Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Zhou et al, The Lancet, Vol 395, Issue 10229, 28 Mar–3 Apr 2020, p 1054-1062
Goals:
• Identify risk factors for mortality
• Describe clinical course and dynamics of viral shedding
Methods:

- Retrospective cohort study
- 2 hospitals
- Adults (≥18 y) who were either discharged or died between Dec 29, 2019 and Jan 31, 2020

Approved by Ethics Board

Informed consent waived
Methods (contd.)

• 4 institutions were involved with detection of SARS-CoV-2 – used next-generation seq or real-time RT-PCR

• Throat swabs for SARS-CoV-2 PCR every other day after remission of symptoms – only qualitative data

• Criteria for discharge – no fever x 3 d, improvement on chest CT, 2 throat samples – at least 24 h apart – negative by PCR

• Blood tests – CBC, coagulation, serum chemistry, renal, hepatic, CPK, LDH, myocardial enzymes, D-dimer, IL-6, ferritin, procalcitonin
Definitions

Fever – temp >37.3 (axillary)

Sepsis / septic shock – per Third international Consensus Definition for Sepsis and Septic Shock (*described in next slide*)

Definitions for secondary infection – clinical symptoms or signs of pneumonia or bacteremia, *and* +ve culture from lower resp tract or blood

Definitions of AKI, ARDS, cardiac injury, coagulopathy..

Illness severity of COVID-19 – according to Chinese management guideline for COVID-19 (version 6.0)
**Sepsis-related organ failure (SOFA) and quick SOFA (qSOFA) scores**

**SOFA score** – Respiratory, CNS, cardiovascular, liver, coagulation and renal criteria. Scores of 0-4 assigned to each criteria

Max SOFA score | Mortality  
--- | ---  
0 – 6 | <10%  
7 – 9 | 15 – 20%  
10 – 12 | 40 – 50%  
13 – 14 | 50 – 60%  
15 | >80%  
16 – 24 | >90%  

**qSOFA score** – bedside prompt that may identify patients with suspected infection who are at greater risk for a poor outcome outside the ICU. Only 3 criteria - one point each for low blood pressure (SBP≤100 mmHg), high respiratory rate (≥22 breaths per min), or altered mentation (Glasgow coma scale<15)
Statistical analysis

Continuous variable – presented as median (interquartile range [IQR])

Categorical variables – presented as number – n (%)

Comparisons between survivors and non-survivors – Mann-Whitney U test, Chi-square ($\chi^2$), or Fisher’s exact test

### Parametric Tests
- Assume that sample data usually come from a normal (Gaussian) distribution requires a large sample size
- Differences between individual values in a sample and are more powerful
- Able to identify smaller differences than are nonparametric tests and should be used whenever possible

### Nonparametric Tests
- Make no assumptions about the distribution of originating data
- Therefore ignores absolute values of data points and focus instead on ordinal properties (e.g., which is smallest, which is most common)
- More difficult to demonstrate statistical significance with a nonparametric test (i.e., the difference between the 2 groups must be larger) than with a parametric test.

From Winters et al - Ochsner J. 2010 Fall; 10(3): 213–216.

### Table: Parametric vs. Nonparametric Tests

| Parametric               | Nonparametric                  |
|--------------------------|--------------------------------|
| Chi-square test<sup>a</sup> | Fisher exact test              |
| Paired Student $t$ test  | Wilcoxon signed rank test      |
| Unpaired Student $t$ test| Mann-Whitney $U$ test          |
| ANOVA by sum of squares  | ANOVA by rank                  |
| Pearson product moment coefficient | Spearman rank correlation coefficient |

ANOVA: analysis of variance.

<sup>a</sup> Chi-square is a nonparametric test. Some authors propose thinking of it as parametric, as it works with the sample distribution, mathematically speaking.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096219/
Excellent simple overview!
Statistical analysis (contd.)

Risk factors associated with in-hospital death:
- Univariable (univariate) and Multivariable (multivariate) logistic regression models

Total number of deaths – 54. Thus only 5 variables were chosen (based on previous data) for multivariate analysis to avoid ‘overfitting’ (i.e., too many parameters for the data set). Focused on data that are likely to be readily available in emergency settings.

Used generalized linear model adjust for possible differences in pt characteristics and differences in Rx between the 2 centers.
Results

831 pts hospitalized with COVID-19 – 613 excluded (still hospitalized as of Jan 31, 2020, or not confirmed by SARS-CoV-2 RNA detection

Table 1. Demographic, clinical, lab and radiologic findings on admission
Table 1. Demographic, clinical, lab and radiologic findings on admission

| Demographics and clinical characteristics | Total (n=191) | Non-survivor (n=54) | Survivor (n=137) | p-value |
|------------------------------------------|--------------|---------------------|------------------|---------|
| Respiratory rate ≥24 breaths per min     | 56 (29%)     | 34 (63%)            | 22 (16%)         | <0.0001 |
| Pulse ≥125 beats per min                 | 2 (1%)       | 2 (4%)              | 0                | 0.024   |
| Systolic blood pressure < 90 mm Hg       | 1 (1%)       | 1 (1%)              | 0                | 0.53    |
| Fever (temperature ≥37.3°C)              | 180 (94%)    | 51 (94%)            | 129 (94%)        | 0.94    |
| Cough                                    | 151 (79%)    | 39 (72%)            | 112 (82%)        | 0.35    |
| Sputum                                   | 44 (23%)     | 14 (26%)            | 30 (22%)         | 0.35    |
| Myalgia                                  | 29 (15%)     | 8 (15%)             | 21 (15%)         | 0.93    |
| Fatigue                                  | 44 (23%)     | 15 (28%)            | 29 (21%)         | 0.33    |
| Diarrhoea                                | 9 (5%)       | 2 (4%)              | 7 (5%)           | 0.67    |
| Nausea or vomiting                       | 7 (4%)       | 3 (6%)              | 4 (3%)           | 0.40    |
| SOFA score                               | 2.0 (1.0-4.0) | 4.5 (4.0-6.0)      | 1.0 (1.0-2.0)    | <0.0001 |
| qSOFA score                              | 1.0 (0.0-1.0) | 1.0 (1.0-2.0)      | 0.0 (0.0-1.0)    | <0.0001 |
| CURB-65 score                            | 0.0 (0-2.0)  | 2.0 (1-3.0)        | 0.0 (0-1.0)      | <0.0001 |
| 0-1                                      | 141/188 (75%) | 16 (30%)           | 125/134 (93%)    | <0.0001 |
| 2                                        | 32/188 (17%)  | 23 (43%)           | 9/134 (7%)       |        |
| 3-5                                      | 15/188 (8%)   | 15 (28%)           | 0/134            |        |
| Disease severity status                  |              |                     |                  |        |
| General                                  | 72 (38%)     | 0                   | 72 (53%)         | <0.0001 |
| Severe                                   | 66 (35%)     | 12 (22%)            | 54 (39%)         |        |
| Critical                                 | 53 (28%)     | 42 (78%)            | 11 (8%)          |        |
| Time from illness onset to hospital admission, days | 11.0 (8.0-14.0) | 11.0 (8.0-15.0) | 11.0 (8.0-13.0) | 0.53    |
### Results

**Table 1 (contd).** Demographic, clinical, lab and radiologic findings on admission

| Demographics and clinical characteristics | Total (n=191) | Non-survivor (n=54) | Survivor (n=137) | p-value |
|------------------------------------------|--------------|---------------------|------------------|---------|
| **Laboratory findings**                  |              |                     |                  |         |
| White blood cell count, \times 10^9 per L |              |                     |                  |         |
| <4                                       | 32 (17%)     | 5 (9%)              | 27 (20%)         | <0.0001 |
| 4–10                                     | 119 (62%)    | 24 (44%)            | 95 (69%)         |         |
| >10                                      | 40 (21%)     | 25 (46%)            | 15 (11%)         |         |
| Lymphocyte count, \times 10^9 per L      | 1.0 (0.6–1.3)| 0.6 (0.5–0.8)       | 1.1 (0.8–1.5)    | <0.0001 |
| <0.8                                     | 77 (40%)     | 41 (76%)            | 36 (26%)         | <0.0001 |
| Haemoglobin, g/L                          | 128.0 (119.0–140.0) | 126.0 (115.0–138.0) | 128.0 (120.0–140.0) | 0.30    |
| Anaemia                                  | 29 (15%)     | 14 (26%)            | 15 (11%)         | 0.0094  |
| Platelet count, \times 10^9 per L        | 206.0 (155.0–262.0) | 165.5 (107.0–229.0) | 220.0 (168.0–271.0) | <0.0001 |
What is the utility of breaking the data down into ranges?

Table 1 (contd). Demographic, clinical, lab and radiologic findings on admission.
Results

Table 1 (contd). Demographic, clinical, lab and **radiologic** findings on admission

| Demographics and clinical characteristics | Total (n=191) | Non-survivor (n=54) | Survivor (n=137) | pvalue |
|------------------------------------------|--------------|---------------------|------------------|--------|
| **Imaging features**                      |              |                     |                  |        |
| Consolidation                            | 112 (59%)    | 40 (74%)            | 72 (53%)         | 0.0065 |
| Ground-glass opacity                     | 136 (71%)    | 44 (81%)            | 92 (67%)         | 0.049  |
| Bilateral pulmonary infiltration         | 143 (75%)    | 45 (83%)            | 98 (72%)         | 0.090  |
Results

Table 2. Treatments and outcomes

| Treatments                      | Total (n=191) | Non-survivor (n=54) | Survivor (n=137) | p value  |
|---------------------------------|---------------|---------------------|------------------|----------|
| Antibiotics                     | 181 (95%)     | 53 (98%)            | 128 (93%)        | 0.15     |
| Antiviral treatment             | 41 (21%)      | 12 (22%)            | 29 (21%)         | 0.87     |
| Corticosteroids                 | 57 (30%)      | 26 (48%)            | 31 (23%)         | 0.0005   |
| Intravenous immunoglobulin      | 46 (24%)      | 36 (67%)            | 10 (7%)          | <0.0001  |
| High-flow nasal cannula oxygen therapy | 41 (21%)  | 33 (61%)            | 8 (6%)           | <0.0001  |
| Non-invasive mechanical ventilation | 26 (14%)    | 24 (44%)            | 2 (1%)           | <0.0001  |
| Invasive mechanical ventilation | 32 (17%)      | 31 (57%)            | 1 (1%)           | <0.0001  |
| ECMO                            | 3 (2%)        | 3 (6%)              | 0                | 0.0054   |
| Renal replacement therapy       | 10 (5%)       | 10 (19%)            | 0                | <0.0001  |

Sicker patients likely to receive drugs and supportive treatment
### Table 2. Treatments and outcomes

| Outcomes                              | Total (n=191) | Non-survivor (n=54) | Survivor (n=137) | p value |
|---------------------------------------|---------------|---------------------|------------------|---------|
| Sepsis                                | 112 (59%)     | 54 (100%)           | 58 (42%)         | <0.0001 |
| Respiratory failure                   | 103 (54%)     | 53 (98%)            | 50 (36%)         | <0.0001 |
| ARDS                                  | 59 (31%)      | 50 (93%)            | 9 (7%)           | <0.0001 |
| Heart failure                         | 44 (23%)      | 28 (52%)            | 16 (12%)         | <0.0001 |
| Septic shock                          | 38 (20%)      | 38 (70%)            | 0                | <0.0001 |
| Coagulopathy                          | 37 (19%)      | 27 (50%)            | 10 (7%)          | <0.0001 |
| Acute cardiac injury                  | 33 (17%)      | 32 (59%)            | 1 (1%)           | <0.0001 |
| Acute kidney injury                   | 28 (15%)      | 27 (50%)            | 1 (1%)           | <0.0001 |
| Secondary infection                   | 28 (15%)      | 27 (50%)            | 1 (1%)           | <0.0001 |
| Hypoproteinaemia                      | 22 (12%)      | 20 (37%)            | 2 (1%)           | <0.0001 |
| Acidosis                              | 17 (9%)       | 16 (30%)            | 1 (1%)           | <0.0001 |
| ICU admission                         | 50 (26%)      | 39 (72%)            | 11 (8%)          | <0.0001 |
| ICU length of stay, days              | 8.0 (4.0-12.0)| 8.0 (4.0-12.0)      | 7.0 (2.0-9.0)    | 0.41    |
| Hospital length of stay, days         | 11.0 (7.0-14.0)| 7.5 (5.0-11.0)     | 12.0 (9.0-15.0)  | <0.0001 |
| Time from illness onset to fever, days| 1.0 (1.0-1.0) | 1.0 (1.0-1.0)      | 1.0 (1.0-1.0)    | 0.16    |
| Time from illness onset to cough, days| 1.0 (1.0-3.0) | 1.0 (1.0-1.0)      | 1.0 (1.0-4.0)    | 0.90    |
| Time from illness onset to dyspnoea, days| 7.0 (4.0-9.0)| 7.0 (4.0-10.0)      | 7.0 (4.0-9.0)    | 0.51    |
| Time from illness onset to sepsis, days| 9.0 (7.0-13.0)| 10.0 (7.0-14.0)     | 9.0 (7.0-12.0)   | 0.22    |
| Time from illness onset to ARDS, days | 12.0 (8.0-15.0)| 12.0 (8.0-15.0) | 10.0 (8.0-13.0) | 0.65    |
| Time from illness onset to ICU admission, days| 12.0 (8.0-15.0)| 12.0 (8.0-15.0) | 11.5 (8.0-14.0) | 0.88    |
| Time from illness onset to corticosteroids treatment, days| 12.0 (10.0-16.0)| 13.0 (10.0-17.0) | 12.0 (10.0-15.0)| 0.55    |
| Time from illness onset to death or discharge, days | 21.0 (17.0-25.0)| 18.5 (15.0-22.0) | 22.0 (18.0-25.0) | 0.0003 |
| Duration of viral shedding after COVID-19 onset, days | 20.0 (16.0-23.0)| 18.5 (15.0-22.0) | 20.0 (17.0-24.0) | 0.024   |
Table 3. Risk factors associated with in-hospital death

| Demographic and clinical characteristics | Univariable OR (95% CI) | p value | Multivariable OR (95% CI) | p value |
|-----------------------------------------|------------------------|---------|---------------------------|---------|
| Age, years*                             | 1.14 (1.09-1.18)       | <0.0001 | 1.10 (1.03-1.17)          | 0.0043  |
| Female sex (vs male)                    | 0.61 (0.31-1.20)       | 0.15    | ..                        | ..      |
| Current smoker (vs non-smoker)          | 2.23 (0.65-7.63)       | 0.20    | ..                        | ..      |
| Comorbidity present (vs not present)   |                        |         |                           |         |
| Chronic obstructive lung disease        | 5.40 (0.96-30.40)      | 0.056   | ..                        | ..      |
| Coronary heart disease                  | 21.40 (4.64-98.76)     | <0.0001 | 2.14 (0.26-17.79)         | 0.48    |
| Diabetes                                | 2.85 (1.35-6.05)       | 0.0062  | ..                        | ..      |
| Hypertension                            | 3.05 (1.57-5.92)       | 0.0010  | ..                        | ..      |
| Respiratory rate, breaths per min       |                        |         |                           |         |
| ≤24                                     | 1 (ref)                |         | ..                        | ..      |
| >24                                     | 8.89 (4.34-18.19)      | <0.0001 | ..                        | ..      |
| SOFA score                              | 6.14 (3.48-10.85)      | <0.0001 | 5.65 (2.61-12.23)         | <0.0001 |
| qSOFA score                             | 12.00 (5.06-28.43)     | <0.0001 | ..                        | ..      |

Results
### Results

**Table 3.** Risk factors associated with in-hospital death.

**Laboratory values**

| Laboratory findings | Univariable OR (95% CI) | p value | Multivariable OR (95% CI) | p value |
|---------------------|--------------------------|---------|---------------------------|---------|
| **White blood cell count, x 10⁹ per L** | | | | |
| <4                  | 0.73                     | 0.56    | ...                       | ...     |
| (0.26–2.10)         |                          |         |                           |         |
| 4–10                | 1 (ref)                  | ...     | ...                       | ...     |
| (3.02–14.41)        |                          |         |                           |         |
| >10                 | 6.60                     | <0.0001 | ...                       | ...     |
| (3.02–14.41)        |                          |         |                           |         |
| **Lymphocyte count, x 10⁹ per L** | 0.02                     | <0.0001 | 0.19                      | 0.13    |
| (0.01–0.08)         |                          |         | (0.02–1.62)               |         |
| **ALT, U/L**        | | | | |
| ≤10                 | 1 (ref)                  | ...     | ...                       | ...     |
| (1.48–5.57)         |                          |         |                           |         |
| >10                 | 2.87                     | 0.0018  | ...                       | ...     |
| (1.48–5.57)         |                          |         |                           |         |

(Continued from previous column)

| Laboratory values | Univariable OR (95% CI) | p value | Multivariable OR (95% CI) | p value |
|-------------------|--------------------------|---------|---------------------------|---------|
| **Creatinine, μmol/L** | ≤133                     | 1 (ref) | ...                       | ...     |
| >133              | 4.39                     | 0.048   | ...                       | ...     |
| (1.01–19.06)      |                          |         |                           |         |
| **Lactate dehydrogenase, U/L** | ≤245                     | 1 (ref) | ...                       | ...     |
| >245              | 42.42                    | 0.0002  | ...                       | ...     |
| (6.10–338.44)     |                          |         |                           |         |
| **Creatine kinase, U/L** | ≤185                     | 1 (ref) | ...                       | ...     |
| >185              | 2.56                     | 0.043   | ...                       | ...     |
| (1.02–6.36)       |                          |         |                           |         |
| **High-sensitivity cardiac troponin I, pg/mL** | ≤28                      | 1 (ref) | ...                       | ...     |
| >28               | 80.07                    | <0.0001 | ...                       | ...     |
| (10.34–520.36)    |                          |         |                           |         |

|                  | Univariable OR (95% CI) | p value | Multivariable OR (95% CI) | p value |
|------------------|-------------------------|---------|---------------------------|---------|
| **D-dimer, pg/mL** | ≤0.5                    | 1 (ref) | ...                       | ...     |
| >0.5             | 1.96                    | 0.32    | 2.14                      | 0.52    |
| (0.52–7.43)      | (0.21–21.39)            |         |                           |         |
| **Prothrombin time, s** | <16                     | 1 (ref) | ...                       | ...     |
| ≥16               | 4.62                    | 0.019   | ...                       | ...     |
| (2.29–16.50)     |                          |         |                           |         |
| **Serum ferritin, μg/L** | ≤200                     | 1 (ref) | ...                       | ...     |
| >200              | 9.10                    | 0.0038  | ...                       | ...     |
| (2.04–4.56)      |                          |         |                           |         |
| **IL-6, pg/mL** | ≤12                     | 1 (ref) | ...                       | ...     |
| ≥12               | 1.12                    | 0.0080  | ...                       | ...     |
| (1.03–1.23)      |                          |         |                           |         |
| **Procalcitonin, ng/mL** | ≤1.75                     | 1 (ref) | ...                       | ...     |
| >1.75             | 2.75                    | 0.011   | ...                       | ...     |
| (2.81–10.40)     |                          |         |                           |         |
Results

Figure 1: Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19. Figure shows median duration of symptoms and onset of complications and outcomes. ICU = intensive care unit. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. ARDS = acute respiratory distress syndrome. COVID-19 = coronavirus disease 2019.
Figure 2: Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19. Figure shows temporal changes in d-dimer (A), lymphocytes (B), IL-6 (C), serum ferritin (D), high-sensitivity cardiac troponin I (E), and lactate dehydrogenase (F). Differences between survivors and non-survivors were significant for all timepoints shown, except for day 4 after illness onset for d-dimer, IL-6, and high-sensitivity cardiac troponin I. For serum ferritin (D), the median values after day 16 exceeded the upper limit of detection, as indicated by the dashed line. COVID-19=coronavirus disease 2019. IL-6= interleukin-6.
Discussion points

Strengths
• Fairly large numbers (largest to date)
• Two centers
• Identifies prognostic indicators of poor outcome/mortality despite ICU care – can this help allocation of resources during a crisis? Ethical dilemma!
• Dynamics of viral shedding

Limitations
• Retrospective study
• Not all patients had all the lab tests performed
• Various treatments tried in a non-controlled manner - could influence outcomes
• Lack of quantitative SARS-CoV-2 measurements
• Findings in Wuhan may not necessarily apply to other populations