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REVIEW

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East–West differences in clinical manifestations of COVID-19 patients: A systematic literature review and meta-analysis

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic is currently not under control. We aimed to assess whether there are differences in clinical manifestations between COVID-19 patients from the East (East and South-East Asian countries including China, South Korea, and Thailand) and the West (North American, European, and Middle East countries, including the United States, Italy, France, and Iran). For this meta-analysis, we searched for eligible studies about COVID-19 in three databases: PubMed, EMBASE, and the Cochrane Library. Studies were divided into two cohorts for analysis: the East and the West. Stata 13.1 software was used for the meta-analysis. Of the 1527 studies initially identified by the literature search, 169 full-text articles were retrieved and screened for eligibility. Fifty-seven of these, describing 19,353 patients, were deemed eligible for inclusion. Of these, 45 studies with 8416 patients were from the East while 12 studies with 10,937 patients were from the West. The results indicated that the incidences of cough, headache, dizziness, nasal congestion, and digestive symptoms in COVID-19 patients from the East were lower than those in the West. The laboratory data showed that there were no significant differences in the levels of lymphocytes, leukocytes, C-reactive protein, and platelet counts between the two groups. In addition, our results also showed that the incidence of cardiac and kidney injury, as well as increased levels of creatinine, alanine transaminase, and aspartate transaminase, were significantly higher in patients from the West than from the East. Our meta-analysis indicated that there are differences in the clinical manifestations of COVID-19 in patients from the East and the West. COVID-19 patients from the West appear to suffer more severe liver, kidney, and heart damage due to SARS-CoV-2.

KEYWORDS
antiviral agents, coronavirus, drug specificity, genetics, mutation, virus classification

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] The first case of COVID-19, from Wuhan, Hubei, China, was reported to the World Health Organization (WHO) by the Chinese authorities on December 31, 2019. Subsequently, COVID-19 cases were reported across a wide geographic distribution around the globe. In January and February 2020, Asian countries represented by China and South Korea were the regions most

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affected by COVID-19.[2,3] After March, Europe and North America gradually became the epicenters of the disease.[4] To date, SARS-CoV-2 has swept into over 200 countries with over 35 million cases and more than 1 million deaths. This is a public health emergency that all countries should take seriously.

Typical clinical symptoms, laboratory abnormalities, and radiological imaging tests are of great importance for the screening and diagnosis of COVID-19.[5–8] The clinical features commonly range from mild respiratory illness to severe acute respiratory disease. According to reports, the most common clinical symptoms of COVID-19 were fever, cough, expectoration, dyspnea, fatigue, and myalgia while gastrointestinal symptoms, and smell and taste dysfunction were rare.[9,10]

It is generally accepted that viral mutations occur during the transmission and spread of a virus. It has been reported that the SARS-Cov-2 viruses currently circulating in the world can be divided into three or more lineage clusters based on the results of gene sequencing and phylogenetic network analysis. Forster et al.[11] described three central variants distinguished by amino acid changes, and named them A, B, and C. The A and C types were found in significant proportions outside East Asia, in Europeans and Americans. In contrast, the B type was the most common in East Asia. This suggests that differences in geography, time of infection, race, and changes in the pathogen itself may result in different clinical characteristics and therapeutic responses in COVID-19 patients. However, at present, there are no research data to verify this hypothesis. Due to the importance of this issue in better understanding COVID-19, tracing the origin of the virus, and optimizing patient treatment strategies, we aimed to determine whether there are differences in clinical manifestations between COVID-19 patients from the East and beyond.

2 | METHODS

2.1 | Search strategy and selection criteria

Our meta-analysis was conducted according to PRISMA and MOOSE guidelines. We searched for eligible studies on COVID-19 in three databases, PubMed, EMBASE, and the Cochrane Library. The search results were updated on May 18, 2020. Our search terms contained "COVID-19," "complications," "comorbidities," and "clinical characteristics." The references of identified reviews and meta-analyses were screened for additional eligible studies.

Two authors (Xiucheng Liu and Xiang Li) independently assessed the eligibility of studies after reading the titles, abstracts, and full texts. One senior investigator arbitrated the disagreements and made final decisions. Studies were selected according to the following criteria:

(1) The majority of participants were COVID-19 patients. Studies involving puerperants or infants were excluded because of atypical symptoms. Studies with external limitations on patients' characteristics such as severe disease only or acute respiratory distress syndrome (ARDS) only were excluded.
(2) No restrictions were applied to the study design, study type, region, and race of participants.
(3) Included studies should report at least one pre-existing comorbidity, as well as the clinical characteristics, laboratory findings, radiologic findings, medical treatments, or outcomes of the COVID-19 patients.
(4) Studies with sample sizes smaller than four were excluded.
(5) The languages of studies were limited to English and Chinese.

2.2 | Data extraction and quality assessment

Two authors (Xiang Li and Yeqing Zhou) independently extracted the relevant data, including the name of the first author, study design, region, duration of recruitment, sample size, mean or median age, history of smoking (including current smokers), medical comorbidities, clinical characteristics, laboratory findings, radiologic findings, complications, treatments, and clinical outcomes of the COVID-19 patients. We classified patients with elevated levels of troponin T as having acute cardiac injury and ICU patients as severe cases in the absence of other relevant data.

The methodological quality of the included studies was assessed by the quality assessment tool for case series studies published by the National Institutes of Health (NIH; www.nih.gov). This tool includes nine items, with a score of 0 or 1 for each item. The overall quality of a study was measured by the sum of the scores for all items, ranging from 0 to 9. Included studies were classified as having a low (7–9), moderate (5–6), or high risk of bias (0–4). Disagreements were settled by the chief investigators.

2.3 | Statistical analyses

Data analysis was performed with Stata 13.1 software (Stata Corporation). A random-effects model was applied to calculate the pooled estimated prevalence with 95% confidence intervals of pre-existing comorbidities, clinical characteristics, laboratory findings, radiologic findings, complications, treatments, and clinical outcomes of the COVID-19 patients. We selected the Stata METAPROP module and the Freeman-Tukey double arcsine transformation to prevent the exclusion of studies with extremely small or extremely large prevalence estimates and minimize their impacts on the results before analyzing the data.

We calculated the heterogeneity among studies using I^2. If I^2>75% (high heterogeneity), we conducted subgroup analysis to determine the possible source of the heterogeneity, using the following variables: age, region, and sex. The differences in prevalence were also analyzed by these subgroups. We assessed the publication bias by Egger's test.

3 | RESULTS

3.1 | Study selection and characteristics

Our initial search identified 1527 publications. Of these, 193 were duplications. Of the remaining studies, 1165 records were excluded after reviewing the title and abstract, leaving 169 studies eligible for the full-text review. We also included eight additional studies identified through other sources. Among these 177 full-text papers, 41 had external limitations on participants' characteristics, 8 did not report original data, 15 did not report clinical characteristics, comorbidities, or complications of COVID-19, 10 had a sample size smaller than four, 5 were irrelevant to our topic, 3 described puerperants or infants, and 1 was the erratum of an already-included study. One publication was excluded due to a low-quality assessment score. As over half of the studies were conducted in China, we performed a further screening of Chinese publications. The further exclusion criteria for Chinese studies were a quality assessment score below 7 or a sample size of less than 50. Finally, 57 studies[3,12-67] with 19,353 patients were eligible for inclusion. Of these, 45 studies[3,12-55] with 8416 patients were from the East (East and South-East Asian countries, including China, South Korea, and Thailand). Twelve studies[56-67] with 10,937 patients were from the West (North American, European, and Middle East countries, such as the United States, Italy, France, and Iran). The period of enrollment ranged from December 11, 2019 to April 5, 2020. Our selection process is illustrated in Figure 1 and the characteristics of the included studies are summarized in Table 1.

3.2 | Quality assessment

The details of the quality assessment are summarized in Table S1. All 57 studies described a clear study question and study population while only 16 studies enrolled patients consecutively. The subjects of 52 studies were comparable. Clearly described interventions were presented in 42 studies and clear outcome measures were reported in 49 studies. Thirty-four studies reported an adequate length of follow-up. Most studies provided detailed statistical methods ($n = 48$) and detailed and comprehensive results ($n = 56$).

3.3 | Overall perspective of the clinical manifestations of COVID-19

A total of 57 studies involving 19,353 COVID-19 patients were included. We conducted a meta-analysis of the prevalence of 14 clinical symptoms of COVID-19. The incidence of these symptoms was as follows: fever (0.76; 95% CI, 0.68–0.84), cough (0.64; 95% CI, 0.58–0.70), expectoration (0.31; 95% CI, 0.25–0.37), dyspnea (0.30; 95% CI, 0.24–0.37), fatigue (0.29; 95% CI, 0.23–0.35), myalgia (0.20; 95% CI, 0.17–0.24), sore throat (0.18; 95% CI, 0.13–0.24), digestive symptoms (0.17; 95% CI, 0.12–0.21), headache (0.13; 95% CI, 0.10–0.15]), ecphysesis (0.13; 95% CI, 0.05–0.20), chest pain (0.12; 95% CI, 0.08–0.16), dizziness (0.10; 95% CI, 0.06–0.14), nasal congestion (0.07; 95% CI, 0.05–0.09), and hemoptysis (0.02; 95% CI, 0.01–0.02) (Figure S1A).

The results of the clinical laboratory tests of the COVID-19 patients showed increased levels of C-reactive protein (CRP) (0.55; 95% CI, 0.47–0.63), lactate dehydrogenase (LDH) (0.48; 95% CI, 0.34–0.62), brain natriuretic peptide (BNP) (0.41; 95% CI, 0.30–0.53), D-dimer (0.26; 95% CI, 0.18–0.35), troponin T (0.26; 95% CI, 0.19–0.33), aspartate aminotransferase (AST) (0.23; 95% CI, 0.12–0.35), and alanine aminotransferase (ALT) (0.20; 95% CI, 0.11–0.29), and decreased numbers of lymphocytes (0.41; 95% CI, 0.30–0.52), leukocytes (0.25; 95% CI, 0.18–0.32), and platelets, all of which were common laboratory

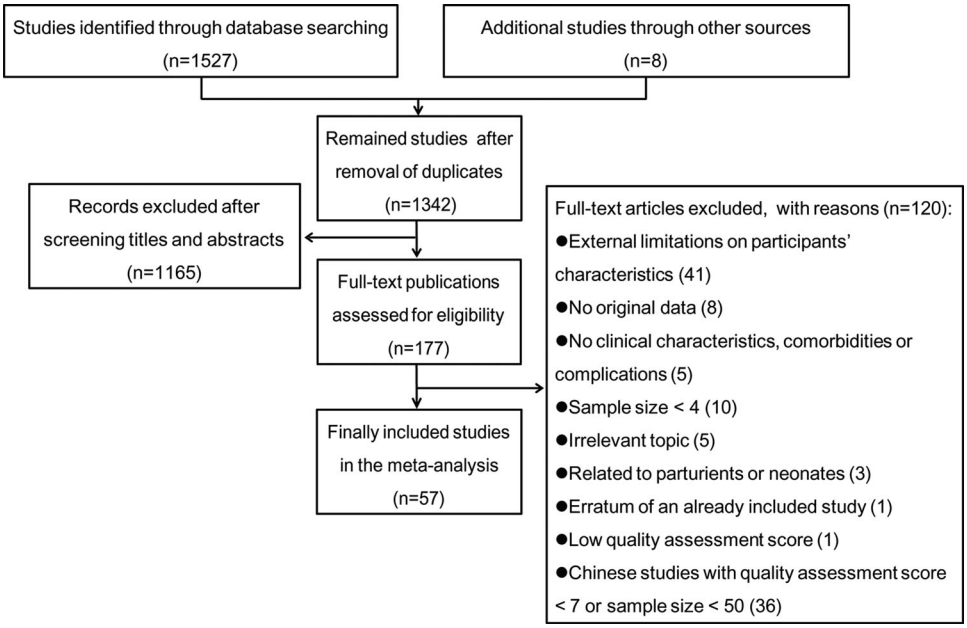


FIGURE 1 Study selection

TABLE 1 Demographics of the included studies

								Severity				Underlying Comorbidities							
Study	Enrollment duration	Region	Study design	Quality score	*N*	Males (%)	Age	Asymptomatic (%)	Mild to moderate (%)	Severe (%)	Critical (%)	Any (%)	Hypertension (%)	Diabetes (%)	Malignance (%)	Liver disease (%)	Kidney disease (%)	Coronary heart disease (%)	COPD (%)
Lian, J.	01.17–02.12	China Hangzhou	RCS	8	788	407 (51.7)	45.83 (14.88)	0 (0.0)	710 (90.1)	61 (7.7)	17 (2.2)	218 (27.7)	126 (16.0)	57 (7.2)	6 (0.8)	31 (3.9)	7 (0.9)	11 (1.4)	3 (0.4)
Shi, S.	01.20–02.10	China Wuhan	RCS	8	416	205 (49.3)	64 (21–95)	NR	NR	NR	NR	NR	127 (30.5)	60 (14.4)	9 (2.2)	4 (1.0)	14 (3.4)	44 (10.6)	12 (2.9)
Guo, T.	01.23–02.23	China Wuhan	RCS	8	187	91 (48.7)	58.5 (14.66)	NR	NR	NR	NR	NR	61 (32.6)	28 (15.0)	13 (7.0)	NR	6 (3.2)	21 (11.2)	4 (2.1)
Yang, W.	01.17–02.10	China Wenzhou	RCS	8	149	81 (54.4)	45.11 (13.35)	NR	NR	NR	NR	NR	NR	NR	2 (1.3)	NR	NR	NR	1 (0.7)
Wang, D.	01.01–01.28	China Wuhan	RCS	8	138	75 (54.3)	56 (42–68)	NR	NR	36 (26.1)	NR	64 (46.3)	43 (31.2)	14 (10.1)	10 (7.2)	4 (2.9)	4 (2.9)	20 (14.5)	4 (2.9)
Guan, W. J.	12.11–01.29	China Mutli-city	RCS	8	1099	640 (58.2)	47 (35–58)	0 (0.0)	926 (84.3)	173 (15.7)	NR	261 (23.7)	165 (15.0)	81 (7.4)	10 (0.9)	23 (2.1)	8 (0.7)	27 (2.5)	12 (1.1)
Wu, J.	01.22–02.14	China Jiangsu	RCS	8	80	39 (48.8)	46.1 (15.42)	0 (0.0)	77 (96.3)	3 (3.8)	0 (0.0)	38 (47.5)	NR	NR	1 (1.2)	1 (1.2)	1 (1.3)	NR	1 (1.3)
Mo, P.	01.01–02.05	China Wuhan	RCS	8	155	86 (55.5)	54 (42–66)	0 (0.0)	63 (40.6)	55 (35.5)	37 (23.9)	NR	37 (23.9)	15 (9.7)	7 (4.5)	7 (4.5)	6 (3.9)	15 (9.7)	5 (3.2)
Cao, J.	01.03–02.01	China Wuhan	RCS	8	102	53 (52.0)	54 (37–67)	NR	NR	18 (17.6)	NR	47 (46.1)	28 (27.5)	11 (10.8)	4 (3.9)	2 (2.0)	4 (3.9)	5 (4.9)	10 (9.8)
Wang, Z.	01.16–01.29	China Wuhan	RCS	8	69	32 (46.4)	42 (35–62)	NR	NR	NR	NR	NR	9 (13.0)	7 (10.1)	4 (5.8)	1 (1.4)	NR	8 (11.6)	4 (5.8)
Liu, K.	01.01–02.15	China Hainan	RCS	7	56	31 (55.4)	53.75 (13.78)	NR	NR	NR	NR	NR	10 (17.9)	4 (7.1)	NR	1 (1.8)	1 (1.8)	2 (3.6)	NR
Xu, X. W.	01.10–01.26	China Wuhan	RCS	7	62	35 (56.5)	41 (32–52)	NR	NR	1 (1.6)	NR	20 (32.3)	5 (8.1)	1 (1.6)	NR	7 (11.3)	1 (1.6)	NR	1 (1.6)
Chen, J.	01.20–02.06	China Shanghai	RCS	8	249	126 (50.6)	51 (36–64)	7 (2.8)	NR	22 (8.8)	NR	90 (36.1)	NR	NR	1 (0.4)	2 (0.8)	NR	55 (22.1)	5 (2.0)
Cai, Q.	01.11–02.06	China Shenzhen	RCS	8	298	145 (48.7)	47.5 (33–61)	30 (10.1)	210 (70.5)	58 (19.5)	NR	NR	47 (15.8)	18 (6.0)	4 (1.3)	28 (9.4)	NR	25 (8.4)	NR
Wu, J.	01.20–02.20	China Yancheng	RCS	7	280	151 (53.9)	43.12 (19.02)	NR	NR	83 (29.6)	NR	NR	NR	NR	5 (1.8)	7 (2.5)	3 (1.1)	29 (10.4)	1 (0.4)
Qian, G. Q.	01.20–02.21	China Zhejiang	RCS	7	91	37 (40.7)	50 (36.5–57)	0 (0.0)	82 (90.1)	9 (9.9)	NR	NR	15 (16.5)	8 (8.8)	NR	NR	NR	3 (3.3)	NR
Chen, N.	01.01–01.20	China Wuhan	RCS	8	99	67 (67.7)	55 (13.1)	NR	NR	23 (23.2)	NR	50 (50.5)	NR	NR	1 (1.0)	NR	NR	40 (40,4)	1 (1.0)
Wu, C.	12.25–01.26	China Wuhan	RCS	8	201	128 (63.7)	51 (43–60)	NR	NR	53 (26.4)	NR	NR	39 (19.4)	22 (10.9)	1 (0.5)	7 (3.5)	2 (1.0)	8 (4.0)	5 (2.5)
Chen, T.	01.01–02.10	China Wuhan	RCS	8	203	108 (53.2)	54 (20–91)	0 (0.0)	96 (47.3)	73 (36.0)	34 (16.7)	88 (43.4)	43 (21.2)	16 (7.9)	7 (3.4)	8 (3.9)	8 (3.9)	16 (7.9)	8 (3.9)
Feng, Y.	01.01–02.15	China Multi-city	RCS	7	476	271 (56.9)	53 (40–64)	0 (0.0)	352 (73.9)	54 (11.3)	70 (14.7)	205 (43.1)	113 (23.7)	49 (10.3)	12 (2.5)	NR	NR	38 (8.0)	22 (4.6)
Dai, H.	01.10–02.07	China Jiangsu	RCS	7	234	136 (58.1)	44.6 (7–82)	0 (0.0)	219 (93.6)	13 (5.6)	2 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR
Shi, H.	12.20–1.23	China Wuhan	RCS	7	81	42 (51.9)	49.5 (11)	NR	NR	NR	NR	21 (25.9)	12 (14.8)	10 (12.3)	4 (4.9)	7 (8.6)	3 (3.7)	8 (9.9)	9 (11.1)
Li, X.	01.26–02.05	China Wuhan	RCS	8	548	279 (50.9)	60 (48–69)	NR	NR	NR	NR	NR	166 (30.3)	83 (15.1)	24 (4.4)	5 (0.9)	10 (1.8)	34 (6.2)	17 (3.1)
Du, W.	01.23–02.15	China Shandong	RCS	7	53	26 (49.1)	41.47 (NR)	0 (0.0)	52 (98.1)	1 (1.9)	0 (0.0)	NR	NR	NR	NR	NR	NR	NR	NR
Liu, K. C.	01.21–02.03	China Anhui	RCS	7	73	41 (56.2)	37.38 (14.26)	3 (4.1)	46 (63.0)	21 (28.8)	3 (4.1)	NR	NR	NR	NR	NR	NR	NR	NR
Qi, X.	01.23–02.18	China Mutli-city	PS	7	70	39 (55.7)	NR	NR	NR	NR	NR	11 (15.7)	8 (11.4)	3 (4.3)	2 (2.9)	NR	NR	2 (2.9)	NR
Chu, Y.	01.17–02.10	China Wenzhou	RCS	9	149	81 (54.4)	45.11 (13.35)	NR	149 (100)	NR	NR	NR	NR	NR	2 (1.3)	NR	NR	NR	1 (0.7)
Chen, Q.	01.01–03.11	China Taizhou	RCS	7	145	79 (54.5)	47.5 (14.6)	0 (0.0)	102 (70.3)	43 (29.7)	0 (0.0)	NR	22 (15.2)	14 (9.7)	3 (2.1)	6 (4.1)	3 (2.1)	NR	6 (4.1)

TABLE 1 (Continued)

								Severity				Underlying Comorbidities							
Study	Enrollment duration	Region	Study design	Quality score	*N*	Males (%)	Age	Asymptomatic (%)	Mild to moderate (%)	Severe (%)	Critical (%)	Any (%)	Hypertension (%)	Diabetes (%)	Malignance (%)	Liver disease (%)	Kidney disease (%)	Coronary heart disease (%)	COPD (%)
Pan, L.	01.18–02.28	China Hubei	RCS	8	204	107 (52.5)	52.91 (15.98)	NR	NR	16 (7.8)	NR	NR	NR	NR	13 (6.4)	NR	NR	NR	NR
Zhao, X. Y.	01.16–02.10	China Hubei	RCS	8	91	49 (53.8)	46 (NR)	0 (0.0)	61 (67.0)	30 (33.0)	0 (0.0)	21 (23.1)	18 (19.8)	3 (3.3)	3 (3.3)	NR	1 (1.1)	NR	1 (1.1)
Sun, L.	01.20–02.15	China Beijing	RCS	7	55	31 (56.4)	44 (34–56)	NR	NR	NR	NR	18 (32.7)	8 (14.5)	5 (9.1)	NR	3 (5.5)	1 (1.8)	1 (1.8)	NR
Zhang, R.	01.10–02.10	China Wuhan	RCS	7	120	43 (35.8)	45.4 (15.6)	NR	NR	NR	NR	32 (26.7)	19 (15.8)	7 (5.8)	7 (5.8)	1 (0.8)	NR	9 (7.5)	4 (3.3)
Zheng, Y.	01.16–02.04	China Hubei	RCS	8	73	40 (54.8)	NR	0 (0.0)	43 (58.9)	28 (38.4)	2 (2.7)	24 (32.9)	NR	NR	1 (1.4)	NR	NR	NR	NR
Guan, C. S.	01.12–02.28	China Beijing	RCS	7	53	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bi, X.	01.23–02.04	China Taizhou	RCS	7	113	64 (56.6)	46 (37–55)	NR	NR	NR	NR	44 (38.9)	NR	NR	NR	NR	NR	NR	NR
Zhang, J.	01.13–02.16	China Wuhan	RCS	7	111	46 (41.4)	38 (32–57)	NR	NR	NR	NR	37 (33.3)	15 (13.5)	14 (12.6)	8 (7.2)	1 (0.9)	NR	NR	3 (2.7)
Wan, S.	01.26–02.04	China Chongqing	RCS	7	123	55 (44.7)	46.16 (15.15)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pei, G.	01.28–02.09	China Wuhan	RCS	8	333	182 (54.7)	56.3 (13.4)	0 (0.0)	144 (43.2)	133 (40.0)	56 (16.8)	NR	NR	NR	NR	NR	NR	NR	NR
Yao, Q.	01.30–02.11	China Huanggang	RCS	8	108	43 (39.8)	52 (37–58)	0 (0.0)	83 (76.9)	13 (12.0)	12 (11.1)	25 (23.1)	16 (14.8)	5 (4.6)	NR	2 (1.9)	NR	4 (3.7)	3 (2.8)
Yang, R.	12.24–01.24	China Wuhan	RCS	8	212	107 (50.5)	55.6 (40–67)	NR	NR	NR	NR	89 (42.0)	NR	NR	NR	23 (10.8)	11 (5.2)	NR	NR
Qiu, C.	01.22–02.23	China Hunan	RCS	8	104	49 (47.1)	43 (7.54)	5 (4.8)	83 (79.8)	16 (15.4)	0 (0.0)	NR	15 (14.4)	12 (11.5)	NR	NR	NR	7 (6.7)	1 (1.0)
KCDC	01.20–02.14	Korea Mutli-city	SD	4	28	15 (53.6)	NR (20–79)	3 (10.7)	NR	NR	NR	10 (35.7)	NR	NR	1 (3.6)	NR	NR	NR	NR
Pongpirul, W. A.	01.08–01.31	Thailand Bangkok	RCS	5	11	NR	61 (28–74)	NR	NR	NR	NR	7 (63.6)	4 (36.3)	2 (18.2)	0 (0.0)	1 (9.1)	NR	3 (27.3)	0 (0.0)
Kim, E. S.	01.19–02.17	Korea Mutli-city	RCS	8	28	15 (53.6)	42.6 (13.4)	NR	NR	NR	NR	5 (17.9)	0 (0.0)	2 (7.1)	1 (3.6)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hong, K. S.	until 03.29	Korea Daegu	RCS	8	98	38 (38.8)	55.4 (17.1)	NR	NR	NR	NR	NR	30 (30.6)	9 (9.2)	4 (4.1)	1 (1.0)	NR	NR	3 (3.1)
McMichael, T. M.	02.27–03.19	USA Washington	SD	4	167	55 (32.9)	72 (21–100)	NR	NR	NR	NR	NR	74 (44.3)	38 (22.8)	15 (9.0)	6 (3.6)	43 (25.7)	68 (40.7)	36 (21.6)
Goyal, P.	03.03–03.27	USA New York	RCS	7	393	238 (60.6)	62.2 (48.6–73-.7)	NR	NR	NR	NR	NR	197 (50.1)	99 (25.2)	NR	NR	NR	54 (13.7)	20 (5.1)
Richardson, S.	03.01–04.04	USA NewYork	RCS	8	5700	3437 (60.3)	63 (52–75)	NR	NR	1281 (22.5)	NR	5350 (93.9)	3026 (53.1)	1808 (31.7)	320 (5.6)	30 (0.5)	268 (4.7)	595 (10.4)	287 (5.0)
Zaninotto, M.	03.05–03.07	Italy Padova	RCS	6	75	56 (74.7)	67 (56–76)	NR	NR	21 (28.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Duanmu, Y.	3.04–3.23	USA California	RCS	7	100	56 (56)	45 (32–65)	NR	NR	NR	NR	NR	19 (19)	10 (10.0)	3 (3.0)	NR	6 (6.0)	NR	1 (1.0)

(Continues)

TABLE 1 (Continued)

Study	Enrollment duration	Region	Study design	Quality score	*N*	Males (%)	Age	Severity				Underlying Comorbidities							
								Asymptomatic (%)	Mild to moderate (%)	Severe (%)	Critical (%)	Any (%)	Hypertension (%)	Diabetes (%)	Malignance (%)	Liver disease (%)	Kidney disease (%)	Coronary heart disease (%)	COPD (%)
Singh, S.	NR	USA Mutli-city	RCS	5	2780	1070 (38.5)	51.92 (17.56)	NR	NR	NR	NR	NR	1190 (42.8)	640 (23.0)	NR	NR	385 (13.8)	280 (10.1)	NR
Aggarwal, S.	until 04.04	USA Des Moines	RCS	7	16	12 (75)	67 (38–95)	NR	NR	8 (50.0)	NR	NR	9 (56.2)	5 (31.3)	3 (18.8)	NR	6 (37.5)	3 (18.8)	2 (12.5)
Garg, S.	03.01–03.30	USA Mutli-city	RCS	4	180	NR	NR (NR)	NR	NR	NR	NR	159 (88.3)	79 (43.9)	47 (26.1)	NR	10 (5.6)	20 (11.1)	23 (12.8)	17 (9.4)
Moein, S. T.	03.21–04.05	Iran Tehran	RCS	6	60	40 (66.7)	46.55 (12.17)	0 (0.0)	54 (90.0)	6 (10.0)	0 (0.0)	NR	6 (0.1)	8 (13.3)	NR	NR	NR	NR	NR
Gold, J. A. W.	03.01–03.30	USA Georgia	RCS	6	305	NR	NR (NR)	NR	NR	NR	NR	287 (94.1)	206 (67.5)	121 (39.7)	12 (3.9)	7 (2.3)	32 (10.5)	35 (11.5)	16 (5.2)
Javanian, M.	02.25–03.12	Iran Babol	RCS	8	100	51 (51)	60.12 (13.87)	NR	NR	NR	NR	NR	32 (32)	37 (37.0)	4 (4.0)	3 (3.0)	12 (12.0)	NR	12 (12.0)
Million, M.	03.03–03.31	France Marseille	RCS	8	1061	492 (46.4)	43.6 (15.6)	0 (0.0)	1008 (95.0)	25 (2.4)	28 (2.6)	NR	149 (14.0)	78 (7.4)	28 (2.6)	NR	NR	46 (4.3)	NR

*KCDC: Korea Centers for Disease Control and Prevention.

COPD, Chronic obstructive pulmonary disease; NR, not reported.

Age, mean/median [SD/IQR/range], years.

abnormalities. In addition, the radiological imaging results indicated that 61% (95% CI, 0.50–0.71) of patients had bilateral lung lesions, while 25% (95% CI, 0.11–0.38) had lesions in one lung only. The incidence of ground-glass opacity (GGO) and consolidation was 40% (95% CI, 0.19–0.60) and 47% (95% CI, 0.23–0.72), respectively (Figure S1B).

The complications observed in the COVID-19 patients in the included studies are shown in Figure S1C. The results showed that ARDS (0.19; 95% CI, 0.14–0.24), hypoalbuminemia (0.38; 95% CI, 0.09–0.67), cardiac injury (0.18; 95% CI, 0.13–0.23), liver injury (0.11; 95% CI, 0.07–0.16), and kidney injury (0.09; 95% CI, 0.05–0.12) were the common complications of COVID-19.

3.4 | Clinical symptoms, East versus West

To explore whether there were differences in the clinical manifestations of COVID-19 patients between the East and the West, we compared the symptoms of patients from the two regions. The results showed that the incidence of cough (0.62 for the East vs. 0.80 for the West, $p < .001$), headache (0.10 vs. 0.31, $p < .05$), dizziness (0.07 vs. 0.37, $p < .001$), nasal congestion (0.06 vs. 0.16, $p < .001$) (Figure S2), together with dyspnea (0.25 vs. 0.66, $p < .001$), sore throat (0.13 vs. 0.20, $p < .05$), and digestive symptoms (0.13 vs. 0.50, $p < .05$) in patients with COVID-19 in East and South-East Asia were lower than those in North America, Europe, and Middle East. However, the incidence of fever (0.79 vs. 0.65, $p > .05$), ecphysesis (0.15 vs. 0.17, $p > .05$), and chest pain (0.10 vs. 0.24, $p > .05$) were not significantly different between the two groups (Figures S3 and S4).

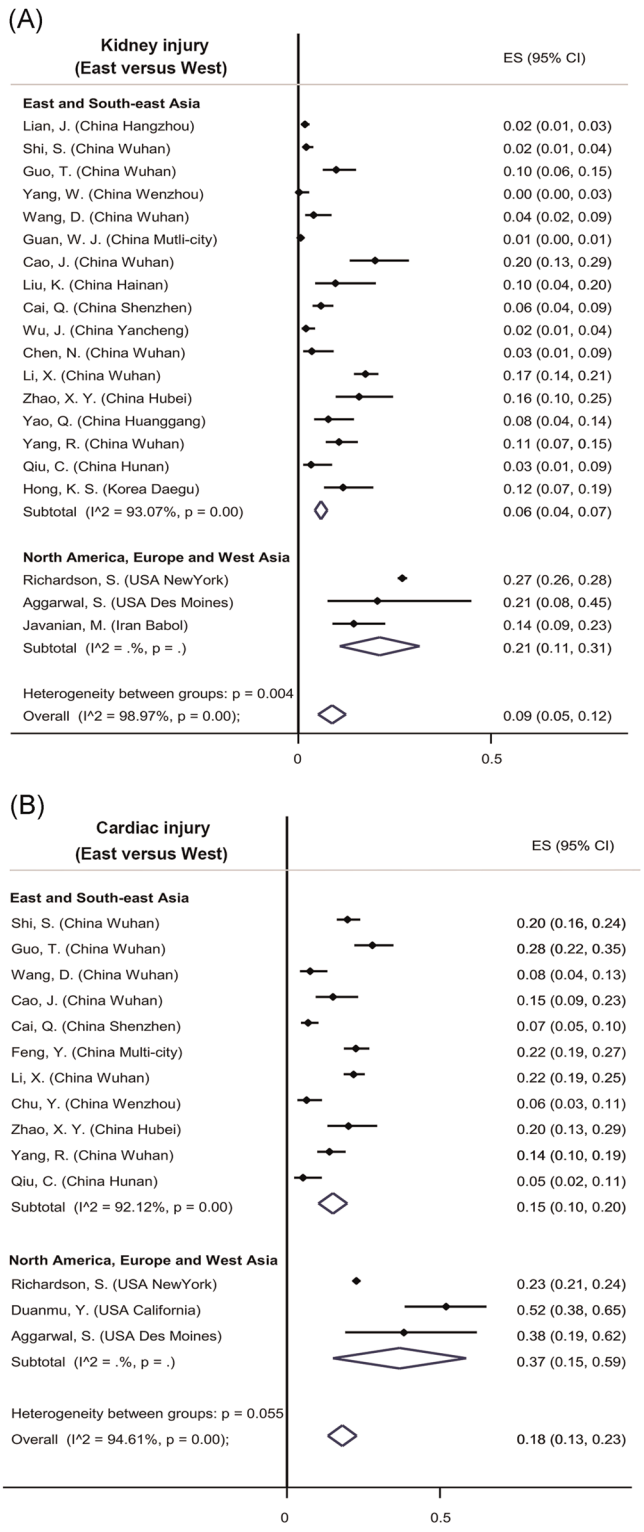
3.5 | Laboratory abnormalities, East versus West

Next, we conducted a meta-analysis of the laboratory data of the COVID-19 patients; the full results are presented in Figures S5 and S6. Specifically, we found that the indicators of significant differences in the laboratory test results between the two groups were ALT (0.18 for the East vs. 0.39 for the West, $p < .001$), AST (0.19 vs. 0.57, $p < .001$), and leukocytopenia (0.26 vs. 0.01, $p < .001$). No differences were observed in the incidence of lymphocytopenia (0.40 for the East vs. 0.48 for the West, $p > .05$) and thrombocytopenia (0.15 vs. 0.18, $p > .05$), nor for the increases in CRP (0.53 vs. 0.71, $p > .05$), D-dimer (0.26 vs. 0.25, $p > .05$), and troponin I (TnI) (0.23 vs. 0.23, $p > .05$) levels.

3.6 | Radiological imaging and complications, East versus West

The radiological images from the included studies (32 studies, a total of 6942 cases) are shown in Figure S7. The results indicated that there was no significant difference in the proportion of COVID-19 patients with normal initial chest radiographs (0.27 for the East vs. 0.24 for the (West, $p > .05$) nor with GGO (0.40 vs. 0.39, $p > .05$) between patients in East Asia and patients in Europe and North America.

In addition, the incidence of acute kidney injury (0.06 for the East vs. 0.21 for the West, $p < .01$) and cardiac injury (0.15 vs. 0.37, $p > .05$) in COVID-19 patients from the East was lower than that in the West (Figure 2).



3.7 | The clinical manifestation of COVID-19 patients in Wuhan and outside Wuhan

Wuhan, Hubei, was the epicenter of the COVID-19 outbreak in China. Most COVID-19 cases were diagnosed in Wuhan (62%) of which most reported Wuhan-related exposure (86%). Here, the results of the subgroup analysis showed that there were no significant differences in clinical symptoms between patients from Wuhan and patients outside Wuhan: cough (0.63 for Wuhan vs. 0.61 for non-Wuhan, $p > .05$), expectoration (0.26 vs. 0.33, $p > .05$), headache (0.10 vs. 0.10, $p > .05$), dizziness (0.05 vs. 0.11, $p > .05$), digestive symptoms (0.14 vs. 0.11, $p > .05$), nasal congestion (0.09 vs. 0.06, $p > .05$), myalgia (0.23 vs. 0.17, $p > .05$), and fatigue (0.33 vs. 0.26, $p > .05$). The laboratory data showed a similar pattern: lymphocytopenia (0.43 vs. 0.39, $p > .05$), thrombocytopenia (0.12 vs. 0.16, $p > .05$), neutropenia (0.14 vs. 0.12, $p > .05$), leukopenia (0.31 vs. 0.25, $p > .05$), leukocytosis (0.12 vs. 0.07, $p > .05$), CRP (0.54 vs. 0.52, $p > .05$), D-dimer (0.37 vs. 0.22, $p > .05$), LDH (0.53 vs. 0.41, $p > .05$), troponin I (0.28 vs. 0.20, $p > .05$), and creatinine (0.12 vs. 0.07, $p > .05$) for Wuhan and non-Wuhan patients, respectively. Similarly, in terms of the radiological imaging, the proportion of patients with GGO (0.37 vs. 0.42, $p > .05$) did not differ significantly between Wuhan and outside Wuhan (Figure S8–S12). However, the mortality rate (0.13 vs. 0.02, $p = .00$) and the proportion of critical cases (0.19 vs. 0.03, $p < .001$) in Wuhan were much higher than those outside Wuhan (Figure S13).

4 | DISCUSSION

The WHO declared COVID-19 a public health emergency of international concern on January 30, 2020, and called on countries to exercise caution. Compared to the other two highly pathogenic coronaviruses, SARS-CoV and MERS-CoV, that have emerged in the 21st century, SARS-CoV-2 has a greater ability to spread or cause severe illness in the human population.[68] At present, COVID-19 cases have spread to five continents with Europe and North America becoming the new epicenters of COVID-19. Here, our meta-analysis included 57 studies with 19,353 patients from December 2019 to May 2020 to systematically review the clinical characteristics of COVID-19 patients. Furthermore, by comparing the data from the East and the West, we found that the clinical manifestations of patients in East and South-East Asia were significantly different from those in Europe, Western Asia, and North America.

The results of this study showed that the most common symptoms seen in COVID-19 patients were fever (76%), cough (64%), expectoration (31%), dyspnea (30%), fatigue (29%), and myalgia (20%). A few patients may have additional symptoms such as digestive symptoms (17%), headache (13%), and hemoptysis (0.02%), amongst others. In terms of laboratory tests, COVID-19 usually caused increased levels of CRP (55%), LDH (48%), BNP (41%), and lymphocytopenia (41%), but had little effect on the level of leukocytes. Imaging examinations revealed unilateral or bilateral pulmonary infiltrates in most patients. In general, the overall manifestation of COVID-19 was consistent with a respiratory virus infection.

The exact origin of the virus that is currently circulating globally remains controversial. A recent study has shown that SARS-CoV-2 has three central variants, suggesting that the etiology, epidemiological characteristics, and clinical manifestations of COVID-19 patients from the East and the West may be different.[11] However, the supporting evidence for this hypothesis is still insufficient. Here, we examined this issue from a global perspective and found that the incidence of major clinical symptoms (including cough and dyspnea but not including fever and chest pain), differed between patients from the East and the West. The laboratory data showed that there were no significant differences in the levels of lymphocytes, leukocytes, CRP, and platelets between the two groups. It should be noted that the results also show that the incidence of cardiac and kidney injury, together with increased levels of creatinine, ALT, and AST in patients in the West were significantly higher than those in the East. In other words, COVID-19 patients in the West appear to have suffered more liver, kidney, and heart damage. In addition, it should be noted that there appears to be a trend in which the prevalence of hypertension, cardiovascular disease, and diabetes are higher among patients from the West. This may be an important contributor to the differences in clinical presentation between COVID-19 patients from the East and the West. Therefore, this conclusion indicates a necessity for healthcare workers in the West to pay more attention to the protection of the heart, liver, and kidneys.

Overall, the above data support the hypothesis to a certain extent, specifically, that the clinical manifestations of COVID-19 in patients from the East and the West may differ. The investigation of these differences is crucial to a better understanding of the origin of the virus, and to tracking its evolution in the population, and designing prevention and control strategies. However, it is difficult to conclude that the differences in clinical manifestations are caused by viral mutations or that the disease presenting in the West is more severe. Race, chronic underlying conditions, epigenetics, geography, the configuration of medical resources, population age structure, local policies, the stages of the epidemic, and even environmental factors may all contribute to these differences in clinical manifestations.

Wuhan was the epicenter of COVID-19 in China. In China, more than 60% of the confirmed cases and 83% of COVID-19-related

FIGURE 2 The incidences of acute kidney injury and cardiac injury in COVID-19 patients, East versus West. A, Forest plots of kidney injury. B, Forest plots of cardiac injury. Acute kidney injury was identified as an increase in serum creatinine by ≥0.3 mg/dl (≥26.5 mol/L) within 48 h or an increase in serum creatinine to ≥1.5 times baseline within the prior 7 days compared with the preceding 1 year of data in acute care medical records. Acute kidney injury is calculated only for patients with record of baseline kidney function data available and without a diagnosis of end-stage kidney disease. Cardiac injury was defined as blood levels of cardiac biomarkers (hs-TNI) above the 99th-percentile upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography

deaths were reported in Wuhan. Recent research by Li et al.[68] and Xu et al.[69] has suggested there may have been differences in clinical symptoms, laboratory abnormalities, and clinical outcomes between patients inside and outside of Wuhan. Data from the Chinese Center for Disease Control and Prevention (CCDC) have also indicated that the case-fatality rate in Hubei Province was higher than that outside the province.[70] Some researchers have hypothesized that this may have been due to a decrease in the pathogenicity of SARS-CoV-2 in the process of transmission. If so, a change in pathogenicity would likely be visible in the presence of significant clinical heterogeneity among studies from the East. Here, our results demonstrated that there were no significant differences in clinical symptoms, laboratory data, and radiological imaging between cases within and outside of Wuhan. As Wuhan was the original location, an initial shortage of healthcare resources may have occurred during the early stages of the outbreak. Hospitals in Wuhan gave priority to admitting patients with severe/critical disease in the early stage of the epidemic. This may be the explanation for the higher mortality and proportion of critical cases in Wuhan.

Our systematic review and meta-analysis suffers from the usual limitations of initial investigations of infections with an emerging novel pathogen. First, the datasets were retrospective studies, which prevented us from ruling out the influence of other confounding factors. Second, more detailed patient information, such as the severity of the relevant clinical symptoms and the presence of underlying disease, was not included in most studies. Third, the meta-analysis showed significant heterogeneity between the included studies. Due to the large number of outcomes, it was not possible to perform subgroup and sensitivity analysis for each of the outcome indicators, an issue that affects the accuracy of the results of a meta-analysis. Lastly, more data from Africa and South America should be included in future research. The conclusions of this meta-analysis require verification by more studies from across the world with increased precision in design and larger sample sizes.

5 | CONCLUSION

The COVID-19 outbreak is currently not under control, with a high risk of global spread. Our meta-analysis indicated that the most common symptoms seen in COVID-19 patients were fever, cough, expectoration, dyspnea, fatigue myalgia. There are differences in the clinical manifestations and mortality of COVID-19 between the East and the West and COVID-19 patients from the West appear to suffer more severe liver, kidney, and heart damage due to SARS-CoV-2. Investigation of these differences is critical for an understanding of the spread of SARS-Cov-2 and the documentation of the diversity in COVID-19 manifestations to improve the detailed management of the disease in different regions. In addition, international cooperation is crucial because it allows countries to fully share data, evidence, and experience so that they can defeat the virus together.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTORS

Hao Zhang designed the study and finally approved the version to be published; Xiucheng Liu write the manuscript & acquired the data; Xiang Li acquired the data and help write the manuscript; Yeqing Zhou acquired the data; Teng Sun prepared the figures.

DATA AVAILABILITY STATEMENT

In accordance with the "DFG Guidelines on the Handling of Research Data," we will make all data available upon request. The data set will be archived for at least 10 years after publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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