臺北市立聯合醫院
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THE LANCET

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

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

- 臨床醫師可由下列**潛在危險因子**，在COVID-19感染的疾病早期辨識**預後不佳**的病患：
  - **年齡較大**
  - **SOFA score高**
  - **d-dimer 大於1μg/L**
- **Viral Shedding 的時間延長**，對於未來隔離感染患者以及最佳抗病毒治療的策略，提供了理論依據

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Methods

- 研究設計：回溯性世代研究
- 研究對象：
  - 2019年12月29日至2020年1月31日之間，在金銀潭醫院及武漢肺科醫院因COVID-19感染而死亡或出院的18歲以上成年患者
  - 這兩家醫院在2020年2月1日前是武漢唯一接受COVID-19感染患者轉診的專責醫院，因此此研究所納入的是在疫情爆發早期所有因COVID-19感染住院且有明確outcome (死亡或出院)的成年患者
  - 出院條件：
    - 沒有發燒至少3天
    - Chest CT檢查顯示雙側肺部實質性的改善
    - 臨床的呼吸道症狀緩解
    - 2次咽喉拭子的SARS-CoV-2 RNA 檢測陰性，2次採檢間隔至少24小時

Methods -- Definitions

項目	定義
Fever	腋溫至少37.3 °C
Sepsis, septic shock	依據2016第三版國際敗血暨敗血性休克定義共識
Secondary infection	當患者有肺炎或菌血症的臨床症狀，並且在住院後從下呼吸道檢體(合格的痰液、氣管內抽吸物或支氣管肺泡灌洗液)或血液樣本的培養出新的病原體
Ventilator-associated pneumonia	依據hospital-acquired 及 ventilator-associated pneumonia 的治療指南來診斷
Acute kidney injury	依據KDIGO 臨床實務指南
ARDS	依據 Berlin Definition
Acute cardiac injury	血清的心肌生化標記(例如high-sensitive cardiac troponin I)高於參考值上限的99百分位，或心電圖和心臟超音波顯示新的異常
疾病嚴重度	依據中國的新型冠狀病毒肺炎診療方案第六版
Coagulopathy	PT延長3秒或aPTT延長5秒
Hypoproteinaemia	血液 Albumin 小於 25 g/L
暴露史	與確診SARS-CoV-2感染者接觸或曾到過武漢海鮮市場

Methods -- Statistical Analysis

- Mann-Whitney U test, χ2 test, or Fisher's exact test: 比較存活者和非存活者之間的差異
- 使用單變量和多變量logistic回歸分析探討與院內死亡相關的危險因素
  - **選擇5個變量進行多變量logistic回歸分析：**

    --考量到此研究中的死亡總數(n = 54)以及為了避免統計模型出現overfitting，因此依據先前研究的發現和臨床限制，選擇5個變項包括 lymphocyte count, d-dimer, SOFA score, coronary heart disease, age
  - **若變量為以下情形則從單變量分析排除：**

    --組間差異不顯著

    --不確定其準確性（例如: 暴露程度是自我報告）

    --事件數量太少而無法計算odds ratios

    --與SOFA score 有共線性

Results

- 截至2020年1月31日，有813名成年患者因COVID-19在金銀潭醫院或武漢肺科醫院住院
  - **此研究最終納入191位患者**：
    - 排除613例仍在住院或未經SARS-CoV-2 RNA檢測確診的患者，以及在病歷中缺少可用關鍵資訊的患者
    - 金銀潭醫院：135位，武漢肺科醫院：56位
    - **住院期間死亡：54位，出院：137位**

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

- **年齡**：
  - ➢範圍為18歲至87歲
  - ➢ 中位數為56.0歲（ IQR 46.0–67.0 ）
- **性別**：大多數患者為男性
- **共病症**：
  - ➢將近一半的患者有共病症
  - ➢ 高血壓為最常見，其次是糖尿病及冠心病

Results

	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%)	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
Laboratory findings				
White blood cell count, ×10⁹ 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, ×10⁹ 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/dL	128·0 (119·0–140·0)	126·0 (115·0–138·0)	128·0 (120·0–140·0)	0·30

(Table 1 continues on next page)

- 入院時的症狀：
  - 最常見為發燒、咳嗽
  - 其次是痰、倦怠
- Lymphocytopenia:
  - 發生在77(40%)位患者

Results

	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

Table 2: **Treatments and outcomes**

- 治療：
  - Systematic corticosteroid 以及intravenous immunoglobulin的使用在非存活者及存活者之間有顯著差異
  - 32(17%)位患者需要mechanical ventilation, 其中有31(97%)位死亡。從發病到接受mechanical ventilation的median time為14.5天(12.0–19.0)
  - 3位患者使用了ECMO，但3位都死亡

Results

	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

Data are median (IQR) or n (%). p values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. COVID-19=coronavirus disease 2019. *Ordered by escalating scale of respiratory support. †Detectable until death.

Table 2: **Treatments and outcomes**

- 從疾病發作(即入院前)
  - ➢ 到出院的median time：22.0天 (IQR 18.0–25.0)
  - ➢ 到死亡的median time：18.5天 (IQR 15.0–22.0)
- 併發症：
  - ➢ 敗血症最常見，其次是呼吸衰竭、ARDS、心臟衰竭和敗血性休克
  - ➢ 一半的非存活者發生secondary infection
  - ➢ 需要mechanical ventilation的32位病患中有10(31%)位發生ventilator-associated pneumonia
  - ➢ 非存活者者的併發症發生頻率高於存活者

	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	..	..
Laboratory findings				
White blood cell count, × 10^9 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, × 10^9 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	..	..

(Table 3 continues in next column)

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
(Continued from previous column)				
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, ng/mL				
≤28	1 (ref)	..	..	..
>28	80·07 (10·34–620·36)	<0·0001	..	..
D-dimer, μg/L				
≤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	..	..

OR=odds ratio. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. *Per 1 unit increase.

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

- 單變量分析：
  - **糖尿病或冠心病患者死亡的風險更高**
  - 其他與死亡相關：年齡、淋巴球減少、白血球增加、ALT升高、LDH、 hs-cardiac troponin I 、CK、D-dimer、serum ferritin、IL-6，PT、 Cre、 Procalcitonin

	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	..	..
Laboratory findings				
White blood cell count, × 10^9 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, × 10^9 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	..	..

(Table 3 continues in next column)

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
(Continued from previous column)				
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, ng/mL				
≤28	1 (ref)	..	..	..
>28	80·07 (10·34–620·36)	<0·0001	..	..
D-dimer, µg/L				
≤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	..	..

OR=odds ratio. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. *Per 1 unit increase.

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

- 多變量邏輯斯迴歸：
  - 納入有完整數據的171位患者的所有變量(53位非存活者和118位存活者)
  - **入院時年齡越大、SOFA score 越高和 d-dimer大於1µg/ L與死亡風險增加相關**

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

Data are median (IQR) or n (%). p values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. COVID-19=coronavirus disease 2019. *Ordered by escalating scale of respiratory support. †Detectable until death.

Table 2: **Treatments and outcomes**

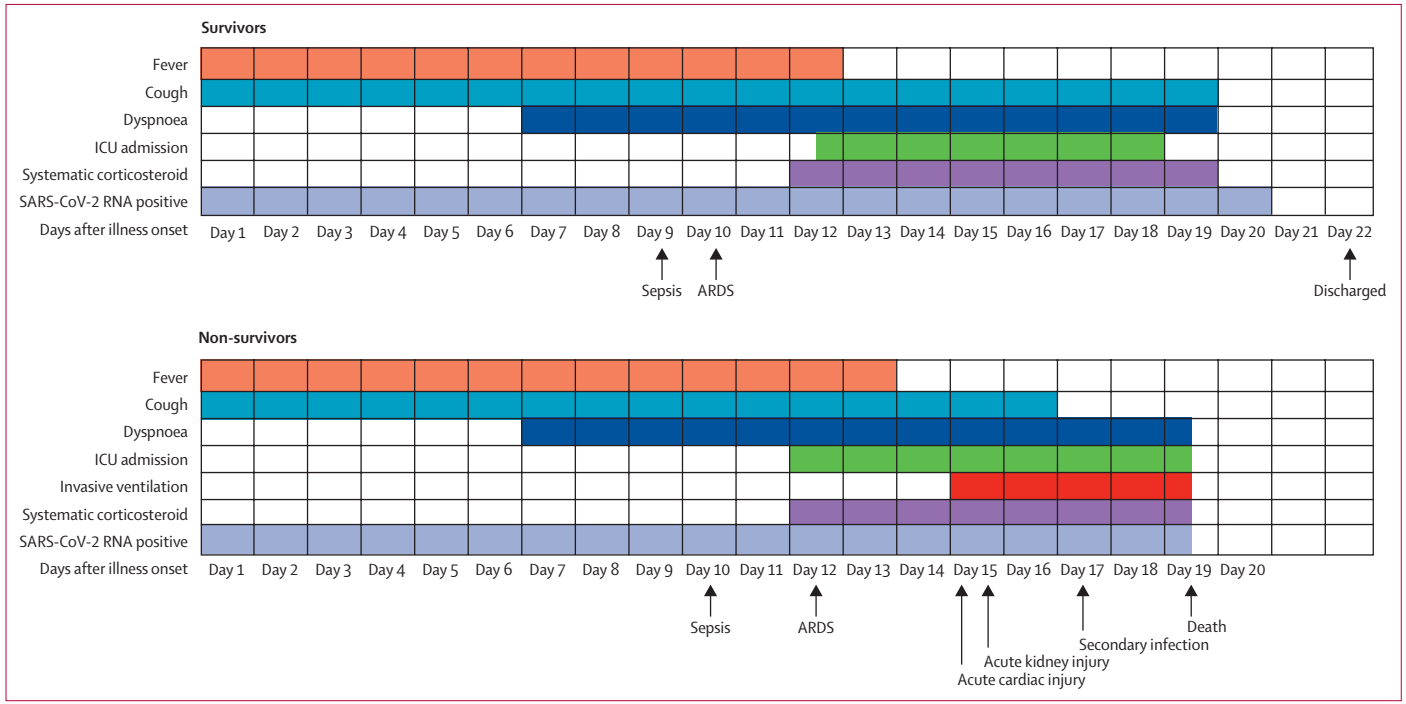


Figure 1: **Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19**
Figure shows median duration of symptoms and onset of complications and outcomes. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019.

- 在存活者，從發病開始到viral shedding的median duration為20.0天(IQR 17.0-24.0)
- 在非存活者中，從開始發病直到死亡，皆可以連續檢測到病毒

Results –Viral Shedding

- 在存活者中，Viral Shedding期間最短為8天，最長為37天
- 在接受lopinavir/ritonavir治療並且出院的29位患者中:
  - 從發病到開始抗病毒治療的median time為14.0天(IQR 10.0–17.0)
  - Viral shedding的median duration為22.0天(18.0–24.0)
- 患者疾病嚴重程度為severe者：Viral shedding的median duration為19.0天(17.0–22.0)
- 患者疾病嚴重程度為critical者： Viral shedding的median duration為24.0天(22.0–30.0)

Results – Changes in Lab Markers

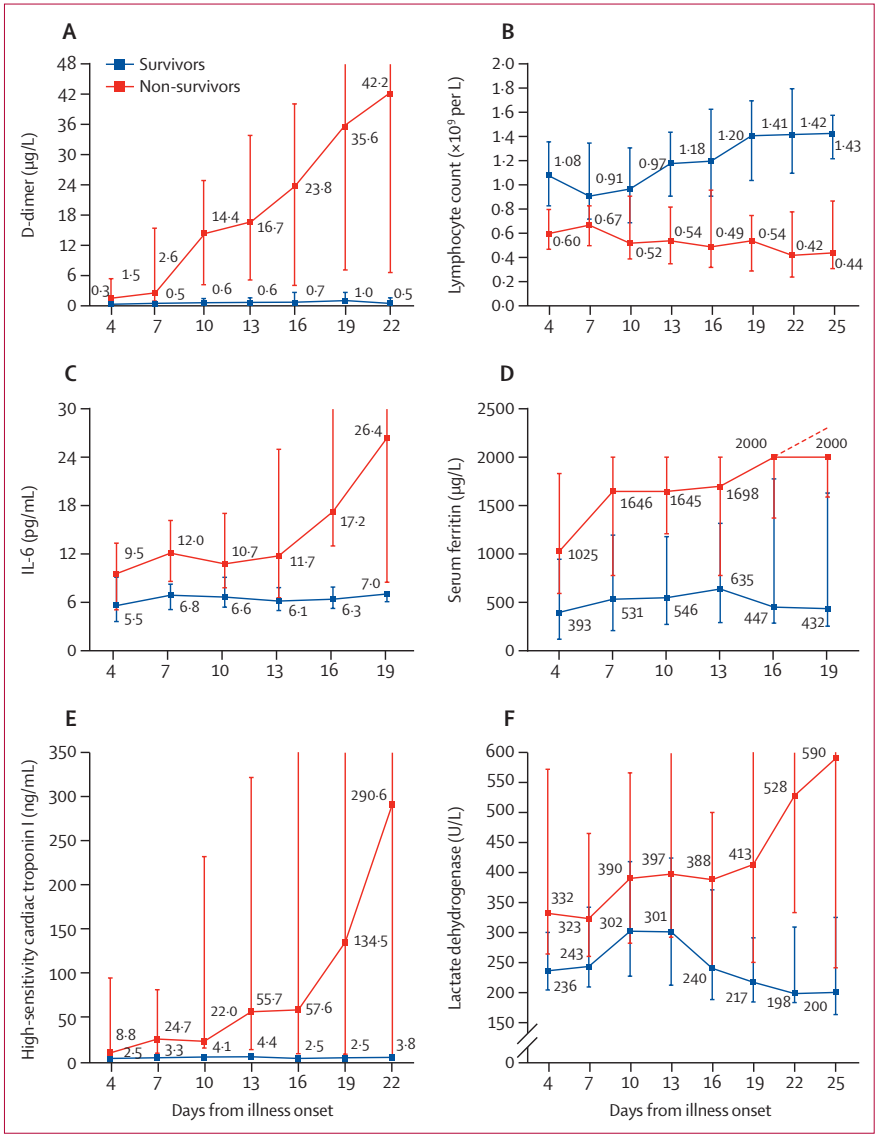


Figure 2: **Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19**
Figure shows temporal changes in d-dimer (A), lymphocytes (B), IL-6 (C), serum ferritin (D), high-sensitivity cardiac troponin I (E), and lactate dehydrogenase (F). Differences between survivors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

- **Lymphocyte:**
  - ➢ 存活者的基線淋巴球數顯著高於非存活者
  - ➢ 存活者在發病後第7天淋巴球數最低，在住院期間有所改善
  - ➢ 非存活者中觀察的嚴重的淋巴球減少直到死亡
- 在臨床過程中與存活者相比，非存活者的D-dimer，hs-cardiac troponin I，serum ferritin，LDH和IL-6的數值明顯上升，且隨著疾病惡化而升高
- **hs-cardiac troponin I:** 在非存活者中，從發病後的第16天開始迅速增加
- **LDH:** 疾病早期在存活者和非存活者均增加，但在存活者從第13天開始下降

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

Data are median (IQR) or n (%). p values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. COVID-19=coronavirus disease 2019. *Ordered by escalating scale of respiratory support. †Detectable until death.

Table 2: **Treatments and outcomes**

- 呼吸困難:
  - ➢ 從發病到呼吸困難的median time在存活者和非存活者相似
  - ➢ 存活者的median duration為13.0天(9.0-16.5)
- 在存活者中發燒的median duration為12.0天(8.0-13.0)，咳嗽為19·0天(12.0-23.0)
- 62(45%)位存活者在出院時仍有咳嗽，39(72%)位非存活者在死亡時仍有咳嗽
- 所有患者發病後到發生其他outcome的 median time:
  - ➢ Sepsis: 9.0天(7.0-13.0)
  - ➢ ARDS: 12.0天(8.0-15.0)
  - ➢ Acute cardiac injury: 15.0天(10.0-17.0)
  - ➢ Acute kidney injury: 15.0天(13.0-19.5)
  - ➢ Secondary infection: 17·0天(13·0-19·0)

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
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
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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
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Data are median (IQR) or n (%). p values were calculated by Mann-Whitney U test, χ^2 test, or Fisher's exact test, as appropriate. ECMO=extracorporeal membrane oxygenation. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. COVID-19=coronavirus disease 2019. *Ordered by escalating scale of respiratory support. †Detectable until death.

Table 2: **Treatments and outcomes**

- 使用corticosteriods的起始時間和持續時間在兩組相似
- 在非存活者中，從發病到發生其他outcome的median time:
  - Sepsis: 10.0天(7.0-14.0)
  - ARDS: 12.0天(8·0-15·0)
  - Acute cardiac injury: 14.5天(9.5-17.0)
  - Secondary infection: 17.0天(13·0-19.0)
- 在存活者中分別有:
  - 一位acute kidney injury: 發病後9天
  - 一位secondary infection:發病後14天
  - 一位acute cardiac injury:發病後21
- 在接受mechanical ventilation的病患中，從呼吸困難到插管的median time為10.0天(5.0-12.5)，從mechanical ventilation到發生ventilator associated pneumonia的時間為8.0天(2.0-9.0)

Discussion

- 此研究發現因COVID-19住院的武漢市成年人，其院內死亡風險較高的相關因素：
  - 年齡較大
  - D-dimer 大於1μg/ L
  - 入院時SOFA score較高
- 在嚴重的COVID-19感染中，常見的實驗室檢查數值變化：
  - IL-6升高
  - high-sensitivity cardiac troponin I 升高
  - LDH升高
  - Lymphopenia
- 在存活者和非存活者的咽喉採檢都可持續檢測出病毒

Discussion

- **此研究顯示，COVID-19患者的年齡增加與死亡相關**
  - 依據過去的報告，老年是SARS和MERS造成死亡的重要獨立預測因子
  - 因年齡而造成的T細胞和B細胞功能缺陷，以及 type 2 cytokines的過度製造，可能導致對病毒複製的控制不足和更長時間的促發炎反應，從而導致不良的結果

- **SOFA score是對sepsis和septic shock良好的診斷指標，也反映了多重器官功能障礙的狀態和程度**
  - 在此研究中，發現一半以上的患者患有敗血症
  - 此外，超過70%的患者白血球數低於10.0×10^9 / L或procalcitonin 低於0.25 ng / mL，且在入院時的檢查未檢測到細菌病原體
  - 敗血症是常見的併發症，可能直接由SARS-CoV-2感染引起，但其致病機轉仍有待進一步研究

Discussion

- **Cardiac complication:**
  - 此研究中，超過一半的死亡者發現住院期間high-sensitivity cardiac troponin I 升高
  - 金銀潭醫院對一名53歲的慢性腎衰竭婦女進行了第一次的屍體解剖，結果顯示急性心肌梗塞(此數據未發表；為私人與中科院病理學家的溝通)
  - 在此研究中發現d-dimer大於1μg/ L與COVID-19的致命後果相關，過去有研究顯示高濃度的d-dimer與在急診發現的感染或敗血症患者的28天死亡率相關。其可能的機轉包括：
    - ✓ 全身性的pro-inflammatory cytokines responses，其為動脈粥樣硬化的介質，直接透過局部發炎反應導致斑塊破裂
    - ✓ 促凝血因子的誘導和血流動力學的變化，容易導致缺血和血栓形成
  - 此外，血管張力素轉化酶2(angiotensin converting enzyme 2) 是SARS-CoV-2的受體，存在於肌細胞和血管內皮細胞上，因此至少在理論上有可能使心臟直接受到病毒感染。值得注意的是，儘管未報導病毒檢測研究，但在COVID-19的致命病例中已發現到心臟組織中的interstitial mononuclear inflammatory infiltrates

Discussion

- **Viral replication:**
  - 感染性病毒複製的程度和持續時間是評估傳播風險和指引患者隔離決策的重要因
  - 因冠狀病毒的RNA檢測較病毒分離更為敏感，因此大多數研究已將定性或定量病毒RNA檢測作為感染性冠狀病毒的潛在標記
  - 對SARS-CoV，約有1/3的患者在發病後的4週內，在呼吸道檢體中可檢測到病毒RNA ;而對MERS-CoV，在下呼吸道檢體中可檢測到病毒RNA的時間至少持續3週。然而**SARS-CoV-2 RNA可檢測的持續時間尚未能歸納出特徵**
  - 此研究發現，**在存活者中可檢測到SARS-CoV-2 RNA的median duration為20天，而在非存活者則一直持續到死亡都可檢測到**。這對於患者隔離決策和抗病毒治療時間的指引上都具有重要意義
  - 有效的抗病毒治療可能會改善COVID-19感染的預後，雖然在此研究中使用lopinavir/ritonavir治療後並未觀察到viral shedding的時間有縮短

Discussion

研究限制：

- 採用回顧性研究設計，並未對所有患者進行所有實驗室檢查，包括LDH、IL-6和serum ferritin，因此可能低估了這些因子在預測院內死亡中的作用
- 患者有時會在疾病晚期才轉到這兩家醫院。缺乏有效的抗病毒藥物，對於標準支持性療法的依從性不足，以及使用高劑量的皮質類固醇，也可能導致某些患者的臨床預後較差
- 對於viral shedding持續時間的估計可能受到呼吸道檢體採集頻率、缺乏定量病毒RNA檢測、以及用咽喉拭子檢測SARS-CoV-2 RNA的陽性率相對較低的限制
- 研究排除了截至2020年1月31日在仍在醫院住院的病患，因此研究對象屬於在較早階段疾病相對較嚴重的，此研究中的病死率無法反映出COVID-19的真實死亡率
- 研究結果的推論可能受到樣本數的限制。但是，此研究包括了兩家指定的COVID-19專責醫院的所有成年患者，因此研究對象應可代表在武漢市被確診和接受治療的病例