Clinical features of middle-aged patients died of 2019 Novel Coronavirus–Infected Pneumonia

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Abstract

Background

Since December, 2019, the emerge of a Novel Coronavirus Disease 2019 (COVID-19) have caused global concern, the majority viewpoints are that the deaths are related to advanced ages, however, the emergence of younger deaths needs immediate attention.

Methods

Clinical characteristics, laboratory results, chest CT scans and treatment measures were retrospectively reviewed for six deceased patients under 60 years old with confirmed COVID-19 who were admitted to Wuhan Pulmonary Hospital in Wuhan, Hubei Province, China, from 6th January to 4th March, 2020.

Results

The age range of the patients was 50.17 ± 3.25 years (45–55 years), none of them had underlying diseases. All of patients presented with the symptoms of fever, respiratory system and digestive system. The level of albumin and lymphocyte counts decreased early in the stages of the disease, and then gradually increased. The neutrophil to lymphocyte ratio (NLR) increased (higher than normal range) in early stage and gradually decreased when the disease progressed. All the six patients showed ground-glass opacity (GGO) and bilateral patchy shadowing in early stage under the computed tomography (CT). All the patients died of severe pneumonia and multiple organ failure.

Conclusions

The decreased level of serum albumin occurred in the early stages of the disease, and delays in the first admission to hospital probably aggravate the disease development. The increase of the NLR in early stage of disease may be a risk of death for COVID-19. These findings may provide useful information for optimizing supportive care for COVID-19 pneumonia.

Background

Since December 2019, an outbreak named Novel Coronavirus Disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, Hubei province have caused global concern. The disease has rapidly spread to other areas of China even all over the world. The World Health Organization (WHO) has declared COVID-19 a public health emergency of international concern [1]. Up to 6 March, 2020, a total of 98,373 COVID-19 cases have been confirmed internationally, among which 3,388 patients died. The fatality rate (3.4%) is in accordance with the national official statistics (3.2%) [2, 3], and significantly lower than those of SARS-COV and MERS-COV infected pneumonia [4, 5].

However, the rapid spread causes a worldwide pandemic, and increase in the numbers of death causes thousands of families huge psychological trauma and economic burden especially for those patients with the age under 60 years old. Previously published articles and expert consensus have demonstrated [6, 7] that, risk of death is much higher in the elderly and those with chronic underlying diseases. Nevertheless, the relatively younger deceased patients have rarely been paid attention to. In this study, we investigated the clinical characteristics of patients died of COVID-19 pneumonia under the age of 60 to reveal risk factors leading to poor clinical outcomes, even death.

Methods

Study design

This was a retrospective, single center, observational study. We assessed the eligibility of 220 laboratory-confirmed COVID-19 patients who were admitted to Wuhan Pulmonary Hospital between 6th January and 4th March, 2020. Only patients under 60 years and died before 4th March were included for the analysis. Confirmed SARS-CoV-2 infection cases are in accordance with the 'new coronary pneumonia diagnosis and treatment plan (trial version 6)' issued by the health commission of the People's Republic of China (PRC) [8]. Medical data were securely sent to the research team of Shanghai for analysis.

Data Collection

Demographic information, medical history, exposure history, underlying comorbidities (including chronic obstructive pulmonary disease, diabetes, chronic hypertension, coronary heart disease, cerebrovascular disease, cancer, chronic renal disease), surgery history, clinical signs and symptoms, laboratory findings and chest computed tomographic (CT) scan or X-ray results and treatment measures were obtained from electronic medical records. Cigarette smoking and alcohol consumption were also extracted. The date of disease onset was defined as the day when symptoms began to appear. The date of death refers to the time when doctors declared clinical death. Patient 4 with short disease duration and few laboratory data available was not included in the figure of the dynamic changes of laboratory parameters. The CT images were not available during the disease progress of patient 1, 4 and 5.

Laboratory Finding And Treatment Measures

Laboratory diagnosis of SARS-CoV-2 infection were confirmed by viral nucleic acid test (NAT) using real-time polymerase-chain-reaction (RT-PCR) amplification of open reading frame 1ab (ORF1ab) and nucleocapsid protein (NP) genes fragments from sputum, pharyngeal swab or lower respiratory tract samples [9]. The double-positive was defined as positive RT-PCR result of both ORF1ab and NP, while double-negative was defined as negative result of the tests. Infection was defined as double-positive test results.

Medical laboratory results includes complete blood count, blood chemical analysis, coagulation testing, blood liver and renal function and measures of electrolytes, C-reactive protein (CRP), procalcitonin (PCT), creatine kinase (CK) and the neutrophil to lymphocyte ratio (NLR). Patient four with short disease duration and few laboratory data available was not included in the figure of the dynamic changes of laboratory parameters.

Treatment measures included antiviral therapy, intravenous antibiotics, antifungal medication, corticosteroid therapy, intravenous immunological therapy. Mechanical ventilation (invasive or noninvasive), extracorporeal membrane oxygenation therapy (ECMO), and kidney replacement therapy were also obtained from medical records of each patient.

Statistical analysis

Statistical analyses were conducted using SPSS, version 24.0 (IBM Corp, Armonk, NY). We presented continuous measurements as a mean $\pm$ standard deviation, and categorical variables as number and percentage.

Results

A total of 220 patients were assessed for eligibility. 169 (76.8%) patients were discharged before 4th March, 2020. Of the 51 patients died of COVID-19, 45 (88.2%) patients were excluded for being more than 60 years old or having insufficient clinical data. Six patients under 60 years old who died of COVID-19 were recruited in the study. A flowchart of the patient selection process was shown in Fig. 1.

Demographic And Clinical Features

The mean age of the six patients was 50.17 ± 3.25 years (range, 45–55 years). Four (67.7%) patients were male. Patients progressed to death within 13–48 days. None of them had underlying diseases. One patient had current smoker with 20 cigarettes a day for 20 years. Demographics and clinical features of the study population are listed in Table 1.

Table 1
Demographics and clinical features of COVID-19 infected patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	N,(%)
Age, (years)	50	49	45	51	55	51	
Sex	male	male	female	female	male	male	
Onset of symptom to, (days)							
Hospital admission	10	6	14	6	4	8	
ICU admission	10	11	14	9	9	8	
Death	22	39	42	13	48	25	
Bilateral large range of GGO damages	12	11	9	10	11	11	
Highest Temperature, (°C)	40	40	39	38.9	37.2	38.5	
Symptoms							
Dyspnea	Yes	Yes	Yes	Yes	Yes	No	5 (83.3)
Chest distress	Yes	Yes	Yes	Yes	No	No	4 (66.7)
Cough	Yes	Yes	No	No	Yes	Yes	4 (66.7)
Poor appetite	No	Yes	No	Yes	No	Yes	3 (50)
Diarrhea	No	No	No	Yes	Yes	Yes	3 (50)
Nausea,vomiting	No	No	No	Yes	No	No	1 (16.7)
Other symptoms	Mild hae-moptysis	Fatigue, Myalgia	Sore throat	Fatigue	Fatigue	Fatigue, Myalgia	
Complications							
Acute respiratory distress syndrome	Yes	Yes	Yes	Yes	Yes	Yes	6 (100)
Multiple organ failure	Yes	Yes	Yes	Yes	Yes	Yes	6 (100)

All patients had a fever, and 5 (83.3%) had the body temperature greater than 38.5. The most commonly experienced symptoms were in respiratory system and digestive system. Regarding the respiratory symptoms, dyspnea and chest distress appeared in five patients, cough in five patients, and one reported a sore throat or mild haemoptysis. In terms of digestive symptoms, four patients indicated poor appetite, three had diarrhea, and one had nausea and vomiting. Other symptoms included fatigue in four patients and myalgia in two patients.

Laboratory and Radiologic findings

The dynamic changes of laboratory parameters were record from the day of disease onset to the day when the patient died (Fig. 2). During the complete clinical course of the disease, the levels of D-dimer, creatine kinase (CK) and C-reaction protein (CRP) were remarkably higher than normal range in most patients. As the disease progressed and clinical status deteriorated, the levels of procalcitonin (PCT), creatinine, leukocyte counts and neutrophil counts progressively increased, while the levels of hemoglobin gradually decreased. The NRL increased (higher than normal range) in early stage and gradually decreased when the disease progressed. Reversely, the level of albumin and lymphocyte counts decreased early in the stages of the disease, and then gradually increased.

In the CT images, all the six patients showed ground-glass opacity (GGO) and bilateral patchy shadowing in early stage, and all rapidly progressed into a large range of GGO damages. The time span from symptom onset to large range of GGO was 9-12d (Fig. 3). Patient 1, 4 and 5 showed a "white lung" in the CT image on day 12, 10 and 11 after symptom onset respectively. Patient 2, 3 and 6 showed a "melted sugar" pattern on day 11, 9 and 11 after symptom onset respectively. As the disease progressed, the CT images showed the lungs in patient 2, 3 and 6 continued to deteriorate.

Treatment And Clinical Outcomes

All of patients received antiviral therapy, intravenous antibiotics, corticosteroid therapy, intravenous immunological therapy, and noninvasive ventilation. Among those, four patients received antifungal therapy, five patients were obtained invasive mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) equipment was performed in three patients. There were two patients with continuous renal replacement therapy. The clinical course and treatment process of the patients were displayed in Fig. 4. All the patients progressed to severe pneumonia and multiple organ failure. More than two organs were identified shutting down in each patient.

Discussion

Previously published studies have showed that severe COVID-19 patients were much older than non-severe patients and associated with higher frequency of comorbidities [6, 7, 10], and those older patients often died of their pre-existing comorbidities. However, none patient in our study had underlying

comorbidities, and they all rapidly progressed to severe pneumonia and multiple organ failure with the age younger than 60 years. Thus, it is necessary to investigate the clinical characteristics of younger adults (under 60 years) without underlying comorbidities who died of COVID-19, so as to provide an implication for physician to identify the potential risk of poor clinical outcomes, as well as take timely prevention and treatment.

In this study, four patients had symptoms of digestive system including poor appetite, diarrhea, nausea and vomiting. Nevertheless, all patients had been reported decreases in albumin level in the early stages. The phenomenon of general digestive system involvement in severe patients was in accordance with previous studies. Wang et al found that patients admitted to the intensive care unit (ICU) were more likely to report abdominal pain, and anorexia [6]. In addition, Zhang et al reported nausea commonly experienced in severe group ($P=0.027$) [7]. Guan W et al showed that the frequency of nausea or vomiting, diarrhea was 6.9%, 5.8% in severe patients, and 4.6%, 3.5% in nonsevere patients respectively [11]. They also demonstrated that severe and death patients have malnutrition caused by digestive symptom in the early stage. It is proposed that malnutrition may promote the development of the diseases, secondary severe infection and multiple organ failure, even if albumin rises at the end of the disease course. Thus, in the early stage of the disease, timely strengthen nutrition and improve digestive system symptoms should be considered to improve the poor prognosis.

Laboratory tests indicated that the levels of D-dimer, CK and CRP were remarkably higher than normal range. The levels of PCT, creatinine, leukocyte counts and neutrophil counts were gradually higher as disease progressed, which is in consistent with recently published results. Wang DW et al showed that, the neutrophil count, D-dimer, blood urea, and creatinine levels continued to increase over the disease progression in the nonsurvivors [6]. In addition, Cao et al reported D-dimer greater than 1 $\mu\text{g/mL}$ at admission to hospital was associated with the risk of death [12]. Zhang et al reported that, higher values of leukocyte count ($P=0.014$), D-dimer ($P<0.001$), CRP ($P<0.001$), PCT ($P<0.001$) were found in severe cases, compared to non-severe cases [7]. The levels of hemoglobin gradually decreased as the development of the disease, which was consistent with the study of Chen et al [10]. The abnormal index of CRP, PCT, leukocyte counts and neutrophil counts may indicate sustained and prominent inflammatory response. The higher D-dimer but the lower hemoglobin levels may attribute to a disturbed coagulation mechanism under the condition of infection with COVID-19. In addition, higher leukocyte count and PCT may be due to secondary bacterial infection. Furthermore, the virus, hypoxia and shock may induce higher serum CK and creatinine levels.

In this study, our result shown an increase in the level of NRL in early stage of disease, and a gradual decrease as the disease progressing, in consistent with previously published studies which showed that [13, 14], NLR levels were significantly higher in non-survivors than in survivors with Community Acquired Pneumonia (CAP), the receiver operating characteristic (ROC) curve of NLR as a predictor of the mortality was better than that of the neutrophil count, white blood cell (WBC) count, lymphocyte count and CRP level. Therefore, the increase of NLR in early stage of disease may have predictive value for death. Nevertheless, the increase in lymphocyte counts was different from the previous studies [6, 12], but was

consistent with the study of Kai et al [15], which found the proportion of lymphocytes decreased in elderly patients was much higher than that of the young and middle-aged patients, perhaps patients under the age of 60 in our study was without underlying diseases, which was different in patients in previous studies. In addition, the small sample size in our study may affect the accuracy of the results.

It takes about 9-12d from the initial symptoms to large range of ground-glass opacity in CT scan in our study, around which they were admitted to the intensive care unit. The first admission to hospitals appeared about 4-14d after the onset of the symptoms, which was similar to the previous studies. Li et al showed that 89% of patients not being hospitalized until at least day five of illness [16]. Zhou et al reported the median time from illness onset to hospital admission on non-survivor patients was 11.0 days (8.0–15.0) [12]. Their clinical status deteriorated rapidly. All patients underwent noninvasive ventilation. Five were further treated with invasive ventilation. ECMO was applied as the last resort to treat three patients. This reminds us to pay attention to the early stage of young and middle-aged patients without chronic underlying diseases, timely and effective therapies should be considered for the severe patients to prevent the deterioration of the disease.

Our study has several limitations. First, the patients who died of COVID-19 were mainly elderly patients with underlying diseases, the number of younger patients who died was less, which would bring limitations to the study sample. Second, we did not report the CT images about the disease progresses of patient 1, 4 and 5, patient 4 was also not included in the figure of the dynamic changes of laboratory parameters, which might cause bias. Third, some patients under 60 years with insufficient clinical data were excluded from the analysis. Therefore, our results may not be generalizable to all patients under 60 years. Fourth, this is only general treatment plans for confirmed patients in a single center hospital, it is necessary to explore specific treatment plans for younger patients without underlying diseases in multicenter studies. Whereas, we believe that the findings reported here are important for understanding the clinical characteristics of COVID-19 in middle-aged patients of high mortality risk.

Generally, there was an increase in lymphocyte counts in patients under 60 years old who died of the COVID-19 pneumonia, which was different from those older patients. In addition, the decreased level of serum albumin in the early course and delays in the first admission to hospital deteriorated the symptoms of the infection. The increase of NLR in early stage of disease might be a risk factor of death. To pay attention to the clinical information and take a timely therapeutic strategy for similar severe patients might be important for physicians to reduce mortality due to the COVID-19 pneumonia.

Abbreviations

COVID-19, Coronavirus Disease 2019; NLR, neutrophil to lymphocyte ratio; GGO, ground-glass opacity; CT, computed tomography; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization; CK, creatine kinase; CRP, C-reaction protein; PCT, procalcitonin; EMCO, extracorporeal membrane oxygenation; ICU, intensive care unit; ROC, receiver operating characteristic; WBC, white blood cell.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine. Due to the respective nature of our study, all patients died before data collection. Thus, written informed consent was obtained from immediate family members of patients.

Consent for publication

Written informed consent for publication of the clinical details and clinical images was obtained from immediate family members of patients.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GC, YW and XL collected the data, CJ and XL accomplished data analysis, GZ and DZ performed imaging processing, YH and MH drafted the manuscript and made literature review, YC, HH and LY designed the study and reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Flowchart of the patient selection process

Figure 2

Dynamic changes in laboratory parameters from disease onset to death. The solid lines in red show the upper normal limit of each parameter, and the solid line in green shows the lower normal limit of lymphocyte count, hemoglobin and albumin.

Figure 3

CT images of COVID-19 related pneumonia. a. CT images on day 12 after symptom onset and 10 days from death (patient 1). b1. CT images on day 11 after symptom onset and 28 days from death (patient2). b2. CT images on day 16 after symptom onset and 23 days from death (patient2). c1. CT images on day 9 after symptom onset and 33 days from death (patient3). c2. CT images on day 18 after symptom onset and 24 days from death (patient3). d. CT images on day 10 after symptom onset and 3 days from death (patient4). e. CT images on day 11 after symptom onset and 37 days from death (patient5). f1. CT images on day 11 after symptom onset and 14 days from death (patient6). f2. CT images on day 16 after symptom onset and 9 days from death (patient6).

Figure 4

The clinical course and treatment process of the patients