



Association Between Ethnicity and Severe COVID-19 Disease: a Systematic Review and Meta-analysis

Antony Raharja¹ · Alice Tamara² · Li Teng Kok¹

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Abstract

Objectives This article evaluates if ethnicity is an independent poor prognostic factor in COVID-19 disease.

Methods MEDLINE, EMBASE, Cochrane, WHO COVID-19 databases from inception to 15/06/2020 and medRxiv. No language restriction. Newcastle-Ottawa Scale (NOS) and GRADE framework were utilised to assess the risk of bias and certainty of evidence. PROSPERO CRD42020188421.

Results Seventy-two articles (59 cohort studies with 17,950,989 participants, 13 ecological studies; 54 US-based, 15 UK-based; 41 peer-reviewed) were included for systematic review and 45 for meta-analyses. Risk of bias was low: median NOS 7 of 9 (interquartile range 6–8). Compared to White ethnicity, unadjusted all-cause mortality was similar in Black (RR: 0.96 [95% CI: 0.83–1.08]) and Asian (RR: 0.99 [0.85–1.16]) but reduced in Hispanic ethnicity (RR: 0.69 [0.57–0.84]). Age- and sex-adjusted risks were significantly elevated for Black (HR: 1.38 [1.09–1.75]) and Asian (HR: 1.42 [1.15–1.75]), but not for Hispanic (RR: 1.14 [0.93–1.40]). Further adjusting for comorbidities attenuated these associations to non-significance: Black (HR: 0.95 [0.72–1.25]); Asian (HR: 1.17 [0.84–1.63]); Hispanic (HR: 0.94 [0.63–1.44]). Subgroup analyses showed a trend towards greater disparity in outcomes for UK ethnic minorities, especially hospitalisation risk.

Conclusions This review could not confirm a certain ethnicity as an independent poor prognostic factor for COVID-19. Racial disparities in COVID-19 outcomes may be partially attributed to higher comorbidity rates in certain ethnicity.

Keywords Ethnicity · COVID-19 · Mortality · Hospitalisation · Acute kidney injury · Intubation

Introduction

Up to 85% of individuals affected by SARS-CoV-2 are asymptomatic or have mild illness, 15% require oxygen and 5% critically ill requiring intensive care unit (ICU) admission [1]. Several risk factors such as age, male sex and comorbidities have been shown to correlate with more severe disease

[2]. Understanding the demographic risk factors for severe disease is of paramount importance not only to inform clinical practice but also to inform risk stratification at workplace and focus public health efforts at protecting vulnerable groups and those most affected by COVID-19 [3].

Multiple studies reported overrepresentation of ethnic minority groups in COVID-19 deaths and ICU admissions [4, 5]. A previous systematic review by Pan et al. highlighted the lack of ethnicity reporting in the literature. There was a consistent evidence of greater infection rates amongst ethnic minorities, but it noted a conflicting evidence on the relationship between ethnicity and mortality [6]. The association between ethnicity and COVID-19 outcomes may be riddled with confounding factors such as age, sex, comorbidities and socioeconomic factors [7]. As such, considerations of covariates are necessary to determine if ethnicity is truly an independent risk factor for poor outcomes in COVID-19.

This systematic review and meta-analysis evaluates the association between ethnicity and poor outcomes (mortality, hospitalisation, ICU admission, advanced respiratory support and kidney failure) in patients with laboratory-confirmed SARS-CoV-2.

Antony Raharja, Alice Tamara and Li Teng Kok are equally contributing co-first authors.

Highlights

- Ethnicity is not an independent poor prognostic factor in COVID-19 disease.
- Racial disparities in COVID-19 outcomes can be attributed to higher rates of medical comorbidities in ethnic minority groups.
- Disproportionate impact of COVID-19 on ethnic minorities is possibly largely driven by increased infection rates amongst ethnic minorities.

✉ Antony Raharja
antony.raharja@nhs.net

¹ Guy's and St Thomas' NHS Foundation Trust, London, UK

² Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Method

This study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement [8]. The protocol of this review was registered in PROSPERO database, CRD42020188421.

Data Sources and Searches

A literature search of databases was conducted from database inception to 31 May 2020, and later updated on 15 June 2020. Databases used were Ovid MEDLINE, Ovid EMBASE, Cochrane COVID-19 Study Register and World Health Organization (WHO) COVID-19 Global Research Database. Medical Subject Headings (MeSH) terms were ‘SARS-CoV-2 OR Covid-19 OR novel coronavirus’ and ‘ethnic OR race OR minority group OR demography’. The *Lancet*, *BMJ* and *JAMA* were reviewed for any relevant articles. Preprint servers (MedRxiv and BioRxiv) were searched for non-peer-reviewed preprint articles. References of included studies and a related systematic review were screened for relevant articles as part of literature snowballing [6]. Citation tracking was carried out using Google Scholar on 24 June 2020 to identify relevant articles which cited any of the included studies. No language restrictions were applied. All steps were carried out by pairs of independent reviewers (AT, LK, AR), and a third reviewer arbitrated for cases without consensus. Full details of search strategies are described in Online Supplementary Appendix S2.

Study Selection

We included studies that reported associations between ethnicity and any of the prespecified outcomes indicative of severe COVID-19 disease in laboratory-confirmed SARS-CoV-2 patients. Primary outcome is all-cause mortality. Secondary outcomes are hospitalisation, critical care admission, advanced respiratory support requirement (such as invasive mechanical ventilation (IMV), extracorporeal membrane oxygenation (ECMO)) and acute kidney injury (any severity or the need for acute renal replacement therapy). In particular, we excluded studies that reported on infection rates alone. Interventional trials, case reports, commentaries and articles from news media were excluded. In this article, we use the term ‘ethnicity’ to describe both ‘ethnicity’ and ‘race’ (Supplementary Methods S1).

Data Extraction and Quality Assessment

A custom spreadsheet was developed and piloted by AR and AT prior to use for data extraction; this recorded study characteristics (name, date, publication status), aim, location,

setting, participant characteristics including age, sex, ethnicity (White, Black, Asian, Hispanic, mixed or missing data), body mass index, smoking status, comorbidities (hypertension, diabetes, chronic kidney disease, pulmonary disease, cardiovascular disease, asthma, COPD, coronary artery disease, heart failure, cancer) and whether the study collected any data on socioeconomic factors. Raw outcome data were extracted, along with any adjusted and unadjusted risk estimates (hazard ratios (HRs), relative risks (RRs) and odds ratios (ORs)).

The Newcastle-Ottawa Scale (NOS) and the modified NOS by Modesti were used to assess risk of bias for longitudinal cohort studies and ecological studies respectively [9, 10]. A maximum score of 9 is possible, with 7 and above being regarded as low risk of bias. Pairs of investigators (AR, AT and LK) independently carried out data extraction and assessed risk of bias. A third investigator resolved any disagreement through discussion. Details of the data extraction form and NOS can be found in Online Supplementary Methods S3 and S4.

GRADE framework was used to assess the quality of evidence, and certainty in the adjusted risk estimates for each ethnicity-outcome association [11]. Observational studies provided high-quality evidence for prognostic factors, and are down-rated for risk of bias, inconsistency, imprecision, indirectness and publication bias or up-rated for strong evidence of association ($RR > 2$ or < 0.5) [12].

Data Synthesis and Analysis

Meta-analysis was carried out if two or more longitudinal cohort studies compared risk of outcomes in Black, Asian or Hispanic ethnic group with White participants (reference group) for each outcome. When multiple articles studied the same patient cohort, we would only use the cohort study reporting the largest number of events in the meta-analysis to avoid double-counting; this assumes a longer follow-up time. Ethnicity-outcome associations in COVID-19 patients were assessed using DerSimonian-Laird random-effects meta-analyses in the R package *meta*, as we expect heterogeneity across prognostic studies. If the risk estimates were not reported but raw data available, we calculated RRs and 95% confidence intervals for cohort and single arms of case-controlled studies. RRs were used as they do not overestimate risks, and outcomes were not rare in most studies [13]. ORs were converted to RRs using the Zhang and Yu formula, as developed in R (*orsk*) for the purpose of meta-analysis if outcome was $> 10\%$ [14]. OR was assumed to approximate RR if the outcome in the study was rare.

Meta-analyses of unadjusted and adjusted risk estimates were carried out separately for each ethnicity-outcome association, with pooled $\log(HR)$ and $\log(RR)$ calculated separately [15, 16]. We present two sets of adjusted estimates: (1) adjusted for age and sex; (2) age, sex and at minimum one

comorbidity. For ease of readership and interpretation, $\log(\text{HR})$ and $\log(\text{RR})$ were converted to HR and RR in the texts. Study heterogeneity was evaluated by I^2 statistic and visual inspection of the forest plots. Forest plots are displayed in Online Supplementary Results S3.

Reasons for heterogeneity were explored; Subgroups analyses stratified by locations (UK or USA) or risks of bias ($\text{NOS} < 7$ or ≥ 7) were conducted, including assessments of interaction. As a post hoc analysis, we calculated pooled risk estimates after excluding small studies ($n < 100$). Funnel plots were examined for publication bias and evaluated for asymmetry using Begg's rank correlation test as data from observational studies were likely to have asymmetric distribution [17]. All statistical analyses were performed in RStudio (version 1.3.959).

Results

The literature search retrieved 5706 articles on the databases, including 1043 duplicates. Additional 296 preprint articles were screened. Titles and abstract screening excluded 4883 articles, and full-text examination excluded 45 articles. Manual searching, reference tracking and citation tracking yielded a further 27 articles. Study selection process is illustrated according to PRISMA flowchart (Fig. 1).

There were 72 articles (59 cohort and 13 ecological studies) included for qualitative synthesis; 41 (57%) studies were peer-reviewed publications at the time of screening. Studies were conducted in the USA (54 studies), the UK (15), Brazil (one) and Israel (one). There was one multinational study based across the USA, Canada and Spain. Fifty-one studies assessed ethnic disparity in risks of mortality, 21 on hospitalisation, 18 on ICU admission, 18 on IMV and 8 on kidney failure. Adjusted analyses were carried out by 40 of 59 cohort studies and 5 of 13 ecological studies. The median NOS score was 7 (interquartile range 6–8, range 4–9). Twenty-four (33%) studies had a NOS score of less than 7, mainly due to failure to control for age or comorbidities or non-representative study sample such as pregnant women, paediatric, cancer or transplant patients (Supplementary Results S1.1–2).

Of the 59 cohort studies, including one case-controlled study in which suitable data was extracted from one of its arms, there were 17,950,989 participants: 11,502,289 (64%) were White; 383,303 (2.1%) were Black; 1,055,396 (5.9%) were Asian; 15,439 (0.086%) were Hispanic; 4,596,081 (26%) had missing ethnicity data. Study characteristics are summarised in Table 1. Forty-five studies were included for meta-analysis. Summary of pooled risk estimates could be found in Table 2. A high level of heterogeneity was observed between studies. Publication bias was not detected (Supplementary Results S4).

Mortality

Fifty-one studies reported ethnicity-aggregated mortality data, including 38 cohort studies comprising 17,501,820 participants (63% White, 2.1% Black, 6.0% Asian, 0.069% Hispanic, 2.9% others and 26% missing ethnicity data). Total sample sizes were more than 100 participants ($n > 100$) in 26 of 28 (93%) cohort studies included in the meta-analysis.

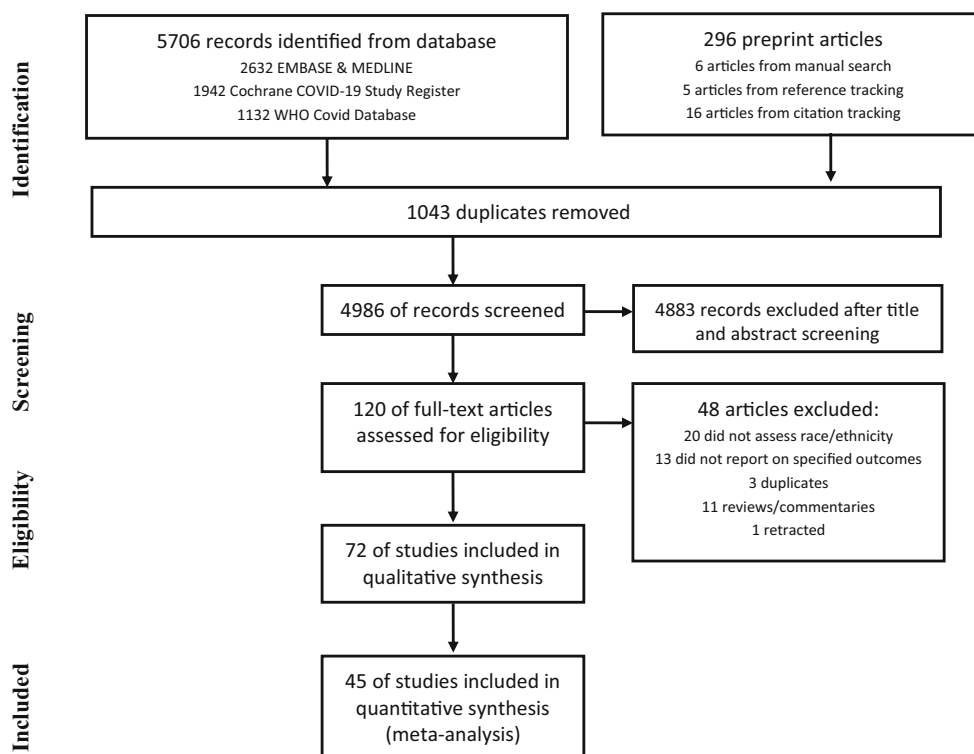
Pooled estimates from hazard ratios and relative risks generally showed similar magnitude, direction of effect and statistical significance. In the unadjusted analyses, compared to White ethnicity, all-cause mortality risk was similar in Black (RR: 0.96 [95% CI: 0.83–1.08], $I^2 = 88$, $k = 25$) and Asian (RR: 0.99 [95% CI: 0.85–1.16], $I^2 = 84$, $k = 14$) but significantly reduced in Hispanic ethnicity (RR: 0.69 [95% CI: 0.57–0.84], $I^2 = 76$, $k = 11$). Age- and sex-adjusted mortality risks were significantly elevated for Black (HR: 1.38 [95% CI: 1.09–1.75], $I^2 = 94$, $k = 5$) and Asian (HR: 1.42 [95% CI: 1.15–1.75], $I^2 = 87$, $k = 3$), but not for Hispanic (RR: 1.14 [95% CI: 0.93–1.40], $I^2 = 0$, $k = 3$). Further adjustment for comorbidities attenuated these associations, rendering associations non-significant; HR (Black): 0.95 [95% CI: 0.72–1.25], $I^2 = 79$, $k = 4$; HR (Asian): 1.17 [95% CI: 0.84–1.63], $I^2 = 73$, $k = 3$; HR (Hispanic): 0.94 [95% CI: 0.63–1.44], $I^2 = 89$, $k = 2$.

Subgroup analysis by location showed a consistent trend towards greater mortality risk estimates in UK ethnic minorities, but difference was not significant. Subgrouping by risk of bias did not demonstrate different effects (Supplementary Results S2).

Ten cohort studies, not included in meta-analysis, echoed similar findings, and did not support ethnicity as an independent risk factor for poor COVID-19 outcomes. Two studies reported non-significant difference in unadjusted mortality risk in Black (vs. non-Black) [18, 19]. Four studies (three unadjusted, one adjusted analyses) did not find an increase in mortality risk amongst non-White ethnicity [20–23]. Four studies reported lower mortality risk in Hispanic patients compared to that in non-Hispanic patients; two reported significant unadjusted analysis, and none reported significant age-adjusted analyses [24–27].

There were 12 US-based ecological design studies, utilising publicly available dataset to draw an indirect association between ethnicity and COVID-19 outcomes. Eight studies illustrated that counties with a greater proportion of African-Americans have higher rates of county-level COVID-19 hospitalisations and deaths [28–32], even after adjusting for a combination of county-level characteristics such as age, poverty, comorbidities, healthcare access and geography [33–36]. One study did not find an increased mortality risk in Asian ethnicity after adjustment for age and geography [35]. Instead, a higher proportion of Asian population was a protective factor to counties [32]. Three studies reported increased age-adjusted mortality in

Fig. 1 Study selection process



the Hispanic population [32, 35–37]. One study noted that ethnic segregation correlated with risks of COVID-19 death [38]. One UK study showed that Black African, Black Caribbean, Pakistani, Bangladeshi and Indian ethnic groups had higher age-standardised and geography-adjusted mortality ratio [39].

Hospitalisation

Twenty-one studies assessed hospitalisation risk in different ethnic groups. There were 20 cohort studies comprising 428,000 patients (90% White, 4.5% Black, 3.4% Asian, 1.6% Hispanic, 3.0% others and 0.19% missing ethnicity data); 14 articles were suitable for meta-analysis. Only one had a small sample size ($n < 100$).

Compared to White ethnicity, crude unadjusted risk of hospitalisation was significantly higher in Black (RR: 1.68 [95% CI: 1.28–2.20], $I^2 = 98$, $k = 13$), but similar for Asian (RR: 1.13 [95% CI: 0.78–1.66], $I^2 = 95$, $k = 8$) and Hispanic (RR: 1.00 [95% CI: 0.95–1.06], $I^2 = 0$, $k = 8$) ethnicity. Age- and sex-adjusted risk was significantly raised in Black (RR: 2.23 [95% CI: 1.54–3.19], $I^2 = 92$, $k = 5$) and Hispanic (RR: 1.49 [95% CI: 1.28–1.75], $I^2 = 0$, $k = 2$), but not Asian (RR: 1.16 [95% CI: 0.64–2.08], $I^2 = 82$, $k = 3$) ethnicity. Weakening of association was noted after further adjustment for comorbidities: Black (RR: 1.40 [95% CI: 0.93–2.12], $I^2 = 95$, $k = 4$), Asian (RR: 1.04 [95% CI: 0.99–1.11], $I^2 = 0$, $k = 3$) and Hispanic (RR: 1.24 [95% CI: 1.02–1.52], $I^2 = 75$, $k = 3$).

Five studies considered further socioeconomic factors in their analysis and showed that adjusting for socioeconomic factors could reduce the disparity in hospitalisation risk [40–44].

Subgroup analysis showed strongly significant interaction p value between UK and US subgroups. The hospitalisation risk of Black and Asian was markedly higher in the UK. For Black ethnicity, RR is 5.47 [95% CI: 2.51–12.06] in UK studies vs. RR 1.36 [95% CI: 1.08–1.72] in US studies with a p value of 0.0008. For Asian ethnicity, RR is 2.95 [95% CI: 1.55–5.53] in UK studies vs. RR 0.90 [95% CI: 0.82–1.66] in US studies with a p value of 0.0003. Subgrouping by location was not possible for Hispanic ethnicity. Subgrouping by NOS did not show significant interaction, although there was a trend towards greater risk in studies with lower NOS (Supplementary Results S2).

Seven studies were not suitable for meta-analyses. In a descriptive unadjusted analysis, three studies reported no differences between the number of Hispanic and non-Hispanic patients [25], Black and non-Black patients [18] and between White and BAME patients [20]. Despite no significant differences, ethnic minorities were still disproportionately represented in COVID-19 admissions [45, 46]. Two other studies reported increased adjusted risks of hospitalisation in non-White ethnic groups in both the USA and the UK [42, 47]. One New York study showed that rates of COVID-19 hospitalisations were higher in areas with greater proportion of ethnic minorities [28].

Table 1 Summary of study characteristics

	Overall	Mortality	Hospitalisation	ICU admission	Kidney failure	IMV
No. of studies	72	51	21	18	8	18
Peer-reviewed	41	27	13	11	4	14
Study location						
UK	15	11	5	5	1	1
USA	55	39	16	13	7	17
Others	4	3	0	0	0	0
Ecological studies	13	13	1	0	0	0
Cohort studies	59	38	20	18	8	18
No of participants in cohort studies (<i>N</i>)	17,950,989*	17,501,820	428,000	30,301	21,999	16,862
White, <i>n</i> (%)	11,502,289 (64)	11,093,885 (63)	385,113 (90)	13,611 (45)	8334 (38)	6958 (41)
Black	383,303 (2.1)	372,020 (2.1)	19,395 (4.5)	9830 (32)	8347 (38)	6914 (41)
Asian	1,055,396 (5.9)	1,045,189 (6.0)	14,726 (3.5)	1289 (4.3)	1137 (5.2)	865 (5.1)
Hispanic	15,439 (0.086)	12,148 (0.069)	6888 (1.6)	2405 (7.9)	2007 (9.1)	657 (3.9)
Mixed or others	529,953 (2.9)	514,340 (2.9)	11,520 (3.0)	1873 (6.2)	2854 (13)	941 (5.6)
Missing data	4,596,081 (26)	4,594,472 (26)	834 (0.19)	1438 (4.7)	610 (2.8)	718 (4.3)
Newcastle-Ottawa scale points, median (IQR), range						
Number of studies with NOS ≥ 7 points, <i>k</i> (%)	48/72 (67)	36/51 (71)	13/21 (62)	14/18 (78)	8/8 (100)	14/18 (78)
Overall	7 (6–8), 4–9	7 (6–8), 4–9	8 (6–8), 4–9	8 (7.25–9), 6–9	8.5 (7.75–9), 7–9	8 (7.25–9), 6–9
Selection of study groups (max 4)	4 (3–4), 2–4	4 (3–4), 2–4	4 (3–4), 2–4	4 (3–4), 3–4	4 (3.75–4), 2–4	4 (3–4), 3–4
Comparability of groups (max 2)	1.5 (0–2), 0–2	1 (0–2), 0–2	2 (0.25–2), 0–2	2 (1.25–2), 0–2	2 (2–2), 0–2	2 (1.25–2), 0–2
Outcome (max 3)	3 (2–3), 1–3	3 (2–3), 1–3	2 (2–3), 1–3	3 (2–3), 2–3	3 (3–3), 2–3	3 (2.25–3), 1–3

*One study was excluded as data derived from the same cohort [41, 42]. Studies may separate ethnicity from race; in such cases, Hispanic and other races are not mutually exclusive

Critical Care Admission

Eighteen studies assessed ethnicity as a risk factor for ICU admission, comprising 30,301 participants (45% White, 32% Black, 7.9% Asian, 7.9% Hispanic and 4.7% with missing ethnicity data). Subgroup analyses by location or NOS scores were not possible as ten of 11 studies included in meta-analyses were US-based, and all have NOS ≥ 7.

Compared to White ethnicity, the unadjusted risks of ICU admission were significantly raised in Black (RR: 1.51 [95% CI: 1.11–2.04], $I^2 = 94$, $k = 10$), similar in Asian (RR: 1.02 [95% CI: 0.51–2.22], $I^2 = 71$, $k = 4$) and lower in Hispanic ethnicity (RR: 0.89 [95% CI: 0.75–1.05], $I^2 = 0$, $k = 6$). However, pooled estimates for Asian included three US-based studies and one UK study. The largest study was UK-based and reported an increased risk for Asian ethnicity [48]. The other three studies were US-based studies, relatively smaller sample sizes, showing non-significant associations.

Risk of ICU admission for Black ethnicity was attenuated to non-significant level after adjusting for age and sex (RR: 1.39 [95% CI: 0.85–2.27], $I^2 = 69$, $k = 3$), and further after accounting for comorbidities (RR: 1.31 [95% CI: 0.84–2.03], $I^2 = 91$, $k = 4$). There was inadequate data for meta-

analysis for Asian ethnicity; one study reported significantly increased age- and sex-adjusted risk of ICU Admission for Asian ethnicity [49]. Only two studies reported age-, sex- and comorbidity-adjusted analysis for Hispanic ethnicity, showing a non-significant association with ICU admission (RR: 0.93 [95% CI: 0.74–1.16], $I^2 = 0$, $k = 2$).

Seven studies were not suitable for meta-analysis. Five UK-based studies reported over-representation of the BAME communities in ICU cohorts [20, 21, 46, 50, 51], with two reporting higher age-adjusted risk for BAME [20, 21]. On the other hand, two US studies did not find a significant difference in risk of ICU admission between Black and non-Black study participants [18, 19].

Respiratory Failure

Eighteen cohort studies comprising 16,862 participants (41% White, 41% Black, 5.1% Asian, 3.9% Hispanic and 4.3% missing ethnicity data) reported ethnicity-aggregated data on the need for advanced respiratory support, i.e. invasive mechanical ventilation (IMV). Thirteen studies were suitable for meta-analysis.

Table 2 Summary estimates for mortality with log (hazard ratio) [95% confidence interval], I^2 and number of studies (k), or log (relative risk) [95% confidence interval], I^2 and number of studies

Ethnicity (White as reference)	Univariate	Multivariate [†]	Multivariate [‡]
Mortality			
Black vs. White, log (HR)	-0.17 [-0.63; 0.30], 94, $k=4$	0.32 [0.09; 0.56]*, 94, $k=5$	-0.05 [-0.33; 0.22], 79, $k=4$
Black vs. White, log(RR)	-0.05 [-0.18; 0.08], 88, $k=25$	0.25 [0.03; 0.46]*, 12, $k=5$	0.06 [-0.05; 0.17], 60, $k=6$
Asian vs. White, log (HR)	0.01 [-0.31; 0.33], 82, $k=4$	0.35 [0.14; 0.56]*, 87, $k=3$	0.16 [-0.18; 0.49], 73, $k=3$
Asian vs. White, log(RR)	-0.01 [-0.16; 0.15], 84, $k=14$	0.42 [0.04; 0.80]*, 0, $k=2$	NA
Hispanic vs. White, log (HR)	NA	NA	-0.06 [-0.47; 0.35], 89, $k=2$
Hispanic vs. White, log(RR)	-0.36 [-0.56; -0.17]*, 76, $k=11$	0.13 [-0.08; 0.34], 0, $k=3$	NA
Hospitalisation			
Black vs. White, log(RR)	0.52 [0.25; 0.79]*, 98, $k=13$	0.80 [0.43; 1.16]*, 92, $k=5$	0.34 [-0.07; 0.75], 95, $k=4$
Asian vs. White, log(RR)	0.13 [-0.25; 0.50], 95, $k=8$	0.15 [-0.44; 0.73], 82, $k=3$	0.04 [-0.01; 0.10], 0, $k=3$
Hispanic vs. White, log(RR)	0.00 [-0.05; 0.05], 0, $k=8$	0.40 [0.25; 0.56]*, 0, $k=2$	0.22 [0.02; 0.42]*, 75, $k=3$
Intensive care unit admission			
Black vs. White, log(RR)	0.41 [0.11; 0.71]*, 94, $k=10$	0.33 [-0.16; 0.82], 69, $k=3$	0.27 [-0.18; 0.71], 91, $k=4$
Asian vs. White, log(RR)	0.02 [-0.67; 0.70], 71, $k=4$	NA	NA
Hispanic vs. White, log(RR)	-0.12 [-0.28; 0.05], 0, $k=6$	NA	-0.07 [-0.29; 0.15], 0, $k=2$
Invasive mechanical ventilation			
Black vs. White, log(RR)	0.25 [-0.11; 0.60], 85, $k=10$	0.34 [0.12; 0.56]*, 0, $k=3$	0.21 [-0.51; 0.92], 91, $k=3$
Asian vs. White, log(RR)	0.33 [0.07; 0.59]*, 14, $k=4$	0.43 [0.16; 0.70]*, 0, $k=2$	NA
Hispanic vs. White, log(RR)	-0.12 [-0.37; 0.14], 0, $k=6$	NA	0.01 [-0.17; 0.19], 0, $k=2$
Acute kidney injury			
Black vs. White, log(RR)	0.30 [0.04; 0.56]*, 92, $k=5$	NA	-0.47 [-0.12; 1.07], 95, $k=2$
Asian vs. White, log(RR)	-0.17 [-0.35; 0.01], 0, $k=2$	NA	NA
Hispanic vs. White, log(RR)	NA	NA	NA

*Statistically significant; [†] Adjusted for age and sex; [‡] Adjusted for age, sex and comorbidities. NA data not available. All forest plots are available in Online Supplementary Results S3

In unadjusted analyses, compared to White ethnicity, risk of IMV was higher in Black (RR: 1.28 [95% CI: 0.90–1.81], $I^2 = 85\%$, $k=10$) and Asian (RR: 1.39 [95% CI: 1.07–1.80], $I^2 = 14$, $k=4$) but lower in Hispanic ethnicity (RR: 0.89 [95% CI: 0.69–1.15], $I^2 = 0$, $k=6$). Age- and sex-adjusted risks were significantly high for Black (RR: 1.40 [95% CI: 1.13–1.75], $I^2 = 0$, $k=3$) and Asian ethnicity (RR: 1.54 [95% CI: 1.17–2.02], $I^2 = 0$, $k=2$); There was only one study reporting non-significantly raised age- and sex-adjusted risk of IMV in Hispanic patients [52]. After full adjustment, the associations were attenuated and non-significant in Black (RR: 1.23 [95% CI: 0.61–2.51], $I^2 = 91$, $k=3$) and Hispanic ethnicity (RR: 1.01 [95% CI: 0.84–1.21], $I^2 = 0$, $k=2$). One study reported a non-significantly lower age-, sex- and comorbidity-adjusted risk of IMV in Asian [53].

Subgrouping by location was not possible as all but one study were US-based. In subgroup analysis by risk of bias, unadjusted risks of IMV for Asian and Hispanic ethnicity were reported higher by studies with low risk of bias, albeit there was no significant interaction of p value between subgroups. Inclusion of studies with high-risk bias did not affect

the direction or the statistical significance of the overall pooled estimate, although it attenuated the magnitude.

Results from studies that were not suitable for meta-analysis further reiterated that ethnicity was not associated with risk of intubation. Four studies showed that Black ethnicity was not independently associated with IMV, or a composite of IMV or death [18, 19, 26, 54]. Two studies reported similar rates of IMV in Hispanic and other ethnicities [25, 26], although one study found non-significantly lower risk of IMV or death in Hispanics [54]. One found non-White ethnicity to be more likely to require high-flow oxygen support or IMV, albeit this was statistically non-significant [47]. We did not find any studies reporting association between ethnicity and ECMO.

Kidney Failure

Eight studies comprising 21,999 participants (38% White, 38% Black, 5.2% Asian, 9.1% Hispanic, 2.8% missing ethnicity data) investigated the association between ethnicity and acute kidney injury (AKI); all had low risk of bias and seven

were US-based studies. Five studies were included in the meta-analysis.

In an unadjusted analysis, Black ethnicity was at a significantly higher risk of AKI (RR: 1.35 [95% CI: 1.04–1.76], $I^2 = 92\%$, $k = 5$). Two separate studies showed that this association remained significant after adjustment of age, sex and comorbidities, but pooled RR was non-significant (RR: 1.60 [95% CI: 0.89–2.90], $I^2 = 95\%$, $k = 2$) most likely due to only two studies being suitable. Three studies reported higher rates of Black patients requiring acute renal replacement therapy, although none showed significant association in adjusted analysis [19, 48, 55].

Two studies reported lower unadjusted risk of AKI in Asian ethnicity (RR: 0.85 [95% CI: 0.71–1.01], $I^2 = 0$, $k = 2$). One study reported non-significantly lower adjusted risk of AKI in Asian ethnicity [56]. Two studies did not find an increased unadjusted risk of AKI in Hispanic ethnicity [25, 57]. There were no studies reporting adjusted risk of AKI for Hispanic ethnicities.

Quality Assessment

The level of evidence was high for Black ethnicity, but low for both Asian and Hispanic ethnicities (Table 3). The certainty in the risk estimates for Asian and Hispanic was down-rated for risk of bias and indirectness due to relatively low number of studies providing age-, sex- and comorbidity-adjusted association, and potential differences between study participants and target population. Detailed assessment is described in Supplementary Results S5.

Discussion

This systematic review and meta-analysis could not confirm ethnicity as an independent risk factor for poor outcomes in COVID-19 patients. Analyses of step-wise adjustments for covariates underlined important factors confounding ethnicity as a risk factor.

Interpretation of ethnicity-stratified data requires considerations of traditional risk factors for poor outcomes in COVID-19. Unadjusted risk ratios crudely quantify risk disparities between different ethnicities, but may misrepresent the true association. For instance, a low unadjusted mortality risk in the Hispanic group was due to a relatively younger Hispanic population included in the studies. This contrasts with the elevated age- and sex-adjusted risks across several outcome measures. Attenuation of these risk estimates with further adjustment for comorbidities indicates that disparities could be partially attributed to a greater burden of comorbidities in ethnic minority groups.

Heterogeneity in the meta-analysis can be attributed to differences in the magnitude rather than the direction of effect. Substantial I^2 is expected in meta-analyses of large observational studies producing narrow confidence intervals [12]. Clinical heterogeneity is expected in risk estimates for Asians since Asian ethnicity is not a homogenous group, consisting of individuals from widely diverse origins such as Indian, Pakistani, Bangladeshi, Chinese and others. Subgrouping by location has provided context-specific risk estimates, whilst sacrificing precision for general applicability in public health policy decision-making. We therefore argue that a high level of heterogeneity has not limited the usefulness of the meta-analyses. Nevertheless, for this reason, we down-rate certainty of risk estimates for Asian and Hispanic ethnicity.

To our knowledge, this is the first meta-analysis quantifying the association between ethnicity and COVID-19 outcomes. Our finding is in keeping with findings from pandemic influenza refuting ethnicity as a risk factor [58]. A more recent study continued to echo findings from this meta-analysis [59]. Whilst this review did not support ethnicity as an independent risk factor, the evidence is consistent on the disproportionate representation of ethnic minorities in COVID-19 mortality and morbidity.

This study has clinical and public health implications. Findings from this review should inform decisions regarding risk stratification at work, shielding advice and future allocation of vaccinations. Given the low-to-high-quality evidence indicating that ethnicity is not an independent risk factor,

Table 3 Quality of evidence assessment. Age, sex and comorbidities adjusted risk estimates for each ethnicity-outcome association, and application of GRADE principles towards rating confidence in risk estimates

	All-cause mortality	Hospitalisation	ICU	Ventilation	AKI or acute RRT	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Strong association	GRADE
Black	Ntrl	Ntrl	Ntrl	Ntrl	↑	–	–	–	–	–	–	High
Asian	Ntrl	Ntrl	NA	NA	NA	Down	–	–	Down	–	–	Low
Hispanic	Ntrl	↑*	Ntrl	Ntrl	NA	Down	–	–	Down	–	–	Low

GRADE Grading of Recommendations Assessment, Development and Evaluation, *Ntrl* neutral association, *NA* not applicable. ↑*Significant risk factor; ↑Potential risk factor; non-significant risk ratio > 1.5; risk ratio between 0.67 and 1.5; ↓Potentially protective; non-significant risk ratio < 0.67; ↓*Significant protective

COVID-19 risk assessment should only consider ethnicity in conjunction with other risk factors such as age or comorbidities. Nevertheless, public campaigns need to continue to target ethnic minority groups to reduce rates of infection and medical comorbidities amongst ethnic minorities; both appeared to be the driving forces behind the overrepresentation of racial minorities in COVID-19 mortality.

Our study has several strengths. Search strategy was comprehensive, covering a large number of published peer-reviewed and preprint articles. A further six of 31 preprint articles went on to be published in peer-review journals by 15/08/2020. A large number of studies were included in the meta-analysis with only several small study sizes ($n < 100$); Omission of these studies in post hoc analysis did not affect the direction and statistical significance of analyses. Multiple indicators of poor outcomes, i.e. mortality, hospitalisation, ICU admission, intubation and kidney failure, were considered. Taken together, the balance of evidence weighs against ethnicity as an independent risk factor for poor outcomes in patients with laboratory-confirmed SARS-CoV-2 infection. Lastly, separate pooling of unadjusted and adjusted risk estimates improves our understanding of ethnicity-outcome association.

Our study is limited by certain gaps in currently available evidence: substantial number of ethnicity data missing in studies; limited number of articles on socioeconomic factors as a confounding factor to ethnicity; minimal articles studying adjusted risks in Hispanic, Asian and native populations. There was a minimal involvement of paediatric patients in our meta-analysis, and so findings should not be extrapolated to paediatric patients. Given reports of association between SARS-CoV-2 and Kawasaki-like disease, this area needs to be explored further. We did not investigate whether ethnicity is associated with risk of SARS-CoV-2 infection as this relates to incidence rather than severity. Besides, this has been explored in a previous systematic review [6].

Despite these limitations, our rigorous study updates current evidence on the association between ethnicity and poor COVID-19 outcomes, and identifies gaps in evidence that future studies can work towards.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Reproducible Research Statement Study protocol: see “Method” and Supplement. Statistical code: see “Method.” Data set: All included studies are publicly available; additional data are available upon request from corresponding author.

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