

# Coagulation tests In COVID-19

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- Supervisor in charge of Coagulation section, in Tongji clinical laboratory;
- Published more than 20 papers in SCI journal;
- Research Interests: Lab diagnosis of hemophilia, thrombophilia and TMA.





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# **Coagulation Tests**

**1. Coagulation feature of COVID-19**

**2. Guidance of coagulopathy management**

**3. Use in special cases**

## Sepsis 3.0 = Infection + SOFA $\geq$ 2

**Table 3** The SOFA score

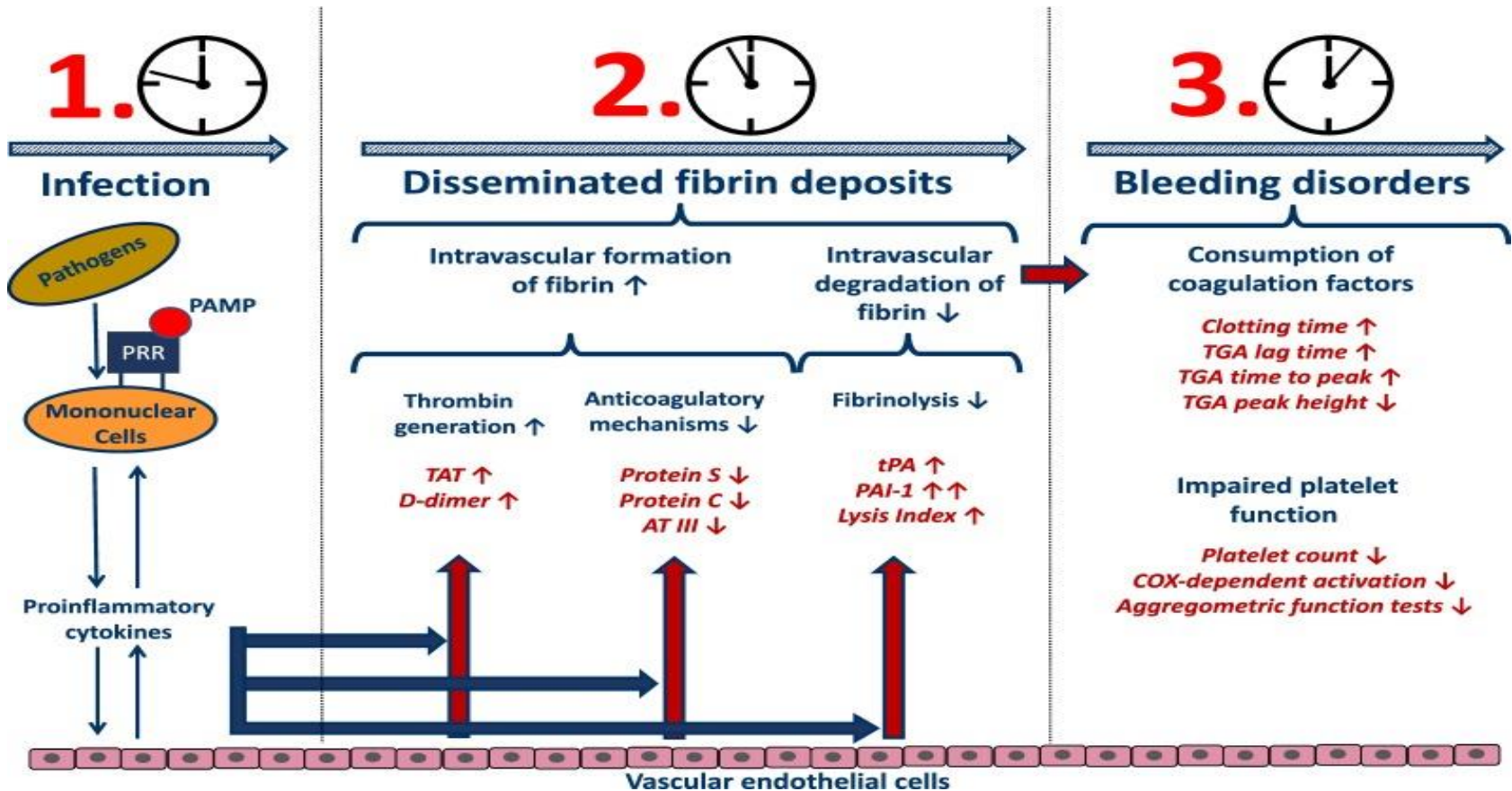
SOFA score	1	2	3	4
<i>Respiration</i>				
PaO <sub>2</sub> /FiO <sub>2</sub> , mmHg	< 400	< 300	< 200 —— with respiratory support ——	< 100
<i>Coagulation</i>				
Platelets × 10 <sup>3</sup> /mm <sup>3</sup>	< 150	< 100	< 50	< 20
<i>Liver</i>				
Bilirubin, mg/dl ( $\mu$ mol/l)	1.2 – 1.9 (20 – 32)	2.0 – 5.9 (33 – 101)	6.0 – 11.9 (102 – 204)	> 12.0 (> 204)
<i>Cardiovascular</i>				
Hypotension	MAP < 70 mmHg	Dopamine $\leq$ 5 or dobutamine (any dose) <sup>a</sup>	Dopamine > 5 or epinephrine $\leq$ 0.1 or norepinephrine $\leq$ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
<i>Central nervous system</i>				
Glasgow Coma Score	13 – 14	10 – 12	6 – 9	< 6
<i>Renal</i>				
Creatinine, mg/dl ( $\mu$ mol/l) or urine output	1.2 – 1.9 (110 – 170)	2.0 – 3.4 (171 – 299)	3.5 – 4.9 (300 – 440) or < 500 ml/day	> 5.0 (> 440) or < 200 ml/day

<sup>a</sup> Adrenergic agents administered for at least 1 h (doses given are in  $\mu$ g/kg·min)

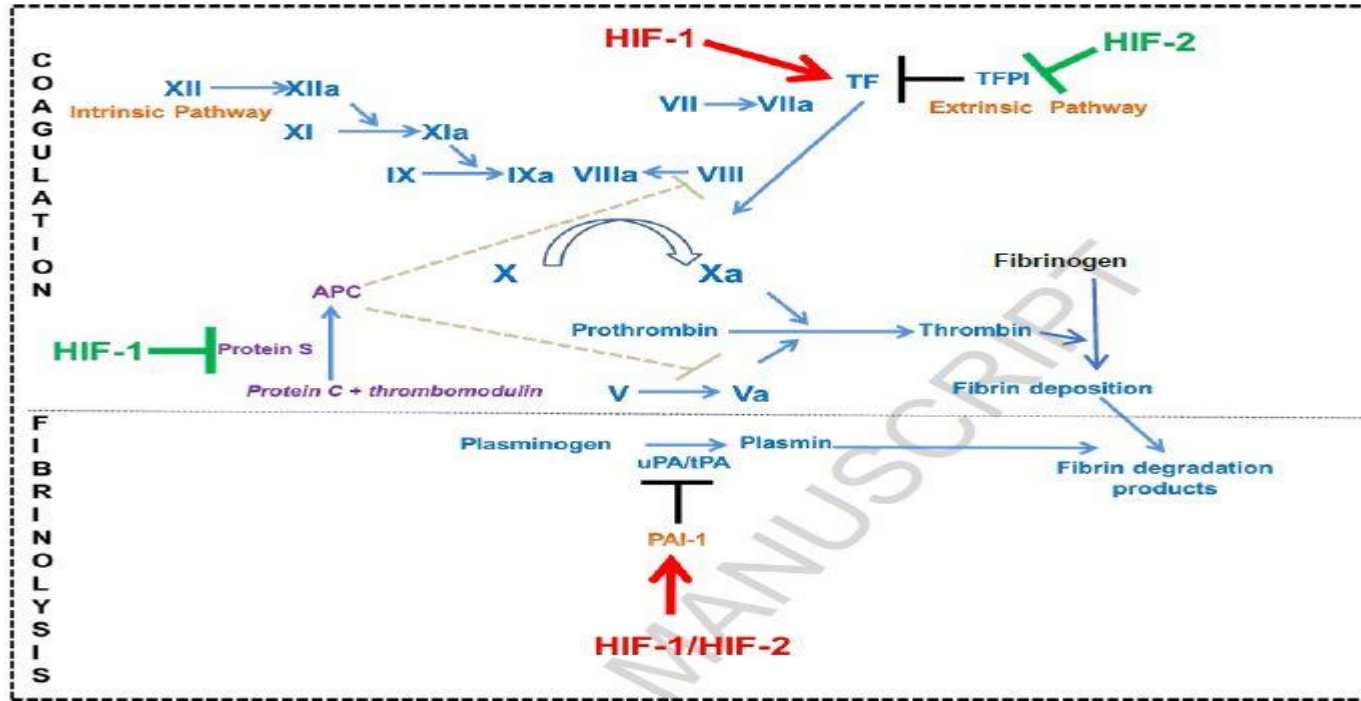


Many severe COVID-19 patients meet the sepsis criteria

# Sepsis-induced coagulopathy



# The stimulation of thrombosis by hypoxia :



A critical COVID-19 patient suffered thromboangiitis



BRIEF REPORT

### Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

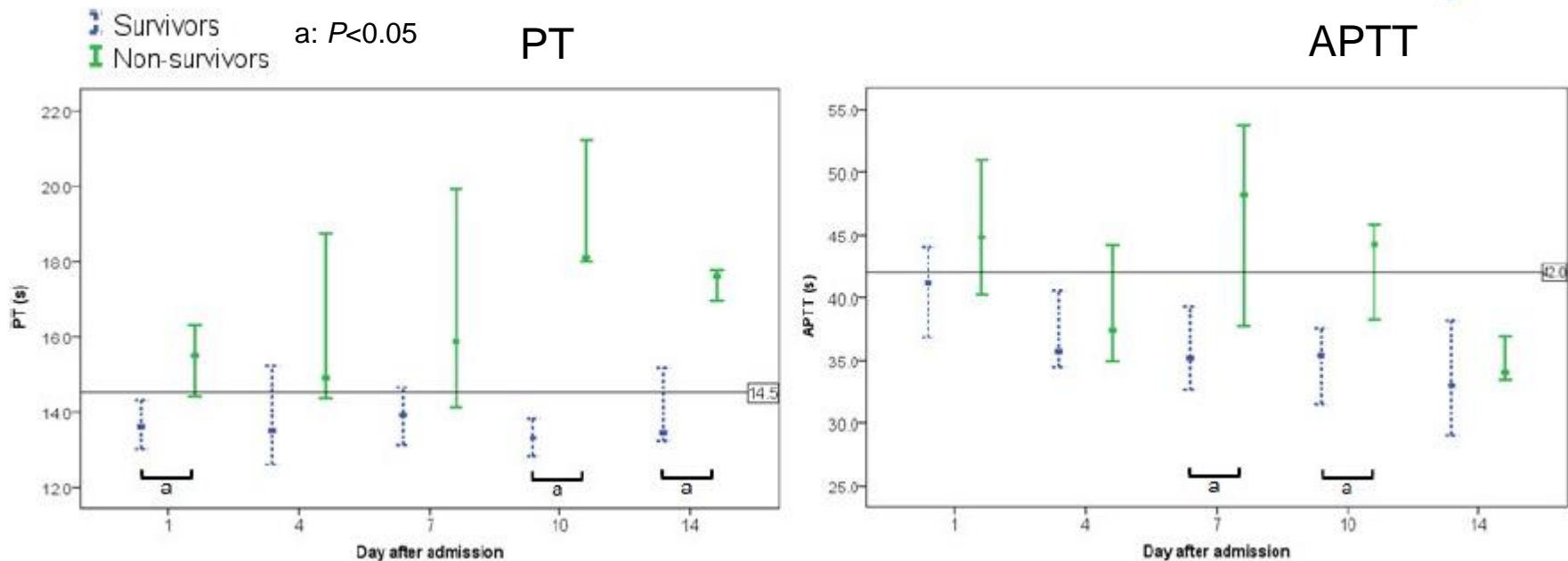
Ning Tang<sup>1</sup> | Dengju Li<sup>2</sup> | Xiong Wang<sup>1</sup> | Ziyong Sun<sup>1</sup>

TABLE 1 Coagulation parameters of NCP patients on admission

Parameters	Normal range	Total (n = 183)	Survivors (n = 162)	Non-survivors (n = 21)	P values
Age (years)		54.1 ± 16.2	52.4 ± 15.6	64.0 ± 20.7	<.001
Sex (male/female)		98/85	82/80	16/5	.035
With underlying diseases		75 (41.0%)	63 (38.9%)	12 (57.1%)	.156
On admission					
PT (sec)	11.5-14.5	13.7 (13.1-14.6)	13.6 (13.0-14.3)	15.5 (14.4-16.3)	<.001
APTT (sec)	29.0-42.0	41.6 (36.9-44.5)	41.2 (36.9-44.0)	44.8 (40.2-51.0)	.096
Fibrinogen (g/L)	2.0-4.0	4.55 (3.66-5.17)	4.51 (3.65-5.09)	5.16 (3.74-5.69)	.149
D-dimer (μg/mL)	<0.50	0.66 (0.38-1.50)	0.61 (0.35-1.29)	2.12 (0.77-5.27)	<.001
FDP (μg/mL)	<5.0	4.0 (4.0-4.9)	4.0 (4.0-4.3)	7.6 (4.0-23.4)	<.001
AT (%)	80-120	91 (83-97)	91 (84-97)	84 (78-90)	.096

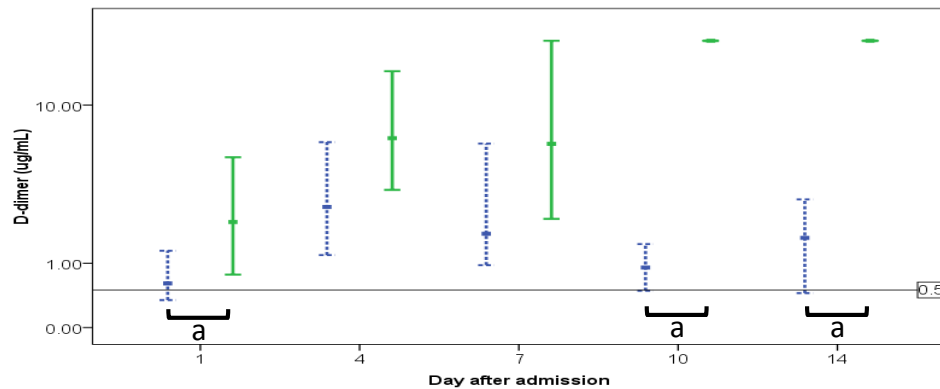
# Our data

## Dynamic of the coagulation results during hospital stay



# Our data

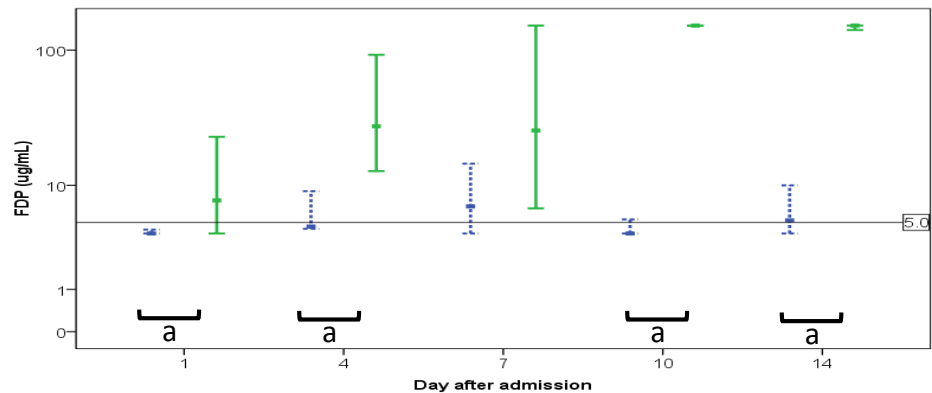
## D-dimer



Survivors  
Non-survivors

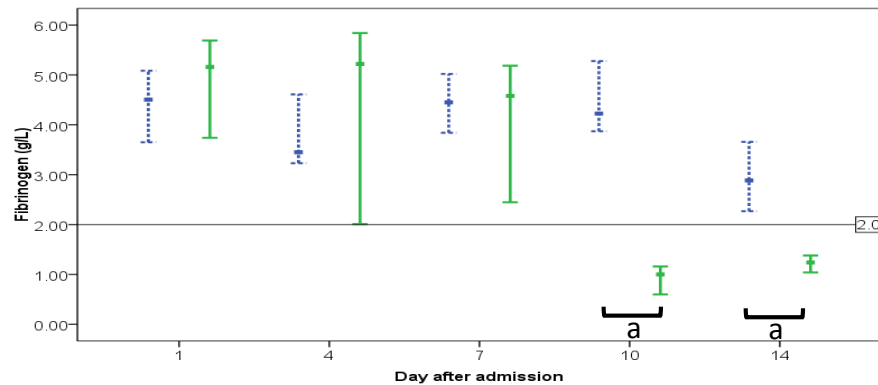
a:  $P < 0.05$

## FDP



# Our data

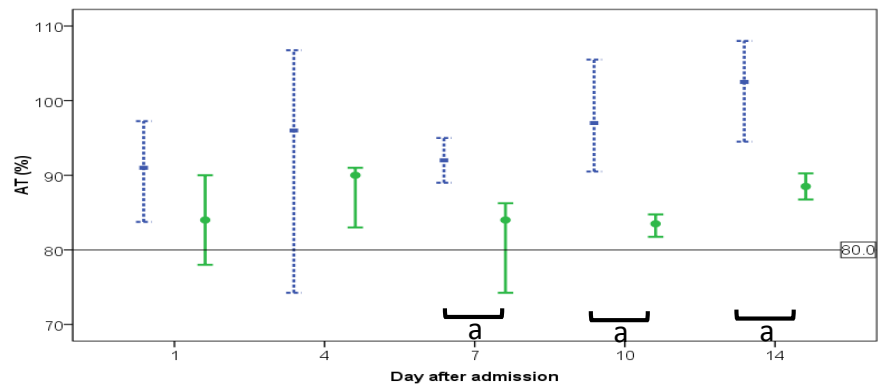
FIB



Survivors  
Non-survivors

a:  $P < 0.05$

AT



# Our data

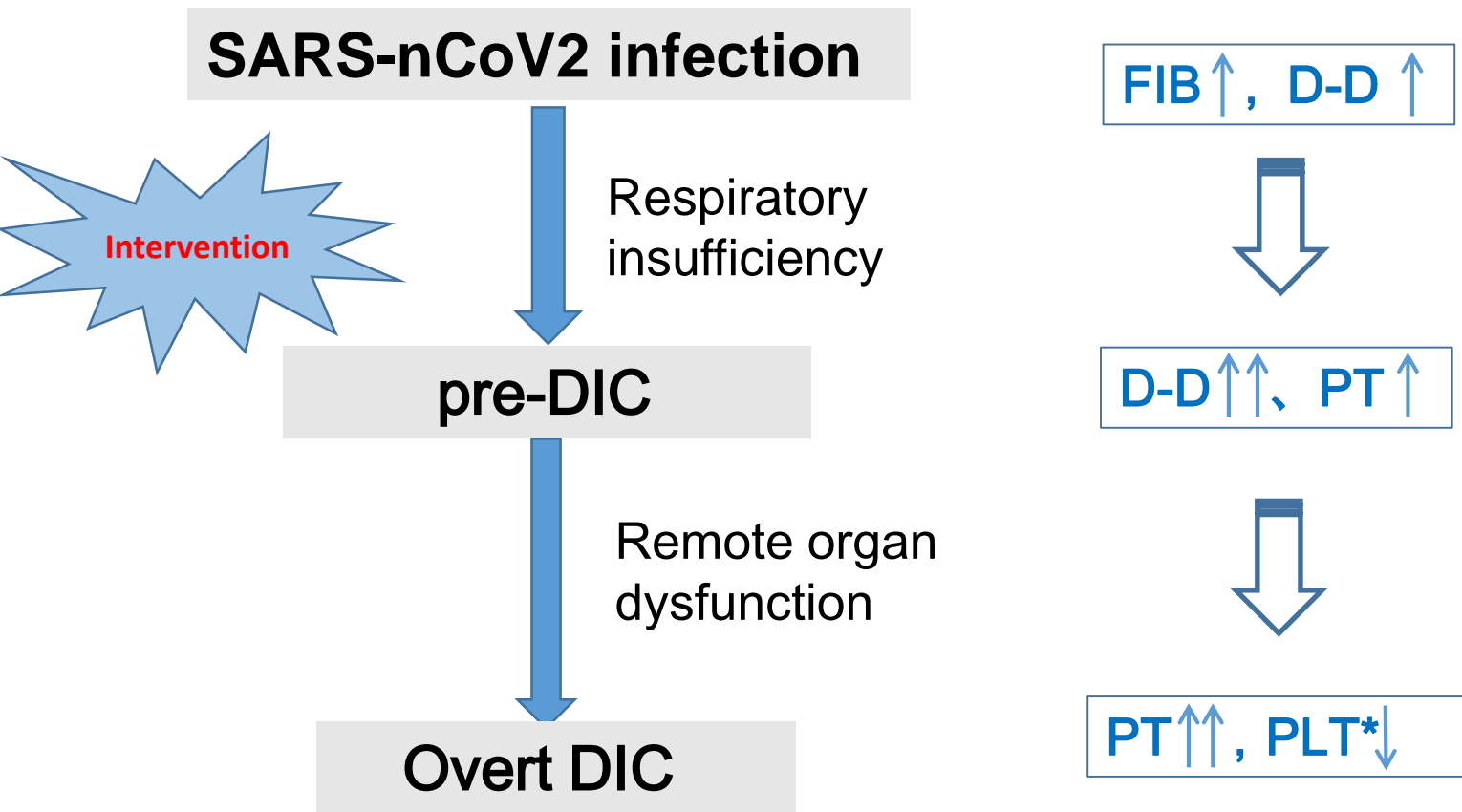
## The grade of DIC in Non-survivors with COVID-2019 (n=21)

	Number of patients (%)
Platelet counts ( $\times 10^9/L$ )	
50-100 (1 point)	7 (33.3)
<50 (2 points)	5 (23.8)
D-dimer ( $\mu g/mL$ )	
1.0-3.0 (2 points)	3 (14.3)
>3.0 (3 points)	18 (85.7)
Fibrinogen (g/L)	
<1.0 (1 point)	6 (28.6)
Prolongation of PT (sec)	
3-6 (1 point)	5 (23.8)
>6 (2 points)	10 (47.6)
Meeting the ISTH criteria of DIC (Total points $\geq 5$ )	15 (71.4)



**In survivors , only 0.6% patients meet the DIC criteria**

# Evolution of coagulopathy in COVID-19 described by coag marker



*\* , PLT count is insensitive for pre-DIC of COVID*

**Case:** 65y male with confirmed COVID-19, ARDS.

	Day 1 (Pre-DIC)	Day 4 (Overt DIC)	Reference range
PT	15.2	18.3	11.5-14.5 s
APTT	32.4	41.6	29.0-42.0 s
FIB	2.74	4.17	2.0-4.0 g/L
D-Dimer	5.21	>21.0	<0.5 ug/mL
PLT count	224	142	125-350 × 10 <sup>9</sup> /L
Anti-thrombin	101	69	80-120%
VWF activity	226	575	50-200%
Plasminogen	67	48	80-132%
Factor VIII	175	214	60-150%



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**2. Guidance of coagulopathy management**

3. Use in special cases

## Could severe COVID-19 patients benefit from anticoagulant treatment?

- ◆ Expert consensus statement from Shanghai (in Chinese): **clearly recommends heparin treatment in COVID-19.**
- ◆ However, no specific inclusion or exclusion criteria has been pointed out.

- Sepsis-induced coagulopathy (SIC)  $\geq 4$  points:  
Screening out sepsis patient who can benefit from anticoagulant treatment.

**Table 3** Scoring for the diagnosis of sepsis-induced coagulopathy

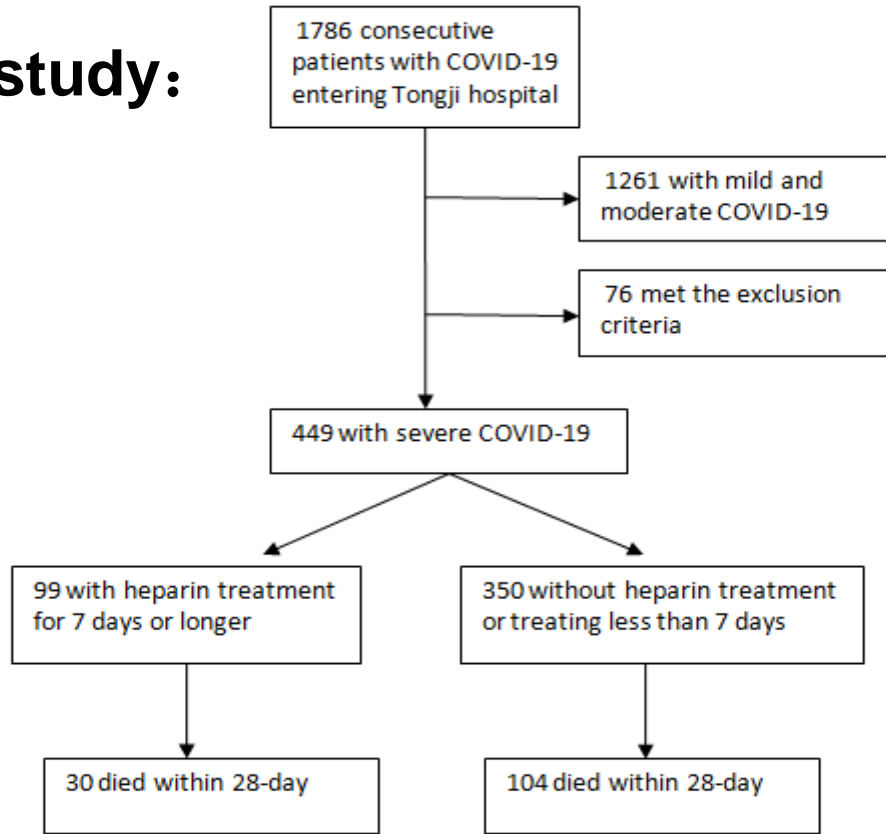
Category	Parameter	0 point	1 point	2 points
Prothrombin time	PT-INR	$\leq 1.2$	$> 1.2$	$> 1.4$
Coagulation	Platelet count ( $\times 10^9/L$ )	$\geq 150$	$< 150$	$< 100$
Total SOFA	SOFA four items	0	1	$\geq 2$

Iba T, et al. *BMJ Open* 2017;7:e017046.

**Usefulness of SIC criteria in stratification of COVID-19?**

# Our retrospective study:

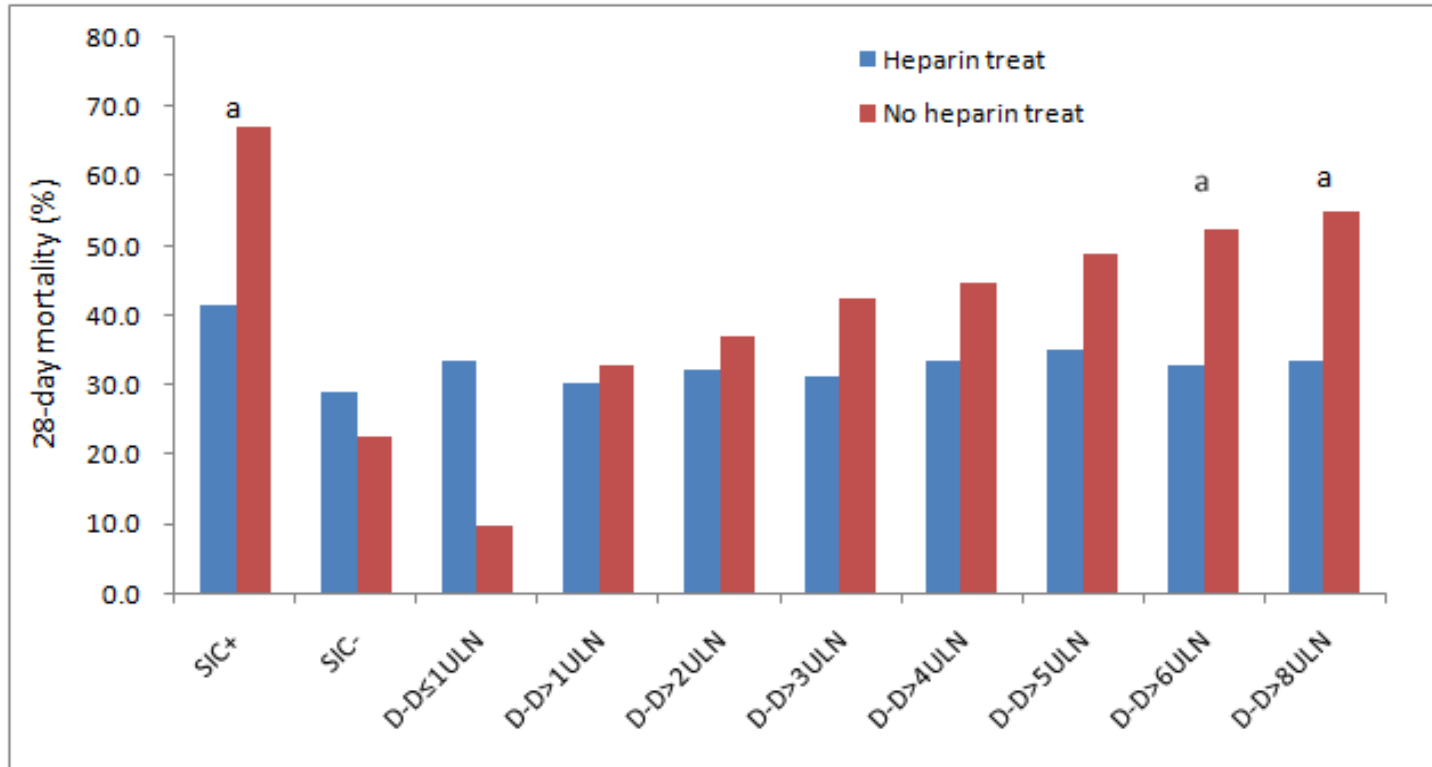
*Has been received by  
J Thromb Haemost*



Mortality: 30.3% vs 29.7%,  $P=0.910$

**Anticoagulant may not benefit to the unselected patients !**

● The severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer may benefit from LMWH treatment



SIC: sepsis-induced coagulopathy; ULN: Upper limit of normal (0.5 ug/mL);  
a,  $P < 0.05$  between heparin users and nonusers.

## ISTH interim guidance on recognition and management of coagulopathy in COVID-19

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1. D-dimer\*
2. Prothrombin time
3. Platelet count
4. Fibrinogen\*\*

1. D-dimer markedly raised\*\*\*
2. Prothrombin time prolonged
3. Platelet count  $100 \times 10^9/L$
4. Fibrinogen  $<2.0 \text{ g/L}$

1. D-dimer not markedly raised\*\*\*
2. Prothrombin time normal
3. Platelet count normal
4. Fibrinogen elevated

Admit (even if no other concerns)  
Monitor once or twice daily

If admitted for other clinical reasons,  
Monitor daily

If discharged, use as baseline for  
if re-presenting with symptoms

In all patients  
Start prophylactic dose  
low molecular weight heparin

Worsening

- Blood products as per protocol (see box on the right)
- Consider experimental therapies

- In non-bleeding patients, keep
- platelet count above  $20 \times 10^9/L$
  - fibrinogen above  $2.0 \text{ g/L}$
- In bleeding patients, keep
- platelet count above  $50 \times 10^9/L$
  - fibrinogen above  $2.0 \text{ g/L}$
  - PT ratio  $<1.5$  (not the same as INR)

# Is heparin treatment effective and safe?

## Monitoring Markers:

- **APTT、ACT** (For UFH) ;
- **Anti-FXa activity** (For UFH/LMWH) ;

*Notice the timing of collecting sample: 2~4h after injection*

- **Antithrombin level** (Remaining above 60% commonly);
- **Platelet count**; if progressively decrease, screening HIT antibody.



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## Case

62y male confirmed COVID-19, progressively dyspnea combined with renal dysfunction, prepared to treat with CRRT.

However, recurrent thrombosis occurred when CRRT.

Thrombophilia related tests:

Protein C: 12%

Protein S: 72%

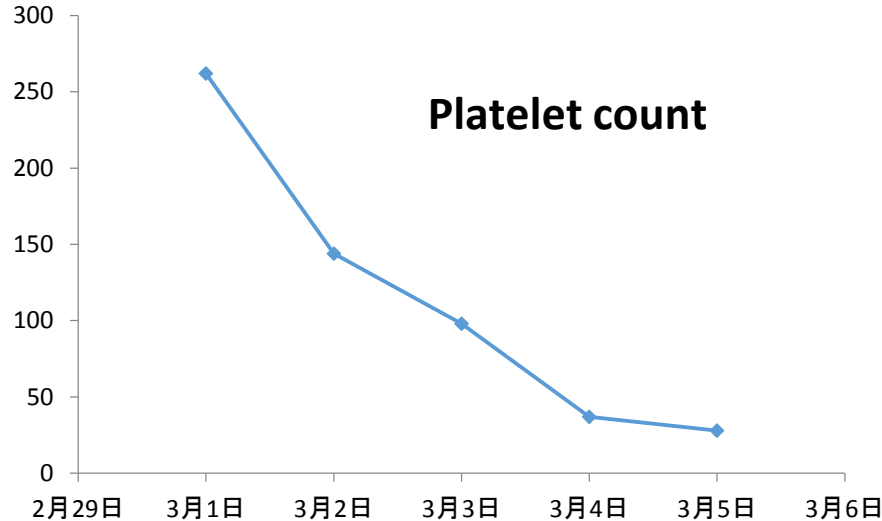
Antithrombin: 75%

Antiphospholipid antibody(LA, ACA, A $\beta_2$ GPI): All negative

**COVID-19 combined Protein C deficiency** was considered

## Case

65y female with confirmed COVID-19, history of hypertension, treated with CVVH. Using UFH、LMWH>5 days.



Recommended heparin-PF4 antibody test, Result: 2.0 U/mL (Ref<1.0).

**Heparin-induced thrombocytopenia (HIT)** was considered.

# Differential diagnosis of COVID-19 induced coagulopathy

- **Heparin interference:** *TEG (heparinase), Anti-FXa*
- **Vitamin K deficiency:** *Coagulation factor II, VII, IX, X*
- **TTP/HUS/ HIT:** *ADAMTS13, CFH, Hep-PF4 antibody...*
- **APS/CAPS:** *Antiphospholipid antibody*

# Conclusions

- ➡ **Hypercoagulability has been found in (early) severe COVID-19, and indicates the risk of DIC and VTE;**
- ➡ **Patients meeting SIC criteria or with markedly elevated D-dimer may benefit from anticoagulant therapy ;**
- ➡ **The value of special coagulation tests on monitoring and differential diagnosis of coagulopathy ;**

# THANKS

