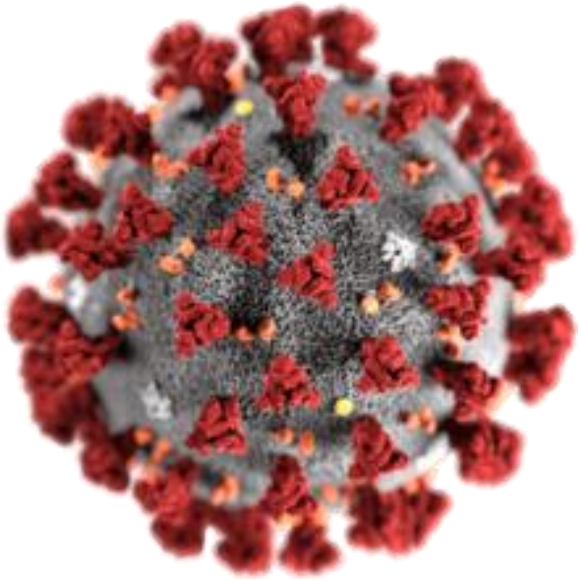
Management of COVID-19



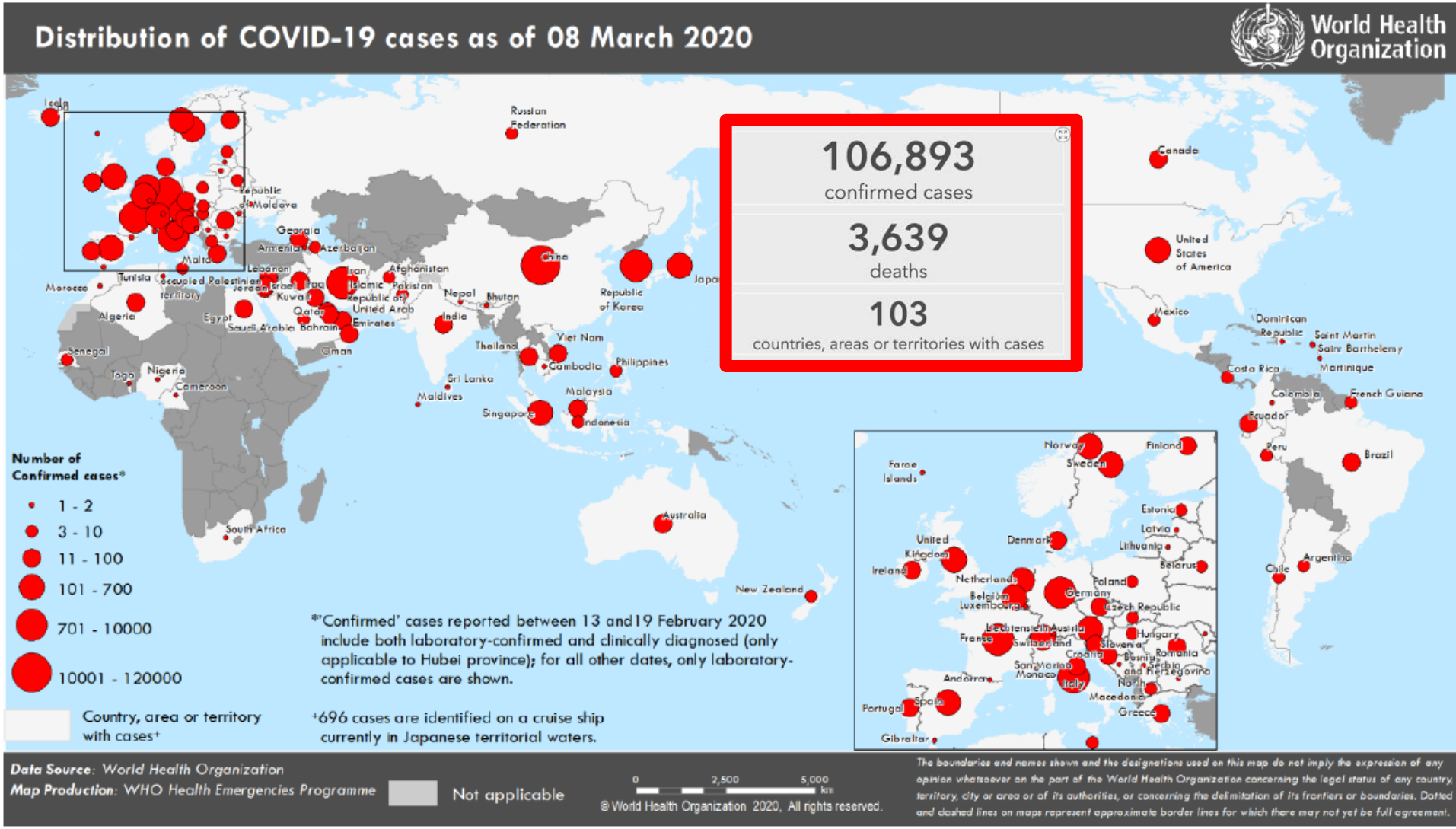
Dr Owen Tsang

Princess Margaret Hospital, Hong Kong

8 Mar 2020 (**day 46 into the outbreak**)

World situation as of 8 Mar 2020

Figure 1. Countries, territories or areas with reported confirmed cases of COVID-19, 08 March 2020



Situation in China

(as of 8 Mar 2020: 80,735 cases, 3119 deaths)

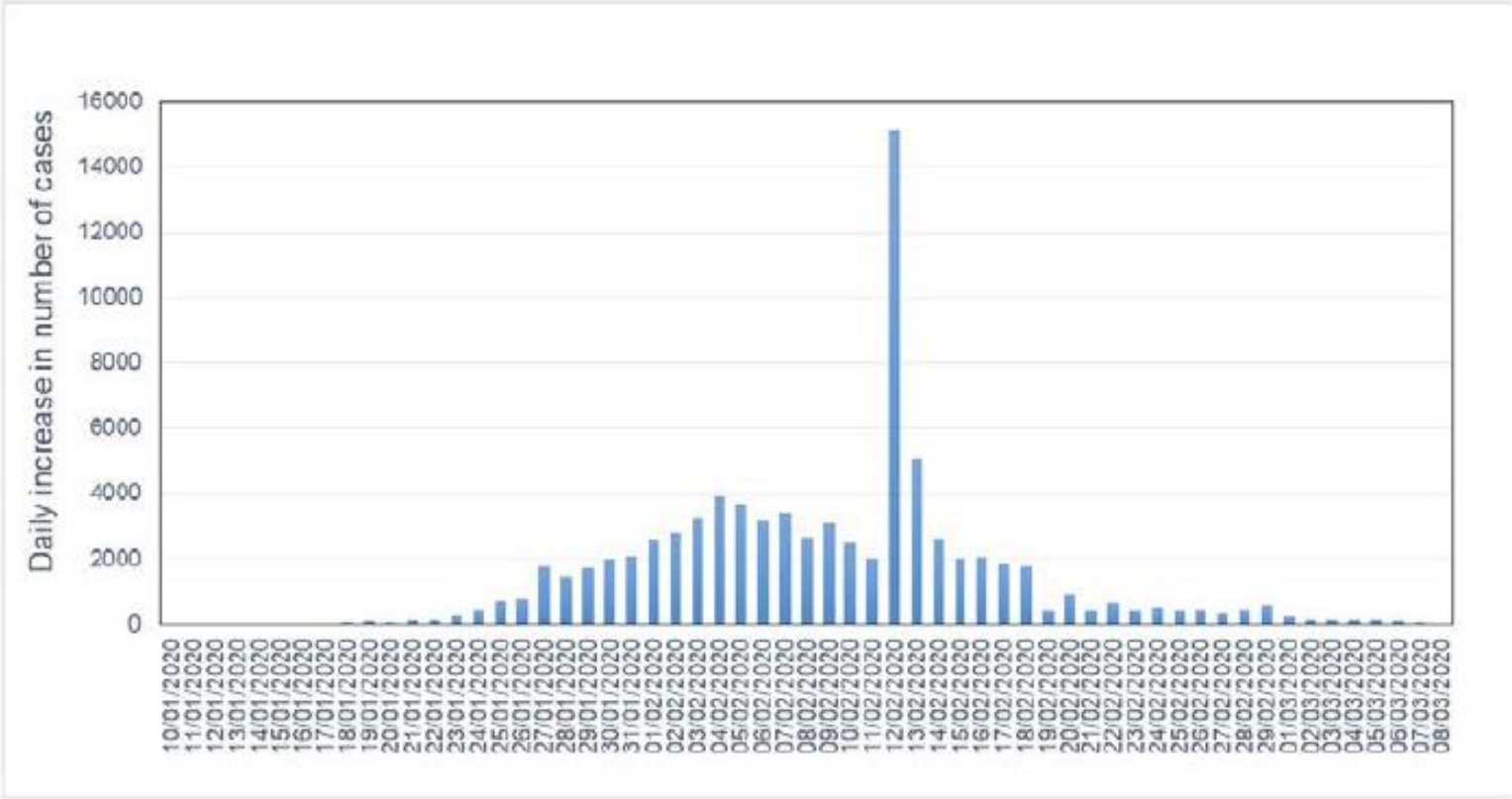


Figure 1 - Daily number of newly reported cases in Mainland China since January 10, 2020 (including cases based on clinical diagnosis from Hubei Province since February 12, 2020)

CHP data

Situation in Guangdong

(as of 8 Mar 2020: 1352 cases, 8 deaths)

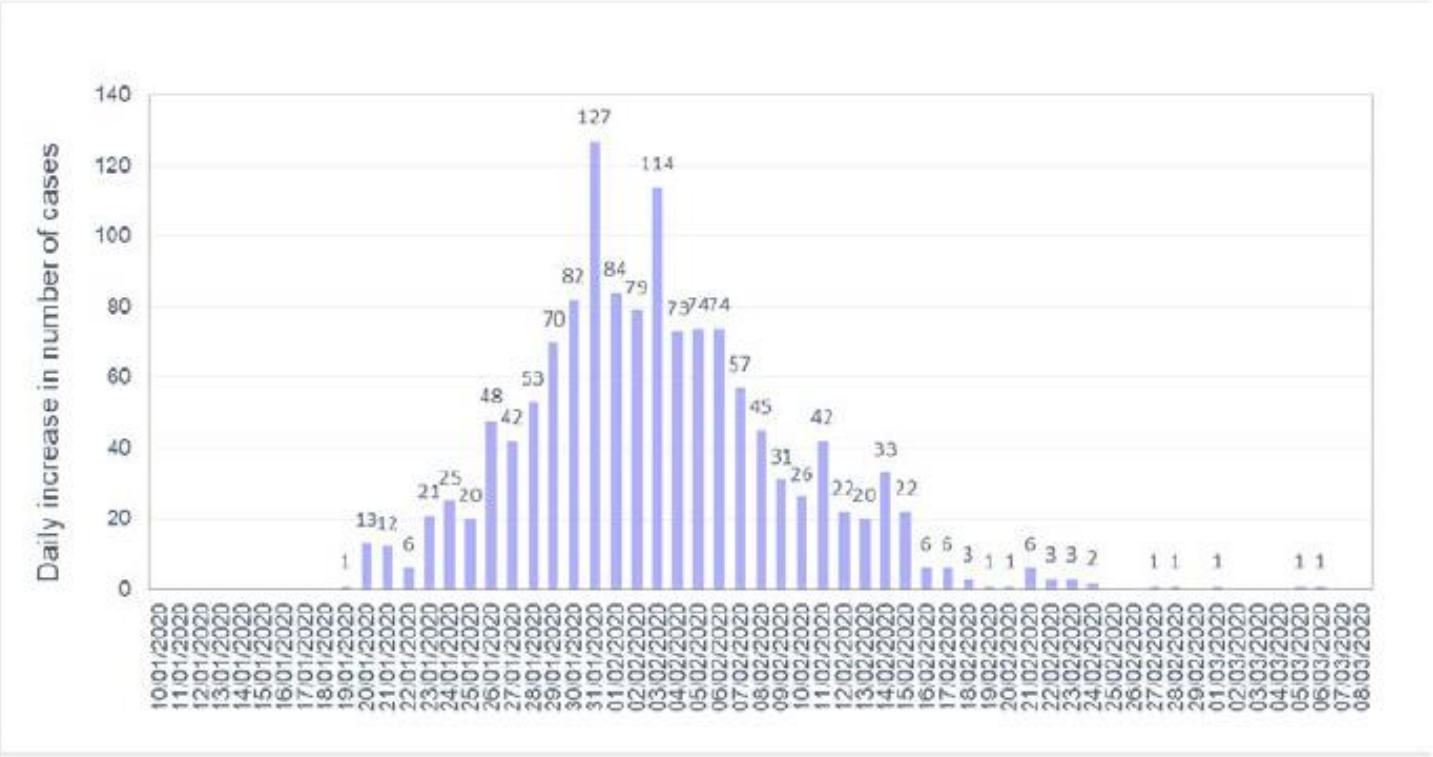
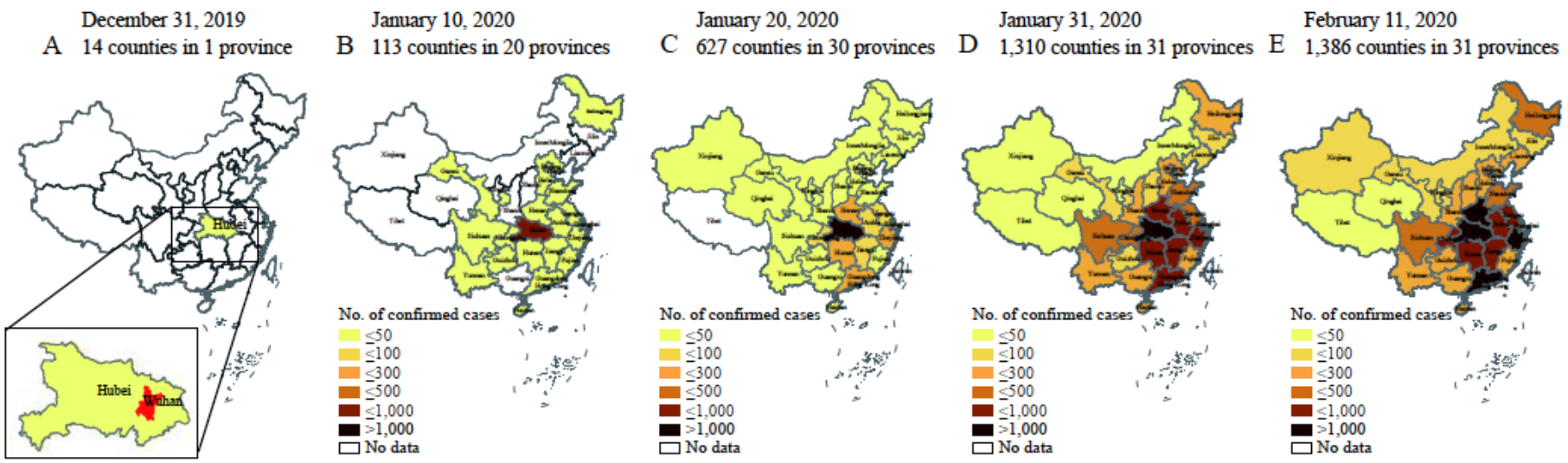
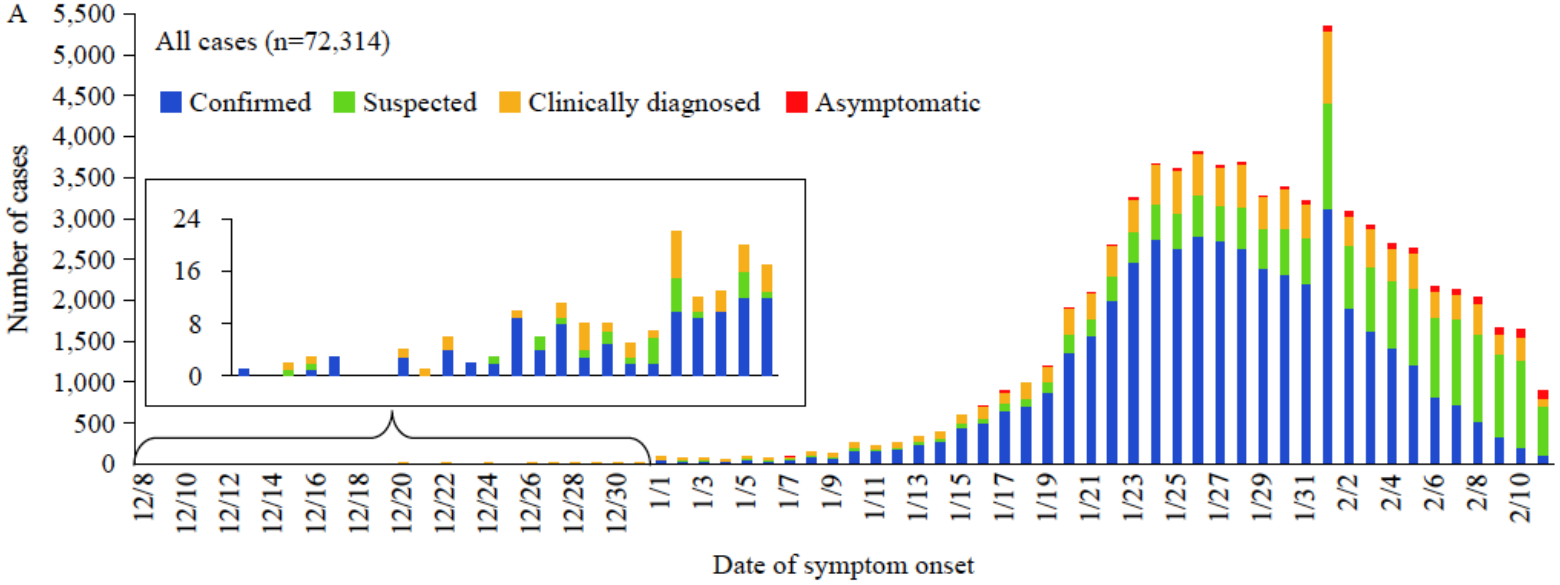


Figure 3 - Daily number of newly confirmed cases reported in Guangdong Province since January 10, 2020

CHP data

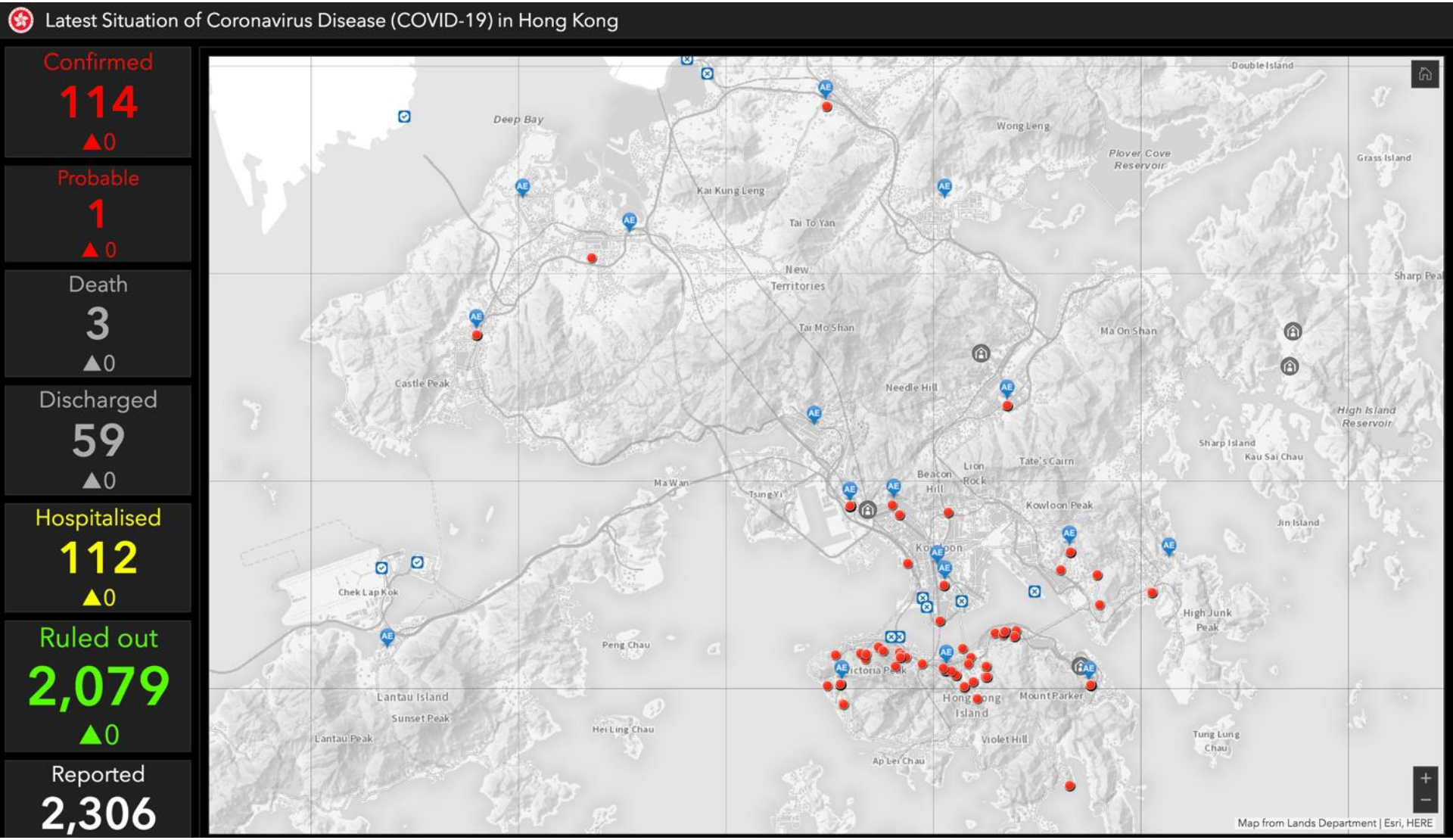
Situation in China (as of 11 Feb 2020)





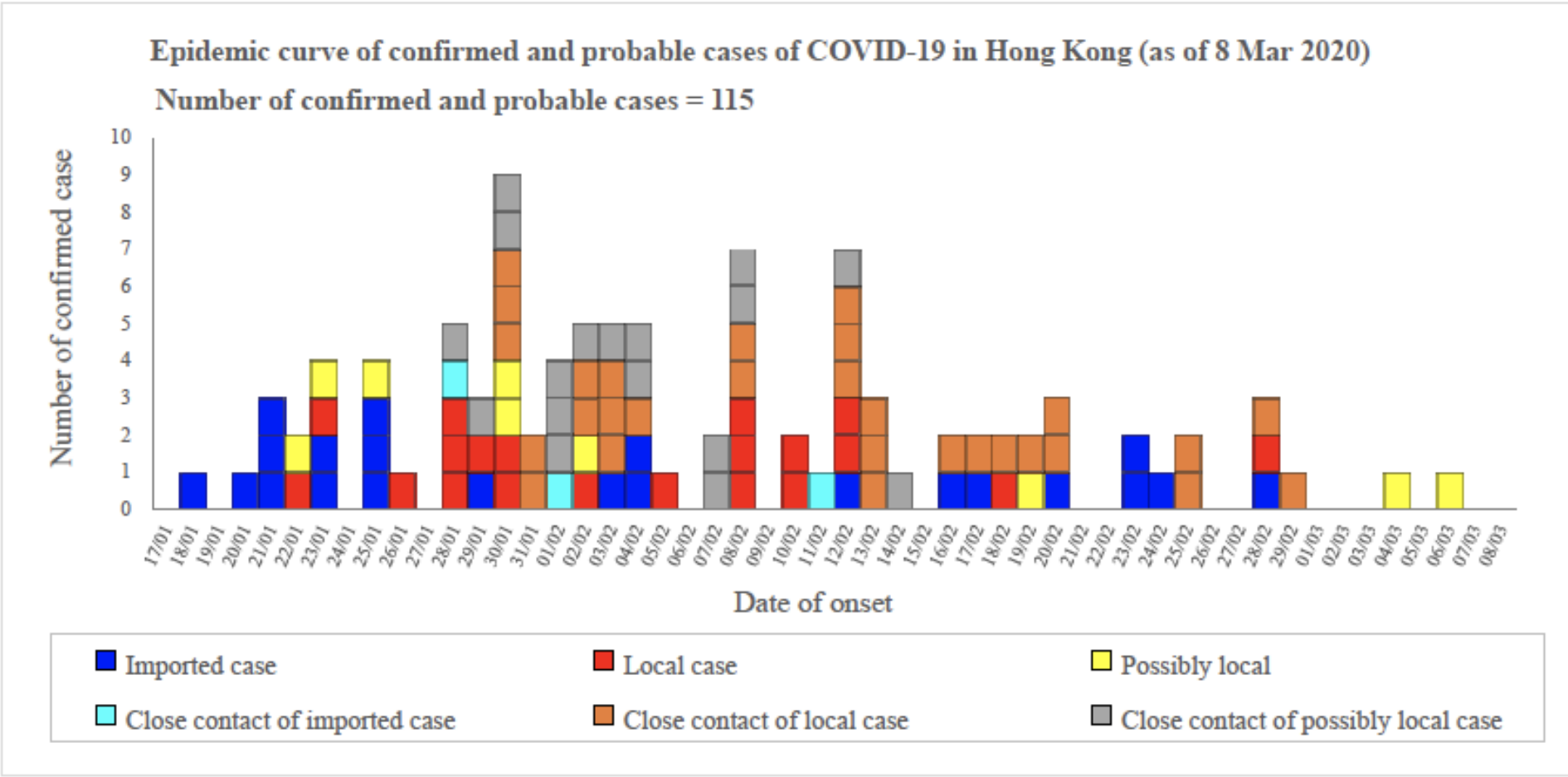
The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. ***China CDC Weekly****. 2020;2 (8): 113-122*

Hong Kong situation (As of 8 Mar 2020)

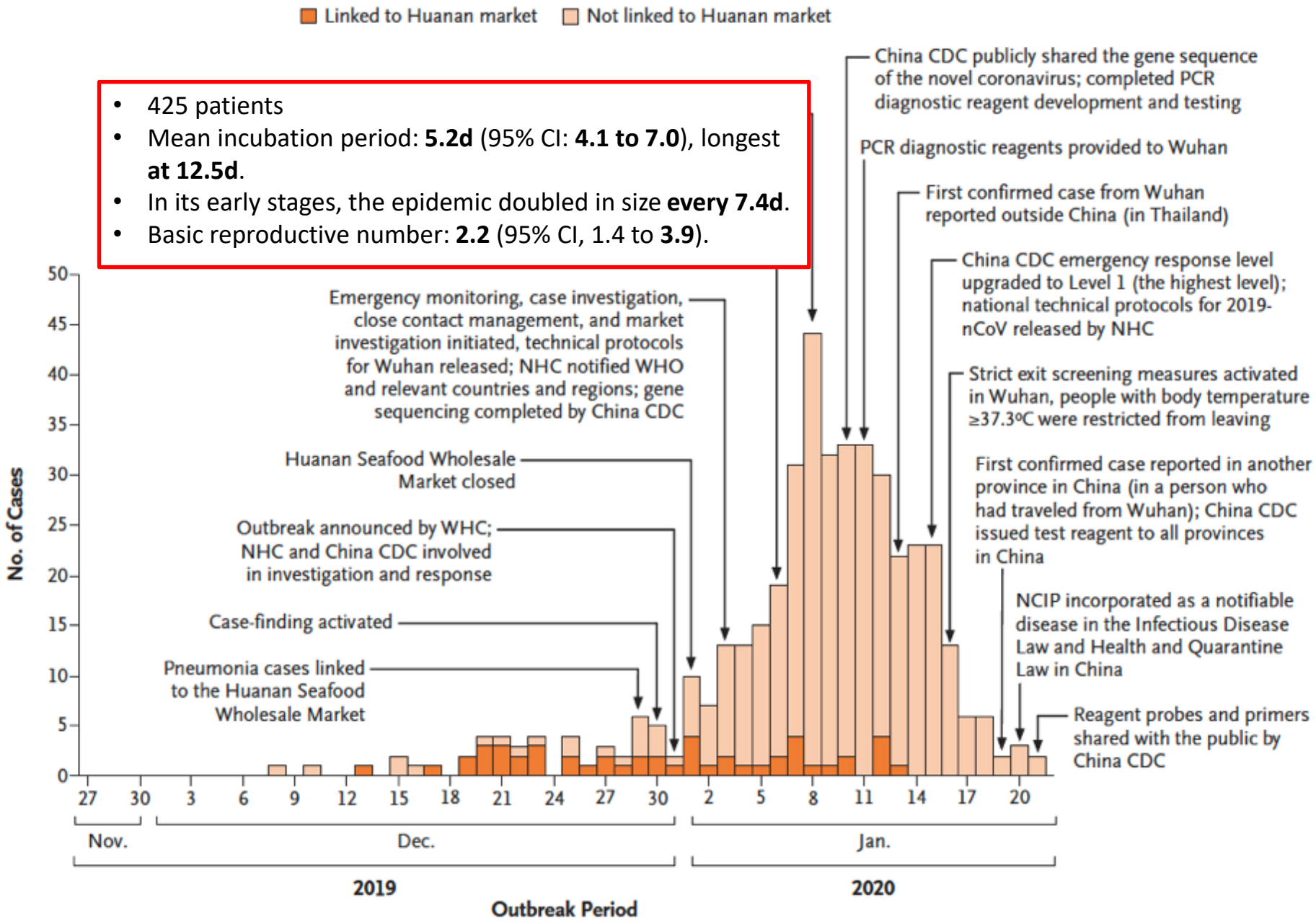


https://chp-dashboard.geodata.gov.hk/covid-19/en.html

Hong Kong situation (As of 8 Mar 2020)



CHP data



Li Q et al. ***N Engl J Med****. Published online on 2020 Jan 29*

Case fatality rate of COVID-19 in China

Baseline characteristics	Confirmed cases, N (%)	Deaths, N (%)	Case fatality rate, %
Overall	44,672	1,023	2.3
Age, years			
0–9	416 (0.9)	–	–
10–19	549 (1.2)	1 (0.1)	0.2
20–29	3,619 (8.1)	7 (0.7)	0.2
30–39	7,600 (17.0)	18 (1.8)	0.2
40–49	8,571 (19.2)	38 (3.7)	0.4
50–59	10,008 (22.4)	130 (12.7)	1.3
60–69	8,583 (19.2)	309 (30.2)	3.6
70–79	3,918 (8.8)	312 (30.5)	8.0
≥80	1,408 (3.2)	208 (20.3)	14.8
Sex			
Male	22,981 (51.4)	653 (63.8)	2.8
Female	21,691 (48.6)	370 (36.2)	1.7
Occupation			
Service industry	3,449 (7.7)	23 (2.2)	0.7
Farmer/laborer	9,811 (22.0)	139 (13.6)	1.4
Health worker	1,716 (3.8)	5 (0.5)	0.3
Retiree	9,193 (20.6)	472 (46.1)	5.1
Other/none	20,503 (45.9)	384 (37.5)	1.9

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. ***China CDC Weekly****. 2020;2 (8): 113-122*

Clinical info

- **1099** patient in China
  - Median Age 47.0 years,
  - 42% were females.
- Direct contact with **wildlife**: 1.18%
- Travel to Wuhan 31.3%
- Contacted with people from Wuhan 71.8%
- Symptoms:
  - **Fever on admission: 43.8**%
  - **Fever during hospitalization: 88.7**%
  - Cough 67.8%
  - Fatigue 38%
  - Sputum 33.7%
  - SOB 18.7%
  - Myalgia/Arthralgia: 14.9%
  - Vomiting 5%
  - Diarrhoea 3.7%
- Median **incubation** period**: 4d** (IQR 2-7d)
- HCW 3.5%

- **Severe case**: 173 (**15.7%**)
- CT abnormality on admission: 86.2%
  - ground-glass opacity 56.4%
  - Bilateral patchy shadowing 51.8%
  - Local patchy shadowing: 41.9%
  - Interstitial abnormality: 14.7%
- Lab info:
  - Lymphopenia 83.2%
  - Thrombocytopenia 36.2%
  - LDH > 250: 41%
  - ALT > 40: 21.3%
  - CK > 200 IU: 13.7%
  - Cr > 133 1.6%
- Outcome:
  - ARDS 3.4%
  - needed oxygen 41.3%
  - NIV 5.1%
  - IMV 2.3%
  - ICU 5%
  - Died **1.4%**

Guan W, et al. ***N Eng J Med*** *published online on 28 Feb 2020 (Nan-Shan Zhong group)*

Comparison vs MERS & SARS

	2019-nCoV*	MERS-CoV	SARS-CoV
Demographic			
Date	December, 2019	June, 2012	November, 2002
Location of first detection	Wuhan, China	Jeddah, Saudi Arabia	Guangdong, China
Age, years (range)	49 (21–76)	56 (14–94)	39·9 (1–91)
Male:female sex ratio	2·7:1	3·3:1	1:1·25
Confirmed cases	835†	2494	8096
Mortality	25† (2·9%)	858 (37%)	744 (10%)
Health-care workers	16‡	9·8%	23·1%
Symptoms			
Fever	40 (98%)	98%	99–100%
Dry cough	31 (76%)	47%	29–75%
Dyspnoea	22 (55%)	72%	40–42%
Diarrhoea	1 (3%)	26%	20–25%
Sore throat	0	21%	13–25%
Ventilatory support	9·8%	80%	14–20%

Wang C. et al. ***Lancet*** *Published Online January 24, 2020*

Infection in HCW

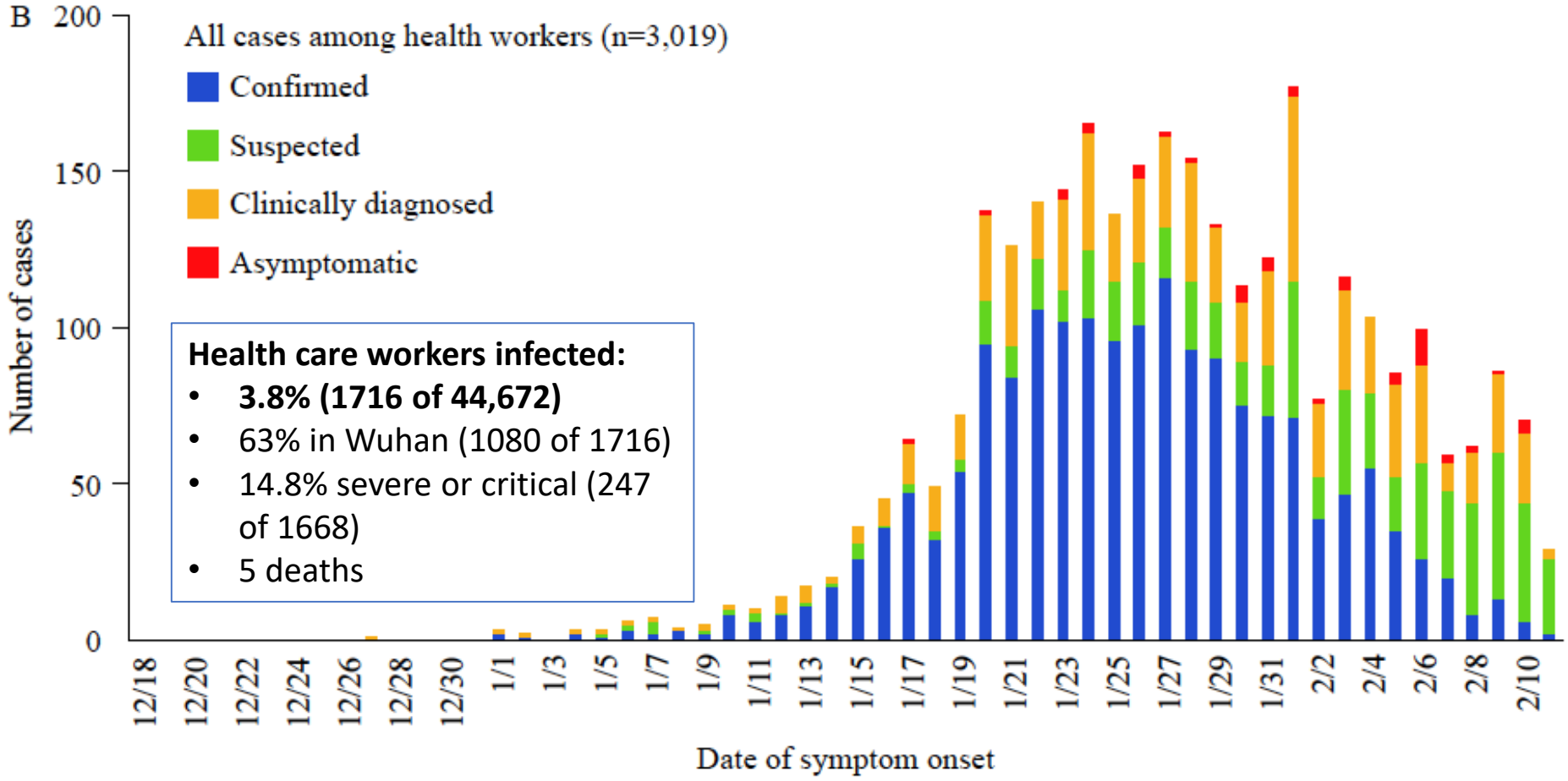
Table 1. Characteristics of Patients with Novel Coronavirus–Infected Pneumonia in Wuhan as of January 22, 2020.*

Characteristic	Before January 1 (N = 47)	January 1 –January 11 (N = 248)	January 12 –January 22 (N = 130)
Median age (range) — yr	56 (26–82)	60 (21–89)	61 (15–89)
Age group — no./total no. (%)			
<15 yr	0/47	0/248	0/130
15–44 yr	12/47 (26)	39/248 (16)	33/130 (25)
45–64 yr	24/47 (51)	106/248 (43)	49/130 (38)
≥65 yr	11/47 (23)	103/248 (42)	48/130 (37)
Male sex — no./total no. (%)	31/47 (66)	147/248 (59)	62/130 (48)
Exposure history — no./total no. (%)			
Wet market exposure	30/47 (64)	32/196 (16)	5/81 (6)
Huanan Seafood Wholesale Market	26/47 (55)	19/196 (10)	5/81 (6)
Other wet market but not Huanan Seafood Wholesale Market	4/47 (9)	13/196 (7)	0/81
Contact with another person with respiratory symptoms	14/47 (30)	30/196 (15)	21/83 (25)
No exposure to either market or person with respiratory symptoms	12/47 (26)	141/196 (72)	59/81 (73)
Health care worker — no./total no. (%)	0/47	7/248 (3)	8/122 (7)

Li Q et al. ***N Engl J Med****. Published online on 2020 Jan 29*

COVID-19 in HCW in China

(as of 11 Feb 2020)



Health care workers infected:

- **3.8% (1716 of 44,672)**
- 63% in Wuhan (1080 of 1716)
- 14.8% severe or critical (247 of 1668)
- 5 deaths

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. ***China CDC Weekly****. 2020;2 (8): 113-122*

COVID-19 IN pregnant women

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
Clinical characteristics										
Date of admission	Jan 20	Jan 25	Jan 27	Jan 26	Jan 27	Jan 27	Jan 28	Jan 29	Jan 30	..
Age (years)	33	27	40	26	26	26	29	28	34	..
Gestational age on admission	37 weeks, 2 days	38 weeks, 2 day	36 weeks	36 weeks, 2 days	38 weeks, 1 day	36 weeks, 3 days	36 weeks, 2 days	38 weeks	39 weeks, 4 days	..
Epidemiological history	Yes (exposure to relevant environment)*	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)*	Yes (exposure to relevant environment)*	Yes (contact with infected person)	Yes (contact with infected person)	Yes (contact with infected person)	Yes (exposure to relevant environment)†	9 (100%)
Other family members affected	No	Yes	Yes	No	No	Yes	No	Yes	No	4 (44%)
Onset to delivery (days)	1	6	4	3	1	4	2	2	7	..
Complications	Influenza	None	Gestational hypertension	Pre-eclampsia	Fetal distress	None	PROM	Fetal distress	PROM	..
Signs and symptoms										
Fever on admission	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	7 (78%)
Post-partum fever	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	6 (67%)
Myalgia	No	Yes	No	No	Yes	Yes	No	No	No	3 (33%)
Malaise	No	No	No	No	Yes	Yes	No	No	No	2 (22%)
Rigor	No	No	No	No	No	No	No	No	No	0
Cough	Yes	Yes	Yes	No	No	Yes	No	No	No	4 (44%)
Dyspnoea	No	No	No	Yes	No	No	No	No	No	1 (11%)
Sore throat	No	No	No	No	No	Yes	Yes	No	No	2 (22%)
Diarrhoea	No	No	No	Yes	No	No	No	No	No	1 (11%)
Chest pain	No	No	No	No	No	No	No	No	No	0

Chen H, ete al. ***Lancet*** *Published online February 12, 2020*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	n (%)
Gestational age at delivery	37 weeks, 2 days	38 weeks, 3 days	36 weeks	36 weeks, 2 days	38 weeks, 1 day	36 weeks, 3 days	36 weeks, 2 days	38 weeks	39 weeks, 4 days	..
Birthweight (g)	2870	3730	3820	1880	2970	3040	2460	2800	3530	..
Low birthweight (<2500 g)	No	No	No	Yes	No	No	Yes	No	No	2 (22%)
Premature delivery	No	No	Yes	Yes	No	Yes	Yes	No	No	4 (44%)
Apgar score (1 min, 5 min)	8, 9	9, 10	9, 10	8, 9	9, 10	9, 10	9, 10	9, 10	8, 10	..
Severe neonatal asphyxia	No	No	No	No	No	No	No	No	No	0
Neonatal death	No	No	No	No	No	No	No	No	No	0
Fetal death or stillbirth	No	No	No	No	No	No	No	No	No	0

Table 2: **Neonatal outcomes**

Amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples from six patients were tested for SARS-CoV-2, and all samples tested negative for the virus.

Chen H, ete al. ***Lancet*** *Published online February 12, 2020*

Transmission of COVID-19 from asymptomatic contact in Germany

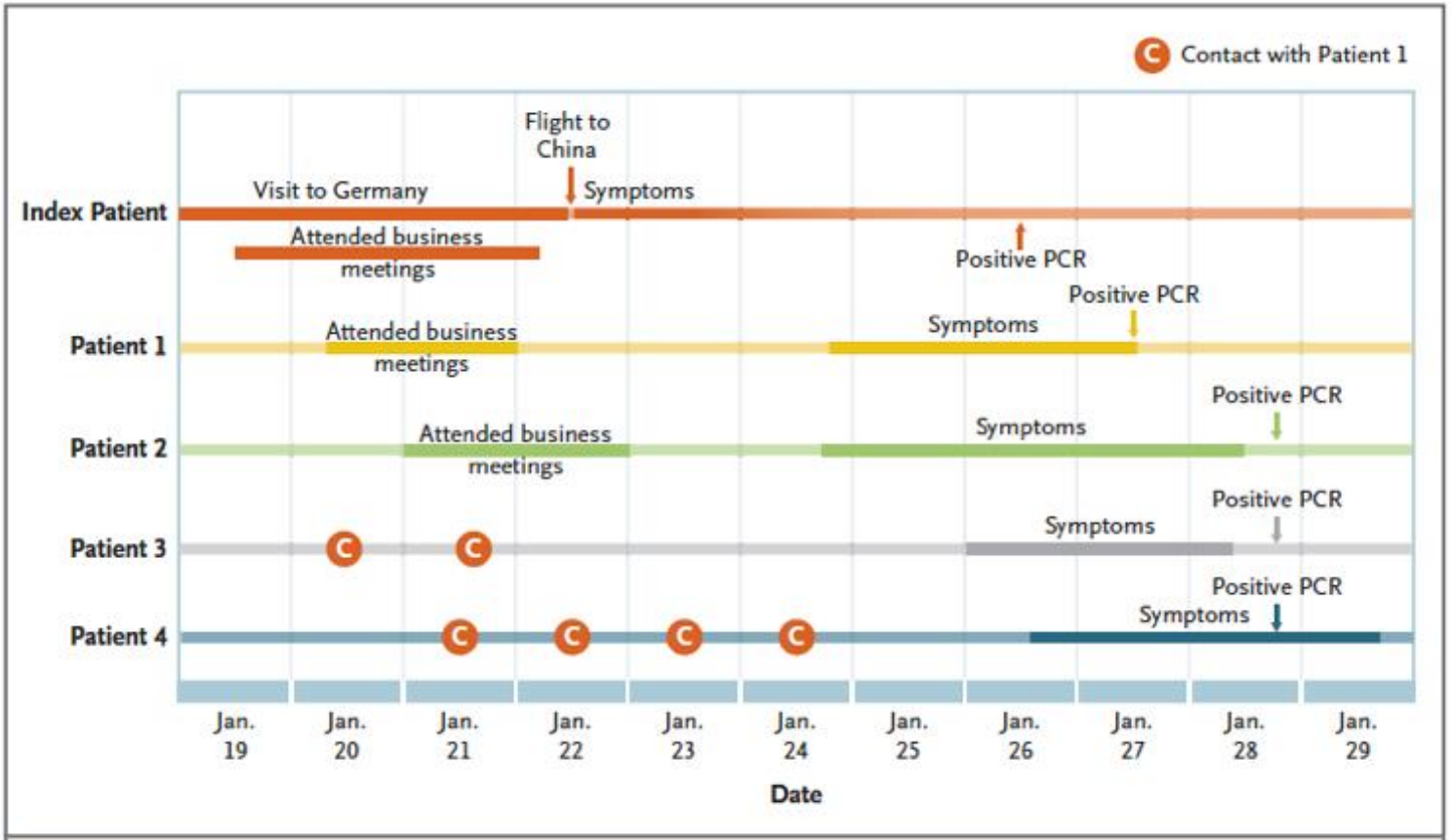


Figure 1. Timeline of Exposure to Index Patient with Asymptomatic 2019-CoV Infection in Germany.

Salient points:

- Asymptomatic carrier can potentially transmit the virus
- High sputum viral load in convalescent patient:
- prolonged shedding or dead virus

Rothe C, et al. ***N Eng J Med*** *published on January 30, 2020*

PMH experience

Definition of Severe: ICU care or death

Demographics, clinical and laboratory characteristics and outcomes of severe & non-severe nCoV cases

	nCoV cases (N=26)		
Characteristics	**Severe cases (n=6)**	**Non- severe cases (n=20)**	**P-value**
	no. (%)	**no. (%)**	
Demographics			
Age (years)	59.8 (mean) 63 (median) 39- 70 (range) 11.3 (SD)	55.1 (mean) 58 (median) 25- 80 (range) 16.4 (SD)	0.533
Gender (male)	3 (50.0)	11 (55.0)	0.596
Suspected transmission route			0.754
Local transmission	2 (33.3)	10 (50.0)	
Import cases from Wuhan	3 (50.0)	8 (40.0)	
Import cases from other Chinese province	1 (16.7)	2 (10.0)	
Family member contact	0	8 (40.0)	0.08
Hospital/ clinic visit in China	1 (16.7)	3 (15.0)	0.676
Wet market visit in China	0	2 (10.0)	0.585
Contact with sick person in China	0	1 (5.0)	0.769
Medical history			
HT	1 (16.7)	5 (25.0)	0.572
DM	2 (33.3)	2 (10.0)	0.218
Gout	1 (16.7)	1 (5.0)	0.415
Hyperlipidemia	2 (33.3)	0	0.046*
CKD	1 (16.7)	0	0.231
COPD	0	1 (5.0)	0.769
IHD	0	1 (5.0)	0.769

Symptoms

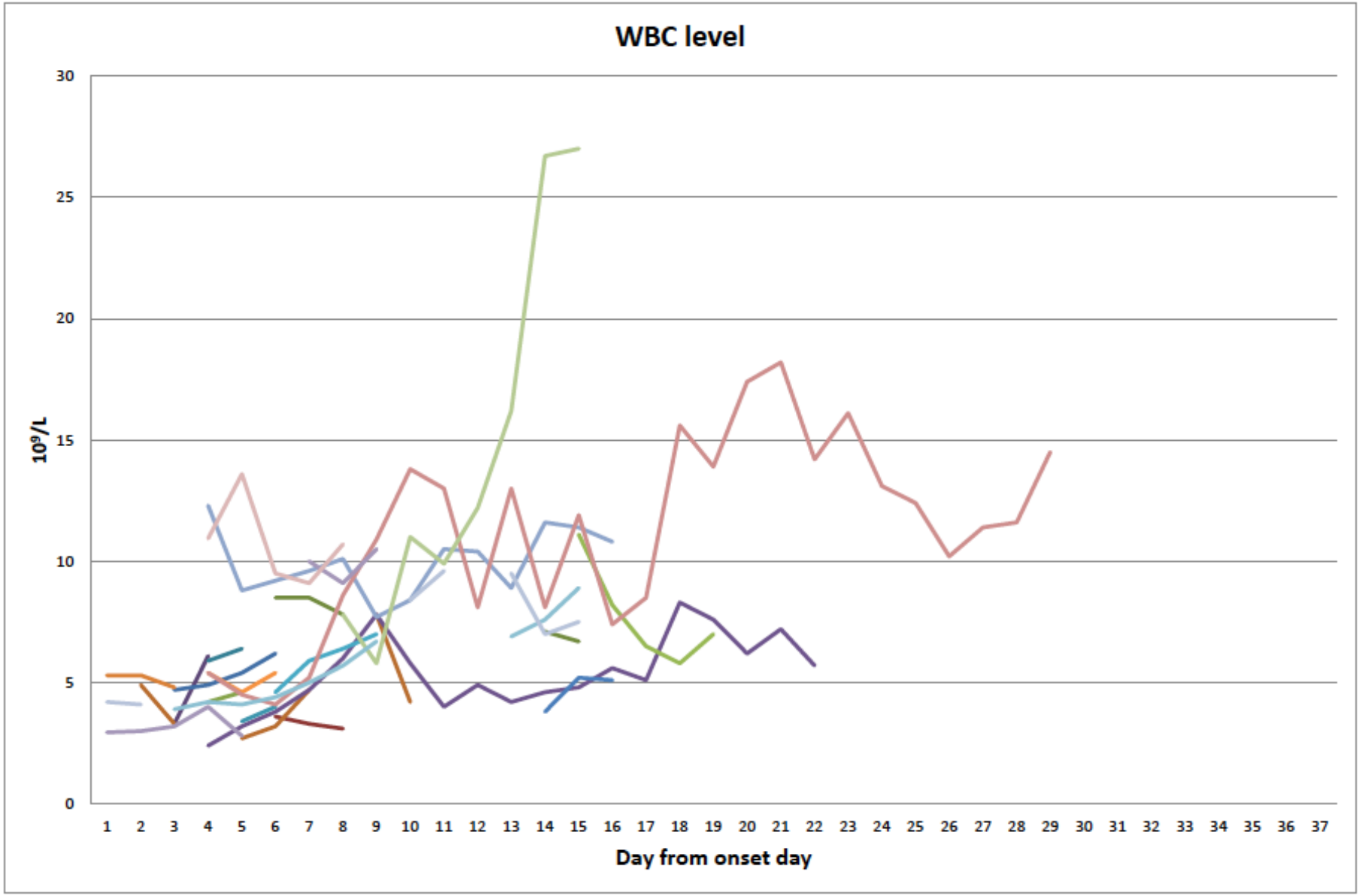
Symptoms			
Fever	6 (100.0)	19 (95.0)	0.769
Cough	0	7 (35.0)	0.118
Chill	1 (16.7)	3 (15.0)	0.676
Dyspnea	3 (50.0)	1 (5.0)	0.028*
Sore throat	0	3 (15.0)	0.438
Diarrhea	1 (16.7)	1 (5.0)	0.415
Myalgia	1 (16.7)	1 (5.0)	0.415
Malaise	1 (16.7)	1 (5.0)	0.415
Rigor	1 (16.7)	1 (5.0)	0.415
Blocked nose	0	1 (5.0)	0.769
Chest pain/ discomfort	1 (16.7)	0	0.231
Loss of appetite	0	1 (5.0)	0.769
Nausea	0	1 (5.0)	0.769
Runny nose	0	1 (5.0)	0.769

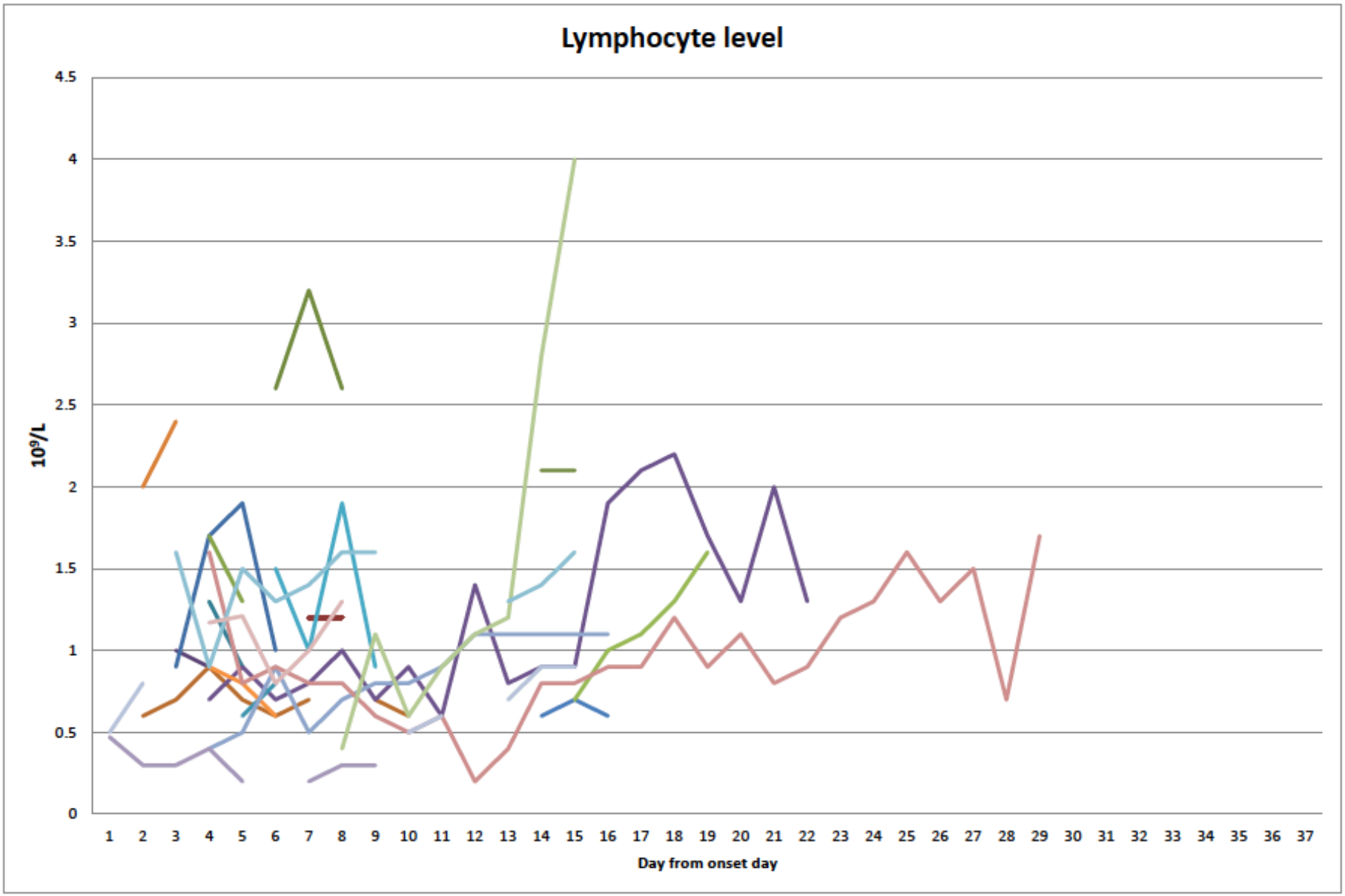
Laboratory result

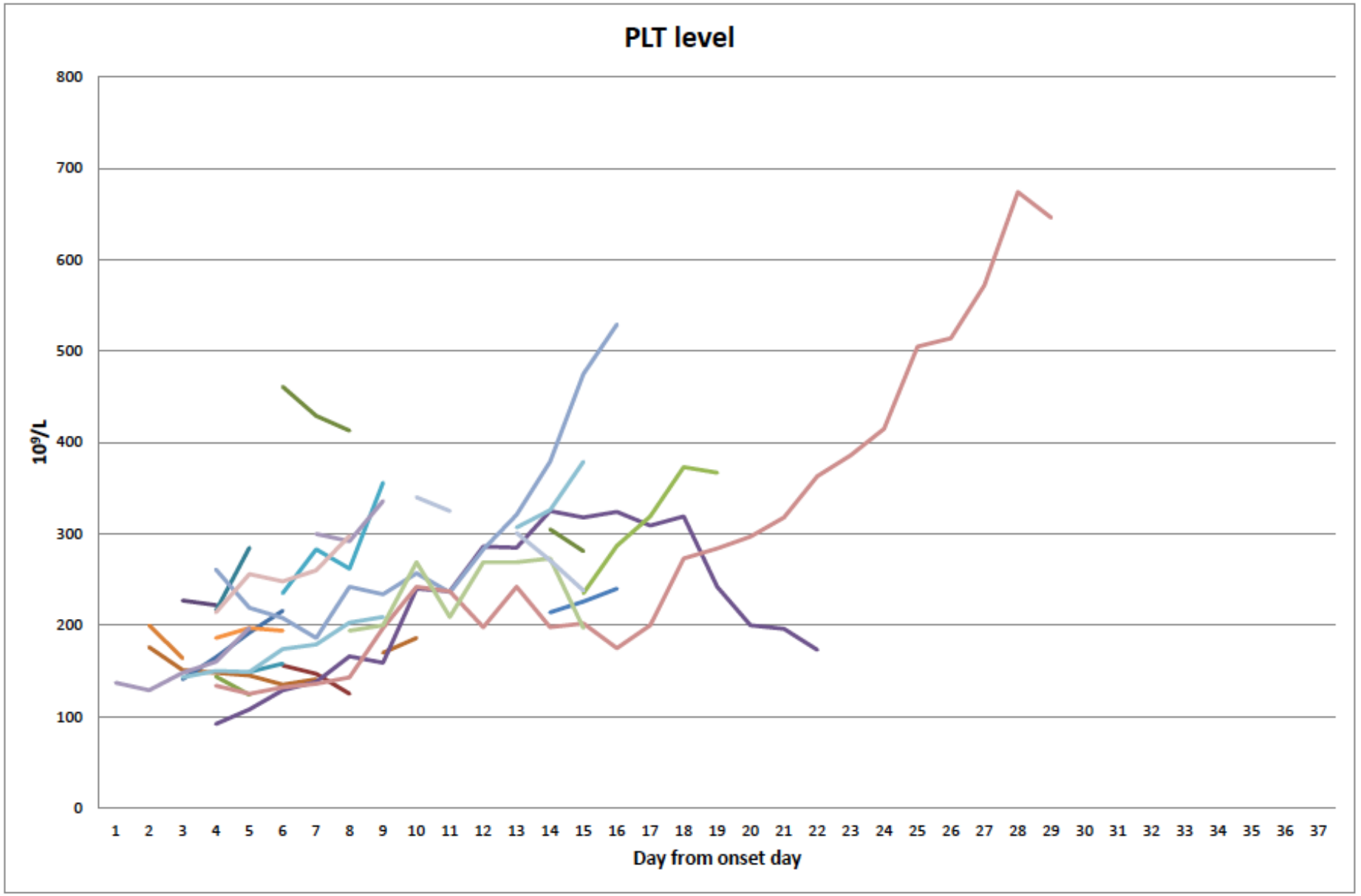
Lab results upon admission Mean (range)			
Haemoglobin (g/dL)	12.9 (11.4- 14.5)	13.3 (10.2- 15.9)	0.545
PLT (10^9/L)	165.8 (92.0- 261.0)	179.5 (101.0- 356.0)	0.596
WBC (10^9/L)	7.0 (2.4- 12.3)	5.0 (3.0- 10.9)	0.081
Neutrophil (10^9/L)	5.9 (1.3-11.7)	3.4 (1.7- 9.0)	0.025*
Lymphocyte (10^9/L)	0.77 (0.45-1.60)	1.10 (0.47- 2.00)	0.167
Creatinine (umol/L)	73.8 (46.0- 119.0)	70.6 (52.0- 108.0)	0.711
Bilirubin (umol/L)	6.0 (4.0- 10.0)	8.4 (3.0- 22.0)	0.257
Albumin (g/L)	30.8 (22.0- 37.0)	37.7 (31.0- 50.0)	0.011*
Globulin (g/L)	39.3 (30.0- 47.0)	34.9 (28.0- 47.0)	0.074
ALP (IU/L)	90.5 (61.0- 141.0)	64.9 (38.0- 115.0)	0.020*
ALT (IU/L)	27.3 (16.0- 40.0)	47.6 (9.0- 197.0)	0.309
CK (U/L)	236.8 (35.0- 1097)	114.2 (41.0- 324.0)	0.216
CRP (mg/L)	149.5 (33.2- 284.0)	26.2 (0.7- 144.0))	<0.001***
LDH (U/L)	463.8 (266.0- 874.0)	235.1 (130.0- 431.0)	0.001**
Urea (mmol/L)	4.4 (2.6- 9.6)	4.36 (2.2- 9.4)	0.949
Procalcitonin	5.4 (0.08- 29.4)	0.10 (0.05- 0.67)	0.065
Troponin I	128.2 (10.0- 652.0)	10.6 (10.0- 18.9)	0.081

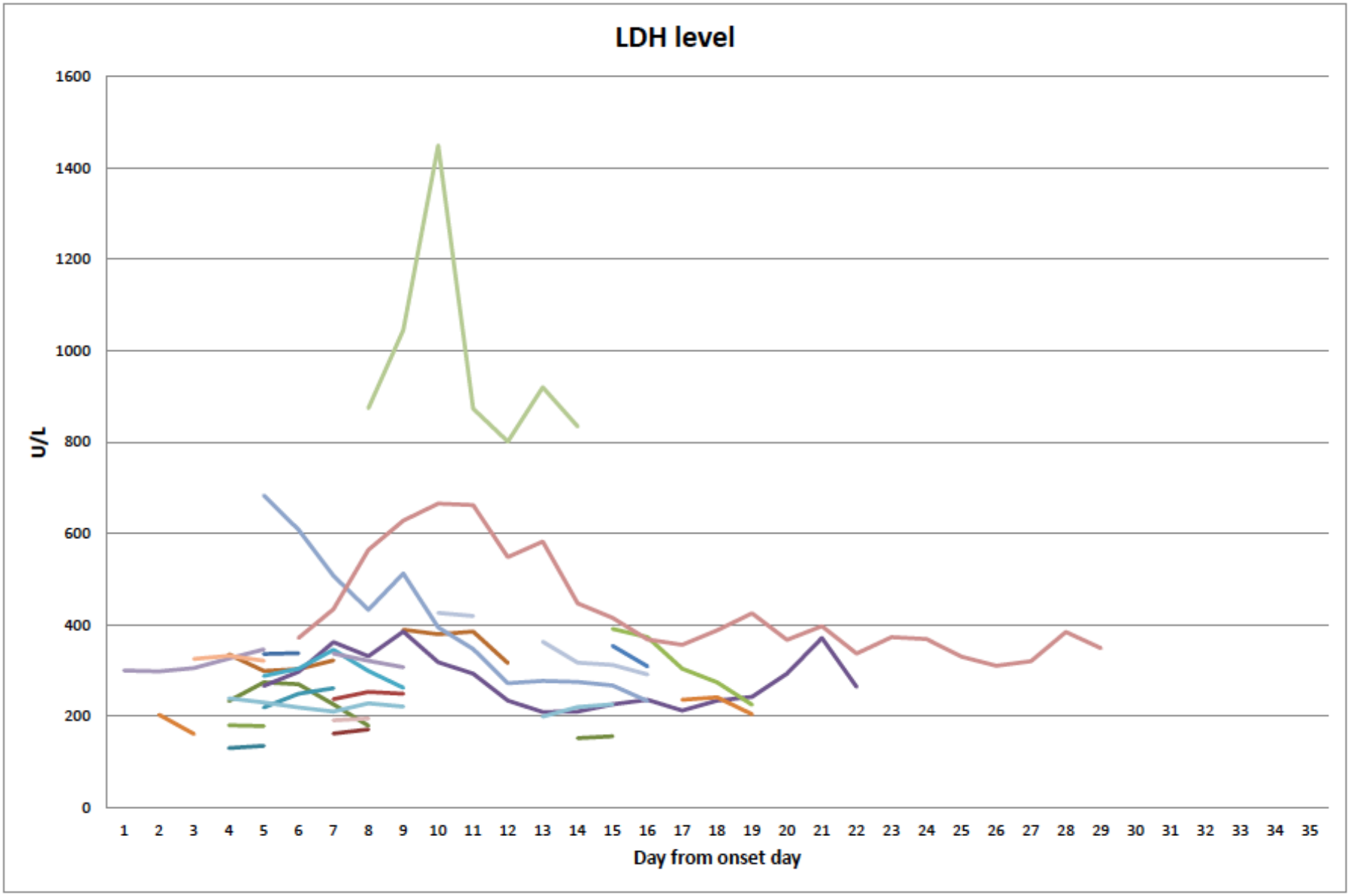
Outcome

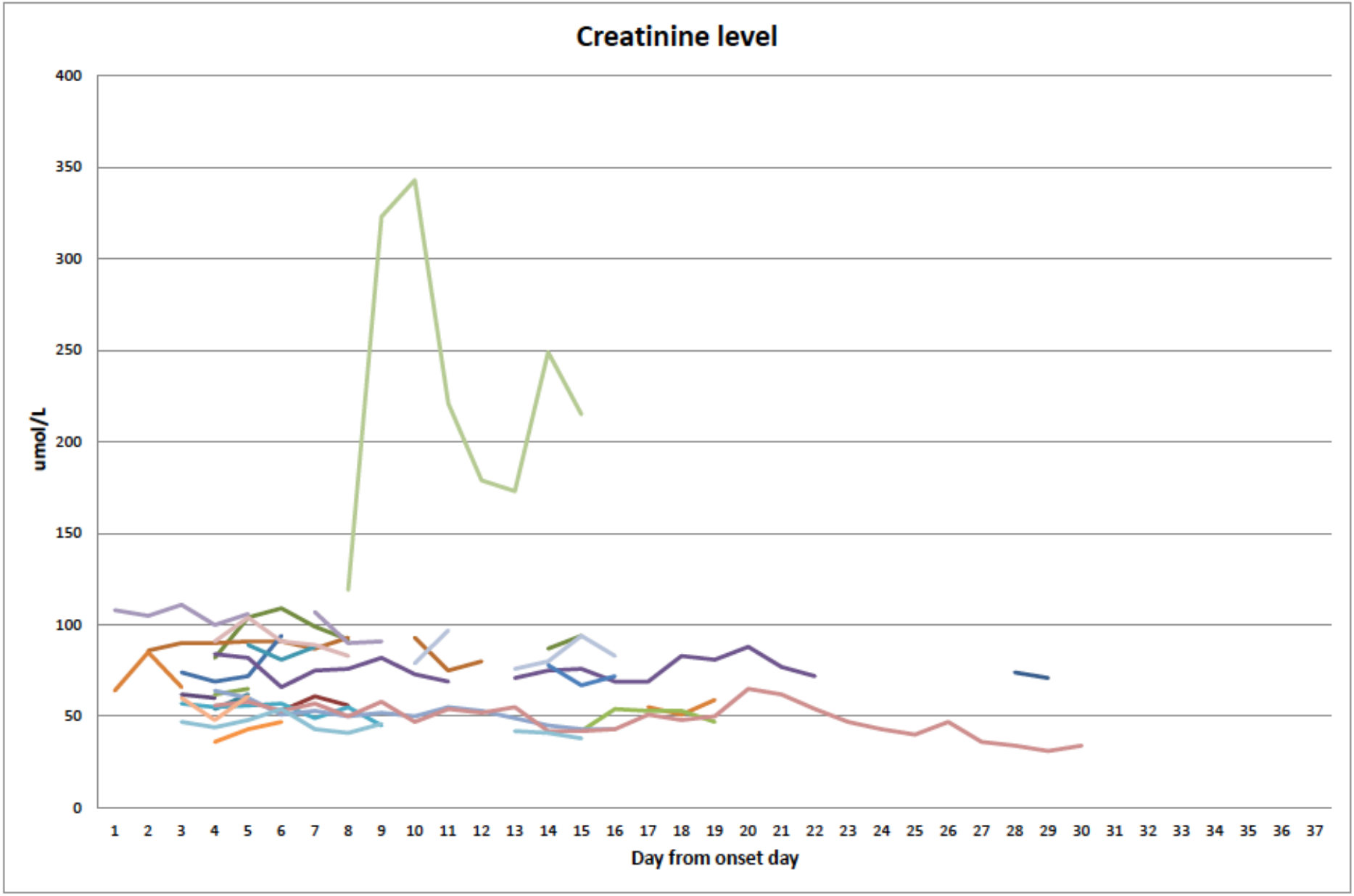
Outcomes			
Required ICU care	5 (83.3)	0	0.231
Discharged	1 (16.7)	6 (30.0)	0.471
Deceased	2 (33.3)	0	0.231

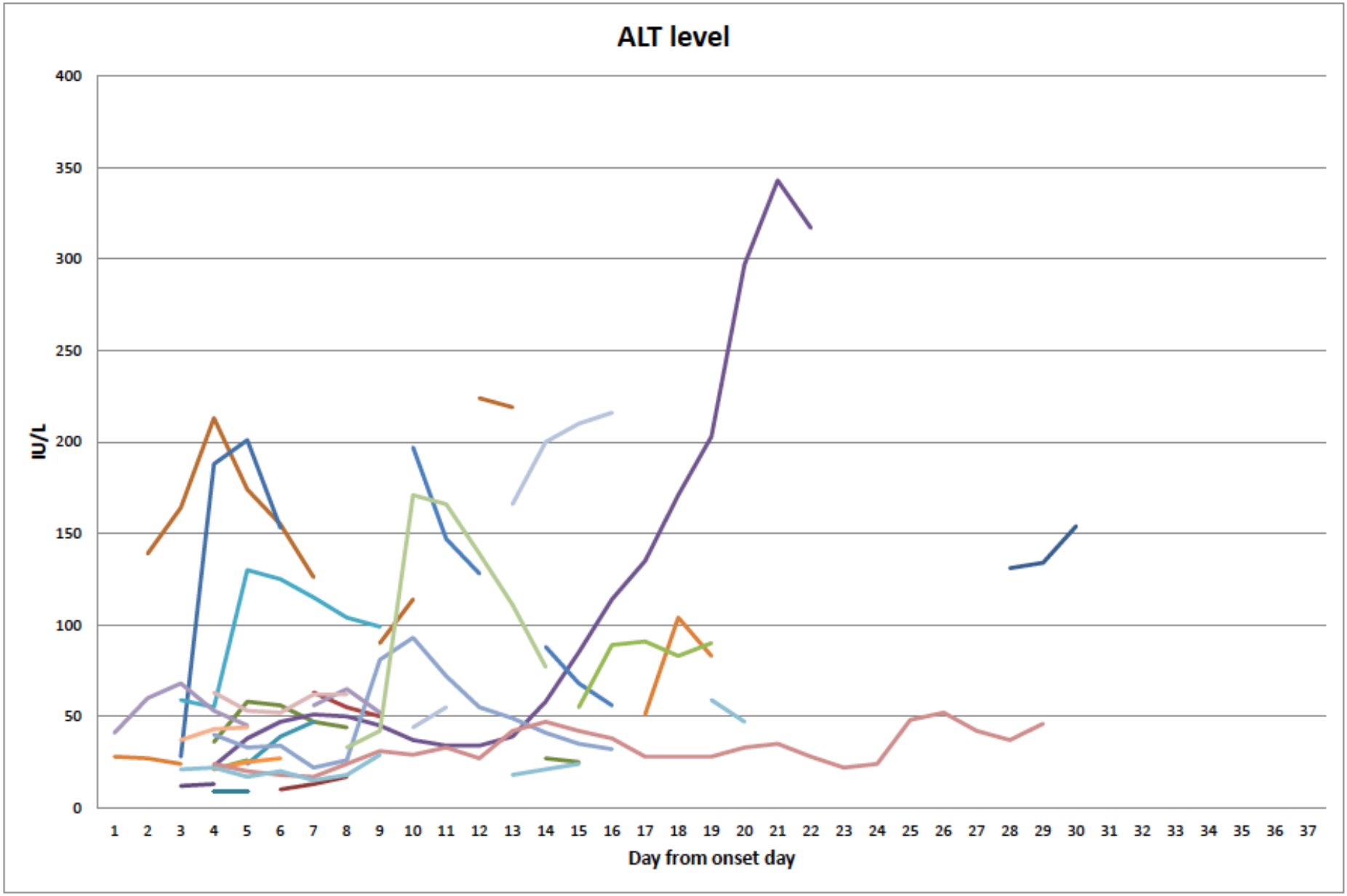

WBC level
30
25
20
15
10
5
0
10⁹/L
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Day from onset day


Lymphocyte level
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
10⁹/L
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Day from onset day


PLT level
800
700
600
500
400
300
200
100
0
10⁹/L
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Day from onset day


LDH level
1600
1400
1200
1000
800
600
400
200
0
U/L
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
Day from onset day


Creatinine level
umol/L
400
350
300
250
200
150
100
50
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Day from onset day

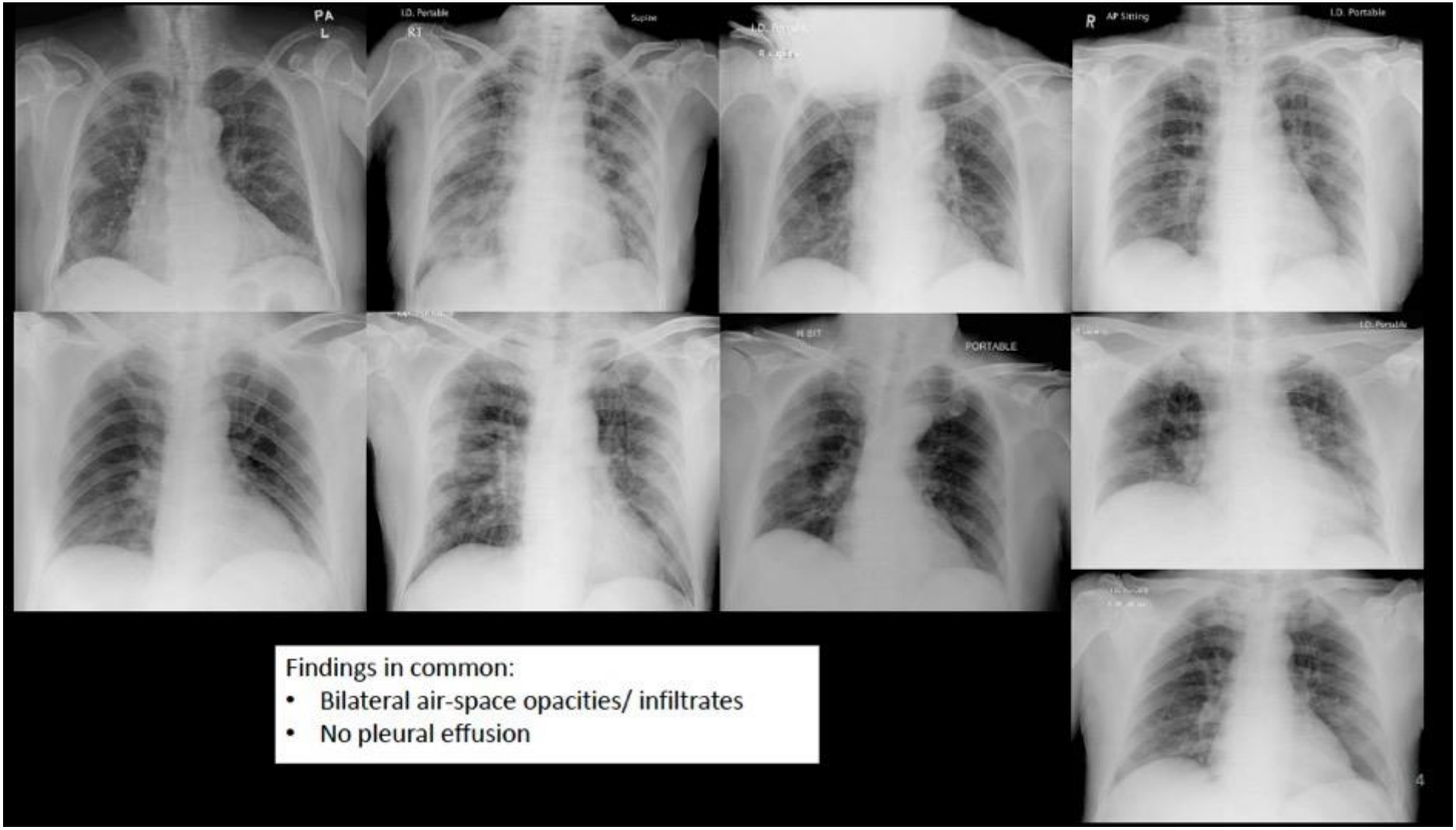

ALT level
400
350
300
250
200
150
100
50
0
IU/L
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37
Day from onset day

Summary of clinical info of PMH cases

- **Typical for viral pneumonitis**
- **WBC N or low, Lymphopenia, even for severe case**
- **ALT slightly up**
- **LDH correlate with disease activities**
- CRP high for severe case
- Could have mild myositis
- Normal: RFT (except for 1 requiring CVVH), Clotting, PCT
- Viral load High in NTS/TS for severe cases also viraemia in severe case

Radiological findings

Typical CXR findings



Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

The Key +ve CT Findings

1. Ground-glass opacities (100%)
2. Involvement of multiple lobes (100%)
3. Subpleural or peripheral distribution (often central-sparing) (100%)
4. Consolidations (77.8%)
5. Septal thickening (55.6%)
6. Bronchial dilation and wall thickening (55.6%)

Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

The Important –ve CT Findings

1. Pleural effusion (0%)
2. Lymphadenopathy (0%)
3. Lung nodule (0%)
4. Specific zonal predominance (variable)

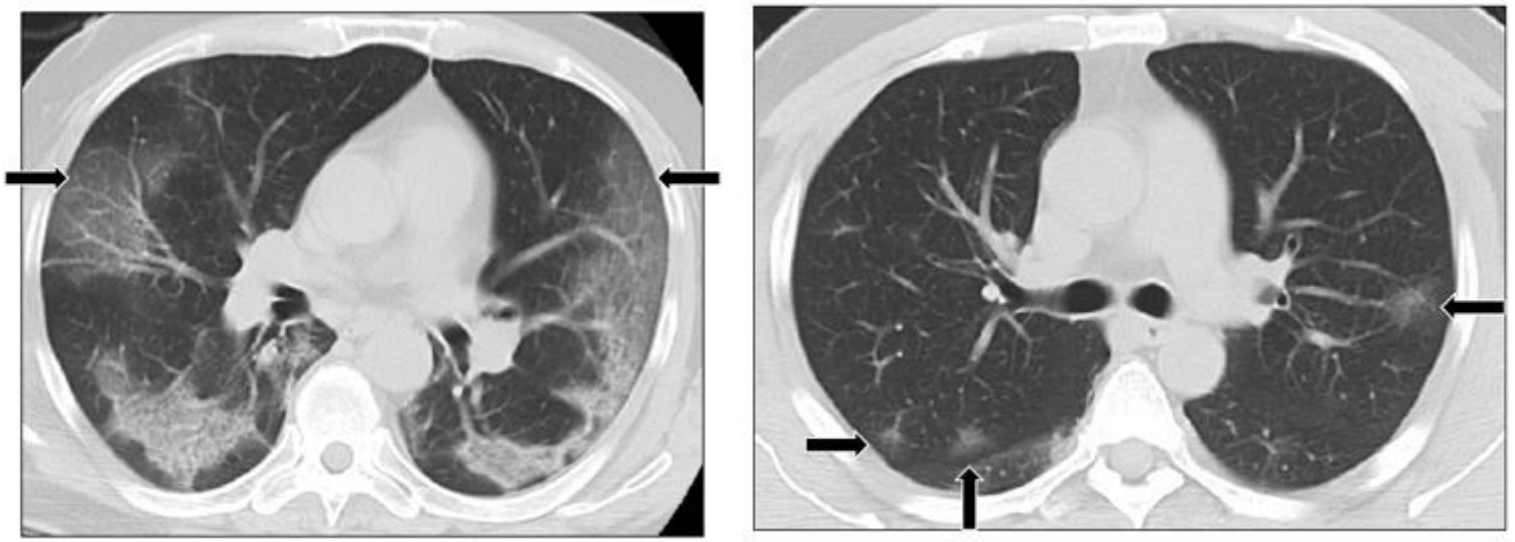
Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

Patient demographics and imaging features	
Total scans included	9
Age	63.7 (39-75)
Sex	
Male	6
Female	3
Days from diagnosis to CT	2.8
CT technique	
HRCT	7
Conventional CT	2
CT findings	
GGO	9 (100%)
All lobes involvement	8 (88.9%)
Upper lobes sparing	1
Peripheral subpleural distribution	9 (100%)
Zonal predominance	
Upper	3 (33.3%)
Basal	3 (33.3%)
Diffuse	3 (33.3%)
Interlobular/ intralobular septal thickening	5 (55.6%)
Consolidation	7 (77.8%)
Bronchial wall thickening or dilatation	5 (55.6%)
Centrilobular nodule	0 (0%)
Pleural effusion	0 (0%)
Lymph node enlargement	0 (0%)

Age and days expressed in means with range in brackets
CT findings expressed in case number with proportions in brackets

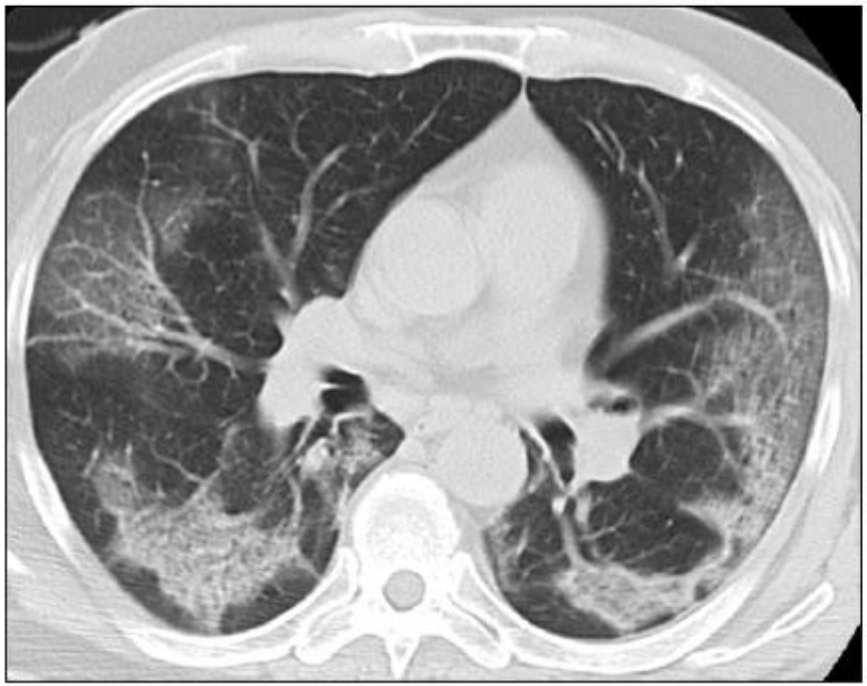
Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

Ground-glass opacities (GGO)



Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

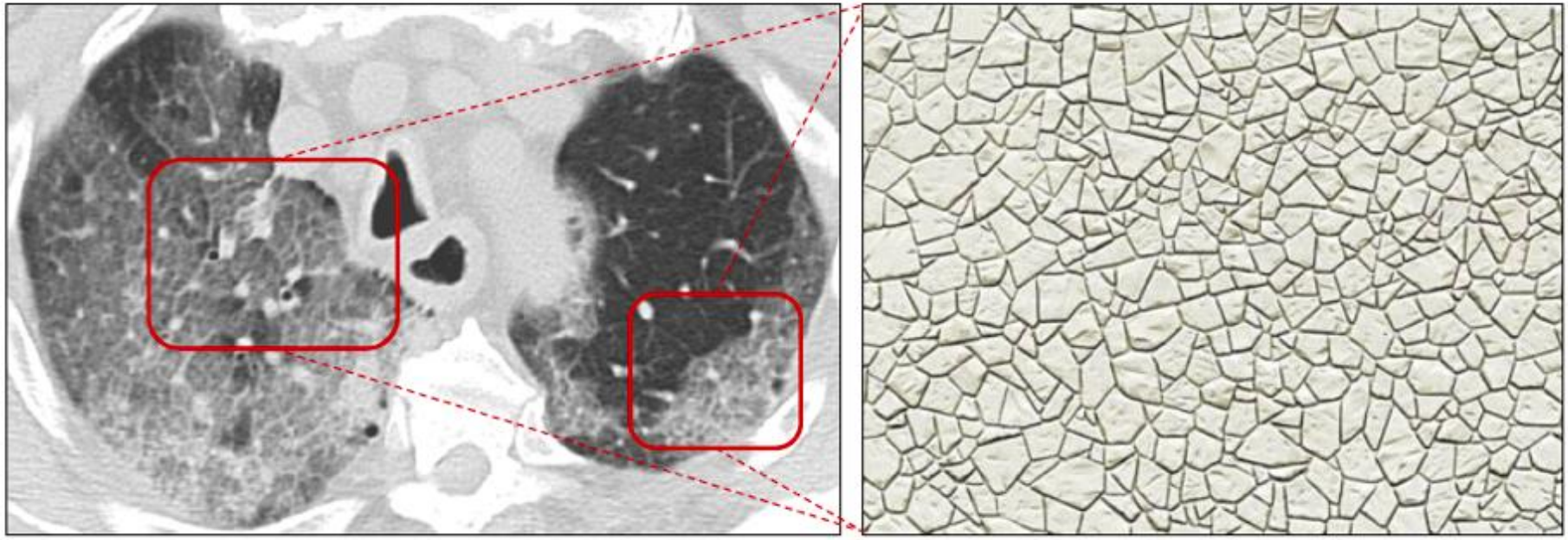
Peripheral/ subpleural distribution



- Peripheral/ subpleural regions are almost invariably involved
- Central regions are often spared/ or involved in a later stage

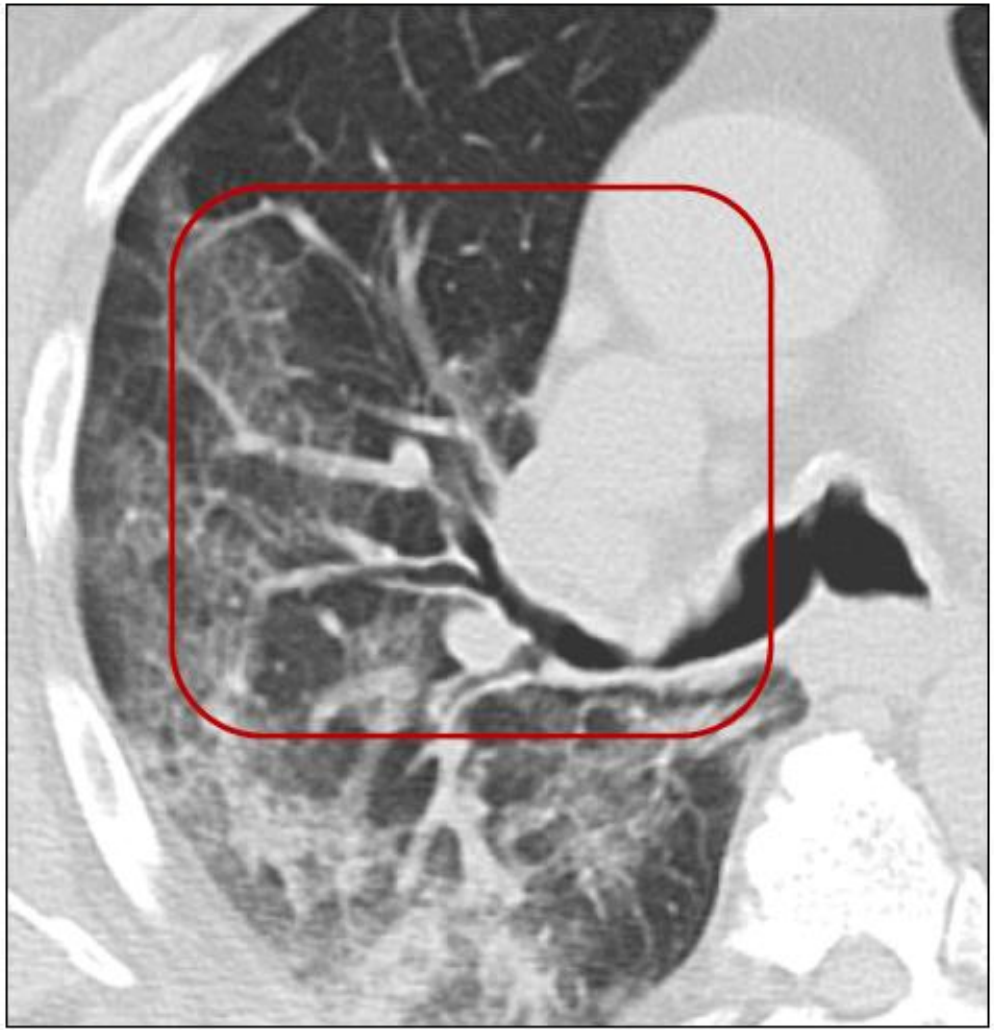
Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

Septal thickening + GGO → crazy-paving pattern



Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

Bronchial dilatation + wall thickening

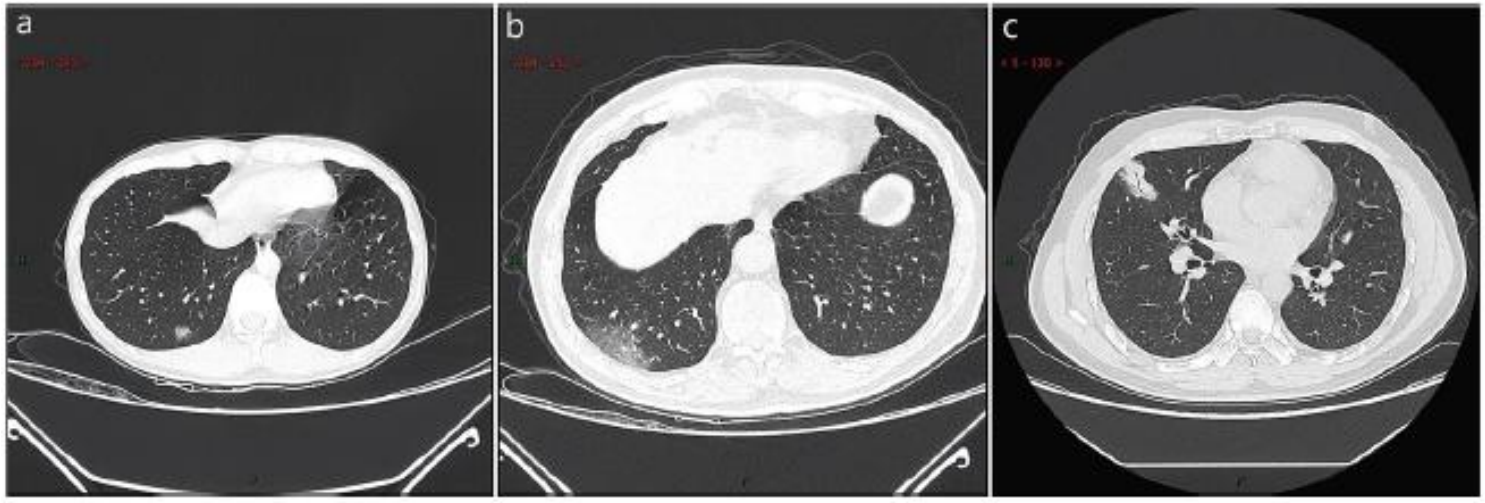


Courtesy of Dr SK Li & Dr YC Lee (Department of Radiology, PMH)

Staging by CT: Ultra- early stage

- 1-2 weeks after exposure
- No clinical manifestation
- -ve laboratory test
- +ve throat swab

- **Radiologic findings**:
  - Single, double or scattered focal ground-glass opacity
  - Nodules located in central lobule surrounded by patchy ground-glass opacities
  - patchy consolidation and sign of intra-bronchial air-bronchogram, which was dominant in the middle and lower pleura



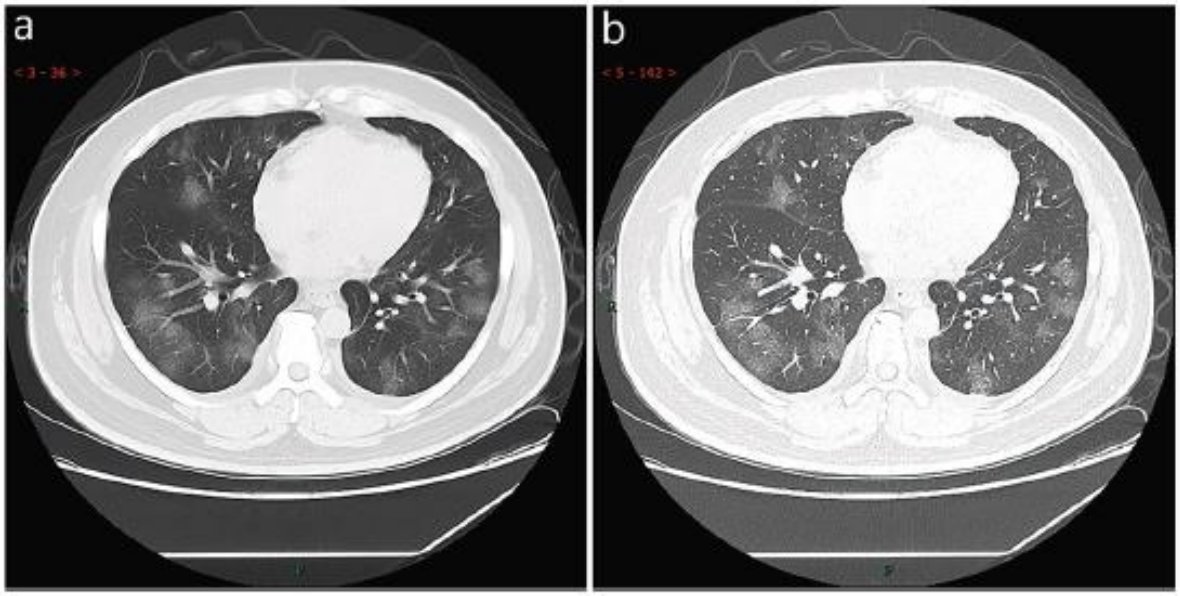
Jin YH, et al. ***Mil Med Res*** *2020;7(1) online 2020 Feb 6*

Staging by CT: Early stage

- 1–3 days after onset (fever, cough, dry cough, etc.).
- **Pathology**: dilatation and congestion of alveolar septal capillary, exudation of fluid in alveolar cavity and interlobular interstitial edema.

Radiologic findings:

- single or multiple scattered patchy or agglomerated **ground-glass opacities**, separated by honeycomb-like or grid-like **thickened of interlobular septa**



Jin YH, et al. ***Mil Med Res*** *2020;7(1) online 2020*

Staging by CT: Rapid progressive stage

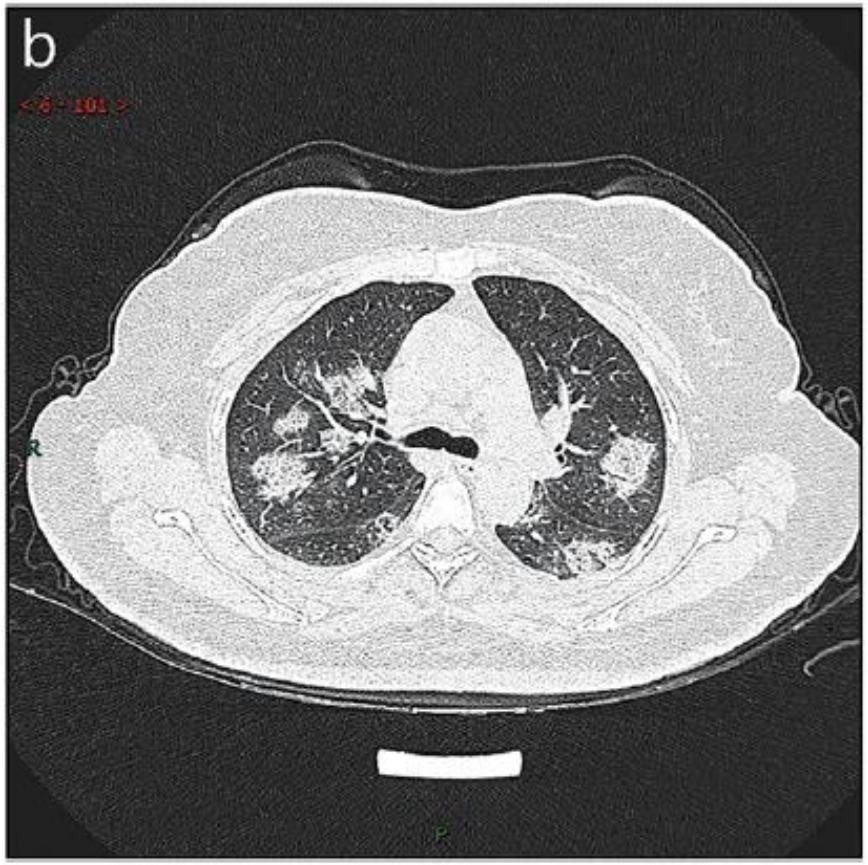
- 3–7 days after onset

Pathology:

- accumulation of a large number of cell-rich exudates in the alveolar cavity,
- vascular expansion and exudation in the interstitium,
- both lead to further aggravation of alveolar and **Interstitial edema**.
- The fibrous exudation connects each alveolus through the inter-alveolar space to form a fusion state.

Radiologic findings:

- A fused and large-scale **light consolidation** with **air-bronchogram** inside



Jin YH, et al. ***Mil Med Res*** *2020;7(1) online 2020*

Staging by CT: Consolidation stage

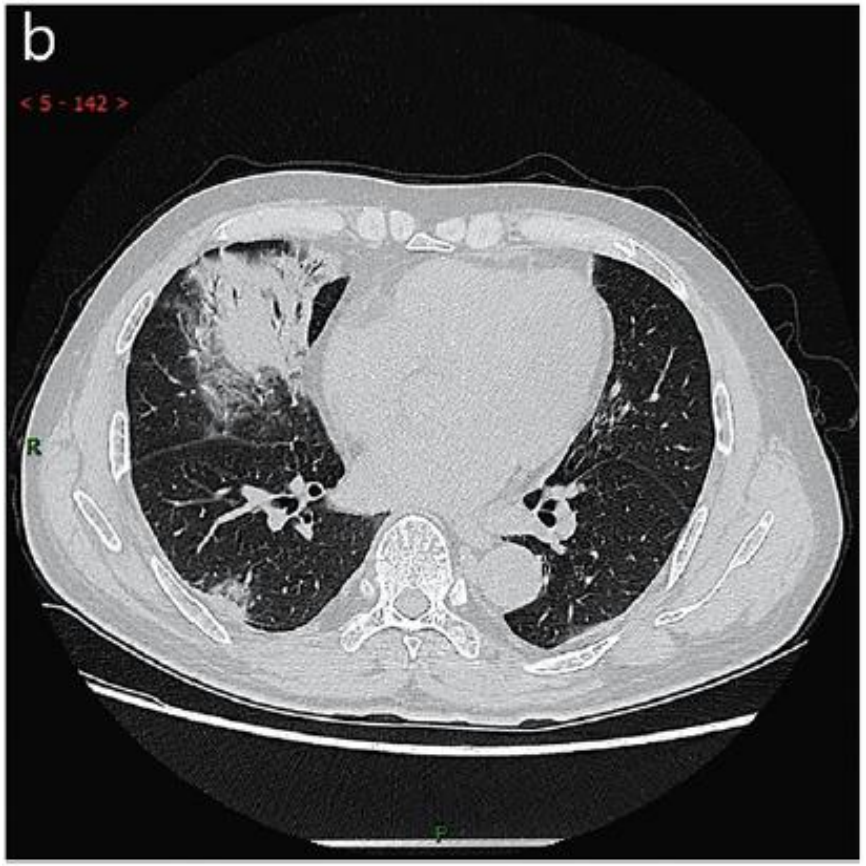
- 7-14 days after onset

Pathology:

- fibrous exudation of the alveolar cavity and the disappearance of capillary congestion in the alveolar wall.

Radiologic findings:

- multiple patchy **consolidations** in slighter density and smaller range than that of the previous stage



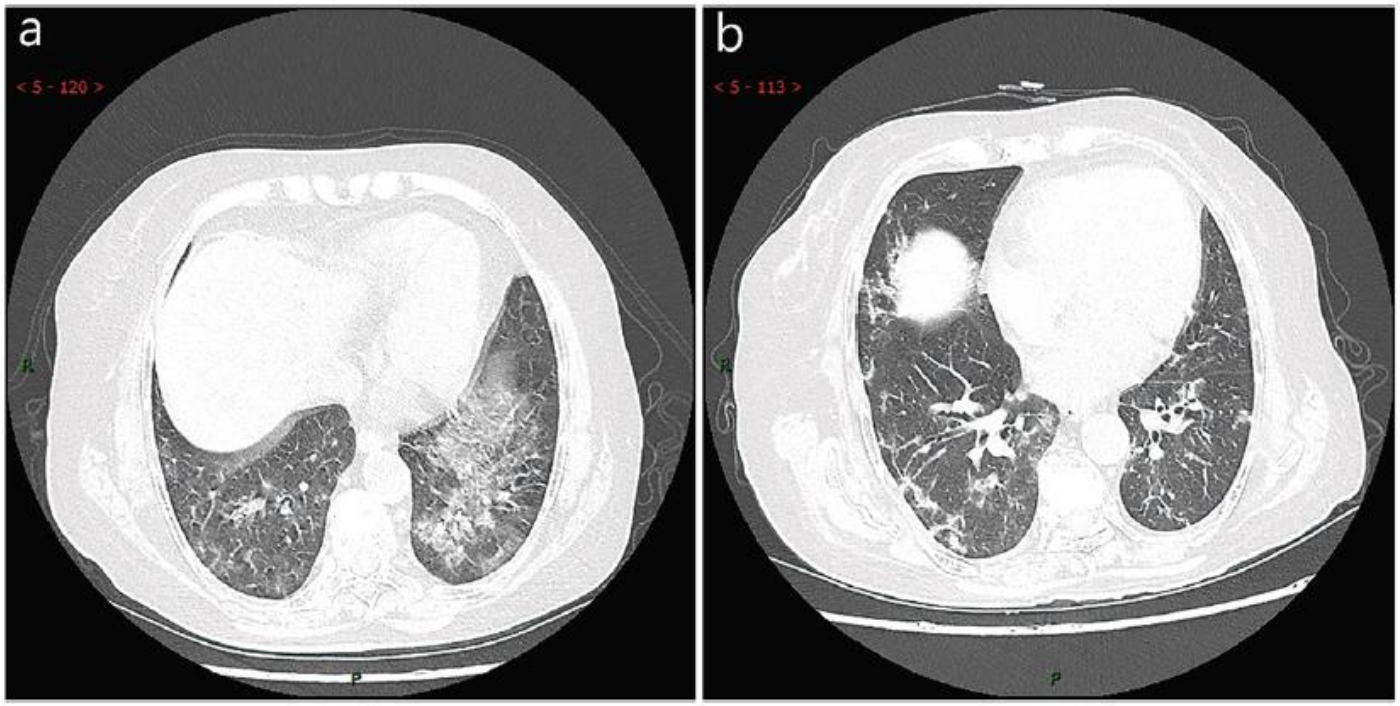
Jin YH, et al. ***Mil Med Res*** *2020;7(1) online 2020*

Staging by CT: Dissipation stage

- 2 and 3 weeks after the onset
- Range of lesions was further reduced.

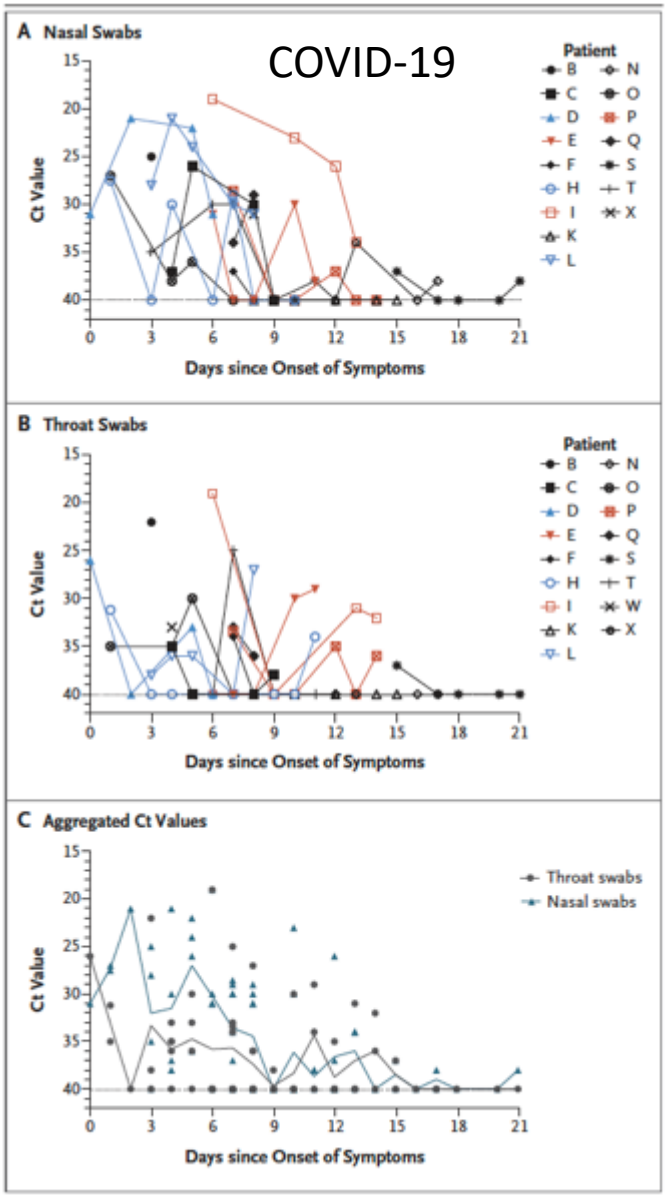
Radiologic findings:

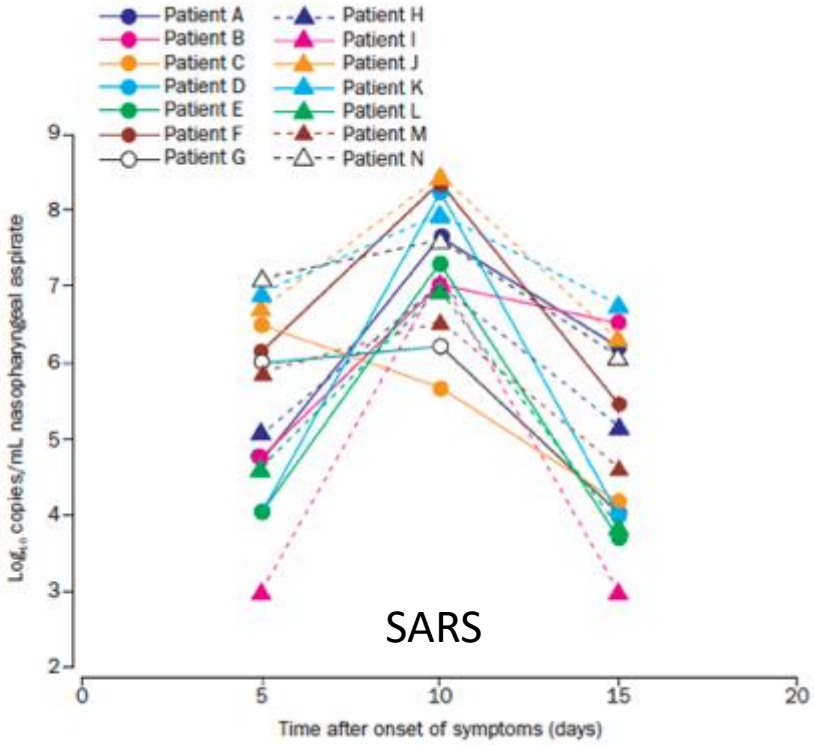
- patchy consolidation or strip-like opacity.
- As time goes on, it showed **grid-like thickening of interlobular septum**, thickening and strip-like twist of bronchial wall and a few scattered **patchy consolidations**



Jin YH, et al. ***Mil Med Res*** *2020;7(1) online 2020*

Viral shedding





- In general, downward trend for COVID-19.
- Vs SARS peaked at day 10

Peiris JS, dt al. ***Lancet*** *2003; 361: 1767–72.*
Zou L, et al. ***N Eng J Med*** *2020 Feb 19 [Online ahead of print]*

Clinical management

Clinical Management

- **General Clinical Management**
  - Monitor vital signs and organ functions, and recognize complication(s) early
  - Liaise with ICU early for intensive care if anticipate clinical deterioration
  - Provide supportive treatments
    - Antibacterial
    - Oxygen
    - *High-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) should only be used in selected patients with hypoxemia respiratory failure.*
    - IV fluid
    - Inotropic support +/-steroid* (septic shock)
    - Mechanical ventilation +/-ECMO (respiratory failure)

* ***Use of corticosteroids***
- *Do not routinely give systemic corticosteroids*
- *Use of short-period, stress dose steroids (hydrocortisone 200mg max daily) for refractory septic shock or other clinical indications on physician discretion*

Specific Treatment for **SARS and MERS**

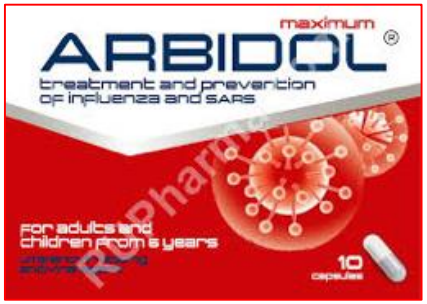
Treatment Modalities	Study focus	Safety profile	Order of recommendation
Convalescent Plasma	**SARS**: Clinical, in vitro, animal **MERS**: in vitro, animal	**Good**	***1***
Interferon	**SARS**: Clinical, in vitro, animal **MERS**: Clinical, in vitro, animal	**Well established**	***1***
Protease inhibitors	**SARS**: Clinical, in vitro, animal **MERS**: Clinical, in vitro, animal	**Well established,** mild GI & liver toxicity	***1***
Monoclonal & polyclonal neutralizing Ab	**SARS**: in vitro, animal **MERS**: Clinical, in vitro, animal	**MERS:** SAB-301 (Safe)	***1***
Interferon + Ribavirin	**SARS**: Clinical, in vitro, animal **MERS**: Clinical, in vitro, animal	Hemoptysis with ribavirin	2
Nitazoxanide	**MERS**: in vitro	**Well established**	2
Chloroquine	**SARS**: in vitro, animal **MERS**: in vitro, animal	**Well established**	2
Corticosteroids	**SARS**: Clinical, animal **MERS**: Clinical	Prolonged viremia, nosocomial infection, VAP, increase mortality	3
IVIG, MMF or ribavirin monotherapy	Not conclusive in in vitro, animal or clinical	**Well established**	3

Evidence base for specific therapies for MERS-CoV infection :
1: **Benefit is likely to exceed risk**
2: **Data is inadequate for assessment**
3: **Risk is likely to exceed benefit**

*ISARIC. **Treatment of MERS-CoV: Decision Support Tool. Clinical Decision Making Tool for Treatment of MERS-CoV v**.4.0, 16 /8/2017*

Clinical trials on **COVID-19** in China (>85)

- **Remdesivir**: Anti Ebola Rx
- **Kaletra**: HIV drug
- **Interferons**
- Influenza drugs:
  - **Oseltamivir**
  - **Baloxavir**
  - **Umifenovir (Arbidol)**
- **Chloroquine**: malaria drug
- **Novaferon**: Anti tumor IFN
- **Tenofovir:** HBV Rx
- **Traditional Chinese medicine**: lianhua qingwen



Potential specific anti-viral agents with available stocks in HA pharmacy

- **Kaletra** (Lopinavir/ritonavir): Anti-HIV Rx
- **Interferons** (interferon-*β,* interferon- γ)
- **Ribavirin**: synergistic effect with kaletra
- **Remdesivir**:
  - Improve both lung fx of Mice and reduce viral load
  - Clinical trail in China has been completed, pending for 28d outcome
  - 3 sites in HK for Gilead sponsored clinical trials: PMH, QMH and PWH

Chu CM, et al. ***Thorax*** *2004;59(3):252-6.*
Cinatl J, et al. ***Lancet*** *2003; 362: 293–94*
Sheahan TP, et al. ***Nat Commun*** *2020; 11(1): 222 doi: 10.1038/s41467-019-13940-6.*

Remdesivir in cell culture (**MERS**)

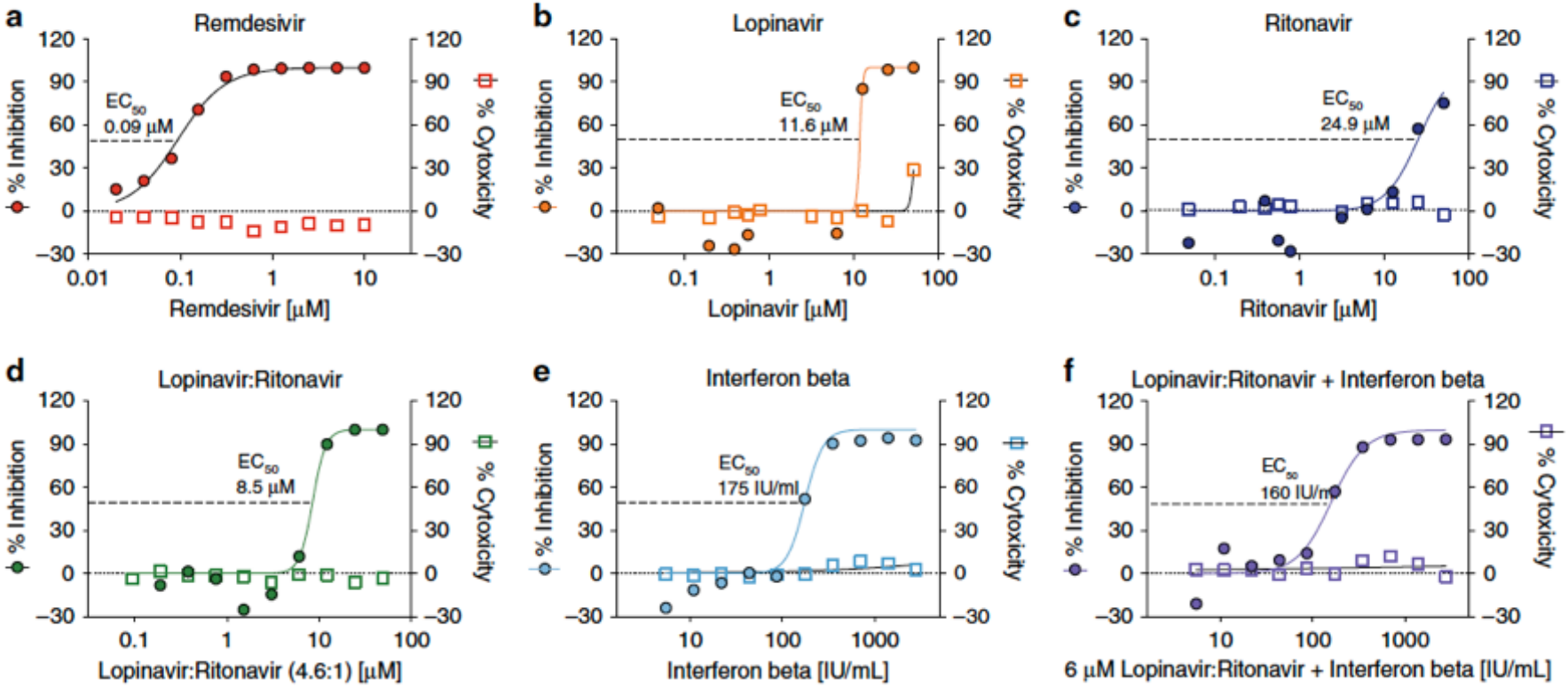
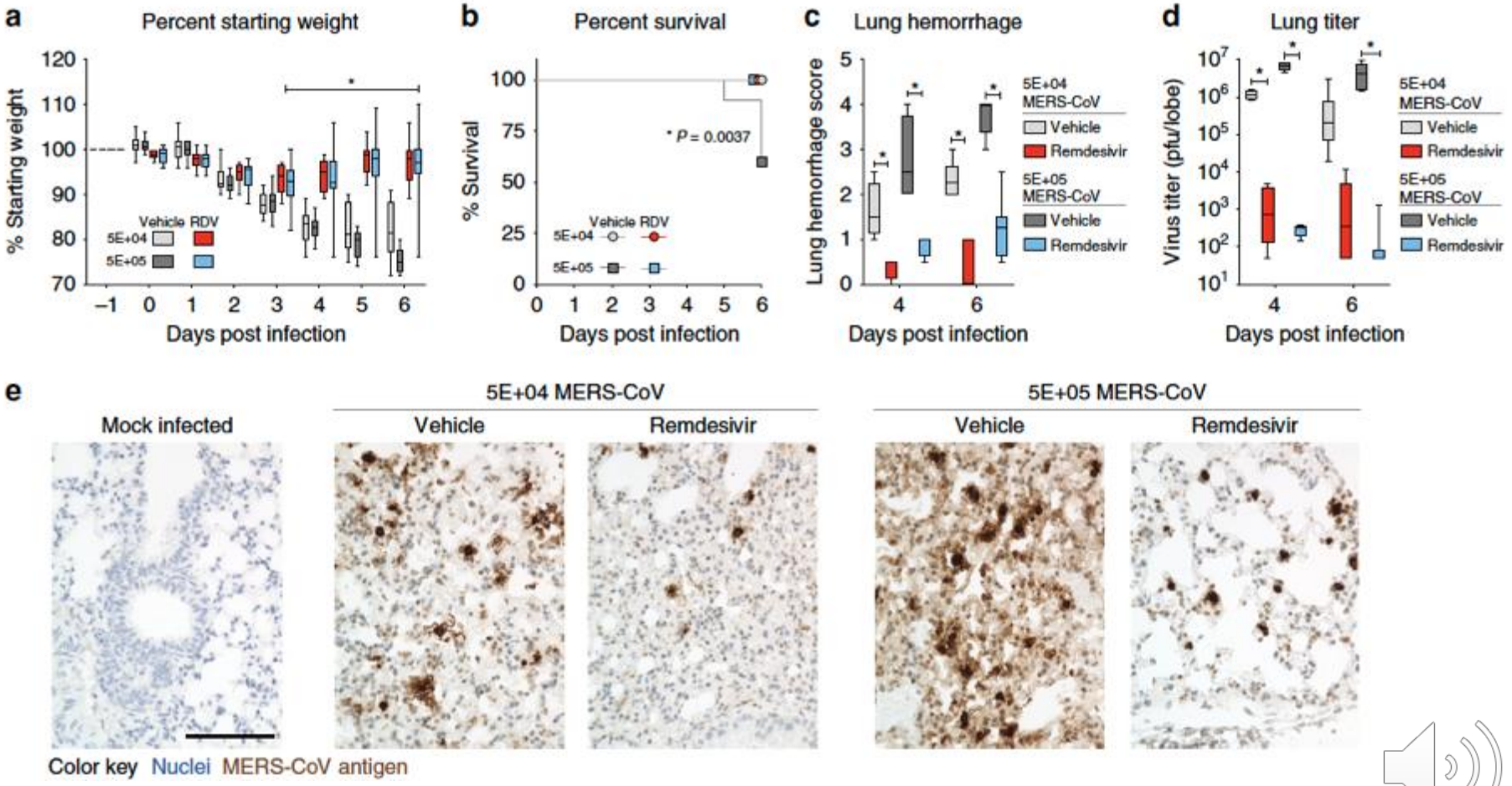


Fig. 1 RDV and IFNb have superior antiviral activity to LPV and RTV. Graphs depict mean % inhibition of MERS-CoV replication (left *Y*-axis) and % cytotoxicity (right *Y*-axis) of antivirals. Calu-3 cells were infected in sextuplicate with MERS-CoV nanoluciferase (nLUC) at a multiplicity of infection (MOI) of 0.08 in the presence of a dose response of drug for 48 h, after which replication was measured through quantitation of MERS-CoV–expressed nLUC. Cytotoxicity was measured in similarly treated but uninfected cultures via Cell-Titer-Glo assay. Representative data are shown from four independent experiments.

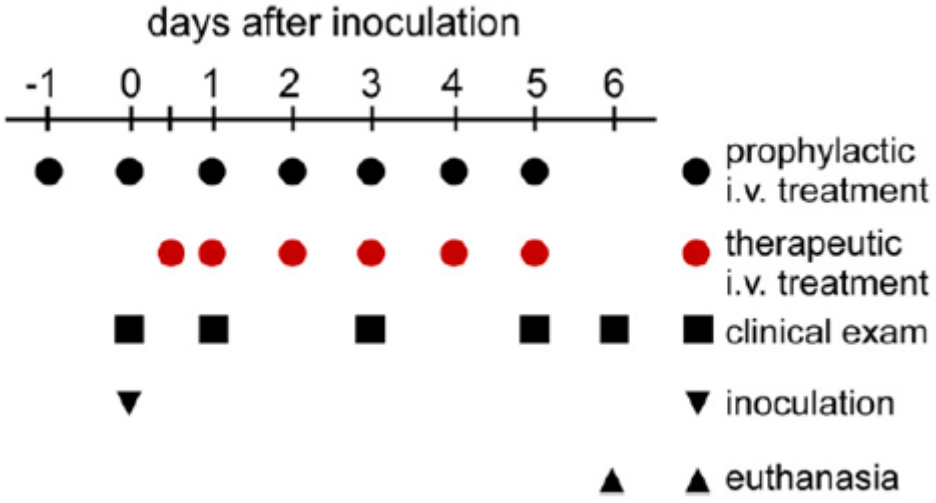
Sheahan TP, et al. ***Nat Commun*** *2020;11:222*

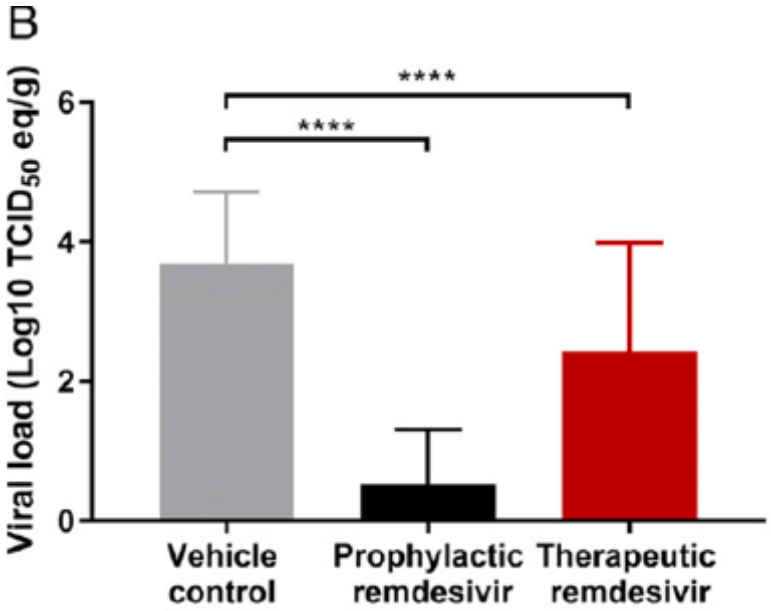
Remdesivir in mice (**MERS**)



Sheahan TP, et al. ***Nat Commun*** *2020;11:222*

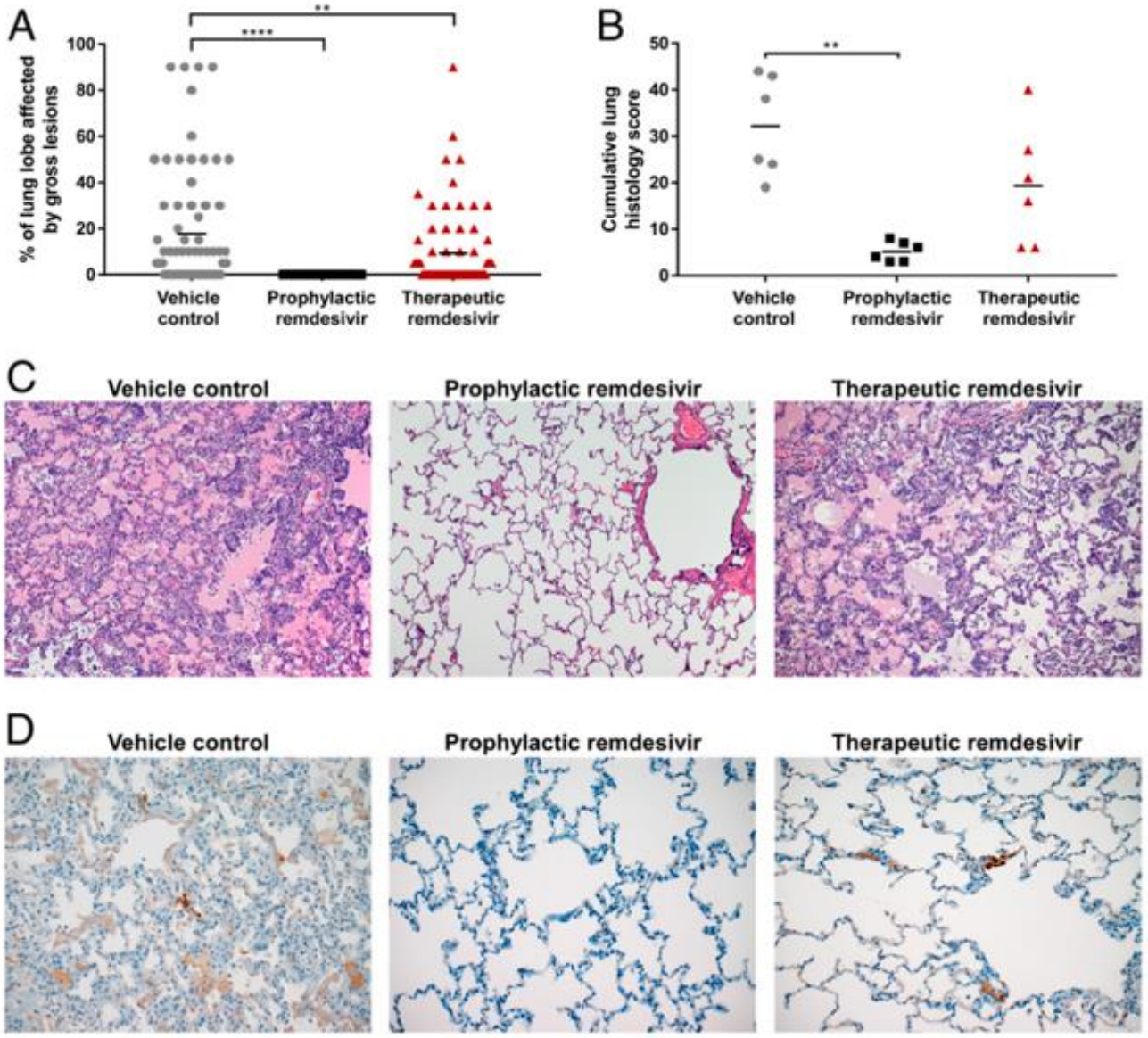
Remdesivir in non-human primates (**MERS**)





de Wit E, et al. Proc Natl Acad Sci U S A. 2020 Feb 13. [Epub ahead of print]

Remdesivir in non-human primates (**MERS**)



de Wit E, et al. Proc Natl Acad Sci U S A. 2020 Feb 13. [Epub ahead of print]

Remdesivir used in 1 US COVID-19 patient

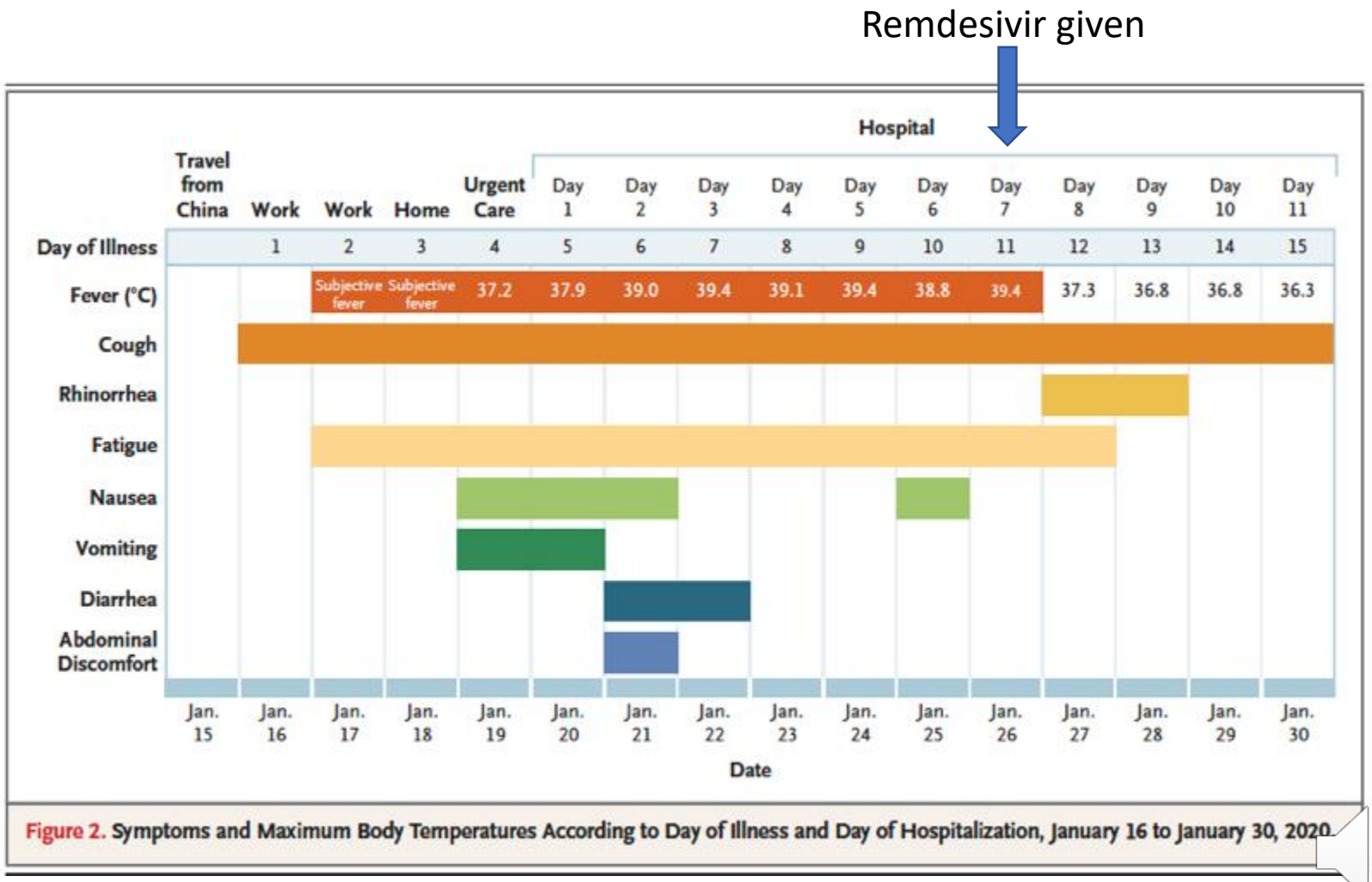


Figure 2. Symptoms and Maximum Body Temperatures According to Day of Illness and Day of Hospitalization, January 16 to January 30, 2020.

Holshue ML, et al. ***N Eng J Med*** *published on January 31, 2020*

Remdesivir

Table 2. Results of Real-Time Reverse-Transcriptase–Polymerase-Chain-Reaction Testing for the 2019 Novel Coronavirus (2019-nCoV).*

Specimen	Illness Day 4	Illness Day 7	Illness Day 11	Illness Day 12
Nasopharyngeal swab	Positive (Ct, 18–20)	Positive (Ct, 23–24)	Positive (Ct, 33–34)	Positive (Ct, 37–40)
Oropharyngeal swab	Positive (Ct, 21–22)	Positive (Ct, 32–33)	Positive (Ct, 36–40)	Negative
Serum	Negative	Negative	Pending	Pending
Urine	NT	Negative	NT	NT
Stool	NT	Positive (Ct, 36–38)	NT	NT

- No adverse events were observed
- Supplemental oxygen was discontinued
- SaO2 improved to 94 to 96% n room air
- Previous bilateral lower-lobe rales were no longer present

Holshue ML, et al. ***N Eng J Med*** *published on January 31, 2020*

Kaletra for **SARS**: retrospective human study

(*Protease inhibitor)*

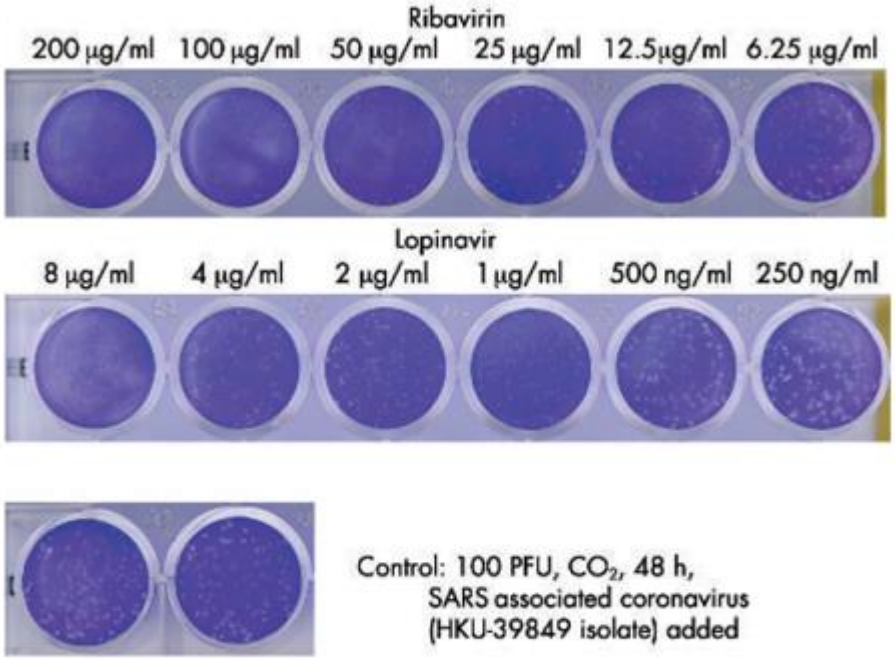


Figure 1 Dose dependent antiviral effects of ribavarin and lopinavir on SARS coronavirus. In vitro antiviral susceptibility testing showed that the cytopathic effect was inhibited by lopinavir at 4 μg/ml and ribavirin at 50 μg/ml after 48 hours of incubation.

Table 3 Adjustment of odds ratio of lopinavir/ritonavir treatment for lactate dehydrogenase (LDH) level with respect to the adverse outcome of death or development of acute respiratory distress syndrome (ARDS) requiring intensive care within 21 days

Variables	Adjusted odds ratio (95% CI)	p value
Treatment		
Controls	1.000	–
Treatment group	0.076 (0.01 to 0.589)	0.014
LDH level (per 100 IU/l increase)	1.155 (0.953 to 1.401)	0.142

- **SARS**: Kaletra (n=41) vs Ribavirin (n=111)
  - ARDS & death 2.4% vs 28.8% (P< 0.001);
- **MERS** study using **Kaletra + IFN** ongoing (**MIRACLE** Trial)

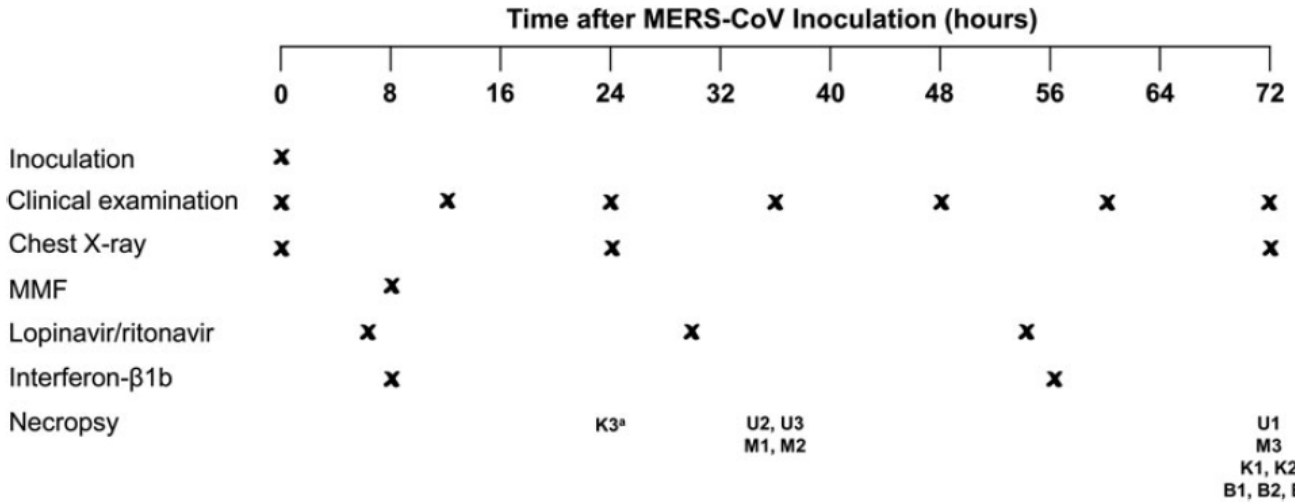
Chu CM, et al. ***Thorax*** *2004;59(3):252-6.*

Arabi YM, et al. ***MIRACLE trial****: study protocol for a RCT. Trials 2018;* ***19:*** *81.*

Kaletra in **MERS:** Non-human primates study

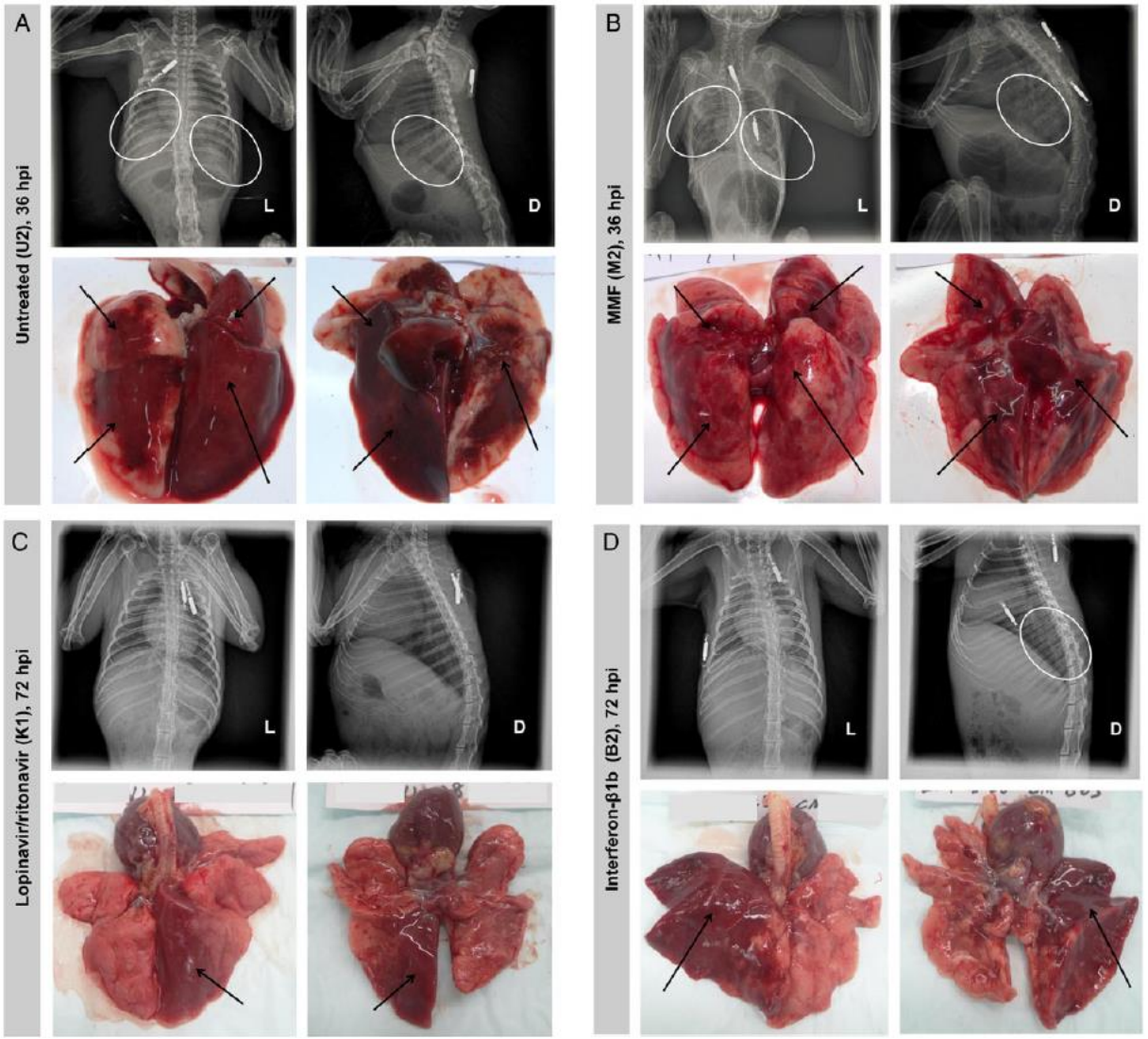
Group	Common Marmoset	Treatment Regimen
1	U1, U2, U3	Untreated (sham treatment with comparable volume per kg body weight of sterile saline)
2	M1, M2, M3	CellCept (25 mg/kg of MMF given ip once at 8 hpi)
3	K1, K2, K3	Kaletra (12 mg/kg/day of lopinavir + 3 mg/kg/day of ritonavir given orally once daily at 6, 30, and 54 hpi)
4	B1, B2, B3	Betaferon (0.267 million IU/kg of interferon-β1b given sc at 8 hpi and at 56 hpi)

Abbreviations: hpi, hours postinoculation; ip, intraperitoneal; MMF, mycophenolate mofetil; sc, subcutaneous.



JF Chan et al. ***J Infect Dis*** *2015:212 (12), 1904-13.*

Kaletra in **MERS:** Non-human primates study



Kaletra & IFN

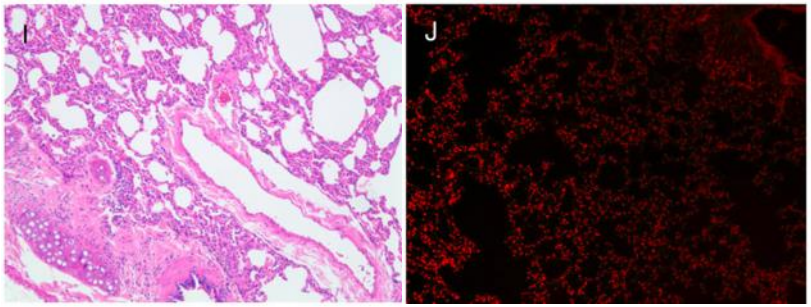
- improved clinical (mean clinical scores ↓50.9%–95.0%
- ↓weight loss
- XR: minimal pulmonary infiltrates
- Pathological: mild bronchointerstitial pneumonia
- Lower mean viral loads in necropsied lung (↓0.59–1.06 log copies/glyceraldehyde 3-phosphate dehydrogenase [GAPDH]; $P < .050$) and extrapulmonary tissue

MMF:

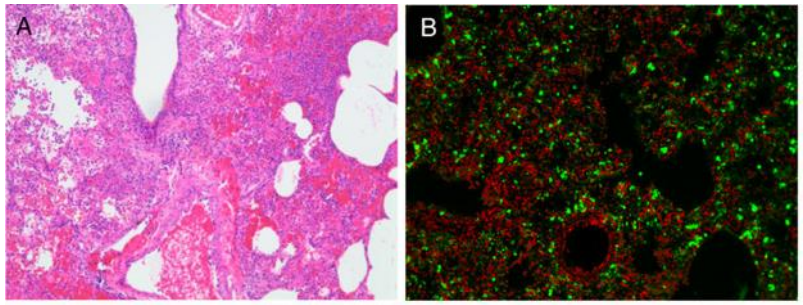
- All animals developed severe and/or fatal disease
- higher mean viral loads (↑0.15–0.54 log copies/GAPDH)

JF Chan et al. ***J Infect Dis*** *2015:212 (12), 1904-13.*

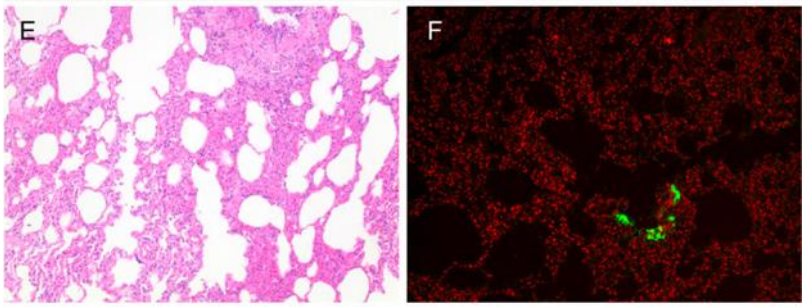
Kaletra in **MERS:** Non-human primates study



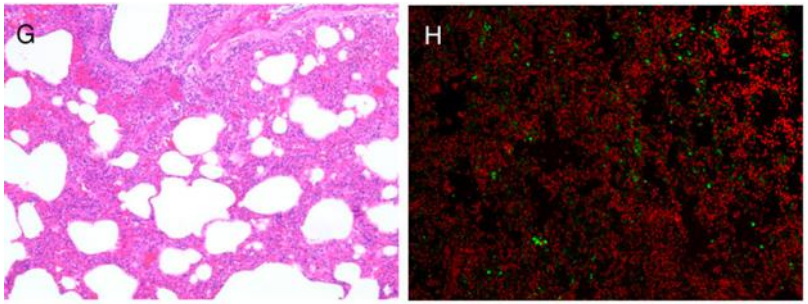
Healthy control



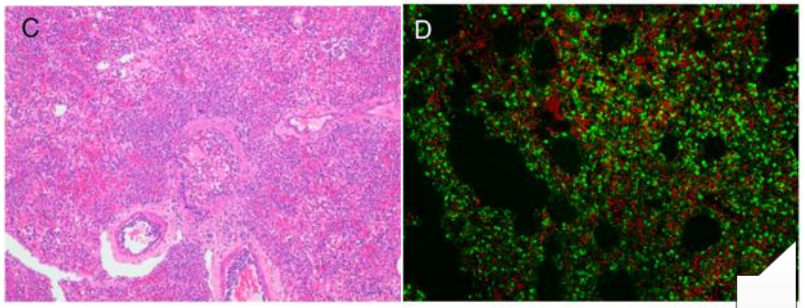
Untreated MERS infected



Kaletra treated



IFN treated



MMF treated

JF Chan et al. ***J Infect Dis*** *2015:212 (12), 1904-13.*

Arabi *et al. Trials* (2020) 21:8
https://doi.org/10.1186/s13063-019-3846-x

Trials

UPDATE Open Access

Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial

Yaseen M. Arabi[1,2*], Ayed Y. Asiri[3], Abdullah M. Assiri[4], Hani A. Aziz Jokhdar[5], Adel Alothman[1,6], Hanan H. Balkhy[1,7], Sameera AlJohani[1,8], Shmeylan Al Harbi[9,10], Suleiman Kojan[1,6], Majed Al Jeraisy[9,10], Ahmad M. Deeb[11,12], Ziad A. Memish[13,14], Sameeh Ghazal[3], Sarah Al Faraj[3], Fahad Al-Hameed[15,16], Asim AlSaedi[15,17], Yasser Mandourah[18], Ghaleb A. Al Mekhlafi[19], Nisreen Murad Sherbeeni[20], Fatehi Elnour Elzein[20], Abdullah Almotairi[21], Ali Al Bshabshe[22], Ayman Kharaba[23], Jesna Jose[24], Abdulrahman Al Harthy[25], Mohammed Al Sulaiman[26], Ahmed Mady[27,28], Robert A. Fowler[29,30], Frederick G. Hayden[31], Abdulaziz Al-Dawood[1,2], Mohamed Abdelzaher[32,33], Wail Bajhmom[34], Mohamed A. Hussein[12,24] and and the Saudi Critical Care Trials group

Still recruiting patients in the middle east

Chinese study on Kaletra/Arbidol for **COVID-19**

项目	洛匹那韦利托那韦组（n=52）	阿比多尔组（n=34）	对照组（n=48）
	Kaletra	Arbidol	SOC

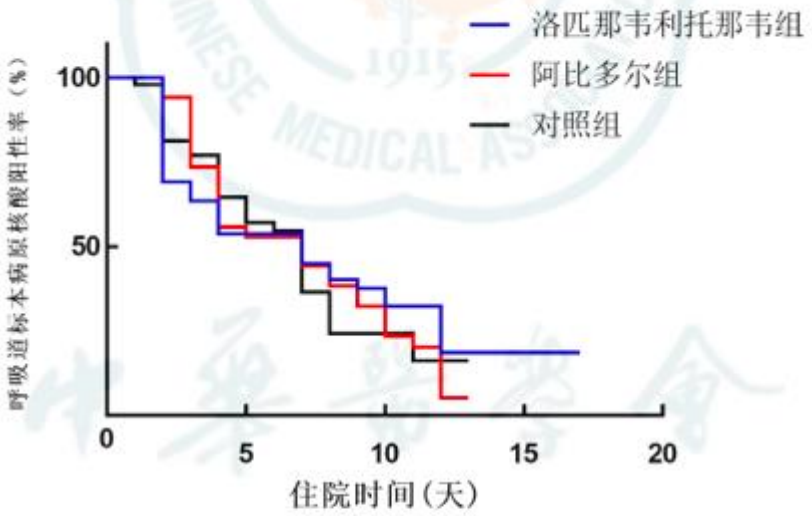


图 1　阿比多尔组、洛匹那韦利托那韦组和对照组患者呼吸道标本病毒核酸转阴时间

Duration of Rx: 5 days

组别	体温恢复正常中位时间	7 天治疗核酸转阴率	不良反应发生率
对照组	4 天	77.1%	8.3%
洛匹那韦利托那韦组	6 天	71.8%	17.8%
阿比多尔组	6 天	82.6%	8.8%

SOC
Kaletra
Arbidol

中华传染病杂志 **2020**年 上海市公共卫生临床中心感染与免疫科

An open-label randomized controlled trial on lopinavir/ ritonavir, ribavirin and interferon β-1b combination versus lopinavir/ ritonavir alone, as treatment for 2019-novel-coronavirus (2019-n-CoV) infection

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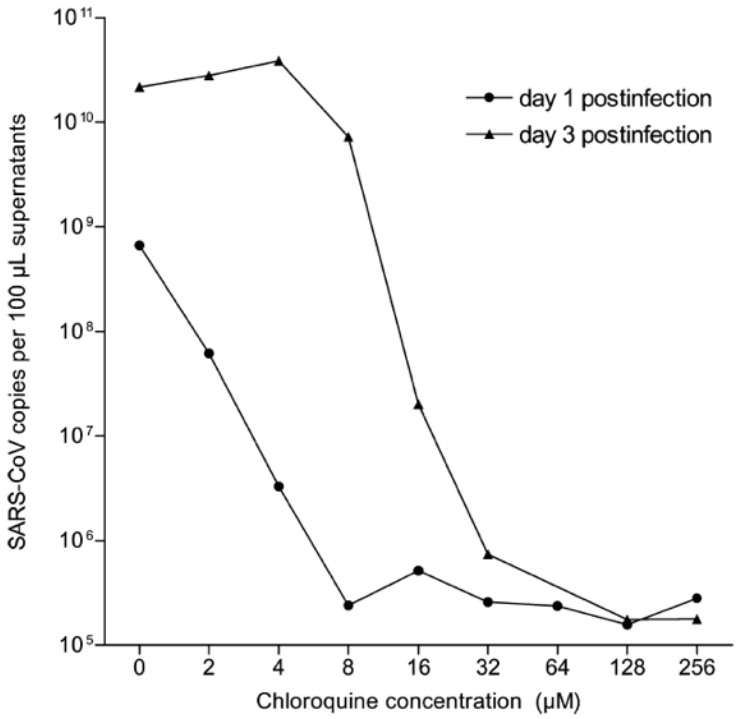
Department of Medicine/ Department of Microbiology

University of Hong Kong

Chloroquine (Antimalaria therapy) in **SARS**

In vitro

SARS-CoV-infected **Vero E6 cells**

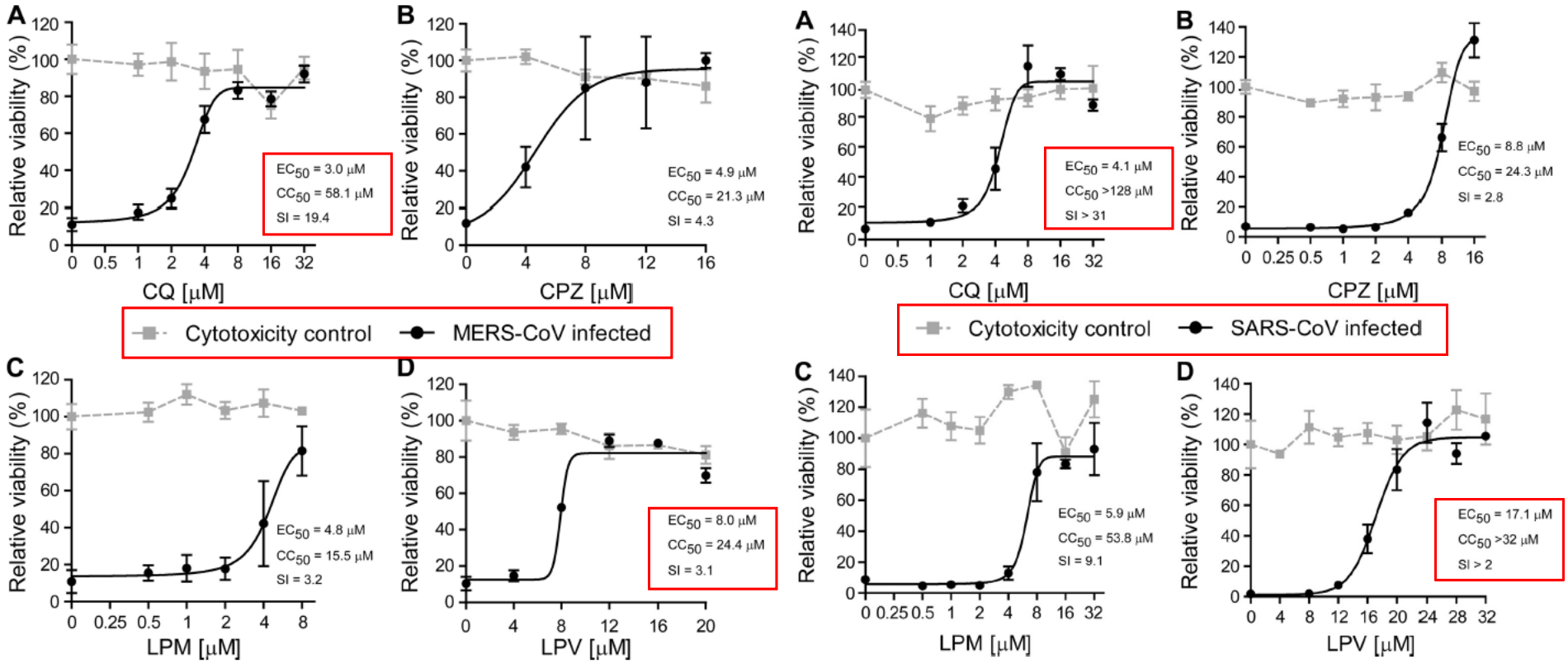


Animal

Compound	Mice/group, *n*	**SARS-CoV** i.p. administration: Treatment, mg/kg	Day 3 virus titre, $\log_{10}$ $CCID_{50}$/g*
Chloroquine†	15	50	4.9 ±0.4
		10	4.9 ±0.3
		1	5.1 ±0.1
		Placebo	4.7 ±0.3
Amodiaquin†	15	75	4.9 ±0.9
		37.5	4.7 ±0.4
		18.8	4.5 ±1.2
		9.4	4.6 ±0.5
		Placebo	4.6 ±0.5
Pentoxifylline†	15	100	5.5 ±0.3
		32	5.2 ±0.2
		10	5.5 ±0.4
		Placebo	5.8 ±1.5

Barbard DL, et al. ***Antivir Chem Chemother*** *2006;17 (5), 275-84.*
E Keyaerts et al. ***Biochem Biophys Res Commun*** *2004;323 (1), 264-8.*

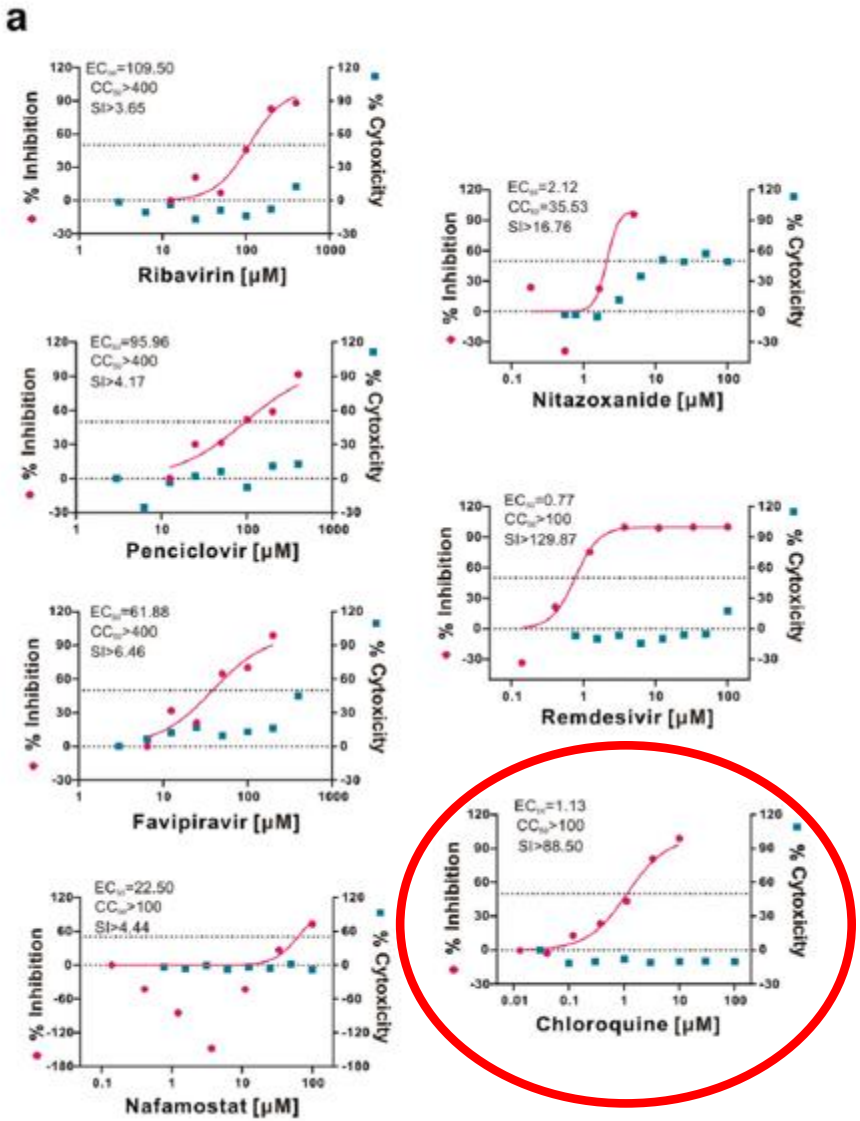
Chloroquine in **SARS & MERS**

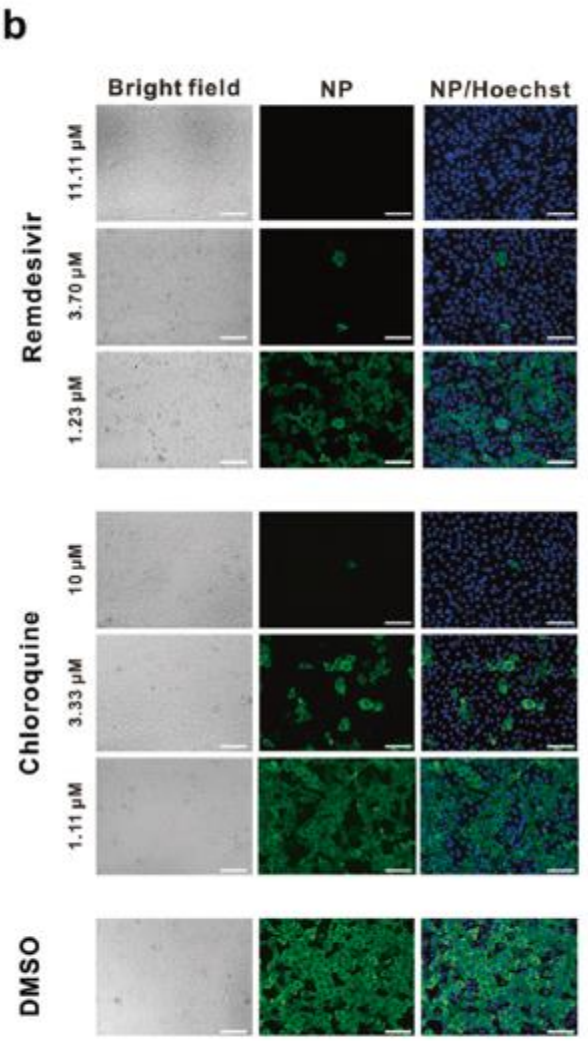


CQ: Chloroquine **CPZ**: chlorpromazine **LPM**: Loperamide **LPV**: Lopinavir

De Wilde AH, et al. ***Antimicrob Agents Chemother*** *2014;58 (8): 4875-84*

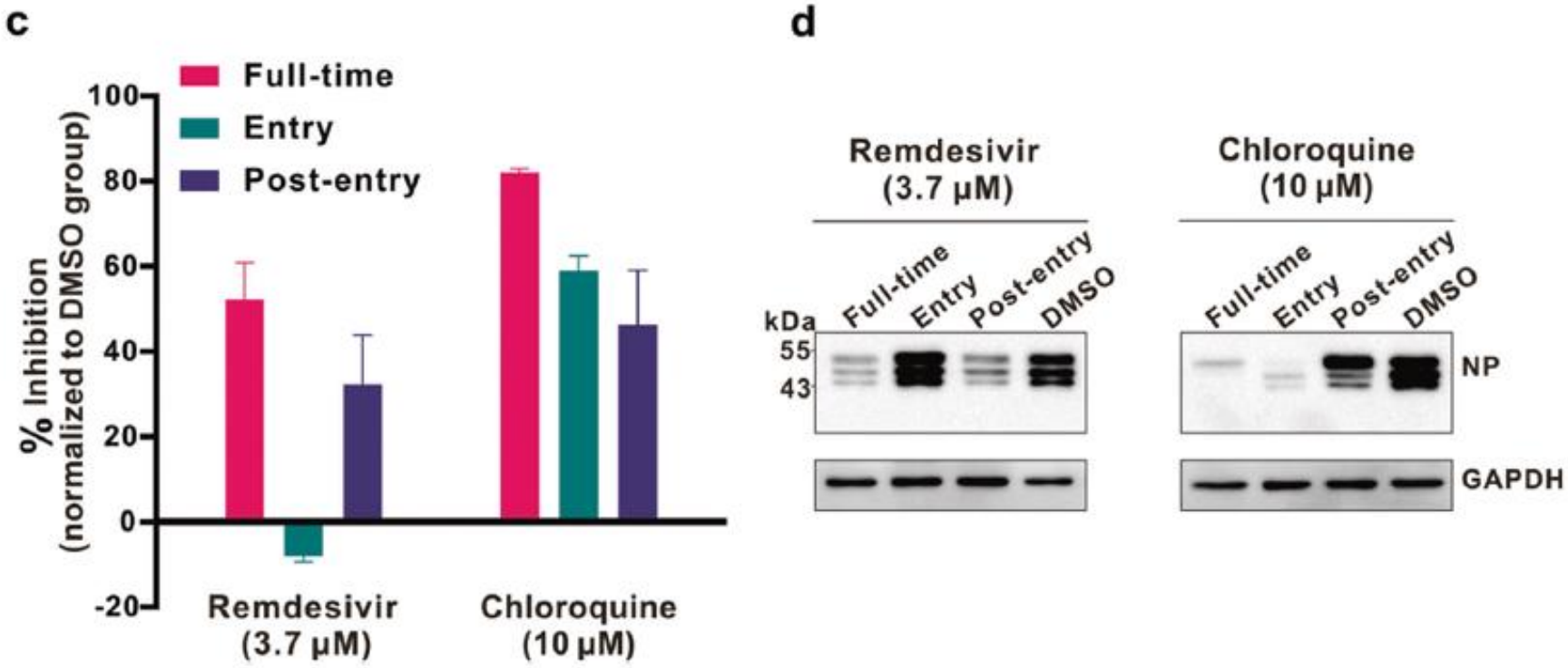
Chloroquine on **COVID-19**



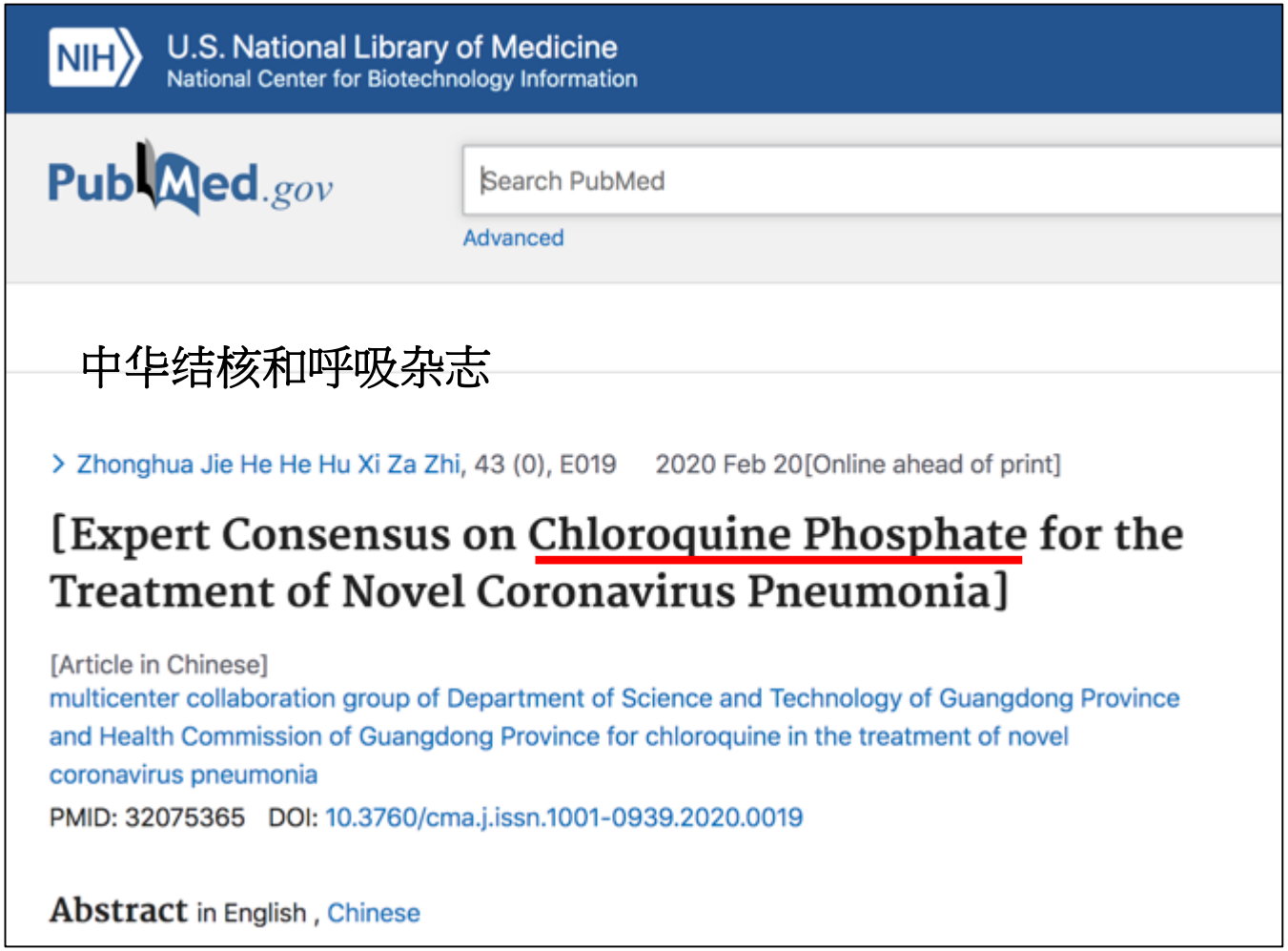


Wang M, et al. ***Cell Res*** *2020 Feb 4[Online ahead of print]*

Chloroquine on **COVID-19**

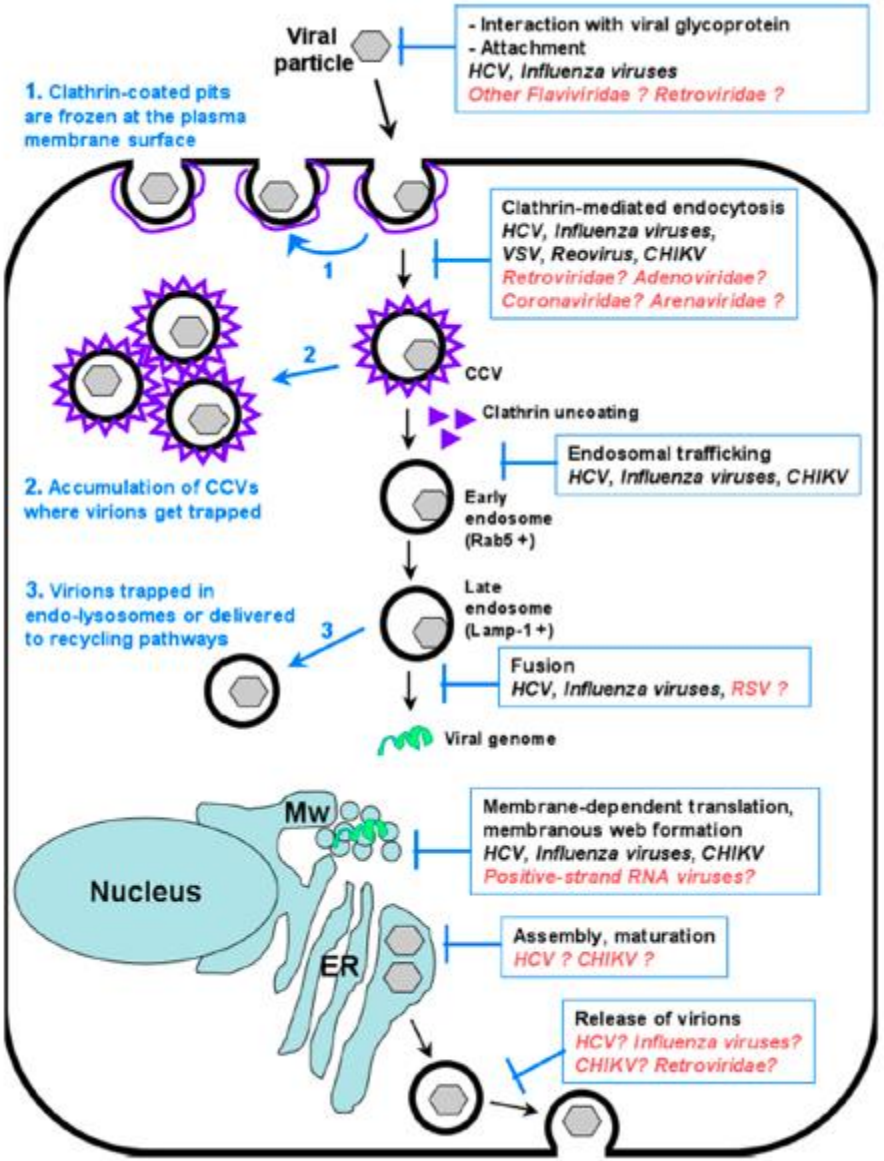


Wang M, et al. ***Cell Res*** *2020 Feb 4[Online ahead of print]*



- Chloroquine phosphate 500mg BD for 10 days
- Chloroquine mediates the **increase of lysosome pH** in vivo, **weakens transferrin** release of iron ions, **reduces intracellular iron** ion content, and then **interferes with intracellular DNA replication and gene expression**

Arbidol (Umifenovir)



- **inhibits membrane fusion** of virus
- **Immunomodulating effect**: stimulates a humoral immune response, induces IFN, and stimulates the phagocytic function of macrophages

Chinese management guideline version 7 (3 Mar 2020)

中华人民共和国中央人民政府
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关于印发新型冠状病毒肺炎诊疗方案（试行第七版）的通知

国卫办医函〔2020〕184号

各省、自治区、直辖市及新疆生产建设兵团卫生健康委、中医药管理局：

为进一步做好新型冠状病毒肺炎病例诊断和医疗救治工作，我们组织专家在对前期医疗救治工作进行分析、研判、总结的基础上，对诊疗方案进行修订，形成了《新型冠状病毒肺炎诊疗方案（试行第七版）》。现印发给你们，请参照执行。各有关医疗机构要在医疗救治工作中积极发挥中医药作用，加强中西医结合，完善中西医联合会诊制度，促进医疗救治取得良好效果。

附件：新型冠状病毒肺炎诊疗方案（试行第七版）

国家卫生健康委办公厅
国家中医药管理局办公室
2020年3月3日

Antiviral treatment:

- Ribavirin + interferon-**α** (Inhalation) **or** lopinavir / ritonavir, for < 10 days
- **Chloroquine** phosphate (500mg, BD) for **7 days**
- **Arbidol** (200mg, tds) for < 10 days
- Continue to evaluate the efficacy of these drugs during use
- It is not recommended to use 3 or more antiviral drugs at the same time.
- Stop drugs when there are side effects

** Chloroquine & Arbidol are unregistered drugs in HK. Chloroquine is used for treatment of malaria but the quantity is small in HA. Arbidol is not available in HK*

Chloroquine use:

- Should be used strictly in accordance with the **expert consensus** and the **recommended dosage and duration** of use in the **6th edition** of treatment guideline
- The scope, dose and time of medication **should not be expanded**
- During the use of the drug, close observation is required.
- Adjust or discontinue when severe **adverse reactions** occur
- Clinical studies on chloroquine phosphate are carried out under the **guidance of designated hospitals**, scientific researchers and clinical doctors
- Limited to the treatment of **confirmed patients** who meet the eligibility criteria.
- **Prophylaxis therapy is not necessary** and is not indicated.

Interim Recommendation on Clinical Management of Adult Cases with Coronavirus Disease 2019 (COVID-19)

Version	Effective Date
1	13 February 2020

Document Number	CCIDER-COVID19-001(v1)
Author	HA Task Force on Clinical Management on Infection (TFCM)
Custodian	Central Committee on Infectious Diseases and Emergency Response (CCIDER)
Approved by	Central Committee on Infectious Diseases and Emergency Response (CCIDER)
Approval Date	13 February 2020
Next Review Date	13 February 2023

http://ha.home/ho/cico/Interim_Recommendation_on_Clinical_Management_of_Adult_Cases_with_COVID-19.pdf

Specific Antiviral treatment: principle

- There is no current evidence from randomized controlled trials to recommend any specific anti-COVID-19treatment for patients with confirmed COVID-19infection.
- Unlicensed treatment should be given under ethically-approved clinical trials as far as possible.
- In the absence of appropriate clinical trials, the following treatment regimens **may** be considered.
- These regimens are determined based on evidence extrapolated from research performed for other coronaviruses, expert opinion, as well as the availability of therapeutics in Hong Kong.
- This serves as an **interim** guidance, and will be updated according to the availability of new evidence or drug availability.

HA Antiviral Treatment guideline

lopinavir/ ritonavir 400mg/100mg (Kaletra) BD po for 14 days

+/-

Ribavirin 400mg BD po for 14 days

+/-

Interferon beta-1b 0.25mg subcutaneous every alternate day for 3 doses (D1-2, D3-4, D5-6 of symptom onset)

- Kaletra is considered as the backbone therapy.
- Additional use of other two drugs is based on in-charge hospital/ cluster Infectious Diseases Physician's discretion.
- Omit the remaining doses of interferon beta-1b when the symptom onset is beyond 7 days (e.g. if the patient presents on day 6 of symptoms onset, only one dose of interferon should be given)
- If patient presents with symptoms beyond 7 days, only ribavirin and kaletra should be given

Pre-treatment workup

6.3.6.1. Check blood x CBP, LRFT, RG, LDH, CK, HBsAg, anti-HCV, anti-HIV

6.3.6.2. + blood x TFT, ANA (for starting interferon)

6.3.6.3. CXR (+/- HRCT thorax if indicated)

6.3.6.4. ECG (if preexisting cardiac abnormalities or disease or clinically indicated). For patients with underlying pre-existing cardiac problems, follow-up monitoring of the cardiac condition is suggested.

6.3.6.5. Pregnancy test for females with reproductive potential (Before starting interferon or ribavirin)

6.3.6.6. Check any drug interactions with concomitant medications (in particular with ritonavir)

6.3.6.7. Obtain consent for treatment

Thanks