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Epidemiological and clinical characteristics analysis of COVID-19 in the surrounding areas of Wuhan, Hubei Province in 2020

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ABSTRACT

Aim: Since December 2019, new COVID-19 outbreaks have occurred and spread around the world. However, the clinical characteristics of patients in other areas around Wuhan, Hubei Province are still unclear. In this study, we performed epidemiological and clinical characteristics analysis on these regional cases.

Methods: We retrospectively investigated COVID-19 patients positively confirmed by nucleic acid Q-PCR at Taihe Hospital from January 16 to February 4, 2020. Their epidemiological, clinical manifestations, and imaging characteristics were analysed.

Results: Among the 73 patients studied, 12.3 % developed symptoms after returning to Shiyan from Wuhan, and 71.2 % had a history of close contact with Wuhan personnel or confirmed cases. Among these patients, 9 cases were associated with family clustering. The first main symptoms presented by these patients were fever (84.9 %) and cough (21.9 %). The longest incubation period was 26 days, and the median interval from the first symptoms to admission was 5 days. Of the patients, 67.1 % were originally healthy people with no underlying diseases, others mostly had common comorbidities including hypertension (12.3 %) and diabetes (5.5 %), 10.9 % were current smokers, 30.1 % had low white blood cell counts and 45.2 % showed decreased lymphocytes at the first time of diagnosis. CT scans showed that multiple patchy ground glass shadows outside of the patient lungs were commonly observed, and a single sub-pleural sheet of ground glass shadow with enhanced vascular bundles was also found located under the pleura. Patient follow-up to February 14 presented 38.4 % severe cases and 2.7 % critical cases. After follow-up, the parameter of lymphocyte counts below 0.8×10^9/L cannot be used to predict severe and critical groups from the ordinary group, and a lower proportion of smokers and higher proportion of diabetes patients occur in the poor outcome group. Other co-morbidities are observed but did not lead to poor outcomes.

Conclusion: The epidemiological characteristics of patients in the area around Wuhan, such as Shiyan, at first diagnosis are described as follows: Patients had histories of Wuhan residences in the early stage and family clustering in the later period. The incubation period was relatively long, and the incidence was relatively hidden, but the virulence was relatively low. The initial diagnosis of the patients was mostly ordinary, and the percentage of critical patients who evolved into the ICU during follow-up is 2.7 %, which is lower than the 26.1 % reported by Wuhan city. According to the Shiyan experience, early diagnosis with multiple swaps of the Q-PCR test and timely treatment can reduce the death rate. Diabetes could be one of the risk factors for progression to severe/critical outcomes. No evidence exists that smoking protects COVID-19 patients from developing to severe/critical cases, and the absolute number of lymphocytes at initial diagnosis could not predict the progression risk from severe to critical condition. Multivariate regression analysis should be used to further guide the allocation of clinical resources.

Since December 2019, new cases of COVID-19 have occurred in Hubei province (China), Hong Kong, Macau, China, Korea, Japan, the

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Philippines, Singapore, and the United States etc. [1,2]. At this moment, clinical characteristics analysis of the cases surrounding areas of Wuhan city, Hubei province has not yet been reported. Shiyan is located in the northwest of Hubei province and is a regional central city adjacent to Hubei, Henan, Shanxi, and Chongqing with approximately 3.5 million people. This area is also one of the main battlefields against COVID-19. The aim of this article is to analyse the epidemiological and clinical characteristics of patients with COVID-19 diagnosed at Taihe Hospital, Shiyan, Hubei province from January 16 to February 4, 2020, with follow-up performed until February 14, 2020.

1. Data collection and research method

According to the COVID-19 diagnosis and treatment protocol (fifth edition of the trial operation) [3], we combined and applied epidemiological history, clinical manifestation, imaging detection and Q-PCR of the respiratory specimens as tools to confirm positive cases. From January 16 to February 4, 2020, a total of 73 patients diagnosed with COVID-19 in Taihe Hospital at Shiyan were identified as the research subjects. This study was approved by the Ethics Committee of Taihe Hospital, and written informed consent was waived due to the rapid emergence of this infectious disease. Follow-up examinations were performed until February 14, 2020, and the epidemiological and clinical characteristics of the above patients were retrospectively analysed.

2. Q-PCR method

Extraction of viral nucleic acid from respiratory specimens was performed using the EZ1 virus mini kit v2.0 (Qiagen). The RNA was eluted in 60 μl of AVE buffer and used as a template for all assays. Two specific real-time RT-PCR methods targeting N and ORF1ab were designed to detect the presence of 2019-nCoV in clinical samples. The ORRlab gene primer sequences are listed as follows. The forward primer sequence is CCCTGTGGGTTTTACACTTAA, the reverse primer sequence is ACGATTGTGCATCAGCTGA, and the probe sequence is 5'-FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3'. For the N gene, the forward primer sequence is GGGGAACTTCTCCTGCTAGAAT, the reverse primer sequence is CAGACATTTTGCTCTCAAGCTG, and the probe sequence is 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'. Thermal cycling was performed at 50 °C for 20 min for reverse transcription, followed by 95 °C for 15 min, 50 cycles of 94 °C for 5 s and 55 °C for 1 min. The result was confirmed as negative if no Ct value or Ct value > 40 was obtained. Positive cases were confirmed if Ct value < 37, and suspicious cases were defined if Ct value was between 37 and 40. For suspicious samples, the experiment was repeated multiple times with multiple swaps of sample for final confirmation.

3. Results

3.1. Demographic characteristics

This study included 73 patients with COVID-19, of which 9 were clustered in families. Of these patients, 61 were travelling back from Wuhan or had a history of close contact with confirmed cases. One of the patients ate a meal near the Huanan China Seafood Market, but it is worth noting that 12 cases had no clear contact history. All of the above are non-medical workers. The average age is 43 years old, and 23 people had chronic underlying diseases, including diabetes, hypertension, oesophageal cancer surgery, bilateral femoral head necrosis, and lower extremity vein thrombosis (Table 1).

3.2. Clinical manifestations at first diagnosis

Most patients had fever as the first symptom for admission. Other symptoms included cough, fatigue, hoarseness and diarrhoea. Certain patients did not have fever at the time of consultation, and most were not accompanied by organ damage (Table 2).

Table 1
Characteristics of COVID-19 patients.

	Patients (n = 73)
Age (Years)	
Intervals	21 – 76
20 – 29	11(15.7 %)
30 – 39	16(21.9 %)
40 – 49	24(32.9 %)
50 – 59	12(16.4 %)
60 – 69	7(7.6 %)
70 – 79	3(4.1 %)
Gender	
Female	33(45.2 %)
Male	40(54.8)
Epidemiological history	
From Wuhan	9(12.3 %)
Close contact with Wuhan personnel	52(71.2 %)
Unknown	12(16.4 %)
Any comorbidity	
Cardiovascular disease[1]	12(16.4 %)
Endocrine disease[2]	4(5.5 %)
Respiratory disease[3]	4(5.5)
Digestive system disease[4]	3(4.1 %)
Malignant tumour	1(1.4 %)
Other	8(11.0 %)
Patients without underlying disease	49(67.1 %)
Smoking history	
Yes	8(10.9 %)
No	65(89.1 %)

Note: [1] Of the cardiovascular disease patients, 9 cases (12.3 %) had *hypertension*, 1 case had cardiac disease, 1 case had coronary heart disease, and 1 case had cerebral infarction. [2] Of the endocrine disease patients, 4 cases had diabetes [3]. Of the respiratory disease patients, 3 cases had sinusitis, and 1 case had pleurisy, but none of them had chronic obstructive pulmonary disease [4]. Of the patients with digestive system disease, 2 cases were HBV carriers, and 1 case had chronic pancreatitis.

Table 2
Clinical characteristics of patients at the first diagnosis.

	Patient (n = 73)
Initial symptoms and characteristics	
Fever on admission	62(84.9 %)
Cough	16(21.9 %)
Fatigue	7(9.6 %)
Sore throat and hoarseness	6(8.2 %)
Fatigue & poor appetite	3(4.1 %)
Myalgia or joint pain	2(2.7 %)
Chest pain	1(1.4 %)
Diarrhoea	1(1.4 %)
Headache	1(1.4 %)
Body temperature (°C)	
Below 37.3	37(50.7 %)
37.3 – 38	24(32.8 %)
38.1 – 39	7(9.6 %)
39.1 – 41	5(6.8 %)
Clinical classification	
Ordinary	73(100 %)
Severe	0
Critical	0

Note: Clinical classification is based on the COVID-19 diagnosis and treatment protocol (fifth edition of the trial operation) issued by the National Health Commission of the People's Republic of China; ECMO, extracorporeal membrane oxygenation.

3.3. Laboratory examination

The total number of white blood cells of the patients was analysed at the time of admission. Of the patients, 30.1 % showed decreased total white blood cell counts, and 45.2 % showed decreased lymphocyte

Table 3
Laboratory diagnostic test result of COVID-19 patients.

	Patients (n = 73)
White blood cell count (x 10^9/normal range 3.5 − 9.5)	
Decrease	22(30.1 %)
Normal	50(68.5 %)
Increase	1(1.4 %)
Neutrophil count (x 10^9/normal range 1.1 − 3.2)	
Decrease	33(45.2 %)
Normal	40(54.8 %)
Increase	0(0 %)
No. of throat swab tests to confirm positive diagnosis	
1	59(80.8 %)
2	10(13.7 %)
≥3	4(5.5 %)

counts. Most patients were positively diagnosed with a single throat swab in the Q-PCR test, but a small number of patients required multiple sampling to confirm the diagnosis (Table 3).

3.4. Outcome

Newly diagnosed patients confirmed with positive throat swap Q-PCR test were transferred to the designated hospitals. After follow-up, 2.7 % of patients were defined as critical, 38.4 % were defines as severe, and 58.9 % were defined as ordinary. Additionally, 10 % of the severe/critical patients had comorbidity of diabetes, and 2.3 % of the ordinary patients had comorbidity of diabetes (Table 4).

3.5. Treatment of patients

All newly diagnosed patients at the mild or ordinary condition were prescribed 5 million units of aerosolized interferon-alpha via inhalation twice per day and 2 capsules of lopinavir/ritonavir orally twice daily for antiviral treatment (a treatment course for 10 days) and levofloxacin at 0.4 g/day by intravenous infusion to prevent bacterial infection. An amount of 3 mL of nebulized acetylcysteine solution was given twice per day by inhalation as an expectorant and cough treatment. Patients showing continuous fever for more than 1 week, showing rapid progression as observed by imaging within 3–5 days, or showing progression into severe and critical conditions were given glucocorticoid methylprednisolone at 1 mg/kg for anti-inflammation (a treatment course of 5–10 days). Intravenous infusion of levofloxacin at 0.4 g/day was applied for severe patients to prevent bacterial infection. Maintenance of water and electrolyte balance and supplying symptomatic treatment of basic diseases and complications are also important [5,6]

3.6. Follow-up of patients on lymphocyte counts

The number of patients with lymphocyte counts less than 0.8×10^9/L in the severe/critical group was not significantly different from that of the ordinary group. (Table 5)

Table 4
Outcomes of follow-up patients.

Follow up	Patients (n = 73)
Ordinary	43(58.9 %)
Severe	28(38.4 %)
Critical	2(2.7 %)
Severe/Critical in combination with diabetes	3(10 %)
Ordinary in combination with diabetes	1(2.3 %)

Table 5
Comparative analysis of lymphocyte counts between severe/critical patients and ordinary patients.

White blood cell count (10^9/L; normal range 1.1 − 3.2)		
Type	≤0.8	> 0.8
Severe/critical	8(26.7 %)	22(73.3 %)
Ordinary	10(23.3 %)	33(76.7 %)

Note: Comparing severe/critical patients with ordinary patients, the absolute value of lymphocyte count was not statistically significant at the absolute number of 0.8×10^9/L ($\chi 2 = 0.111$, $P > 0.05$).

Table 6
Comparative analysis of diabetes association among severe/critical and ordinary patients.

Type	Comorbidity with diabetes	
	Diabetes patients	Non-diabetes patients
Severe/critical	3(10.0 %)	27(90.0 %)
Ordinary	1(2.3 %)	42(97.7 %)

Note: Compared with severe/critical patients and ordinary patients, patients with diabetes mellitus had a higher proportion in the severe/critical illness group than in the ordinary group, but the difference was not statistically significant ($\chi 2 = 2.010$, $P > 0.05$).

3.7. Follow-up of patients on comorbidities

In comparing patients classified as severe/critical with ordinary patients, patients with diabetes mellitus incidence in the severe/critical group was not significantly different from the ordinary group (Table 6).

3.8. Follow-up of patients on smoking history

Comparing the patients classified as severe/critical with patients classified as ordinary, the proportion of patients with smoking histories in the severe/critical group was not significantly different from that of the ordinary group (Table 7).

3.9. Chest imaging features at first diagnosis

All patients received thin-layer CT of the chest, and most had multiple strips of ground-glass shadowing in the lungs, mainly located in the outer boundary, or single-piece ground glass shadowing with enhanced blood vessel bundles located under the pleura, the corresponding CT images were shown in Fig. 1.

4. Discussion

Coronavirus is one of the main pathogens of respiratory infections [4]. There have been three major outbreaks of coronavirus in the 21 st century, namely, SARS-CoV, MERS-Cov, and COVID-19, all of which can cause severe respiratory distress syndrome in humans [7]. After

Table 7
Comparative analysis of smoking history association among severe/critical and ordinary patients.

Type	Smoking history	
	Smoker	Non-smoker
Severe/critical	2(6.7 %)	28(93.3 %)
Ordinary	6(14.0 %)	37(86.0 %)

Note: Comparing the smoking history ratio with ordinary group, the proportion of patients in the severe/critical group was lower, but the difference was not statistically significant ($\chi 2 = 0.962$, $P > 0.05$).

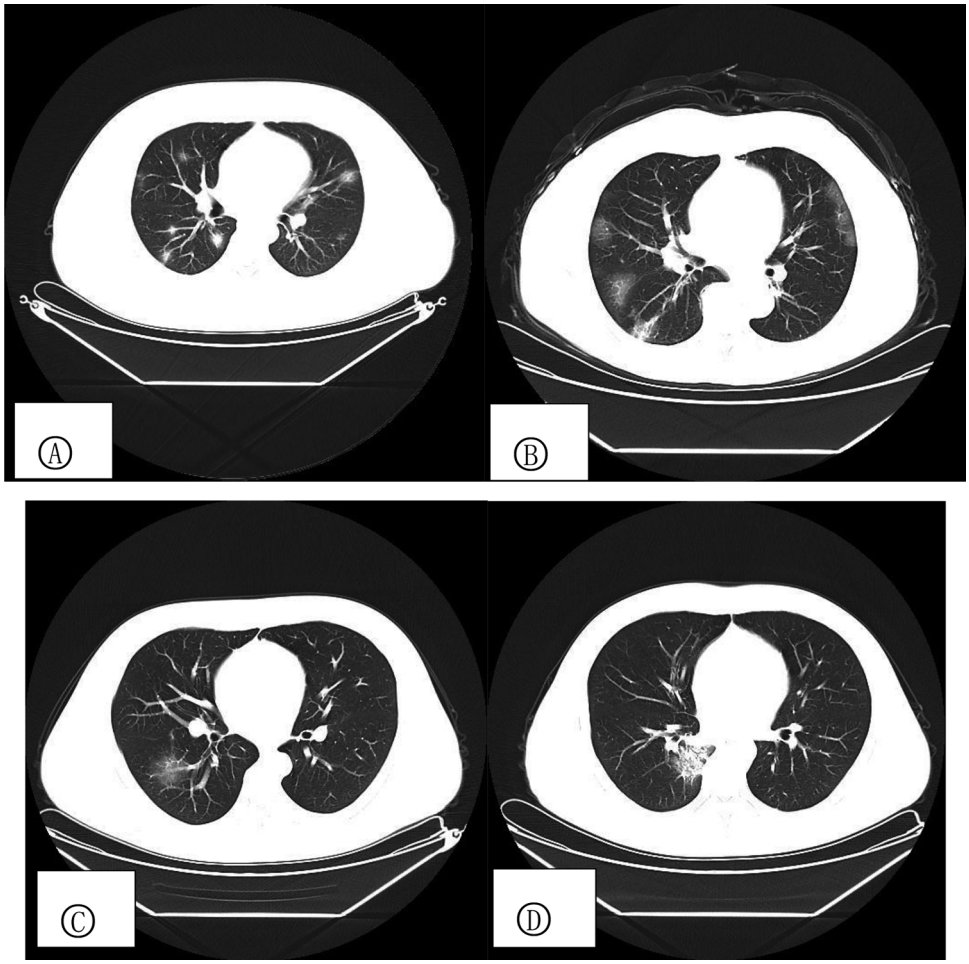

Fig. 1. A & B) Multi-window sheet-like ground glass shadow of both lungs, C & D) single sheet ground glass shadow with vascular bundle enhancement.

analysis of the virus sequence, the natural host inferred by COVID-19 might be bat [8], pangolin and other wild animals. The number of infected people in China reached 63,946 as of February 14, 2020, far exceeding those of SARS and MERS.

This study analysed the clinical characteristics of new coronavirus pneumonia in Shiyan, Hubei Province and found the following: 1) Male patients have higher prevalence, similar to the conclusion of Nanshan Chen [9]. The reason for the gender difference might be related to female oestrogen and X chromosome factors [7,10,11] and social gender roles because it is mostly men who go to work and travel more frequently in the culture of China; 2) The patients with COVID-19 outside Wuhan, Hubei province mostly had a history of living in Wuhan in the early stage (referred to as the first generation of patients), and later on, the second generation and third generations primarily showed clustered onset, which is consistent with the current report [9]. However, there were also patients who did not have contact with any people from Wuhan, but had the occupation of salesperson or window unit staff. This result indicated that the public spreading power of the virus is strong and that the survivability of the virus is long lasting [12]. However, we still need additional information on the epidemiological history and related life histories to draw a conclusion [13]. 3) The majority of young patients had ages of 30–49 years, and comorbidities of hypertension and diabetes were common in patients, but no patients had COPD. The median interval between the first symptom and admission to the hospital is 5 days, and the longest incubation period is 26 days, longer than the 24 days reported by academician Zhong Nanshan [14].

Among all patients, only 10.9 % were smokers, but in the severe/critical group, 6.7 % were smokers, which is not significantly lower than that of the ordinary group with 14.0 %. This result indicated that smoking is not a protective factor for COVID-19 patients, consistent with the TH Rainer studies [15]. Currently, there are no confirmed cases of medical staff infection in our hospital, indicating that as long as the medical staff are properly protected, the chance of infection can be effectively blocked [16]; 5) The majority of the patients present with fever and cough, and most patients have intermittent fever and low fever, but a subset are characterized by fatigue, sore throat, and hoarseness, and accompanying symptoms include one case diarrhoea and one case of headache, similar to that reported by Wuhan [9]. One patient had no abnormal clinical manifestation, but this patient was previously in close contact with a person from another confirmed case, indicating that these unidentified symptom-less patients are a potentially horrible source of chain infection. 6) The proportion of severe/critical cases accounted for 41.1 %, and the severe cases accounted for 38.4 %. The critical cases that required admission to the ICU accounted for 2.7 %, which is lower than the 26 % currently reported in Wuhan [17]. The difference could be based on the different diagnostic criteria used because the new diagnostic standard, respiratory failure, shock, and other functional failures are viewed as critical criteria [3], which will significantly increase the proportion of severe cases. The proportion of patients with lymphocyte counts less than 0.8 attributed to critical illness showed no significance difference compared with that of the ordinary group, and thus we could not only rely on low lymphocyte count as a single factor to predict progression risk factors for critical illness [17].

In addition, 19.2 % of patients needed multiple throat swabs to

obtain Q-PCR positive results, suggesting that the sensitivity of the throat swab test is limited. For patients with high clinical suspicion, multiple sampling or combined sputum and alveolar lavage fluid might help to decrease the false negative rate [18]. Imaging is often reveals multiple patchy and ground-glass shadows in the lungs, which is common in the subpleural or peripheral regions of the lungs, whereas only one lesion occurred mostly in the early phase [19]. The clinical manifestations are not in parallel with the imaging changes. Imaging changes showed a 3–5 day delay relative to clinical symptom presentation. Certain patients have poor absorption and also display pneumonia or fibrosis, which are similar to viral pneumonia syndromes [20–22].

After follow-up, from the current recovery condition of the patients, the proportion of severe cases is low, and there are no deaths. The reasons are considered as follows: 1) The viral pathogenicity and toxicity are slightly higher in the first-generation patients, whereas the second-generation and third-generation patients consist mostly of mild and moderate cases, indicating that the transmission and viability of COVID-19 is notably strong under specific circumstances, which is consistent with the report by Qun Li [23]. The pathogenicity gradually weakens during the transmission process, and the reason for this observation needs to be further investigated; 2) Beginning in mid-January, greater attention was focused nationwide on the prevention and treatment of COVID-19. Patients in the surrounding areas of Wuhan cooperated with the government and took the initiative to go to the hospital for early diagnosis and treatment. 3) Shiyan has sufficient medical facilities and medical staff, with 5 first-class hospitals at grade 3A, and the medical resources per capita are high. Patients receiving timely and proper treatment is one of the reasons. 4) Patients were given nebulized acetylcysteine to inhale as an expectorant to protect their airways. At the same time, for patients with a strong inflammatory response and acute progression as observed on pulmonary imaging, the short-term use of low-dose glucocorticoid for anti-inflammation might be one of the reasons for achievement of good treatment outcomes.

It is also worth noting that M. Dryden et al. reported [24] that people with low immune function, such as the elderly and patients with diabetes, are at high risk for progression to severe/critical condition, but statistical significance was not achieved for use of diabetes as a risk factor, perhaps because the number of patients recruited in this study is not sufficiently large. As such, comorbidity of diabetes and the absolute number of lymphocytes cannot be separately used as risk factors for severe/critical outcomes at the initial diagnosis.

Although this study is limited because it did not fully cover all of the COVID-19 cases in Shiyan, all of the samples from the CDC of Shiyan will be collected at a later stage for further future studies. At this moment, a lack of data exists on the time required for the virus to turn negative as an indicator of the recovery of the patients.

In summary, it was found that diagnosis of COVID-19 patients in Shiyan is primarily based on the travel history questionnaire in Wuhan at the initial stage and family clustering in the later stage. Obviously, the virus incubation period is long, the virulence is relatively low, and the onset is relatively secretive. At initial diagnosis, most of patients are classified as ordinary patients, whereas the number of patients who become severe and critical are lower than that reported in Wuhan. Diabetes might be one of the risk factors for progression to severe and critical manifestations. However, multivariate regression analysis should be explored to predict the factors for development into severe and critical conditions and to guide the allocation of clinical resources.

Contributors

Zheng Yi, Xiong Chang, Liu Yuquan, Qian Xin and Tang Yijun collected the epidemiological and clinical data and processed statistical data. Zheng Yi and Wang Meifang drafted the manuscript. Liang Liu, Elaine Lai-Han Leung and Wang Meifang wrote and revised the final manuscript.

Declaration of Competing Interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104821.

References

[1] C.-N.I.R.S. Team, COVID-19, Australia: epidemiology report 2 (Reporting week ending 19:00 AEDT 8 February 2020), Commun. Dis. Intell. 44 (2020) (2018).
[2] F. Wu, S. Zhao, B. Yu, Y.M. Chen, W. Wang, Z.G. Song, Y. Hu, Z.W. Tao, J.H. Tian, Y.Y. Pei, M.L. Yuan, Y.L. Zhang, F.H. Dai, Y. Liu, Q.M. Wang, J.J. Zheng, L. Xu, E.C. Holmes, Y.Z. Zhang, A new coronavirus associated with human respiratory disease in China, Nature 579 (7798) (2020) 265–269, https://doi.org/10.1038/s41586-020-2008-3 Epub 2020 Feb 3.
[3] NHC-China, SATCM-China, The guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia, Chin. J. Integr. Tradit. Western Med. (2020) 1–3.
[4] H.-D. Song, C.-C. Tu, G.-W. Zhang, S.-Y. Wang, K. Zheng, L.-C. Lei, Q.-X. Chen, Y.-W. Gao, H.-Q. Zhou, H. Xiang, H.-J. Zheng, S.-W.W. Chern, F. Cheng, C.-M. Pan, H. Xuan, S.-J. Chen, H.-M. Luo, D.-H. Zhou, Y.-F. Liu, J.-F. He, P.-Z. Qin, L.-H. Li, Y.-Q. Ren, W.-J. Liang, Y.-D. Yu, L. Anderson, M. Wang, R.-H. Xu, X.-W. Wu, H.-Y. Zheng, J.-D. Chen, G. Liang, Y. Gao, M. Liao, L. Fang, L.-Y. Jiang, H. Li, F. Chen, B. Di, L.-J. He, J.-Y. Lin, S. Tong, X. Kong, L. Du, P. Hao, H. Tang, A. Bernini, X.-J. Yu, O. Spiga, H.-Y.P. Zong-Ming Guon, W.-Z. He, J.-C. Manuguerra, A. Fontanet, A. Danchin, N. Niccolai, Y.-X. Li, C.-I. Wu, G.-P. Zhao, Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human, Proc. Natl. Acad. Sci. U. S. A. 102 (7) (2005) 2430–2435.
[5] G.U. Meduri, L. Bridges, M.C. Shih, P.E. Marik, R.A.C. Siemieniuk, M. Kocak, Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature, Intensive Care Med. 42 (5) (2016) 829–840.
[6] F. Lamontagne, M. Briel, G.H. Guyatt, D.J. Cook, N. Bhatnagar, M. Meade, Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials, J. Crit. Care 25 (3) (2010) 420–435.
[7] A. Badawi, S.G. Ryoo, Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis, Int. J. Infect. Dis. 49 (2016) 129–133.
[8] B. Hu, L.P. Zeng, X.L. Yang, X.Y. Ge, W. Zhang, B. Li, J.Z. Xie, X.R. Shen, Y.Z. Zhang, N. Wang, D.S. Luo, X.S. Zheng, M.N. Wang, P. Daszak, L.F. Wang, J. Cui, Z.L. Shi, Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus, PLoS Pathog. 13 (11) (2017) e1006698.
[9] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J.a. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China- a descriptive study, Lancet (London, England) 0 (2020) 1–7.
[10] S. Jaillon, K. Berthenet, C. Garlanda, Sexual dimorphism in innate immunity, Clin. Rev. Allergy Immunol. 56 (3) (2019) 308–321.
[11] R. Channappanavar, C. Fett, M. Mack, T.E. Patrick, P.M. David, K.S. Perlman, Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection, J. Immunol. 198 (10) (2017) 4046–4053.
[12] S. Zhao, Q. Lin, J. Ran, S.S. Musa, G. Yang, W. Wang, Y. Lou, D. Gao, L. Yang, D. He, M.H. Wang, Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak, Int. J. Infect. Dis. 92 (2020) 214–217.
[13] M.L. Holshue, C. DeBolt, S. Lindquist, K.H. Lofy, J. Wiesman, H. Bruce, C. Spitters, K. Ericson, S. Wilkerson, A. Tural, G. Diaz, A. Cohn, L. Fox, A. Patel, S.I. Gerber, L. Kim, S. Tong, X. Lu, S. Lindstrom, M.A. Pallansch, W.C. Weldon, H.M. Biggs, T.M. Uyeki, S.K. Pillai, V.C.I.T. Washington state -nCo, first case of 2019 novel coronavirus in the United States, N. Engl. J. Med. 382 (2020) 929–936, https://doi.org/10.1056/NEJMoa2001191.
[14] W.-j. Guan, Z.-y. Ni, Y. Hu, W.-h. Liang, C.-q. Ou, J.-x. He, L. Liu, H. Shan, C.-l. Lei, D.S.C. Hui, B. Du, L.-j. Li, G. Zeng, K.-Y. Yuen, R.-c. Chen, C.-l. Tang, T. Wang, P.-y. Chen, J. Xiang, S.-y. Li, J.-l. Wang, Z.-j. Liang, Y.-x. Peng, L. Wei, Y. Liu, Y.-h. Hu, P. Peng, J.-m. Wang, J.-y. Liu, Z. Chen, G. Li, Z.-j. Zheng, S.-q. Qiu, J. Luo, C.-j. Ye, S.-y. Zhu, N.-s. Zhong, Clinical characteristics of 2019 novel coronavirus infection in China, medRxiv (2020) 02.06.20020974.
[15] T. Rainer, D. Smit, P. Cameron, Smoking and severe acute respiratory syndrome, Hong Kong J. Emerg. Med. 11 (3) (2004) 143–145.
[16] J. Riou, C.L. Althaus, Pattern of early human-to-human transmission of Wuhan

2019 novel coronavirus (2019-nCoV), December 2019 to January 2020, Euro Surveill. 25 (4) (2020).
[17] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069, https://doi.org/10.1001/jama.2020.1585 Online ahead of print.
[18] Y. Li, B. Sun, X. Tang, Y.L. Liu, H.Y. He, X.Y. Li, R. Wang, F. Guo, Z.H. Tong, Application of metagenomic next-generation sequencing for bronchoalveolar lavage diagnostics in critically ill patients, Eur. J. Clin. Microbiol. Infect. Dis. 39 (2) (2020) 369–374.
[19] C. Lei, L. Huiguo, L. Wei, L. Jing, L. Kui, S. Jin, D. Yan, W. Shuang, Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia, Chin. J. Tuberculosis Respir. Dis. 43 (00) (2020) E005.
[20] W.J. Liu, M. Zhao, K. Liu, K. Xu, G. Wong, W. Tan, G.F. Gao, T-cell immunity of SARS-CoV: implications for vaccine development against MERS-CoV, Antiviral Res. 137 (2017) 82–92.
[21] K. Frazer, J.E. Callinan, J. McHugh, S. van Baarsel, A. Clarke, K. Doherty, C. Kelleher, Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption, Cochrane Database Syst. Rev. 2 (2016) CD005992.
[22] L. Min, H. Peng, L. Huiguo, W. Xiaojiang, L. Fajiu, C. Shi, L. Jie, C. Bo, L. Jianhua, L. Chenghong, Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia, Chin. J. Tuberculosis Respir. Dis. 43 (00) (2020) E016.
[23] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S.M. Leung, E.H.Y. Lau, J.Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Li, W. Tu, C. Chen, L. Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T.T.Y. Lam, J.T.K. Wu, G.F. Gao, B.J. Cowling, B. Yang, G.M. Leung, Z. Feng, Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. 382 (13) (2020) 1199–1207, https://doi.org/10.1056/NEJMoa2001316 Epub 2020 Jan 29.
[24] M. Dryden, M. Baguneid, C. Eckmann, S. Corman, J. Stephens, C. Solem, J. Li, C. Charbonneau, N. Baillon-Plot, S. Haider, Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections, Clin. Microbiol. Infect. 21 (Suppl. 2) (2015) S27–32.