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RESEARCH ARTICLE

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Detection and analysis of clinical features of patients with different types of coronavirus disease 2019

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Abstract

This study was designed to investigate the change of various indexes in patients with different types of coronavirus disease 2019 (COVID-19). Seventy-five patients with COVID-19 were collected from the First Affiliated Hospital, Zhejiang University School of Medicine, and they were classified into moderate, severe and critically severe types according to the disease severity. The basic information, blood routine, pneumonia-related blood indexes, immune-related indexes along with liver, kidney and myocardial indexes in patients with different types were analyzed. The analysis of immune-related indexes showed that the proportions of critically severe patients with abnormal interleukin-2 (IL-2) and IL-4 were higher than those of severe and moderate patients. In addition, the proportion of patients with abnormal total cholesterol increased as the severity of disease increased, and the proportion in critically severe patients was significantly higher than that in moderate patients. The patients with a more severe COVID-19 are older and more likely to have a history of hypertension. With the progression of COVID-19, the abnormal proportion of total white blood cell, neutrophils, lymphocytes, IL-2, IL-4, and total cholesterol increased. The change of these indexes in patients with different COVID-19 types could provide reference for the disease severity identification and diagnosis of COVID-19. In addition, the change in the total cholesterol level suggested that COVID-19 would induce some liver function damage in patients.

KEYWORDS

clinical features, coronavirus, coronavirus disease 2019 (COVID-19), laboratory index, symptoms

1 | INTRODUCTION

In December 2019, a case of unknown pneumonia occurred in Wuhan, Hubei, China, which was initially named novel coronavirus pneumonia (NCP). The World Health Organization officially named NCP coronavirus disease 2019 (COVID-19), which is a kind of acute infectious disease caused by a new coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]). Coronaviruses are enveloped, positive single-stranded RNA viruses that are widely distributed in humans and animals throughout the world.[1] SARS-CoV-2 belongs to β-coronavirus, which is usually pleomorphic and contains virions with a single positive RNA genome and a diameter of about 50 to 200 nm.[2] Within months of the first report of SARS-CoV-2, it has spread to a pandemic level in China and around the world. COVID-19 causes massive human casualties and huge economic losses and has become a global threat. Therefore, understanding the clinical features of current patients with COVID-19 as soon as possible will help to carry out the treatment and contain the spread of the virus to protect people's health.

Studies have indicated that some important basic information of patients is vital in the diagnosis of many diseases, such as coronavirus

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disease 2019. For example, Chen et al[3] found that male patients were more than female patients in an analysis of 99 cases with COVID-19. According to the statistics, male patients were more than female patients among people who got infected with Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV, which may be due to the protection by X chromosome and sex hormones, making women less sensitive to virus infection.[4,5] Another study also showed an increased mortality risk in older patients with COVID-19 (>65 years old) with complications and acute respiratory distress syndrome, and some significant risk factors, such as allergic disease, asthma, and chronic obstructive pulmonary disease.[6] This suggests that in the treatment of COVID-19 and other diseases, the diagnosis and treatment risks caused by age and some underlying diseases should be noticed. Besides, studies have found that SARS-CoV-2 is more likely to infect adult males with chronic diseases due to their weakened immune function.[4,5,7,8] At the same time, the detection of blood and other clinical indexes can also provide important reference for the diagnosis and treatment. A Study has reported that the large reduction in the total number of lymphocytes indicates that the coronavirus depletes a lot of immune cells and inhibits cellular immune function of the body, thus the low absolute value of lymphocyte count can be used as an indicator for the clinical diagnosis of SARS-CoV-2 infection.[9] Study of change in routine blood indexes has found that the decrease in lymphocyte count and its percentage in severe patients with COVID-19 are more common than those in mild patients.[1,10] In conclusion, screening out indexes with remarkable differences from various clinical indexes is of great importance for the diagnosis, treatment and prognosis of COVID-19 patients.

At present, the clinical routine indexes, blood routine and other pneumonia-related blood indexes, immune-related indexes, liver, kidney, and myocardial indexes of different COVID-19 types have not been fully reported, while these indexes are important references for determining the disease severity of COVID-19. This study included 75 patients with COVID-19 who were admitted to the Zhejiang University School of Medicine First Affiliated Hospital. Basic information including body temperature, gender, age, and underlying diseases, as well as various clinical indexes including blood routine, pneumonia-related blood indexes, immune-related indexes, liver, kidney and myocardial indexes of patients in each group was analyzed. This study improved the clinical information and physicochemical indexes of patients with COVID-19, which helps doctors accurately determine the severity of patients in clinical practice and formulate effective treatment plans.

2 | MATERIALS AND METHODS

2.1 | Patient collection and classification

The data of 75 patients with COVID-19 from 22 January to 15 March 2020 were collected, including cases in the charge of Dr. Zhao Yi during his visit to Wuhan and cases admitted to the First Affiliated Hospital, Zhejiang University School of Medicine. Nucleic acid samples were collected from the respiratory tract of all patients and tested positive for novel coronavirus-RNA by quantitative reverse transcription-polymerase chain reaction. The patients consisted of 41 males and 34 females with an average age of 51.65 ± 15.95 years old. Among the 75 patients, 21 cases had hypertension complications and five cases had diabetes complications. The average body temperature of the patients at admission was 37.45 ± 0.91.

After nucleic acid samples of all the patients were tested positive, patients were divided into mild (n = 4), moderate (n = 22), severe (n = 39), and critically severe (n = 10) cases based on the following criteria.[11] (a) Mild cases: the clinical symptoms are mild, and no manifestations of pneumonia are found in imaging; (b) moderate cases: fever and respiratory symptoms are present in patients, and manifestations of pneumonia can be seen in imaging; (c) severe cases: adults who meet any of the following conditions: respiratory rate ≥30 breaths/min; oxygen saturation ≤93% at resting; arterial partial pressure of oxygen/fraction of inspiration ≤300 mm Hg; patients with pulmonary imaging showing significant lesion progression >50% within 24 to 48 hours are treated as severe cases; (d) critically severe cases: Patients who meet any of the following conditions: occurrence of respiratory failure requiring mechanical ventilation; occurrence of shock; other organ failure requiring monitoring and treatment in intensive care unit. As the sample size of mild cases was small with little statistical significance, so the mild cases were studied together with moderate cases and they were collectively called moderate cases. Blood, fecal, urine, and conjunctival secretions were collected from the patient on day 3 to 5 after disease classification.

2.2 | Evaluation indexes

(1) Clinical features: the body temperature, gender and underlying diseases (including hypertension and diabetes) of patients at the time of admission were recorded in detail and the patients with missing data were excluded.
(2) Blood routine and other blood indexes: peripheral blood samples were collected for testing the indexes, including total hemoglobin (Hb, g/L), total white blood cell (WBC, 10^9/L), neutrophil count (10^9/L), lymphocyte count (10^9/L), procalcitonin (PCT, ng/mL), C-reactive protein (CRP, mg/L).
(3) Immune-related indexes: serum samples of the patients were collected and the following indexes were examined, including tumor necrosis factor γ (TNF-γ) (pg/mL), interleukin-10 (IL-10) (pg/mL), IL-6 (pg/mL), IL-2 (pg/mL), IL-4 (pg/mL), Immunoglobulin M (mg/dL), Immunoglobulin A (mg/dL), and Immunoglobulin G (mg/dL).
(4) Liver, kidney, and myocardial-related indexes: peripheral blood samples were collected to test total cholesterol (mmol/L), albumin (g/L), total bilirubin (μmol/L), direct bilirubin (μmol/L), alanine aminotransferase (ALT) (U/L), aspartate aminotransferase (AST) (U/L), creatine kinase isoenzyme (U/L), creatine phosphate kinase (CPK) (U/L), glomerular filtration rate (GFR) (mL/min).

2.3 | Statistical methods

All data were statistically analyzed using SPSS 22.0 software. Clinical data of patients with different disease classifications were compared and analyzed using Fisher exact test. Partial measurement data were expressed as mean ± standard deviation and analyzed using the *t* test. Statistically, $P < .05$ was considered to have a significant difference, and $P < .01$ represented an extremely significant difference.

3 | RESULTS

3.1 | Comparison of clinical features of patients with different COVID-19 types

Because of different clinical features of patients with different COVID-19 types, we conducted statistical analysis of patients with different disease classifications based on the clinical features, such as age, sex, underlying diseases, and body temperature (Table 1). It was found that the ages of critically severe and severe patients were generally older than that of moderate patients ($P < .05$), and there was no significant difference in the age between critically severe and severe patients ($P > .05$). According to the statistics of patients with hypertension, the proportion of patients with hypertension in all critically severe cases was remarkably higher than that in moderate cases ($P < .01$). However, no significant difference of the proportion was found between severe cases and moderate cases or critically severe cases ($P > .05$). Moreover, it was discovered that there was no significant difference in sex, diabetes, and body temperature among the three types of patients ($P > .05$). These results indicated that age and hypertension were two important indexes affecting the disease severity, which presented that patients in an advanced age or with hypertension tended to have a more severe disease, while sex, diabetes, and body temperature were not significantly different in patients with different COVID-19 types.

3.2 | Comparison of blood routine and other pneumonia-related blood indexes of patients with different COVID-19 types

Blood routine and disease-related blood indexes are commonly used for disease diagnosis, which are of great significance. To study the differences in blood routine and other pneumonia-related blood indexes of patients with different COVID-19 types, we firstly compared and analyzed the blood indexes in patients with different types (Table 2). In terms of total Hb count, there was no significant difference between moderate and critically severe cases, moderate and severe cases, or critically severe and severe cases ($P > .05$). For total WBC, the proportions of patients with abnormal WBC in critically severe and severe cases were higher than that in moderate cases ($P < .05$). Similar results could be observed concerning abnormal neutrophil count ($P < .05$) and lymphocyte count ($P < .01$), but there

TABLE 1 Comparison of clinical features of patients with different COVID-19 types

Project Indicators	Moderate type				Severe type				Critically severe type				*P* value	
	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	(Moderate vs severe)	(Moderate vs critically severe)	(Severe vs critically severe)
Age	26	45.63	15.46		39	53.10	14.11		10	61.57	13.01		.0487	.0055	.0951
Sex	26	12	14	0.5385	39	22	17	0.4359	10	7	3	0.3000	.4564	.2742	.4959
Hypertension	26	23	3	0.1154	39	27	12	0.3077	10	4	6	0.6000	.0821	.0062	.1407
Diabetes	26	26	0	0.0000	39	35	4	0.1026	10	9	1	0.1000	/	/	1.0000
Temperature	26	37.72	0.78		34	37.30	0.97		10	37.27	1.02		.0885	.1652	.8943

Notes: Normal reference values: blood pressure (systolic pressure, 90-139mm Hg; diastolic pressure, 60-89mm Hg); fasting blood glucose (3.9-6.1 mmol/L). Beyond or below the normal reference value is considered abnormal.
Abbreviation: COVID-19, coronavirus disease 2019.

TABLE 2 Comparison of blood routine and other pneumonia-related blood indicators of patients with different COVID-19 types

Project Indicators	Moderate type				Severe type				Critically severe type				*P* value		
	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	(Moderate vs severe)	(Moderate vs critically severe)	(Severe vs critically severe)
Total Hb	23	15	8	0.3478	34	19	15	0.4412	10	5	5	0.5000	.5858	.4611	1.0000
Total WBC count	26	18	8	0.3077	38	13	25	0.6579	10	5	5	0.5000	.0103	.4402	.4682
Neutrophil count	26	17	9	0.3462	37	14	23	0.6216	10	2	8	0.8000	.0420	.0248	.4568
Lymphocyte count	26	24	2	0.0770	38	18	20	0.5263	10	1	9	0.9000	.0002	<.0001	.0654
PCT	23	13	10	0.4348	37	17	20	0.5405	10	4	6	0.6000	.5959	.4646	1.0000
CRP	15	4	11	0.7333	21	2	19	0.9048	6	1	5	0.8333	.2100	1.0000	.5453

Notes: Normal reference values: Total Hb, 131 to 172 g/L; total WBC, 4 to 10×10^9/L; neutrophil count, 2 to 7×10^9/L; lymphocyte count, 0.8 to 4.0×10^9/L; PCT, 0.00 to 0.05 ng/mL; CRP, 0.00-8.00 mg/L. Beyond or below the normal reference value is considered abnormal.

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Hb, hemoglobin; PCT, procalcitonin; WBC, white blood cell.

was no significant difference between severe cases and critically severe cases ($P > .05$). These results suggested that total WBC, neutrophil count, and lymphocyte count were associated with the severity of COVID-19.

In addition, we measured the levels of PCT and CRP of patients with different classifications. These two indexes are commonly used to reflect inflammation in clinical practice. The elevation of PCT indicates bacterial infection, while the elevation of CRP indicates inflammation in the body.[12] It could be observed from Table 2 that there were no significant differences in the proportions of patients with abnormal PCT and CRP among the three groups ($P > .05$). This indicated that PCT and CRP were lowly correlated with the disease severity of COVID-19.

3.3 | Comparison of immune-related indexes of patients with different COVID-19 types

Studies have shown that "cytokine storm" (also known as hypercytokinemia) is present in severe infections with SARS, MERS, H5N1, and H7N9, and is associated with the severity of disease as a predictor of death.[13,14] We made a comparative analysis on various immune-related indexes of patients with different COVID-19 types to investigate their differences (Table 3). In the statistical analysis of cytokines, it was found that the proportion of patients with abnormal IL-2 and IL-4 in all critically severe cases was higher than that in moderate cases and severe cases. There were no significant differences in the proportions of patients with abnormal TNF-γ, IL-10, IL-6, IGM, and IGG among the three groups ($P > .05$). These results indicated that IL-2 and IL-4 were the two immune-related indexes associated with the progression of COVID-19, and they would gradually increase with the aggravation of the disease.

3.4 | Comparison of liver, kidney and myocardial indexes of patients with different COVID-19 types

Liver, kidney and myocardial indexes are of great value in disease diagnosis. We compared the liver, kidney, and myocardial-related indexes of patients with different COVID-19 types to study their differences (Table 4). The study on total cholesterol found that the proportion of patients with total cholesterol abnormality in critically severe cases was higher than that in moderate patients ($P < .01$). While concerning total bilirubin, albumin, direct bilirubin, ALT, AST, creatine kinase isozyme, CPK, and GFR, no significant differences were observed in patients with different COVID-19 types ($P > .05$). These results indicated that total cholesterol was a relevant index of COVID-19 progression.

4 | DISCUSSION

This study intended to explore the abnormal changes of various routine indexes, blood routine and other pneumonia-related blood

TABLE 3 Comparison of immune-related indicators of patients with different COVID-19 types

Project Indicators	Moderate type				Severe type				Critically severe type				*P* value		
	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	(Moderate *VS* Severe)	(Moderate *VS* Critically severe)	(Severe *VS* Critically severe)
TNF-γ	13	9	4	0.3077	17	12	5	0.2941	8	5	3	0.3750	1.0000	1.0000	1.0000
IL-10	18	5	13	0.7222	25	6	19	0.7600	10	2	8	0.8000	1.0000	1.0000	1.0000
IL-6	18	4	14	0.7778	24	4	20	0.8333	10	3	7	0.7000	.7061	.6744	.3943
IL-2	18	17	1	0.0556	23	23	0	0.0000	8	0	8	1.0000	/	/	/
IL-4	18	17	1	0.0556	24	24	0	0.0000	8	0	8	1.0000	/	/	/
IGM	17	17	0	0.0000	29	28	1	0.0345	10	9	1	0.1000	/	/	.4521
IGA	17	9	8	0.4706	29	27	2	0.0690	10	9	1	0.1000	.0026	.0912	1.0000
IGG	16	13	3	0.1875	29	22	7	0.2414	10	9	1	0.1000	1.0000	1.0000	.6526

Notes: Normal reference values: TNF-γ, 0-20.06 pg/mL; IL-10, 0 to 2.31 pg/mL; IL-6, 0 to 6.61 pg/mL; IL-2, 0 to 4.13 pg/mL; IL-4, 0 to 8.37 pg/mL; LGM, 30 to 220 mg/dL; IGA, 100 to 420 mg/dL; LGG, 860 to 1740 mg/dL. Beyond or below the normal reference value is considered abnormal.

Abbreviations: COVID-19, coronavirus disease 2019; IGA, Immunoglobulin A; IGG, Immunoglobulin G; IGM, Immunoglobulin M; IL, interleukin; TNF-γ, tumor necrosis factor γ.

indexes, immune-related indexes, liver, kidney, and myocardial-related indexes in patients with different COVID-19 types, and to conduct a comparative descriptive analysis of clinical features. Through reviewing the general features of the novel coronavirus, we could better understand COVID-19 and promote the development of a better treatment strategy.

Fever is the most obvious index of coronavirus infection. The most obvious symptom of SARS is the body temperature over 38℃ within 2 weeks. In addition, 60% of MERS patients developed fever.[15] Therefore, in the course of clinical diagnosis and treatment, patients with a high fever of a long duration and rapid progression should be closely monitored to avoid the complications caused by high fever, which would lead to a poor prognosis.[16] Age, diabetes, and other complications are also important predictors of COVID-19 morbidity and mortality.[17] In addition, about half of patients with COVID-19 have chronic underlying diseases, mainly cardiovascular and cerebrovascular diseases as well as diabetes, which is similar to patients with MERS.[7] Our study found that age and hypertension were significantly correlated with the severity of disease. The older the age, the higher the severity of disease. Hypertension would also accelerate the malignant progression of the disease. However, the differences in gender and diabetes were not significant in patients with different COVID-19 types.

In addition to the routine clinical features, some blood routine indexes are also important for disease progression in patients. Tissue damage caused by infection or malignant disease can lead to a change in the WBC count. Neutrophils are primarily involved in nonspecific immunity,[18] and lymphocytopenia is a sign of hypoimmunity. A study reported that lymphopenia (56.5%), increased CRP level (73.6%), and elevated PCT level (17.5%) were observed in patients with COVID-19.[19] Our research showed that the total WBC, neutrophil count and lymphocyte count were three blood routine indexes associated with progression of COVID-19. The proportions of patients with these three abnormal indexes in severe and critically severe cases were significantly higher than that in moderate patients, with no significant difference between critical cases and severe cases. These results revealed that SARS-CoV-2 may act mainly on lymphocytes, especially on T lymphocytes, like SARS-CoV.

A study has shown that cytokines/chemokines (such as IL-2, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP1A, and TNF-α) are significantly higher in intensive care unit (ICU) patients with COVID-19 than those in non-ICU patients.[20] Study on SARS indicated that IL-1, IL-6, IL-8, IL-12, IFN-γ, IP-10, and MCP-1 are associated with inflammation and extensive lung damage.[21] Besides, elevated levels of IFN-γ, IL-15, IL-17, and TNF-α are also features of MERS-CoV infection.[22] Therefore, inhibition of excessive inflammatory response in patients with COVID-19 is critical to reduce the mortality of severe and critically severe patients. All these studies demonstrate that the change in the levels of cytokines and inflammatory factors in patients is of reference value for guiding pharmacy. Here, we found that IL-2 and IL-4 were highly correlated with the progression of COVID-19, and the proportions of patients with abnormal IL-2 and IL-4 in critically severe cases were higher than that in moderate or severe patients

TABLE 4 Comparison of liver, kidney, and myocardial indicators of patients with different COVID-19 types

	Moderate type				Severe type				Critically severe type				*P* value		
Project Indicators	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	Cases	Normal (mean)	Abnormal (SD)	Abnormal proportion	(Moderate vs severe)	(Moderate vs critically severe)	(Severe vs critically severe)
Total cholesterol	22	16	6	0.2727	33	29	4	0.1212	8	6	2	0.2500	0.1747	<0.0001	0.5777
Albumin	23	13	10	0.4348	37	13	24	0.6486	9	3	6	0.6667	0.1179	1.0000	1.0000
Total bilirubin	24	22	2	0.0833	38	38	0	0.0000	9	7	2	0.2222	/	0.2952	/
Direct bilirubin	24	21	3	0.1250	37	30	7	0.1892	9	7	2	0.2222	0.7261	0.5971	1.0000
ALT	23	21	2	0.0870	37	30	7	0.1892	9	7	2	0.2222	0.4604	0.5568	0.5568
AST	23	17	6	0.2609	37	26	11	0.2973	9	6	3	0.3333	1.0000	0.6853	1.0000
Creatine kinase isoenzyme	24	21	3	0.1250	34	32	2	0.0588	9	7	2	0.2222	0.6396	0.5971	0.1878
CPK	24	16	8	0.3333	34	23	11	0.3235	9	6	3	0.3333	1.0000	1.0000	1.0000
GFR	21	94.6	21.11		36	90.53	25.11		8	97.58	7.52		0.5356	0.7023	0.4402

Notes: Normal reference values: total cholesterol, 3.14 to 5.86 mmol/L; albumin, 40 to 55 g/L; total bilirubin, 0 to 26 μmol/L; direct bilirubin, 0 to 8 μmol/L; ALT, 9 to 50 U/L; AST, 15 to 40 U/L; creatine kinase isoenzyme, 2 to 25 U/L; CPK, 50 to 310 U/L. Beyond or below the normal reference value is considered abnormal.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CPK, creatine phosphate kinase; GFR, glomerular filtration rate.

with a significant difference, which is consistent with the study made by Zhang et al.[20] This suggests that our study could provide reference for real-time monitoring of abnormal changes in IL-2 and IL-4 of patients with COVID-19.

In addition, many studies have explored that liver, kidney and myocardial indexes have important predictive functions in the severity of disease. For example, both SARS and MERS are linked to acute myocarditis, acute myocardial infarction and fast-onset heart failure.[23] Since the emergence of COVID-19, many studies have been carried out on the clinical features of this disease.[24,25] Of the 138 recently reported hospitalized patients with COVID-19, 7.2% developed acute cardiac injury.[26] Han et al found that 31.6%, 35.4% and 5.1% patients with COVID-19 had elevated levels of ALT, AST and bilirubin, respectively.[27] In the present study, we found that total cholesterol was associated with COVID-19 progression, which could also be found in the study made by Han et al. Our study provides information for real-time monitoring of abnormal change in total cholesterol of critically severe and severe patients by evaluating clinical features.

Since COVID-19 was firstly discovered in Wuhan, it has spread rapidly and shown widespread severity. Early isolation, early diagnosis and early management contribute to better control of disease progression. Our study found that age, hypertension, total WBC count, neutrophil count, lymphocyte count, IL-2, IL-4, and total cholesterol were highly correlated with COVID-19 disease progression, which had certain reference value. Proper monitoring of patients' physiological and biochemical indexes is conducive for effective treatment of patients with different COVID-19 types, thus reducing the complications and mortality of COVID-19. The data in this study can be used to determine the disease progression of patients with COVID-19 and to conduct disease classification. Besides, the change in total cholesterol of patients with different classifications suggests that COVID-19 may also have a negative effect on liver function of patients.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

CONSENT FOR PUBLICATION

All authors consent to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

HGW, JSH, and LHP both contributed to the conception and design, YJZ, JC, WW, JZ, and YZ contributed to the article drafting and revising. HH is the guarantors for the article who takes full responsibility for the work.

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