2020-04-02

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

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Et al.

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)*

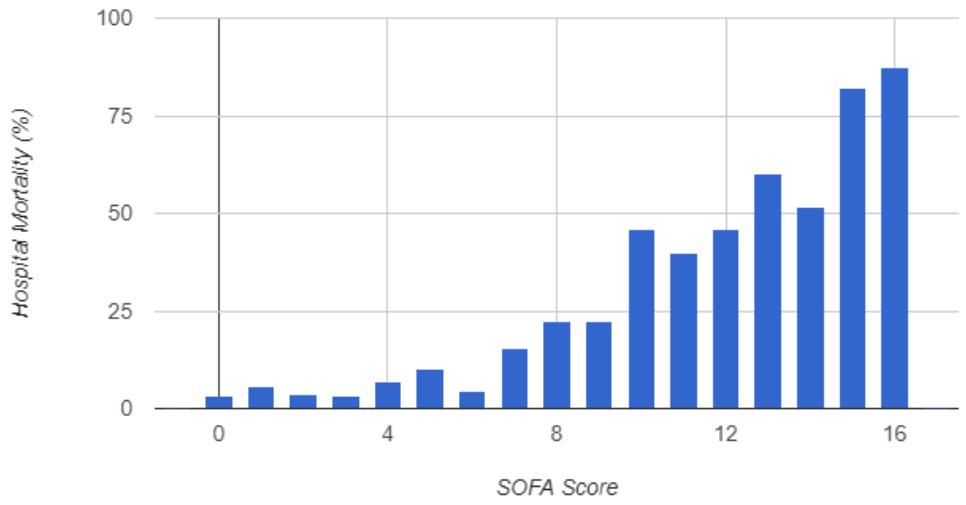
Definitions for secondary infection – clinical symptoms or signs of pneumonia or bacteremia, *and* +ve culture from lower resp tract or blood

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

Illness severity of COVID-19 – according to Chinese management guideline for COVID-19 (version 6.0)

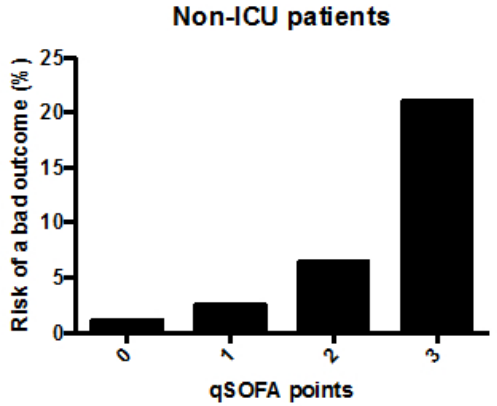
Sepsis-related organ failure (SOFA) and quick SOFA (qSOFA) scores

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 (χ^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 (eg, which is smallest, which is most common)
- more difficult to demonstrate statistical significance with a nonparametric test (ie, 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.

Parametric	Nonparametric
Chi-square test[a]	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.

[a] 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

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	pvalue
Demographics and clinical characteristics				
Age, years	56·0 (46·0–67·0)	69·0 (63·0–76·0)	52·0 (45·0–58·0)	<0·0001
Sex	..	..	..	0·15
Female	72 (38%)	16 (30%)	56 (41%)	..
Male	119 (62%)	38 (70%)	81 (59%)	..
Exposure history	73 (38%)	14 (26%)	59 (43%)	0·028
Current smoker	11 (6%)	5 (9%)	6 (4%)	0·21
Comorbidity	91 (48%)	36 (67%)	55 (40%)	0·0010
Hypertension	58 (30%)	26 (48%)	32 (23%)	0·0008
Diabetes	36 (19%)	17 (31%)	19 (14%)	0·0051
Coronary heart disease	15 (8%)	13 (24%)	2 (1%)	<0·0001
Chronic obstructive lung disease	6 (3%)	4 (7%)	2 (1%)	0·047
Carcinoma	2 (1%)	0	2 (1%)	0·37
Chronic kidney disease	2 (1%)	2 (4%)	0	0·024
Other	22 (12%)	11 (20%)	11 (8%)	0·016

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

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
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%)	0	1 (1%)	0·53
Fever (temperature >37·3°C)	180 (94%)	51 (94%)	129 (94%)	0·94
Cough	151 (79%)	39 (72%)	112 (82%)	0·15
Sputum	44 (23%)	14 (26%)	30 (22%)	0·55
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 (1·0–1·0)	0·0 (0·0–1·0)	<0·0001
CURB-65 score	0·0 (0·0–2·0)	2·0 (1·0–3·0)	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	..	..	..	<0·0001
General	72 (38%)	0	72 (53%)	..
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

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Laboratory findings				
White blood cell count, × 10^9 per L	6·2 (4·5–9·5)	9·8 (6·9–13·9)	5·2 (4·3–7·7)	<0·0001
<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, × 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, × 10^9 per L	206·0 (155·0–262·0)	165·5 (107·0–229·0)	220·0 (168·0–271·0)	<0·0001

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

What is the utility of breaking the data down into ranges?

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Albumin, g/L	32·3 (29·1–35·8)	29·1 (26·5–31·3)	33·6 (30·6–36·4)	<0·0001
ALT, U/L	30·0 (17·0–46·0)	40·0 (24·0–51·0)	27·0 (15·0–40·0)	0·0050
>40	59/189 (31%)	26 (48%)	33/135 (24%)	0·0015
Creatinine >133 µmol/L	8/186 (4%)	5 (9%)	3/132 (2%)	0·045
Lactate dehydrogenase, U/L	300·0 (234·0–407·0)	521·0 (363·0–669·0)	253·5 (219·0–318·0)	<0·0001
>245	123/184 (67%)	53 (98%)	70/130 (54%)	<0·0001
Creatine kinase, U/L	21·5 (13·0–72·4)	39·0 (19·5–151·0)	18·0 (12·5–52·1)	0·0010
>185	22/168 (13%)	11/52 (21%)	11/116 (9%)	0·038
High-sensitivity cardiac troponin I, pg/mL	4·1 (2·0–14·1)	22·2 (5·6–83·1)	3·0 (1·1–5·5)	<0·0001
>28	24/145 (17%)	23/50 (46%)	1/95 (1%)	<0·0001
Prothrombin time, s	11·6 (10·6–13·0)	12·1 (11·2–13·7)	11·4 (10·4–12·6)	0·0004
<16	171/182 (94%)	47 (87%)	124/128 (97%)	0·016*
≥16	11/182 (6%)	7 (13%)	4/128 (3%)	–
D-dimer, µg/mL	0·8 (0·4–3·2)	5·2 (1·5–21·1)	0·6 (0·3–1·0)	<0·0001
≤0·5	55/172 (32%)	4 (7%)	51/118 (43%)	<0·0001*
>0·5 to ≤1	45/172 (26%)	6 (11%)	39/118 (33%)	–
>1	72/172 (42%)	44 (81%)	28/118 (24%)	–
Serum ferritin, µg/L	722·0 (377·2–1435·3)	1435·3 (728·9–2000·0)	503·2 (264·0–921·5)	<0·0001
>300	102/128 (80%)	44/46 (96%)	58/82 (71%)	0·0008
IL-6, pg/mL	7·4 (5·3–10·8)	11·0 (7·5–14·4)	6·3 (5·0–7·9)	<0·0001
Procalcitonin, ng/mL	0·1 (0·1–0·1)	0·1 (0·1–0·5)	0·1 (0·1–0·1)	<0·0001
<0·1	114/164 (70%)	19/51 (37%)	95/113 (84%)	<0·0001*
≥0·1 to <0·25	30/164 (18%)	16/51 (31%)	14/113 (12%)	–
≥0·25 to <0·5	6/164 (4%)	3/51 (6%)	3/113 (3%)	–
≥0·5	14/164 (9%)	13/51 (25%)	1/113 (1%)	–

Results

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

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
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

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Treatments*				
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 immunoglobin	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**

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Outcomes				
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)	0·30
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

Results

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
Demographics and clinical characteristics				
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

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

Laboratory values

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Laboratory findings				
White blood cell count, × 10⁹ per L				
<4	0·73 (0·26–2·10)	0·56	..	..
4–10	1 (ref)	..	..	..
>10	6·60 (3·02–14·41)	<0·0001	..	..
Lymphocyte count, × 10⁹ per L*	0·02 (0·01–0·08)	<0·0001	0·19 (0·02–1·62)	0·13
ALT, U/L				
≤40	1 (ref)	..	..	..
>40	2·87 (1·48–5·57)	0·0018	..	..
Creatinine, µmol/L				
≤133	1 (ref)	..	..	..
>133	4·39 (1·01–19·06)	0·048	..	..
Lactate dehydrogenase, U/L				
≤245	1 (ref)	..	..	..
>245	45·43 (6·10–338·44)	0·0002	..	..
Creatine kinase, U/L				
≤185	1 (ref)	..	..	..
>185	2·56 (1·03–6·36)	0·043	..	..
High-sensitivity cardiac troponin I, pg/mL				
≤28	1 (ref)	..	..	..
>28	80·07 (10·34–620·36)	<0·0001	..	..
D-dimer, µg/mL				
≤0·5	1 (ref)	..	1 (ref)	..
> 0·5	1·96 (0·52–7·43)	0·32	2·14 (0·21–21·39)	0·52
> 1	20·04 (6·52–61·56)	<0·0001	18·42 (2·64–128·55)	0·0033
Prothrombin time, s				
<16	1 (ref)	..	..	..
≥16	4·62 (1·29–16·50)	0·019	..	..
Serum ferritin, µg/L				
≤300	1 (ref)	..	..	..
>300	9·10 (2·04–40·58)	0·0038	..	..
IL-6, pg/mL*	1·12 (1·03–1·23)	0·0080	..	..
Procalcitonin, ng/mL*	13·75 (1·81–104·40)	0·011	..	..

Results

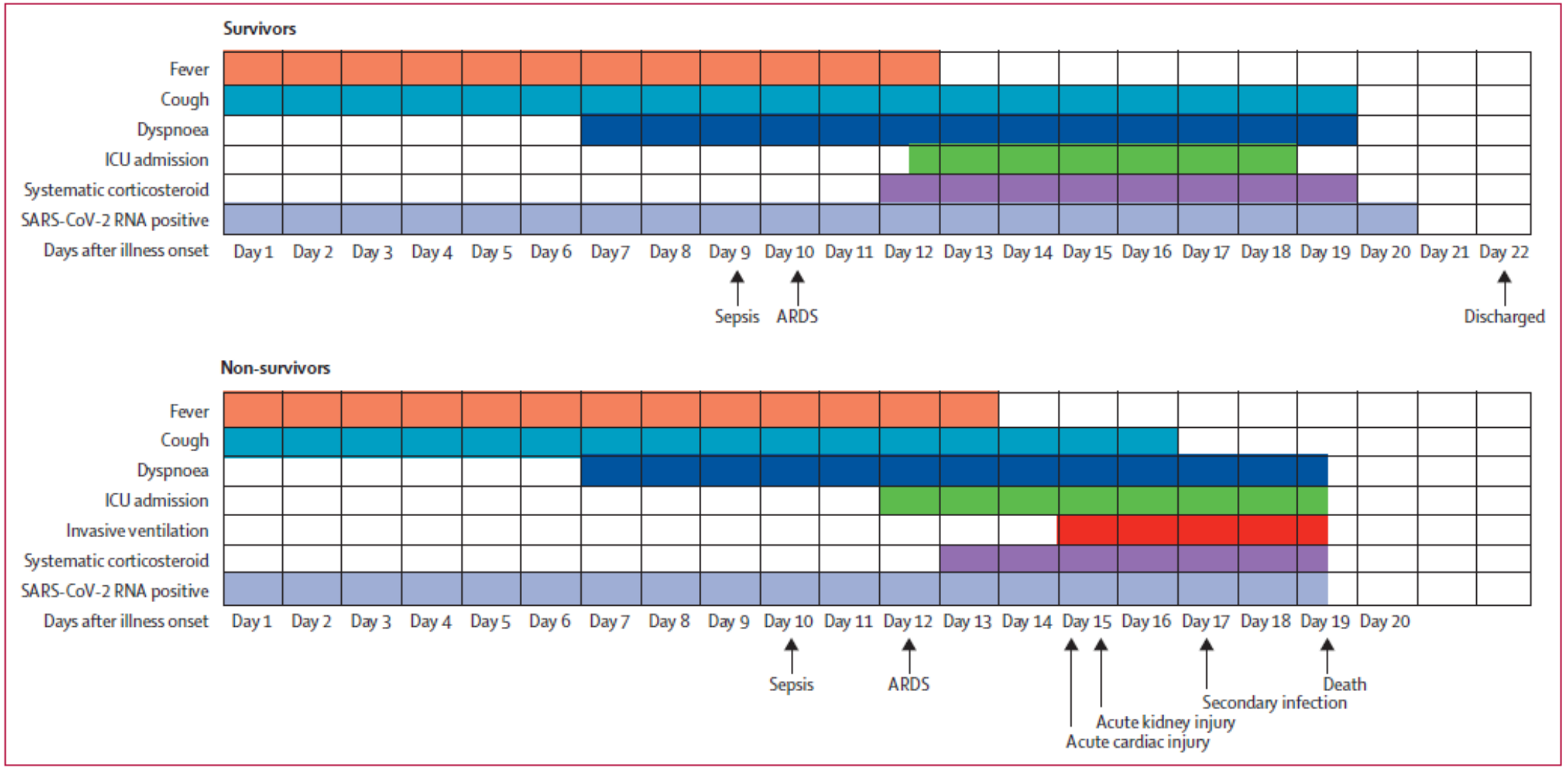
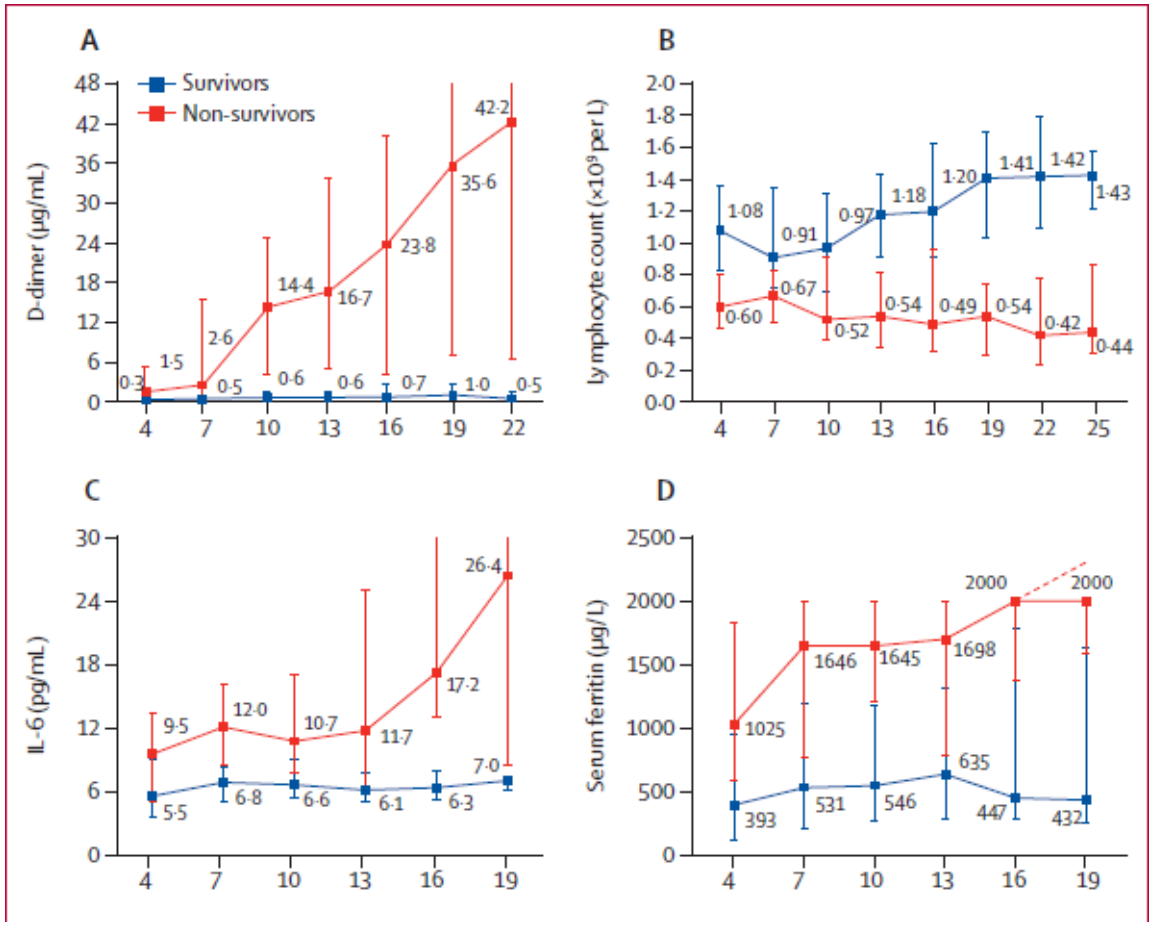


Figure 1: **Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19**

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.

Results



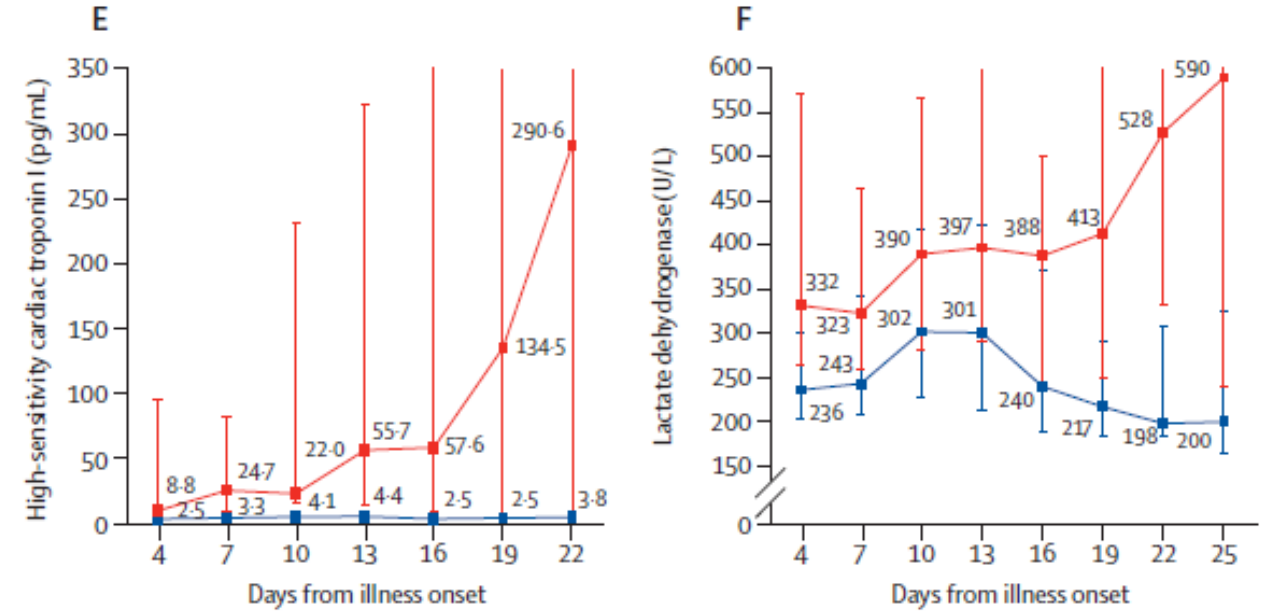


Figure 2: **Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19**
Figure shows temporal changes in d-dimer (A), lymphocytes (B), IL-6 (C), serum ferritin (D), high-sensitivity cardiac troponin I (E), and lactate dehydrogenase (F). Differences between survivors 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