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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Review

Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: A systematic review and meta-analysis

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ABSTRACT

Introduction: Since December 2019, a novel coronavirus (SARS-CoV-2) has triggered a world-wide pandemic with an enormous medical and societal-economic toll. Thus, our aim was to gather all available information regarding comorbidities, clinical signs and symptoms, outcomes, laboratory findings, imaging features, and treatments in patients with coronavirus disease 2019 (COVID-19).

Methods: EMBASE, PubMed/Medline, Scopus, and Web of Science were searched for studies published in any language between December 1st, 2019 and March 28th, 2020. Original studies were included if the exposure of interest was an infection with SARS-CoV-2 or confirmed COVID-19. The primary outcome was the risk ratio of comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatments, outcomes, and complications associated with COVID-19 morbidity and mortality. We performed random-effects pairwise meta-analyses for proportions and relative risks, I^2, T^2, and Cochrane Q, sensitivity analyses, and assessed publication bias.

Results: 148 studies met the inclusion criteria for the systematic review and meta-analysis with 12′149 patients (5′739 female) and a median age of 47.0 [35.0–64.6] years. 617 patients died from COVID-19 and its complication. 297 patients were reported as asymptomatic. Older age (SMD: 1.25 [0.78–1.72]; $p < 0.001$), being male (RR = 1.32 [1.13–1.54], $p = 0.005$) and pre-existing comorbidity (RR = 1.69 [1.48–1.94]; $p < 0.001$) were identified as risk factors of in-hospital mortality. The heterogeneity between studies varied substantially (I^2; range: 1.5–98.2%). Publication bias was only found in eight studies (Egger's test: $p < 0.05$).

Conclusions: Our meta-analyses revealed important risk factors that are associated with severity and mortality of COVID-19.

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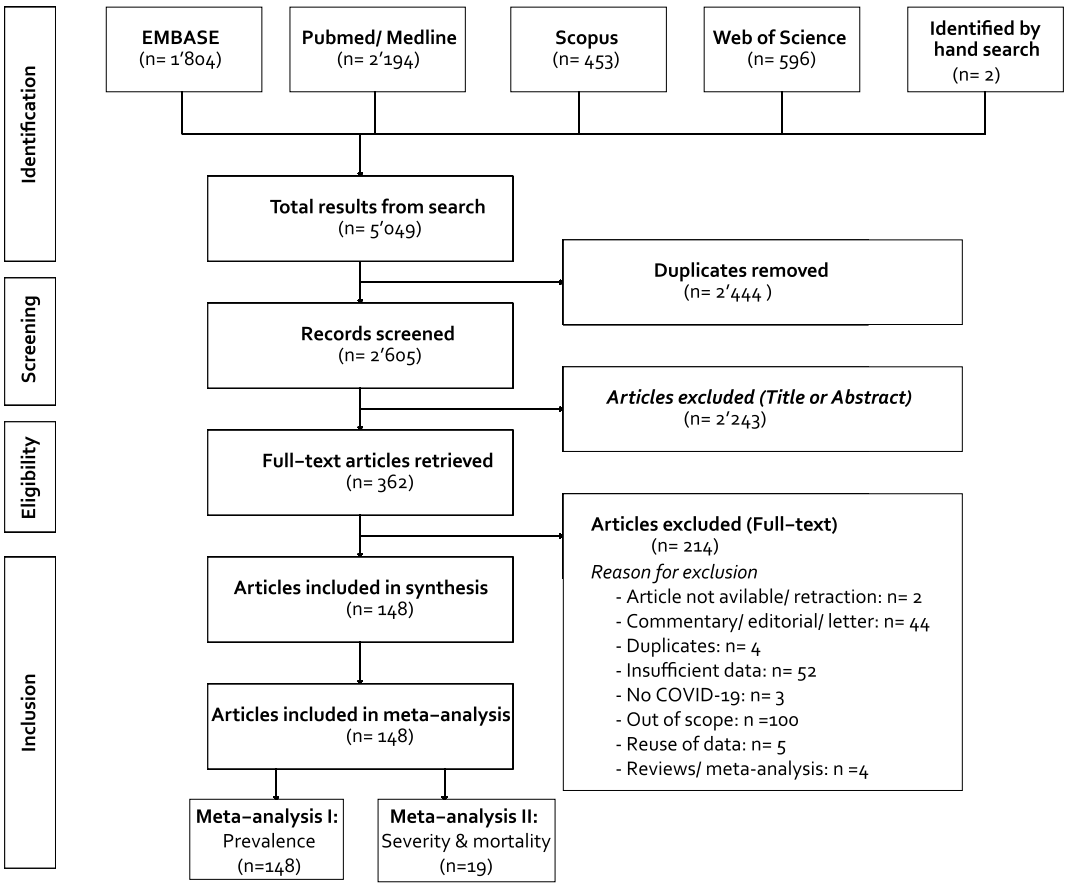

Fig. 1. Flow-chart of the search strategy. A total of 148 studies were eligible for the literature review and the first part of the meta-analysis (i.e., prevalence). Nineteen studies were included in the second part of the meta-analysis (i.e., severity and mortality).

1. Introduction

The severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) initially emerged in Wuhan, Hubei, People's Republic of China and has been identified as the causative agent of coronavirus disease 2019 (COVID-19). It's pandemic spread presents a substantial medical challenge with an enormous societal and economic toll [1,2]. Similar to influenza and SARS-CoV-1, SARS-CoV-2 is considered a "crowd disease" that spreads most easily when individuals are packed together at high densities. Phylogenetic data implicate a zoonotic origin [3] and the rapid spread suggests ongoing person-to-person transmission [4]. Additional factors contributing to the rapid spread constitute the duration of the incubation period [5] and infectiousness peaking on or before symptom onset [6] contribute to the rapid spread of SARS-CoV-2. Another factor contributing to the rapid spread and alarmingly high number of infected people is the SARS-CoV-2 nature of initial dormancy of symptoms. The most common symptoms associated with COVID-19 include a sudden onset of fever, coughing, and dyspnea [2,7,8]. Complications comprise acute respiratory distress syndrome (ARDS), pneumonia, kidney failure, bacterial superinfections, coagulation abnormalities and thromboembolic events, sepsis, and even death [9,10]. So far, only a few demographic and clinical factors, such as older age, diabetes, and cardiovascular diseases, have been linked with poor outcome and increased risk of mortality [11,12]. This knowledge gap extends to the risk of infections, disease progression, and outcomes in vulnerable patient populations, including newborns, children, pregnant, and elderly patients. A better understanding of the risks for these vulnerable patient populations is critical in order to optimize their protection and tailor prevention and treatment strategies. Thus, the aim of our systematic review and meta-analysis was to gather available information in the literature and determine the most prevalent comorbidities, clinical signs and symptoms, imaging features, laboratory parameters, treatments, outcomes, and complications arising in patients with COVID-19. We stratified our systematic reviews and meta-analysis by different cohorts, namely pediatric/neonatal and adult COVID-19 patients including pregnant women. Furthermore, we aimed to assess current evidence for the associations between risk factors and in-hospital mortality. Based on previous reports, we addressed the hypothesis that male sex, older age, as well as pre-existing hypertension and diabetes mellitus are risk factors of morbidity and mortality in patients with COVID-19.

2. Methods

Our systematic review and meta-analysis adhere to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [13] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [14].

2.1. Search strategy and selection criteria

Four bibliographic databases were systematically searched: EMBASE, PubMed/Medline, Scopus, and Web of Science. Our search was not restricted by language. We searched for studies published from December 1st, 2019 to March 28th, 2020, with search terms related to COVID-19 ("COVID-19", "SARS-CoV-2", "coronavirus disease 2019", "severe acute respiratory syndrome coronavirus 2", "2019 novel coronavirus", "2019-nCoV", "coronavirus", and "corona virus"). The full search strategy is provided in Appendix 1. Manual searching was also performed, reviewing reference lists of relevant studies and

comprehensive review articles. Records were managed by EndNote X 8.0 software to exclude duplicates.

2.2. Selection of studies

Two investigators (CRJ and MW) independently screened the titles and abstracts to determine whether studies should be included. Eligibility criteria were also applied to the full-text articles during the final selection. In case multiple articles reported on a single study, the article that provided the most data was selected for further synthesis. We quantified the inter-rater agreement for study selection using Cohen's κ coefficient [15]. Articles written in Chinese were reviewed by our two native speaking authors (BT and CW) and if the inclusion criteria were met, these authors also extracted the specified data. All disagreements were discussed and resolved at a consensus meeting.

2.3. Inclusion and exclusion criteria

All full-text, peer-reviewed articles that described case-control, cohort studies, or case studies investigating the epidemiological and clinical features, comorbidities, laboratory parameters, imaging features, treatment, and/or outcomes (e.g., death) of patients that were diagnosed with COVID-19. We excluded duplicate publications, non-peer reviewed articles (e.g., preprints), reviews, meta-analyses, abstracts or conference proceedings, editorials, commentaries, letters with insufficient data, studies on non-human species, or out-of-scope studies (e.g., comparison with other infections, case-fatality reports). In case multiple studies published data from the same cohort, we included the article representing the most inclusive information on the population to avoid overlap. Lastly, studies that did not report demographics (i.e., age and sex) were also excluded. Fig. 1 outlines our search strategy and application of inclusion and exclusion criteria.

2.4. Data extraction and synthesis

Data extraction tables were created with the following information: 1) publication information (i.e., author, date, language of article, country where the study was performed, study design [case study, case series, or cohort study] [16], study population [pediatric/neonatal and adult COVID-19 patients including pregnant women); 2) demographics (i.e., age, sex); 3) clinical signs and symptoms (e.g., cough, fatigue, fever, sputum); 3) comorbidities (e.g., hypertension, diabetes, cardiovascular diseases); 4) therapies administered to treat COVID-19 (e.g., antibiotics, antivirals, invasive mechanical ventilation); 5) clinical outcomes (e.g., death, survival, recovery); and 6) complications associated with COVID-19 (e.g., sepsis and shock, ARDS). In case studies provided data for multiple patient groups (e.g., pediatric and adult patient), we extracted this information separately for each group. A full list of extracted variables is provided in Supplementary Table 1.

2.5. Statistical analysis

For the studies reporting mean and standard deviation (SD) for extracted variables, we computed the median and interquartile ranges (IQR) assuming a normal distribution (i.e., using the formula: IQR ~SD*1.35). To test if there is a bias by including the studies for which we computed the median and IQR (i.e., quartiles, Q1 and Q3), we performed a sensitivity analyses in which we calculated the median and IQR under the assumption of right-skewed and left-skewed distribution (see Appendix 2). We compared the results of the different distributions to test the robustness of our findings. Descriptive statistics (median, IQR, n, and %) were used to characterize the studies and patients included as well as the laboratory parameters. Weighted by study sample size, the pooled median and 95% confidence interval (CI) were computed for continuous variables. Normality approximation of the binomial was used to construct an approximate confidence interval (R package *metamedian* [17]). Welch's two-sample *t*-test was employed to test if there are significant differences in the proportion of male and female patients across studies.

Our meta-analysis was structured in two parts. In the first part, we performed meta-analyses of all 148 studies to define the prevalence of comorbidities, clinical signs and symptoms, imaging features, treatments, outcomes, and complications associated with COVID-19. Using the *metaprop* function of the R package *metafor* [18], we calculated the overall prevalence from studies reporting a single prevalence. Our meta-analysis was stratified by patient group (pediatric/neonatal [$\leq$17 years of age], pregnant, and adult COVID-19 patients). Heterogeneity between studies was assessed visually by Forest plots, and analytically by I^2, Tau (T^2), and Cochrane Q. Briefly put, I^2 describes the percentage of variation across studies that is due to heterogeneity rather than chance [19]: 0% indicates no heterogeneity, whereas 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively. The CIs for I^2 were calculated using the iterative non-central chi-squared distribution method of Hedges and Piggott [20]. Tau (T^2) represents the absolute value of the true variance (heterogeneity) and is the estimated SD of underlying true effects across studies. Cochran's Q is the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method (i.e., sample size) [21]. The second part comprised meta-analyses to calculate the relative risk (RR) of certain comorbidities, clinical signs and symptoms, imaging features, laboratory parameters, complications, and outcomes in patients with severe vs. those with non-severe disease condition (12 studies) as well as deceased vs. survivors (7 studies). The categorization into severe and non-severe COVID-19 disease was consistent with the groups reported by the reviewed studies (Supplementary Table 2). Owing to our judgment that considerable clinical and statistical heterogeneity exists among the studies (statistical heterogeneity was confirmed by the computed I^2, T^2, and Cochrane Q), we calculated pooled RRs with 95% CIs using random-effects models with inverse-variance weighting (*metabin* function from R package *meta*). For continuous outcome data (e.g., age, laboratory parameters, and time from symptoms onset to hospital admission), we estimated the standardized mean difference (SMD) by means of a random-effects models with inverse variance weighting for pooling (*metacont* function from R package meta). To calculate the SMD, we converted medians, Q1s, and Q3s into means and standard deviations. The SMD, 95% CIs, and p values were reported. We produced Forest plots to visualize the results from the random-effects models (R function: *forest*). Publication bias was assessed visually by funnel plots (R function: *funnel*) and analytically by the Egger test (R function: *regtest*). An Egger test $p < 0.05$ indicates a significant publication bias. All statistical analyses were performed in R (version 3.6.3) for MacOS X (Mojave, 10.14.4) with the packages meta (version 4.11–0) and *dmetar* (version 0.0.90) [18]. The code used for the analysis and to create figures and tables is provided in our GitHub repository (https://github.com/jutzca/Corona-Virus-Meta-Analysis-2020).

2.6. Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Study selection and study characteristics

Our systematic literature search yielded 5′049 articles (including articles identified by manual searching). Upon removal of duplicates and exclusion of studies on the basis of their abstracts or following screening their full text, 148 met the inclusion criteria and were

Table 1
Included studies of adults with COVID-19.

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Ai et al., 2020 [32]	Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases	32101510	S1	China	English	Cohort Study	Adult	1014	51 (15)	467 (46)	547 (54)
Albarello et al., 2020 [159]	2019-novel Coronavirus severe adult respiratory distress syndrome in two cases in Italy: An uncommon radiological presentation	32112966	S2	Italy	English	Case series	Adult	2	66.5 [66.25–66.75]	1 (50)	1 (50)
An et al., 2020 [94]	CT Manifestations of Novel Coronavirus Pneumonia: A Case Report	32157862	S3	China	English	Case Study	Adult	1	50	0 (0)	1 (100)
Arentz et al., 2020 [59]	Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State	32191259	S4	USA	English	Cohort Study	Adult	21	70 [43–92]	11 (52)	10 (48)
Bai et al., 2020 [128]	Analysis of the first cluster of cases in a family of novel coronavirus pneumonia in Gansu Province	32064855	S5	China	Chinese	Case series	Adult	7	53.4	3 (43)	4 (57)
Chan et al., 2020 [4]	A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster	31986261	S6_adult	China	English	Case series	Adult	5	50 [36.25–64.50]	2 (40)	3 (60)
Chang et al., 2020 [131]	Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China	32031568	S7	China	English	Cohort Study	Adult	13	34 [34–48]	10 (77)	3 (33)
Chen et al., 2020 [95]	Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia	32164089	S8	China	Chinese	Cohort Study	Adult	29	56 [range 26–79]	21 (72)	8 (28)
Chen et al., 2020 [67]	Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19	32141280	S9_severe	China	Chinese	Cohort Study	Adult (severe)	24	68.5 (13.6)	18 (75)	6 (25)
Chen et al., 2020 [67]	Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19	32141280	S9_nonsevere	China	Chinese	Cohort Study	Adult (non-severe)	126	57.1 (15.6)	66 (52)	60 (48)
Chen et al., 2020 [39]	Clinical progression of patients with COVID-19 in Shanghai, China	32171869	S10	China	English	Cohort Study	Adult	249	51 [36–64]	126 (51)	123 (49)
	Epidemiological and clinical	32007143	S11	China	English	Cohort Study	Adult	99	55.5 (13.1)	67 (68)	32 (32)

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Table 1 (*continued*)

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Chen et al., 2020 [140]	characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study										
Chen et al., 2020 [161]	Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study	32217556	S12	China	English	Cohort Study	Adult	274	62 [44–70]	171 (62)	103 (38)
Cheng et al., 2020 [149]	Epidemiological characteristics of novel coronavirus pneumonia in Henan	32118390	S13	China	Chinese	Cohort Study	Adult	1079	46 [IQR: 24]	573 (53)	506 (47)
Cheng et al., 2020 [62]	Clinical Features and Chest CT Manifestations of Coronavirus Disease 2019 (COVID-19) in a Single-Center Study in Shanghai, China	32174128	S14	China	English	Cohort Study	Adult	11	50.36 (15.5)	8 (73)	3 (27)
Cheng et al., 2020 [157]	First case of Coronavirus Disease 2019 (COVID-19) pneumonia in Taiwan	32113824	S15	Taiwan	English	Case Study	Adult	1	55	0 (0)	1 (100)
[b] [69]	Early Epidemiological and Clinical Characteristics of 28 Cases of Coronavirus Disease in South Korea	32149037	S16	Korea	English	Cohort Study	Adult	28	42.6 [range 20–73]	15 (54)	13 (46)
Dai et al., 2020 [105]	CT Imaging and Differential Diagnosis of COVID-19	32129670	S17	China	English	Case Series	Adult	4	50 [47.75–55.125]	4 (100)	0 (0)
Deng et al., 2020 [68]	Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study	32209890	S18_death	China	English	Cohort Study	Adult and pediatric	109	69[62–74]	73 (67)	36 (33)
Deng et al., 2020 [68]	Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study	32209890	S18_survival	China	English	Cohort Study	Adult and pediatric	116	40[33–57]	51 (44)	65 (56)
Ding et al., 2020 [72]	The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China	32196707	S19	China	English	Case Series	Adult	5	49 [47–50]	2 (40)	3 (60)
Ding et al., 2020 [28]	A cured patient with 2019-nCoV pneumonia	32205073	S20	China	English	Case Study	Adult	1	57	0 (0)	1 (100)
Dong et al., 2020 [106]	Epidemiological characteristics of confirmed COVID-19 cases in Tianjin	32164400	S21	China	English	Cohort Study	Adult	135	48.62 (16.83)	72 (53)	63 (47)
Duan and Qin 2020 [144]	Pre- and Posttreatment Chest CT Findings - 2019 Novel Coronavirus (2019-nCoV) Pneumonia	32049602	S22	China	English	Case Study	Adult	1	46	0 (0)	1 (100)

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Table 1 (*continued*)

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Fan et al., 2020 [49]	Perinatal Transmission of COVID-19 Associated SARS-CoV-2: Should We Worry?	32182347	S23	China	English	Case Series	Adult	2	31.5 [30.25–32.75]	0 (0)	2 (100)
Fang et al., 2020 [93]	Changes of CT findings in a 2019 novel coronavirus (2019-nCoV) pneumonia patient	32073631	S24	China	English	Case Study	Adult	1	47	1 (100)	0 (0)
Fang et al., 2020 [88]	Comparisons of nucleic acid conversion time of SARS-CoV-2 of different samples in ICU and non-ICU patients	32209381	S25	China	English	Cohort Study	Adult	32	41	16 (50)	16 (50)
Fang et al., 2020 [115]	CT Manifestations of Two Cases of 2019 Novel Coronavirus (2019-nCoV) Pneumonia	32031481	S26	China	English	Case Series	Adult	2	38.5 [35.25–41.75]	1 (50)	1 (50)
Gautret et al., 2020 [127]	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial	32205204	S27	France	English	Case Series	Adult	36	47 [24.5–61.5]	15 (42)	21 (58)
Gross et al., 2020 [112]	CT appearance of severe, laboratory-proven coronavirus disease 2019 (COVID-19) in a Caucasian patient in Berlin, Germany	32193883	S28	Germany	English	Case Study	Adult	1	61	1 (100)	0 (0)
Guan et al., 2020 [25]	Epidemiological investigation of a family clustering of COVID-19	32149484	S29	China	Chinese	Case Series	Adult	7	53.43	3 (43)	4 (57)
Guan et al., 2020 [138]	Clinical Characteristics of Coronavirus Disease 2019 in China	32109013	S30	China	English	Cohort Study	Adult	1099	47 [35–58]	639 (58)	460 (42)
Guan et al., 2020 [142]	CT Findings of Coronavirus Disease (COVID-19) Severe Pneumonia	32208010	S31	China	English	Case Study	Adult	1	59	0 (0)	1 (100)
Guan et al., 2020 [120]	Imaging Features of Coronavirusdisease 2019 (COVID-19): Evaluationon Thin-Section CT	32204990	S32	China	English	Cohort Study	Adult	53	42 [range 1–86]	25 (47)	28 (53)
Han et al., 2020 [137]	Early Clinical and CT Manifestations of Coronavirus Disease 2019 (COVID-19) Pneumonia	32181672	S33	China	English	Cohort Study	Adult	108	45	38 (35)	70 (65)
Han et al., 2020 [104]	The course of clinical diagnosis and treatment of a case infected with coronavirus disease 2019	32073161	S34	China	English	Case Study	Adult	1	47	1 (100)	0 (0)
Hao, 2020 [30]	Clinical features of atypical 2019 novel coronavirus pneumonia with an initially negative RT-PCR assay	32092387	S35	China	English	Case study	Adult	1	58	1 (100)	0 (0)
He et al., 2020 [52]	Impact of complicated myocardial injury on the clinical outcome	32171190	S36	China	Chinese	Cohort Study	Adult	54	68 [59.8–74.3]	34 (63)	20 (37)

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Table 1 (*continued*)

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
	of severe or critically ill COVID-19 patients										
Hill et al., 2020 [118]	The index case of SARS-CoV-2 in Scotland: a case report	32205138	S37	Scotland	English	Case Study	Adult	1	51	1 (100)	0 (0)
Holshue et al., 2020 [113]	First Case of 2019 Novel Coronavirus in the United States	32004227	S38	USA	English	Case Study	Adult	1	35	1 (100)	0 (0)
Hosoda et al., 2020 [57]	SARS-CoV-2 enterocolitis with persisting to excrete the virus for about two weeks after recovering from diarrhea: A case report	32188528	S39	Japan	English	Case Study	Adult	1	81	0 (0)	1 (100)
Hu et al., 2020 [119]	Clinical characteristics of 24 asymptomatic infections with COVID19 screened among close contacts in Nanjing, China	32146694	S40	China	English	Cohort Study	Adult	24	32.5 [19.0–57.0]	8 (33)	16 (64)
Hu et al., 2020 [102]	CT imaging of two cases of one family cluster 2019 novel coronavirus (2019-nCoV) pneumonia: inconsistency between clinical symptoms amelioration and imaging sign progression	32190575	S41	China	English	Case Series	Adult	2	42.5 [40.25–44.75]	1 (50)	1 (50)
Huang et al., 2020 [76]	Clinical characteristics of laboratory confirmed positive cases of SARS-CoV2 infection in Wuhan, China: A retrospective single center analysis	32114074	S42	China	English	Cohort Study	Adult	34	56.24 (17.14)	14 (41)	20 (59)
Huang et al., 2020 [66]	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	31986264	S43	China	English	Cohort Study	Adult	41	49 [41–58]	30 (73)	11 (27)
Huang et al., 2020 [109]	Use of Chest CT in Combination with Negative RT-PCR Assay for the 2019 Novel Coronavirus but High Clinical Suspicion	32049600	S44	China	English	Case Study	Adult	1	36	1 (100)	0 (0)
Jin et al., 2020 [63]	Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms	32213556	S45_withGI	China	English	Cohort Study	Adult - with GI Symptoms	74	46.14 (14.19)	37 (50)	37 (50)
Jin et al., 2020 [63]	Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms	32213556	S45_noGI	China	English	Cohort Study	Adult - No GI Symptoms	577	45.09 (14.45)	294 (51)	283 (49)
		32198005	S46	Vietnam	English		Adult	1	46	0 (0)	1 (100)

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Table 1 (*continued*)

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Lee et al., 2020 [54]	A case of COVID-19 and pneumonia returning from Macau in Taiwan: Clinical course and anti-SARS-CoV-2 IgG dynamic					Case study					
Leung et al., 2020 [47]	Clinical features of deaths in the novel coronavirus epidemic in China	32175637	S47	China	English	Cohort Study	Adult	46	70.6 (12.63)	31 (67)	15 (33)
Li et al., 2020 [114]	CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19)	32215691	S48	China	English	Cohort Study	Adult	78	44.6 (17.9)	38 (49)	40 (51)
Li et al., 2020 [99]	Characteristics of peripheral blood leukocyte differential counts in patients with COVID-19	32114745	S49	China	Chinese	Cohort Study	Adult	10	46.5 [36.5–64.3]	5 (50)	5 (50)
Li et al., 2020 [96]	Comparison of epidemic characteristics between SARS in 2003 and COVID-19 in 2020 in Guangzhou	32159317	S50	China	Chinese	Cohort Study	Adult	346	48 [range 3 months–90 yo]	167 (48)	179 (52)
Li et al., 2020 [111]	Comparison of the clinical characteristics between RNA positive and negative patients clinically diagnosed with 2019 novel coronavirus pneumonia	32087623	S51	China	Chinese	Cohort Study	Adult	31	54	15 (48)	16 (52)
Lian et al., 2020 [77]	Analysis of Epidemiological and Clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan	32211844	S52_young	China	English	Cohort Study	Adult (young and middle-aged < 60 years)	652	41.15 (1.38)	349 (54)	303 (46)
Lian et al., 2020 [77]	Analysis of Epidemiological and Clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan	32211844	S52_old	China	English	Cohort Study	Adult (elderly>=60 years)	136	68.28 (7.31)	58 (43)	78 (57)
Lin et al., 2020 [40]	Novel coronavirus pneumonia outbreak in 2019: Computed tomographic findings in two cases	32056397	S53	China	English	Case Series	Adult	2	37 [36–38]	2 (100)	0 (0)
Liu et al., 2020 [147]	Clinical feature of COVID-19 in elderly patients: a comparison with young and middle-aged patients	32171866	S54_old	China	English	Cohort Study	Adult (elderly>=60 years)	18	68.00 [65.25–69.75]	12 (67)	6 (33)
Liu et al., 2020 [147]	Clinical feature of COVID-19 in elderly patients: a comparison with young and middle-aged patients	32171866	S54_young	China	English	Cohort Study	Adult (young and middle-aged < 60 years)	38	47 [35.75–51.25]	19 (50)	19 (50)
Liu et al., 2020 [153]	Gross examination of report of a COVID-19 death autopsy	32198987	S55	China	Chinese	Case Study	Adult	1	85	1 (100)	0 (0)
Liu et al., 2020 [90]	Clinical characteristics of 30 medical workers	32062957	S56	China	Chinese	Cohort Study	Adult	30	35 [21–59]	10 (33)	20 (67)

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Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
	infected with new coronavirus pneumonia										
Liu et al., 2020 [81]	Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease	32118640	S57	China	English	Cohort Study	Adult	78	38 [33–57]	39 (50)	39 (50)
Liu et al., 2020 [74]	Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury	32048163	S58_adult	China	English	Case Series	Adult	12	63 [53.5–65]	8 (67)	4 (33)
Liu et al., 2020 [133]	Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province.	32044814	S59	China	English	Cohort Study	Adult	137	57 [range 20–83]	61 (45)	76 (55)
Liu et al., 2020 [146]	Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children	32171865	S60_adult	China	English	Cohort Study	Adult	14	33.5 [range 27-58]	5 (36)	9 (64)
Mo et al., 2020 [98]	Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China	32173725	S61	China	English	Cohort Study	Adult	155	54 [42–66]	86 (55)	69 (45)
Pan et al., 2020 [132]	Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China	32055945	S62	China	English	Cohort Study	Adult	63	44.9 (15.2)	33 (52)	30 (48)
Peng et al., 2020 [145]	Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nVoC	32120458	S63_severe	China	Chinese	Cohort Study	Adult (severe)	16	57.5 [54–63]	9 (56)	7 (44)
Peng et al., 2020 [36]	Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nVoC	32120458	S63_nonsevere	China	Chinese	Cohort Study	Adult (non-severe)	96	62 [55–67.5]	44 (46)	52 (54)
Qian et al., 2020 [80]	A COVID-19 Transmission within a family cluster by presymptomatic infectors in China	32201889	S64_adult	China	English	Case series	Adult	7	57.5 [44.5–59]	3 (43)	4 (57)
Qian et al., 2020 [156]	Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series	32181807	S65	China	English	Cohort Study	Adult	91	50 [36.5–57]	37 (41)	54 (59)
Qu et al., 2020 [61]	Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19	32181903	S66	China	English	Cohort Study	Adult	30	50.5 [36–65]	16 (53)	14 (47)
		32004165	S67	China	English		Adult	5	52 [49–61]		2 (40)

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Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Ren et al., 2020 [165]	Identification of a novel coronavirus causing severe pneumonia in human - a descriptive study					Case Series				3 (60)	
Ruan et al., 2020 [130]	A case of 2019 novel coronavirus infected pneumonia with twice negative 2019-nCoV nucleic acid testing within 8 days	32149771	S68	China	English	Case study	Adult	1	47	0 (0)	1 (100)
Shi et al., 2020 [44]	Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China	32211816	S69	China	English	Cohort Study	Adult	416	64 [range 21–90]	205 (49)	211 (51)
Shi et al., 2020 [51]	Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study	32105637	S70	China	English	Cohort Study	Adult	81	49.5 (11)	42 (52)	39 (48)
Shi et al., 2020 [103]	Evolution of CT Manifestations in a Patient Recovered from 2019 Novel Coronavirus (2019-nCoV) Pneumonia in Wuhan, China	32032497	S71	China	English	Case Study	Adult	1	42	1 (100)	0 (0)
Silverstein et al., 2020 [91]	First imported case of 2019 novel coronavirus in Canada, presenting as mild pneumonia	32061312	S72	Canada	English	Case Study	Adult	1	56	1 (100)	0 (0)
Song et al., 2020 [60]	SARS-CoV-2 induced diarrhea as onset symptom in patient with COVID-19	32139552	S73	China	English	Case Study	Adult	1	22	1 (100)	0 (0)
Song et al., 2020 [164]	Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia	32027573	S74	China	English	Cohort Study	Adult	51	49 (16)	25 (49)	26 (51)
Spiteri et al., 2020 [31]	First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020	32156327	S75	Europe	English	Cohort Study	Adult	38	42 [range 2–81]	25 (66)	13 (34)
Stoecklin et al., 2020 [160]	First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020	32070465	S76	France	English	Case Series	Adult	3	31 [30.5–39.5]	2 (67)	1 (33)
Sun et al., 2020 [134]	Epidemiological and Clinical Predictors of COVID-19	32211755	S77	Singapore	English	Cohort Study	Adult	54	42 [34–54]	29 (54)	25 (46)
Sun et al., 2020 [89]	Evolution of Computed Tomography Manifestations in Five Patients Who Recovered from Coronavirus Disease 2019 (COVID-19) Pneumonia.	32174054	S78	China	English	Case Series	Adult	5	45 [range 20–55]	2 (40)	3 (60)
Tang et al., 2020 [108]	Abnormal coagulation parameters are associated with poor prognosis in patients with novel	32073213	S79	China	English	Cohort Study	Adult	183	54.1 (16.2)	98 (54)	85 (46)

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Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
	coronavirus pneumonia										
Tian et al., 2020 [148]	Characteristics of COVID-19 infection in Beijing	32112886	S80	China	English	Cohort Study	Adult	262	47.5 [range 1–94]	127 (48)	135 (52)
Tian et al., 2020 [84]	Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer	32114094	S81_case1	China	English	Case Study	Adult	1	73	1 (100)	0 (0)
Tian et al., 2020 [84]	Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer	32114094	S81_case2	China	English	Case Study	Adult	1	84	0 (0)	1 (100)
Tong et al., 2020 [38]	Potential Presymptomatic Transmission of SARS-CoV-2, Zhejiang Province, China, 2020	32091386	S82	China	English	Case Series	Adult	6	23.00 [15.00–41.75]	3 (50)	3 (50)
Van Cuong et al., 2020 [154]	The first Vietnamese case of COVID-19 acquired from China	32085849	S83	Vietnam	English	Case Study	Adult	1	25	0 (0)	1 (100)
Wan et al., 2020 [70]	Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing	32198776	S84	China	English	Cohort Study	Adult	135	47 [36–55]	72 (53)	63 (47)
Wang et al., 2020 [56]	Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment	32037389	S85	China	English	Case series	Adult	4	47.5 [28.75–63]	3 (75)	1 (25)
Wang et al., 2020 [139]	Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China	32031570	S86	China	English	Cohort Study	Adult	138	56 [42–68]	75 (54)	63 (46)
Wang et al., 2020 [100]	Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China	32176772	S87	China	English	Cohort Study	Adult	69	42 [35–62]	32 (46)	37 (54)
Wang et al., 2020 [45]	Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China	32179910	S88	China	English	Cohort Study	Adult	55	49 [range 2–69]	22 (40)	33 (60)
Wang et al., 2020 [26]	The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China	32139464	S89	China	English	Cohort Study	Adult	18	39 [29–55]	10 (56)	8 (44)
Wu et al., 2020 [125]	Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A	32109279	S90	China	English	Cohort Study	Adult	80	46.1(15.42)	39 (49)	41 (51)

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Table 1 (*continued*)

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
	Multicenter Descriptive Study										
Wu et al., 2020 [85]	Biological characters analysis of COVID-19 patient accompanied with aplastic anemia	32145715	S91	China	Chinese	Case Study	Adult	1	48	1 (100)	0 (0)
Xie et al., 2020 [82]	Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplification tests	32114193	S92	China	English	Case Series	Adult	9	34 [26–45]	4 (44)	5 (56)
Xiong et al., 2020 [50]	Clinical and High-Resolution CT Features of the COVID-19 Infection: Comparison of the Initial and Follow-up Changes	32134800	S93	China	English	Cohort Study	Adult	42	49.5 (14.1)	25 (60)	17 (40)
Xu et al., 2020 [73]	Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2	32109443	S94	China	English	Cohort Study	Adult	50	43.9 (16.8)	29 (58)	21 (42)
Xu et al., 2020 [22]	Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2	32107577	S95	China	English	Cohort Study	Adult	90	50 [range 18–86]	39 (43)	51 (57)
Xu et al., 2020 [64]	Pathological findings of COVID-19 associated with acute respiratory distress syndrome	32085846	S96	China	English	Case Study	Adult	1	50	1 (100)	0 (0)
Xu et al., 2020 [8]	Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series	32075786	S97	China	English	Cohort Study	Adult	62	41 [32–52]	35 (56)	27 (44)
Xu et al., 2020 [41]	Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19	32179140	S98_imported	China	English	Cohort Study	Adult	15	35	10 (67)	5 (33)
Xu et al., 2020 [41]	Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19	32179140	S98_secondary	China	English	Cohort Study	Adult	17	37	7 (41)	10 (59)
Xu et al., 2020 [41]	Clinical features and dynamics of viral load in imported and non-importedpatients with COVID-19	32179140	S98_tertiary	China	English	Cohort Study	Adult	19	53	8 (42)	11 (58)
Yang et al., 2020 [126]	Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China	32112884	S99	China	English	Cohort Study	Adult	149	45.11 (13.35)	81 (54)	68 (46)
		32105632	S100	China	English		Adult	52	59.7 (13.3)		17 (33)

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Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Yang et al., 2020 [9]	Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study					Cohort Study				35 (67)	
Yao et al., 2020 [42]	Clinical characteristics and influencing factors of patients with novel coronavirus pneumonia combined with liver injury in Shaanxi region	32153170	S101	China	Chinese	Cohort Study	Adult	40	53.87 (15.84)	25 (63)	15 (37)
Yao et al., 2020 [143]	Epidemiological characteristics of 2019-ncoV infections in Shaanxi, China by February 8, 2020	32139462	S102	China	English	Cohort Study	Adult	195	44.13 (15.8)	129 (66)	66 (34)
Ye et al., 2020 [23]	Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation	32171867	S103	China	English	Case series	Adult	5	31 [30–32]	2 (40)	3 (60)
Yoon et al., 2020 [141]	Chest Radiographic and CT Findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of Nine Patients Treated in Korea	32100485	S104	South Korea	English	Cohort Study	Adult	9	54	4 (44)	5 (56)
Young et al., 2020 [79]	Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore	32125362	S105	Singapore	English	Cohort Study	Adult	18	47 [31–71]	9 (50)	9 (50)
Yu et al., 2020 [150]	A Familial Cluster of Infection Associated With the 2019 Novel Coronavirus Indicating Possible Person-to-Person Transmission During the Incubation Period	32067043	S106	China	English	Case series	Adult	4	72 [68–78.25]	2 (50)	2 (50)
Yuan et al., 2020 [55]	Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China	32191754	S107	China	English	Cohort Study	Adult	27	60 [47–69]	12 (44)	15 (56)
Zhang et al., 2020 [71]	CT image of novel coronavirus pneumonia: a case report	32189175	S108	China	English	Case Study	Adult	1	64	1 (100)	0 (0)
Zhang et al., 2020 [27]	Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing	32164091	S109	China	Chinese	Cohort Study	Adult	9	36 [15–49]	5 (56)	4 (44)
Zhang et al., 2020 [34]	Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China	32077115	S110	China	English	Cohort Study	Adult	140	57 [range 25–87]	71 (51)	69 (49)
Zhang et al., 2020 [155]	Epidemiological, clinical characteristics of cases of SARS-CoV-2	32205284	S111	China	English	Cohort Study	Adult	573	46.65 (13.83)	295 (51)	278 (49)

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Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
	infection with abnormal imaging findings.										
Zhang et al., 2020 [117]	High-resolution CT features of 17 cases of Corona Virus Disease 2019 in Sichuan province, China	32139463	S112	China	English	Cohort Study	Adult	17	48.6 [range 23–74]	8 (47)	9 (53)
Zhao et al., 2020 [162]	The characteristics and clinical value of chest CT images of novel coronavirus pneumonia	32199619	S113	China	English	Cohort Study	Adult	80	44 (1.77)	43 (54)	37 (46)
Zhao et al., 2020 [78]	A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias	32161968	S114	China	English	Cohort Study	Adult	19	48 [27–56]	11 (58)	8 (42)
Zhou et al., 2020 [48]	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	32171076	S115	China	English	Cohort Study	Adult	191	56 [46.0–67.0]	119 (62)	72 (38)
Zhu et al., 2020 [110]	Comparison of heart failure and 2019 novel coronavirus pneumonia in chest CT features and clinical characteristics	32129583	S116	China	Chinese	Cohort Study	Adult	12	52 [32–73]	8 (67)	4 (33)
Zhu et al., 2020 [58]	Clinical and CT imaging features of 2019 novel coronavirus disease (COVID-19)	32142928	S117	China	English	Case Series	Adult	6	43 [32–56]	0 (0)	6 (100)

[a] Mean(sd) or median[Q1-Q3].
[b] COVID-19 National Emergency Response Center, Epidemiology and Case Management Team, Korea Centers for Disease Control and Prevention, Cheongju, Korea et al., 2020.

considered for the review and meta-analysis (Fig. 1) [4,8,9,11,22–165]. The inter-rater agreement for study selection was very high (κ = 0.94 [95% CI: 0.91–0.96], 97.0% agreement [11/362 studies with disagreement]). Detailed information on the included studies are provided in Tables 1–3. Included studies were conducted in 15 countries between December 1st, 2019 and March 28th, 2020 (Supplementary Table 3) and enrolled between 1 and 1′099 patients (median 12.5 [1.00–56.75]). The majority of the articles were written in English (123 studies, 83.1%) and the remainder in Chinese (25 studies, 16.9%). We classified studies according to their design [16]: cohort study (76 studies, 51.4%), case study/report (41 studies, 27.7%), and case series (31 studies, 20.9%). While all studies reported information on demographics (148, 100%), the number of studies reporting information on comorbidities (84 studies, 56.8%), clinical sign and symptoms (130 studies, 87.8%), laboratory parameters (113 studies, 76.4%), imaging features (118 studies, 79.7%), treatments (91, 61.5%), outcomes (118 studies, 79.3%), and complications (59 studies, 39.9%) varied markedly.

In terms of study population, 114 studies included only adult participants, 6 only pregnant women, 22 only children and neonates, and 6 included mixed cohorts. Of the total 12′149 patients included, 6′410 (52.8%) were male and 5′739 were female (47.2%, Fig. 2A and B). The median age of adult (11′058 patients, 91.0%), pregnant (35 patients, 0.3%), and pediatric (1′056 patients, 8.7%; including neonates) patients was 47.0 years [35.0–65.3] (Fig. 3A), 30.0 [26.0–33.0] (Fig. 3B), and 10.0 [2.0–13.0] (Fig. 3C), respectively. Approximately 7.8% (297/3′822 patients) were reported to be asymptomatic and 7.7% (617/8′047) died during hospitalization due to complications related to the infection with SARS-CoV-2. With the exception of one 10-month old child, all deaths were non-pregnant adult COVID-19 patients.

3.2. Adult patients

Higher proportions of male than female patients were reported to be infected with SARS-CoV-2 (t = 2.678, df = 202, p = 0.008; Fig. 2A) across all studies. Comorbidities were present in ~31% of the adult patients (2′329/7′608), with hypertension being the most prevalent one (1′352/6′460 patients, 20.93%), followed by heart failure (37/354 patients, 10.5%), diabetes mellitus (678/6′535 patients, 10.4%), and coronary heart disease (194/2′388 patients, 8.5%) (Fig. 4A, Table 4, Supplementary Fig. 1). The most frequent clinical signs and symptoms were fever (6′955/8′859 patients, 78.5%), cough (4′778/8′885 patients, 53.8%), and fatigue (1′996/7′980 patients, 25.0%) (Fig. 4B, Table 4). A little over five percent of the adult COVID-19 patients were asymptomatic (148/2′749 patients, 5.4%). Over 6′969 patients (89.6%) had abnormal CT imaging features. The most common patterns of CT abnormalities were indicating pneumonia (unilateral or bilateral; 6′620/7′917 patients, 83.6%), including air bronchogram (264/523 patients, 50.5%), and ground-glass opacity (GGO) with consolidation (153/323 patients, 47.4%) and without (2′446/5′591 patients, 43.8%) (Table 4, Supplementary Fig. 2). In terms of laboratory parameters, inflammatory markers, such as interleukin 6 (22 pg/mL [4.68–51.8]), and erythrocyte sedimentation rate (32.5 mm/h [17.3–53.8]) were elevated across the

Table 2
Included studies of pregnant women with COVID-19.

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Chen et al., 2020 [29]	Pregnant women with new coronavirus infection: a clinical characteristics and placental pathological analysis of three cases	32114744	S118	China	Chinese	Case Series	Pregnant	3	29.6	0 (0)	3 (100)
Chen et al., 2020 [75]	Chest computed tomography images of early coronavirus disease (COVID-19)	32162211	S119	China	English	Case Study	Pregnant	1	27	0 (0)	1 (100)
Chen et al., 2020 [11]	Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records	32151335	S120	China	English	Case series	Pregnant	9	28 [26–33]	0 (0)	9 (100)
Dong et al., 2020 [46]	Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn	32215581	S121_pregnant	China	English	Case Study	Pregnant	1	29	0 (0)	1 (100)
Liao et al., 2020 [122]	Chest CT Findings in a Pregnant Patient with 2019 Novel Coronavirus Disease	32212578	S122	China	English	Case Study	Pregnant	1	25	0 (0)	1 (100)
Liu et al., 2020 [146]	Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children	32171865	S60_pregnant	China	English	Cohort Study	Pregnant	16	30 [26–35]	0 (0)	16 (100)
Wang et al., 2020 [123]	A case of 2019 Novel Coronavirus in a pregnant woman with preterm delivery	32119083	S123	China	English	Case study	Pregnant	1	28	0 (0)	1 (100)
Wang et al., 2020 [152]	A case report of neonatal COVID-19 infection in China	32161941	S124_pregnant	China	English	Case study	Pregnant	1	34	0 (0)	1 (100)
Wen at al, 2020 [124]	A patient with SARS-CoV-2 infection during pregnancy in Qingdao, China	32198004	S125	China	English	Case study	Pregnant	1	31	0 (0)	1 (100)
Xia et al., 2020 [136]	Emergency Caesarean delivery in a patient with confirmed coronavirus disease 2019 under spinal anaesthesia	32192711	S126	China	English	Case Study	Adult	1	27	0 (0)	1 (100)

[a] Mean(sd) or median[Q1-Q3].

adult population. Moreover, markers of coagulation, namely D-dimer (0.5 μg/mL [0.3–1.08]), fibrinogen (4.5 g/L [3.66–5.1]), and cell damage were also elevated (i.e., lactate dehydrogenase, U/L; 213 [173–268]). An overview of all laboratory parameters is provided in Supplementary Table 4. As shown in Fig. 4D, the most common treatments were antivirals (4′475/6′068 patients, 73.8%), oxygen therapy (1′300/1′872 patients, 69.4%), and antibiotics (2′518/4′825 patients, 52.2%). Detailed information on all treatments is provided in Table 4. Eight percent (616/7′727 patients) of the adults died during the hospitalization due to complications related to COVID-19. Amongst the survivors (7′111/7′727 patients, 92.0%), a total of 3′025 (68.7%) remained hospitalized, 1′751 (32.4%) were discharged, and 1′012 (27.1%) reportedly recovered (Fig. 4C, Table 4). Important to note, for some patients it was stated that they both, recovered and were discharged (i.e., one patient can fall in multiple categories). The median duration between symptoms onset and hospitalization was 8 days [7–9.5]. A total of 195 (6.8%) patients were admitted to the intensive care unit (ICU). The most frequently reported complications associated with COVID-19 were pneumonia (1′032/1′489 patients, 69.2%), respiratory failure (141/413 patients, 34.1%), acute cardiac injury (242/1′250 patients, 19.4%), and ARDS (759/5′122 patients, 14.8%), (Fig. 4D, Table 4).

3.3. Pregnant woman

Studies investigating the effect of COVID-19 in pregnant women reported that only five pregnant women had any history of comorbidities. Hypothyroidism, allergies, or influenza were reported each for one pregnant woman (in two cases the exact nature of comorbidity was not reported) (Supplementary Table 5). Fever (25/35 patients, 71.4%), cough (12/29 patients, 41.4%), and myalgia (3/9 patients, 33.3%) were the three most common symptoms observed in pregnant women that were infected with SARS-CoV-2 (Supplementary Fig. 3, Supplementary Table 5). Abnormal CT features were evident in 88.6% (31/35 patients) of pregnant women diagnosed with COVID-19. Pneumonia (unilateral or bilateral, 31/35 patients, 88.6%), GGO (29/34 patients, 85.3%), and consolidation (8/16 patients, 50.0%) were among the most common patterns of CT abnormalities (Supplementary Fig. 4, Supplementary Table 5). Inflammatory markers, such as C-reactive protein (19.25 mg/L [12.35–25.7]), procalcitonin (0.187 ng/mL), and neutrophil count (9.14×10^9/L) were elevated in this patient population. Along this line, lactate dehydrogenase concentrations were increased (544 U/L) reflecting cellular damage. An overview of all laboratory parameters is provided in Supplementary Table 4. Moreover, antibiotics (14/14 patients, 100.0%), antivirals (11/14 patients, 78.6%) and oxygen therapy

Table 3
Included studies of pediatric and neonatal patients with COVID-19Type a message.

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Cai et al., 2020 [65]	First case of 2019 novel coronavirus infection in children in Shanghai	32102141	S127	China	Chinese	Case Study	Pediatric	1	7	1 (100)	0 (0)
Chan et al., 2020 [4]	A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster	31986261	S6_pediatric	China	English	Case series	Pediatric	1	10	1 (100)	0 (0)
Chen et al., 2020 [101]	First case of severe childhood novel coronavirus pneumonia in China	32135586	S128	China	Chinese	Case Study	Pediatric	1	1.1	1 (100)	0 (0)
Cui et al., 2020 [33]	A 55-Day-Old Female Infant Infected With 2019 Novel Coronavirus Disease: Presenting With Pneumonia, Liver Injury, and Heart Damage	32179908	S129	China	English	Case study	Neonatal	1	55 (days)	0 (0)	1 (100)
Dong et al., 2020 [46]	Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn	32215581	S121_pediatric	China	English	Case Study	Neonatal	1	0	0 (0)	1 (100)
Dong et al., 2020 [92]	Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China	https://doi.org/10.1542/peds.2020-0702	S130	China	English	Cohort Study	Pediatric	731	10 [2–13]	420 (57)	311 (43)
Fan et al., 2020 [158]	Anal swab findings in an infant with COVID-19	DOI: 10.1002/ped4.12186	S131	China	English	Case Study	Neonatal	1	0.25	0 (0)	1 (100)
Feng et al., 2020 [87]	Analysis of CT features of 15 children with 2019 novel coronavirus infection	32061200	S132	China	Chinese	Case series	Pediatric	15	7 [range 4–14]	5 (33)	10 (67)
Ji et al., 2020 [135]	Clinical features of pediatric patients with COVID-19: a report of two family cluster cases	32180140	S133	China	English	Case Series	Pediatric	2	12.0 [10.5–13.5]	2 (100)	0 (0)
Le et al., 2020 [24]	The first infant case of COVID-19 acquired from a secondary transmission in Vietnam	32213326	S134	Vietnam	English	Case Study	Neonatal	1	0.25	0 (0)	1 (100)
Liu et al., 2020 [74]	Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury	32048163	S58_pediatric	China	English	Case Study	Pediatric	1	10	1 (100)	0 (0)
Liu et al., 2020 [86]	Detection of Covid-19 in Children in Early January 2020 in Wuhan, China	32163697	S135	China	English	Case Series	Pediatric	6	3 [3–3.75]	2 (33)	4 (67)
Liu et al., 2020 [146]	Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children	32171865	S60_pediatric	China	English	Cohort Study	Pediatric	4	3.0 [0.7–6.0]	2 (50)	2 (50)
		32187458	S136	China	English		Pediatric	171	6.7 [2–9.8]		67 (39)

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Table 3 (*continued*)

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
Lu et al., 2020 [37]	SARS-CoV-2 Infection in Children					Cohort Study				104 (61)	
Park et al., 2020 [163]	First Pediatric Case of Coronavirus Disease 2019 in Korea	32193905	S137	South Korea	English	Case Study	Pediatric	1	10	0 (0)	1 (100)
Qian et al., 2020 [80]	A COVID-19 Transmission within a family cluster by presymptomatic infectors in China	32201889	S64_pediatric	China	English	Case study	Pediatric (asymptomatic)	1	1.1	0 (0)	1 (100)
Sun et al., 2020 [116]	Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study	32193831	S138	China	English	Case series	Pediatric	8	10.2 [5.04–13.54]	6 (75)	2 (25)
Tang et al., 2020 [43]	Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China	32150527	S139	China	English	Case Study	Pediatric	1	10	1 (100)	0 (0)
Wang et al., 2020 [83]	SARS-CoV-2 infection with gastrointestinal symptoms as the first manifestation in a neonate	32204755	S140	China	Chinese	Case Study	Neonatal	1	19 (days)	1 (100)	0 (0)
Wang et al., 2020 [152]	A case report of neonatal COVID-19 infection in China	32161941	S124_pediatric	China	English	Case study	Neonatal	1	0	1 (100)	0 (0)
Wang et al., 2020 [107]	Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China	32118389	S141	China	Chinese	Cohort Study	Pediatric	31	7.1 [0.6–17]	15 (48)	16 (52)
Wei et al., 2020 [53]	Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China	32058570	S142	China	English	Case Series	Neonatal	9	0.58 [0.33–0.75]	2 (22)	7 (78)
Xia et al., 2020 [151]	Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults	32134205	S143	China	English	Cohort Study	Pediatric	20	2 [range 1 day–14 years 7 months]	13 (65)	7 (35)
Xu et al., 2020 [35]	Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding	PMCID: PMC7095102	S144	China	English	Case Series	Pediatric	10	6.63 [2.17–13.4]	6 (60)	4 (40)
Zeng et al., 2020 [97]	First case of neonate infected with novel coronavirus pneumonia in China	32065520	S145	China	Chinese	Case Study	Neonatal	1	17 (days)	1 (100)	0 (0)
Zhang et al., 2020 [145]	2019-novel coronavirus infection in a three-month-old baby	32043842	S146	China	Chinese	Case study	Neonatal	1	0.25	0 (0)	1 (100)
Zheng et al., 2020 [129]	Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China	32207032	S147	China	English	Cohort Study	Pediatric	25	3 [2–9]	14 (56)	11 (44)
Zhou et al.,	Clinical features and chest CT findings of	32204756	S148	China	Chinese	Case Series	Pediatric	9		4 (44)	5 (56)

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Table 3 (*continued*)

Authors	Title	PMID	Unique study ID	Country	Language	Study type	Study population	Sample size	Age[a]	Male (%)	Female (%)
2020 [121]	coronavirus disease 2019 in infants and young children								1 [range 7 months-3 years]		

[a] Mean(sd) or median[Q1-Q3].

(high flow nasal cannula; 3/12 patients, 25.0%) were used to treat pregnant COVID-19 patients (Supplementary Table 5). None of the pregnant COVID-19 patients died. Lastly, one patient was admitted to the ICU (Supplementary Table 5).

3.4. Pediatric and neonatal patients

Similar to the adult cohort, the proportion between female and male patients were comparable in the pediatric/neonatal cohort ($t = 1.169$, $df = 26$, $p = 0.253$; Fig. 2B). Fourteen percent of the children and neonates were asymptomatic (149/1′054). With the exception of two children, no comorbidities were reported for any of the pediatric or neonatal patients (Supplementary Table 6). Similar to the adult and pregnant COVID-19 patients, children and neonates frequently presented with fever (170/320 patients, 53.1%), cough (149/311 patients, 47.9%), and sputum (14/51 patients, 27.5%) (Supplementary Fig. 6 and Supplementary Table 6). Sixty-five percent of the pediatric and neonatal patients presented with CT abnormalities, including pneumonia (194/298 patients), GGO (108/278 patients, 38.9%), and local patchy shadowing (52/223 patients, 23.3%) (Supplementary Fig. 7, Supplementary Table 6). An overview of all laboratory parameters is provided in Supplementary Table 7. As the reference values vary considerably within the pediatric/neonatal patient population, the results of the laboratory parameters have to be interpreted with caution. In terms of treatment, children and neonates received antibiotics (31/43 patients, 72.1%), oxygen therapy through high flow nasal cannula (5/9 patients, 55.6%), and alpha interferon aerosol inhalation therapy (31/52, 59.6%) to treat COVID-19 and its complications (Supplementary Fig. 8, Supplementary Table 6). With the exception of a 10-month-old child that died four weeks after admission of multi-organ failure, all children survived. Less than 30% remained hospitalized (90/293 patients), 74.5% were discharged (216/290 patients) and 87.4% reportedly recovered (236/270 patients) (Supplementary Fig. 9, Supplementary Table 6). The median duration between symptoms onset and hospitalization was 6 days [4.0–8.5]. Fifteen percent (6/39 patients) had to be admitted to the ICU. Complications associated with COVID-19 comprised pneumonia (16/26 patients, 61.5%), secondary bacterial infection (12/21 patients, 57.1%), and respiratory failure (10/33 patients, 30.3%) (Supplementary Table 6).

3.5. Non-severe vs. severe

Twelve studies (2′596 patients) provided separate data for patients with a severe (500 patients, 19.3%) and non-severe disease status (2′096, 80.7%). No differences regarding sex were found between severe ($t = 0.604$, $df = 16.645$, $p = 0.554$; male: 278 patients [55.6%] and female: 210 patients [42.0%]; unknown sex: 12 patients [2.4%]) and non-severe disease status group ($t = 0.217$, $df = 16.393$, $p = 0.831$; male: 1′059 patients [50.5%] and female: 925 patients [49.5%]) (Supplementary Fig. 10). In terms of age, patients with non-severe COVID-19 were significantly younger (median age in years = 45.0 [34.0–57.0]) than those with a severe disease progression (61.4 [44.5–75.5], Fig. 5). Our meta-analysis revealed that older age (SMD: 0.68 [0.40–0.97]; $p < 0.001$), being male (RR = 1.11 [1.01–1.22]; $p = 0.039$), and preexisting comorbidities (RR = 2.11 [1.02–4.35], $p = 0.046$) were associated with a higher risk of increased disease severity. Specifically, hypertension (RR = 2.15 [1.64–2.81], $p < 0.001$), diabetes mellitus (RR = 2.56 [1.50–4.39], $p = 0.005$), any heart condition (RR = 4.09 [2.45–6.84], $p < 0.001$), and chronic obstructive pulmonary disease (COPD, RR = 5.10 [3.08–8.45], $p < 0.001$) (Fig. 6, Table 5) were associated with worse outcome (i.e., severe disease). To test if the increased risk of heart conditions is attributable to the study that has classified their patients into severe and non-severe based on the presence or absence of cardiac injuries, we conducted a sensitivity analysis excluding this study [44]. The risk of any heart condition remained significantly elevated in the severe disease patient cohort (RR = 3.87 [1.85–8.11], $p = 0.005$). Numerous laboratory parameters were significantly different between the non-severe and severe patient cohorts. Patients with severe disease status presented with decreased levels of albumin (SMD = 1.60 [-2.97 - (−0.24)]; $p = 0.022$), hemoglobin (SMD = −0.23 [-0.41- (−0.06)]; $p = 0.001$), and thrombocytes (SMD = −0.57 [-0.68-(-0.45)]; $p < 0.001$) in comparison to patients with non-severe disease status. Additionally, C-reactive protein (SMD = 1.47 [0.88–2.07]; $p < 0.001$), lactate dehydrogenase (SMD = 1.71 [1.08–2.34]; $p < 0.001$), and aspartate transaminase levels (SMD = 0.85 [0.61–1.09]; $p < 0.001$) were elevated in patients with severe disease status. In terms of complications, patients with severe COVID-19 disease were at an elevated risk of developing ARDS (RR = 10.59 [2.44–46.01], $p = 0.014$, Fig. 6). The heterogeneity between the studies varied substantially (Table 5). Publication bias, measured by means of the Egger's test, was only evident in three analyses. However, Egger's test may lack the statistical power to detect bias when the number of studies is small (i.e., fewer than 10) as we only included 4–8 studies.

3.6. Survivor vs. non-survivors

Seven studies (957 patients) provided disaggregated data for COVID-19 survivors (617 patients, 64.5%) and non-survivors (340, 35.5%). No differences regarding sex were found in the survivor group ($t = 0.258$, $df = 11.879$, $p = 0.801$; male: 326 patients [52.8%] and female: 291 patients [47.2%]), but a significantly higher proportion of male patients were amongst the deceased cohort ($t = 4.30$, $df = 12$, $p = 0.001$; male: 236 patients [69.4%] and female: 104 patients [30.6%]) (Supplementary Fig. 10). In terms of age, COVID-19 patients that survived were significantly younger (median age in years = 52.0 [35.0–66.0]) than non-survivors (68.0 [62.0–76.0], Fig. 5). The meta-analysis yielded older age (SMD: 1.25 [0.78–1.72]; $p < 0.001$), being male (RR = 1.32 [1.13–1.54], $p = 0.005$), and pre-existing comorbidities (RR = 1.69 [1.48–1.94]; $p < 0.001$) as potential risk factors of in-hospital mortality. Pre-existing cerebrovascular diseases (RR = 36.88 [8.50–160.04]; $p = 0.009$), heart conditions (RR = 3.95 [1.03–15.20], $p = 0.047$, Fig. 7A), and hypertension (RR = 2.09 [1.65–2.64]; $p = 0.001$) were found to be associated with the highest risks of mortality. Clinical signs and symptoms as well as imaging features were comparable between survivors and non-survivors. In terms of treatments, non-survivors were more frequently mechanically ventilated than survivors (RR = 6.05 [1.41–26.05]; $p = 0.026$, Fig. 7B) and more commonly received extracorporeal membrane oxygenation (RR = 4.39 [1.64–11.78], $p = 0.014$). Non-survivors had higher risks of complications, particularly acute kidney injury (RR = 20.77 [2.43–177.44], $p = 0.017$; Fig. 7C) and ARDS

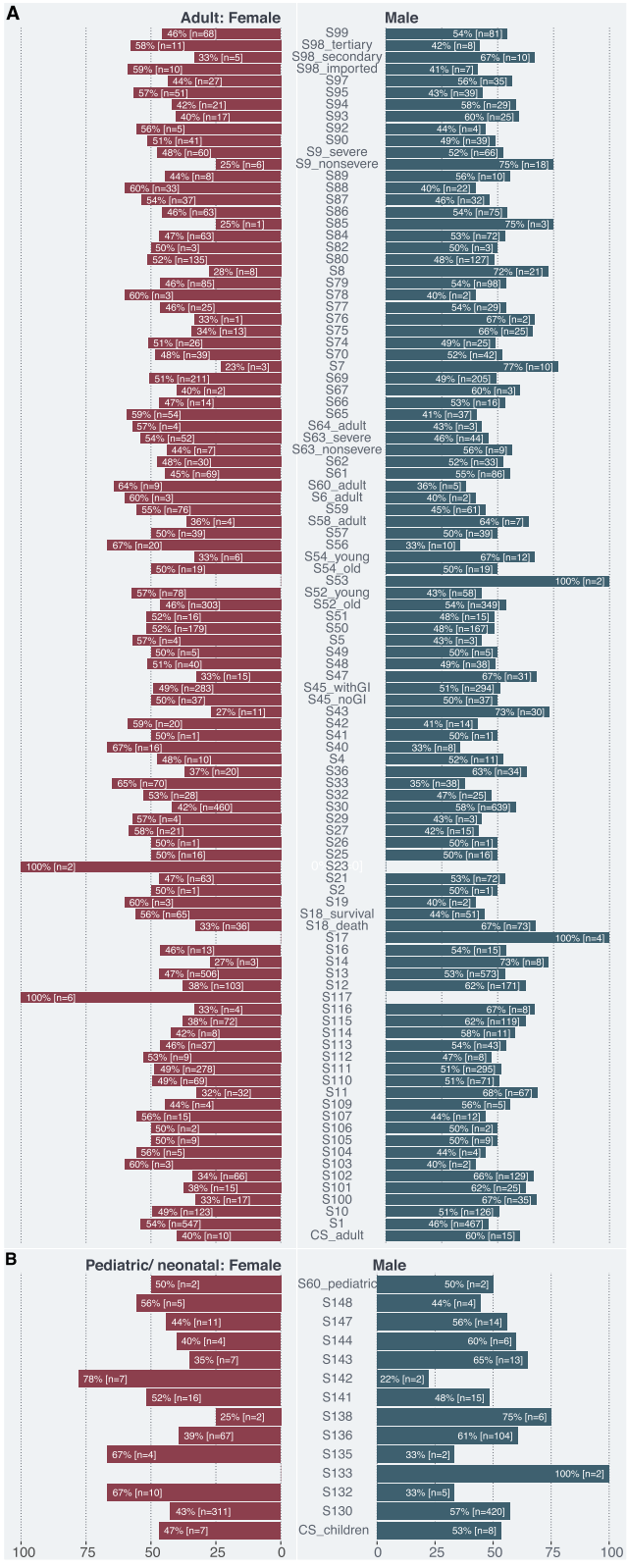

Fig. 2. Proportion of female and male patients in adult (A) and pediatric/neonatal cohort (B). All case studies/reports were pooled together for visualization (CS_adult, and CS_children [pediatric/neonatal]). The key to the study identifier can be found in Table 1 (adults) and Table 3 (children).

(RR = 4.24 [1.30–13.83], p = 0.026, Fig. 7D). Low levels of albumin (SMD = −1.13 [-1.41 – (−0.85)]; p < 0.001) and lymphocytes (SMD = −0.92 [-1.3 – (−0.55)]; p < 0.001) as well as elevated level of interleukin 6 (SMD = 1.21 [0.93–1.5]; p < 0.001), leucocytes (SMD = 2.21 [0.61–3.64]; p = 0.06), and prolonged prothrombin time (SMD = 7.99 [4.64–11.34]; p < 0.01) were associated with death (Table 5). Publication bias, measured by means of the Egger's test, was only evident in five analyses.

4. Discussion

As of May 1st, 2020, more than 3.3 million confirmed cases of COVID-19 and more than 230′000 deaths attributable to the disease, have been reported worldwide [166,167]. In-depth knowledge of clinical, laboratory, and imaging factors that are associated with the disease progression and outcome is critical to inform clinical decision making and pandemic preparedness initiatives. An ever-growing number of research studies have been performed, but thus far the meta-analytical evidence is sparse. To address this paucity, we conducted a systematic review and meta-analysis of 148 studies involving over 12′000 patients providing an unprecedently comprehensive overview of comorbidities, clinical signs and symptoms, laboratory parameters, CT imaging features, treatment, outcomes, and complications in adult, pregnant, and pediatric/neonatal COVID-19 patients. Approximately eight percent of the patients were reported to be asymptomatic. However, this low number does not appear to reflect the reality as the vast majority of the included studies primarily reported on symptomatic patients and were not designed to screen for asymptomatic patients. Furthermore, over seven percent died from complications associated with COVID-19. Recent analysis suggests that up to 75% of the coronavirus infections caused no illness [168–170]. Presumably, the virus has been circulating for longer than generally believed and large swathes of the population have already been exposed. Although our fatality rate lies within previous estimates [171,172], it is important to mention that only a limited number of studies reported on the outcomes of COVID-19 (i.e., death, survival, recovery) and thus, caution has to be exercised when interpreting this number. Through our meta-analysis, we revealed several important risk factors that are associated with severe disease progression and mortality. Among these risk factors were two demographic factors, namely older age and being male. Well-studied consequences of ageing are the decline in the immune function (e.g., T-cell and B-cell function) and excess production of type 2 cytokines [173,174]. These age-dependent changes in the immune response are suspected to cause deficiency in control of viral replication and more prolonged proinflammatory responses, potentially leading to poor outcome [175]. Corroborative evidence stems from preclinical studies that found an age-dependent host innate responses to virus infection in non-human primates inoculated with SARS-CoV-1 [176]. Confirming previous findings [177,178], sex-specific differences in mortality and vulnerability to the disease were evident in the current study. Specifically, men were disproportionately affected by an infection with SARS-CoV-2 (i.e., proportion of men presented with COVID-19 was larger compared to women) and the in-hospital mortality amongst male patients was significantly higher compared to female patients. Emerging evidence pinpoints towards differences in the immune system [140], genetic polymorphism [179], life style factors including smoking [180], personal hygiene habits [181], pre-existing comorbidities [182,183], and expression of angiotensin-converting enzyme 2 (ACE2) [184,185] as potential explanations for the increased vulnerability in men. This sex difference in vulnerability has also been observed for SARS-CoV-1 and MERS [186], two previously emerging coronavirus diseases. The lack of sex-disaggregated data in the reviewed studies made it impossible to further explore these potential explanations for the discrepant findings in men and women. Overall, the preexisting comorbidities, namely hypertension, diabetes mellitus, and any heart condition, were found to be linked with both, more severe diseases status and increased in-hospital

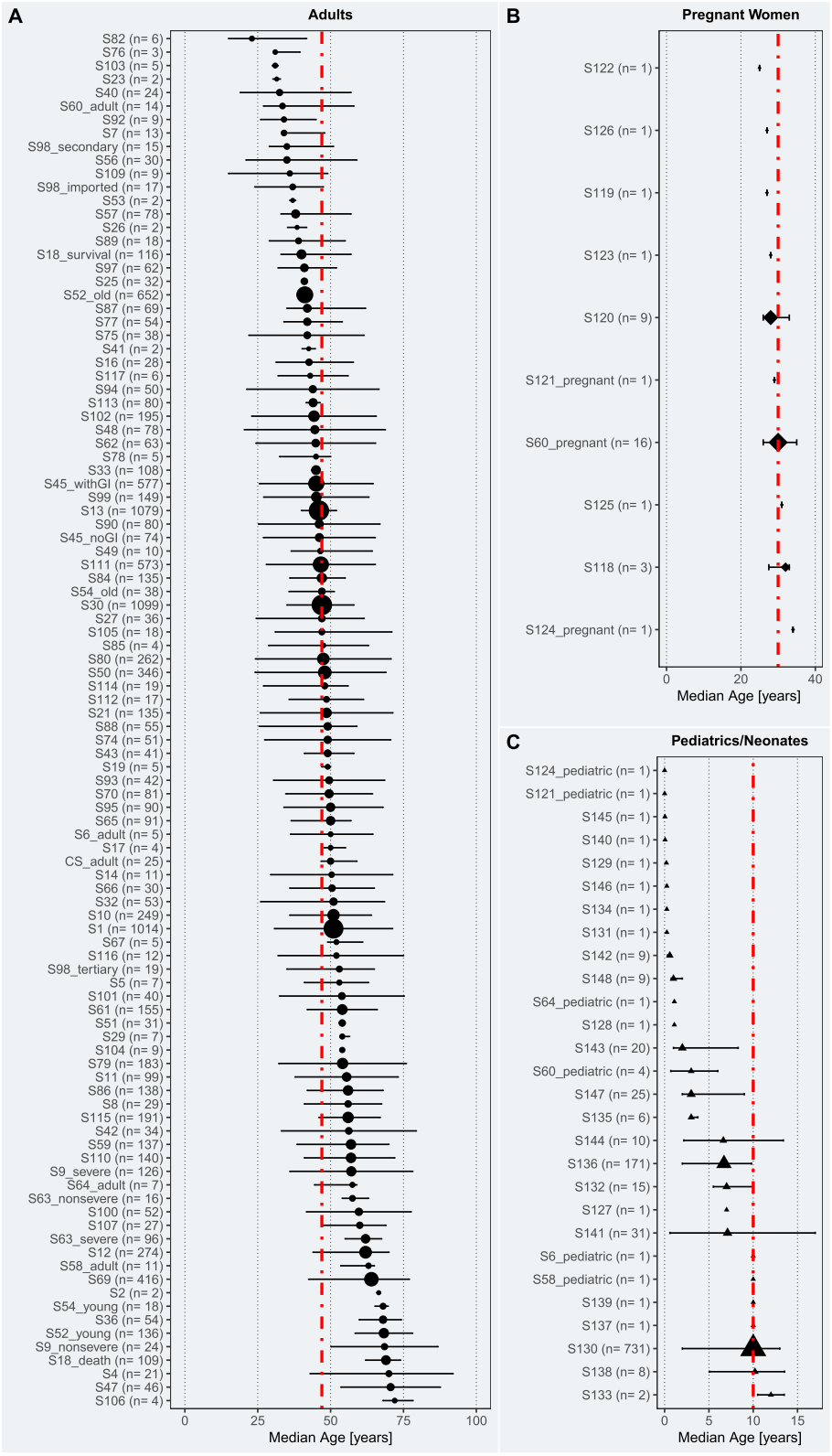

Fig. 3. Age of adult (A), pregnant (B), and pediatric/neonatal COVID-19 patients (C) included in eligible studies. Median age and interquartile ranges (IQR) are represented by the midpoints and error bars, respectively. The studies have been sorted by patients' median age in years. The size of the midpoint (circle, square, triangle) indicates the study sample size. The red line represents the pooled median age of the respective cohort. All adult case studies/reports (CS_adult) were pooled for the visualization reasons. The key to the study identifier can be found in Table 1 (adults), Table 2 (pregnant women), and Table 3 (children). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

mortality. Smoking, by contrast, was not associated with disease severity or mortality. However, the low number of studies reporting smoking status (13/148) cautions against early assumptions. Clinical signs and symptoms were comparable between patients with non-severe and severe COVID-19 as well as survivors and non-survivors. Fever, cough, and myalgia were amongst the most frequent reported symptoms across all groups. Similarly, the present study revealed no differences in the CT imaging features. The majority of the COVID-19 patients presented with pneumonia (bilateral or unilateral) and GGO. These pathological findings are a hallmark of any viral pneumonia, and thus it is not surprising that asymptomatic patients had similar distinctive features [187]. In terms of laboratory parameters, elevated levels of

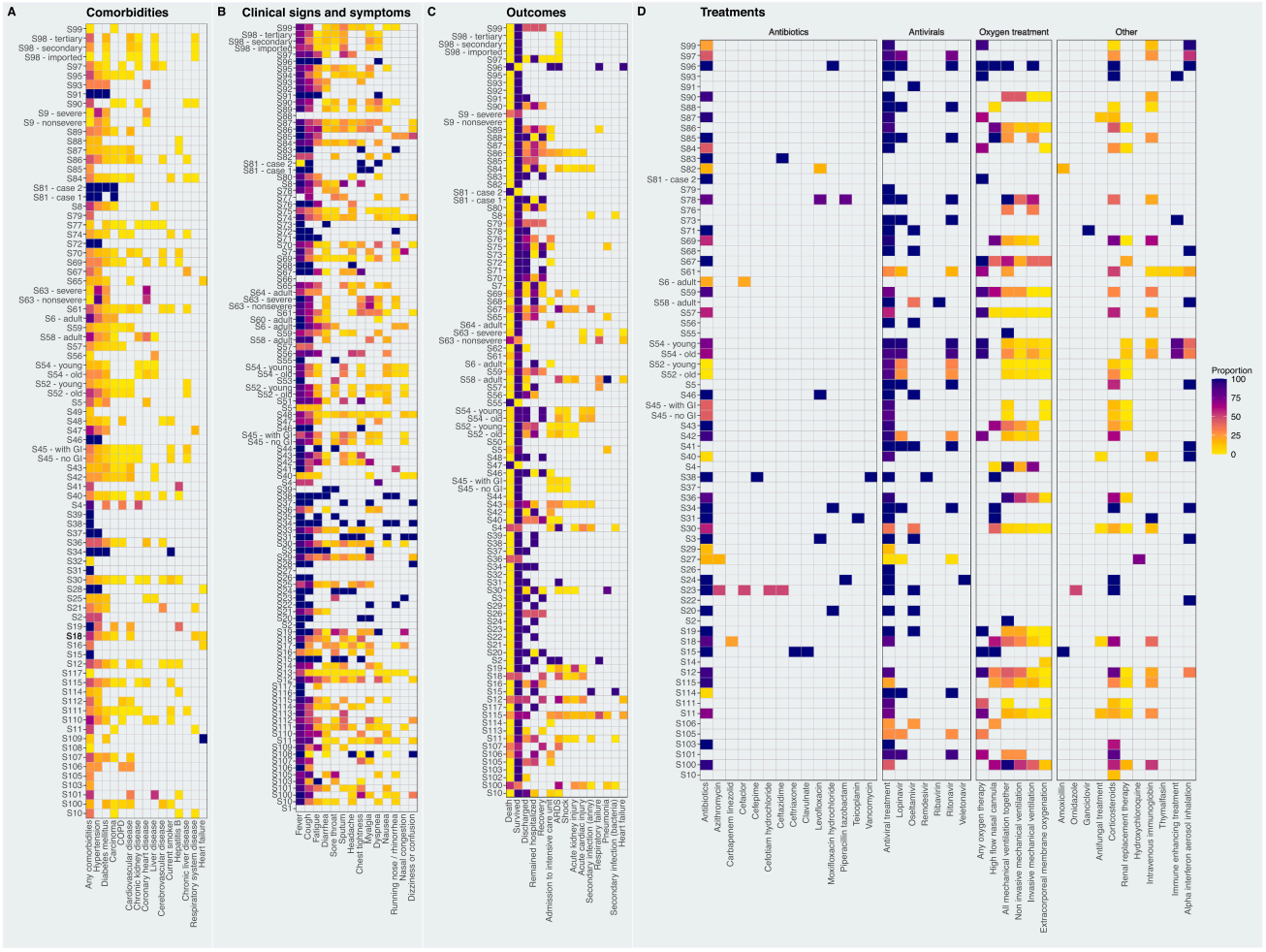

Fig. 4. Comorbidities (A), clinical signs and symptoms (B), outcomes (C), and treatments administered (D) to adult COVID-19 patients. The colors indicated the proportion of patients (%, 0 = yellow, 100 = dark purple). Note: Missing values are colored in white. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Summary for random-effects models for prevalence of comorbidities, clinical signs and symptoms, imaging features, treatments, outcomes and complications in adult CoVID-19 patients.

Variable	Number of studies	Patients	Total patients	Crude prevalence [%]	Random- effects models (REM) Prevalence	REM (lower CI)	REM (upper CI)	T^2	I^2	Q
Comorbidities										
Any comorbidity	85	2′329	7′608	30.61	29.57	24.08	35.71	1.271	95.4	902.92
Hypertension	58	1′352	6′460	20.93	23.24	19.23	27.8	0.585	90.4	517.13
Diabetes mellitus	53	678	6′535	10.37	11.81	10.12	13.72	0.218	70.0	187.38
Carcinoma	36	111	6′033	1.84	2.15	1.56	2.95	0.447	56.7	95.51
Chronic obstructive pulmonary disease	29	86	5′232	1.64	1.70	0.92	3.1	1.976	84.5	147.80
Cardiovascular disease	28	180	3′747	4.80	6.09	4.04	9.10	1.014	85.0	208.10
Chronic kidney disease	20	56	3′521	1.59	1.85	0.93	3.63	1.536	79.4	84.55
Coronary heart disease	17	194	2′388	8.12	9.32	4.53	18.21	2.167	94.3	294.63
Any liver disease	15	51	580	8.79	3.85	1.44	9.89	2.215	83.5	95.23
Cerebrovascular disease	13	112	2′568	4.36	3.95	2.12	7.23	1.025	87.5	143.74
Current smoker	13	266	3′400	7.82	5.79	4.32	7.72	0.156	68.8	62.4
Hepatitis B	12	54	2′333		2.72	1.41	5.16	0.724	71.5	34.60
Chronic liver disease	11	95	2′576	3.69	3.69	3.03	4.49	0	0	15.53
Any respiratory system disease	10	49	1′020	4.80	2.95	1.28	6.67	1.045	78.8	45.62
Heart failure	5	37	354	10.45	20.12	2.25	73.36	5.885	95.6	43.48
Immunodeficiency	5	6	418	1.44	1.62	0.18	12.8	3.889	81.3	19.40
Clinical signs and symptoms										
Asymptomatic	69	148	2′749	5.38	0.4	0.07	2.21	11.535	93.6	664.40
	65	1′936	2′597	74.55	98.03	92.48	99.51	9.123	96.2	864.92

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Table 4 (*continued*)

Variable	Number of studies	Patients	Total patients	Crude prevalence [%]	Random- effects models (REM) Prevalence	REM (lower CI)	REM (upper CI)	T^2	I^2	Q
Patients reported with any sign or symptom										
Fever	110	6′955	8′859	78.51	82.96	79.13	86.21	0.968	91.6	1′096.03
Cough	102	4′778	8′885	53.78	58.38	53.92	62.70	0.528	90.1	1′671.74
Fatigue	69	1′996	7′980	25.01	29.25	24.03	35.07	0.918	94.2	1′140.98
Diarrhea	58	465	6′475	7.18	8.32	6.63	10.4	0.497	76.9	343.2
Sore throat	49	726	6′538	11.10	13.04	10.0	16.84	0.683	88.7	357.51
Sputum	48	1′437	6′118	23.49	25.06	19.68	31.35	0.850	94.3	904.12
Headache	48	710	7′564	9.39	10.4	8.29	12.97	0.511	86.0	326.48
Chest tightness	46	885	4′596	19.26	24.21	17.02	33.21	1.737	95.3	882.92
Myalgia	46	808	5′284	15.29	18.99	14.69	24.19	0.779	90.7	411.98
Dyspnea	39	705	5′730	12.30	15.20	10.54	21.43	1.446	94.8	881.01
Nausea	31	329	5′361	6.14	7.06	4.87	10.11	0.837	88.0	211.11
Running nose (rhinorrhea)	25	113	2′513	4.50	7.30	4.57	11.46	0.676	71.3	115.97
Nasal congestion	20	219	4′487	4.88	9.32	4.7	17.65	2.089	94.7	166.83
Dizziness or confusion	18	97	1′054	9.20	13.6	6.92	24.97	1.376	84.8	85.04
Hemoptysis	13	65	3′298	1.97	2.37	1.62	3.44	0.170	44.2	23.26
Anorexia	10	205	1′202	17.05	14.21	7.3	25.84	1.132	93.9	131.95
Emesis or vomiting	6	38	857	4.43	4.43	3.24	6.04	0	0	4.42
Chest pain	6	64	832	7.69	7.78	2.97	18.86	1.389	90.8	90.01
Abdominal pain	7	38	740	5.14	5.11	2.93	8.77	0.223	46.2	22.04
Imaging features										
Pathologic findings	93	6′969	7′780	89.58	97.83	95.38	99.00	5.934	97.4	952.20
Pneumonia	93	6′620	7′917	83.62	96.87	93.71	98.47	5.885	98.1	1′610.32
Ground glass opacity (GGO)	62	2′446	5′591	43.75	69.13	56.74	79.27	2.900	97.9	1′126.68
Bilateral pneumonia	48	2′745	4′247	64.63	77.29	70.08	83.17	1.173	94.6	931.56
Unilateral pneumonia	32	799	3′745	21.34	19.27	16.46	22.43	0.154	73.0	86.28
Consolidation	30	771	2′022	38.13	38.33	26.94	51.16	1.265	92.1	271.44
GGO with consolidation	15	153	323	47.37	49.53	40.35	58.73	0.174	43.1	26.58
Local patchy shadowing	8	424	1′161	36.52	35.79	15.64	62.63	1.426	75.4	28.40
Bilateral patchy shadowing	12	577	1′341	43.03	56.15	23.58	84.16	1.659	92.6	58.37
Nodular lesions	13	70	1′345	5.20	15.39	7.31	29.55	1.339	83.3	93.73
Air bronchogram	10	264	523	50.48	49.43	41.59	57.29	0.129	59.5	23.29
Pleural effusion	10	52	666	7.81	7.88	5.04	12.11	0.292	55.6	24.46
Reticulation/interlobular septal thickening	7	81	1′244	6.51	21.88	5.10	59.34	4.467	95.8	296.72
Interstitial abnormalities	5	163	1158	14.08	21.39	10.88	37.75	0.419	70.4	20.65
Crazy paving pattern	5	59	210	28.10	30.75	13.89	55.00	0.690	75.2	26.42
Treatments										
Antiviral treatment	57	4′475	6′068	73.75	92.74	85.65	96.47	5.031	98.4	2′064.73
Antibiotics	47	2′518	4′825	52.19	74.94	54.38	88.24	7.244	99.0	2′226.02
Corticosteroids	34	1′715	5′828	29.43	39.08	27.24	52.37	2.185	98.1	1′647.19
All mechanical ventilation	32	807	5′228	15.44	29.24	16.42	46.51	3.963	98.3	1′248.53
Invasive mechanical ventilation	25	238	3′506	6.79	8.84	4.39	16.97	2.969	95.6	356.53
High flow nasal cannula	20	1′298	2′745	47.29	47.39	27.93	67.67	2.654	98.3	499.24
Non-invasive mechanical ventilation	23	502	3′838	13.08	14.23	8.60	22.65	1.650	96.1	590.79
Intravenous immunoglobin	20	781	3′162	24.70	21.67	15.47	29.50	0.070	94.0	486.21
Alpha interferon aerosol inhalation	15	367	745	49.26	89.41	55.01	98.31	6.313	97.4	331.79
Lopinavir	19	510	1′284	39.72	87.54	56.52	97.44	8.618	98.4	428.93
Ritonavir	19	510	1′284	39.72	87.54	56.52	97.44	8.618	98.4	428.93
Oxygen therapy	20	1300	1′872	69.44	83.83	72.76	90.96	1.519	95.2	406.24
Extracorporeal membrane oxygenation	22	31	4′651	0.67	0.51	0.16	1.63	4.517	86.9	93.79
Oseltamivir	13	443	1′159	38.22	96.39	41.42	99.9	9.269	91.8	89.74
Renal replacement therapy	18	62	4′572	1.36	1.35	0.48	3.78	4.010	92.7	154.71
Immune enhancing treatment	5	103	254	40.55	86.21	25.17	99.15	7.827	96.1	1′96.76
Antifungal treatment	5	70	1′516	4.62	6.81	3.68	12.28	0.401	81.7	32.66
Outcomes										
Death	99	616	7′727	7.97	1.28	0.54	2.99	8.559	97.0	1′806.30
Survived	99	7′111	7′727	92.03	98.72	97.01	99.46	8.559	97.0	1′806.30
Discharged	56	1′751	5′401	32.42	52.15	35.25	68.58	5.257	98.5	2′161.24
Remained hospitalized	48	3′025	4′405	68.67	66.99	53.27	78.32	3.008	97.6	1′440.97
Recovery	34	1′012	3′741	27.05	53.76	32.35	73.87	5.495	98.5	1′685.14
Complications										
Admission to intensive care unit	23	195	2′877	6.78	9.68	5.41	16.73	1.685	91.4	314.57
Acute respiratory distress syndrome	27	759	5′122	14.82	22.97	12.69	37.94	3.121	98.0	1321.27
Shock	18	140	4′291	3.26	2.41	1.10	5.22	2.267	93.0	301.37
Acute kidney injury	18	241	4′113	5.86	7.17	3.75	13.28	1.889		335.95

(*continued on next page*)

Table 4 (*continued*)

Variable	Number of studies	Patients	Total patients	Crude prevalence [%]	Random- effects models (REM) Prevalence	REM (lower CI)	REM (upper CI)	T^2	I^2	Q
									95/0	
Acute cardiac injury	13	242	1′250	19.36	13.54	8.58	20.72	0.631	88.2	109.82
All secondary infections	11	62	630	9.84	9.73	6.11	15.15	0.358	58.9	30.69
Respiratory failure	8	141	413	34.14	29.94	11.28	58.95	2.224	92.5	108.36
Pneumonia	7	1′031	1′489	69.24	33	8.36	72.68	4.67	98.2	476.86
Secondary infections (bacteria)	5	5	202	2.48	2.48	1.03	5.81	0	0	9.06
Heart failure	6	91	589	15.45	10.34	2.74	32.07	2.254	94.8	43.99

interleukin 6, leucocytes, D-dimer, and lactate dehydrogenase as well as hypoalbuminemia and lymphopenia were more commonly seen in patients with severe COVID-19 illness and non-survivors. High levels of D-dimer have a reported association with 28-day mortality in patients with infections or sepsis admitted to the intensive care unit [188]. Systemic pro-inflammatory cytokine responses (e.g., interleukin 6 and other components) contribute to host defense against infections, such as SARS-CoV-2 [189–191]. However, exaggerated synthesis of interleukin 6 can lead to an acute, severe systemic inflammatory response syndrome (SIRS) known as 'cytokine storm' [192]. In addition to SIRS, hypoalbuminemia and lymphopenia were previously shown to be associated with increased odds of severe infection and infection-related death [193–195]. Complications were very common amongst patients with severe COVID-19 disease (over 50%) and non-survivors (more than two thirds). Acute cardiac injury, ARDS, and acute kidney injury were strongly linked to the outcomes. Widely used treatments for COVID-19 and associated complications comprised antibiotics, antivirals, and oxygen therapy. Patients with severe COVID-19 disease required more often mechanical ventilation and renal replacement therapy compared to those with non-severe COVID-19. Moreover, corticosteroids have been commonly administered to hospitalized patients with severe illness, although their benefit is highly disputed. Evidence from MERS or influenza suggests that patients who were given corticosteroids had prolonged viral replication, receive mechanical ventilation, and have higher mortality [196–199]. Administration of antibiotics and antivirals was independent of disease-severity.

Pregnant women as well as pediatric and neonatal patients may be less vulnerable to complications of COVID-19. Comorbidities were almost non-existent in these patient cohorts. Clinical signs and symptoms, laboratory parameters, imaging features, and treatments were

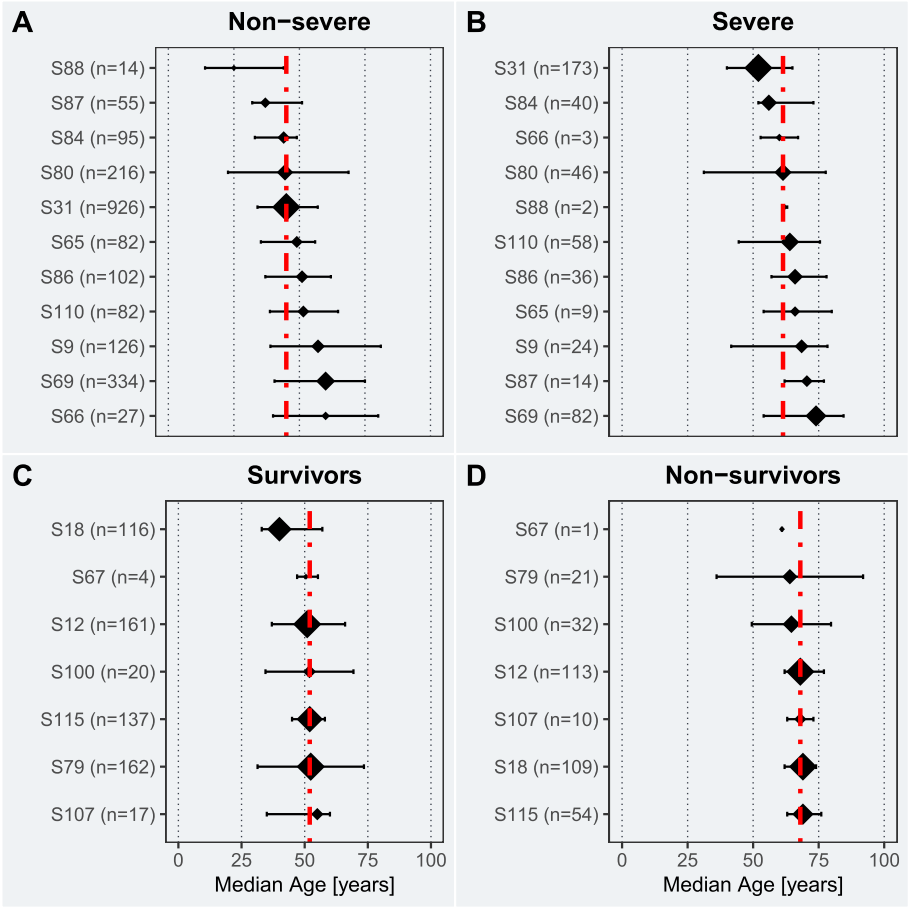

Fig. 5. Age of non-severe (A), severe (B), survivor (C), and non-survivor (D) COVID-19 patients included in eligible studies. The median age and Interquartile ranges (IQR) are represented by the midpoints and error bars, respectively. The studies have been sorted by patients' median age in years. The size of the midpoint indicates the study sample size. The red line indicates the pooled median age of the respective cohort. The key to the study identifier can be found in Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

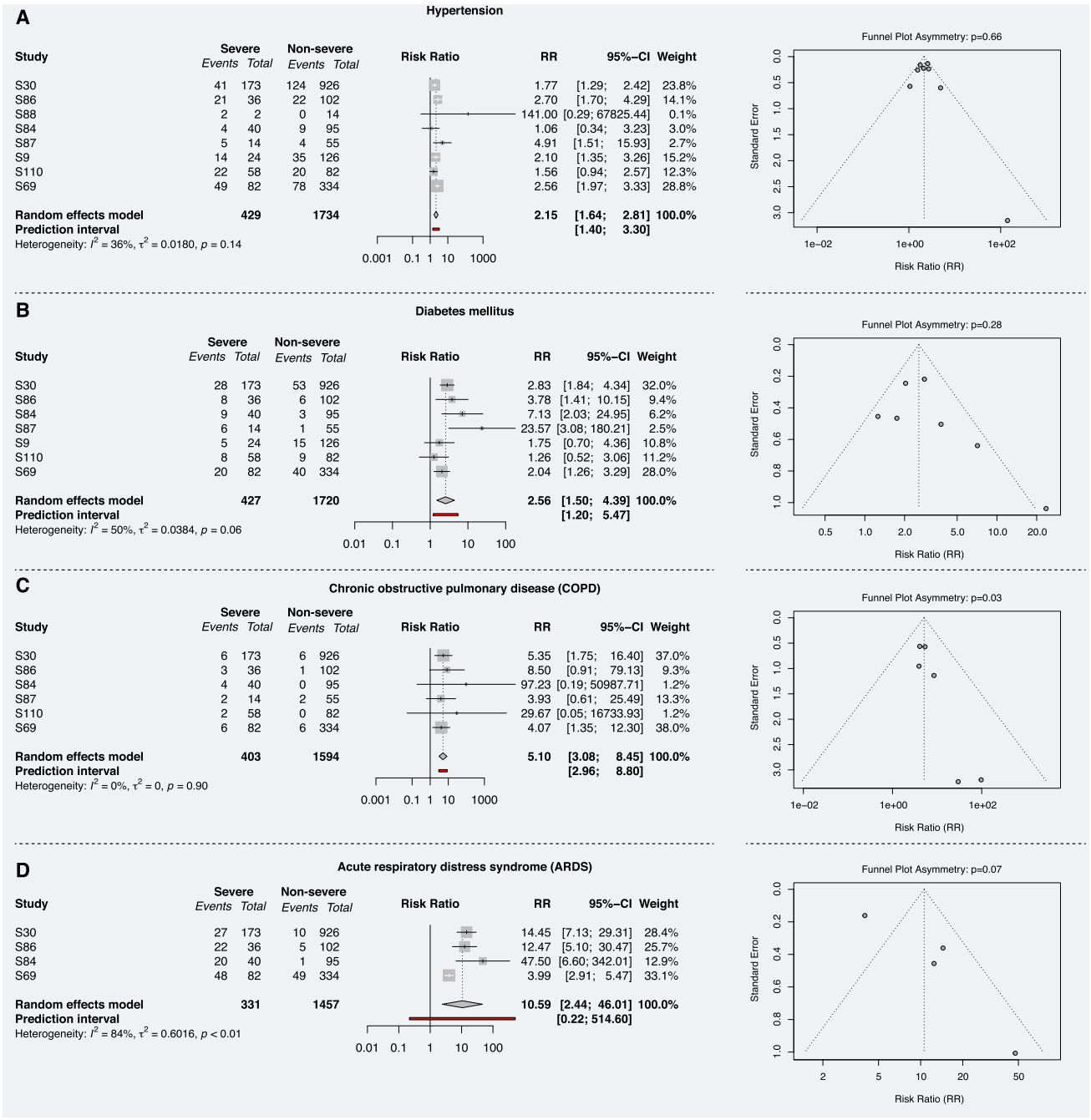

Fig. 6. Relative risks of comorbidities (i.e., hypertension, diabetes mellitus, and COPD) and complications (i.e., ARDS) in patients with a severe COVID-19 disease progression. Funnel plots indicate the potential of publication bias. The key to the study identifier can be found in Table 1.

comparable to the adult (non-pregnant) cohort. While there was a considerable proportion of children and neonates with SARS-CoV-2 infections reported, most of these patients did not need hospitalization and recovered quite well. With the exception of a 10-month old neonate, no children were amongst the deaths reported. All pregnant women included in our study survived COVID-19 and associated complications.

4.1. Limitations of review

A limitation of the current review was that literature search was limited to articles listed in EMBASE, PubMed/Medline, Scopus, Web of Science, or identified by hand searches. Considering the pace at which the research in this area is moving forward, it is likely that the findings of the publications described in this paper will be quickly complemented by further research. The literature search also excluded grey literature (e.g., preprints, reports, conference proceedings), the importance of which to this topic is unknown, and thus might have introduced another source of search bias. There is also a probability of publication bias, as well as potential for a search bias. Publication bias is likely to result in studies with more positive results being preferentially submitted and accepted for publication. Moreover, geographical bias cannot be ruled out as the majority of the studies (129/148) were conducted in China. While symptoms might be quite comparable across countries, comorbidities, treatments, and outcomes potentially depend on the country (and its healthcare system). There is also a considerable risk for a reporting bias towards comorbidities, clinical signs and symptoms, laboratory parameters, imaging features, treatment, outcomes, and complications that are present. Specifically, only a minority of studies

Table 5
Results of meta-analyses for patients with severe and non-severe disease outcomes as well as survivors and non-survivors.

	Number of Studies	Number of events/ Number of severe	Number of events/ Number of non-severe	RR [95% CI]	p-value	T^2	I^2	Cochranes Q	Egger's test (p-value)
Severe (cases) vs non-severe CoVID-19 disease (controls)									
Demographics									
Sex: male	10	278/488	1059/1987	1.11 [1.01–1.22]	0.039	0.004	0%	7.67	0.763
Sex: female	10	210/488	925/1987	0.95 [0.82–1.10]	0.450	0.006	18.6%	11.05	0.395
Age	11	487	2059	SMD: 0.68 [0.40–0.97]	<0.001	0.154	81.8%	55.05	0.012
Comorbidities									
Any comorbidity	4	167/307	291/1205	2.11 [1.02–4.35]	0.046	0.160	79.8%	14.86	0.122
Hypertension	8	158/429	292/1734	2.15 [1.64–2.81]	<0.001	0.018	35.8%	10.91	0.664
Diabetes mellitus	7	84/427	127/1720	2.56 [1.50–4.39]	0.005	0.038	49.7%	11.92	0.279
Any heart condition	7	64/427	58/1720	4.09 [2.45–6.84]	<0.001	0.032	22.7%	7.76	0.548
Chronic obstructive pulmonary disease (COPD)	6	23/403	15/1594	5.10 [3.08–8.45]	<0.001	0	0%	1.59	0.034
Carcinoma	5	15/345	19/1512	3.13 [0.63–15.64]	0.120	0.696	42.9%	7.00	0.339
Symptoms and signs									
Fever	8	399/462	1588/1847	1.02 [0.99–1.06]	0.187	<0.001	41.3%	11.92	0.644
Fatigue	8	199/462	611/1847	1.21 [0.99–1.48]	0.059	0.004	46.0%	12.95	0.011
Myalgia	5	53/318	237/1454	1.01 [0.66–1.56]	0.929	<0.001	20.7%	5.04	0.702
Headache	7	47/404	187/1765	1.14 [0.94–1.39]	0.146	<0.001	0.0%	1.65	0.625
Cough	8	290/462	1051/1847	1.14 [1.02–1.27]	0.026	0.006	15.1%	8.25	0.633
Sputum	6	85/385	384/1549	1.05 [0.79–1.39]	0.460	<0.001	14.8%	5.87	0.873
Dyspnea	6	91/207	56/587	4.67 [0.99–21.91]	0.050	1.156	76.2%	21.03	0.148
Sore throat/Pharyngalgia	6	41/358	182/1549	1.40 [0.62–3.17]	0.337	0.218	50.9%	10.19	0.831
Diarrhea	6	41/403	77/1594	1.76 [0.72–4.32]	0.164	0.296	53.7%	10.80	0.384
Treatment									
Antibiotics	4	254/309	743/1410	1.63 [0.67–3.96]	0.177	0.285	93.5%	45.93	0.807
Antiviral treatment	6	249/347	888/1526	1.05 [0.90–1.22]	0.490	0.011	77.7%	22.45	0.604
Corticosteroids	5	200/345	416/1512	2.26 [1.32–3.87]	0.014	0.174	93.7%	63.66	0.211
Imaging features (i.e., CT)									
Pathological findings	7	400/416	1372/1631	1.06 [0.96–1.18]	0.192	0.009	90.1%	60.32	0.085
Pneumonia	5	373/389	1290/1539	1.05 [0.94–1.18]	0.299	0.008	92.1%	50.58	0.176
Complications									
Acute respiratory distress symptom (ARDS)	4	117/331	65/1457	10.59 [2.44–46.01]	0.014	0.606	84.1%	18.90	0.067
Acute kidney injury	4	16/331	8/1457	6.60 [0.37–116.33]	0.128	2.075	65.0%	8.56	0.909
Laboratory parameter	**Number of studies**	**Number of severe**	**Number of non-severe**	**SMD [95% CI]**	**p-value**	T^2	I^2	**Cochranes Q**	**Egger's test (p-value)**
Albumin	3	131	511	−1.60 [-2.97 - (−0.24)]	0.022	1.385	96%	50.01	0.790
Alanine aminotransferase (ALT)	6	184	695	0.27 [0.06–0.47]	0.011	0.014	22.1%	6.42	0.545
Aspartate transaminase (AST)	6	184	695	0.85 [0.61–1.09]	<0.001	0.031	36.5%	7.88	0.942
Creatinine	6	205	794	0.59 [0.12–1.07]	0.015	0.298	87.3%	39.30	0.501
C-reactive protein (CRP)	6	227	774	1.47 [0.88–2.07]	<0.001	0.487	91.2%	56.50	0.296
D-dimer	4	143	361	0.55 [0.22–0.89]	0.001	0.066	59.4%	7.39	0.632
Hemoglobin	6	342	1618	−0.23 [-0.41- (−0.06)]	0.001	0.016	37.2%	7.96	0.927
Lactate dehydrogenase (LDH)	4	93	279	1.71 [1.08–2.34]	<0.001	0.294	77.3%	13.20	0.599
Leucocytes	7	412	1676	0.49 [-0.24-1.21]	0.187	0.905	97.0%	202.83	0.175
Lymphocytes	8	415	1703	−0.59 [-0.88 - (−0.30)]	<0.001	0.118	79.1%	33.54	0.986
Monocytes	3	59	239	−0.10 [-0.39- 0.19]	0.519	0	0%	0.58	0.180
Neutrophils	4	99	334	0.94 [0.27–1.61]	0.006	0.384	85.6%	20.8	0.409
Potassium	4	304	1437	−0.21 [-0.40 - (−0.02)]	0.034	0.015	41.2%	5.1	0.502
Procalcitonin	4	194	566	0.72 [0.06–1.38]	0.032	0.410	92.0%	37.55	0.848
Sodium	4	304	1437	−0.26 [-0.67-0.15]	0.201	0.137	86.3%	21.97	0.533
Thrombocytes	7	357	1621	−0.57 [-0.68- (-0.45)]	<0.001	0	0.0%	3.47	0.127
Others									
Time since onset of symptoms to admission	5	236	789	0.14 [-0.12- 0.41]	0.291	0.056	64.8%	11.36	0.465
	Number of Studies	**Number of events/ Number of non-survivors**	**Number of events/Number of survivors**	**RR [95% CI]**	**p-value**	T^2	I^2	**Cochranes Q**	**Egger's test (p-value)**

(*continued on next page*)

Table 5 (*continued*)

Non-survivors (cases) vs survivors (controls)									
Demographics									
Sex: male	7	236/340	326/617	1.32 [1.13–1.54]	0.005	0.002	21.8%	7.67	0.700
Sex: female	7	104/340	291/617	0.65 [0.53–0.83]	0.005	0	1.6%	6.10	0.540
Age	7	340	617	SMD: 1.25 [0.78–1.72]	<0.001	0.294	85.7%	41.97	0.012
Comorbidities									
Any comorbidity	6	207/308	234/597	1.69 [1.48–1.94]	<0.001	0	1	2.91	0.115
Hypertension	5	125/287	90/435	2.09 [1.65–2.64]	0.001	<0.001	0%	2.08	0.545
Diabetes mellitus	5	71/318	53/451	1.88 [1.26–2.81]	0.012	<0.001	0%	2.88	0.141
Any heart condition	5	48/318	15/451	3.95 [1.03–15.20]	0.047	.477	45.5%	7.35	0.666
Cerebrovascular disease	3	12/155	0/198	36.88 [8.50–160.04]	0.009	0	0%	0.07	0.305
Any lung disease	4	39/308	14/434	3.03 [0.61–15.04]	0.115	.429	49.8%	5.97	0.811
Carcinoma	5	12/318	8/451	2.26 [0.67–7.61]	0.136	0	0%	2.84	0.020
Current smoker	4	13/200	13/322	2.02 [0.61–6.72]	0.160	<0.001	0%	2.65	0.136
Symptoms and signs									
Fever	6	288/319	407/455	1.00 [0.95–1.05]	0.974	0	0%	4.9	0.022
Fatigue	3	109/276	129/414	1.24 [1.14–1.36]	0.009	0	0%	0.09	0.991
Myalgia	5	35/210	66/339	0.97 [0.61–1.55]	0.895	0.026	0%	3.14	0.385
Headache	4	19/255	29/301	0.83 [0.64–1.09]	0.120	0	0%	0.26	0.930
Cough	6	196/319	196/455	1.37 [0.58–3.24]	0.385	0.605	92.3%	64.86	0.389
Sputum	4	84/277	93/418	1.43 [0.65–3.15]	0.245	0.182	62.4%	7.99	0.886
Dyspnea	4	178/264	85/314	2.60 [0.58–11.65]	0.137	0.561	86%	21.49	0.611
Diarrhea	3	48/277	71/418	0.96 [0.38–2.43]	0.860	0.077	27.6%	2.76	0.838
Treatment									
Antibiotics	5	280/309	395/438	1.03 [0.99–1.07]	0.114	0	0%	2.09	0.293
Antiviral treatment	5	222/329	446/596	0.94 [0.79–1.13]	0.426	0.006	67.7%	12.38	0.260
Corticosteroids	4	229/308	227/434	1.29 [0.66–2.54]	0.321	0.136	80.6%	15.44	0.873
Immunoglobulin	4	143/308	122/434	1.88 [0.36–9.69]	0.309	0.979	92.5%	40.23	0.213
Oxygen nasal (high flow)	4	154/308	139/434	2.16 [0.09–50.50]	0.493	3.843	98.1%	158.98	0.030
All mechanical ventilation	5	298/319	115/455	6.05 [1.41–26.05]	0.026	1.126	84.5%	25.75	0.686
Non-invasive mech. ventilation	5	181/309	45/438	5.33 [1.52–18.71]	0.021	0.565	66.7%	12.02	0.765
Invasive mech. ventilation	5	89/309	5/438	14.14 [138–145.09]	0.034	2.080	59.7%	9.92	0.181
Renal replacement therapy	4	22/200	1/322	10.36 [0.98–110.07]	0.051	0.194	0%	1.92	0.057
Extracorporeal membrane oxygenation	5	12/309	2/438	4.39 [1.64–11.78]	0.014	0	0%	1.35	0.033
Imaging features (i.e, CT)									
Pathological findings	6	562/577	325/335	0.97 [0.87–1.09]	0.588	0.006	75.9%	20.71	0.675
Pneumonia	3	159/168	254/302	1.07 [0.97–1.17]	0.089	<0.001	0%	1.34	0.680
Complications									
ARDS	6	298/319	115/455	4.24 [1.30–13.83]	0.026	1.115	92.8%	69.92	0.197
Shock	4	98/277	0/418	242.79 [23.70–2487.07]	0.005	0	0%	0.64	0.300
Acute cardiac injury	4	178/308	23/434	13.21 [0.70–248.38]	0.068	2.783	81.8%	16.48	0.435
Acute kidney injury	5	88/309	5/435	20.77 [2.43–177.44]	0.017	2.301	67.7%	12.37	0.229
Laboratory parameter	**Number of Studies**	**Number of cases**	**Number of controls**	**SMD [95% CI]**	**p-value**	T^2	I^2	**Cochranes Q**	**Egger's test (p-value)[a]**
Albumin	2	110	120	−1.14 [-1.41 – (−0.85)]	<0.001	0	0%	0	n.a.
ALT	3	223	281	0.45 [0.08–0.82]	0.016	0.056	62.7%	6.37	0.984
AST	2	114	165	0.17 [-0.07 – 0.41]	0.168	0	0%	0.76	n.a.
Creatinine	4	200s	322	2.24 [-0.56 – 5.03]	0.117	7.719	98.8%	244.97	0.460
CRP	2	114	165	0 [-0.24 – 0.24]	1.0	0	0%	0	n.a.
D-dimer	4	174	274	1.54 [-0.17 – 3.25]	0.077	2.370	96.8%	94.99	0.672
Hemoglobin	3	142	140	−0.08 [-0.32 – 0.16]	0.504	0	0%	0.61	0.610
LDH	2	110	120	1.61 [1.31–1.91]	<0.001	0	0%	0.3	n.a.
Leucocytes	4	277	418	2.21 [0.61–3.64]	0.006	1.989	97.9%	144.57	0.421
Lymphocytes	4	255	301	−0.92 [-1.3 – (−0.55)]	<0.001	0.079	64.6%	8.47	
Neutrophils	2	55	141	3.6 [3.12–4.08]	<0.001	0	0%	0.17	n.a.
Potassium	2	55	141	0.41 [0.1–0.77]	0.01	0	0%	0.01	n.a.
Thrombocytes	4	196	277	0.9 [-2.09 – 3.88]	0.556	8.916	99%	309.32	0.487
Partial thromboplastin time (PTT)	5	206	294	7.99 [4.64–11.34]	<0.001	13.245	98.9%	370.17	0.194
Activated partial thromboplastin time (APTT)	3	65	158	21.73 [4.34–39.13]	0.014	231.933	99.5%	363.82	0.386
Interleukin 6 (IL-6)	2	110	120	1.21 [0.93–1.5]	<0.001	0	0%	0.44	n.a.
Others									

(*continued on next page*)

Table 5 (*continued*)

Time since onset of symptoms to admission	3	195	273	0.47 [-0.09 – 1.02]	0.098	0.201	85.8%	14.05	0.797

[a] Egger's test cannot be performed with less than three studies. Abbreviation: SMD: Standardize mean difference (negative number indicate lower values in cases, positive number indicate higher number in cases).

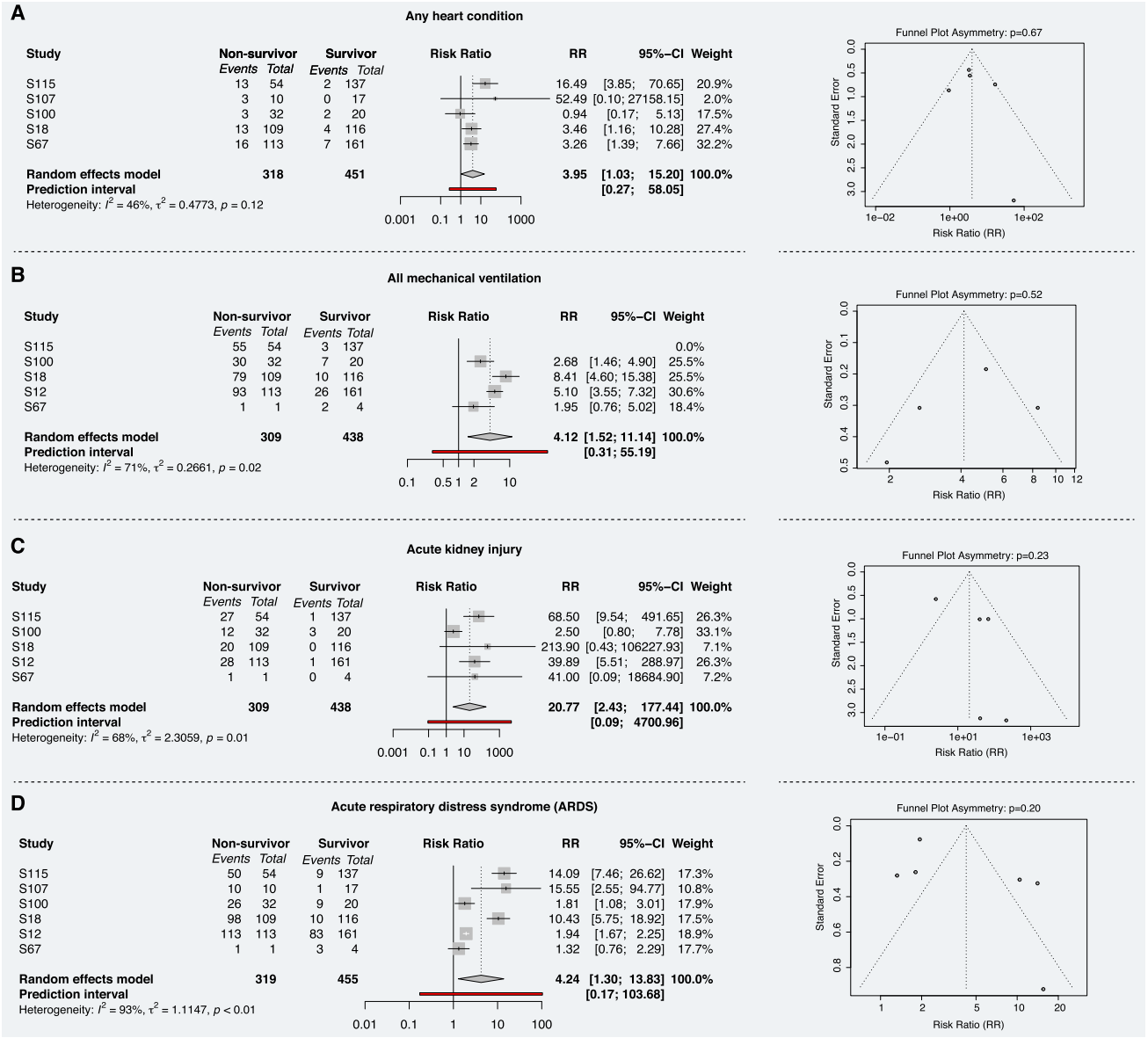

Fig. 7. Relative risks of comorbidity (i.e., any heart condition), treatment (i.e., mechanical ventilation), and complications (i.e., acute kidney injury and ARDS) in survivors and non-survivors. Funnel plots indicate the potential of publication bias. The key to the study identifier can be found in Table 1.

reported a zero when this information was assessed, but absent in patients. Lack of data on absent clinical signs and symptoms might lead to distorted estimates of proportion. Furthermore, the low number of asymptomatic patients must be considered with caution. The meta-analysis of severity and mortality could only be performed with a small number of studies as the minority of the 148 provided data separately for different disease severity groups (e.g., non-severe, severe, survivors, non-survivors). This needs to be considered when interpreting the results, including the publication bias as the Egger's test may lack the statistical power to detect bias when the number of studies is small (i.e., <10). Lastly, the criteria to classify patients in severe and non-severe COVID-19 disease cohorts varied between studies leading to additional heterogeneity between studies. By virtue of low number of studies available, we could not assess this heterogeneity nor adjust for it.

4.2. Conclusion and future directions

In conclusion, this unprecedentedly comprehensive systematic review and meta-analysis of the literature published during the first 120 days of the COVID-19 pandemic yields important information regarding the comorbidities, clinical signs and symptoms, laboratory parameters, imaging features, treatment, outcomes, and complications. Male sex, older age, and pre-existing comorbidities are major risk factors for in-hospital mortality and complications. This study revealed a fatality

rate of 7.7% and found that approximately 8% of the patients were reportedly asymptomatic. Based on recent reports, the latter number is likely 6- to 10-fold higher as only a few asymptomatic patients are captured by the health care system as they do not seek medical attention due to the lack of symptoms [168] or are not hospitalized and thus, included in studies. Unnoticed asymptomatic cases of COVID-19 are likely a major source of ongoing transmission. Children and neonates appear to be the least vulnerable cohort. Forthcoming studies are needed that provide sex-disaggregated data to better characterize risk factors that affect both sexes or are specific to men or women, respectively.

Authors' contribution

Catherine Jutzeler: Substantial contributions to the conception and design of the study; acquisition, analysis, and interpretation of data, drafting the manuscript, final approval of version to be published.

Lucie Bourguignon: Substantial contributions to acquisition, analysis, and interpretation of data, drafting the manuscript, final approval of version to be published.

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Declaration of competing interest

The authors do not report any (financial or otherwise) conflict of interest.

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Appendix A. Supplementary data

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