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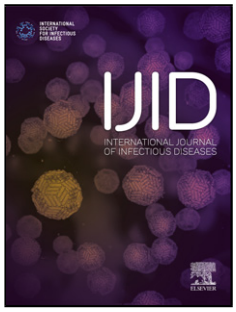

Risk-adapted Treatment Strategy For COVID-19 Patients

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PII: S1201-9712(20)30179-X

DOI: https://doi.org/10.1016/j.ijid.2020.03.047

Reference: IJID 4053

To appear in: *International Journal of Infectious Diseases*

Received Date: 19 March 2020

Revised Date: 21 March 2020

Accepted Date: 23 March 2020

Please cite this article as: { doi: https://doi.org/

Risk-adapted Treatment Strategy For COVID-19 Patients

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Length of abstract: 250

The length of the paper: 1846

Highlights

1. There are no clear expert consensus or guidelines on how to treat COVID-19.
2. We developed a risk-adapted treatment approach according to the illness severity.
3. This strategy was effective in symptoms alleviation and chest CT recovery.
4. This strategy is a useful and efficient approach for COVID-19 patients.

Abstract

Background: There are no clear expert consensus or guidelines on how to treat 2019 coronavirus disease (COVID-19). The objective of this study is to investigate the short-term effect of risk-adapted treatment strategy on patients with COVID-19.

Methods: We collected the medical records of 55 COVID-19 patients for analysis. We divided these patients into mild, moderate and severe groups, and risk-adapted treatment approaches were given according to the illness severity.

Results: Twelve patients were in mild group and 22 were in moderate group (non-severe group, n=34), and 21 patients were in severe group. At the end of the first two weeks after admission, clinical manifestations had completely despeared in 31(91.2%)patients in non-severe group, and 18(85.7%) patients in severe group (p=0.85). Both groups had a satisfied chest CT imaging recovery, which includes 22(64.7%) patients in non-severe group and 12(57.1%) patients in severe group recovered at least 50% of the whole leisions in the first week, and 28(82.4%) and 16(76.2%) recovered at least 75% in the second week, respectively. There were no significant differences in SARS-CoV-2 RNA clearance between two group (p=0.92). There were also no significant differences in the levels of SARS-CoV-2-IgM and IgG antibody production between the two groups (p=0.13, 0.62). There were 45 cases were discharged from the hospital, and no patients died at the time of this clinical analysis.

Conclusions: Risk-adapted treatment strategy was associated with significant clinical manifestations alleviation and clinical imaging recovery. In severe COVID-19 patients, early and short-term use of low-dose methylprednisolone was beneficial and did not delay SARS-CoV-2 RNA clearance and influence IgG antibody production.

Key words

COVID-19; novel coronavirus pneumonia; risk-adapted treatment strategy; antiviral treatment; low-dose corticosteroid

Introduction

The novel coronavirus-associated pneumonia, which was named 2019 coronavirus disease (COVID-19) by WHO, began to spread in Wuhan, China, in December 2019 and has now become a global public health crisis. As of March 3rd, 2020, there were a total of 80270 cumulative confirmed patients and 2981 cumulative deaths in China, and according to the WHO report, there were a total of 10566 confirmed patients and 166 deaths outside China. The limited clinical data indicated that COVID-19 was associated with high incidence of intensive care unit (ICU) admission and high mortality[1-5]. However, until now, there are no clear expert consensus or guidelines on how to treat COVID-19. We developed a risk-adapted treatment approach according to the illness severity; and the objective of this study is to investigate the short-term effect of this risk-adapted treatment strategy on clinical manifestations alleviation, clinical imaging recovery and SARS-CoV-2 RNA clearance.

Methods

Patients selection

This is a retrospective study and we collected the medical records of 55 COVID-19 patients for analysis. All these patients were admitted to the Unit Z6 (total of 64 beds) in Cancer center of Wuhan Union Hospital on February 15th, 2020 (from 13:00 to 23:00, Beijing time) according to the unified arrangements of the local Government. Medical records include clinical characteristics, laboratory parameters, treatment approaches, and

clinical outcomes. This study was approved by the First Affiliated Hospital of University of Science and Technology of China institutional review board and the need for informed consent was obtained.

Clinical characteristics include patient's age, sex, first clinical symptoms, days from onset of symptoms to hospital, respiratory rate, heart rate, oxygen saturation (SpO2), etc. Laboratory Parameters included tests of blood routin, liver and kidney function, coagulation, C-reactive protein and procalcitonin, peripheral blood CD3+T-cells percentage, interleukin-6 level and SARS-CoV-2-IgG and IgM antibodies, etc. Nasal and pharyngeal swab specimens were collected for detecting SARS-CoV-2 RNA which were tested by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) at least three times within 2 weeks.

Clinical classification

We divided these 55 confirmed patients into three types: mild COVID-19– fever and mild respiratory symptoms, with pulmonary imaging such as computed tomography (CT) showing no obvious or only mild pneumonia; moderate COVID-19 – obvious respiratory symptoms such as fever and cough, and pulmonary CT indicates typical coronavirus pneumonia with overall lesions less than 30%; however, moderate patients have stable vital signs, and oxygen saturation＞93% without oxygen support; and severe COVID-19 – at least 1 of clinical features which including reapiratory rate more than 30 breaths/minute at rest, oxygen saturation ≤93% without oxygen support, arterial oxygen partial pressure/fractional inspired oxygen (PaO2/FiO2) ≤ 300 mmHg, the total lesions on chest CT ≥30% or rapid progress ≥50% in next 72 hours (which were evaluated by two physicians and two radiologist).

Risk-adapted treatment

Risk-adapted treatment approaches were adopted for these patients. For mild COVID-19 patients, intermitted low-flow oxygen therapy (⩽3L/min) and antiviral treatment with one of the oral antiviral regimens (such as arbidol tablets, 200mg three times daily) are given. For moderate COVID-19 patients, continuous middle-flow oxygen therapy (3~ 5L/min),

triple antiviral treatment of an oral antiviral regimen, ribavirin (500mg every 12 h, intravenously) and recombinant interferon-α2b (5 million units twice daily, aerosol) are given. Traditional Chinese medicine (TCM) is also recommended for mild or moderate COVID-19 patients. For severe COVID-19 patients, treatment approach is comprised of oxygen support including mask oxygen(＞5L/min), high flow nasal oxygen therapy (HFNO), or non-invasive ventilation (NIV); triple antiviral treatment including an oral antiviral regimen, ribavirin and recombinant interferon-α2b (usage and dosage same as above). The recommended duration of antiviral treatment is 10 days. For severe patients, corticosteroid (methylprednisolone 0.5mg~1mg/kg.d×5 days) should be given immediately on admission or within the first three days of hospitalization. Empirical antibiotic treatment is considered for all types if bacteria infection was suspected. Treatment-failure patients should be prepared early for intubation and invasive mechanical ventilation, and even considered with extracorporeal membrane oxygenation (ECMO) [6].

Statistical methods

Variables of clinical characteristics, laboratory parameters, treatment approaches, and clinical outcomes, such as categorical variables were measured using χ^2 test, and continuous variables were measured using Mann-Whitney U test between non-severe group (including mild and moderate patients) and severe group. Statistical analyses were conducted using R statistical software (R Foundation for Statistical Computing, Version 3.4.3). Differences with $p< 0.05$ were considered significant.

Results

This study includes 55 hospitalized patients with confirmed COVID-19 including 12 patients in mild group and 22 in moderate group (non-severe group, n=34), and 21 patients were in severe group (table1). The median age was 59(29-77) years in non-severe group and 62(29-91) years in severe group (p=0.37). There are 47.1%(n=16) male patients in non-severe group and 38.1% (n=8) in severe group (p=0.58). The most

common symptoms at onset of illness were fever (26[76.5%] in non-severe group and 19[90.5%] in severe group) and cough (13[38.2%] in non-severe group and 11[52.4%] in severe group). The median Days from onset of symptoms to hospital presentation were 11(3-40) in non-severe group and 10(1-30) in severe group (p=0.89).

Patients in severe group had a faster respiratory rate and heart rate (p=0.015, 0.012), and a lower SpO2 than patients in non-severe group (p=0.045). There are significant higher levels of fibrinogen, D-dimer, and fibrin/fibrinogen degradation products (FDP) in in severe group (p＜0.001,＜0.001,＜0.001), and there are also significant higher levels of lactate dehydrogenase, C-reactive protein, creatine kinase, and hypersensitive troponin I in severe group than those in non-severe group (p=0.004,＜0.001, 0.01, 0.007), respectively. Patients in severe group have a very lower lymphocyte count and CD3-T cells percentage than that in non-severe group (p=0.008, 0.002). The severe group also had a higher interleukin-6 level than that in non-severe group (p=0.02) (tabe 1). There were no significant differences between two groups in terms of white blood cell count (4.95[2.28-8.44]×10^9/L vs 5.25[1.47-10.92]×10^9/L,p=0.31), platelet count (215[110-436]×10^9/L vs 211[118-367]×10^9/L,p=0.79), alanine ainotransferase(24.5[8-137] U/Lvs 32[8-498]U/L,p=0.48) and creatinine(72[48-97]μmol/L vs 67[56-133] μmol/L,p=0.68).

All patients received chest CT scans on admission, and 100% had abnormal findings. Nodular or peripheral ground-glass opacity and bilateral patchy shadowing were found in 16(47.1%) paients in non-severe group (overall lesions＜30%) and 8(38.1%) patients in severe group (overall lesions≥30%). Bilateral multiple lobular or subsegmental areas of consolidation were found in 12 patients (35.3%) in non-severe group (overall lesions＜30%) and 11 patients (52.4%) in severe group (overall lesions≥30%).

At the end of the first two weeks after admission (as of Mar 1st), clinical manifestations had completely despeared in 31(91.2%)patients in non-severe group, and 18(85.7%) patients in severe group (p=0.85). Chest CT was re-examined with an interval of 5- 14 days. It was found that patients in both groups had a satisfied radiologic imaging recovery, which includes 22(64.7%) patients in non-severe group and 12(57.1%) patients

in severe group recovered at least 50% of the whole leisions in the first week, and 28(82.4%) patients in non-severe group and 16(76.2%) patients in severe group recovered at least 75% of the whole leisions in the second week. There were no significant differences in the proportion of patients who had SARS-CoV-2 RNA clearance between the non-severe group (33[97.1%]) and the severe group (20[95.2%]) (p=0.92). There were also no significant differences in the levels of SARS-CoV-2-IgM(35.1[0.92-292.8]AU/ml vs 62.8[0.3-621.0]AU/ml) and IgG antibody production(162.8[0.86-195.1]AU/ml vs 145.7[1.8-204.1]AU/ml) between the two groups (p=0.13, 0.62). There were 45 cases were discharged from the hospital, and no patients died at the time of this clinical analysis.

Discussion

In this study, we developed a risk-adapted treatment approach for COVID-19 according to the illness severity (mild, moderate and severe). Our study indicates that use of risk-adapted treatment approach in patients with COVID-19 was associated with significant clinical manifestations alleviation and clinical imaging recovery; and in patients with severe COVID-19, early and short-term use of low-dose methylprednisolone did not delay SARS-CoV-2 RNA clearance and influence the IgG type antibody production when compared with non-severe patients.

COVID-19 is characterized by fever, dry cough and fatigue, and a few patients have symptoms of nausea or vomiting and diarrhea, etc[1-5]. However, in clinical practice, COVID-19 and other viral infections like influenza need to be further differentiated. Influenza is also a contagious respiratory illness caused by influenza viruses that infect upper respiratory tract, and sometimes the lungs; the main symptoms of influenza are sudden high fever, headache, myalgia, general malaise; It can cause mild to severe illness, and at times can lead to death[7-9]. In this study, severe patients had abnormal hematological manifestations including significant lower lymphocytes and CD3+T cells, increased fibribogen, D-dimer and fibrin/fibrinogen degradation products (FDP) levels; a

very high interleukin-6 level which demonstrated that cytokines storm might exsit. Some clinical studies also found acute cardiac injury and acute renal injury in severe patients [1-3]. These findings indicated that COVID-19 is a systemic disease, not just pneumonia. However, critical influenza may also cause complications with high morbidity and mortality, such as pneumonia, myocarditis, central nervous system disease and death [9]. In this situation, we recommend to use a broad-spectrum molecular diagnostic panel for rapid detection of the most common respiratory pathogens to make a differential diagnosis [10]. In clinical emergency or intensive care unit, pneumonia with unknown cause is accompanied by lymphocytopenia, elevated interleukin-6 level and other obvious abnormal laboratory parametres, clinicians should ask if the patients or their families have any contact history with COVID-19 patient, and SARS-CoV-2 nucleic acid should be detected timely [10].

For the diagnosis and treatment of COVID-19, clinicians need to conduct clinical classification based on patient's clinical symptoms and laboratory test results (including chest CT). Different clinical types indicate that patients have different pathophysiological processes or are at different stages of disease development, and therefore require tailored treatment aproaches. Although the efficacy of antiviral therapy is still uncertain, combination treatment based on the inhibition of viral replication might reduce the inflammatory injury, and can allow the body to gradually produce enough virus-specific antibodies to clear the virus through the immune response, and ultimately cure the disease. There is a great debate on the use of corticosteroids for coronavirus infection such as severe acute respiratory syndrome (SARS)[11,12] and Middle East respiratory ryndrome (MERS)[13,14], and the data of systemic corticosteroid treatment in critical COVID-19 are lacking. The findings of this study support the use of corticosteroids in severe COVID-19. Early use (immediately on admission or within the first three days of hospitalization) might relatively rapid control the disease progress or avoid disease further deterioration. Short-term and low-dose administration (methylprednisolone 0.5mg~1mg/kg.d×5 days) could avoid the corticosteroid's potential risks; on the other hand, such cortocosteroid use does not influence the SARS-CoV-2 RNA clearance and

SARS-CoV-2 IgG antibody production.

In conclusion, we established a risk-adapted treatment strategy for COVID-19, and this strategy could be considered a useful and efficient approach for these patients based on our short-term observation. However, this study has certain limitations. It is a retrospective study in a single center, and the sample is relatively small, and the observation time is short; continued evaluations of this risk-adapted treatment strategy are needed.

Funding.

This research received no external funding.

Ethical approval.

Ethical approval was obtained from the ethics committees of the First Affiliated Hospital of University of Science and Technology of China. This is a retrospective and observational study and the informed consent was obtained.

Conflicts of interest.

The authors declare no conflict of interest.

Acknowledgments.

The authors thank Yin-Ling Liu, Yu-Lan Wang, Fei Yu, Can Zhang, Xiao-Jing Wang, Jing Li, Jun Chen, Kai-Di Song, Xiao-Bing Wang, Chun-Lin Xie, Wei-De Zhou, Fei Tong, Ben-Jie Shan, Xu-Han Zhang, Juan Zhang, Jun Jiang, Zhan Zhang, Xiao-Wan Zhou, Hao Tang, Song Wei, Fei Ye, Jin-Sheng Hua for their clinical practice work in COVID-19 patients.

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Table 1 Patient's characteristics and clinical outcomes

Characteristics	**Non-severe COVID-19**	**Severe COVID-19**	***p***
Total (n)	34	21	
Respiratory rate, median (range)	20(18-26)	28(22-36)	0.015
Heart rate, median (range)	81(60-108)	88(54-140)	0.012
Oxygen saturation on admission, median (range)	97(94-99)	94(88-98)	0.045
Neutrophil count, median (range) ($\times10^9$/L)	2.77(0.93-5.93)	3.46(0.56-9.29)	0.06
Lymphocyte count, median (range) ($\times10^9$/L)	1.55(0.74-2.0)	1.09(0.57-2.18)	0.008
CD3-T cells, median (range) (%)	76.8(62.9-89.6)	70.5(39.5-86.8)	0.002
Aspartate aminotransferase, median (range) (U/L)	23(10-66)	40(16-346)	0.005
Total bilirubin, median (range) (mmol/L)	10.2(6.9-47.4)	13.4(7.4-35.7)	0.06
Lactate dehydrogenase, median (range) (U/L)	194(114-293)	247(143-437)	0.004
Creatine kinase, median (range) (U/L)	53(24-152)	74(32-2324)	0.01
Hypersensitive troponin I, median (range) (pg/mL)	1.6(0-9.4)	5.3(0.5-4428)	0.007
C-reactive protein, median (range) (mg/L)	6.14(0.08-103)	29.9(3.14-114)	＜0.001
Fibrinogen, median (range) (g/L)	3.4(2.4-5.7)	5.3(3.3-8.1)	＜0.001
Fibrin/Fibrinogen degradation products, median (range) (mg/L)	1.35(1-15.2)	2.9(1-18.2)	＜0.001
D-dimer, median (range) (mg/L)	0.24(0.2-2.9)	1.0(0.2-5.0)	＜0.001
Interleukin-6, median (range) (ng/L)	27.6(3.6-280)	64.3(3.8-439)	0.02