Risk Factors for Severe Cases of Inpatients with COVID-19 in Henan Province, China: A Multicenter Retrospective Cohort Study

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Research

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Abstract

Rationale: Our pilot study suggested that coexisting cerebrovascular diseases on admission with respiratory rate greater than 24 breaths per min, and LDH greater than 245U/L may be risk factors for death among hospitalized COVID-19 patients in Henan province, China. Whether these risk factors are associated with severe illness in inpatients with COVID-19 is yet unclear.

Background: To explore risk factors associated with severe cases in hospitalized COVID-19 patients in Henan province, China

Methods: This study was a multicenter retrospective cohort study. A total of 112 patients with COVID-19 were admitted to Henan Provincial People's Hospital and Anyang Infectious Disease Hospital from February 3 to March 31, 2020. These patients were confirmed by SARS-CoV-2 nucleic acid test. Demographic, epidemiological, clinical and laboratory data, imaging changes, and definite severity typing of illness (severe cases or non-severe cases) were extracted from electronic medical records and compared between severe cases and non-severe cases. Univariate and multivariate logistic regression methods were used to explore the risk factors associated with in-hospital severe cases.

Results: A total of 104 patients (55 from Henan Provincial People's Hospital and 57 from Anyang Infectious Disease Hospital) were included in this study, of whom 62 (59.6%) were non-severe cases and 42 (40.4%) were severe cases. Multivariate regression showed increasing odds of in-hospital severe cases associated with age ≥65 years (odds ratio 6.535 [95% CI, 1.365-31.295]; p=0.019), coexisting diabetes (11.165 [1.142-109.172], p=0.038), cough (17.494 [2.971-102.995]; p=0.002), increased procalcitonin (0.05-0.25ng/L) (9.640 [2.162-42.982]; p=0.003) and LDH greater than 245U/L (11.040 [2.661-45.808]; p=0.001) on admission.

Conclusions: Age ≥65 years, coexisting diabetes, cough, increased PCT, and LDH greater than 245U/L on admission may be risk factors for severe cases among hospitalized COVID-19 patients in Henan Province, China.

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus (CoV) SARS-CoV-2 and is causing substantial morbidity and mortality [1]. A total of 18761363 confirmed cases and 330279 deaths have been reported only in the United States as of December 26th, 2020 [2]. According to the WHO and China's joint investigation team, the fatality rate was 5.8% in Wuhan and 0.7% in the rest of China [3]. Outside China, COVID-19 mortality varies from country to country, with Bangladesh reporting the highest (11.36%) and Israel the lowest (0.3%) [4].

The clinical manifestations of COVID-19 are varied and include the asymptomatic carrier status, acute respiratory disease (ARD), and pneumonia [5, 6]. Patients with pneumonia have respiratory symptoms and positive findings in chest imaging. Severe pneumonia can present as acute respiratory distress syndrome (ARDS) leading to severe hypoxia, respiratory failure, multi-organ failure, shock and death [5, 7].

There are four clinical types of COVID-19: mild, common, severe, and critical [8]. According to a report by the Chinese Center for Disease Control and Prevention, the estimated proportion of cases of varying severity is 81% for mild and common cases, 5% for severe cases and 14% for critical severe cases [9].

To reduce mortality from COVID-19, research works focusing on the identification of risk factors associated with death or severe cases from COVID-19 is needed. It is well known that patients with severe illness have a high mortality rate, while non-severe cases have a relatively low mortality rate. Studying the risk factors associated with severe illness can lead to earlier intervention and improved outcomes. The risk factors associated with death of patients with COVID-19 have been studied widely. Unfortunately, the risk factors associated with severe illness are frequently overlooked or less reported. The majority of COVID-19 deaths are generally considered to be among the elderly or those patients with underlying diseases, including cardiovascular disease, diabetes, chronic lung disease, hypertension and cancer [9]. In a recent study involving 191 inpatients confirmed as COVID-19, Chinese scholars found that older age, high SOFA score, and D-dimer greater than 1µ g/L were independent risk factors for COVID-19 [10]. This study also found that some laboratory tests, such as lymphocytopenia, an increase in serum lactate dehydrogenase (LDH), cardiac troponin I (CTNI) and interleukin-6 (IL-6), were more common in critically ill patients [10].

Whether the factors mentioned above are also associated with severe illness in patients with COVID-19 is not clear. Therefore, in this study demographic, epidemiological, clinical, and laboratory data, imaging changes, and final outcome of hospitalized patients confirmed by SARS-CoV-2 nucleic acid from designated hospitals in Henan province of China, were investigated retrospectively to explore risk factors associated with severe cases of COVID-19 patients so as to help the clinician in early recognition and intervention, and to improve the prognosis.

Patients And Methods

Patients and study design
A total of 112 patients with COVID-19 and hospitalized in Henan People's Hospital and Anyang Infectious Disease Hospital between February 3, 2020 and March 31, 2020 were included in this retrospective cohort study, including 55 cases from Henan People's Hospital and 57 cases from Anyang Infectious Disease Hospital. SARS-CoV-2 nucleic acid test were confirmed in all patients, who had a definite illness severity typing and outcome of death or survival within the study period. A final sum of 104 patients were enrolled in our study.

According to the Chinese management guideline for COVID-19 (version 7.0), clinical classification of COVID-19 illness was defined as following[8] in our study: severe cases included severe and critical cases, on the other hand, mild and normal cases were defined as non-severe cases.

Data Collection

Clinical data of interest, including age, sex, clinical manifestations, laboratory, imaging, treatment, outcome, and epidemiological data were collected. All data were extracted by two researchers alone in the same standard form.

Laboratory Procedures

As it was reported that the laboratory confirmation of SARS-CoV-2 infection was detected SARS-CoV-2 in respiratory specimens by real-time RT-PCR [11]. All the enrolled patients underwent nucleic acid detection by Throat-swab. After clinical symptoms relieved, the re-examination of SARS-CoV-2 PCR were done every other day in order to obtain qualitative data.

Statistical analysis

Continuous and categorical variables were expressed as median (IQR) and percentages, the Mann-Whitney U test, chi-square test, or Fisher’s exact test were performed to compared differences between non-severe cases and severe cases. Univariate and multivariate logistic regression were used to identify risk factors. The univariate logistic regression was performed first, the variables were excluded if the differences were small and the number of events was too small to calculate odds ratios. The rest factors were analysed in the multivariate analysis. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software version 22.0(SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the patients

A total of 112 confirmed COVID-19 patients were transferred to Henan Provincial People's Hospital (55 cases) or Anyang Infectious Disease Hospital (57 cases) for treatment. Excluding 8 cases with incomplete clinical data, 104 cases were included as study subjects. All subjects had a clear severity typing during the study period with 62 (59.6%) non-severe cases and 42 (40.4%) severe cases. The median age of the study subjects was 50.5 years (IQR 42–59), and most of the subjects were females (56, 53.8%). The proportion of people aged ≥ 60 years in severe cases was higher than that in non-severe cases (42.9% vs. 9.7%, p < 0.05). The median days from onset to diagnosis was 4 (3–7) days in non-severe cases and 7 (4–10) days in severe cases (p < 0.05; Table 1).

Table 1: Demographic, clinical, laboratory, and radiographic findings of inpatients with COVID-19 on admission
|                              | Total | Non-severe cases | Severe cases | P   |
|------------------------------|-------|------------------|--------------|-----|
|                              | n=104 | n=62             | n=42         |     |
| Demographic and clinical characteristics |       |                  |              |     |
| Age/years                    | 50.5(42-59) | 48(34-55.2)      | 57.5(47.8-71.3) | <0.001 |
| Age/years ≥60                | 24(23.1%) | 6(9.7%)          | 18(42.9%)    | <0.001 |
| Sex                          |       |                  |              |     |
| Male                         | 48(46.2) | 31(50.0%)        | 17(40.5%)    | >0.05 |
| Female                       | 56(53.8) | 31(50%)          | 25(59.5%)    |     |
| Time from illness onset to diagnosis, days | 5.5(3-8.75) | 4(3-7)           | 7(4-10)     | <0.05 |
| Exposure history             | 95(91.3) | 54(87.1%)        | 41(97.6%)    | >0.05 |
| Coexisting underlying diseases at admission |       |                  |              |     |
| Diabetes                     | 18(17.3%) | 2(3.2%)          | 6(38.1%)     | <0.001 |
| Hypertension                 | 30(28.8%) | 16(25.8%)        | 14(33.3%)    | >0.05 |
| Coronary heart disease       | 9(8.7%) | 3(4.8%)          | 6(14.3%)     | >0.05 |
| Cerebrovascular disease      | 9(8.7%) | 3(4.8%)          | 6(14.3%)     | >0.05 |
| Hepatopathy                  | 4(3.8%) | 3(4.8%)          | 1(2.4%)      | >0.05 |
| Pulmonary disease            | 9(8.7%) | 3(4.8%)          | 6(14.3%)     | >0.05 |
| Tumor                        | 2(1.9%) | 1(1.6%)          | 1(2.4%)      | >0.05 |
| Fever (temperature ≥37.3°C)  | 87(83.7%) | 52(83.9%)       | 35(83.3%)    | >0.05 |
| Headache                     | 11(10.06%) | 7(11.3%)       | 4(9.3%)      | >0.05 |
| Muscular soreness            | 16(15.4%) | 8(12.9%)        | 8(19%)       | >0.05 |
| Fatigue                      | 46(44.2%) | 25(40.3%)       | 21(50.0%)    | >0.05 |
| Rhinobyon                    | 7(6.7%) | 6(9.7%)          | 1(2.4%)      | >0.05 |
| Rhinorrhoea                  | 5(4.8%) | 3(4.8%)          | 2(4.8%)      | >0.05 |
| Sore throat                  | 11(10.6%) | 9(14.5%)       | 2(4.8%)      | >0.05 |
| Cough                        | 62(59.6%) | 28(45.2%)       | 34(81%)      | <0.001 |
| Sputum                       | 30(28.8%) | 10(16.1%)       | 20(47.6%)    | <0.001 |
| Dyspnea                      | 33(31.7%) | 5(8.1%)         | 28(66.7%)    | <0.001 |
| Diarrhoea                    | 8(7.7%) | 4(6.5%)          | 4(9.5%)      | >0.05 |
| Disturbance of consciousness | 7(6.7%) | 0(0.0%)         | 7(16.7%)     | <0.05 |
| Respiratory rate >24 breaths per min | 5(4.8%) | 1(1.6%) | 4(9.5%) | >0.05 |
| Pulse ≥100 beats per min     | 14(13.5%) | 7(11.3%)        | 7(16.7%)     | >0.05 |
| Systolic pressure mmHg       | 123(117-134) | 120(118-131) | 127(114-141) | >0.05 |
| **Diastolic pressure** (mmHg) | 79(70-84) | 80(72-85) | 76(61-83) | >0.05 |
|---|---|---|---|---|
| **Death** | 7(6.7%) | 0(0.0%) | 7(16.7) | <0.05 |

**Laboratory findings**

| **Laboratory** | **Value** | **Value** | **Value** | **p** |
|---|---|---|---|---|
| **White blood cell count**, ×10^9/L | 4.71(3.71-6.67) | 4.5(3.4-5.8) | 5.6(3.8-8.1) | <0.05 |
| **Lymphocyte count**, ×10^9/L | 1.13(0.87-1.55) | 1.25(0.91-1.58) | 1.05(0.82-1.41) | >0.05 |
| **Monocyte count**, ×10^9/L | 0.43(0.28-0.54) | 0.42(0.28-0.51) | 0.45(0.29-0.62) | >0.05 |
| **Procalcitonin**, ng/mL | <0.001 | ≤0.05 | 68(65.4%) | 52(83.9%) | 16(38.1%) |
| | <0.25 | 27(26%) | 9(14.5%) | 18(42.9%) |
| | <0.5 | 5(4.8%) | 0(0.0%) | 5(11.9%) |
| | ≥0.5 | 4(3.8%) | 1(1.6%) | 3(7.1%) |
| **CRP, mg/L** | 18.0(7.0-62.9) | 14.2(3.4-46.2) | 31.3(10.3-85.7) | <0.05 |
| **ALT, U/L** | 19(18.3%) | 11(17.7%) | 8(19%) | >0.05 |
| >40 | 23(22.1%) | 12(19.4%) | 11(26.2%) | >0.05 |
| **AST, U/L** | 32(30.8%) | 11(17.7%) | 21(50%) | <0.05 |
| >40 | 11(10.6%) | 6(9.7%) | 5(11.9%) | >0.05 |
| **TBIL, umol/L** | 11.2(8.8-15.6) | 11.6(9.1-17.5) | 10.4(7.0-14.1) | >0.05 |
| **LDH, U/L** | 32(30.8%) | 11(17.7%) | 21(50%) | <0.05 |
| >245 | 11(10.6%) | 6(9.7%) | 5(11.9%) | >0.05 |
| **CK, umol/L** | 3.9(3.1-5.0) | 3.6(2.9-4.5) | 4.3(3.2-5.7) | <0.05 |
| >185 | 55.0(47.2-65.0) | 59.5(50.0-72.0) | 50.5(44.8-56.0) | <0.05 |
| **BUN, mmol/L** | 5.9(4.8-7.3) | 5.5(4.8-6.6) | 6.4(4.8-9.5) | <0.05 |
| **CREA, mmol/L** | 86(82.7%) | 51(82.3%) | 35(83.3%) | >0.05 |
| **d-dimer, ug/L** | 34(32.7%) | 15(24.2%) | 19(45.2%) | <0.05 |
| >0.5 | 24(23.1%) | 5(8.1%) | 19(45.2%) | <0.05 |
| **Blood glucose, mmol/L** | 17(14-22) | 16(12-19) | 20(15-25) | <0.05 |

**Duration of viral shedding after COVID-19 onset, days**

| **Duration** | **Value** | **Value** | **Value** |
|---|---|---|---|
| 17(14-22) | 16(12-19) | 20(15-25) | <0.05 |

**Imageological change**

**Sites of imaging abnormalities**

| **Lesion** | **Value** | **Value** | **Value** |
|---|---|---|---|
| No lesion on either side | 8(7.7%) | 7(11.3%) | 1(2.4%) | >0.05 |
| Unilateral lesion | 10(9.6%) | 7(11.3%) | 3(7.1%) |
| Bilateral lesions | 86(82.7%) | 48(77.4%) | 38(90.5%) |

**Morphology of the imaging changes**

| **Change** | **Value** | **Value** | **Value** |
|---|---|---|---|
| Ground-glass opacity | 86(82.7%) | 51(82.3%) | 35(83.3%) | >0.05 |
| Consolidation | 34(32.7%) | 15(24.2%) | 19(45.2%) | <0.05 |
| Interstitial change | 24(23.1%) | 5(8.1%) | 19(45.2%) | <0.05 |
| Other changes | 5(4.8%) | 1(1.6%) | 4(9.5%) | >0.05 |
Data are median (IQR) or n (%). p values were calculated by Mann-Whitney U test, χ² test, or Fisher’s exact test, as appropriate.

COVID-19: coronavirus disease 2019. CRP: C reactive protein, ALT: alanine aminotransferase, AST: aspartic transaminase, TBIL: total bilirubin, LDH: lactate dehydrogenase, CK: creatinine kinase, BUN: blood urea nitrogen, CREA: creatinine.

Eighty one patients had a comorbidity, with hypertension being the most common (30 [28.8%] patients), followed by diabetes (18 [17.3%] patients), coronary heart disease (9 [8.7%] patients), cerebrovascular disease (9 [8.7%] patients). The proportion of severe cases with diabetes was higher than that of non-severe cases (38.1% vs. 3.2%, p < 0.001). There was no difference in the proportion of hypertension, coronary heart disease and cerebrovascular disease between the non-severe group and the severe group (all p > 0.05). Fever (83.7%), cough (59.6%) and fatigue (44.2%) were common symptoms at admission. Compared with non-severe group, there was no significant difference in severe group presented with symptoms at admission such as fever, headache, muscle soreness, fatigue, nasal congestion, runny nose, sore throat, diarrhea, respiratory rate, pulse, and blood pressure (all p > 0.05). The proportion of inpatients with cough, sputum, dyspnea, disturbance of consciousness were higher in severe group than non-severe group (81.0% vs. 45.2%), (47.6% vs. 16.1%), (66.7% vs. 8.1%), and (16.7% vs. 0.0%), respectively (all p < 0.05; Table 1).

The death proportion in the severe group was higher than that in the non-severe group (16.7% vs. 0.0%, p < 0.05) (Table 1).

Comparison of laboratory findings between non-severe group and severe group

The count of white blood cell (WBC) (×10⁹/L) 5.6 [3.8–8.1] vs. 4.5 [3.4–5.8]) and the levels of serum C-reactive protein (CRP) (mg/L) (31.3 [10.30-85.72] vs. 14.23 [3.40–46.20]), blood urea nitrogen (BUN) (mmol/L) (4.31 [3.23–5.70] vs. 3.57 [2.87–4.46]), blood glucose (mmol/L) (6.44 [4.80–9.53] vs. 5.57 [4.78–6.56]), and proportion of inpatients with LDH greater than 245 U/L (50.0% vs. 11.7%), and D-dimer greater than 0.5µg/L (47.6% vs. 14.5%) were higher in severe group than non-severe group (all p < 0.05). The level of serum creatinine (CREA) (mg/L) (50.50 [44.75-56.00] vs. 59.5 [50.00–72.00]) was lower in severe group than non-severe group (p < 0.05). There was no difference in the count of lymphocyte (L), mononuclear cell (M), total bilirubin (TBIL), and the proportion of inpatients with alanine aminotransferase (ALT) greater than 40 U/L, Aspartic transaminase (AST) greater than 40 U/L, creatine phosphokinase (CK) greater than 185µ mol/L between the two groups (all p > 0.05; Table 1).

The median duration of viral shedding in severe group were longer than non-severe group (20 [15–25] vs. 16 [12–19]) (p < 0.05).

Comparison of imaging changes between non-severe group and severe group

Compared with non-severe group, there were no difference in the proportion of site, ground-glass opacity and other imaging abnormalities in severe group (all p > 0.05). The proportion of inpatients with consolidation and interstitial change were higher in severe group than non-severe group (45.2% vs. 24.2%) and (45.2% vs. 8.1%), respectively (all p < 0.05; Table 1).

Analysis Of Risk Factors Associated With Severe Cases

In univariate analysis, odds of severe cases was higher in patients with age ≥ 65 years, coexisting diabetes, cough, increased PCT (0.05–0.25 ng/L), and LDH greater than 245 U/L on admission (all p < 0.05, Table 2). The time from illness onset to diagnosis, d-dimer > 0.5µ g/L, sputum, dyspnea, WBC count, CRP, CREA, blood glucose, duration of viral shedding after COVID-19 onset, consolidation and interstitial change were also associated with severe cases (all p < 0.05, Table 2).
| Demographics and clinical characteristics | Univariable OR(95% CI) | P   | Multivariable OR(95% CI) | p   |
|------------------------------------------|------------------------|-----|--------------------------|-----|
| Age, years                               | 7.000                  | 0.000 | 6.535                   | 0.019 |
| ≥ 60                                     | (2.473–19.811)         |     | (1.365–31.295)          |     |
| Sex                                      | 0.680                  | 0.340 | ..                      | ..   |
|                                          | (0.308–1.501)          |     |                         |     |
| Time from illness onset to Diagnosis, days* | 1.139                  | 0.013 | ..                      | ..   |
|                                          | (1.028–1.262)          |     |                         |     |
| Exposure history                         | 6.074                  | 0.095 | ..                      | ..   |
|                                          | (0.730–50.509)         |     |                         |     |

| Coexisting underlying diseases at admission | Univariable OR(95% CI) | P   | Multivariable OR(95% CI) | p   |
|--------------------------------------------|------------------------|-----|--------------------------|-----|
| Hypertension                               | 1.437                  | 0.407 | ..                      | ..   |
|                                           | (0.610–3.388)          |     |                         |     |
| Diabetes                                   | 18.462                 | 0.000 | 11.165                   | 0.038 |
|                                           | (3.957–86.143)         |     | (1.142–109.172)         |     |
| Coronary heart disease                     | 3.278                  | 0.108 | ..                      | ..   |
|                                           | (0.772–13.926)         |     |                         |     |
| Cerebrovascular disease                    | 3.278                  | 0.108 | ..                      | ..   |
|                                           | (0.772–13.926)         |     |                         |     |
| Hepatopathy                                | 0.480                  | 0.531 | ..                      | ..   |
|                                           | (0.048–4.775)          |     |                         |     |
| Pulmonary disease                          | 3.278                  | 0.108 | ..                      | ..   |
|                                           | (0.772–13.926)         |     |                         |     |
| Tumor                                      | 1.488                  | 0.781 | ..                      | ..   |
|                                           | (0.090–24.465)         |     |                         |     |
| Fever (temperature ≥ 37.3 °C)              | 0.962                  | 0.942 | ..                      | ..   |
|                                           | (0.334–2.766)          |     |                         |     |
| Headache                                   | 0.827                  | 0.774 | ..                      | ..   |
|                                           | (0.226–3.023)          |     |                         |     |
| Muscular soreness                          | 1.588                  | 0.397 | ..                      | ..   |
|                                           | (0.545–4.629)          |     |                         |     |
| Fatigue                                    | 1.480                  | 0.330 | ..                      | ..   |
|                                           | (0.672–3.259)          |     |                         |     |

OR: odds ratio; CRP: C reactive protein, ALT: alanine aminotransferase, AST: Aspartic transaminase, TBIL: total bilirubin, LDH: lactate dehydrogenase, CK: creatinine kinase, BUN: blood urea nitrogen, CREA: creatinine. * Per 1 unit increase
| Condition                      | Univariable OR(95% CI) | $P$  | Multivariable OR(95% CI) | $p$  |
|-------------------------------|------------------------|------|--------------------------|------|
| Rhinobyon                    | 0.228 (0.026–1.964)    | 0.178 | ..                       | ..   |
| Rhinorrhea                   | 0.983 (0.157–6.153)    | 0.986 | ..                       | ..   |
| Sore throat                   | 0.294 (0.060–1.438)    | 0.131 | ..                       | ..   |
| Cough                         | 5.161 (2.060–12.928)   | 0.000 | 17.494 (2.971–102.995)   | 0.002|
| Sputum                        | 4.727 (1.906–11.722)   | 0.001 | ..                       | ..   |
| Dyspnea                       | 22.8 (7.463–69.656)    | 0.000 | ..                       | ..   |
| Diarrhoea                     | 1.526 (0.360–6.474)    | 0.566 | ..                       | ..   |
| Disturbance of consciousness  | 2861698293 (0–.)       | 0.999 | ..                       | ..   |
| Respiratory rate              |                        |      |                          |      |
| > 24 breaths per min          | 6.421 (0.692–59.621)   | 0.102 | ..                       | ..   |
| Pulse ≥ 100 beats per min     | 1.571 (0.508–4.865)    | 0.433 | ..                       | ..   |
| Systolic pressure, mmHg *     | 1.012 (0.998–1.038)    | 0.331 | ..                       | ..   |
| Diastolic pressure, mmHg *    | 0.970 (0.938–1.003)    | 0.070 | ..                       | ..   |

**Laboratory findings**

| Test                          | Univariable OR(95% CI) | $P$  | Multivariable OR(95% CI) | $p$  |
|-------------------------------|------------------------|------|--------------------------|------|
| White blood count, 10^9/L *   | 1.276 (1.056–1.542)    | 0.012 | ..                       | ..   |
| Neutrophil count, 10^9/L *    | 0.465 (0.201–1.075)    | 0.073 | ..                       | ..   |
| Lymphocyte count, 10^9/L < 0.8| 2.143 (0.729–6.297)    | 0.166 | ..                       | ..   |

OR: odds ratio. CRP: C reactive protein, ALT: alanine aminotransferase, AST: Aspartic transaminase, TBIL: total bilirubin, LDH: lactate dehydrogenase, CK: creatinine kinase, BUN: blood urea nitrogen, CREA: creatinine. * Per 1 unit increase
|                          | Univariable OR(95% CI) | $P$ | Multivariable OR(95% CI) | $p$ |
|--------------------------|------------------------|-----|--------------------------|-----|
| Monocyte count, ×10^9/L* | 4.172 (0.536–32.46)    | 0.172 | ..                       | ..  |
| Procalcitonin, ng/mL     | 0.001                  |     | 0.022                    |     |
| ≤ 0.05                   | 1(ref)                 |     |                          |     |
| < 0.25                   | 6.500 (2.447–17.264)   | 0.000 | 9.640 (2.162–42.982)     | 0.003|
| < 0.5                    | 5250293311 (0.000–..)  | 0.999 | 6794498033 (0.000–..)    | 0.999|
| ≥ 0.5                    | 9.750 (0.947–100.361)  | 0.056 | 16.577 (0.155–1775.468)  | 0.239|
| CRP, mg/L*               | 1.011 (1.003–1.019)    | 0.009 | ..                       | ..  |
| ALT, U/L                 | 1.091 (0.398–2.992)    | 0.866 | ..                       | ..  |
| > 40                     |                        |     |                          |     |
| AST, U/L                 | 1.479 (0.582–3.758)    | 0.411 | ..                       | ..  |
| > 185                    |                        |     |                          |     |
| TBIL, μmol/L*            | 1.000 (0.999–1.001)    | 0.965 | ..                       | ..  |
| LDH, U/L                 | 4.636 (1.906–11.279)   | 0.001 | 11.040 (2.661–45.808)    | 0.001|
| > 245                    |                        |     |                          |     |
| CK, μmol/L               | 1.261 (0.359–4.435)    | 0.717 | ..                       | ..  |
| > 185                    |                        |     |                          |     |
| BUN, mmol/L*             | 1.057 (0.961–1.164)    | 0.254 | ..                       | ..  |
| CREA, mmol/L*            | 0.967 (0.942–0.993)    | 0.013 | ..                       | ..  |
| d-dimer, ug/L            | 5.354 (2.111–13.577)   | 0.000 | ..                       | ..  |
| > 0.5                    |                        |     |                          |     |
| Blood glucose, mmol/L*   | 1.221 (1.026–1.454)    | 0.024 | ..                       | ..  |
| Duration of viral shedding after COVID-19 onset, days* | 1.006 (1.008–1.127) | 0.026 | ..                       | ..  |

OR: odds ratio, CRP: C reactive protein, ALT: alanine aminotransferase, AST: Aspartic transaminase, TBIL: total bilirubin, LDH: lactate dehydrogenase, CK: creatinine kinase, BUN: blood urea nitrogen, CREA: creatinine. * Per 1 unit increase
| Image change | Univariable OR(95% CI) | P       | Multivariable OR(95% CI) | p       |
|--------------|------------------------|---------|--------------------------|---------|
| Sites of imaging abnormalities | 0.219 | .. | .. | .. |
| No lesion on either side | 1(ref) | .. | .. | .. |
| Unilateral lesion | 0.180 | (0.021–1.531) | 0.116 | .. | .. |
| Bilateral lesions | 0.541 | (0.131–2.235) | 0.396 | .. | .. |

| Morphology of the imaging changes | Univariable OR(95% CI) | P       | Multivariable OR(95% CI) | p       |
|----------------------------------|------------------------|---------|--------------------------|---------|
| Ground-glass opacity             | 1.078 | (0.381–3.053) | 0.887 | .. | .. |
| Consolidation                    | 2.588 | (1.116–6.001) | 0.027 | .. | .. |
| Interstitial change              | 9.417 | (3.142–28.226) | 0.000 | .. | .. |
| Other changes                    | 6.421 | (0.692–59.621) | 0.102 | .. | .. |

OR: odds ratio. CRP: C reactive protein, ALT: alanine aminotransferase, AST: Aspartic transaminase, TBIL: total bilirubin, LDH: lactate dehydrogenase, CK: creatinine kinase, BUN: blood urea nitrogen, CREA: creatinine. * Per 1 unit increase

We included 104 patients with complete data (42 severe cases and 62 non-severe cases) for all the variables that make sense in the multivariate logistic regression model. We found that age ≥ 65 years (OR 6.535 [95% CI 1.365–31.295], p = 0.019), coexisting diabetes (11.165 [1.142–109.172], p = 0.038), cough (17.494 [2.971–102.995], p = 0.002), increased PCT (0.05–0.25 ng/L) (9.640 [2.162–42.982], p = 0.003) and LDH greater than 245 U/L (11.040 [2.661–45.808], p = 0.001) on admission were associated with increased odds of severe cases (Table 2).

**Discussion**

In this retrospective cohort study, logistic regression models were used to identify several independent risk factors for severe cases in inpatients with COVID-19 in Henan province, China. Specifically, age ≥ 65 years, coexisting diabetes, cough, increased PCT, and LDH greater than 245 U/L on admission were associated with higher odds of severe cases among hospitalized COVID-19 patients.

This study found that age ≥ 65 years on admission was associated with increased odds of severe cases among hospitalized COVID-19 patients. Severe SARS-CoV-2 infection can occur in any age group, but is most often associated with middle-aged and elderly people. According to a report by the Chinese Center for Disease Control and Prevention, among about 44,500 confirmed infected patients, 87% were between 30 and 79 years old, and older patients were also associated with increased mortality. The fatality rates of patients aged 70–79 and ≥ 80 years were 8% and 15%, respectively [9]. In the United States, 67% of the cases were diagnosed at the age ≥ 45, and similar to the cases in China, the elderly had the highest mortality rate with 80% of the patients dying among patients aged ≥ 65 years [12]. The findings of this study were in accord with the above reports. The mechanism by which advanced age leads to severe illness is unclear. Previous studies in
macaques inoculated with SARS-CoV found that older macaques had stronger host innate responses to virus infection than younger adults with an increase in differential expression of genes associated with inflammation and a reduction in the expression of type I interferon beta [13]. The age-dependent defects in T-cell and B-cell function and the excess production of type 2 cytokines could lead to a deficiency in control of viral replication and more prolonged proinflammatory responses potentially leading to poor outcome [14].

This study found that coexisting diabetes mellitus (DM) on admission was associated with increased odds of severe cases among hospitalized COVID-19 patients. It is now well recognized that older age and the presence of DM, hypertension, and severe obesity (BMI ≥ 40 kg/m²) increases morbidity and mortality in patients with COVID-19 [5]. Plasma glucose levels and DM are independent predictors for mortality and morbidity in patients with SARS [15]. Certain racial groups such as African Americans, Hispanics, and Native Americans are highly prone to develop DM and disparities in health care make these groups more vulnerable. Potential mechanisms that may increase the susceptibility for COVID-19 in patients with DM include: a) higher affinity cellular binding and efficient virus entry, b) decreased viral clearance, c) diminished T cell function, d) increased susceptibility to hyperinflammation and cytokine storm syndrome, and e) presence of cardiovascular disease [1]. Identification of clinical and biochemical parameters using multiomics approaches that predict severity of the COVID-19 in DM using large data sets is urgently needed.

In this study, we found that cough at admission was associated with in-hospital severe cases in patients with COVID-19. The presentation of cough often indicates that the respiratory system is involved. The mechanism of pulmonary involvement may be that SARS-CoV-2 virus enters alveolar epithelial cells by binding to ACE2 receptors and triggers a systemic inflammatory response, creating an immune dysfunction with a hyperactivity of T lymphocytes and the release of proinflammatory cytokines such as IL-2, IL-6, IL-7, MCP1 and TNF alpha [16]. If the inflammation is protective initially, it appears secondarily that most cellular and tissue lesions are more the result of hyperinflammation than of the direct effect of the virus [16]. These two phenomena may favor at the respiratory level, pulmonary lesions, by hypercapillary permeability and pulmonary edema, leading to acute respiratory distress [17]. Hyperinflammation at the systemic level may lead to vascular, thrombotic and cytokines’ toxicity phenomena, resulting in multisystemic lesions [18, 19].

This study found that increased PCT on admission was associated with increased odds of severe cases among hospitalized COVID-19 patients. PCT is an emerging prognostic marker in COVID-19. Increasing data suggest a link between serum PCT levels and disease severity in patients with COVID-19 [20, 21]. Elevated PCT was also associated with adverse outcomes (OR 13.1; 95% CI [7.37–23.1]). PCT was increased in 22.8% and 30.6% of patients with the severe course and adverse outcome, respectively [22]. PCT is increased in a subset of COVID-19 patients at risk for clinical deterioration and adverse outcome [22]. Our data are consistent with the findings mentioned above. Variance in PCT levels have previously been proposed to differentiate systemic inflammation of bacterial origin from viral origin in community acquired pneumonia and sepsis, with a significant rise indicating bacterial infection [23, 24]. Therefore, most researchers suggest that raised procalcitonin observed in COVID-19 could be due to bacterial co-infection which can cause increased severity and drives systemic sepsis. However, some researchers think that PCT levels in deteriorating patients are increased because of target organ injury. PCT is also associated with altered liver function tests, cardiac injury, and ocular symptoms [25, 26]. Patients with severe COVID-19 infection can develop immune hyperactivation and cytokine release syndrome (CRS) with a massive release of IL-6 [19]. Therefore, whether PCT levels in deteriorating patients are increased because of bacterial infections or target organ injury needs further study.

This study also found that LDH greater than 245 U/L at admission was associated with in-hospital severe cases in COVID-19 patients. LDH is widely distributed in heart, liver, lung and human tissues. Once the tissue is damaged, the serum LDH concentration increased. LDH is one of the predictor of many pulmonary inflammatory diseases, such as obstructive disease, lung infection disease and interstitial lung disease [27, 28]. This study found an association between increased LDH and severe cases in inpatients with COVID-19, which is consistent with the findings of other study [29]. The elevated LDH is due to the direct damage of lung tissue once COVID-19 infected, and on the other hand, hypoxia causes cell damage and increases the permeability of cell membrane, which aggravate the release of LDH. The continuous increase of LDH indicates the exacerbated of the disease. In the course of COVID-19, the elevated of serum LDH can not only be used as a reference index of lung damage, but also reflect the severity of the disease.

Our study is the first to focus on COVID-19 inpatients in Henan province, central China. The findings of this study may be applicable to the general population in China's most populous province. Our study is also one of the few studies on the risk factors associated with severe illness in COVID-19 inpatients, and our data are of great significance for early identification of these risk factors.

Despite the above significant findings, there were still some deficiencies in our study. First, this study was a retrospective study, and some laboratory tests that might be meaningful were not collected, such as IL-6, serum ferritin, T-lymphocyte subset, and the correlation between these indicators and severe illness was not studied as a result. Second, since some patients with incomplete data were excluded from this study, the sample size of this study was small which may limit the promotion of the conclusions of this study in the general hospitalized population. Therefore, prospective multi-center studies with large samples should be carried out in the future to further verify the conclusions of this study.
Conclusions

In summary, our study found that age $\geq 65$ years, coexisting diabetes, cough, increased PCT and LDH greater than 245 U/L may be independent risk factors for severe cases in hospitalized COVID-19 patients in Henan province, China. The recognition of these risk factors is helpful for clinicians to identify patients with poor prognosis in the early stage so as to strengthen organ monitoring and therapeutic intervention in the early stage and improve the poor prognosis.

Abbreviations

COVID-19 Coronavirus disease 2019
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
CRP C reactive protein
ALT Alanine aminotransferase
AST Aspartic transaminase
TBIL Total bilirubin
LDH Lactate dehydrogenase
CK Creatinine kinase
BUN Blood urea nitrogen
CREA Creatinine

Declarations

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Authors' contributions

ZY contributed conception and design of the study. XL, JW, KL and XL collected the data and contributed to the literature searches. JW and XL participated in the design and performed the statistical analysis. XL, ZY, and XL drafted the initial manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

The study was approved by the Research Ethics Commission of Henan People's Hospital and the requirement for informed consent was waived by the Ethics Commission.

Consent for publication

Consent for publication was obtained for this report.

Competing interests
We declare no competing interests.

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References

1. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736–41. doi:10.1152/ajpendo.00124.2020.

2. Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE): Johns Hopkins Coronavirus Resource Center.

3. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). February 16–24, 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (Accessed on March 04, 2020).

4. Oke J, Heneghan C. Oxford Covid-19 Evidence Service. 2020 [cited 2020 March 27]; Available from: https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/.

5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708–1720. doi:10.1056/NEJMoa2002032. Epub 2020 Feb 28.

6. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061–1069. doi:10.1001/jama.2020.1585.

7. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, Liu W, Bi Y, Gao GF. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol. 2016 Jun;24(6):490–502. doi:10.1016/j.tim.2016.03.003. Epub 2016 Mar 21.

8. National Health Commission of the People's Republic of China. Diagnosis and treatment of COVID-19 in china (version 7.0). Available at https://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7de4cef80dc7f5912eb1989/files/ce3e6945832a438eeae415350a8ce964pdf.

9. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42. doi:10.1001/jama.2020.2648.

10. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054–1062. doi:10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. Erratum in: Lancet. 2020 Mar 28;395(10229):1038.

11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30.

12. Centers for Disease Control and Prevention. Severe outcomes among patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2. (Accessed on March 19, 2020).

13. Smits SL, de Lang A, van den Brand JM, Leijten LM, van IJcken WF, Eijkemans MJ, van Amerongen G, Kuiken T, Andeweg AC, Osterhaus AD, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog. 2010 Feb 5;6(2):e1000756. doi:10.1371/journal.ppat.1000756.

14. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis. 2005 Nov 15;41 Suppl 7:S504-12. doi:10.1086/432007. PMID: 16237654.

15. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, Sun GZ, Yang GR, Zhang XL, Wang L, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med. 2006 Jun;23(6):623–8. doi:10.1111/j.1464-5491.2006.01861.x.
16. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, Duan G. Virology. Epidemiology, Pathogenesis, and Control of COVID-19. Viruses. 2020 Mar 27;12(4):372. doi: 10.3390/v12040372.

17. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020 May;109:102433. doi:10.1016/j.jaut.2020.102433. Epub 2020 Feb 26.

18. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020 Jun;215:108427. doi:10.1016/j.clim.2020.108427. Epub 2020 Apr 20.

19. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033–1034. doi: 10.1016/S0140-6736(20)30628-0. Epub 2020 Mar 16.

20. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020 Jun;505:190–1. doi:10.1016/j.cca.2020.03.004. Epub 2020 Mar 4.

21. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020 Aug;81(2):e16–25. doi:10.1016/j.jinf.2020.04.021. Epub 2020 Apr 23.

22. Zazzana N, Dipaola F, Ognibene S. Procalcitonin and secondary bacterial infections in COVID-19: association with disease severity and outcomes. Acta Clin Belg. 2020 Sep 23:1–5. doi: 10.1080/17843286.2020.1824749. Epub ahead of print.

23. Müller B, Becker KL, Schächinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med. 2000 Apr;28(4):977–83. doi:10.1097/00003246-200004000-00011.

24. Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, Nusbaumer C, Tamm M, Christ-Crain M. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis. 2007 Mar 2;7:10. doi: 10.1186/1471-2334-7-10.

25. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, Zhang Y, Huang S, Liu Z, Cheng J. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol. 2020 Oct;18(10):1887–91. doi:10.1016/j.cgh.2020.05.002. Epub 2020 Apr 10.

26. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020 Jul;5(7):802–10. doi:10.1001/jamacardio.2020.0950.

27. Norikazu I, Naoyuki M, Shunji H, Atsushi K, Yoko F, Aki S, Eisuke K, Hideto T, Tokio W, Hiroto A, et al. Management of refractory Mycoplasma pneumoniae pneumonia: utility of measuring serum lactate dehydrogenase level. J Infect Chemother. 2014 Apr;20(4):270–273. doi: 10.1016/j.jiac.2014.01.001.

28. Drent M, Cobben NA, Henderson RF, Wouters EF, Dieijen VM. Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation. Eur Respir J. 1996 Aug;9(8):1736–41. doi:10.1183/09031936.96.09081736.

29. Zhang ZL, Hou YL, Li DT, et al. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scand J Clin Lab Invest. 2020 Oct;80(6):441–7. doi:10.1080/00365513.2020.1768587.