Research Article

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The relationship between oxygen therapy, drug therapy, and COVID-19 mortality

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Abstract: Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19). We conducted a retrospective study of COVID-19 inpatients in Wuhan Pulmonary Hospital (Wuhan, China) from January 1 to February 29, 2020. The subjects were divided into four groups due to different treatment regimes. We used the Kaplan–Meier method to determine the cumulative rates of in-hospital death and the Cox proportional hazard model to calculate the risk factors and corresponding hazard ratios. A total of 185 patients were included in this study. The median age of the patients was 62 years, including 94 men and 91 women. Kaplan–Meier analysis demonstrated that mortality was higher in older patients, higher in men, and lower in the low-flow oxygen therapy group. Body mass index (BMI) had no influence on mortality, as well as high flow oxygen therapy, Lopinavir–ritonavir (LPV/r) therapy, and the interferon-alpha add LPV/r therapy. Cox proportional hazard regression confirmed that the low flow oxygen therapy was independent protective factor for in-hospital death after adjusting for age, gender, and BMI. In conclusion, the mortality was higher in older patients, higher in men, and lower in the low-flow oxygen therapy group. BMI had no influence on mortality, as well as high flow oxygen therapy, LPV/r therapy, and interferon-alpha add LPV/r therapy.

Keywords: drugs treatment, COVID-19, pneumonia, mortality

1 Introduction

On December 31, 2019, the World Health Organization (WHO) was notified a cluster of cases of pneumonia with unknown etiology in Wuhan, Hubei Province, China. Chinese specialists rapidly isolated the novel coronavirus on January 7 and shared viral genome data with the international community [1]. The highly pathogenic virus is now called SARS-CoV-2 (initially called 2019-nCoV) [2]. The disease was named COVID-19 by the WHO [3]. With reports of thousands of new cases of SARS-CoV-2 infection in China and evidence of person-to-person transmission in the United States and other countries [4,5]; on January 30, the WHO declared the epidemic outbreak of a public health emergency of international concern. Specific treatment and prevention options, such as targeted antiviral drugs and vaccines, were not yet available. Several preexisting and potential drug candidates, including Lopinavir–ritonavir (LPV/r) and interferon-alpha, have been applied to the clinical antiviral treatment of the COVID-19. In this single-center retrospective study of COVID-19 adult patients in Wuhan Pulmonary Hospital, which was designated for COVID-19 cases by local government, we aimed to illuminate the relationship between different treatment regimens and inpatient all-cause mortality of COVID-19 patients.
2 Methods

2.1 Study design and participants

We included 185 patients with laboratory-confirmed COVID-19 from Wuhan Pulmonary Hospital (Wuhan, China), who had been discharged or had died by February 29, 2020. Laboratory diagnosis of SARS-CoV-2 is based on the positive viral nucleic acid test result on throat swab samples. Diagnosis and treatment are given according to the guidance provided by the Chinese National Health Commission. On March 11, 2020, the French government announced the launch of a clinical trial of treatment for pneumonia caused by SARS-CoV-2 to test the effectiveness of four different treatments. Inspired by the French clinical trial, we divided patients into four groups: the high-flow oxygen therapy group, the low-flow oxygen therapy group, the LPV/r group, and the interferon-alpha add LPV/r group.

Ethics approval and consent to participate: The study was approved by the Research Ethics Committee of Wuhan Pulmonary Hospital and Xin Hua Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Written informed consent was waived by the Ethics Commission of the designated hospital for this retrospective study. For patients whose data were collected, the Ethics Committee of Shanghai Jiao Tong University School of Medicine approved the Research Ethics Committee of Wuhan Pulmonary Hospital and Xin Hua Hospital a retrospective study. Written informed consent was obtained from all patients or their legal guardians.

2.2 Data collection

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records. The data were reviewed by a trained team of physicians.

2.3 Definition

The date of disease onset was defined as the day when the symptom was noticed. Based on the epidemiological definition of the course, we did not simply take discharge as the endpoint of the survivor’s course, but for the first time the nucleic acid negative time after the patient’s symptoms improve (excluding the delay in hospitalization due to other diseases and the interval wait for discharge). For non-survivors, the end time of the course is the time of death. The course of COVID-19 was accurately recorded. According to the oxygen inhaled per minute, we divided oxygen inhalation therapy into low flow 1–3 L/min and high flow 4–8 L/min.

2.4 Statistical analysis

Continuous and categorical variables were presented as median (interquartile range) and n (%), respectively. A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using the SPSS (version 22.0). Cumulative rates of in-hospital death were determined using the Kaplan–Meier method. The risk factors and corresponding hazard ratios (HRs) were calculated using the Cox proportional hazard model.

3 Results

3.1 Baseline characteristics

We included 185 inpatients in the final analysis. Forty-three patients died during hospitalization and 142 were discharged. The median age was 62 years, the number of people in each age subgroup is 42 (22.7%) for <50 years, 128 (69.2%) for 50–70 years, and 15 (8.1%) for ≥75 years, and 50.8% were males. The median body mass index (BMI) was 22.96 and 119 (64.3%) cases were classified as severe (i.e., dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24–48 h) at admission, among whom 81 (57%) survived and 38 (88.4%) died. Course of disease was 21 (16–24) days for survivors and 25 (18–31) days for non-survivors (p value = 0.001). More than half of the patients presented with fever (162 [87.6%]), dry cough (96 [51.9%]), and fatigue (98 [53.0%]). Other symptoms include chest stuffiness (70 [37.8%]), poor appetite (67 [36.2%]), sputum production (63 [34.1%]), shortness of breath (57 [30.8%]), myalgia (53 [28.6%]), diarrhea (35 [18.9%]), headache (31 [16.8%]), nausea and vomiting (21 [11.4%]), hemoptysis (12 [6.5%]), nasal congestion (10 [5.4%]), and pharyngalgia (7 [3.8%]). Patients with preexisting comorbidities conditions are as follows: 22.3% for diabetes, 37.8% for hypertension, 12.4% for cardiovascular disease, 13.5% for hyperlipemia, 3.8% for chronic obstructive pulmonary disease, 3.2% for chronic kidney disease, 4.3% for cerebrovascular disease, 4.9% for chronic liver...
Table 1: Baseline characteristics

|                                | Total (n, %) | Survivor (n, %) | Non-survivor (n, %) | p value |
|--------------------------------|-------------|----------------|--------------------|---------|
|                                | 185         | 142            | 43                 |         |
| Age, year                      |             |                |                    |         |
|                               | 62.00 (50.00–68.00) | 57.00 (49.00–65.75) | 69.00 (64.50–72.00) | <0.001  |
| Male                           | 94 (50.8%)  | 64 (45.1%)     | 30 (69.8%)         | 0.005   |
| Female                         | 91 (49.2%)  | 78 (54.9%)     | 13 (30.2%)         |         |
| BMI                            | 22.96 (21.05–25.30) | 22.86 (20.70–25.29) | 23.44 (21.77–25.33) | 0.558   |
| Smoking history                | 27 (14.6%)  | 16 (11.3%)     | 11 (25.6%)         | 0.020   |
| History of surgery             | 53 (28.6%)  | 41 (28.9%)     | 12 (27.9%)         | 0.902   |
| Drug allergy history           | 14 (7.6%)   | 10 (7%)        | 4 (9.3%)           | 0.742   |
| Severe disease, %              | 119 (64.3%) | 81 (57%)       | 38 (88.4%)         | <0.001  |
| Course of disease              | 21.00 (16.00–26.00) | 21.00 (16.00–24.00) | 25.00 (18.00–31.00) | 0.001   |
| **Signs and symptoms**         |             |                |                    |         |
| Fever, >37.3°C                 | 162 (87.6%) | 122 (85.9%)    | 40 (93%)           | 0.216   |
| Nasal congestion               | 10 (5.4%)   | 9 (6.3%)       | 1 (2.3%)           | 0.803   |
| Fatigue                        | 98 (53.0%)  | 75 (52.8%)     | 23 (53.5%)         | 0.938   |
| Pharyngalgia                   | 7 (3.8%)    | 7 (4.9%)       | 0 (0.0%)           | 0.204   |
| Chest stuffiness               | 70 (37.8%)  | 51 (35.9%)     | 19 (44.2%)         | 0.185   |
| Shortness of breath            | 57 (30.8%)  | 38 (26.8%)     | 19 (44.2%)         | 0.030   |
| Cough                          | 96 (51.9%)  | 71 (50%)       | 25 (58.1%)         | 0.349   |
| Sputum production              | 63 (34.1%)  | 50 (35.2%)     | 13 (30.2%)         | 0.896   |
| Hemoptysis                     | 12 (6.5%)   | 8 (5.6%)       | 4 (9.3%)           | 0.478   |
| Myalgia                        | 53 (28.6%)  | 43 (30.3%)     | 10 (23.3%)         | 0.612   |
| Headache                       | 31 (16.8%)  | 27 (19.0%)     | 4 (9.3%)           | 0.135   |
| Poor appetite                   | 67 (36.2%)  | 45 (31.7%)     | 22 (51.2%)         | 0.020   |
| Nausea and vomiting            | 21 (11.4%)  | 15 (10.6%)     | 6 (14.0%)          | 0.539   |
| Diarrhoea                      | 35 (18.9%)  | 24 (16.9%)     | 11 (25.6%)         | 0.203   |
| Heart rate at admission, >100 bpm | 76.00 (65.00–100.00) | 76.00 (65.00–100.00) | 78.00 (68.00–102.00) | 0.226   |
| Systolic blood pressure at admission, >130 mmHg | 121.00 (111.50–133.50) | 121.00 (113.00–133.00) | 118.50 (107.50–137.25) | 0.590   |
| **Comorbidities**              |             |                |                    |         |
| Any comorbidity                | 63 (34.1%)  | 45 (31.7%)     | 18 (41.9%)         | 0.218   |
| Diabetes                       | 41 (22.3%)  | 23 (16.3%)     | 18 (41.9%)         | 0.002   |
| Hypertension                   | 70 (37.8%)  | 42 (29.6%)     | 28 (65.1%)         | <0.001  |
| Cardiovascular disease         | 23 (12.4%)  | 11 (7.7%)      | 12 (27.9%)         | <0.001  |
| Hyperlipemia                   | 25 (13.5%)  | 25 (17.6%)     | 0 (0.0%)           | 0.003   |
| Chronic obstructive pulmonary disease | 7 (3.8%)    | 4 (2.8%)       | 3 (7.0%)           | 0.210   |
| Chronic kidney disease         | 6 (3.2%)    | 3 (2.1%)       | 3 (7.0%)           | 0.139   |
| Cerebrovascular disease        | 8 (4.3%)    | 5 (3.5%)       | 3 (7.0%)           | 0.391   |
| Tumor                          | 11 (5.9%)   | 10 (7.0%)      | 1 (2.3%)           | 0.462   |
| Chronic liver disease          | 9 (4.9%)    | 8 (5.6%)       | 1 (2.3%)           | 0.687   |
| **Complications**              |             |                |                    |         |
| Hypoproteinemia                | 53 (28.6%)  | 35 (24.6%)     | 18 (41.9%)         | 0.029   |
| Respiratory failure            | 39 (21.1%)  | 13 (9.2%)      | 26 (60.5%)         | <0.001  |
| Acute respiratory distress syndrome | 33 (17.8%)  | 8 (5.6%)       | 25 (58.1%)         | <0.001  |
| Liver dysfunction              | 64 (34.6%)  | 48 (33.8%)     | 16 (37.2%)         | 0.681   |
| Electrolyte disturbances       | 59 (31.9%)  | 40 (28.2%)     | 19 (44.2%)         | 0.048   |
| Acute kidney injury            | 10 (5.4%)   | 0 (0.0%)       | 10 (23.3%)         | <0.001  |
| **Laboratory findings**        |             |                |                    |         |
| White blood cell count, ×10⁹/L |             |                |                    |         |
| <4                             | 5.98 (3.91–9.54) | 5.43 (3.69–8.57) | 8.86 (5.37–12.93) | <0.001  |
| 4–10                           | 45 (46.9%)  | 40 (31.5%)     | 5 (12.5%)          | <0.001  |
| >10                            | 89 (53.3%)  | 70 (55.1%)     | 19 (47.5%)         |         |
| Monocytes count, ×10⁹/L         |             |                |                    |         |
| >0.6                           | 0.32 (0.20–0.43) | 0.31 (0.20–0.41) | 0.34 (0.26–0.47) | 0.094   |
| 3–10                           | 14 (8.4%)   | 10 (7.9%)      | 4 (10%)            | 0.745   |
| Mononuclear cell ratio         |             |                |                    |         |
| <3                             | 5.45 (3.32–7.88) | 5.87 (3.62–8.00) | 4.00 (2.48–6.85) | 0.014   |
| 3–10                           | 37 (22.3%)  | 22 (17.5%)     | 15 (37.5%)         | 0.017   |

(Continued)
3.2 Association of treatments with in-hospital death

The in-hospital death occurred in 43 (23.2%) patients in our study. Kaplan–Meier analysis demonstrated that mortality was higher in older patients \( (p = 0.001) \), higher in men than in women \( (p = 0.021) \), and lower in the low-flow oxygen therapy group than in the non-low-flow oxygen therapy group. BMI had no influence on mortality \( (p = 0.058) \), as well as high flow oxygen therapy, LPV/r therapy, and interferon-alpha add LPV/r therapy (Figure 1). \( p \) values of each group are as follows: high-flow oxygen therapy group \( (p = 0.799) \), low-flow oxygen therapy group \( (p = 0.003) \), the LPV/r group \( (p = 0.888) \), and the interferon-alpha add LPV/r group \( (p = 0.575) \). Cox proportional hazard regression confirmed that the low-flow oxygen therapy was an independent
protective factor for in-hospital death after adjusting for age, gender, and BMI (Table 2): the high-flow oxygen therapy group (HR: 0.909, 95% CI: 0.479–1.724, p = 0.770), the low-flow oxygen therapy group (HR: 0.369, 95% CI: 0.170–0.801, p = 0.012), the LPV/r group (HR: 0.798, 95% CI: 0.252–2.524, p = 0.701), the interferon-alpha add LPV/r group (HR: 1.556, 95% CI: 0.641–3.777, p = 0.328), gender (HR: 2.105, 95% CI: 1.031–4.295, p = 0.041), age (HR: 1.084, 95% CI: 1.042–1.127, p < 0.001), and BMI (HR: 1.093, 95% CI: 0.979–1.219, p = 0.114).

### Table 2: Cox proportional hazard regression confirmed that the low-flow oxygen therapy was independent protective factor for in-hospital death after adjusting for age, gender, and BMI

| All-cause mortality                      | HR (95% CI) | p value |
|-----------------------------------------|-------------|---------|
| Gender (male vs female)                 | 2.105 (1.031–4.295) | 0.041   |
| Age (years)                             | 1.084 (1.042–1.127) | <0.001  |
| BMI                                     | 1.093 (0.979–1.219) | 0.114   |
| High flow oxygen therapy                | 0.909 (0.479–1.724) | 0.770   |
| Low flow oxygen therapy                 | 0.369 (0.170–0.801) | 0.012   |
| LPV/r                                   | 0.798 (0.252–2.524) | 0.701   |
| Interferon add LPV/r                    | 1.556 (0.641–3.777) | 0.328   |

4 Discussion

In this retrospective study, 185 patients with confirmed COVID-19 admitted to Wuhan Pulmonary Hospital from January 1 to February 29, 2020, were enrolled. We selected several types of antiviral drugs that are now clinically concerned and applied to clinical treatment and divided subjects into two groups: the LPV/r group and the interferon-alpha add LPV/r group. In addition to the above two treatment methods, we studied the correlation between high-flow oxygen therapy and low-flow oxygen therapy with in-hospital mortality of COVID-19 patients. Results showed that mortality was higher in older patients, higher in men than in women, and lower in the low-flow oxygen therapy group than in the non-low-flow oxygen therapy group. BMI had no influence on mortality, as well as high flow oxygen therapy, LPV/r therapy, and interferon-alpha add LPV/r therapy.
China also indicated that the treatment of LPV/r is ineffective for COVID-19 [7]. Interferon is a biological response regulator. Interferon has the effect of antiviral enhancement of immunity and is widely used in clinical antiviral therapy. The combination of interferon and LPV/r is often used in the clinical antiviral therapy, but in this study, the treatment of interferon-alpha add LPV/r had no effect on hospitalization mortality in patients with COVID-19. The study gave the conclusions that the mortality was lower in the low-flow oxygen therapy group than in the group without using low-flow oxygen therapy, and the mortality of inpatients with COVID-19 was not affected by high-flow oxygen therapy. It is not difficult to understand that patients with low-flow oxygen therapy were less ill, so the prognosis is better. In addition, our study found that mortality was higher in older patients, higher in men than in women. BMI had no influence on mortality. The same conclusion has been drawn from many existing studies [8–12]. Because advanced age is an independent risk factor and older patients may have multi-system underlying diseases and a decline in autoimmunity, both will lead to high mortality after suffering from COVID-19. Many studies on the clinical characteristics of COVID-19 have also confirmed that the mortality of COVID-19 in male patients is higher than that in female patients. BMI is an important international measure of obesity and health but had no effect on mortality in this study. There were some limitations in this study. First, this is a single-center retrospective observational study with limitations of study number and region; thus, the multicenter and prospective studies should be performed to further clarify the correlation between drug therapy and the mortality rate of COVID-19 inpatients. Second, the number of COVID-19 case in this study is still less; the large sample study is more likely to reduce the potential bias of the sample itself. Although we tried to adjust for many confounders, there may exist confounders either unmeasured or unknown that could explain our observed results.

5 Conclusions

The mortality was higher in older patients, higher in men than in women, and lower in the low-flow oxygen therapy group than in the non-low-flow oxygen therapy group. BMI had no influence on mortality, as well as high flow oxygen therapy, LPV/r therapy, and interferon-alpha add LPV/r therapy. The low-flow oxygen therapy was an independent protective factor for in-hospital death after adjusting for age, gender, and BMI.

Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| BMI          | body mass index |
| CI           | confidence interval |
| COVID-19     | coronavirus disease 2019 |
| HR           | hazard ratio |
| SARS-CoV-2   | severe acute respiratory syndrome coronavirus 2 |
| WHO          | World Health Organization |

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Author contributions: L. Han, G. Chen, and Y. An designed the study. L. Han, Y. An, Y. Chen, X. Lan, and Y. Wang collected the data. L. Han, Y. Chen, and C. Xu prepared the figures and tables. X. Li, C. Ji, L. Han, Y. Chen, and C. Xu contributed analytical tools. L. Han and Y. An wrote the paper. Y. Cai, H. Huang, and L. Yang conceived the project and supervised and coordinated all the work. All authors read and approved the final article.

Conflict of interest: The authors declare that they have no competing interest.

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