SYSTEMATIC REVIEWS

Comparative profile for COVID-19 cases from China and North America: Clinical symptoms, comorbidities and disease biomarkers

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Abstract

BACKGROUND
Large inter-individual and inter-population differences in the susceptibility to and outcome of severe acute respiratory syndrome coronavirus 2 or coronavirus disease 2019 (COVID-19) have been noted. Understanding these differences and how they influence vulnerability to infection and disease severity is critical to public health intervention.

AIM
To analyze and compare the profile of COVID-19 cases between China and North America as two regions that differ in many environmental, host and healthcare factors related to disease risk.

METHODS
We conducted a meta-analysis to examine and compare demographic information, clinical symptoms, comorbidities, disease severity and levels of disease biomarkers of COVID-19 cases from clinical studies and data from China (105 studies) and North America (19 studies).

RESULTS
COVID-19 patients from North America were older than their Chinese counterparts and with higher male: Female ratio. Fever, cough, fatigue and dyspnea were the most common clinical symptoms in both study regions (present in about 30% to 75% of the cases in both regions). Meta-analysis for the prevalence of comorbidities (such as obesity, hypertension, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, cancer, and chronic kidney diseases) in

COVID-19 patients were all significantly more prevalent in North America compared to China. Comorbidities were positively correlated with age but at a significantly younger age range in China compared to North American. The most prevalent infection outcome was acute respiratory distress syndrome which was 2-fold more frequent in North America than in China. Levels of C-reactive protein were 4.5-fold higher in the North American cases than in cases from China.

CONCLUSION
The differences in the profile of COVID-19 cases from China and North America may relate to differences in environmental-, host- and healthcare-related factors between the two regions. Such inter-population differences-together with intra-population variability-underline the need to characterize the effect of health inequities and inequalities on public health response to COVID-19 and can assist in preparing for the re-emergence of the epidemic.

Key Words: COVID-19; Symptoms; Comorbidities; China; North America; Adults

Core Tip: The study evaluates the inter-population differences in the susceptibility to acute respiratory syndrome coronavirus-2 or coronavirus disease 2019 (COVID-19) between China and North America. Fever, cough, fatigue and dyspnea were the most common clinical symptoms of COVID-19 in both study regions. Hypertension, diabetes and cancer were the most prevalent comorbidities in COVID-19 cases from China whereas obesity, hypertension and diabetes were the most prevalent in North America. Prevalence of comorbidities in COVID-19 cases increased with age but was at younger ages in cases from China compared to those from North America. Inflammatory markers such as C-reactive protein were 4.5-fold higher in the North American cases than in cases from China. The differences in COVID-19 profile between China and North America reflects the differences in environmental-, host- and healthcare-related factors between the two regions.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) is a novel, zoonotic, positive-sense, single-stranded RNA b-coronavirus that belongs-together with SARS-CoV and Middle Eastern respiratory syndrome (MERS)-CoV-to the *Coronaviridae* family, sub-family *Orthocoronaviridae*[1]. In December 2019, COVID-19 infection began to spread from Wuhan, Hubei, China where it was declared on January 30, 2020 as a public health emergency of international concern by the World Health Organization (WHO)[2], a status that was raised to its highest level on February 28 and the disease was declared a global pandemic on March 11, 2020[2]. That pandemic status was declared when the number of cases was increased 13 times (outside China) than the initial number of cases, reporting > 118000 infections with triple the number of countries primarily involved (114 countries) and with > 4000 deaths[2]. Presently, *i.e.*, within less than 6 mo, the number of COVID-19 cases has increased by approximately 200-fold with a similar increase in the number of deaths[3].

The clinical manifestations of the disease severity have shown great inter-individual variation in response to infection[4] with 81%, 14% and 5% of the cases were, respectively manifested with mild, severe and critical outcomes[4-6]. The rapid global spread of the disease, together with the inter-individual variation in response to infection, underlines the need for systematic analysis of global datasets from clinical

research to better characterize the potential risk factors that play a role in population vulnerability to development of severe disease.

As of mid-August 2020, there are over 6 million cases and 235000 deaths in North America (United States, Mexico and Canada) and approximately 90000 cases and 5000 deaths in China[3]. Taken together, at that time, over 30% of the world's confirmed cases and deaths were reported in North America (mainly the United States) and China. Given this high prevalence, it is unsurprising that most of the epidemiological, clinical, etiological, and immunological studies on COVID-19 have so far emerged from clinical research in these two regions. However, East Asia and North America have significant differences in lifestyle and sociodemographic factors, and population characteristics which may differently affect response to infection. Understanding these inter-population differences may highlight factors that influence population vulnerability and facilitate a better understanding of the disease etiology. Therefore, the present study was undertaken to systematically analyze, summarize and compare findings from China and North America as two highly affected populations with COVID-19. The outcome of this study may permit designing population-based prevention and control measures for COVID-19 and other infectious diseases caused by coronaviruses.

MATERIALS AND METHODS

Study selections

A systematic literature search was conducted in conformity with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Table 1). The studies examined here were selected from the Aggregated Dataset of Clinical Outcomes for COVID-19 Patients – a publicly accessible dataset which aggregates data from published clinical studies and preprints released between December 2019 and April 2020[7]. This dataset is largely derived from studies conducted in hospitals in the countries affected with COVID-19. Reports in this aggregated dataset were collected from 17 countries (Australia, Chile, China, France, Germany, Iceland, Italy, Japan, Korea, Mexico, Netherlands, Scotland, Singapore, South Korea, United Kingdom and United States) representing the regions of East Asia, Europe, and the Americas. The studies were observational, randomized clinical trials and case reports. For each paper in the aggregated dataset, an MIT researcher reads the paper and gathers the relevant numerical data from the tables and text into a standard format. In the present study, we excluded case reports and studies with patients from countries other than China and North America. The inclusion of case studies would have added more heterogeneity to the meta-analysis findings (see below). Only reports with adult cases were included. As shown in Figure 1, we included 124 studies and reports – 105 from China and 19 from North America (Supplementary Table 2).

Data extracted for the purpose of this study included demographic information (number of patients, age, gender, and ethnicity), frequency of clinical symptoms (fever, cough, dyspnea, headache, expectoration, myalgia, fatigue, diarrhea, vomiting or nausea, sore throat and chills), prevalence of comorbidities [obesity, hypertension, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), cancer, liver diseases and chronic kidney diseases], infection outcomes [acute respiratory distress syndrome (ARDS), heart failure, septic shock, acute kidney injury and secondary infection] and levels of standard disease biomarkers [white blood cell count (10^9/L), lymphocyte count (10^9/L), aspartate aminotransferase (U/L), total bilirubin (μmoL/L), creatine kinase (U/L), C-reactive protein (CRP) (mg/L) and procalcitonin (ng/mL)].

Statistical analysis and meta-analysis

Weighted average and 95% confidence intervals (CI) were used to calculate the mean age and percentages of males, ethnicity, disease severity, the prevalence of infection outcome and average levels of biomarkers in COVID-19 cases from the selected studies. Meta-analysis tests were conducted-by Comprehensive Meta-Analysis software (CMA), version 3.9 (Englewood, NJ, United States)[8] – on the comorbidities prevalence and clinical symptoms frequency. Pooling of the variance in proportions or percentages (raw) were based on a binary random effects model[9]. This was due to the heterogeneity of the examined populations and the possible across-population variability in the relationships between COVID-19 and the evaluated factors (*e.g.*, comorbidities or clinical symptoms). Comparisons between the assessed factors in the
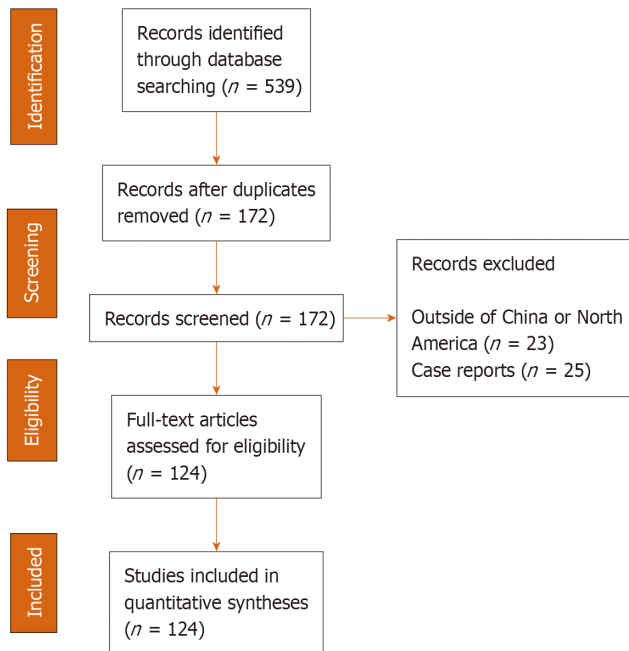
Identification

Records identified through database searching (*n* = 539)

Screening

Records after duplicates removed (*n* = 172)

Records screened (*n* = 172)

Records excluded

Outside of China or North America (*n* = 23)
Case reports (*n* = 25)

Eligibility

Full-text articles assessed for eligibility (*n* = 124)

Included

Studies included in quantitative syntheses (*n* = 124)

Figure 1 Flowchart of study selection and systematic literature review process. The flow diagram describes the systematic review of literature evaluating the prevalence of comparative profile for coronavirus disease 2019 (COVID-19) cases from China and North America from studies selected from Aggregated Dataset of Clinical Outcomes for COVID-19 Patients[7]. Quantitative analysis is developed from 124 studies from China (*n* = 105) and North America (*n* = 19).

two evaluated populations was carried out using the Chi-squared test as previously recommended[10,11]. Comparisons of the average age and levels of disease markers were carried out by Student's *t*-test. Pearson's correlation coefficient (*r*) was used to measure of the association between the proportion of the examined comorbidities and age in the examined regions. We used SPSS Statistics, Version 21.0 (SPSS Inc., Chicago, IL, United States) for all statistical tests (two-sided).

Heterogeneity among the selected studies was assessed by the Q test[12]. Information provided by the Q test conveys if heterogeneity is present or absent. However, this test does not inform on the heterogeneity level besides it has insufficient power to detect heterogeneity, especially when there is small number of assessed studies (*e.g.*, for some comorbidities). Consequently, I^2 index was calculated as a complement to the Q test and to define the extent of between-study heterogeneity[13]. I^2 index values are typically categorized as considerable (> 90%), substantial (60%-90%), moderate (30%-60%) and low (< 30%)[14]. True heterogeneity was also examined by assessing τ^2 that informs on the within-study variance in the used random-effects model[15]. Publication bias (Supplementary Table 3) was assessed as described earlier[15] by Egger's test and to examine the tendency for an effect estimated from studies with a small sample size to be different from that obtained from large studies. Kendall's tau with continuity correction test (Begg and Mazumdar rank correlation test) was however used to test the correlation between the ranks of effect sizes and the ranks of their variances across the selected studies.

RESULTS

In the present study we examined the data of 72025 COVID-19 cases from 124 reports from China (105 studies) and North America (19 studies). The number of entries from the reports from North America was 1.28-fold higher than those from China. Data collected from these studies were obtained from the "Aggregated Dataset of Clinical Outcomes for COVID-19 Patients" and were compared between patients from the two regions for demographic information, frequency of clinical symptoms, prevalence of comorbidities and levels of standard disease biomarkers. As shown in Table 1, COVID-19 cases from North America were older than their Chinese counterparts and with higher male: Female ratio. Reports from North America examined Hispanics (approximately 50%), Whites (approximately 30%), and African Americans and Asians

Table 1 Characteristics of the study populations with coronavirus disease 2019 from China and North America

Characteristic	China		North America		P^3 value
	Number of cases (n)[1]	Mean[2] (95%CI)	Number of cases (n)[1]	Mean[2] (95%CI)	
Age	23088	50.6 (50.4-50.8)	37293	55.5 (55.4-55.6)	< 0.001
Male (%)	29755	52.6 (52.5-52.7)	36298	54.4 (54.2-54.5)	< 0.001
Severity (%)	26810	18.7 (12.8-24.6)	7824	25.1 (19.1-31.3)	< 0.001
Infection outcome (%)					
ARDS	13524	14.5 (14.1-14.9)	1849	34.9 (33.9-36.1)	< 0.001
Heart failure	4847	10.6 (10.2-11.1)	2654	2.5 (2.4-2.6)	< 0.001
Septic shock	10886	4.0 (3.8-4.2)	2266	28.4 (27.3-29.5)	< 0.001
Acute kidney injury	12767	5.5 (5.4-5.7)	4761	26.7 (26.4-27.1)	< 0.001
Secondary infection	4617	15.3 (14.7-15.9)	807	5.3 (5.1-5.6)	< 0.001

[1]n is the number of subjects assessed for each characteristic as per the source database[7].

[2]Weighted mean.

[3]Student's *t*-test or Chi Square test. ARDS: Acute respiratory distress syndrome.

(approximately 20%) whereas reports from China, as expected, examined only Chinese (100%) patients (data not shown). As for the infection outcomes, significantly ($P <$ 0.001) higher rates of cases from North America were found to develop ARDS, septic shock and acute kidney injury compared to their Chinese counterparts but had lowers rates of heart failure and secondary infection. In China, the most prevalent infection outcomes were ARDS and secondary infection which occurred in about 15% of the cases (95%CI: 14.1%-14.9% and 14.7%-15.9%; respectively). Similarly, in North America, ARDS was the chief infection complication (34.9%, 95%CI: 33.9-36.1), followed by septic shock (28.4%; 95%CI: 27.3-29.5).

Meta-analysis for the frequency of clinical symptoms associated with COVID-19 in both study populations is shown in Table 2. Fever, cough, fatigue and dyspnea were the most common clinical symptoms in COVID-19 cases, but with varying frequencies between the studies regions. These symptoms were present in about 30% to 75% of the cases in both regions. Also, about 10% to 30% of the cases in both regions had expectoration, myalgia, diarrhea, headache, sore throat, chills, vomiting and/or nausea. Significantly lower rates of fever and expectoration were noted in North America compared to China ($P <$ 0.001) whereas similar frequencies of cough, headache, fatigue and sore throat were observed in both study areas. From the selected reports, the mortality rates of COVID-19 (± SD) was 5.9 ± 13.4% in China, not significantly different from rates of 13.9 ± 14.8% in North America. Substantial to considerable I^2 values (60%-> 90%) were obtained for the combined frequency of the majority of clinical symptoms from the evaluated reports, indicating a high degree of heterogeneity among studies. On the other hand, the combined frequency from studies reporting fatigue, sore throat and chills have shown low among-studies level of heterogenicity (I^2: 18%-51%).

Meta-analysis for the prevalence of comorbidities in COVID-19 cases from studies in China and North America is shown in Table 3. Except for liver diseases and cancer, the prevalence of all comorbidities was significantly higher in North America compared to China ($P <$ 0.001). The prevalence of liver diseases (any, *e.g.*, alcohol-related liver disease, hepatitis, cirrhosis, hemochromatosis, liver Cysts, non-alcoholic fatty liver disease) was similar in both regions whereas that of cancer was 1.5-fold higher in China than in North America ($P <$ 0001). Hypertension followed by diabetes were the most prevalent comorbidities in both regions with the North American cases having on average 2.5-fold higher prevalence on the two diseases than cases from China. Although obesity was the third most prevalent co-existing medical condition in COVID-19 cases from North America (approximately 35% of the cases), it was the least prevalent comorbidity in China (only 2% of the cases). Similar to hypertension and diabetes, cardiovascular diseases were 2.5-fold higher in cases from North America (21%) than in those from China (8%). Chronic kidney diseases and COPD were, respectively 5.6- and 3.5-fold significantly ($P <$ 0.001) more prevalent in COVID-19 cases from North America than China. Substantial to considerable I^2 values (60%->

Table 2 Meta-analyses for the frequency of clinical symptoms in coronavirus disease 2019 cases from China and North America

Symptoms	China						North America						P^2 value
	Number of cases (*n*)[1]	Meta-analysis		Heterogenicity			Number of cases (*n*)	Meta-analysis		Heterogenicity			
		Frequency (%)	95%CI	r^2	Q	I^2		Frequency (%)	95%CI	r^2	Q	I^2	
Fever	25223	77.5	75.8-79.2	0.015	3591	93	4,502	43.3	30.8-56.1	0.099	5023	96	< 0.001
Cough	24105	59.6	56.9-62.4	0.041	4843	95	3766	58.3	44.7-71.9	0.951	1997	98	0.131
Dyspnea	20558	29.4	26.7-32.1	0.028	9566	98	3711	38.9	24.3-53.5	0.103	4636	99	< 0.001
Headache	13627	9.8	8.6-11.1	0.003	726	85	2483	8.9	6.4-11.4	0.001	36	64	0.163
Expectoration	14426	28.1	25.3-30.7	0.018	1719	93	2024	8.2	5.5-10.9	0.002	14	72	< 0.001
Myalgia	16.184	19.1	17.1-21.2	0.012	3596	96	1224	22.5	12.8-32.3	0.019	159	94	< 0.001
Fatigue	19561	36.3	33.2-39.4	0.038	5004	97	21	48.3	20.1-76.5	0.032	4	51	0.253
Diarrhea	20535	10.4	9.3-11.6	0.004	2210	92	3719	12.9	7.6-18.2	0.012	538	96	< 0.001
Vomiting and nausea	14974	7.2	6.1-8.3	0.003	1485	91	2198	11.6	6.1-17.1	0.006	108	91	< 0.001
Sore throat	11379	9.1	7.7-10.4	0.002	476	84	2542	8.3	6.8-9.8	0.001	16	23	0.202
Chills	5949	7.5	5.2-9.8	0.003	386	94	2108	17.7	16.1-19.3	0.001	5	18	< 0.001

[1]*n* is the number of subjects assessed for each clinical symptom as per the source database[7].

[2]Chi Square test for the difference between symptom frequency in China and North America.

90%) were obtained for the combined prevalence of each comorbidity from the examined reports, indicating high among-studies heterogeneity in the evaluated conditions in reports from both regions. Analysis for the correlation between comorbidities and age in COVID-19 cases from China and North America is shown in Figure 2. All comorbidities were positively correlated with age in both study regions except for rates of obesity in North America that were steady along the examined age range. Although the overall average age was comparable between cases from the two regions, comorbidities were reported at a significantly younger age range in China compared to North American.

The average levels of biomarkers in COVID-19 cases from China and North America is shown in Table 4. Studies from both regions showed levels within the reference clinical range for white blood cell count, lymphocyte count and total bilirubin. In both regions, however, levels significantly higher than the reference range were reported in aspartate aminotransferase, creatine kinase, CRP, and procalcitonin and were higher in cases from North America compared to China. For example, aspartate amino-

Table 3 Meta-analyses for the prevalence of comorbidities in the study populations of coronavirus disease 2019 cases from China and North America

Comorbidities	China						North America						P^2 value
	Number of cases (n)[1]	Meta-analysis		Heterogenicity			Number of cases (n)	Meta-analysis		Heterogenicity			
		Frequency (%)	95%CI	τ^2	Q	I^2		Frequency (%)	95%CI	τ^2	Q	I^2	
Obesity	666	2.1	0.1-4.3	0.001	54	91	26895	22.9	18.1-27.9	0.016	2130	99	< 0.001
Hypertension	22650	25.6	23.8-27.4	0.013	2154	91	34442	47.6	41.0-54.2	0.034	5347	99	< 0.001
Diabetes	23770	11.8	10.9-12.6	0.002	980	79	35384	34.1	30.1-38.2	0.015	3169	98	< 0.001
Cardiovascular diseases	22439	7.9	7.1-8.7	0.002	1339	86	33459	20.8	18.4-23.3	0.005	4379	99	< 0.001
COPD	17263	3.3	2.8-3.7	0.001	540	78	29697	11.6	10.1-13.1	0.001	716	94	< 0.001
Cancer	16527	9.7	7.1-12.2	0.017	19185	99	24564	6.6	5.5-7.6	0.001	254	89	< 0.001
Liver diseases (any)	11087	3.3	2.8-3.9	0.001	276	68	9706	3.1	2.1-4.2	0.001	98	83	0.414
Chronic kidney diseases	16394	2.1	1.7-2.4	0.001	236	59	30761	11.8	10.0-13.6	0.002	1082	86	< 0.001

[1]n is the number of subjects assessed for each comorbidity as per the source database[7].

[2]Chi Square test for the difference between prevalence of comorbidity in China and North America. COPD: Chronic obstructive pulmonary disease.

transferase and creatine kinase were approximately 1.4-fold significantly higher in North American cases than Chinese cases whereas CRP levels were 4.5-fold higher ($P < 0.001$).

DISCUSSION

The present study provides an insight into population-related differences in the clinical features of COVID-19 between China and North America. On the first of April 2020, the case fatality rate (CFR) of the disease was 4.02% in China, 1.74% in the United States, 1.15% in Canada and 2.56% in Mexico (averaging 1.7% for the three North American countries)[2,16]. These rates, however, changed over time as the pandemic evolved with the CFRs in North America superseding those in China. As of the end of August 2020, the CFR has increased in both world regions to 5.23% in China, 3.14% in the United States, 7.31% in Canada and 10.87% in Mexico (averaging 7.1% in North America)[2,16]. In general, these CFRs of COVID-19 are still lower than that of the other two coronavirus epidemics, namely, SARS (10%)[17-19] and MERS-CoV (38%)[20]. The regional changes and differences in COVID-19 CFRs are thought to be due to the varying rates of disease severity and the different diagnostic tools and detection

Table 4 Average levels of biomarkers in coronavirus disease 2019 cases from China and North America

Biomarker	China		North America		*P*[3] value	Reference range
	Number of cases (*n*)[1]	Mean[2] (95%CI)	Number of cases (*n*)[1]	Mean[2] (95%CI)		
White blood cell count (10^9/L)	21703	5.47 (5.4-5.6)	9094	7.53 (7.51-7.55)	< 0.0001	3.4-9.6
Lymphocyte count (10^9/L)	22053	1.04 (1.0-1.3)	8653	0.88 (0.87-0.89)	< 0.0001	0.95-3.07
Aspartate aminotransferase (U/L)	15495	30.8 (30.5-31.3)	8627	45.2 (45.1-45.3)	< 0.0001	8-20
Total bilirubin (μmoL/L)	10824	10.7 (10.6-10.8)	281	1.4 (1.1-1.7)	< 0.0001	2-17
Creatine kinase (U/L)	11382	85.3 (84.7-85.8)	9033	115 (113-117)	< 0.0001	M: 25-90 F: 10-70
C-reactive protein (mg/L)	16144	25.9 (25.5-26.4)	12059	116 (115-117)	< 0.0001	0-8
Procalcitonin (ng/mL)	12050	2.44 (2.2-2.6)	11661	0.70 (0.68-0.72)	< 0.0001	0-0.15

[1]*n* is the number of subjects assessed for a given characteristic as per the source database[7].

[2]Weighted mean; [3]Student's *t*-test.

protocols between the two populations[21]. Moreover, climate (*e.g.*, temperature and humidity), immune status, age, gender, genetic profile, prevalence of comorbidities, and the healthcare services and facilities can be also important factors affecting the differences in COVID-19 profile[22-26]. These factors differ markedly not only between but also within the studied regions[27]. Furthermore, research has shown that the expression of angiotensin I converting enzyme 2 (ACE2) receptors may play a role in the severity of coronavirus infection in different populations[28]. Variations in *ACE2* gene expression have been proposed to be associated with different ACE2 activity and population-related differences in COVID-19 risk[28]. For example, East Asian populations have been shown to have high allele frequency of the eQTL variants (expression quantitative trait loci, the genomic loci that explain disparity in mRNA expression) associated with higher *ACE2* tissue expression[29] and the possible subsequent population-related differences in susceptibility (or response) to COVID-19[28].

As a newly emerging infectious disease, the entire population is expected to be vulnerable to COVID-19. However, studies have shown that the median age of patients infected with COVID-19 has been between 42 to 59 years[30-33]. The average age range of 50 (China) to 55 (North America) years reported here falls within that most susceptible age interval. It seems however that COVID-19 cases from North America tend to be slightly – but significantly – older than their counterparts from China. Older patients (> 60 years) with underlying diseases were found to be more vulnerable to severe illness that progresses to death[34,35]. This observation was apparent in the cases from North America where patients with co-existing medical conditions were, on average, older (40-80 years) than their counterparts from China (18-75 years). In the present study, the incidence of the disease was higher in men than in women in both study regions. Although sex-related difference in disease incidence were not statistically significant, confirming earlier findings[32], a study by Wei *et al*[36] reported that males have higher odds ratio (OR) of disease-related morbidity (OR: 1.12), severity (1.63), and mortality (1.71) than females.

Based on symptoms, disease indicators and imaging results, the clinical manifestations of the disease severity has been divided into mild (non- or mild-pneumonia; occurred in 81% of the cases); severe (dyspnea, ≥ 30/min respiratory frequency, ≤ 93% blood oxygen saturation, and/or more than 50% lung infiltrates within 1-2 d; in 14% of the cases) and critical (respiratory failure, septic shock, and/or multiple organ dysfunction or failure; in 5% of the cases)[5]. Typical clinical symptoms of COVID-19 include fever, fatigue, and dry cough while expectoration, headache, nausea, vomiting, and diarrhea are among the atypical symptoms[21]. Although some confirmed cases are asymptomatic or have low typical clinical symptoms and are recovered within one week without presenting with pneumonia[32,37,38], many cases have shown some signs of bilateral lung injury[39]. In severe cases, however, the infection can progress rapidly to ARDS, septic shock, metabolic acidosis, coagulopathy, acute myocardial injury, injury to the kidney and even multiple organ failure[31,33,40] that collectively may eventually be fatal. In the present study the frequency of case severity was significantly higher in North America than China. This
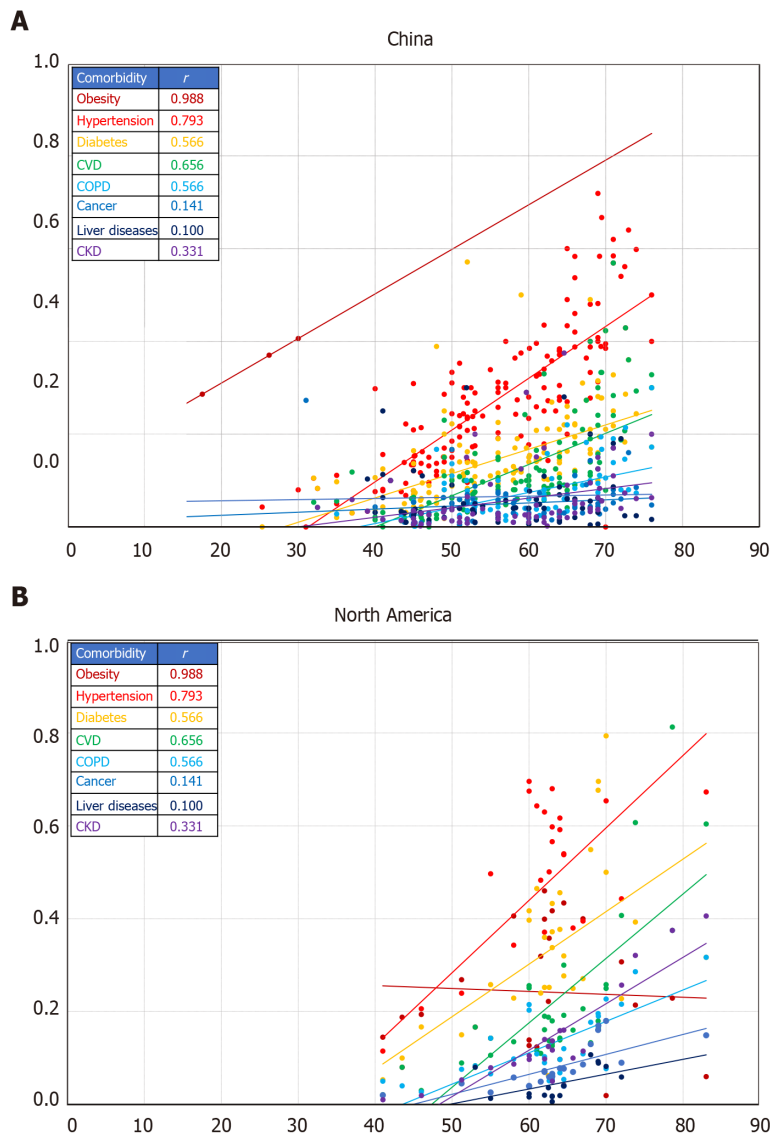
Figure 2 Comparative profile for the correlation between comorbidities (proportion) and age (years) in coronavirus disease 2019 cases from China and North America. A: China; B: North America. Lines represent linear regression between the proportion of comorbidity and age. Colors correspond to the comorbidity in the insert table with the related Pearson correlation coefficient (*r*). Each data marker represents one entry. All *r* values are significant at *P* < 0.05 for the corresponding number of entries shown. Number of entries is per the source database[7].

was apparently due to the higher rates of ARDS, septic shock and acute kidney injury that were all in higher rates in cases from North America compared to those from China. This may be due to the higher rates of clinical symptoms such as dyspnea, myalgia, diarrhea and chills noted in the North American cases. Dyspnea is associated with severe pneumonia or ARDS whereas symptoms such as diarrhea may indicate an involvement in gastrointestinal tract, particularly in patients with non-severe cases. Currently, there is no firm evidence to suggest that severity of digestive symptoms corresponds to severity of COVID-19 clinical course. These symptoms are known to be associated with inflammatory syndrome, pneumonia and/or respiratory infections[41]. In a retrospective cohort study, critically ill COVID-19 patients were presented with high levels of inflammation associated with fever, coughing, dyspnea, diarrhea together with lymphopenia and hypoalbuminemia[41]. In this respect, we noted that levels of CRP, the acute phase reactant and the downstream factor in the innate immunity-related inflammatory pathway[42], were 4.5-fold higher in the cases from North America than in those from China. Therefore, subsequent to infection, and in response to the individual's immune status, high levels of innate immunity-related inflammation may emerge to combat the disease leading to a range of clinical symptoms that may manifest into an array of disease complications and severe

outcomes. In line with this proposition, early stages of COVID-19 are characterized by a decrease in the absolute number of peripheral blood lymphocytes that progressively decline as the disease develops into its severe outcome[43-46]. This state is suggested to result in inflammatory lesions in the lungs and extensive inflammatory reactions and necrosis in the spleen, lymph nodes and blood vessels that may lead to fatal complications[6].

Of the populations vulnerable to increased risk of infection and severe outcomes of COVID-19 are those with pre-existing medical conditions such as hypertension, diabetes, cardiovascular disease and other underlying conditions[30,31,40]. In a meta-analysis of 11 reports with 521 mild COVID-19 cases and 704 severe cases[47-57], we found severe COVID-19 cases to have a 3-fold higher prevalence of cardiovascular diseases, hypertension and diabetes than mild cases (unpublished data). These comorbidities were all significantly higher in the cases from North America compared to those from China. Interestingly, in both study regions, the most common comorbidities were hypertension followed by diabetes and cardiovascular diseases. This was also noted in a number of studies reported in a recent meta-analysis of 656 COVID-19 patients from 19 studies[39]. Hypertension, diabetes and cardiovascular diseases are all metabolic syndrome-related conditions known to be at higher prevalence in North America than in East Asia. For example, the 2019 trends of age-specific incidence of diagnosed diabetes have shown a lower diseases prevalence in China[58] compared to United States[59] at the same age group ($\geq$ 65 years). In general, the metabolic syndrome related conditions are usually linked to endothelial dysfunction, attenuation of anti-inflammatory responses and generation of a pro-inflammatory state; features that are also common in many infectious disorders[60,61]. Overproduction of cytokines and acute-phase reactants[6], such as CRP, related to chronic comorbidities may lead to endothelial dysfunction and subsequent complications including pericardial effusion, vascular leakage, allergy and ascites[62]. Furthermore, inadequate secretion of insulin and hyperglycemia can deteriorate the functions of lymphocyte and macrophage causing a state of diminished acquired immunity[63]. The latter was associated with 60% higher risk of complications related to pneumonia[64]. Indeed, the etiological link between severity of COVID-19 and chronic diseases has not been fully elucidated. However, it is rational to propose that in infected patients, chronic comorbidities can synergistically (with the infection) downregulate both the individual's innate and adaptive immune responses[65,66]. Such a synergism between infection and chronic diseases may also impair other critical components of immunity such as the activity of neutrophils, phagocytosis and chemotaxis and attenuate the functions of neutrophils and T cells[65,66] to aggravate the severity of infectious diseases outcome.

Several limitations can be identified in the present study. Across the selected studies, sub-cohort divisions may have followed different criteria which may be of independent interest[7]. These include severity of disease (*e.g.*, severe *vs* mild), death (*e.g.*, survivors *vs* non-survivors) and comorbidity (*e.g.*, diabetic *vs* non-diabetic). This subgrouping was not considered here as we were attentive only to COVID-19 cases and comparing the profile of the disease in the two study regions. Moreover, studies in this dataset are designed with different objectives which may have affected data reporting. For example, some studies will only report data from non-survivors, some studies will focus on the profile of the disease clinical symptoms with little information on its outcome and some reports will vary in their definition to disease severity. Therefore, data points may exhibit a high proportion of missing or re-reported features and hence the different number of examined subjects for the assessed disease characteristics[7]. Additionally, the diverse methodologies used to define the disease characteristics may have contributed to the large among-studies variation in each region. Furthermore, selected papers were not consistent in reporting the mortality or discharge rates[7]. Some only report mortality whereas others report discharges rates while many patients remain in the hospital at the conclusion of the study. Additionally, the studies from the examined database aggregates data from different locations and hospitals within each of the two regions. This may have led to different reporting standards even within the same study. Furthermore, the large difference between the number of studies from China and North America may have influenced the degree of among-studies heterogeneity in the combined frequency of findings within the studied regions. Sources of heterogeneity may also relate to the large variation among studies in the sample size and the different study designs, objectives, and outcome measures.

CONCLUSION

In conclusion, marked differences in the profile of COVID-19 have been observed between cases from China and North America in terms of disease severity, clinical symptoms, prevalence of comorbidities and levels of disease markers. These differences may relate to both environmental- and host-related factors as well as differences in the diagnostic and detection protocols between the two study regions. Furthermore, the varied prevalence of comorbidities and status of healthcare services between China and North America may be other important factors affecting the COVID-19 profile difference[67]. Indeed, a possible convergence between chronic and infectious diareses may influence the severity of COVID-19 in subjects with pre-existing medical conditions[68]. These observations underline the necessity to conduct more systematic population-based epidemiological assessments to elucidate both environmental-, socioeconomic- and host-related factors in disease etiology. The distinct disease profile among different world regions underlines the need to characterize the effect of health inequities and inequalities on public health response to COVID-19 and address the influence of inter- and intra-population differences on health.

ARTICLE HIGHLIGHTS

Research background

Large inter-individual and inter-population differences in the susceptibility to and outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) have been noted. Understanding these differences and how they influence vulnerability to infection and disease severity is critical to public health intervention.

Research motivation

To evaluates the inter-population differences in the SARS-CoV-2 or COVID-19 between China and North America.

Research objectives

The objective of this systematic review and meta-analysis is to analyze and compare the profile of COVID-19 cases between China and North America as two regions that differ in many environmental, host and healthcare factors related to disease risk.

Research methods

We conducted a meta-analysis to examine and compare demographic information, clinical symptoms, comorbidities, disease severity and levels of disease biomarkers of COVID-19 cases from clinical studies and data from China (105 studies) and North America (19 studies).

Research results

Fever, cough, fatigue and dyspnea were the most common clinical symptoms of COVID-19 in both study regions. Hypertension, diabetes and cancer were the most prevalent comorbidities in COVID-19 cases from China whereas obesity, hypertension and diabetes were the most prevalent in North America. Prevalence of comorbidities in COVID-19 cases increased with age but was at younger ages in cases from China compared to those from North America. Inflammatory markers such as C-reactive protein were 4.5-fold higher in the North American cases than in cases from China.

Research conclusions

The differences in COVID-19 profile between China and North America reflects the differences in environmental-, host- and healthcare-related factors between the two regions.

Research perspectives

Inter-population differences – together with intra-population variability – underline the need to characterize the effect of health inequities and inequalities on public health response to COVID-19 and can assist in preparing for the re-emergence of the epidemic.

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