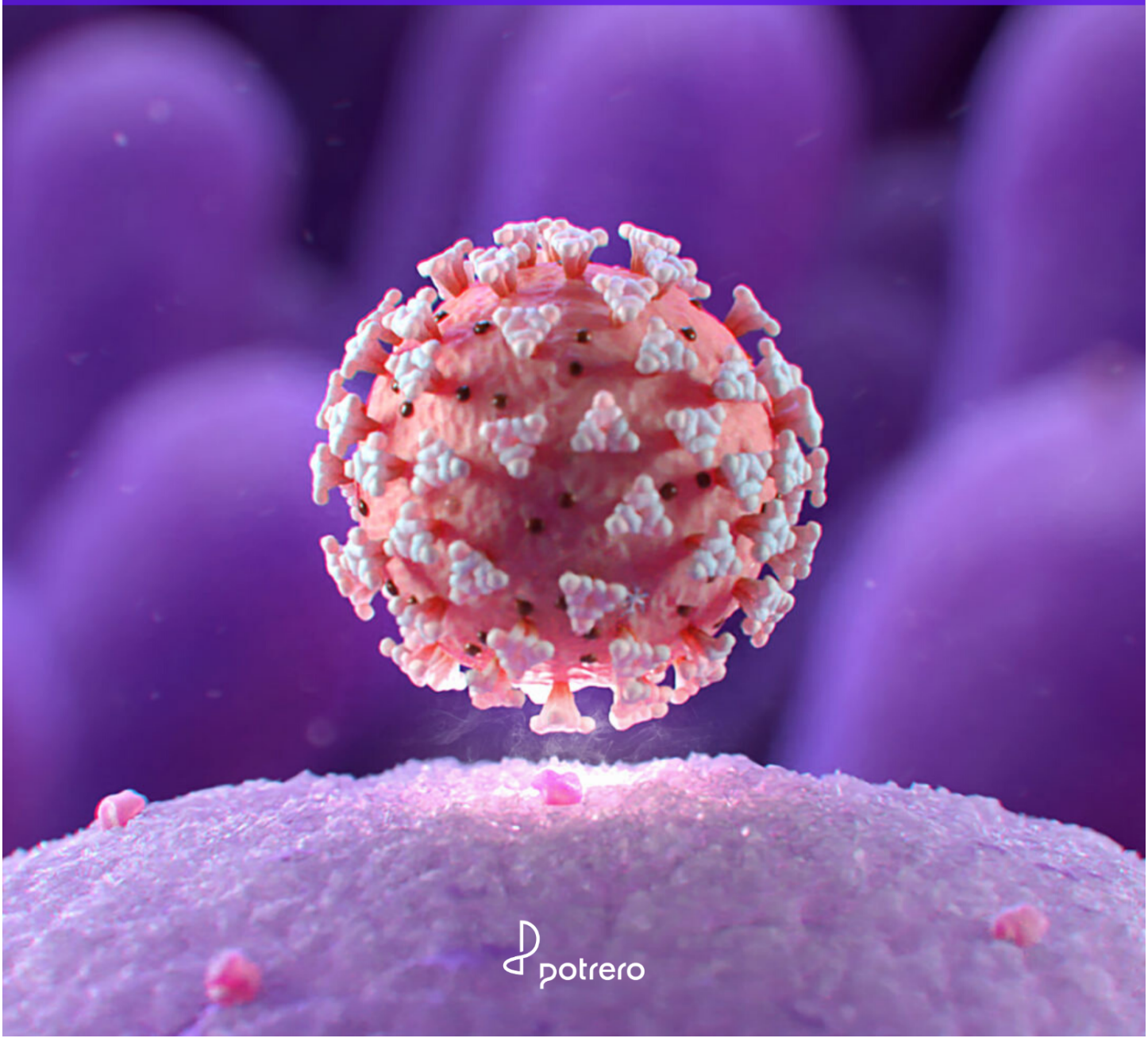
GLOBAL COVID-19 UPDATE

Dr. Zhiyong Peng, MD PhD

Chair & Professor of Critical Care Medicine at Zhongnan Hospital

Vice-Director of Center of Clinical Trials of Wuhan University



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Amid the coronavirus pandemic, physicians and healthcare workers have shown great resilience and dedication to fighting the pandemic globally.

Dr. Zhiyong Peng,Chair & Professor of Critical Care Medicine at Zhongnan Hospital & Vice-Director of Center of Clinical Trials of Wuhan University, shares what his hospital has done in managing COVID 19 patients and details on what we can expect in the near future.

Disclaimer: The following is a white paper highlighting his recent webinar. All information has been transcribed and converted from Dr. Peng's slide deck and webinar.

The top priority in facing the outbreak is personal protection and optimizing compliance in using it within hospitals.

Setting protocols for protective personal equipment of how protective gear is put on and removed is paramount during this time.

Additional Medical Resources Needed for COVID-19

- Medical and ICU beds
- Human Resources
- Medical Equipment
- Teams

With limited medical resources, mobilizing through the help of local authorities and the government is essential in handling the corona virus crisis.

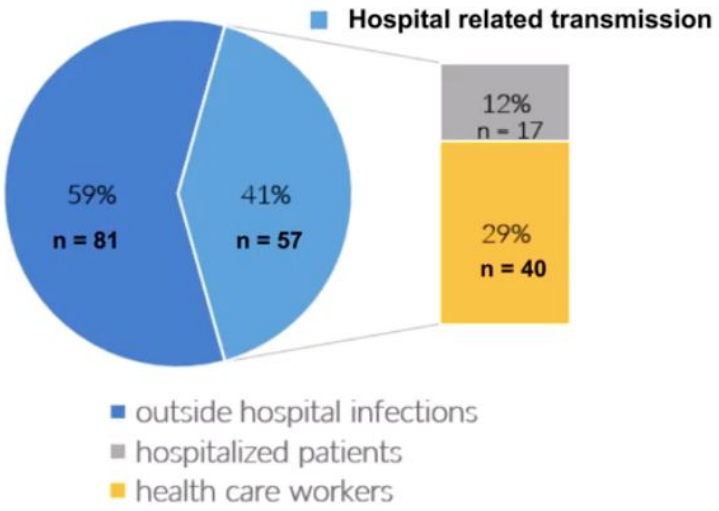
Top COVID-19 Priority: Personal Protective Equipment (PPE)

- PPE: cap, surgical gloves, fluid-resistant gown/protective suits, fit-tested respirator(N95 or FFP3), goggles(anti-fog), face shield/full hood
- Precautions for droplet, close contact and airborne
- Protocols for wearing PPE and taking off PPE
- Environment monitoring for virus

In order to flatten the curve, healthcare workers in hospitals should be aware of the importance of personal protection. Setting protocols for personal protective equipment around how protective gear is put on and removed is vital.

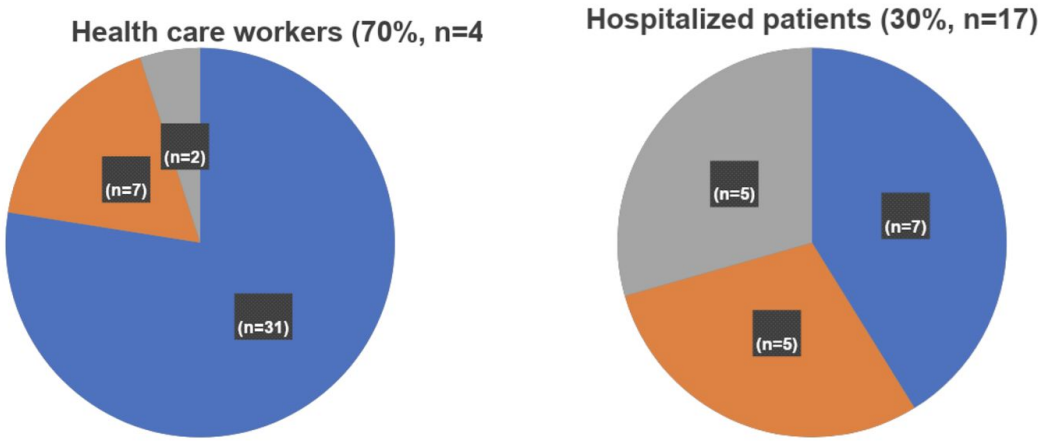
Features of COVID-19 Hospital Related Transmission

- The human-to-human transmission was frequent, especially in hospitals.



Case study: https://jamanetwork.com/journals/jama/fullarticle/2761044

Hospital related transmission



Wang D, et al. JAMA 2020;Feb7.

While many healthcare workers are on the front lines fighting this virus for the public, their risk of contracting the virus is at a higher presentation due to the pathogenic environment of hospitals and their work environment.

It has been found that 29% of healthcare workers have been infected with the virus.

Transmission is frequent , characterized with hospital related infection but low morality.

It has been estimated that atypical patients were the main source of transmission.

In a single-center case series involving 138 patients with NCIP, 26% of patients required admission to the intensive care unit and 4.3% died. Presumed human-to-human hospital-associated transmission of 2019-nCoV was suspected in 41% of patients.

In this case series in Wuhan, China, NCIP was frequently associated with presumed hospital-related transmission, 26% of patients required intensive care unit treatment, and mortality was 4.3%.

Epidemiology of COVID-19 Patient

	Total (n=138)	**ICU (n=36)**	**Non-ICU (n=102)**	**P value**
Age, years	56 (42-68)	66 (57-78)	51 (37-62)	<0.001
Gender, Male	75(54.3%)	22 (61.1%)	53(52.0%)	0.343
Comorbidities	64(46.4%)	26 (72.2%)	38(37.3%)	<0.001
Hypertension	43(31.2%)	21 (58.3%)	22(21.6.0%)	<0.001
Diabetes	14(10.1%)	8 (22.2%)	6(5.9%)	0.009
Cardiovascular disease	20(14.5%)	9(25.0%)	11(10.8%)	0.0037
Cerebrovascular disease	7(5.1%)	6 (16.7%)	1(1.0%)	0.001
COPD	4(2.9%)	3 (8.3%)	1(1.0%)	0.054
CKD	4(2.9%)	2 (5.6%)	2 (2.0%	0.279
Chronic liver disease	4(2.9%)	0 (0%)	4 (3.9%)	0.573
Malignancy	10 (7.2%)	4 (11.1%)	6(5.9%(	0.287
HIV infection	2(1.45)	0 (0%)	2(2.0%(	1.000

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It was likely to infect older persons with comorbidities

Wang D, et al. JAMA 2020;Feb7.

Signs and Symptoms of COVID-19

Of 138 hospitalized patients with NCIP, the median age was 56 years (interquartile range, 42-68; range, 22-92 years) and 75 (54.3%) were men.

Hospital-associated transmission was suspected as the presumed mechanism of infection for affected health professionals (40 [29%]) and hospitalized patients (17 [12.3%]). Common symptoms included fever (136 [98.6%]), fatigue (96 [69.6%]), and dry cough (82 [59.4%]).

Most common symptoms at onset were found to be:

Symptom (% of Patients with Symptom)

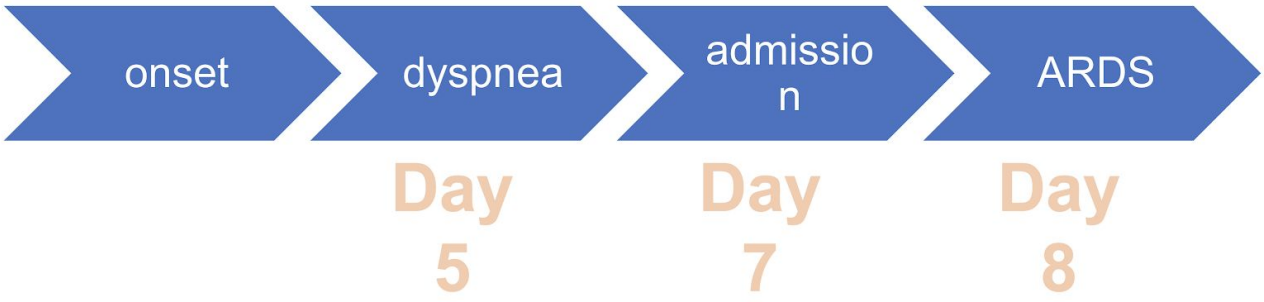
Fever (98.6%)	Myalgia (34.8%)
Fatigue (69.6%)	Dyspnea (31.2%)
Dry Cough (59.4%)	

- 10% of patients presented initially with diarrhea 1-2 days prior to development of fever and dyspnea.

- Dyspnea, dizzy, abdominal pain and anorexia frequently occurred in ICU patients.

COVID-19 Clinical Process

The time from onset to dyspnea was 5.0 days, 7.0 days to hospital admission, and 8.0 days to ARDS.



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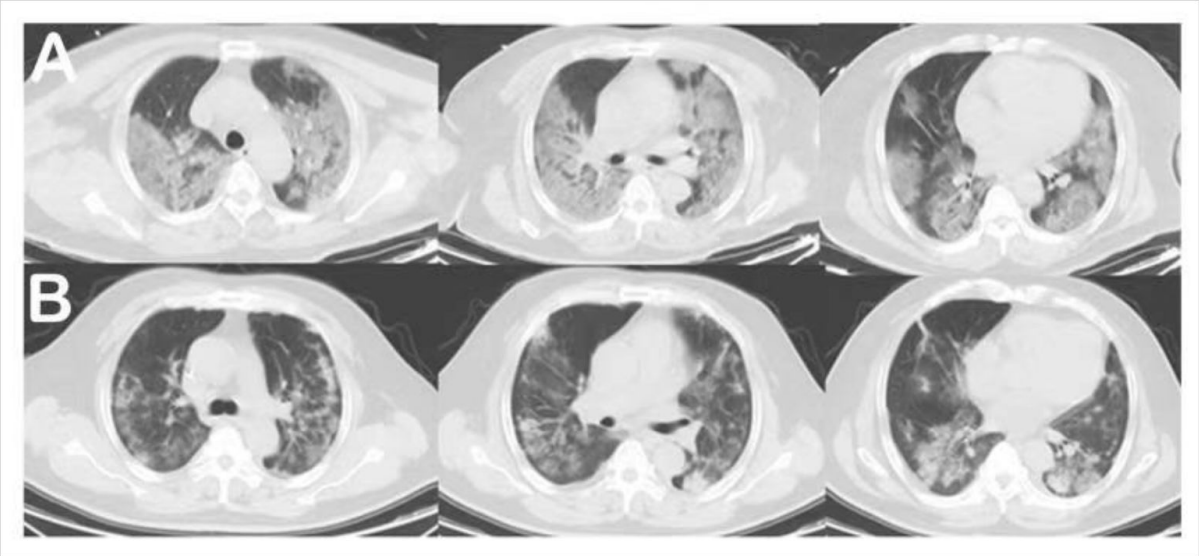
Typical COVID-19 Chest CT: Ground-Glass Opacity



Chest CT images of a 52-year-old patient infected with 2019-nCoV

(A) Chest CT obtained on Jan 7 showed ground-glass opacity in both lungs on day 5 after symptoms onset. (B) Images taken on Jan 21 showed the absorption of bilateral ground-glass opacity after the treatment of ECMO during Jan 7 to 12 in ICU.

COVID-19 Laboratory Results

	Normal range	Total (n=138)	ICU (n=36)	Non-ICU (n=102)	*P* value
White blood cell count, × 10^9/L	3.5-9.5	4.5(3.3-6.2)	6.6(3.6-9.8)	4.3(3.3-5.4)	0.003
Neutrophil count, × 10^9/L	1.8-6.3	3.0(2.0-4.9)	4.6(2.6-7.9)	2.7(1.9-3.9)	<0.001
Lymphocyte count, × 10^9/L	1.1-3.2	0.8(0.6-1.1)	0.8(0.5-0.9)	0.9(0.6-1.2)	0.033
Monocyte count, × 10^9/L	0.1-0.6	0.4(0.3-0.5)	0.4(0.3-0.5)	0.4(0.3-0.5)	0.955
Platelet count, × 10^9/L	125-350	163(123-191)	142(119-202)	165(125-188)	0.775
Prothrombin time, s	9.4-12.5	13.0(12.3-13.7)	13.2(12.3-14.5)	12.9(12.3-13.4)	0.373
Activated partial thromboplastin time, s	25.1-36.5	31.4(29.4-33.5)	30.4(28.0-33.5)	31.7(29.6-33.5)	0.093
D-dimer, mg/L	0-500	203(121-403)	414(191-1324)	166(101-285)	<0.001
Creatine kinase, U/L	<171	92(56-130)	102(62-252)	87(54-121)	0.076
Creatine kinase-MB, U/L	<25	14(10-18)	18(12-35)	13(10-14)	<0.001
Lactate dehydrogenase, U/L	125-243	261(182-403)	435(302-596)	212(171-291)	<0.001
Alanine aminotransferase, U/L	9-50	24(16-40)	35(19-57)	23(15-36)	0.007
Aspartate aminotransferase, U/L	15-40	31(24-51)	52(30-70)	29(21-38)	<0.001
Total bilirubin, mmol/L	5-21	9.8(8.4-14.1)	11.5(9.6-18.6)	9.3(8.2-12.8)	0.016
Urea, mmol/l	2.8-7.6	4.4(3.4-5.8)	5.9(4.3-9.6)	4.0(3.1-5.1)	<0.001
Creatinine, μmol/L	64-104	72(60-87)	80(66-106)	71(58-84)	0.037
Hypersensitive troponin I, pg/mL	<26.2	6.4(2.8-18.5)	11.0(5.6-26.4)	5.1(2.1-9.8)	0.004

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COVID-19 Diagnosis Criterion

Diagnostic Test	**Results**
Epidemiological History	
Typical Symptoms and Signs	Febrile, Fatigue, Dyspnea
Labs	Lymphopenia, Flu-Test (-)
Chest CT	Multiple patches starting from outer parts
Virus Test	Low Sensitivity
Serum AB Test	Suspect if negative virus test

Confirmed COVID-19 Diagnosis:

- Symptoms/Signs + Lab Test + Typical Chest
- CT + Positive Viral Test

Clinical Presentation - ICU Patients

	Normal range	ICU (n=36)
Onset of symptom to ICU admission (d)	NA	10 (6-12)
GCS	NA	15 (9-15)
APACHE II	NA	17 (10-22)
SOFA	NA	5 (3-6)
PH	7.35-7.45	7.43 (7.39-7.47)
Lactate, mmol/l	0.5-1.6	1.3 (0.7-2.0)
PaO2, mm/Hg	83-108	68 (56-89)
PaO2/FiO2, mm/Hg	400-500	136 (103-234)
PaCO2, mm/Hg	35-48	34 (30-38)

COVID-19 Organ Injury and Complications

- ICU patients had higher incidence of complications
- The common complications were ARDS, cardiac injury and shock.

COMPLICATIONS	Total (n=138)	ICU (n=36)	Non-ICU (n=102)	P value
Shock	12(8.7%)	11(30.6%)	1(1.0%)	<0.001
Acute Cardiac Injury	10(7.2%)	8(22.2%)	2(2.0%)	<0.001
Arrhythmia	23(16.7%)	16(44.4%)	7(6.9%)	<0.001
Acute Respiratory Distress Syndrome (ARDS)	27(19.6%)	22(61.1%)	5(4.9%)	<0.001
Acute Kidney Injury (AKI)	5(3.6%)	3(8.3%)	2(2.0%)	0.111

ICU patients had higher levels of APACHE , SOFA, PaO2/FiO2 and experienced an increasingly higher incidence of complications.

COVID-19 Patient Ventilation Support

Treatment	Total (n=138)	ICU (n=36)	Non - ICU (n=102)
High- flow oxygen	106 (76.81%)	4 (11.11%)	102 (100%)
NIV	15 (10.9%)	15 (41.7%)	0 (0.0%)
IMV	17 (12.32%)	17 (47.22%)	0 (0.0%)
ECMO	4 (2.9%)	4 (11.1%)	0 (0.0%)

- Half of patients who were critically ill needed invasive ventilation and four of them switched to ECMO, meaning 10% of the patients switched to

Data from Current COVID -19 Patients at ICU admission (February 7 - March 6, 2020) - Hu B, et al. Under review.

Treatments and outcomes	**Patients (number with percentage , n=50)**
PaO2/FiO2 (mmHg)	115(87-190)
Cstat (ml/cmH20)	22.5(17.0-40.50
IL-6(pg/m)	62.2(18.2-129.5)
Lymphocyte count (x10^9/L)	0.59(0.32-0.85)
Modes of respiratory supports	
HFNC+NIMV	14(28.0)
IMV	19(38.0)
IMV+ECMO	17(34.0)
IMV+ Prone ventilation	15(30.0)
Medications	
Antiviral Therapy	37(74.0)
Glucocorticoid therapy	38(76.0)
Antibiotics	45(90.0)
Complications	
ARDS	47(94.0)
Shocks	22(44.0)
Arrhythmia	19(38.0)
Acute cardiac injury	13(26.0)
AKI	11(22.0)
Secondary infection	17(34.0)

- Patients admitted were very ill with severe lung injury
- 28% patients recovered with only NIMV
- 72% requiring IMV, and half of them switched to ECMO
- 64% patients complicated with heart problems

Key Points for COVID-19 Ventilation Support

1. Lung protective approach is extremely important

2. Prone the patients as early as possible

3. Evaluate the mode/parameters set frequently and switch/change appropriate

4. Titrate PEEP and tidal volume based on the transpulmonary pressure. Keep driving pressure <15, and Pplat <28

5. Prevent Acute Cor Pulmonale

6. Be careful of lung RM. Set highest PEEP at 20

Placing patients in a prone position as early as possible is the first step in creating an efficient environment.

In ensuring safety and ventilation support, a lung protective approach is extremely important.

Ventilation is not the cure for covid patients, but ventilators are able to enhance and support patients if used correctly. Evaluating the modes that are set frequently and making sure that driving pressure is I<15 and Pplat <28

When to Switch the Modes of Ventilation

- **HFNC**: recommend in the room with negative-pressure
- If P/F 200-300mmHg, set flow rate at 40-50L/min, FiO2 100%, for 2 hr
- Evaluate the efficacy based on the ROXI[RR-(SpO2/FiO2)]
- If SpO2>93% and RR<25, or ROXI>3.85, continue HFNC; if SpO2<93% and RR>30, or ROXI<2.85, stop HFNC, and the go to NIV (if conscious) or intubation
- If the values between the ranges, continue for another 2 hr, and the re-evaluate

NIV

- If P/F 150-200, start NIV, however BiPAP may worsen the lung injury,
- High RR or/ and tidal volume will increase trans-pulmonary or driving pressure, worsen lung injury and pulmonary edema and induce pulmonary fibrosis
- Initial set IPAP 12, EPAP 5-8,FiO2 80-100% for 2 h, follow the tidal volume (TV), if TV<9ml/kg, continue; if TV>12, intubate

IMV

- IF P/F< 150, go to IMV
- First, test if RM is available , set the highest PEEP at 20 , if not and driving pressure>15, then paralyze the patients with prone position
- Follow the lung compliance
- If FiO2>60, P/F<150 or Ppleuto>35, PaCO2>50 and PH<7.25, go to ECMO

COVID-19 NIV in the Last 9 Days

NIV	FiO2	PS (cmH2O)	PEEP (cmH2O)	SPO2	RR (n/min)
-D9	60%	14	5	93%	33
-D8	55%	16	5	92%	32
-D7	50%	16	5	92%	32
-D6	50%	16	5	92%	30
-D5	60%	18	5	92%	28
-D4	50%	18	8	93%	32
-D3	55%	18	8	92%	32
-D2	60%	18	8	90%	44
-D1	60%	23	8	88%	42

COVID-19 Detailed Treatments from ECMO

VV-ECMO	Rotation speed (r/min)	Blood flow (L/min)	Sweep rate (L/min)	FiO2
D1	3000	3.5	3.5	100%
D2	3400	3.8	3.5	80%
D3	3370	3.7	3.5	80%
D4	3360	3.7	3.5	70%
D5	3400	3.9	3.5	70%
D6	3400	3.8	3.5	50%
D7	3065	3.3	3.5	40%
D8	3100	3.4	3.5	30%
D9	2500	2.5	3.5	21%

Weaning ECMO and switched to SIMV

V-SIMV	Fi02	PS (cmH2O)	Peep (cmH2O)	Pplat (CmH2)	Compliance (ml/cmH2O)	Prone position
D10	55%	10	5	20	24	Yes
D11	40%	10	5	20	24	Yes
D12	40%	10	5	20	28	Yes
D13	40%	8	4	22	35	Yes
D14	30%	8	4	22	36	No

Case Report

- F/64 yr, transferred to ICU from outside hospital due to severe dyspnea, and tachycardia.
- Diagnosed with COVID-19 in outside hospital
- Previously healthy.
- Tx in outside hospital:
    - Antiviral & antibiotics for 5 days
    - Corticosteroids for 7 days
    - NIV for 9 days

NIV	FiO_2	PS(cmH_2O)	PEEP (cmH_2O)	SPO_2	RR (n/min)
-D9	60%	14	5	93%	33
-D8	55%	16	5	92%	32
-D7	50%	16	5	92%	32
-D6	50%	16	5	92%	30
-D5	60%	18	5	92%	28
-D4	50%	18	8	93%	32
-D3	55%	18	8	92%	32
-D2	60%	18	8	90%	44
-D1	60%	23	8	88%	42

Vital sign at ICU Admission:

- HR 130bpm
- SpO_2 82% (with 6L/min)
- RR 46/min
- NBP 130/82mmHg.

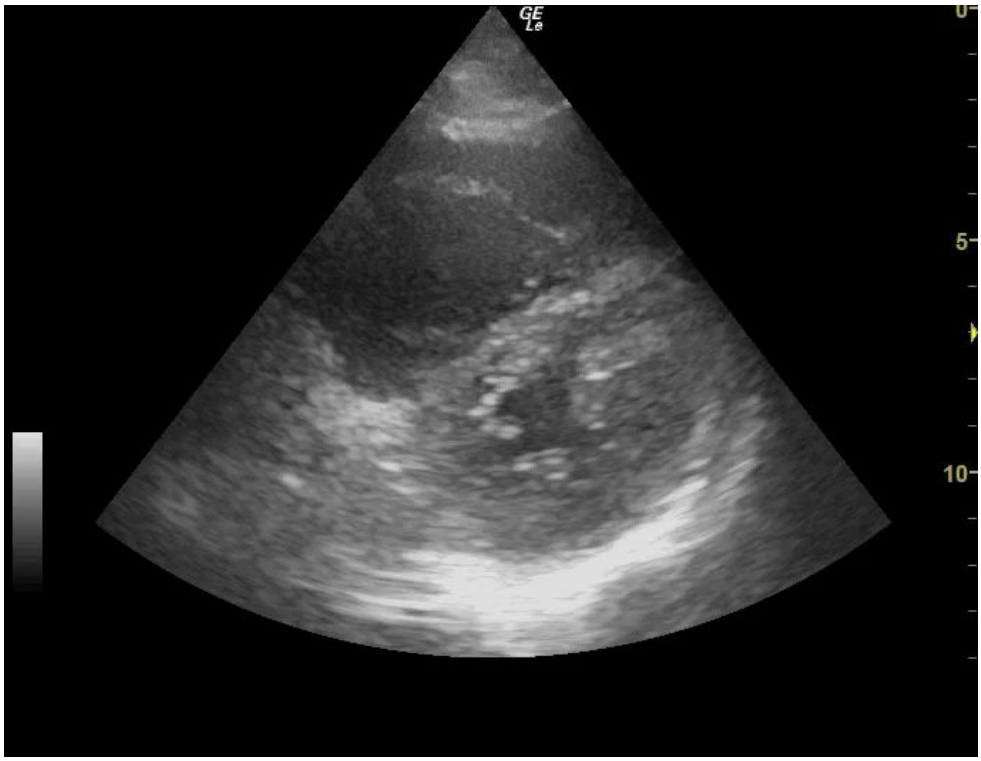
- We gave her NIV with FiO_2 100% immediately, and prepared for intubation
- ABG :
  - pH 7.26
  - $PaCO_2$ 55 mmHg
  - PaO_2 49mmHg
  - FiO_2 100%

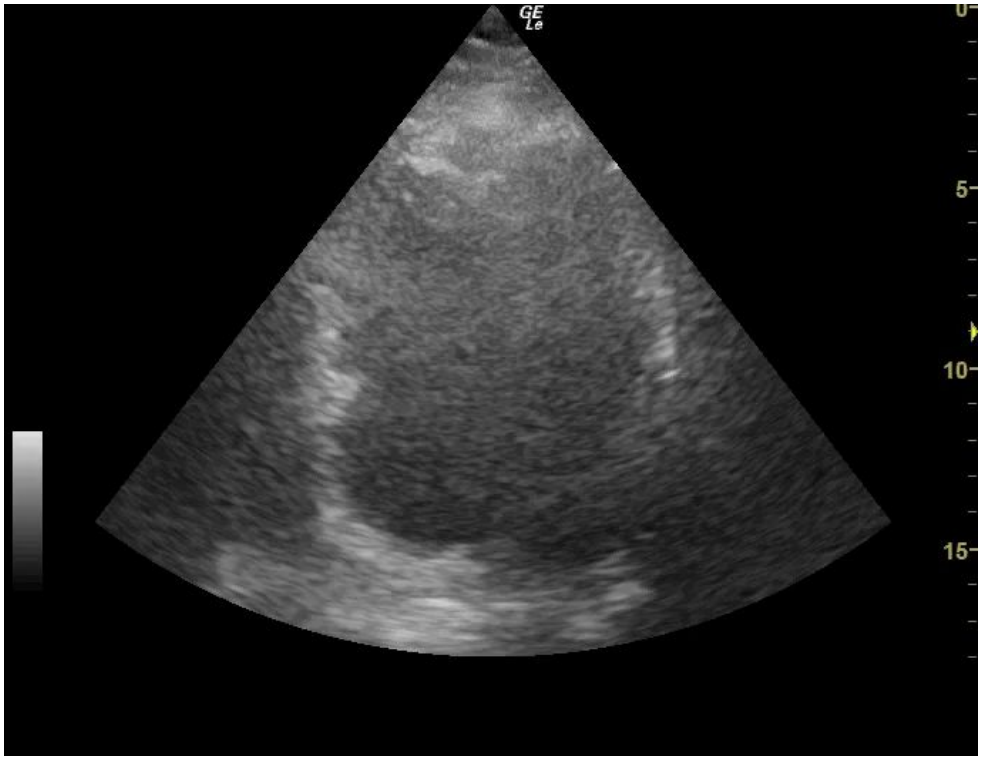
Next Steps

- Intubated and supported with V-SIMV mode, tidal volume 400mL, FiO2 90%, PEEP 5cmH_2O, PS 12cmH_2O, (detected Pplat 26cmH_2O and Compliance 20ml/cmH_2O).
- Subsequently paralyzed with prone position ventilation for 12 hrs
- Not improved , P/F<60 for 4 hrs with hypercapnia, and hypotension requiring vasopressors, then switched to v-v ECMO

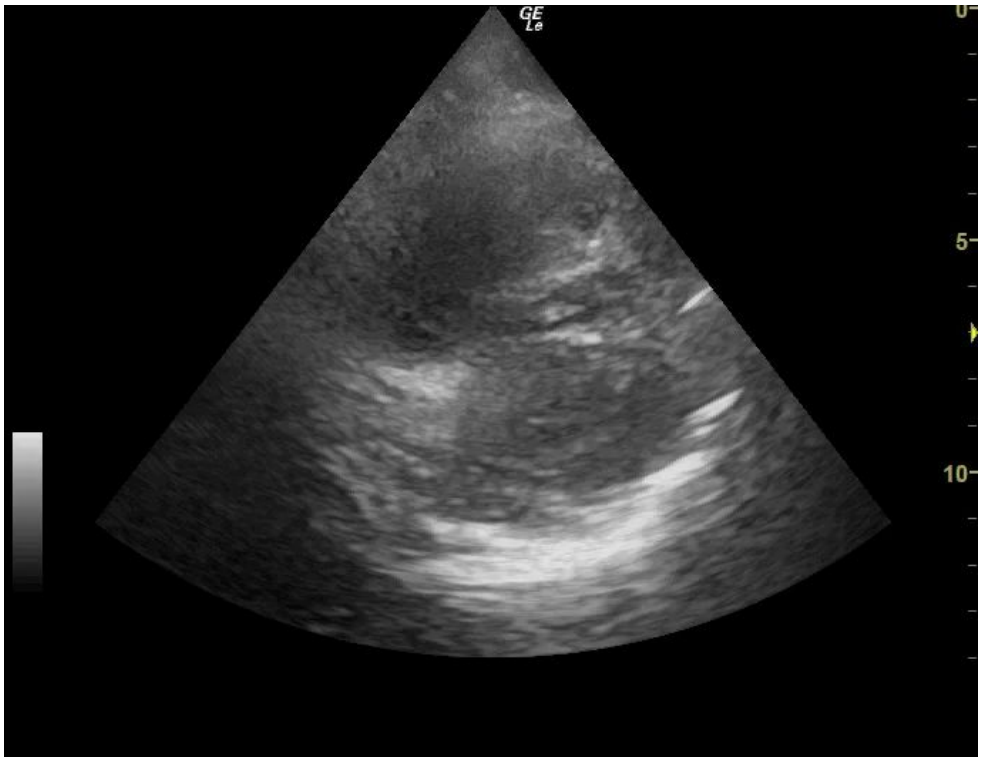
In providing efficient care for patients, ventilation care is important for the fact that it can prevent acute Cor Pulmonale induced by severe hypoxemia.

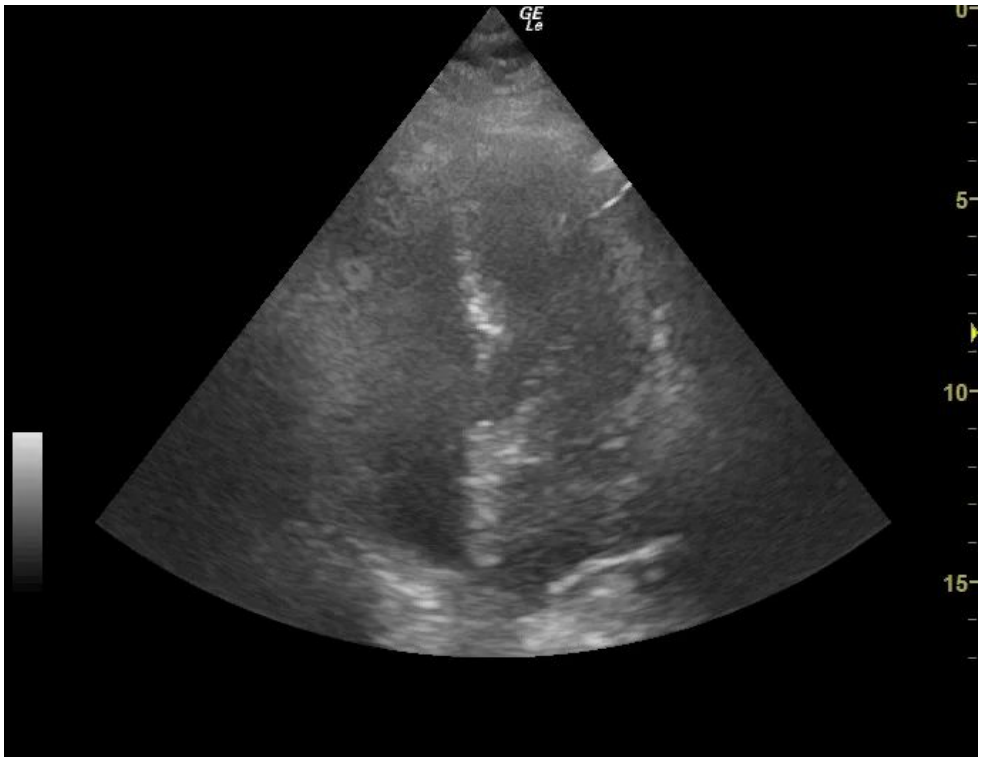
Patient Complicated with Acute Cor Pulmonale - Before VV-ECMO support, NE 1μg/min·kg





Acute Cor Pulmonale Improved with Adequate Oxygenation - 10 hr after ECMO, NE 0.3μg/min·kg





Detailed Treatments from ECMO

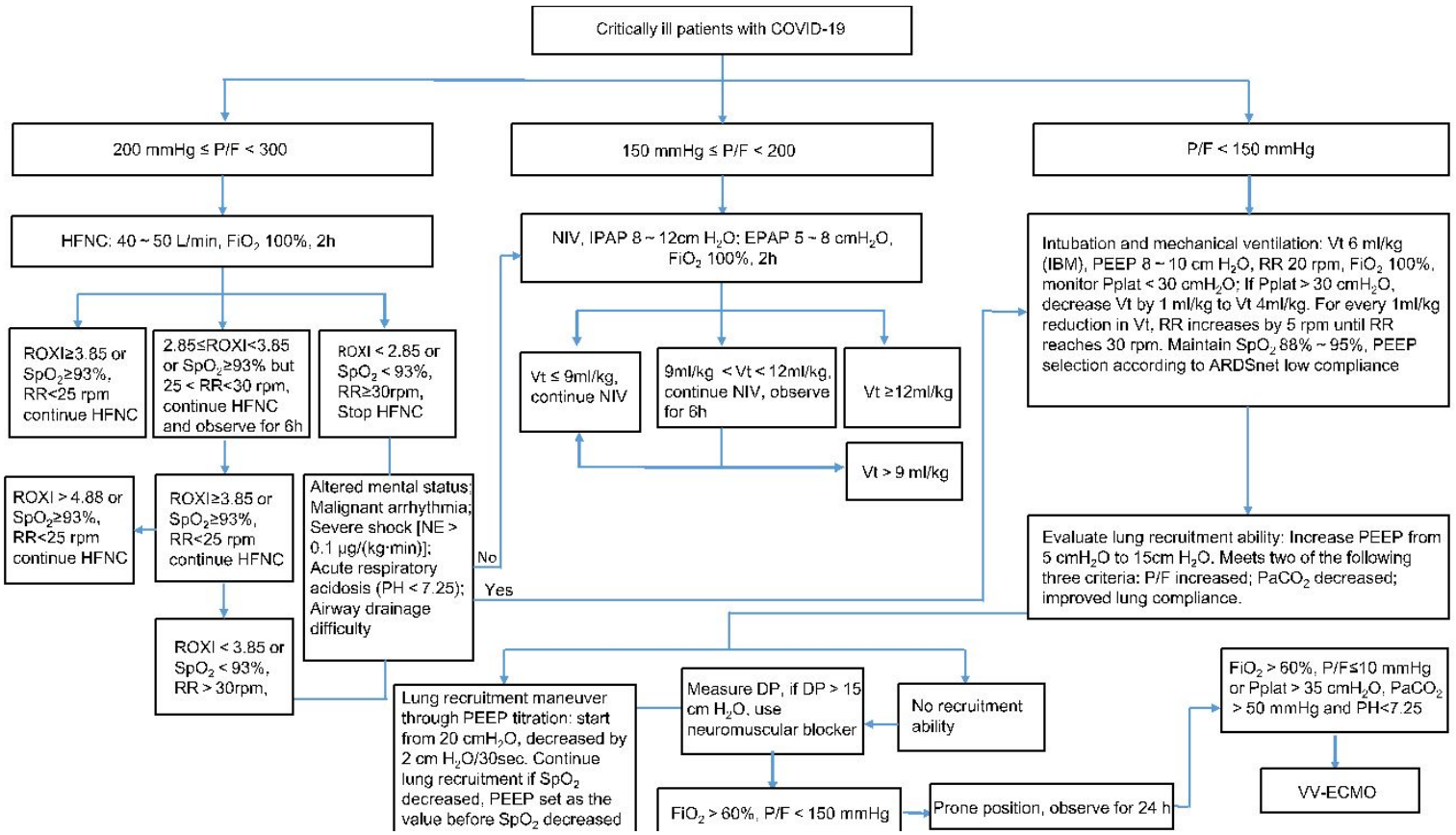
VV-ECMO	Rotation speed (r/min)	Blood flow(L/min)	Sweep rate (L/min)	FiO_2	VV-ECMO
D1	3000	3.5	3.5	100 %	D1
D2	3400	3.8	3.5	80%	D2
D3	3370	3.7	3.5	80%	D3
D4	3360	3.7	3.5	70%	D4
D5	3400	3.9	3.5	70%	D5
D6	3400	3.8	3.5	50%	D6
D7	3065	3.3	3.5	40%	D7
D8	3100	3.4	3.5	30%	D8
D9	2500	2.5	2.5	21%	D9

Weaning ECMO and switched to SIMV

V-SIMV	FiO_2	PS (cmH_2O)	PEEP (cmH_2O)	Pplat (cmH_2O)	Compliance (ml/cmH_2O)
D10	55%	10	5	20	24
D11	40%	10	5	20	24
D12	40%	10	5	20	28
D13	40%	8	4	22	35
D14	30%	8	4	22	36

Lessons Learned

- Need to evaluate the mode/parameters set frequently, and switch/change if not appropriate
- Prevent acute Cor Pulmonale induced by severe hypoxemia



Prognosis of COVID-19 Patients

At the end of February 8, 2020

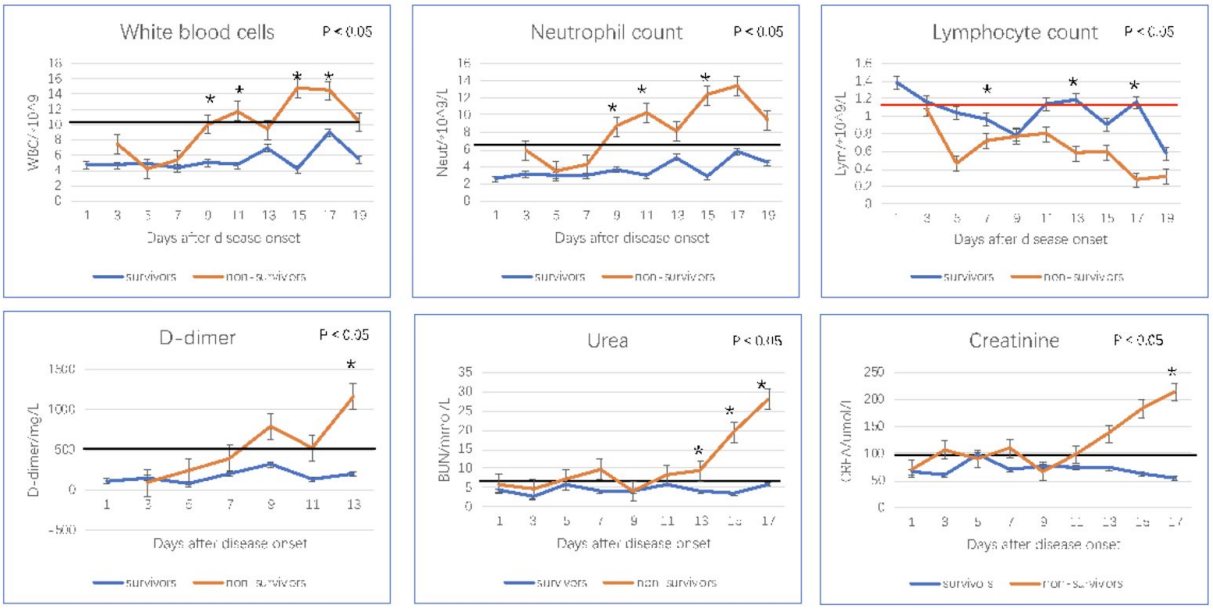
1. 58 (42.03%) patients were still in hospitalization
2. 72 (52.17.10%) patients had been discharged
3. 8 (5.79%) patients have died
4. ICU mortality was at 18%

From February 8 to March 7, 2020:

1. More than 50 patients admitted in ICU from Feb 8 to March 7
2. 70% of COVId-19 patients needed IMV, 50% switched to ECMO and 7 of them weaned off ECMO
3. The predicted overall ICU mortality increased to 25-30%

Dynamic Changes of Laboratory Tests in Survivors and Non-Survivors in Hospitalized Patients

ICU patients showed higher level of D-dimer (414mg/L [191-1324]), creatine kinase-MB (18U/L [12-35]), lactate dehydrogenase (435U/L [302-596]) than non-ICU patients.



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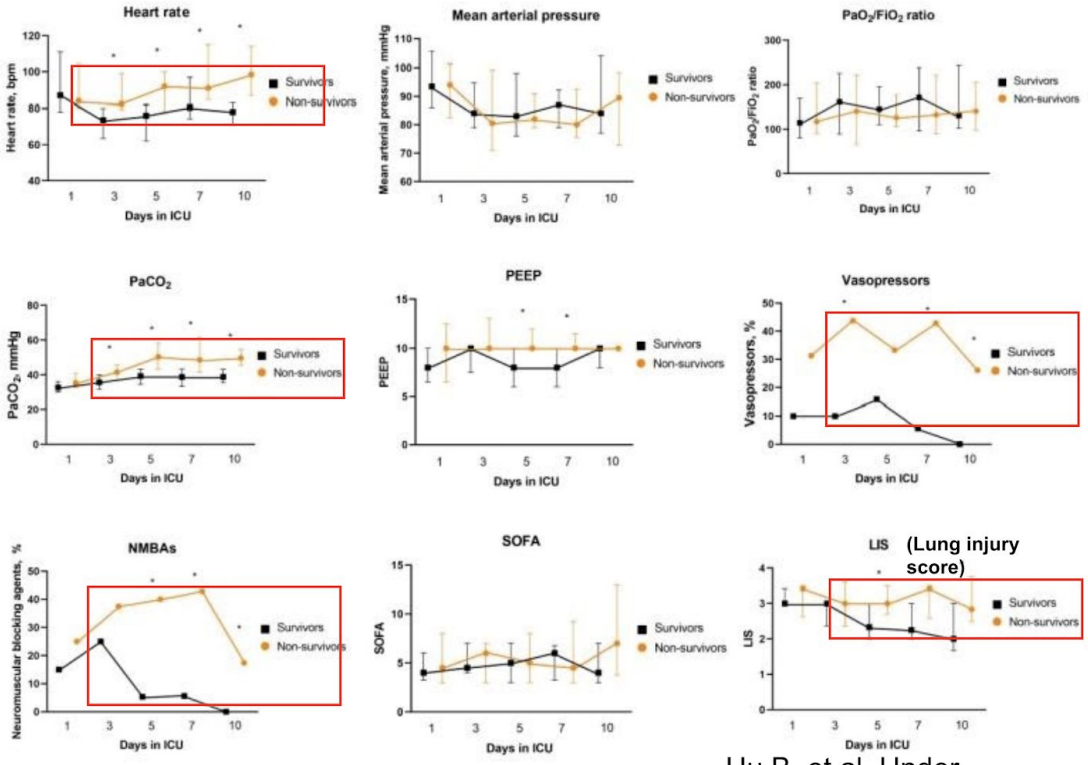
Dynamic Changes of ICU Survivors and Non-Survivors



Hu B, et al. Under

There has been a significant difference in survivors and non survivors of patients who have been hospitalized and in the ICU.

Non Survivors had a higher amount of white blood cells, neutrophil, D-dimer, Urea and creatinine and a lower amount of lymphocytes than survivors hospitalized.

In addition, non survivors had a higher heart rate, vasopressors, NMBAs and overall lung injury score than those who survived.

The lung compliance at ICU admission elevated PACO2 predicted a poor outcome.

Covid-19 Predictors at ICU Admission for Mortality

Characteristics	**All patients (n=50)**	**Survivors (n=20)**	**Non - survivors (n=16)**	**P value**
Age , years	62.0 (49.5-69.0)	56.0 (48.5-67.5)	66.5 (61.3-75.0)	0.043
Male	34 (68.0)	13 (65.0)	11(68.8)	0.813
Scoring system				
APACHE II	13 (11-19)	12.5 (10.5-18.5)	16.5 (12.0-24.3)	0.194
SOFA	5 (4-8)	4.0 (3.3-6.0)	4.5 (3.0-8.0)	0.784
LIS	3.33 (3.00-3.50)	3.0 (3.0-3.42)	3.42 (2.63-3.50)	0.585
Cstat (ml/cmH20)	22.5 (17.0 -40.5)	42.0 (18.0-47.0)	19.5 (14.0 - 24.2)	0.038
PaO2/FiO2	115 (87 -190)	114 (80-170)	117 (91-204)	0.633
PaCO2 (mmHg)	33.8 (31.7 - 38.6)	32.7 (30.2-36.1)	35.4 (32.7-40.9)	0.115
PEEP	10.0 (6.8-10.0)	8.0 (6.5-10.0)	10.0 (6.5-12.5)	0.386
Length of ICU stay (d)	12.0 (8.3-16.8)	10.0 (8.3- 14.0)	12.5 (8.3- 22.0)	0.285
Length of mechanical ventilation (d)	8.5 (5.5-15.3)	6.0 (4.0-9.0)	10.5 (6.9- 21.3)	0.061

Conclusions

- The preparation for the outbreak of COVID-19 is important, as medical resource are always limited.
- The transmission was frequent, characterized with hospital related infection but low mortality. The atypical patients were probably the main source of transmission.
- Critically ill patients tended to be older with comorbidities, specific symptoms and laboratory abnormalities.
- Titrating modes/parameters of ventilation supports with a lung-protective approach is crucial.
- The most common complication was ARDS, arrhythmia and septic shock. Nearly half of the critically ill patients needed invasive ventilation.
- The lung compliance at ICU admission and persistently elevated PaCO2 predicted poor outcome.