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# Epidemiological and clinical characteristics of non-severe and severe pediatric and adult COVID-19 patients across different geographical regions in the early phase of pandemic: a systematic review and meta-analysis of observational studies

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jim-2021-001858).

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Accepted 2 June 2021



**To cite:** Chua PEY, Shah SU, Gui H, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2021-001858

## ABSTRACT

This systematic and meta-review aimed to compare clinical presentation, outcomes, and care management among patients with COVID-19 during the early phase of the pandemic. A total of 77 peer-reviewed publications were identified between January 1, 2020 and April 9, 2020 from PubMed, Google Scholar, and Chinese Medical Journal databases. Subsequently, meta-analysis of 40 non-overlapping studies, comprising of 4844 patients from seven countries, was conducted to see differences in clinical characteristics and laboratory outcomes across patients from different geographical regions (Wuhan, other parts of China and outside China), severity (non-severe, severe and fatal) and age groups (adults and children). Patients from Wuhan had a higher mean age (54.3 years) and rates of dyspnea (39.5%) compared with patients from other parts of China and outside China. Myalgia, fatigue, acute respiratory distress syndrome (ARDS) and fatalities were also significantly more prevalent among Wuhan patients. A significant dose–response increase in prevalence of diabetes, D-dimer, white blood cells, neutrophil levels and ARDS was seen from non-severe to severe and fatal outcomes. A significant increase in mean duration of symptom onset to admission was seen between non-severe cases (4.2 days) and severe and fatal cases (6.3 days and 8.8 days, respectively). Proportion of asymptomatic cases was higher in children (20%) compared with adults (2.4%). In conclusion, patients with COVID-19 from Wuhan displayed more severe clinical disease during the early phase of the pandemic, while disease severity was significantly lesser among pediatric cases. This review suggests that biomarkers at admission may be useful for prognosis among patients with COVID-19.

## INTRODUCTION

Since the first reported cluster in Wuhan, China, in December 2019, COVID-19 has spread worldwide, with varying intensity across countries. Within the USA, state-level differences in incidence and fatality rates have been attributed to public health management and demographic factors.[1] COVID-19 manifests differently in diverse ethnic groups and countries, with answers beyond socioeconomic and cultural explanations.[2] Reports on multisystem inflammatory syndrome in COVID-19 pediatric patients only emerged in Europe and USA, whereas there were no prior reports among Chinese patients.[3] Additionally, WHO guidance identified cardiovascular disease (CVD) and diabetes as risk factors for COVID-19,[4] but this was based on data obtained from China. Obesity is now emerging as a significant risk factor in Western populations and has been linked to higher levels of inflammation.[5] The interplay between virus and host immune factors at the molecular level has also shed light on why the disease affects people differently.[6]

There is currently a wealth of literature on heterogeneous COVID-19 patient populations including those of different country of origins and clinical types. However, there is limited synthesized evidence examining the differences in clinical presentation of patients with COVID-19 in these diverse populations. This review aims to identify key factors associated with COVID-19 clinical severity, presentation in different geographical areas and populations during the early phase of the pandemic.

## MATERIAL AND METHODS

### Search strategy

This systematic review and meta-analysis was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (online supplemental table S1a). A systematic search for peer-reviewed articles using keywords: '**COVID-19**', '**COVID-19**', '**2019-nCoV**', '**SARS-CoV2**', '**新**

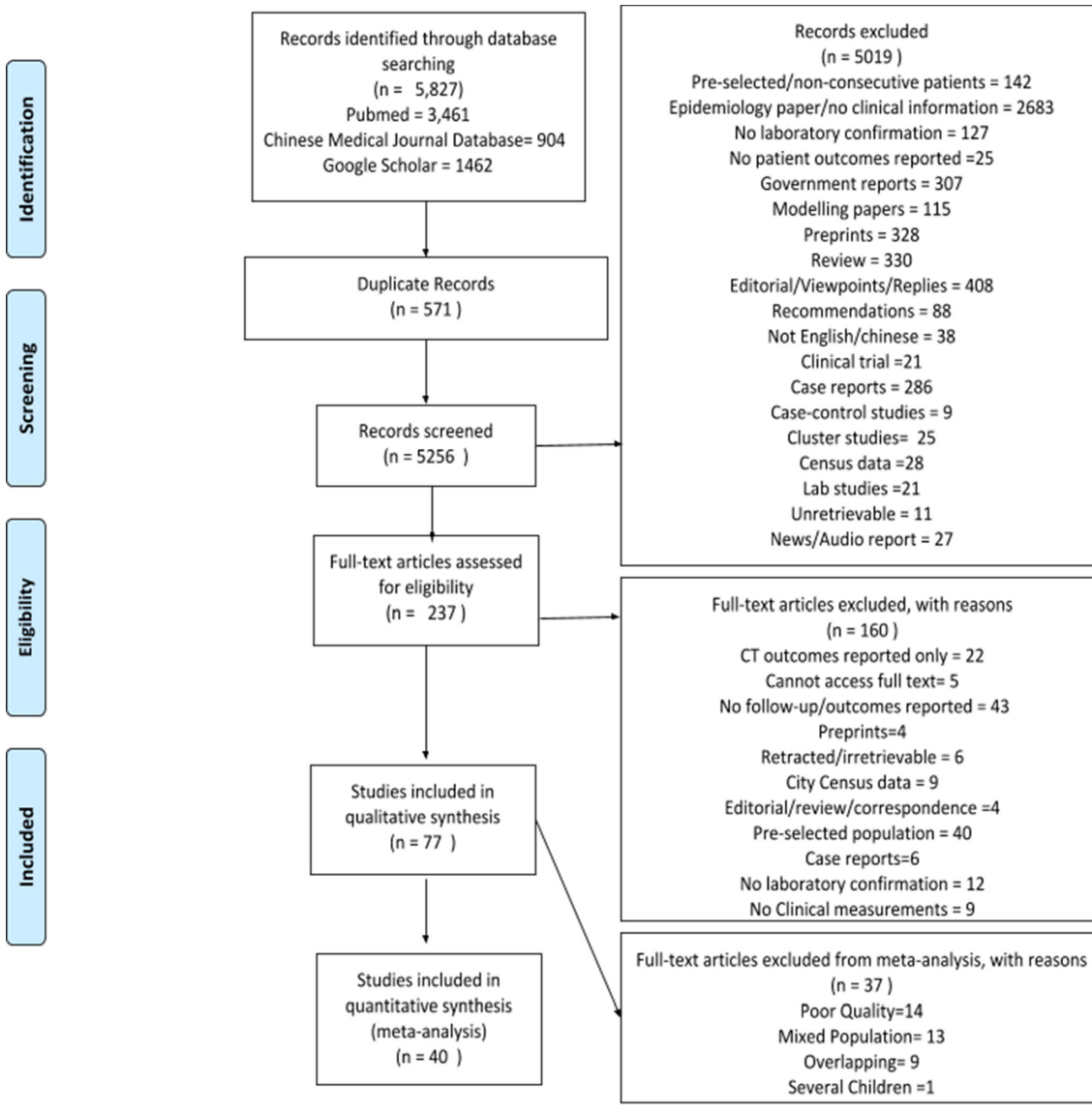


**Figure 1** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

型冠状病毒', '新型肺炎', and '**Wuhan pneumonia**' was conducted in three databases—PubMed, Google Scholar, and Chinese Medical Journal database (figure 1). Articles published from January 1, 2020 to April 9, 2020 in English or Chinese were imported and managed in Endnote V.X9. Primary screening of identified papers was carried out by three authors as per the PICOS tool, while discrepancies were resolved by a fourth author.

Studies selected after full-text screening were observational cohort studies or case series with clinical data (symptoms, laboratory, and chest imaging (CT/X-ray results at admission)) on patients consecutively admitted for laboratory-confirmed COVID-19. Studies focusing on specific groups of patients (with comorbidities, pregnant women) or only CT outcomes or scores were excluded. Included studies had follow-up information over a period or composite endpoint (discharged, death). Editorials, news articles, reviews of selected articles, and case reports (<4 patients) were excluded. Additionally, preprints were excluded due to lack of peer review process which would lower the methodological quality, affecting the findings (online supplemental figure S1).

## Data extraction and quality control

Four reviewers (JK, SUS, PEYC, GH) independently extracted relevant data from eligible studies to an Excel sheet template. Each study was reviewed by two reviewers and any disagreement in extraction was resolved by a third reviewer. The National Heart, Lung, and Blood (NHLB) quality assessment tool[7] was used for cohort studies and case series, focusing on the studies' standardized data collection methodologies (either based on International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) forms or WHO COVID-19 data collection tools). Additionally, the study population had to be well defined (with study period and data cut-off date specified) with consecutively admitted patients recruited and clear inclusion/exclusion criteria. Bias assessment considered whether sufficient time had elapsed between baseline characteristics and clinical

outcome in order to infer any association between exposure and outcome.

### Meta-analysis

Frequencies and proportions of patient characteristics were reviewed. Studies with missing mean and SD were imputed from median, range, and IQR based on a method proposed by McGrath *et al*.[8] Logit and double arcsine transformation methods were used in proportional meta-analysis. The pooled prevalence and means of patient characteristics were calculated with 95% CIs, and forest plots generated using R statistical software V.3.6.3. Statistical heterogeneity was assessed through the $I^2$ statistic and Cochran Q test. Heterogeneity was classified as minimal (<25%), low (25%–50%), moderate (50%–75%), or high (>75%). Considering the variability of epidemiological and clinical characteristics, random-effects model, a more conservative approach, was used. Studies with fair/low risk of bias were considered as moderate/good quality studies and were included in meta-analysis.

Overlapping studies were identified based on study period and study site, while moderate/good quality studies with larger sample size were prioritized for inclusion in this review. Predetermined subgroup analyses with Z-test were conducted to study differences in patient characteristics across different (1) clinical severities (non-severe/severe/fatal), (2) geographical areas (hospitals in Wuhan/other parts of China/outside of China) and (3) age groups (children/adults). In this review, patients were classified based on criteria from the Chinese Diagnosis and Treatment Protocol for COVID-19 (sixth edition) issued by the National Health Commission[9]; severe COVID-19 cases were categorized based on admission into intensive care units (ICUs), while non-severe patients were those not admitted to the ICU or did not receive mechanical invasive/non-invasive ventilation. Fatal group consisted of patients with death as an outcome. For comparison between age groups, studies with non-segregated data based on severity were considered under general adult cohort and compared with children cohort studies. Associations were assessed at $p<0.05$ for test of subgroup differences and pairwise post hoc tests to clarify associations between subgroups with >1 study/data point. Effect sizes such as ORs or mean differences were not pooled as data were not adjusted for confounders; however, significant subgroup differences in pooled prevalence and mean values were described.

Meta-regression was used to examine heterogeneity in case-fatality rate (CFR) due to varying mean age and minimum follow-up duration across different studies and visualized with bubble plots. This was generated with STATA V.16. Publication bias was assessed via visual examination of funnel plot asymmetry, as well as with Egger's test.

## RESULTS

### Literature search results and selected study characteristics

A total of 5827 studies were identified, and based on primary screening, 5590 studies, including 571 duplicates, were excluded and 237 studies were selected for full-text review. A total of 77 studies were shortlisted for qualitative synthesis (figure 1).

Of the 77 studies (N=8832), 66 studies consisted of predominantly adult patients with COVID-19 (n=8677), while remaining studies were on pediatric patients (n=155). Among studies focusing on adult patients from other parts of China (n=27), Zhejiang had most number of studies published (n=6)[10–15] followed by Guangdong (n=4)[16–19] and Chongqing[20–22] and Henan (three each).[23–25] Ten studies were based outside of China: USA (Washington[26] and Seattle),[27] Singapore,[28] France (Lille,[29] Paris and Bordeaux),[30] Italy (Vitoria[31] and Lombardy),[32] Macau,[33] Hong Kong[34] and Thailand[35] (online supplemental table S1b).

All 11 studies on children were from China, with 3 from hospitals in Wuhan. Two studies recruited patients across various cities in China,[36 37] while Guangdong province had the maximum number of pediatric patients (n=25)[38 39] (online supplemental table S1c).

### Risk of bias assessment and stratification into meta-analysis subgroups

Fourteen studies were assessed as having poor quality scores; reasons for high risk of bias included lack of study period and measurement thresholds for laboratory test abnormalities. Of the remaining eligible studies with fair/good quality (n=63), 13 studies with a mixed cohort of children and adults were excluded from meta-analysis as age would introduce substantial heterogeneity in results. Additionally, nine studies with timelines overlapping with other larger sample size studies were excluded (online supplemental table S1b and c). There was only one study on severe cases in children,[40] disallowing meta-analysis to be performed within the children subgroup. Forty studies (n=4884) were eventually used in separate subgroup analyses including studies with patients from hospitals within Wuhan (n=14),[15 41–53] other parts of China (n=8)[10 17 21 23 54–57] and outside of China (n=10).[26–35] A comparison between patients with different clinical severities, which included non-severe (n=5), severe (n=16) and fatal (n=7) COVID-19 outcomes, as well as a stratified analysis by age group (children (n=8)[36 37 39 58–62] and adult (n=21)) were conducted (online supplemental table S1d).

### Adult patient characteristics across different COVID-19 clinical severities (non-severe/severe/fatal)

All seven studies from the fatal subgroup were from Wuhan,[43 47–50 52 63] as well as majority of studies from the non-severe subgroups (five studies).[42 49 53] Conversely, for severe subgroup, 11 out of 16 studies had patient data from hospitals outside of Wuhan including Hong Kong, Shenzhen, Xinyang, Chongqing, Macau, Singapore, Washington, Seattle, Vitoria, Lille and Lombardy region[17 21 23 26 27 29 31–34 36] (online supplemental table S1d).

Directly proportional association was seen between age and severity ($p<0.01$). Mean age of patients increased from 47.1 years (95% CI 42.4 to 51.9) for non-severe cases to 61.8 years (95% CI 60.6 to 63.0) in severe cases, and 69.1 years (95% CI 67.0 to 71.3) for fatal cases ($p<0.01$) (figure 2, online supplemental table S2, figure S2).

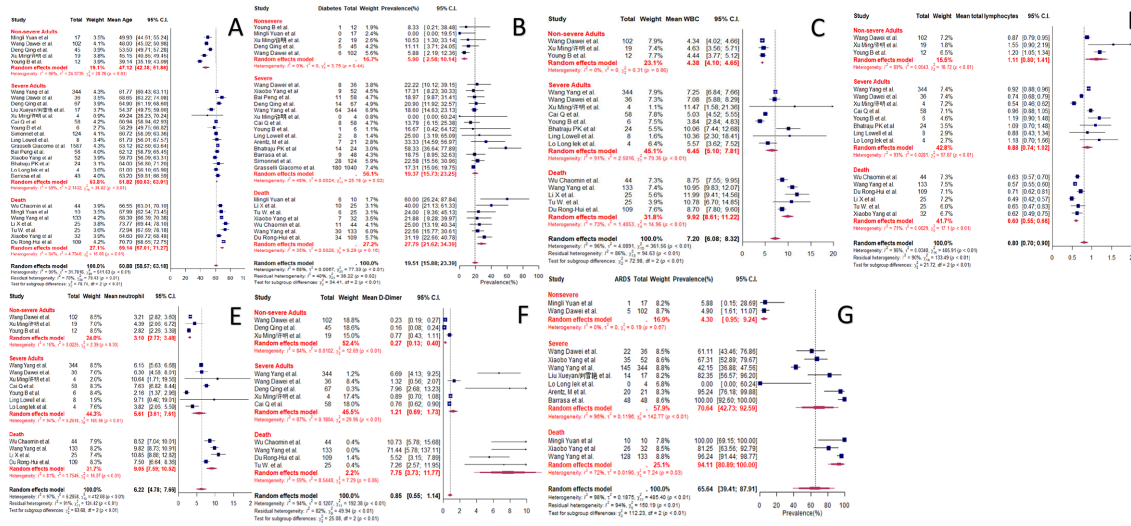

**Figure 2** Patients' characteristics with dose–response relationship across increasing clinical severity: (A) mean age; (B) diabetes; (C) mean white blood cells (WBC); (D) mean total lymphocytes; (E) mean neutrophil; (F) mean D-dimer; (G) acute respiratory distress syndrome (ARDS).

A significantly increased presence of any comorbidity was seen among severe/fatal outcomes compared with non-severe outcomes (p<0.01) (online supplemental table S2). While COPD, CVD, hypertension and diabetes were significantly more prevalent in severe patients compared with non-severe patients (p<0.01), diabetes displayed a dose–response increase in prevalence from non-severe, severe and fatal outcomes (5.9% vs 19.4% vs 27.8%, respectively) (online supplemental table S2, figure S2).

A significant increase in the mean duration of symptom onset to admission (p=0.03) was seen between non-severe cases (4.2 days) and severe and fatal cases (6.3 days and 8.8 days, respectively). Among symptoms assessed at admission, dyspnea/shortness of breath (p<0.01), fatigue (p=0.02) and diarrhea (p=0.02) had subgroup differences, with increased prevalence accompanying more severe outcomes (online supplemental table S2, figure 2). Subsequent pairwise analysis indicated a dose–response increase from non-severe to severe or fatal subgroups, for dyspnea (12% vs 75.2% and 73.2% respectively) and diarrhea (8.7% vs 23.9%), respectively (online supplemental table S2, figure S3).

Among laboratory parameters assessed at admission, mean white blood cells (WBC), total lymphocytes, neutrophil, D-dimer, lactate dehydrogenase (LDH) levels, platelet, C-reactive protein (CRP), bilirubin and creatine kinase differed significantly across subgroups (all p<0.01). Pairwise comparison for mean WBC, neutrophil and D-dimer levels showed a dose–response increase from non-severe to severe to fatal subgroups (online supplemental table S2, figure 2). The proportion of patients admitted with abnormal CXR/CT (p=0.63) and bilateral involvement (p=0.97) did not differ significantly across clinical severity subgroups (online supplemental table S2, figure S4). Mechanical ventilation was observed to be significantly higher in severe and fatal subgroups compared with non-severe subgroup (online supplemental table S2, figure S5). Acute respiratory distress syndrome (ARDS) showed increased prevalence in severe and fatal subgroups compared with non-severe subgroup (p<0.01) (online supplemental table S2, figure 2).

## Adult patient characteristics across hospitals from different geographies

Geographical differences for COVID-19 manifestations were analyzed among patients from Wuhan (n=12),[41–44 47–49 51 53 63–65] other parts of China (n=8, including Shaanxi, Xinyang, Shenyang, Changzhou, Shanghai and Zhejiang)[10 17 21 54–57 66] and outside of China (n=10, including Paris, Bordeaux, Singapore and Bangkok) (online supplemental table S1d).[21 26 27 29 31–36] As of April 9, 2020, published studies based outside of China focused mostly on severe patients or ICU cohorts (n=8, including Hong Kong, Singapore, Washington, Seattle, Vitoria, Lille, Macau and Lombardy) (online supplemental table S3).

Among the overall adult cohort, patients admitted to hospitals in Wuhan had a higher mean age compared with those admitted to hospitals in other parts of China (54.3 years vs 43.6 years, respectively) as well as outside China (50.5 years) (online supplemental table S3, figure 3). A higher proportion of patients outside China showed epidemiological links to Wuhan (98.1%; 95% CI 84.7% to 100%) compared with patients from other parts of China (64.1%; 95% CI 40.6% to 84.6%). Conversely, among severe adult patients, a higher prevalence of epidemiological links to Wuhan was seen in patients from other parts of China (66.0%–95% CI 45.6% to 84.0%) compared with patients outside China (9.5%, 95% CI 0.5% to 24.5%) (online supplemental table S3 figure S6).

Malignancy, hypertension and diabetes were significantly different among adult cohort from the three geographical subgroups (online supplemental table S3, figure 3). In hospitals from other parts of China, including Zhejiang, the presence of malignancy (0.6%, 95% CI 0.2% to 1.3%), hypertension (16.0%, 95% CI 13.7% to 18.6%) and diabetes (6.2%, 95% CI 4.5% to 8.1%) were less common compared with hospitals in Wuhan or outside China (online supplemental table S3, figure S6).

The mean duration of symptom onset to hospitalization was significantly different between geographical subgroups

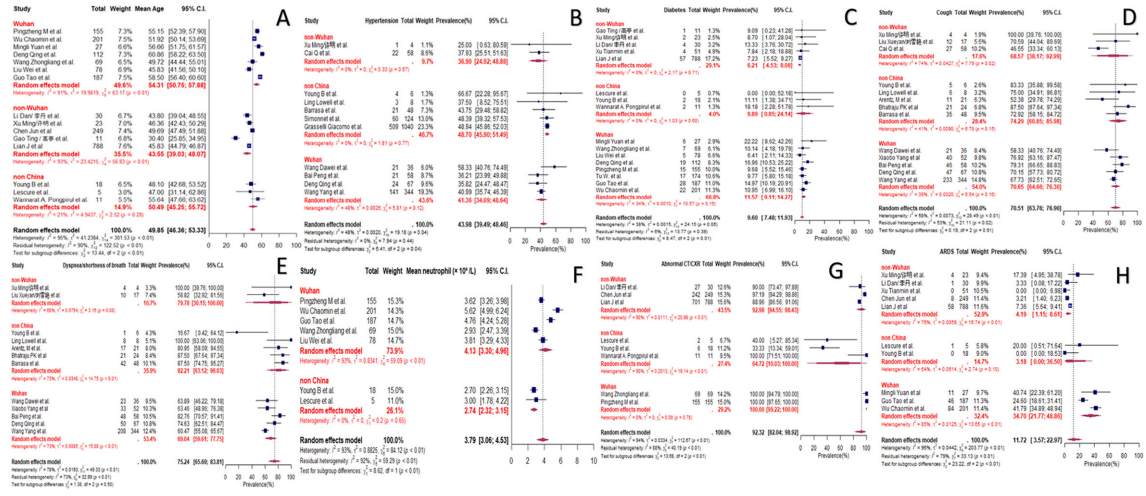

**Figure 3** Forest plots of patient characteristics that differed across all geographical subgroups. (A) Mean age in general adult patients. (B) Hypertension in severe patients. (C) Diabetes in severe patients. (D) Cough in severe patients. (E) Dyspnea in severe patients. (F) Mean neutrophils in general adult patients. (G) Abnormal CT/CXR in severe patients. (H) Acute respiratory distress syndrome (ARDS) in in general adult patients.

(p<0.01). Dyspnea, myalgia and fatigue were significantly more prevalent among patients from Wuhan compared with other parts of China while nausea/vomiting and headache was less common in Wuhan compared with other parts of China (p<0.01) (online supplemental table S3, figure 3).

Mean neutrophil levels were significantly higher in Wuhan patients compared with patients outside of China in general as well as severe cohort (online supplemental table S3, figure 3). Among severe patients, mean platelets were higher in Wuhan compared with patients from outside of China (p<0.01) (online supplemental table S3, figure S6).

Abnormal CT/CXR was more common in Wuhan patients compared with other geographical subgroups (p<0.01). In terms of treatment, glucocorticoid use was more prevalent in Wuhan compared with other geographical areas in the general as well as severe cohort (p<0.01). Conversely, the use of mechanical ventilation among severe patients was significantly higher in patients outside of China (70.8%, 95% CI 58.9% to 81.6%) compared with patients in China (Wuhan and other parts of China; online supplemental table S3). The rate of ARDS and fatality was significantly higher among general adult cohort in Wuhan compared with patients outside of Wuhan (p<0.01) (online supplemental table S3).

## Clinical characteristics among adult and pediatric cohorts

The number of studies with children (n=8)[36 37 39 58–62] was lesser compared with adults (n=17) (online supplemental table S1c). Patient data for children cohort were only available from China and all cases were non-severe. Findings were compared with general adult cohort studies regardless of geographical origin.

The pooled mean age of children and adults was 7.8 (95% CI 7.1 to 8.6) and 49.9 (95% CI 46.4 to 53.3) years. A significantly higher proportions of asymptomatic cases among children were admitted to hospitals (20.6%, 95% CI 6.7% to 38.7%) compared with adults (2.4%, 95% CI 0% to 10%). Most children (83.7%, 95% CI 67.8% to 95.6%) were involved in family clusters, unlike the adult cohort (20.2%, 95% CI14.1% to 27.1%) (online supplemental table S4, figure 4).

There was no significant difference in duration from symptom onset to hospital admission between general adult and pediatric cohorts (4.9 days vs 3.2 days, p=0.51). Prevalence of fever was significantly lower among children (55.5%) compared with adults (84.2%). Lower rates of cough, dyspnea and malaise/fatigue at admission were reported in children compared with the general adult cohort across all geographies (figure 4, online supplemental table S4, figure S7).

Among children, mean levels of WBC, lymphocyte and mean platelet levels were significantly higher compared with general adults (p value<0.0; Online supplemental table S4, figure S7), while similar proportions in both cohorts were discharged (67.6% vs 59.7%) at follow-up. Adults had significantly higher prevalence of abnormal CT/CXR (92%) at admission compared with children (51%) as well as higher prevalence of bilateral involvement and pleural effusion (figure 4, online supplemental table S4, figure S7). All children were classified as non-severe and none underwent mechanical or non-invasive ventilation (online supplemental table S4, figure S7). Similarly, only adult cohorts reported ARDS, ICU admissions (11.7%) and death (CFR 7.8%).

## Effect of age and follow-up time on CFR

A significant positive linear relationship (0.47, 95% CI 0.05 to 0.89; figure 5) between mean age and CFR as well as minimum follow-up duration and CFR (0.58, 95% CI 0.06 to 1.10; figure 5) was seen for 12 adult general cohort studies (p=0.03). Outliers to this trend consisted mostly of patients from Shenyang, Shanghai, Bangkok and Singapore.

## Publication bias

Funnel plot for adult general cohort studies (n=13) shows balanced symmetry, with similar distribution of CFR in

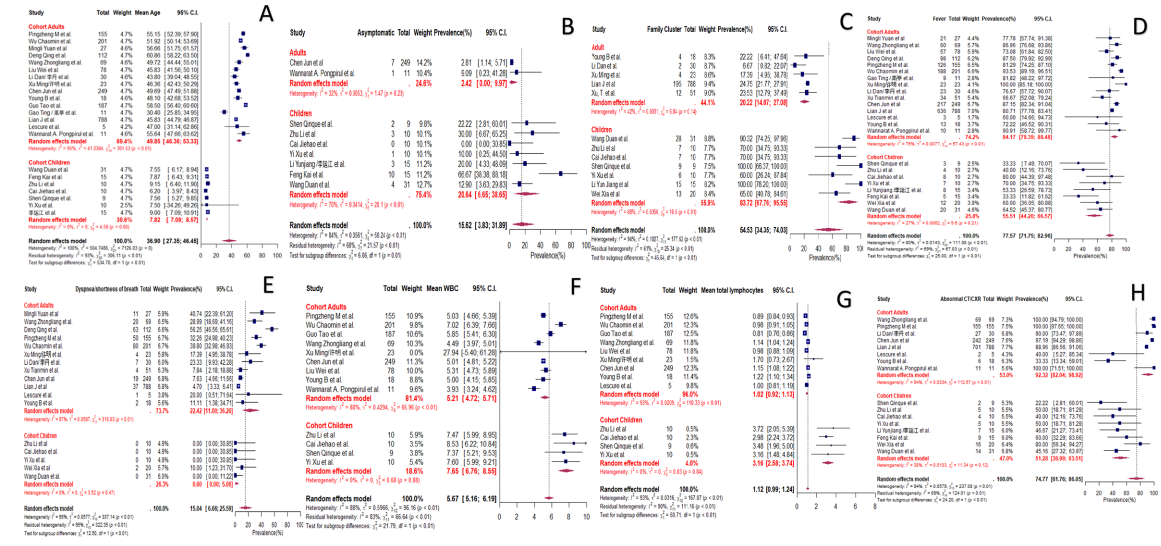

**Figure 4** Forest plots of patients' characteristics of adult and children patient groups. (A) Mean age in years. (B) Asymptomatic cases. (C) Cases with family cluster exposure. (D) Fever. (E) Dyspnea. (F) Mean white blood cells (WBC). (G) Mean total lymphocytes. (H) Abnormal CT/CXR.

smaller, less precise studies (online supplemental figure S8). Egger's test (p=0.38) suggested the absence of publication bias supporting related conclusions for general adult population in our study. Funnel plot for studies reporting severe adult cases (n=11) show balanced symmetry (online supplemental figure S9). Egger's test had a p value of 0.94, suggesting the absence of publication bias among studies exclusively with data on severe cases.

## DISCUSSION

### Demographic and clinical differences across case severities

Based on epidemiologic triad, a susceptible population (host), geographic-specific virus variant (agent) and the local healthcare system (environment) can influence the spread, overall clinical presentation and outcome of COVID-19.[67] Increased age has been recognized as a major risk factor, explainable by physiological changes associated with aging,[68] supporting our analysis. Age profile of patients also correlated with prevalence of comorbidities in Shaanxi and Shanghai, where patients admitted between January and March 2020 had a lower mean age compared with patients in Wuhan. This occurred alongside significantly lower rates age-related diseases like malignancy, hypertension and diabetes.[69]

Our findings were consistent with general understanding that comorbidities including diabetes and hypertension are risk factors for worse outcomes.[4] Although visual inspection of forest plots in this review showed increasing pooled prevalence of CVD with COVID-19 severity, CVD did not show significant differences with increasing clinical severity, contrary to many studies citing CVD as a prognostic factor.[70] Nevertheless, one of the largest studies investigating the effect of comorbidities on serious disease outcomes across China found that CVD was not a risk factor for poor prognosis,[71] while COPD, diabetes, hypertension and malignancy were risk factors after adjusting for age and smoking status. Myocardial injury rather than CVD was seen to be significantly associated with fatal outcome of COVID-19, although myocardial injury is associated with cardiac dysfunction and arrhythmias.[51]

Dyspnea, among various other symptoms at admission, was significantly less common among non-severe compared with severe/fatal cases. This is consistent with well-established prognostic factors for worse COVID-19 outcome.[72] An association between diarrhea and clinical severity observed in this review was scarcely reported in the literature. While one study found that diarrhea was not associated with severe COVID-19,[73] another study showed diarrhea was more common and serious with longer duration and higher frequency in deceased patients than in survivors.[74] Patients with diarrhea were more likely to present with neutrophilia and lymphopenia and develop cytokine storm and multiorgan damage. Several biomarkers, mean WBC, neutrophils, D-dimer, CRP, LDH, bilirubin and platelet levels increased from non-severe to severe/fatal outcomes in this review, while an inverse trend was seen with total lymphocytes. Zhou *et al* reported that raised D-dimer levels were highly associated with COVID-19 fatalities, while age, Sequential Organ Failure Assessment (SOFA) score, and CVD showed similar associations but with smaller risk effect sizes.[75] While these biomarkers can be potential prognostic markers to aid triaging and clinical management, a large independent study to validate the performance of these biomarkers is recommended.

Much research has elucidated how COVID-19 prompts immune cells to release a torrent of chemical signals, ramping up inflammation.[76] In particular, coagulopathy appears to be a key manifestation of severe COVID-19. While most studies associated low platelet levels with worse outcomes,[77] this review found conflicting results with higher platelet counts in fatal compared with non-severe cases. Conversely, Qu *et al* showed that those with worst outcomes presented a peak in the platelet count while the platelet to lymphocyte ratio at the time of platelet peak emerged as an independent prognostic

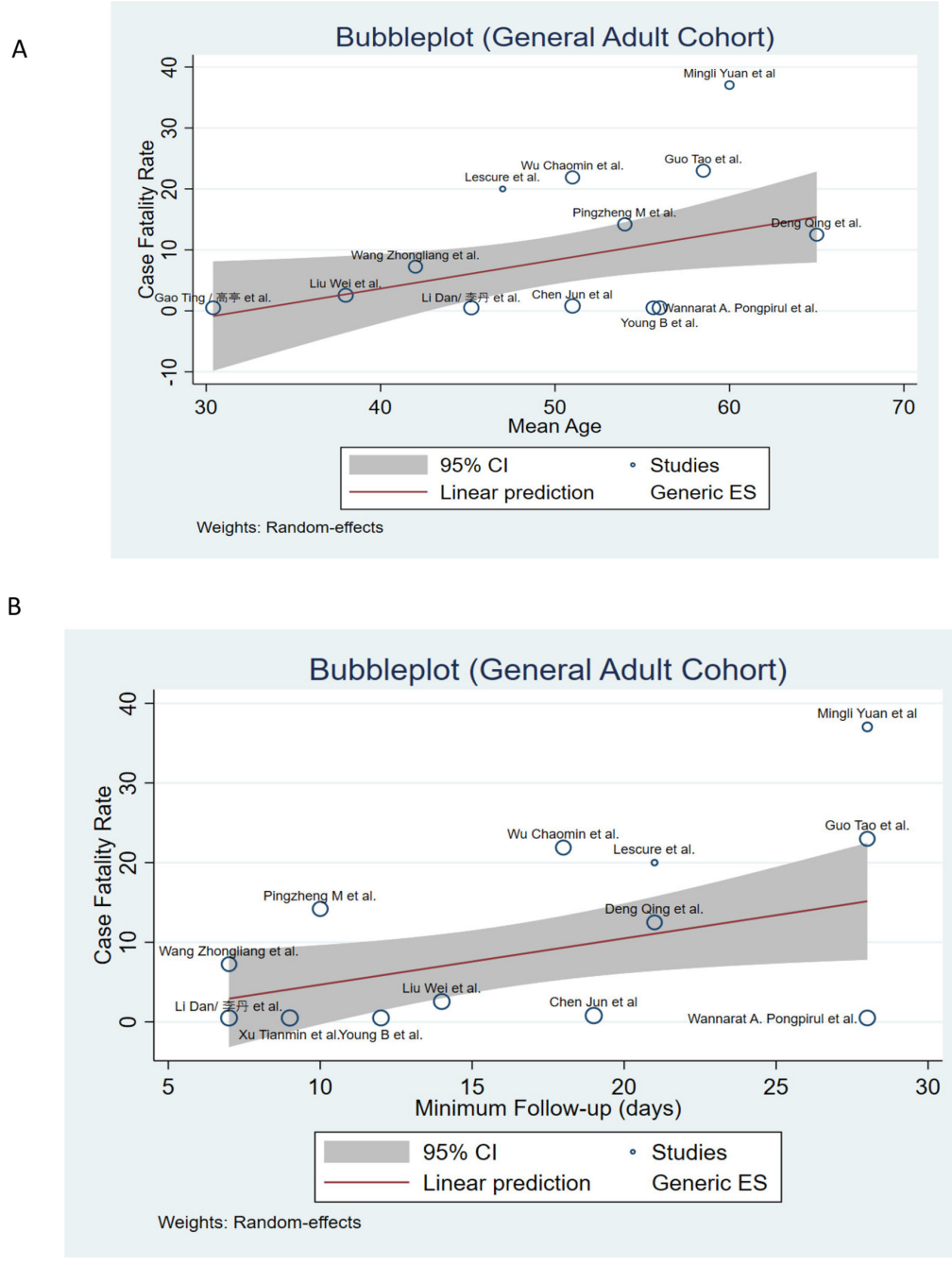


**Figure 5** Bubble plot for meta-regression of (A) age and (B) follow-up duration with case-fatality rate.

factor for prolonged hospitalization.[78] The International Society of Thrombosis and Haemostasis (ISTH) suggests that while there is evidence for thrombocytopenia in COVID-19, it may not be a consistent prognosticator of severe outcomes given variability of results.[79]

## Clinical and severity difference across geographical locations

A significantly higher proportion of patients from Wuhan experienced dyspnea and ARDS in this review, reflecting the general condition of patients presenting to hospitals across different geographies during the study period which is consistent with the progression of the pandemic.[80] While only 1 of 18 patients that were hospitalized in Singapore-based cohort from late January to early February 2020 required mechanical ventilation,[28] Wuhan's hospitals were overwhelmed with patients, and only patients with aggravated symptoms were hospitalized while mild cases were encouraged to self-isolate at home.[81]

ICU fatality rate of hospitalized patients in Hong Kong was much lower than Wuhan, inferring different case severity proportions and ICU resources in these regions.[34] A systematic review noted patients in Hubei Province were more likely to present abnormal liver functions compared with outside Hubei, and that hospitalized patients in Hubei had more severe disease.[82]

This review highlights variation in clinical management and healthcare accessibility across hospitals. Many studies have highlighted disparity in use of mechanical ventilation due to overwhelmed medical system in Wuhan compared with other regions.[49 83 84]

Adult CFR (14.8%) in Wuhan was higher compared with other geographical areas reported in this review. Meta-regression against CFR showed that varying minimum follow-up duration may partially explain differences in CFR. Studies in the UK and USA reported >20% CFR with at least 2 weeks of follow-up[85] or with definite outcomes,[86] suggesting that comparisons of clinical outcomes should take into account follow-up duration.

As more data become available to understand higher rates of disease severity[87] and role of mutations on virulence,[88] more questions on virus–host interactions can be explained.

### Clinical and epidemiological differences among adult and pediatric cases

Number of studies on children were fewer compared with adults. Additionally, this review found that severe COVID-19 clinical presentation and poor outcomes were rare in children and in agreement with health authorities' understanding that children were less susceptible compared with adults.[4] The first city-wide cohort of COVID-19 cases from Jiangsu, Guangzhou and Changsha reported that none required intensive care treatment/mechanical ventilation, and all had relatively normal blood biochemistry and chest imaging.[39 61] Unlike adults, nearly all pediatric cases had normal lymphocyte and leukocyte levels.[60] Chest imaging features in children showed predominantly subpleural changes or nodular ground glass shadows.[38] This difference has been attributed to lower expression of angiotensin-converting enzyme 2 (ACE2) within children's alveolar cells, leading to a reduced potential for SARS-CoV-2 to replicate and to their different immune composition.[89]

Study in Hangzhou hospital found many asymptomatic cases among children which were mostly linked to family cluster/detected through screening.[62] A large-scale systematic review on pediatric cases found 19.3% asymptomatic rate in children, similar to our findings of 20%, highlighting the potential for children to be an undetected source of transmission.[90] In this review, no asymptomatic cases were presented among adult cohort, suggesting the need to screen children with epidemiological linkage to confirmed cases which will help detect subclinical cases and contain the potential spread of COVID-19.

### Limitations

There are some limitations in this review. With limited number of studies from hospitals outside of China as of early April 2020, there was an over-representation of studies from Wuhan wherein the outbreak was first presented. As this review was conducted during the early phase of the pandemic, the epidemic curve in countries outside of China had just begun to rise. Additionally, this review looked at data from patients that were hospitalized. Since the signs and symptoms of COVID-19 varies across severity, asymptomatic patients or those with mild symptoms may not seek medical attention, thus leading to an under-representation of non-severe data. Furthermore, this review was not able to examine other possible risk variables including CD4+ and body mass index/obesity due to insufficient data points for pooling. Although the assessment of bias revealed minimum publication bias, there could be a potential publication bias wherein hospital centres with sensitive data including high CFR may refrain from publishing results. Although this review focused on patients with COVID-19 in the early phase of the pandemic, it provides an insight into the early variant of SARS-CoV-2, guiding future studies that review the differences in clinical severity between the earlier and recent variants of SARS-CoV-2. Nevertheless, strengths of this analysis include the use of 'cleaner' data from hospital centres rather than city-wide census of patient data. The review has also removed overlapping studies to reduce the possibility that the same patient was analyzed twice. With more patient data being published, findings from this review can be updated in the hopes of identifying new patterns of COVID-19 clinical manifestations and epidemiology across time and locations.

## CONCLUSION

Between December 2019 and March 2020, COVID-19 cases presented with greater clinical severity in Wuhan compared with other parts of China and outside China. Differences in clinical management were also observed. Higher prevalence of asymptomatic cases was observed in children compared with adults. The clinical severity presented in hospitals across different geographies was likely attributed by the phase of epidemic spread and the mean age of patients. Potential biomarkers at admission for prognosis of severe disease and fatality among patients with COVID-19 across geographies deserve further validation.

**Acknowledgements** We would like to thank Professor Paul Tambyah, Wang Minxian and Sylvia Gwee for their advice for this manuscript. Additionally, we would like to thank Sylvia Gwee for helping with the final review of the manuscript.

**Contributors** JP: Conceptualization. PEYC, SS, JK, JS and JP: Validation and investigation. HG, SS, PEYC and JK: Formal analysis. PEYC, SS, GH and JK: Data curation. JP, JS, JK, PEYC, HG, and SS: Writing—original draft preparation. JP, JK, PEYC and SS: Writing—review and editing. HG and JK: Visualization. All authors contributed to the article and approved the submitted version.

**Funding** The source of fund comes from the Ministry of Defence (N-608-000-065-001). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

**Competing interests** None declared.

**Patient and public involvement statement** Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Patient consent for publication** Not required.

**Ethics approval** As this was a systematic review, ethical approval was not required as participants were not recruited in the study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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