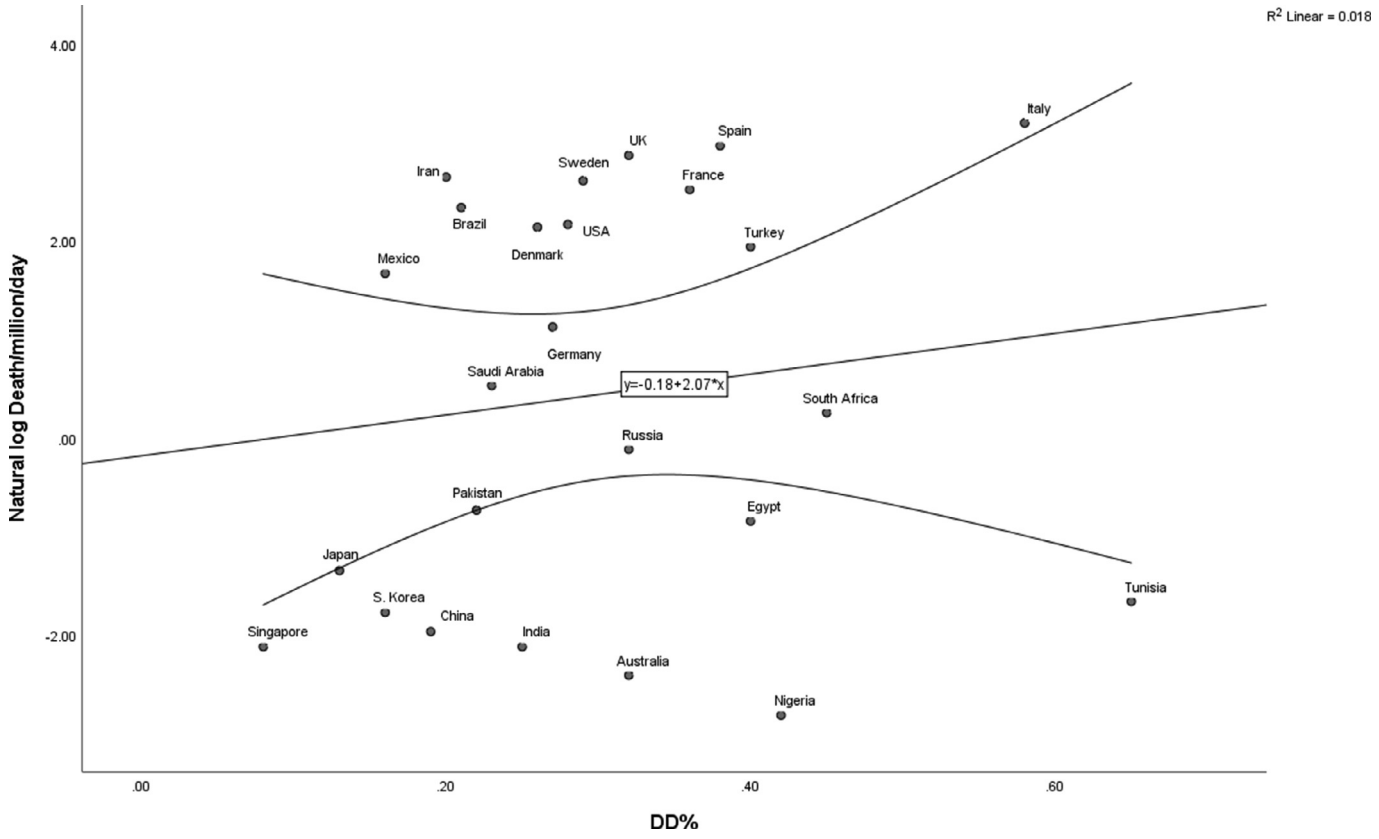

Fig. 1. A. Mortality rate (per million per day, natural log transformed) and DD genotype frequency
B. Mortality rate (per million per day, natural log transformed) and II genotype frequency
Legend: curved lines represent 95% confidence intervals.

Statistical analysis

The outcome of interest was COVID-19-related deaths per million people per day since the first reported case.

We first plotted this outcome (natural log transformed) against percentage of population with DD and II genotypes. We then used multivariable generalised linear models (GLMs) to determine its association with percentage of population with DD and II genotypes, with adjustment for median age of the population, percentage of females within the population and number of diagnostic tests per million people. The models excluded China because data regarding the number of tests conducted in this country could not be sourced. We considered percentage of population with DD and II genotypes as a continuous variable in the primary analyses, and as a categorical variable comprising four quartiles in secondary analyses, with the first (lowest) quartile as the reference category.

Results

The ACE genotype distribution and adjusted mortality rates for each country are shown in Table 1. Overall, the DD genotype frequency was lowest in east Asian countries and highest in African countries. Among European countries, Italy displayed the high prevalence of the DD genotype, at 58%. The II genotype frequency was highest in east Asian countries. Geographical variations in genotype distribution were also noted when genotype frequency data were drawn from sub-populations with existing disease (Table 1).

Fig. 1A and B show the correlation between COVID-19-related deaths per million people per day since the first reported case (natural log transformed) and genotype frequencies. A positive relationship was noted between frequency of the DD genotype and COVID-19 mortality, whereas a negative relationship was observed for frequency of the II genotype.

Table 2 displays incident rate ratios drawn from the GLMs, with and without adjustment for median age, proportion of females and diagnostic tests per million people. Frequency of the II genotype was significantly negatively associated with COVD-19-related mortality rates (incident rate ratio [IRR] 0.02, 95% confidence interval [CI]: 0.0004–0.6, $p = 0.03$), while frequency of the DD genotype did not show any significant correlation (IRR 10.3, 95% CI: 0.4–243.4, $p = 0.15$).

Discussion

COVID-19 has severely challenged governments and healthcare systems worldwide. Variation in mortality does not seem to be adequately explained by differences in country-specific mitigation strategies alone. Our study suggests that differences in COVID-19 mortality may be partially explained by differing frequencies of ACE genotypes, in particular, II genotype.

Most COVID-19 deaths occur from ARDS.[26] At the molecular level, the RAAS system underpins in the pathogenesis of ARDS in COVID-19 infection. High levels of ACE and ACE2 are found in the alveolar epithelial cells and serve as the key regulators of the RAAS system by maintaining pulmonary vascular and immunological homeostasis.[5] Binding of SARS-CoV2 virus spike protein to ACE2 on the surface of epithelial cells leads to downregulation of its activity, thereby permitting unopposed action of ACE and angiotensin II. The consequent pulmonary endothelial cell dysfunction and immune activation results in the inflammatory exudate characterising the onset of ARDS.[6] The different I/D polymorphisms

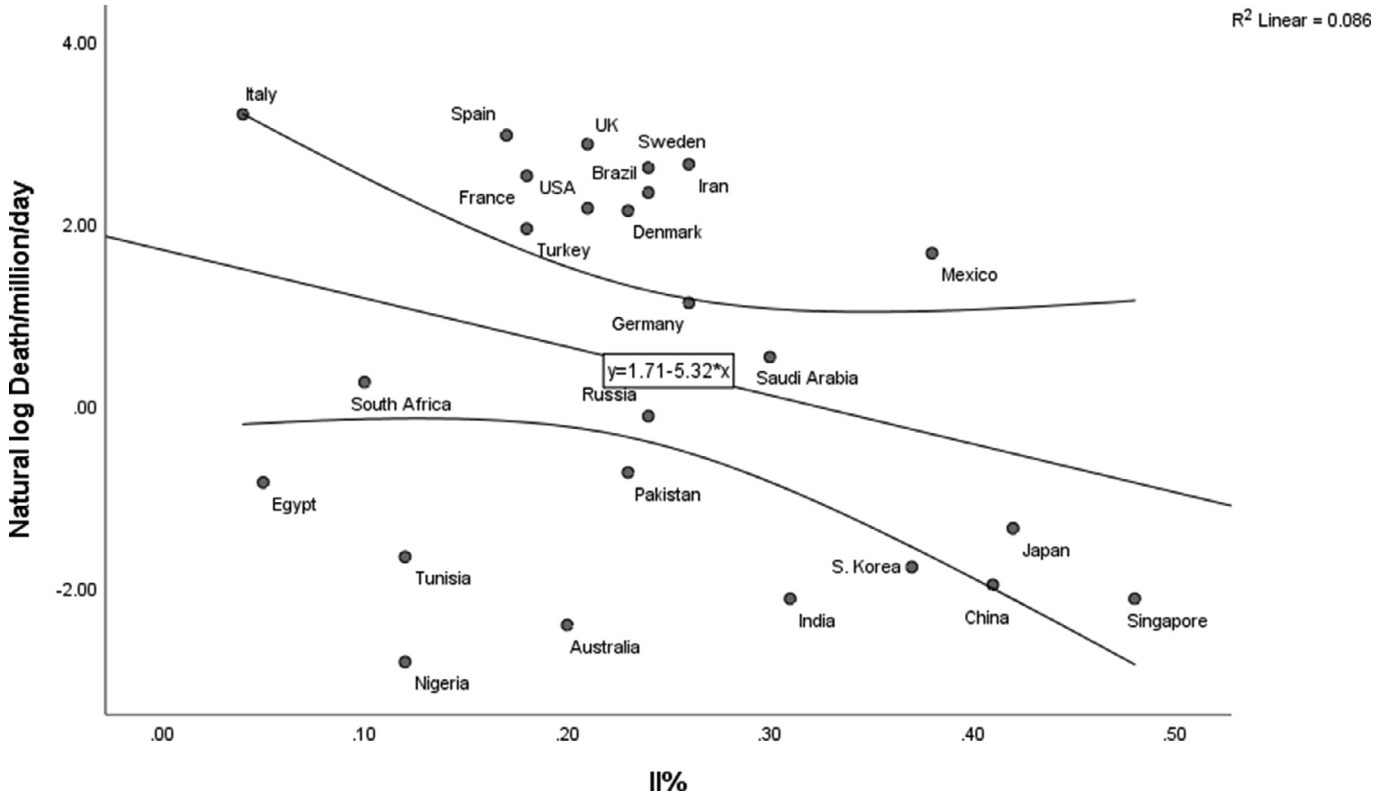

Fig. 1. Continued

Table 2
Incident rate ratios and adjusted incident rate ratios for mortality according to DD and II genotypes.

			IRR (95% CI)		
ACE genotypes	Overall	Q1	Q2	Q3	Q4
DD	10.3 (0.4–243.4), $p=0.15$	1.0 (ref)	1.4 (0.4–5.0), $p=0.6$	5.1 (1.8–14.3), $p=0.002$*	1.6 (0.3–8.8), $p=0.57$
II	0.02 (0.0004–0.6), $p=0.03$*	1.0 (ref)	0.8 (0.2–2.8), $p=0.76$	0.7 (0.2–2.2), $p=0.5$	0.1 (0.02–0.6), $p=0.014$*
			Adjusted IRR (95% CI)		
ACE genotypes	Overall	Q1	Q2	Q3	Q4
DD	4.3 (0.5–41.2), $p=0.2$	1.0 (ref)	0.7 (0.2–3.3), $p=0.7$	2.0 (0.5–8.2), $p=0.3$	1.2 (0.3–4.7), $p=0.8$
II	0.3 (0.002–0.7), $p=0.03$*	1.0 (ref)	1.1 (0.4–3.1), $p=0.9$	0.6 (0.2–1.7), $p=0.3$	0.2 (0.02–1.6), $p=0.1$

CI: confidence interval; IRR: incident rate ratio; Q1: first quartile; Q2: second quartile; Q3: third quartile; Q4: fourth quartile; ref: reference.
IRR was adjusted for median age, sex (% female) and number of tests per million for each country.
* Statistical significance.

alter the concentration of circulating and tissue ACE. In particular, deletion (DD) genotype is associated with higher serum levels of ACE compared to II or ID genotypes, and reduced tissue ACE2 expression, which may explain the reduced prevalence of COVID-19 infections but increasing propensity for a more severe disease.[7,13]

Previous studies have also highlighted the role of ACE in ARDS by demonstrating a direct correlation between measurable serum ACE levels and the course of ARDS.[27] Additionally, ACE gene polymorphisms can determine the risk of ARDS and death from sepsis, with II genotype significantly favouring survival from ARDS at 28 days.[11,12] ACE gene polymorphisms also serve as a risk factor for cardiovascular conditions, including hypertension, ischaemic heart disease, diabetes, renal disease and stroke.[9,16,20,22] Recent large cohort studies demonstrated that patients with these comorbidities are also at a higher risk of death from COVID-19.[26,28] All these findings support the hypothesis that ACE genotype can influence COVID-19 mortality.

There is significant interest in the potential effects of ACE inhibitors on the course of COVID-19.[29,30] To date, no difference in mortality has been observed between COVID-19 patients taking and not taking ACE inhibitors.[29] Furthermore, it is unknown how ACE genotypes affect binding of ACE inhibitors, while the capacity for these medications to affect SARS-CoV2 cellular entry remains unknown. Evaluation of the influence of ACE genotype and the pharmacokinetic properties of ACE inhibitors may be beneficial in the search for potential SARS-CoV2 therapies.

The main limitation of our study stems from use of data from only 25 countries, and some of the samples were over-represented by people with pre-existing diseases. However, the 25 countries are representative of their geographical regions in terms of ACE genotype profiles, as well as COVID-19 burden. The over-representation of people with pre-existing diseases for our ACE genotype data is mitigated by the fact that most COVID-19-related deaths occur among people with comorbidities.[28] Additionally, genotype data in some countries, such as USA, Australia, South Africa and Singapore, may be represented by multiethnic populations. This limitation was overcome by analysis of country-specific mortality data, which included all ethnicities. Lastly, although we adjusted for some of

the potential confounders in our analysis, many factors such as population density, accurate registries, case definitions and mitigation policies may further contribute to observed differences in COVID-19 mortality rates.

The findings from our study may partly explain the differential mortality observed across the world and are aligned with current understanding of SARS-CoV2 and ARDS pathophysiology. The role of ACE genotype as a prognostic factor in COVID-19 warrants further investigation. At a systemic level, knowledge of geographical variations in ACE genotype may allow for better prediction of the course of COVID-19, allowing safeguards to be implemented early, particularly in terms of healthcare resource allocation. At an individual patient level, risk stratification involving ACE genotype may inform more targeted clinical care, ultimately improving patient outcomes to reduce morbidity and mortality from the COVID-19 pandemic.

Declaration of Competing Interest

None to declare.

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Contributors' statement

AKA - conception, literature search, study design, data collection, data analysis, data interpretation, writing and final approval.

TA - conception, literature search, data collection, data analysis, data interpretation, writing and final approval.

BMT - literature search, data collection, data interpretation, writing and final approval.

CY - conception, data interpretation, writing and final approval.

RO - data analysis, data interpretation, writing and final approval.

KLC - conception, study design, data analysis, data interpretation, writing and final approval.

DL - conception, study design, data analysis, data interpretation, writing and final approval.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.11.012.

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