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An analysis of eight family cluster cases in Wuhan, China: Peripheral blood lymphocyte count may predict Covid-19 mortality

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Abstract

Background: Since December 2019, a novel coronavirus (SARS-CoV-2) causing COVID-19 has spread across the world in a global pandemic. Tens of thousands of people were infected, several thousand patients died. However, key risk factors for predicting mortality remain unclear. This study aims to analyze the differences in mortal risk factors between fatal and non-fatal cases within each family, to identify the key risk factors for COVID-19 mortality.

Method: Retrospective, randomly selected eight family clusters consisting of 21 individual cases who had been confirmed positive for SARS-CoV-2 and admitted to the Wuhan Union Hospital, Wuhan, China, from February 6 to March 3, 2020. Clinical characteristics and demographic data were tracked up to March 3.

Results: Among all 8 family cluster cases, 4 families had death cases. All deaths were elderly individuals (range, 77-88 years), all ICU and severe cases were also elderly individuals (72-88 years). Patient 2-M1, who was the oldest of all cases and first confirmed with COVID-19 on January 10, had four critical comorbid conditions including colon cancer, COPD, hypertension, and coronary disease. But he remains in stable condition after more than 50 days of inpatient treatment. We observed that the absolute count of peripheral blood lymphocyte dropped to less than 0.8G/L of all death and ICU cases, ranging from 0.22 G/L to 0.81 G/L.

Conclusions: We found that elderly age is one of the main risk factors for mortality, comorbidities were not predictive of mortality due to COVID-19, although they may extend disease duration. Importantly, we discovered that within our study population the absolute count of peripheral blood lymphocyte is a predictive risk factor for mortality due to COVID-19, establishing that it may be a very important factor for judging a patient's prognosis.

Keywords: COVID-19; Family clusters; Mortality; Risk factors.

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Background

On December 8, 2019, the case of "pneumonia of unknown etiology" was reported in Wuhan, Hubei Province, China. A rapidly increasing rate of patient intake was reported in the fever clinics of almost every hospital of this city. At end of December 2019, a novel coronavirus (SARS-CoV-2) has been proven to be the chief source of this public health emergency [1]. The coronavirus disease 2019 (COVID-19) diffused around the country and resulted in a national outbreak at the end of January. According to the Word Health Organization (WHO) [2], on January 31, 9720 cases of COVID-19 were confirmed in China with 213 deaths; 106 confirmed cases were reported outside of China with 19 countries having been affected. On Feb 27, 2020 the WHO reported that China had 78630 confirmed cases (including 439 new cases in the past 24 hr period) resulting in 2747 (29 new) deaths; outside of China, there were 3664 cases (including 746 new cases) affecting 46 countries and resulting in 57 (13 new) deaths [2]. For the first time, there have been more new cases reported from countries outside of China than from China itself. COVID-19 has caused a global pandemic, and Novel Coronavirus–Infected Pneumonia (NCIP) has led to major health challenges throughout the world.

According to a Chinese Center for Disease Control and Prevention (CDC) report on March 3, 2020 [3], most patients present with non-severe cases, however 3.71% of cases ultimately resulted in death. There is a question as to why some patients presented with milder clinical symptoms and signs, while some cases manifested in organ dysfunction (shock, Acute Respiratory Distress Syndrome (ARDS), acute cardiac injury, and acute kidney injury) and even died. At this moment studies of the phylogenomic traits viral virulence still have reached no certain conclusion [4]. For this study we analyzed the clinical characteristics and predisposing factors of 8 family clustered NCIP cases, including cases in which NCIP resulted in death, in order to identify risk factors for elevated rates of mortality.

Method

This study was approved by the institutional ethics board of the Wuhan Union Hospital of Huazhong University of Science and Technology (2020.0089). The Wuhan Union Hospital is responsible for treating critically ill patients with NCIP and is one of the closest major hospitals to the Huanan seafood market to which many early cases of COVID-19 were associated. On February 6, 2020, we started to participate in treating hospital patients with severe SARS-CoV-2–infected viral pneumonia who were admitted to Wuhan Union Hospital. During our work we found that there are many cases within family clusters, with patients of each family having nearly the same onset date, same living environment, and same diet. However, while some members presented with severe cases resulting in death, others presented with non-severe cases. We collected 8 families (21 cases) as the focus for the study. Oral consent was obtained from family members. All patients were diagnosed with NCIP by their pulmonary CT images and were SARS-CoV-2 positive in throat swab samples confirmed by RT-PCR. Diagnostic criteria were based on recommendations by the Chinese National Institute for Viral Disease Control and Prevention [5]. Clinical characteristics and demographic data were tracked up to March 3.

According to the diagnostic and treatment guidelines for COVID-19 issued by the Chinese National Health Committee (Version 3-7) [5], cases of severe NCIP were defined based on the following criteria: Respiratory frequency ≥30/min, oxygen saturation ≤93% or oxygenation index ≤300 mmHg. The patients who required ICU care met one of the following criteria: Respiratory failure requiring ventilation, development of shock, and/or complications resulting in organ failure. The onset date was identified as the date when patients first noticed symptoms. A detailed analysis of case records was carried out.

Results

The study population included 21 patients within 8 families with confirmed cases of NCIP. The demographic and clinical characteristics are shown in Table 1. Among all 8 family cluster cases, 4 families had death cases (bold in Table 1). All deaths were elderly individuals (range, 77-88 years), all ICU and severe cases were also elderly individuals (72-88 years). These cases had nearly the same age range. In addition, the onset of every group of family cases occurred within the same period. Members from each family were infected by SARS-CoV-2 with virtually identical virulence, however younger patients generally presented as non-severe cases while all deaths occurred in elderly patients over the age of 70.

Out of the 12 patients with comorbid conditions (Table 1 and Figure 1), 2 resulted in deaths, 3 resulted in ICU, 3 resulted in severe cases, and 4 resulted in non-severe cases. In family 1 and 5, each couple had the same onset time, and while both husbands had no comorbid conditions, their wives both had chronic diseases. However, both male patients died while the female patients were still alive after more than 30 days of treatment. In family 4, the elderly parents (4-F1 and 4-M1) became symptomatic on nearly the same date and have the same chronic diseases. However the condition of 4-M1 worsened and he was transferred to the ICU while 4-F1 remained stable. Patient 2-M1, who was the oldest of all cases and first confirmed with COVID-19 on January 10, had four critical comorbid conditions including colon cancer, COPD, hypertension, and coronary disease. But he remains in stable condition after more than 50 days of inpatient treatment.

From these cases, it seems that comorbid conditions are not a major risk factor for mortality, but it most likely to be a key factor that extends the disease duration. Old age is a main risk factor for mortality, but is still not directly related to death of COVID-19. Moreover, although every family has a common living environment, similar dietary structure, same viral infectious condition, and similar onset date, women generally have slower disease progression and stronger living ability.

At the time of admission we collected all patients' blood routine test results and biochemistry and C-reactive Protein (Hs-CRP) results (Table 2). By comparison, we found there were 20 patients with elevated levels of α-hydroxybutyrate dehydrogenase (α-HBDH) and 14 cases of increased Hs-CRP. The level of α-HBDH had a tendency to be elevated in fatal, ICU, and severe cases, however we could not analyze this due to a small sample size.

Interestingly, we observed that the absolute count of peripheral blood lymphocyte dropped to less than 0.8 G/L of all death

and ICU cases , ranging from 0.22 G/L to 0.81 G/L. Except in one non-severe case, the other cases were all within normal range (1.1-3.2 G/L). According to case records, one non-severe (8-F2) patient in family 8, whose count of lymphocyte fell to 0.76 G/L, had her levels return to normal (1.15 G/L) at one week after admission. Furthermore, the aforementioned 94 years old patient with multiple comorbid conditions, was defined as a non-severe case, and remained stable after 52 days of inpatient treatment. His absolute count of peripheral blood lymphocyte was normal (1.55 G/L). In summary, we have identified a decrease in the absolute count of peripheral blood lymphocyte to less than 0.8 G/L as one of the key risk factors for COVID-19 mortality, and this factor has been identified as having a direct relationship with disease progression and prognosis.

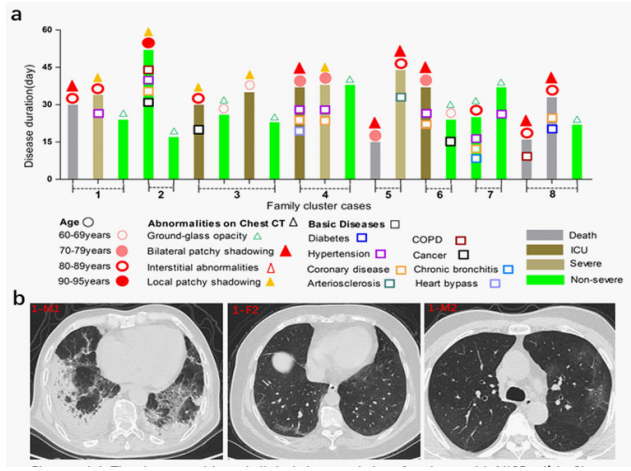

Figure 1: (a) The demographic and clinical characteristics of patients with NICP. (b) Chest computed Tomographic Images of Family One Cases With 2019-nCoV, 1-M1 was fetal case, 1-F2 was service case, 1-M2 was non-severe case.

All 21 cases had received CT scans on admission. The results showed that COVID-19 had caused varying degrees of destruction to every patients' lungs. All non-severe and some severe patients' pulmonary CT presented mild to moderate injury, including local patchy shadowing or ground-glass opacity. All 4 deceased patients' CT images had displayed bilateral patchy shadowing. The patients with reductions in absolute count of peripheral blood lymphocyte also demonstrated large area bilateral patchy shadowing, as well as declining health (Figure 2).

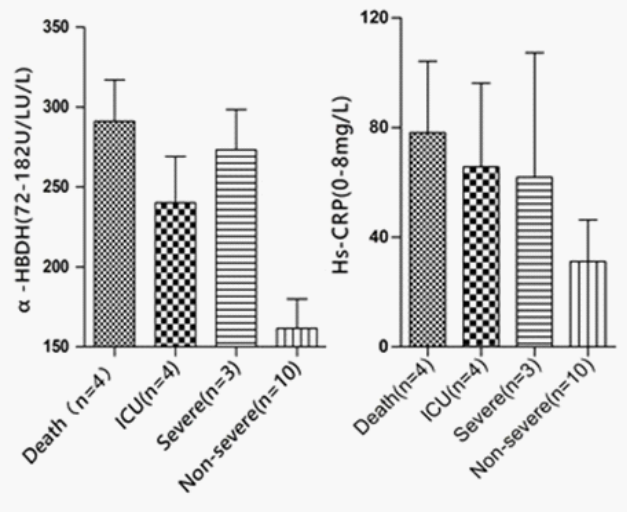

Figure 2: Laboratory findings of α- HBDH and Hs-CRP of cases with conformed with COVID-19. It is can be seen that there are obevious difference between non-severe cases, severe, ICU and death cases, but cause of sample number are not enough.

Table 1: Baseline characteristics of cases infected with SARS-CoV-2.

Family	Member	Age ranges	Sex	Onset of symptoms	Chest CT images	Comorbid factor(s)	Disease (Duration)	Disease severity
1	(M1) Father	80-89	M	1/31/2020	Bilateral patchy shadowing	None	30	Death
	(F1) Mother	80-89	F	1/26/2020	Local patchy shadowing	Hypertension, Deep vein thrombosis	34	Severe
	(M2) Son	50-59	M	1/29/2020	Ground-glass opacity	None	24	Non-severe
2	(M1) Father*	90-95	M	1/10/2020	Local patchy shadowing	COPD, Hypertension, Coronary Disease, Colon Cancer	52	Non-severe
	(M2) Son	60-69	M	2/13/2020	Ground-glass opacity	None	17	Non-severe
3	(M1) Grand-Father	80-89	M	2/6/2020	Local patchy shadowing	Prostate cancer	30	ICU to Non-severe
	(M2) Father	60-69	M	1/29/2020	Ground-glass opacity	None	26	Non-severe
	(F1) Mother	60-69	F	1/28/2020	Local patchy shadowing	None	35	ICU to Non-severe
	(F2) Daughter	30-39	F	2/2/2020	Ground-glass opacity	None	23	Non-severe
4	(M1) Father	70-79	M	1/26/2020	Local patchy shadowing	Hypertension, Coronary Disease, Heart bypass	37	ICU
	(F1) Mother	70-79	F	1/25/2020	Ground-glass opacity	Hypertension, Coronary Disease	38	Severe
	(M2) Son	40-49	M	1/21/2020	Bilateral patchy shadowing	None	38	Non-severe
5	(M1) Husband	70-79	M	1/28/2020	Local patchy shadowing	None	15	Death
	(F1) Wife	80-89	F	1/18/2020	Ground-glass opacity	Arteriosclerosis	44	Severe
6	(M1) Husband	70-79	M	1/25/2020	Bilateral patchy shadowing	Hypertension, Coronary Disease	37	ICU
	(F1) Wife	60-69	F	2/6/2020	Bilateral patchy shadowing	Endometrial cancer	24	Non-severe

7	(F1) Mother	80-89	F	2/6/2020	Bilateral patchy shadowing	Hypertension, Coronary Disease chronic bronchitis	25	Non-severe
	(F2) Daughter	50-59	F	1/31/2020	Ground-glass opacity	Hyperthyroid	37	Non-severe
8	(M1) Father	80-89	M	2/2/2020	Bilateral patchy shadowing	COPD	16	Death
	(F1) Mother	80-89	F	1/28/2020	Bilateral patchy shadowing	Coronary disease Diabets	33	Death
	(F2) Daughter	50-59	F	2/9/2020	Ground-glass opacity	None	22	Non-severe

Table 2: Baseline characteristics of cases infected with SARS-CoV-2.

Family	Member	Lymphocyte (1.1-3.2 G/L)	Lymphocyte% (20-50%)	Leucocyte (3.5-9.5 G/L)	Creatine kinase (24-170 U/L)	CK-MB (0-25 U/L)	a-HBDH (72-182 U/L)	Hs-CRP (0-8 mg/L)
1	(M1) Father	0.73	20.3	3.61	92	10	216	77.53
	(F1) Mother	2.23	33.6	6.64	171	25	235	6.8
	(M2) Son	1.45	35.2	4.11	438	14	206	4.11
2	(M1) Father*	1.55*	24.1	6.43	45	8	176	83.33
	(M2) Son	1.2	25.1	4.77	43	11	67	0.1
3	(M1) Grand-Father	0.65	16.9	3.84	63	10	184	76.65
	(M2) Father	1.36	25.6	5.3	686	21	146	34.76
	(F1) Mother	0.81	29.7	2.74	326	21	235	37.92
	(F2) Daughter	1.58	34.1	4.63	88	8	133	17.19
4	(M1) Father	0.66	17.2	3.85	886	26	221	2.63
	(F1) Mother	1.23	29.2	4.21	271	17	264	26.82
	(M2) Son	2.1	31	3.51	74	21	109	23
5	(M1) Husband	0.68	12.7	3.45	981	30	325	152
	(F1) Wife	1.27	20.6	6.16	78	14	85	32.68
6	(M1) Husband	0.22	17.5	12.83	582	25	321	145.55
	(F1) Wife	1.31	25.9	5.07	145	39	283	22.97
7	(F1) Mother	1.8	26.5	6.81	57	9	146	3.52
	(F2) Daughter	2.03	35	5.78	230	10	182	0.96
8	(M1) Father	0.72	13.8	9.24	663	39	325	44.86
	(F1) Mother	0.34	7.9	4.34	173	14	299	38.38
	(F2) Daughter	0.76	22.3	3.42	43	5	169	0.1

Discussion

At this point in time, COVID-19 has been sweeping the globe for many weeks. We found it useful to look at family cluster cases which have the same viral infectious condition, common living environments, and similar dietary structures. Accounting for external risk factors, the mortal risk factors between fatal and non-fatal cases within each family could be better analyzed. Overall, 4 deaths and 4 ICU patients from 6 families were all elderly parents, with ages ranging from 72 to 88 years. Advanced age is one of the main risk factors for COVID-19 mortality. According to the work of Wu and McGoogan [6] (the largest population-based analysis of COVID-19), out of a total of 44672 confirmed cases, there were 1023 cases that resulted in death. 50.83% (508 of 1023) of fatal cases occurred in patients aged >70 years old. These results are consistent with our family cluster cases.

We note that 2 out of 4 fatal cases had no comorbid factors. 12 patients from 8 families had comorbid factors, however there was no obvious direct correlation between comorbidities and disease severity. Patient 2-M1 remained in stable condition, representing how we can see that comorbidities are not necessarily not the key risk factor for elevated mortality in COVID-19 patients. It is more likely to merely be a factor that extends disease duration. In Dr. Wang's study [7] it was found that the number of cases requiring ICU or non-ICU treatment did not differ based on underlying comorbidities.

Out of 9 cases where the absolute count of peripheral blood lymphocyte dropped to under 0.81 G/L, 4 cases were fatal and 4 were hospitalized in the ICU. 1 case from family 8 had backed to normal after 7 days in hospital. All other cases had normal levels of peripheral blood lymphocyte. Referring again to 94 year old patient 2-M1, although he would be expected to be at high risk for COVID-19 he did not experience a severe drop in blood

lymphocyte levels and remained stable. These findings are supported by a study from Zhou [8] at el. which also found obvious changes in lymphocyte count in COVID-19 death cases.

Conclusions

This study may be one of the first out of the Wuhan epicenter to focus on family clusters of COVID-19 cases. In line with other research, we found that elderly age is one of the main risk factors for mortality, but we did not prove a directly causal relationship between age and death. We also found that comorbidities were not predictive of mortality due to COVID-19, although they may extend disease duration. Importantly, we discovered that within our study population the absolute count of peripheral blood lymphocyte is a predictive risk factor for mortality due to COVID-19, establishing that it may be a very important factor for judging a patient's prognosis.

Declarations

Ethics approval and consent to participate: This study was approved by the institutional ethics board of the Wuhan Union Hospital of Huazhong University of Science and Technology (2020.0089). Oral consent was obtained from all family members.

Consent for publication: Not Applicable.

Availability of data and material: The datasets generated and/or analysed during the current study are not publicly available due to protect patient privacy, but are available from the corresponding author on reasonable request.

Competing interests: None of the authors have any conflict of interest to declare. These patients have not been reported in any other submission by you or anyone else.

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Author contributions: Drs WZ. Wang and Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Idea, design and concept: Drs WZ Wang, D Cui and J Wang; Analysis, interpretation of data and draft manuscript writing: W Wang; Patients' information and clinical record collection: WZ Wang, D Cui, L Zhang, X Zhu, H Fan, R Chen; Critical revision of the manuscript for important intellectual content: JR Wang and J Wang.

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