

COVID-19讀書分享報告

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Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

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Introduction

- In 2019/12, unexplained pneumonia in Wuhan, China → novel coronavirus (**CoV**)
- symptoms similar to severe acute respiratory syndrome CoV (**SARSCoV**) in 2003, angiotensin-converting enzyme 2 (**ACE2**) receptor → **SARS-CoV-2**
- In 2020/2, WHO: coronavirus disease 2019 (**COVID-19**)
- typical symptoms: fever, cough, diarrhea, and fatigue
- lung CT abnormalities

Methods

- retrospective, observational study, from 3 centers in Wuhan, China
- 2020/1/16 ~ 2020/2/19, 214 cases
- defined the degree of severity of COVID-19 (**severe** vs **nonsevere**) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia
- Neurologic manifestations: **CNS, PNS, skeletal muscular injury**
 - CNS: dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure
 - PNS: taste impairment, smell impairment, vision impairment, and nerve pain
 - skeletal muscular injury (muscle pain with elevated CK)

Result

- Demographic and Clinical Characteristics
- Laboratory Findings in Patients With Severe and Nonsevere Infection
- Laboratory Findings in Patients With and Without CNS Symptoms
- Laboratory Findings in Patients With and Without PNS Symptoms
- Laboratory Findings in Patients With and Without Skeletal Muscle Injury

Result

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Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%)			P value ^a
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Age, mean (SD), y	52.7 (15.5)	58.2 (15.0)	48.9 (14.7)	
Age, y				
<50	90 (42.1)	24 (27.3)	66 (52.4)	<.001
≥50	124 (57.9)	64 (72.7)	60 (47.6)	
Sex				
Female	127 (59.3)	44 (50.0)	83 (65.9)	.02
Male	87 (40.7)	44 (50.0)	43 (34.1)	
Comorbidities				
Any	83 (38.8)	42 (47.7)	41 (32.5)	.03
Hypertension	51 (23.8)	32 (36.4)	19 (15.1)	<.001
Diabetes	30 (14.0)	15 (17.0)	15 (11.9)	.29
Cardiac or cerebrovascular disease	15 (7.0)	7 (8.0)	8 (6.3)	.65
Malignancy	13 (6.1)	5 (5.7)	8 (6.3)	.84
Chronic kidney disease	6 (2.8)	2 (2.3)	4 (3.2)	.69

Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%)			P value ^a
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Typical symptoms				
Fever	132 (61.7)	40 (45.5)	92 (73.0)	<.001
Cough	107 (50.0)	30 (34.1)	77 (61.1)	<.001
Anorexia	68 (31.8)	21 (23.9)	47 (37.3)	.04
Diarrhea	41 (19.2)	13 (14.8)	28 (22.2)	.17
Throat pain	31 (14.5)	10 (11.4)	21 (16.7)	.28
Abdominal pain	10 (4.7)	6 (6.8)	4 (3.2)	.21

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Characteristic	No. (%)			P value ^a
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<.001

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Characteristic	No. (%)			P value ^a
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Onset of symptoms to hospital admission, median (range), d				
CNS				
Dizziness	1 (1-30)	1 (1-30)	1 (1-14)	NA
Headache	1 (1-14)	1 (1-3)	3 (1-14)	NA
Impaired consciousness	8 (1-25)	10 (1-25)	1 (1-3)	NA
Acute cerebrovascular disease	9 (1-18)	10 (1-18)	1 (1)	NA
Ataxia	2 (2)	2 (2)	NA	NA
Seizure	2 (2)	2 (2)	NA	NA
PNS				
Impairment				
Taste	2 (1-5)	3 (1-3)	2 (1-5)	NA
Smell	2 (1-5)	1 (1-4)	2 (1-5)	NA
Vision	2 (1-3)	3 (2-3)	1 (1)	NA
Nerve pain	1 (1-1)	1 (1-1)	1 (1)	NA
Skeletal muscle injury	1 (1-11)	1 (1-11)	1 (1-6)	NA

Result

- Demographic and Clinical Characteristics
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- Laboratory Findings in Patients With and Without CNS Symptoms
- Laboratory Findings in Patients With and Without PNS Symptoms
- Laboratory Findings in Patients With and Without Skeletal Muscle Injury

Table 2. Laboratory Findings of Patients With COVID-19

Laboratory finding	Median (range)			P value ^a
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Count, ×10 ⁹ /L				
White blood cell	4.9 (0.1-20.4)	5.4 (0.1-20.4)	4.5 (1.8-14.0)	.008
Neutrophil	3.0 (0.0-18.7)	3.8 (0.0-18.7)	2.6 (0.7-11.8)	<.001
Lymphocyte	1.1 (0.1-2.6)	0.9 (0.1-2.6)	1.3 (0.4-2.6)	<.001
Platelet	209.0 (18.0-583.0)	204.5 (18.0-576.0)	219.0 (42.0-583.0)	.25
C-reactive protein, mg/L	12.2 (0.1-212.0)	37.1 (0.1-212.0)	9.4 (0.4-126.0)	<.001
D-dimer, mg/L	0.5 (0.1-20.0)	0.9 (0.1-20.0)	0.4 (0.2-8.7)	<.001
Creatine kinase, U/L	64.0 (8.8-12216.0)	83.0 (8.8-12216.0)	59.0 (19.0-1260.0)	.004
Lactate dehydrogenase, U/L	241.5 (2.2-908.0)	302.0 (2.2-880.0)	215.0 (2.5-908.0)	<.001
Aminotransferase, U/L				
Alanine	26.0 (5.0-1933.0)	32.5 (5.0-1933.0)	23.0 (6.0-261.0)	.04
Aspartate	26.0 (8.0-8191.0)	34.0 (8.0-8191.0)	23.0 (9.0-244.0)	<.001
Blood urea nitrogen, mmol/L	4.1 (1.5-48.1)	4.6 (1.5-48.1)	3.8 (1.6-13.7)	<.001
Creatinine, μmol/L	68.2 (35.9-9435.0)	71.6 (35.9-9435.0)	65.6 (39.4-229.1)	.03

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- **Laboratory Findings in Patients With and Without CNS Symptoms**
- Laboratory Findings in Patients With and Without PNS Symptoms
- Laboratory Findings in Patients With and Without Skeletal Muscle Injury

Table 3. Laboratory Findings of Patients With COVID-19 With CNS Symptoms^a

Laboratory finding	Median (range)								
	Total			Severe			Nonsevere		
	With CNS symptoms (n = 53)	Without CNS symptoms (n = 161)	P value	With CNS symptoms (n = 27)	Without CNS symptoms (n = 61)	P value	With CNS symptoms (n = 26)	Without CNS symptoms (n = 100)	P value
Count, ×10 ⁹ /L									
White blood cell	4.6 (0.1-12.5)	4.9 (1.8-20.4)	.58	5.3 (0.1-12.5)	5.5 (1.9-20.4)	.77	4.1 (2.4-11.0)	4.6 (1.8-14.0)	.40
Neutrophil	2.6 (0.0-10.9)	3.1 (0.7-18.7)	.41	3.8 (0.0-10.9)	3.6 (0.7-18.7)	>.99	2.2 (0.9-7.4)	2.8 (0.7-11.8)	.11
Lymphocyte	1.0 (0.1-2.3)	1.2 (0.2-2.6)	.049	0.7 (0.1-1.6)	0.9 (0.2-2.6)	.007	1.3 (0.7-2.3)	1.3 (0.4-2.6)	.49
Platelet	180.0 (18.0-564.0)	227.0 (42.0-583.0)	.005	169.0 (18.0-564.0)	220.0 (109.0-576.0)	.04	188.5 (110.0-548.0)	232.0 (42.0-583.0)	.09
C-reactive protein, mg/L	14.1 (0.1-212.0)	11.4 (0.1-204.5)	.31	48.6 (0.1-212.0)	26.1 (0.1-204.5)	.68	7.4 (3.1-111.0)	9.8 (0.4-126.0)	.82
D-dimer, mg/L	0.5 (0.2-9.7)	0.5 (0.1-20.0)	.75	1.2 (0.2-9.7)	0.9 (0.1-20.0)	.42	0.4 (0.2-6.4)	0.4 (0.2-8.7)	.46
Creatine kinase, U/L	79.0 (8.8-12216.0)	60.5 (19.0-1260.0)	.17	104.0 (8.8-12216.0)	64.0 (19.0-1214.0)	.08	52.5 (28.0-206.0)	59.0 (19.0-1260.0)	.56
Lactate dehydrogenase, U/L	243.0 (2.2-880.0)	241.0 (3.5-908.0)	.77	334.0 (2.2-880.0)	299.0 (3.5-743.0)	.32	198.0 (2.5-417.0)	226.0 (121.0-908.0)	.14
Aminotransferase, U/L									
Alanine	27.0 (5.0-261.0)	26.0 (6.0-1933.0)	.21	35.0 (5.0-259.0)	31.0 (7.0-1933.0)	.32	25.5 (13.0-261.0)	23.0 (6.0-135.0)	.68
Aspartate	29.5 (13.0-213.0)	26.0 (8.0-8191.0)	.10	35.5 (14.0-213.0)	34.0 (8.0-8191.0)	.32	23.0 (13.0-198.0)	23.5 (9.0-244.0)	.56
Blood urea nitrogen, mmol/L	4.5 (1.6-48.1)	4.1 (1.5-19.1)	.04	5.0 (2.3-48.1)	4.4 (1.5-19.1)	.04	3.9 (1.6-9.4)	3.8 (1.7-13.7)	.57
Creatinine, μmol/L	71.7 (37.1-1299.2)	66.3 (35.9-9435.0)	.06	71.7 (37.1-1299.2)	68.4 (35.9-9435.0)	.25	72.0 (40.3-133.6)	63.4 (39.4-229.1)	.27

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- Laboratory Findings in Patients With and Without Skeletal Muscle Injury

Table 4. Laboratory Findings of Patients With COVID-19 With PNS Symptoms

Laboratory finding	Median (range)								
	Total			Severe			Nonsevere		
	With PNS symptoms (n = 19)	Without PNS symptoms (n = 195)	<i>P</i> value	With PNS symptoms (n = 7)	Without PNS symptoms (n = 81)	<i>P</i> value	With PNS symptoms (n = 12)	Without PNS symptoms (n = 114)	<i>P</i> value
Count, ×10 ⁹ /L									
White blood cell	4.8 (2.8-7.5)	4.9 (0.1-20.4)	.74	4.5 (3.1-6.8)	5.6 (0.1-20.4)	.11	4.9 (2.8-7.5)	4.4 (1.8-14.0)	.27
Neutrophil	2.8 (1.5-5.4)	3.0 (0.0-18.7)	.74	2.6 (1.5-5.3)	4.1 (0.0-18.7)	.10	2.9 (1.9-5.4)	2.5 (0.7-11.8)	.21
Lymphocyte	1.2 (0.6-2.6)	1.1 (0.1-2.6)	.43	1.2 (0.6-1.6)	0.9 (0.1-2.6)	.26	1.2 (0.7-2.6)	1.3 (0.4-2.4)	.92
Platelet	204.0 (111.0-305.0)	213.0 (18.0-583.0)	.56	204.0 (111.0-245.0)	205.0 (18.0-576.0)	.56	214.5 (155.0-305.0)	219.0 (42.0-583.0)	.81
C-reactive protein, mg/L	12.0 (3.1-81.0)	12.3 (0.1-212.0)	.45	7.5 (3.1-76.4)	43.7 (0.1-212.0)	.13	13.0 (3.1-81.0)	8.8 (0.4-126.0)	.60
D-dimer, mg/L	0.4 (0.2-9.5)	0.5 (0.1-20.0)	.40	0.5 (0.2-9.5)	1.3 (0.1-20.0)	.27	0.4 (0.2-4.5)	0.4 (0.2-8.7)	.99
Creatine kinase, U/L	67.0 (32.0-1214.0)	64.0 (8.8-12216.0)	.41	105.0 (32.0-1214.0)	83.0 (8.8-12216.0)	.76	66.0 (42.0-171.0)	57.5 (19.0-1260.0)	.29
Lactate dehydrogenase, U/L	205.0 (2.5-517.0)	242.0 (2.2-908.0)	.28	170.0 (46.0-517.0)	309.0 (2.2-880.0)	.05	254.0 (2.5-481.0)	215.0 (2.9-908.0)	.67
Aminotransferase, U/L									
Alanine	26.0 (5.0-116.0)	27.0 (6.0-1933.0)	.70	19.0 (5.0-80.0)	35.0 (8.0-1933.0)	.23	26.0 (8.0-116.0)	23.0 (6.0-261.0)	.56
Aspartate	22.0 (8.0-115.0)	27.0 (9.0-8191.0)	.29	22.0 (8.0-53.0)	35.5 (12.0-8191.0)	.13	22.0 (14.0-115.0)	23.5 (9.0-244.0)	>.99
Blood urea nitrogen, mmol/L	4.1 (1.6-8.8)	4.1 (1.5-48.1)	.76	4.2 (3.5-8.8)	4.7 (1.5-48.1)	.96	3.7 (1.6-5.3)	3.9 (1.7-13.7)	.66
Creatinine, μmol/L	62.5 (48.1-121.4)	68.3 (35.9-9435.0)	.46	71.4 (58.3-121.4)	71.7 (35.9-9435.0)	.72	59.9 (48.1-77.3)	66.6 (39.4-229.1)	.24

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Laboratory Findings in Patients With and Without Skeletal Muscle Injury

- With vs without muscle injury (Total):
 - higher neutrophil counts, CRP, D-dimer
 - lower lymphocyte counts
 - increased LDH, AST, ALT, BUN, Cr
- With vs without muscle injury (Severe group):
 - decreased lymphocyte counts
 - increased LDH, AST, ALT, Cr
- With vs without muscle injury (Nonsevere group):
 - increased CRP
 - increased LDH

Discussion

- 214 patients, 88 (41.1%) severe and 126 (58.9%) nonsevere
- 78 (36.4%) had neurologic manifestation (CNS, PNS, skeletal muscle)
- Severe infection:
 - older and had more HTN, but fewer typical symptoms
 - more neurologic manifestations (acute CVD, consciousness disturbance, skeletal muscle injury), occurred early in the illness (median time: 1~2 days)

Discussion

- ACE2 receptor is present in multiple human organs, including nervous system and skeletal muscles
- Autopsy, brain tissue was hyperemic and edematous and some neurons degenerated
- Neurologic injury has been confirmed in the infection of other CoVs such as in SARS-CoV and MERS-CoV

Discussion

- As with other respiratory viruses, SARS-CoV-2 may enter the CNS through the hematogenous or retrograde neuronal route
- higher D-dimer levels in severe group may be the reason why patients with severe infection are more likely to develop cerebrovascular disease

Discussion

- Skeletal muscle injury:
 - elevated CK and LDH, especially in severe cases
 - due to ACE2 receptor?
 - due to elevated cytokines/immune response?

	Severe vs Nonsevere	With vs Without CNS symptoms			With vs Without PNS symptoms	With vs Without muscle injury		
		Total	Severe	N-S	3 groups	Total	Severe	N-S
WBC	↑	-	-	-	-	-	-	-
Neutrophil	↑	-	-	-	-	↑	-	-
Lymphocyte	↓	↓	↓	-	-	↓	↓	-
Platelet	-	↓	↓	-	-	-	-	-
CRP	↑	-	-	-	-	↑	-	↑
D-dimer	↑	-	-	-	-	↑	-	-
CK	↑	-	-	-	-	↑	↑	↑
LDH	↑	-	-	-	-	↑	↑	↑
ALT	↑	-	-	-	-	↑	↑	-
AST	↑	-	-	-	-	↑	↑	-
BUN	↑	↑	↑	-	-	↑	-	-
Cr	↑	-	-	-	-	↑	↑	-

Increased inflammation response, consumptive coagulation system, multiple organ involvement

Limitations

1. Only 214 patients were studied
2. All data were abstracted from the electronic medical records
3. Most patients were still hospitalized at the time of analysis
4. Most of the symptoms were a patient's subjective descriptions

Conclusion

Patients with COVID-19 commonly have neurologic manifestations. During the epidemic period of COVID-19, when seeing patients with neurologic manifestations, clinicians should suspect severe acute respiratory syndrome coronavirus 2 infection as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and lose the chance to treat and prevent further transmission.