Journal Club

Hot Topics of Covid-19

凝固異常／血栓症

2020年6月2日

練馬光が丘病院
総合救急診療科 集中治療部門
木庭 茂／片岡 惇

JSEPTIC Journal Club

NHER ICU GIM
PROUD OF GENERALIST

Menu

凝固検査の異常所見

凝固関連の合併症

病態生理

抗凝固療法

Menu

凝固検査の異常所見

凝固関連の合併症

病態生理

抗凝固療法

BRIEF REPORT

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

Ning Tang[1] | Dengju Li[2] | Xiong Wang[1] | Ziyong Sun[1]

J Thromb Haemost. 2020;18:844-847

- Tongji Hospital of Huazhong University of Science and Technology
- **2020年1月1日～2月3日**までCOVID-19で入院した**183症例**
- PT、APTT、AT、フィブリノゲン、FDP、Dダイマーを測定し、**生存者と死亡者で比較**

- 85人の女性＋98人の男性＝**183**症例
- 平均年齢**54.1**歳（19.4-94歳）
- 75症例（41%）が慢性疾患（心疾患、脳血管疾患、呼吸器疾患、腫瘍、慢性肝疾患、慢性腎臓病など）
- 2月13日時点

  退院：78症例（42.6%）、死亡：21症例（11.5%）、入院継続84症例（45.9%）

TABLE 1 Coagulation parameters of NCP patients on admission

生存者　　非生存者

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

Abbreviations: APTT, activated partial thromboplastin time; AT, antithrombin activity; FDP, fibrin degradation product; NCP, novel coronavirus pneumonia; PT, prothrombin time (PT).

非生存者で入院時に

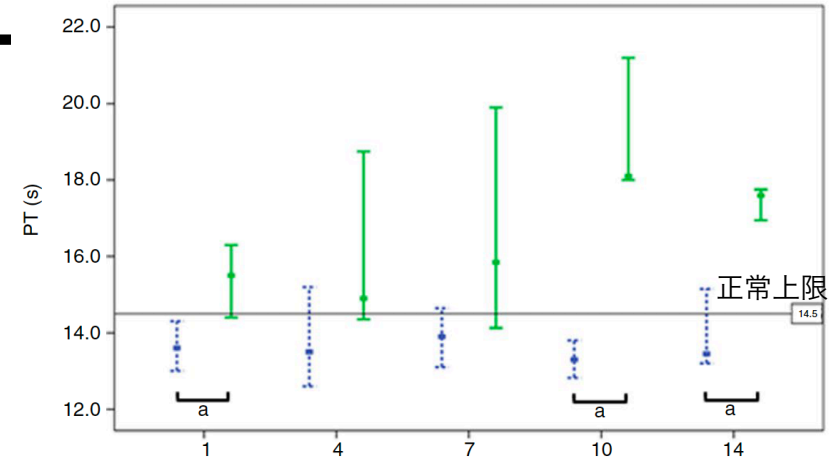
PT延長／Dダイマー上昇／FDP上昇

生存者

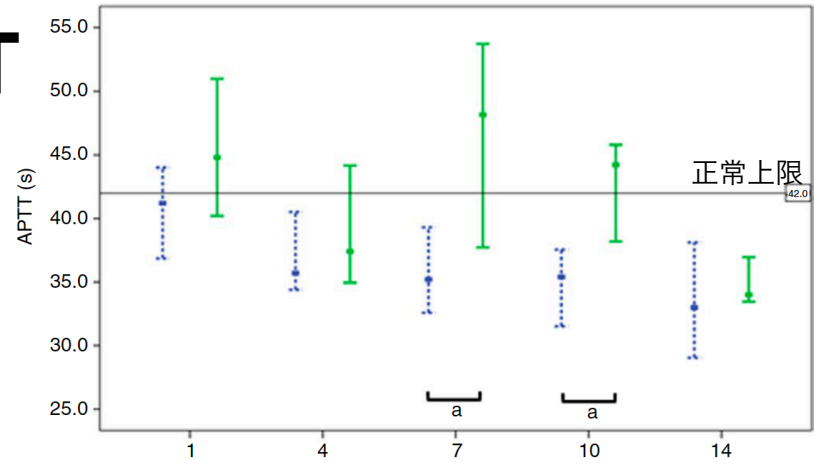
非生存者

a 有意差あり

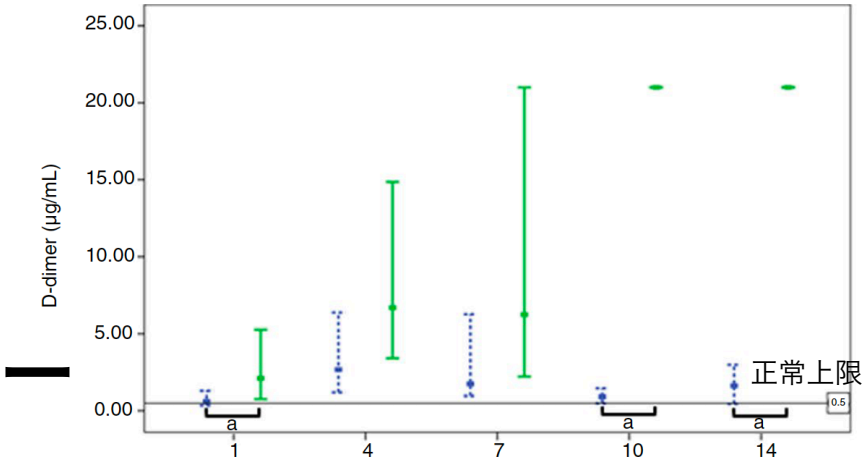
PT



APTT



Dダイマー



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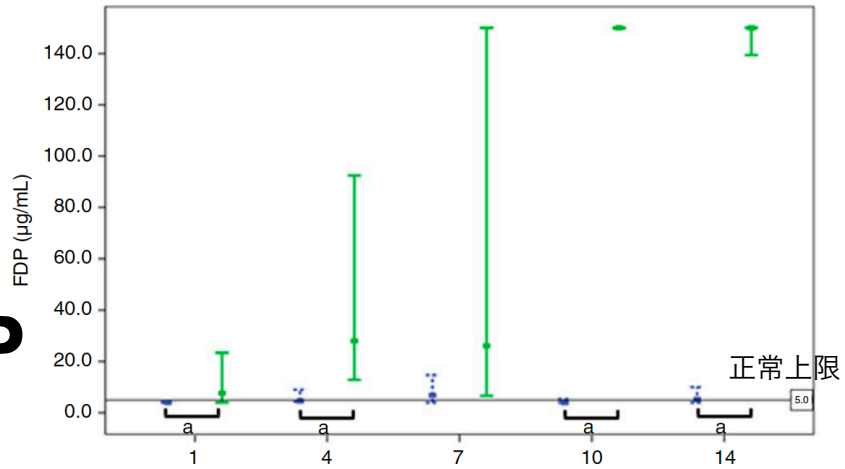
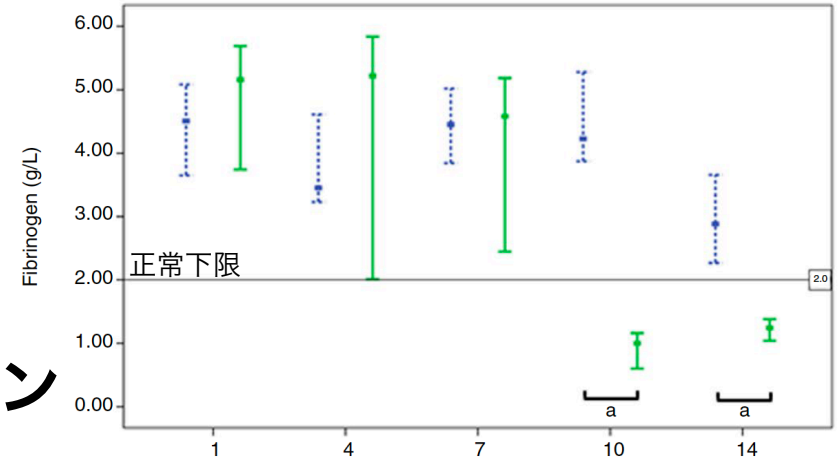


フィブリノゲン



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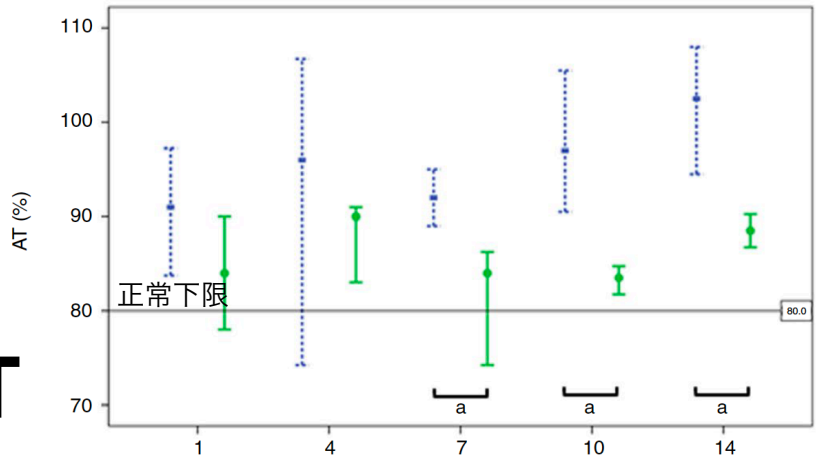
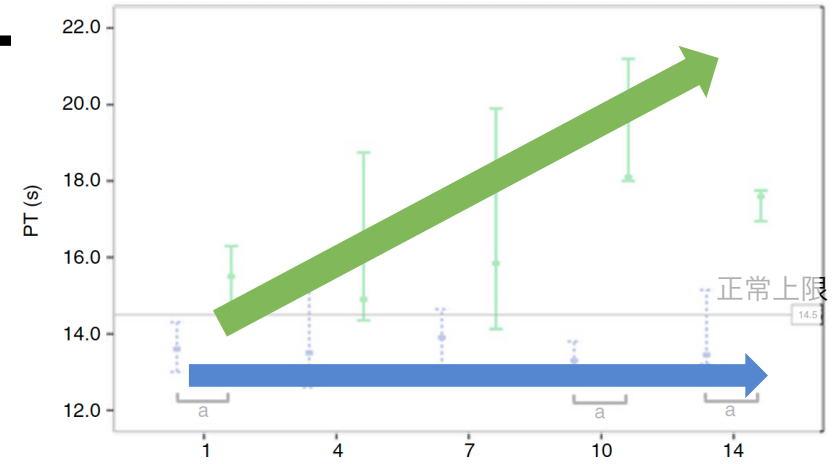


生存者

非生存者

a 有意差あり

PT



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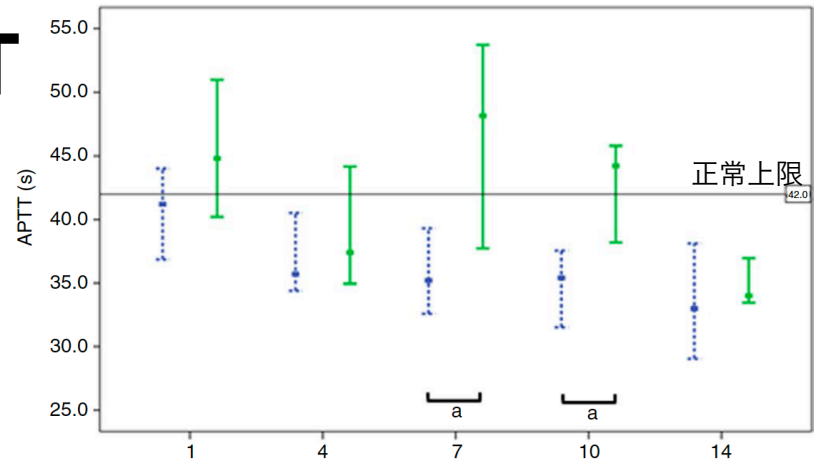
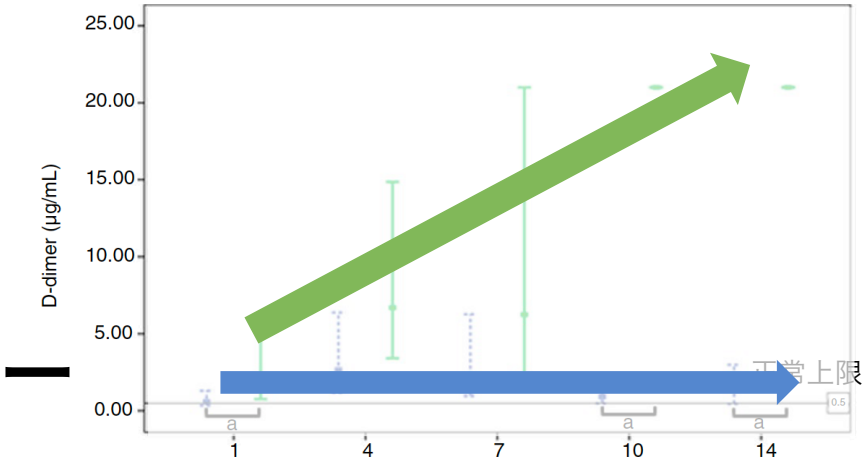


Dダイマー



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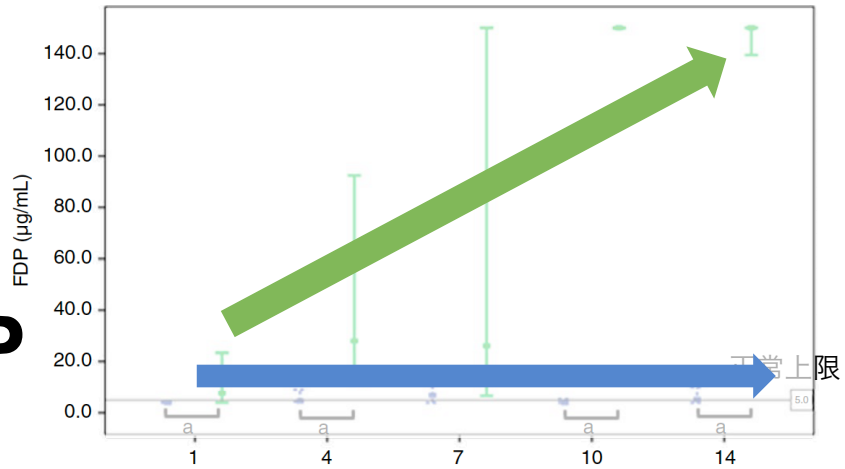

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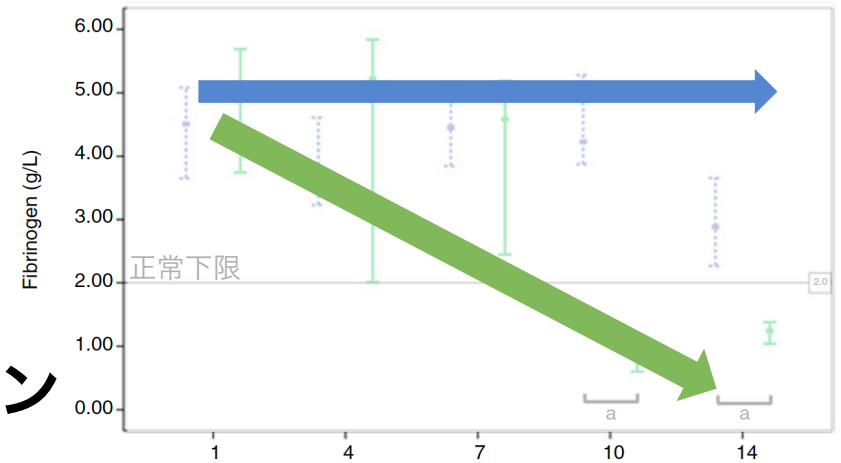

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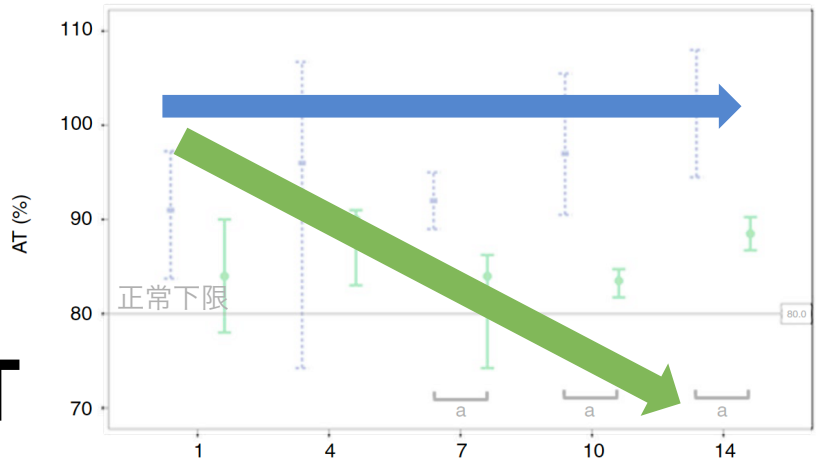

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

April 30, 2020
N Engl J Med 2020; 382:1708-1720
DOI: 10.1056/NEJMoa2002032

1099症例　552の病院@中国

- **Primary Composite End point**
  →ICU入室と人工呼吸器使用もしくは死亡
- **重症度**

年齢の中央値は**47**歳

Primary composite end point：**67**症例（6.1%）

ICU入室：　5%
人工呼吸器：　2.3%
死亡：　1.4%

症状、画像所見、血液検査などについて報告

Table 1. Clinical Characteristics of the Study Patients, According to Disease Severity and the Presence or Absence of the Primary Composite End Point.*

Characteristic	All Patients (N=1099)	Disease Severity		Presence of Primary Composite End Point†	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Age					
Median (IQR) — yr	47.0 (35.0–58.0)	45.0 (34.0–57.0)	52.0 (40.0–65.0)	63.0 (53.0–71.0)	46.0 (35.0–57.0)
Distribution — no./total no. (%)					
0–14 yr	9/1011 (0.9)	8/848 (0.9)	1/163 (0.6)	0	9/946 (1.0)
15–49 yr	557/1011 (55.1)	490/848 (57.8)	67/163 (41.1)	12/65 (18.5)	545/946 (57.6)
50–64 yr	292/1011 (28.9)	241/848 (28.4)	51/163 (31.3)	21/65 (32.3)	271/946 (28.6)
≥65 yr	153/1011 (15.1)	109/848 (12.9)	44/163 (27.0)	32/65 (49.2)	121/946 (12.8)
Female sex — no./total no. (%)	459/1096 (41.9)	386/923 (41.8)	73/173 (42.2)	22/67 (32.8)	437/1029 (42.5)
Smoking history — no./total no. (%)					
Never smoked	927/1085 (85.4)	793/913 (86.9)	134/172 (77.9)	44/66 (66.7)	883/1019 (86.7)
Former smoker	21/1085 (1.9)	12/913 (1.3)	9/172 (5.2)	5/66 (7.6)	16/1019 (1.6)
Current smoker	137/1085 (12.6)	108/913 (11.8)	29/172 (16.9)	17/66 (25.8)	120/1019 (11.8)
Exposure to source of transmission within past 14 days — no./total no.					
Living in Wuhan	483/1099 (43.9)	400/926 (43.2)	83/173 (48.0)	39/67 (58.2)	444/1032 (43.0)
Contact with wildlife	13/687 (1.9)	10/559 (1.8)	3/128 (2.3)	1/41 (2.4)	12/646 (1.9)
Recently visited Wuhan‡	193/616 (31.3)	166/526 (31.6)	27/90 (30.0)	10/28 (35.7)	183/588 (31.1)
Had contact with Wuhan residents‡	442/611 (72.3)	376/522 (72.0)	66/89 (74.2)	19/28 (67.9)	423/583 (72.6)
Median incubation period (IQR) — days§	4.0 (2.0–7.0)	4.0 (2.8–7.0)	4.0 (2.0–7.0)	4.0 (1.0–7.5)	4.0 (2.0–7.0)
Fever on admission					
Patients — no./total no. (%)	473/1081 (43.8)	391/910 (43.0)	82/171 (48.0)	24/66 (36.4)	449/1015 (44.2)
Median temperature (IQR) — °C	37.3 (36.7–38.0)	37.3 (36.7–38.0)	37.4 (36.7–38.1)	36.8 (36.3–37.8)	37.3 (36.7–38.0)
Distribution of temperature — no./total no. (%)					
<37.5°C	608/1081 (56.2)	519/910 (57.0)	89/171 (52.0)	42/66 (63.6)	566/1015 (55.8)
37.5–38.0°C	238/1081 (22.0)	201/910 (22.1)	37/171 (21.6)	10/66 (15.2)	228/1015 (22.5)
38.1–39.0°C	197/1081 (18.2)	160/910 (17.6)	37/171 (21.6)	11/66 (16.7)	186/1015 (18.3)
>39.0°C	38/1081 (3.5)	30/910 (3.3)	8/171 (4.7)	3/66 (4.5)	35/1015 (3.4)
Fever during hospitalization					
Patients — no./total no. (%)	975/1099 (88.7)	816/926 (88.1)	159/173 (91.9)	59/67 (88.1)	916/1032 (88.8)
Median highest temperature (IQR) — °C	38.3 (37.8–38.9)	38.3 (37.8–38.9)	38.5 (38.0–39.0)	38.5 (38.0–39.0)	38.3 (37.8–38.9)
<37.5°C	92/926 (9.9)	79/774 (10.2)	13/152 (8.6)	3/54 (5.6)	89/872 (10.2)
37.5–38.0°C	286/926 (30.9)	251/774 (32.4)	35/152 (23.0)	20/54 (37.0)	266/872 (30.5)
38.1–39.0°C	434/926 (46.9)	356/774 (46.0)	78/152 (51.3)	21/54 (38.9)	413/872 (47.4)
>39.0°C	114/926 (12.3)	88/774 (11.4)	26/152 (17.1)	10/54 (18.5)	104/872 (11.9)
Symptoms — no. (%)					
Conjunctival congestion	9 (0.8)	5 (0.5)	4 (2.3)	0	9 (0.9)
Nasal congestion	53 (4.8)	47 (5.1)	6 (3.5)	2 (3.0)	51 (4.9)
Headache	150 (13.6)	124 (13.4)	26 (15.0)	8 (11.9)	142 (13.8)
Cough	745 (67.8)	623 (67.3)	122 (70.5)	46 (68.7)	699 (67.7)
Sore throat	153 (13.9)	130 (14.0)	23 (13.3)	6 (9.0)	147 (14.2)
Sputum production	370 (33.7)	309 (33.4)	61 (35.3)	20 (29.9)	350 (33.9)
Fatigue	419 (38.1)	350 (37.8)	69 (39.9)	22 (32.8)	397 (38.5)
Hemoptysis	10 (0.9)	6 (0.6)	4 (2.3)	2 (3.0)	8 (0.8)
Shortness of breath	205 (18.7)	140 (15.1)	65 (37.6)	36 (53.7)	169 (16.4)
Nausea or vomiting	55 (5.0)	43 (4.6)	12 (6.9)	3 (4.5)	52 (5.0)
Diarrhea	42 (3.8)	32 (3.5)	10 (5.8)	4 (6.0)	38 (3.7)
Myalgia or arthralgia	164 (14.9)	134 (14.5)	30 (17.3)	6 (9.0)	158 (15.3)
Chills	126 (11.5)	100 (10.8)	26 (15.0)	8 (11.9)	118 (11.4)
Signs of infection — no. (%)					
Throat congestion	19 (1.7)	17 (1.8)	2 (1.2)	0	19 (1.8)
Tonsil swelling	23 (2.1)	17 (1.8)	6 (3.5)	1 (1.5)	22 (2.1)
Enlargement of lymph nodes	2 (0.2)	1 (0.1)	1 (0.6)	1 (1.5)	1 (0.1)
Rash	2 (0.2)	0	2 (1.2)	0	2 (0.2)
Coexisting disorder — no. (%)					
Any	261 (23.7)	194 (21.0)	67 (38.7)	39 (58.2)	222 (21.5)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	6 (3.5)	7 (10.4)	5 (0.5)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Hypertension	165 (15.0)	124 (13.4)	41 (23.7)	24 (35.8)	141 (13.7)
Coronary heart disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (2.3)	4 (6.0)	11 (1.1)
Hepatitis B infection¶	23 (2.1)	22 (2.4)	1 (0.6)	1 (1.5)	22 (2.1)
Cancer‖	10 (0.9)	7 (0.8)	3 (1.7)	1 (1.5)	9 (0.9)
Chronic renal disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)
Immunodeficiency	2 (0.2)	2 (0.2)	0	0	2 (0.2)

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Disease severityは入院時の所見
American thoracic Society
guidelineで計算

Primary composite end point
ICU入室、人工呼吸器、死亡

Table 2. Radiographic and Laboratory Findings.*

Variable	All Patients (N=1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Laboratory findings					
Median Pao_2:Fio_2 ratio (IQR)†	3.9 (2.9–4.7)	3.9 (2.9–4.5)	4.0 (2.8–5.2)	2.9 (2.2–5.4)	4.0 (3.1–4.6)
White-cell count					
Median (IQR) — per mm^3	4700 (3500–6000)	4900 (3800–6000)	3700 (3000–6200)	6100 (4900–11,100)	4700 (3500–5900)
Distribution — no./total no. (%)					
>10,000 per mm^3	58/978 (5.9)	39/811 (4.8)	19/167 (11.4)	15/58 (25.9)	43/920 (4.7)
<4000 per mm^3	330/978 (33.7)	228/811 (28.1)	102/167 (61.1)	8/58 (13.8)	322/920 (35.0)
Lymphocyte count					
Median (IQR) — per mm^3	1000 (700–1300)	1000 (800–1400)	800 (600–1000)	700 (600–900)	1000 (700–1300)
Distribution — no./total no. (%)					
<1500 per mm^3	731/879 (83.2)	584/726 (80.4)	147/153 (96.1)	50/54 (92.6)	681/825 (82.5)
Platelet count					
Median (IQR) — per mm^3	168,000 (132,000–207,000)	172,000 (139,000–212,000)	137,500 (99,000–179,500)	156,500 (114,200–195,000)	169,000 (133,000–207,000)
Distribution — no./total no. (%)					
<150,000 per mm^3	315/869 (36.2)	225/713 (31.6)	90/156 (57.7)	27/58 (46.6)	288/811 (35.5)
Median hemoglobin (IQR) — g/dl‡	13.4 (11.9–14.8)	13.5 (12.0–14.8)	12.8 (11.2–14.1)	12.5 (10.5–14.0)	13.4 (12.0–14.8)
Distribution of other findings — no./total no. (%)					
C-reactive protein ≥10 mg/liter	481/793 (60.7)	371/658 (56.4)	110/135 (81.5)	41/45 (91.1)	440/748 (58.8)
Procalcitonin ≥0.5 ng/ml	35/633 (5.5)	19/516 (3.7)	16/117 (13.7)	12/50 (24.0)	23/583 (3.9)
Lactate dehydrogenase ≥250 U/liter	277/675 (41.0)	205/551 (37.2)	72/124 (58.1)	31/44 (70.5)	246/631 (39.0)
Aspartate aminotransferase >40 U/liter	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)	26/52 (50.0)	142/705 (20.1)
Alanine aminotransferase >40 U/liter	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)	20/49 (40.8)	138/692 (19.9)
Total bilirubin >17.1 μmol/liter	76/722 (10.5)	59/594 (9.9)	17/128 (13.3)	10/48 (20.8)	66/674 (9.8)
Creatine kinase ≥200 U/liter	90/657 (13.7)	67/536 (12.5)	23/121 (19.0)	12/46 (26.1)	78/611 (12.8)
Creatinine ≥133 μmol/liter	12/752 (1.6)	6/614 (1.0)	6/138 (4.3)	5/52 (9.6)	7/700 (1.0)
D-dimer ≥0.5 mg/liter	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)	34/49 (69.4)	226/511 (44.2)

非重症 / 重症

血小板

Dダイマー

Table 3. Complications, Treatments, and Clinical Outcom

Variable	All Patients (N=1099)	Disease Severity		Presence of Composite Primary End Poin	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Complications					
Septic shock — no. (%)	12 (1.1)	1 (0.1)	11 (6.4)	9 (13.4)	3 (0.3)
Acute respiratory distress syndrome — no. (%)	37 (3.4)	10 (1.1)	27 (15.6)	27 (40.3)	10 (1.0)
Acute kidney injury — no. (%)	6 (0.5)	1 (0.1)	5 (2.9)	4 (6.0)	2 (0.2)
Disseminated intravascular coagulation — no. (%)	1 (0.1)	0	1 (0.6)	1 (1.5)	0
Rhabdomyolysis — no. (%)	2 (0.2)	2 (0.2)	0	0	2 (0.2)
Physician-diagnosed pneumonia — no./total no. (%)	972/1067 (91.1)	800/894 (89.5)	172/173 (99.4)	63/66 (95.5)	909/1001 (90.8)
Median time until development of pneumonia (IQR) — d					
After initial Covid-19 diagnosis	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.0 (0.0–3.5)	0.0 (0.0–1.0)
After onset of Covid-19 symptoms	3.0 (1.0–6.0)	3.0 (1.0–6.0)	5.0 (2.0–7.0)	4.0 (0.0–7.0)	3.0 (1.0–6.0)
Treatments					
Intravenous antibiotics — no. (%)	637 (58.0)	498 (53.8)	139 (80.3)	60 (89.6)	577 (55.9)
Oseltamivir — no. (%)	393 (35.8)	313 (33.8)	80 (46.2)	36 (53.7)	357 (34.6)
Antifungal medication — no. (%)	31 (2.8)	18 (1.9)	13 (7.5)	8 (11.9)	23 (2.2)
Systemic glucocorticoids — no. (%)	204 (18.6)	127 (13.7)	77 (44.5)	35 (52.2)	169 (16.4)
Oxygen therapy — no. (%)	454 (41.3)	331 (35.7)	123 (71.1)	59 (88.1)	395 (38.3)
Mechanical ventilation — no. (%)	67 (6.1)	0	67 (38.7)	40 (59.7)	27 (2.6)
Invasive	25 (2.3)	0	25 (14.5)	25 (37.3)	0
Noninvasive	56 (5.1)	0	56 (32.4)	29 (43.3)	27 (2.6)
Use of extracorporeal membrane oxygenation — no. (%)	5 (0.5)	0	5 (2.9)	5 (7.5)	0
Use of continuous renal-replacement therapy — no. (%)	9 (0.8)	0	9 (5.2)	8 (11.9)	1 (0.1)
Use of intravenous immune globulin — no. (%)	144 (13.1)	86 (9.3)	58 (33.5)	27 (40.3)	117 (11.3)
Admission to intensive care unit — no. (%)	55 (5.0)	22 (2.4)	33 (19.1)	55 (82.1)	0
Median length of hospital stay (IQR) — days†	12.0 (10.0–14.0)	11.0 10.0–13.0)	13.0 (11.5–17.0)	14.5 (11.0–19.0)	12.0 (10.0–13.0)

血小板は軽度減少、DICの症例は少ない

Dダイマーは重症例で上昇　PT、FDPなどの記載はなし

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Lancet 2020; 395: 497–506

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S0140-6736(20)30183-5

Chaolin Huang, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†*

2020年1月2日までに入院した**41**症例
＠中国

RT-PCR検査でSARS-CoV-2感染を確認

年齢の中央値は**49**歳
13人（32%）がICUに入院

ICU入院症例と非ICU入院症例で比較

ICU症例は非ICU症例より

	全患者	ICU	非ICU	
	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
White blood cell count, ×10⁹ per L	6·2 (4·1–10·5)	11·3 (5·8–12·1)	5·7 (3·1–7·6)	0·011
<4	10/40 (25%)	1/13 (8%)	9/27 (33%)	0·041
4–10	18/40 (45%)	5/13 (38%)	13/27 (48%)	..
>10	12/40 (30%)	7/13 (54%)	5/27 (19%)	..
Neutrophil count, ×10⁹ per L	5·0 (3·3–8·9)	10·6 (5·0–11·8)	4·4 (2·0–6·1)	0·00069
Lymphocyte count, ×10⁹ per L	0·8 (0·6–1·1)	0·4 (0·2–0·8)	1·0 (0·7–1·1)	0·0041
<1·0	26/41 (63%)	11/13 (85%)	15/28 (54%)	0·045
≥1·0	15/41 (37%)	2/13 (15%)	13/28 (46%)	..
Haemoglobin, g/L	126·0 (118·0–140·0)	122·0 (111·0–128·0)	130·5 (120·0–140·0)	0·20
Platelet count, ×10⁹ per L	164·5 (131·5–263·0)	196·0 (165·0–263·0)	149·0 (131·0–263·0)	0·45
<100 血小板	2/40 (5%)	1/13 (8%)	1/27 (4%)	0·45
≥100	38/40 (95%)	12/13 (92%)	26/27 (96%)	..
Prothrombin time, s PT	11·1 (10·1–12·4)	12·2 (11·2–13·4)	10·7 (9·8–12·1)	0·012
Activated partial thromboplastin time, s	27·0 (24·2–34·1)	26·2 (22·5–33·9)	27·7 (24·8–34·1)	0·57
D-dimer, mg/L Dダイマー	0·5 (0·3–1·3)	2·4 (0·6–14·4)	0·5 (0·3–0·8)	0·0042
Albumin, g/L	31·4 (28·9–36·0)	27·9 (26·3–30·9)	34·7 (30·2–36·5)	0·00066

PTは延長　Dダイマーも上昇

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

Lancet 2020; 395: 1054–62
Published Online March 9, 2020
https://doi.org/10.1016/S0140-6736(20)30566-3

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中国の武漢の2つの病院

→Jinyintan 病院、Wuhan Pulmonary 病院

すべての成人患者をinclude

2020年1月31日までに**生存か死亡**した症例を解析

合計症例：**191**症例

（Jinyintan病院から135症例、Wuhan Pulmonary病院から56症例）

退院：137症例、死亡54症例

91症例（48%）が併存疾患あり

58症例（30%）が高血圧

36症例（19%）が糖尿病

15症例（ 8%）が心血管疾患

非生存　生存

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
(Continued from previous page)				
Anaemia	29 (15%)	14 (26%)	15 (11%)	0·0094
Platelet count, ×10⁹ per L	206·0 (155·0–262·0)	165·5 (107·0–229·0)	220·0 (168·0–271·0)	<0·0001
<100	13 (7%)	11 (20%)	2 (1%)	<0·0001
Albumin, g/L	32·3 (29·1–35·8)	29·1 (26·5–31·3)	33·6 (30·6–36·4)	<0·0001
ALT, U/L	30·0 (17·0–46·0)	40·0 (24·0–51·0)	27·0 (15·0–40·0)	0·0050
>40	59/189 (31%)	26 (48%)	33/135 (24%)	0·0015
Creatinine >133 μmol/L	8/186 (4%)	5 (9%)	3/132 (2%)	0·045
Lactate dehydrogenase, U/L	300·0 (234·0–407·0)	521·0 (363·0–669·0)	253·5 (219·0–318·0)	<0·0001
>245	123/184 (67%)	53 (98%)	70/130(54%)	<0·0001
Creatine kinase, U/L	21·5 (13·0–72·4)	39·0 (19·5–151·0)	18·0 (12·5–52·1)	0·0010
>185	22/168 (13%)	11/52 (21%)	11/116 (9%)	0·038
High-sensitivity cardiac troponin I, pg/mL	4·1 (2·0–14·1)	22·2 (5·6–83·1)	3·0 (1·1–5·5)	<0·0001
>28	24/145 (17%)	23/50 (46%)	1/95 (1%)	<0·0001
Prothrombin time, s	11·6 (10·6–13·0)	12·1 (11·2–13·7)	11·4 (10·4–12·6)	0·0004
<16	171/182 (94%)	47 (87%)	124/128 (97%)	0·016*
≥16	11/182 (6%)	7 (13%)	4/128 (3%)	..
D-dimer, μg/mL	0·8 (0·4–3·2)	5·2 (1·5–21·1)	0·6 (0·3–1·0)	<0·0001
≤0·5	55/172 (32%)	4 (7%)	51/118 (43%)	<0·0001*
>0·5 to ≤1	45/172 (26%)	6 (11%)	39/118 (33%)	..
>1	72/172 (42%)	44 (81%)	28/118 (24%)	..
Serum ferritin, μg/L	722·0 (377·2–1435·3)	1435·3 (728·9–2000·0)	503·2 (264·0–921·5)	<0·0001
>300	102/128 (80%)	44/46 (96%)	58/82 (71%)	0·0008
IL-6, pg/mL	7·4 (5·3–10·8)	11·0 (7·5–14·4)	6·3 (5·0–7·9)	<0·0001
Procalcitonin, ng/mL	0·1 (0·1–0·1)	0·1 (0·1–0·5)	0·1 (0·1–0·1)	<0·0001
<0·1	114/164 (70%)	19/51 (37%)	95/113 (84%)	<0·0001*
≥0·1 to <0·25	30/164 (18%)	16/51 (31%)	14/113 (12%)	..
≥0·25 to <0·5	6/164 (4%)	3/51 (6%)	3/113 (3%)	..
≥0·5	14/164 (9%)	13/51 (25%)	1/113 (1%)	..

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15症例（ 8%）が心血管疾患

- **LDH上昇**
- **PT延長**
- **Dダイマー上昇**
- **フェリチン上昇**

非生存　生存

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
(Continued from previous page)				
Anaemia	29 (15%)	14 (26%)	15 (11%)	0·0094
Platelet count, ×10⁹ per L	206·0 (155·0–262·0)	165·5 (107·0–229·0)	220·0 (168·0–271·0)	<0·0001
<100	13 (7%)	11 (20%)	2 (1%)	<0·0001
Albumin, g/L	32·3 (29·1–35·8)	29·1 (26·5–31·3)	33·6 (30·6–36·4)	<0·0001
ALT, U/L	30·0 (17·0–46·0)	40·0 (24·0–51·0)	27·0 (15·0–40·0)	0·0050
>40	59/189 (31%)	26 (48%)	33/135 (24%)	0·0015
Creatinine >133 μmol/L	8/186 (4%)	5 (9%)	3/132 (2%)	0·045
Lactate dehydrogenase, U/L	300·0 (234·0–407·0)	521·0 (363·0–669·0)	253·5 (219·0–318·0)	<0·0001
>245	123/184 (67%)	53 (98%)	70/130(54%)	<0·0001
Creatine kinase, U/L	21·5 (13·0–72·4)	39·0 (19·5–151·0)	18·0 (12·5–52·1)	0·0010
>185	22/168 (13%)	11/52 (21%)	11/116 (9%)	0·038
High-sensitivity cardiac troponin I, pg/mL	4·1 (2·0–14·1)	22·2 (5·6–83·1)	3·0 (1·1–5·5)	<0·0001
>28	24/145 (17%)	23/50 (46%)	1/95 (1%)	<0·0001
Prothrombin time, s	11·6 (10·6–13·0)	12·1 (11·2–13·7)	11·4 (10·4–12·6)	0·0004
<16	171/182 (94%)	47 (87%)	124/128 (97%)	0·016*
≥16	11/182 (6%)	7 (13%)	4/128 (3%)	..
D-dimer, μg/mL	0·8 (0·4–3·2)	5·2 (1·5–21·1)	0·6 (0·3–1·0)	<0·0001
≤0·5	55/172 (32%)	4 (7%)	51/118 (43%)	<0·0001*
>0·5 to ≤1	45/172 (26%)	6 (11%)	39/118 (33%)	..
>1	72/172 (42%)	44 (81%)	28/118 (24%)	..
Serum ferritin, μg/L	722·0 (377·2–1435·3)	1435·3 (728·9–2000·0)	503·2 (264·0–921·5)	<0·0001
>300	102/128 (80%)	44/46 (96%)	58/82 (71%)	0·0008
IL-6, pg/mL	7·4 (5·3–10·8)	11·0 (7·5–14·4)	6·3 (5·0–7·9)	<0·0001
Procalcitonin, ng/mL	0·1 (0·1–0·1)	0·1 (0·1–0·5)	0·1 (0·1–0·1)	<0·0001
<0·1	114/164 (70%)	19/51 (37%)	95/113 (84%)	<0·0001*
≥0·1 to <0·25	30/164 (18%)	16/51 (31%)	14/113 (12%)	..
≥0·25 to <0·5	6/164 (4%)	3/51 (6%)	3/113 (3%)	..
≥0·5	14/164 (9%)	13/51 (25%)	1/113 (1%)	..

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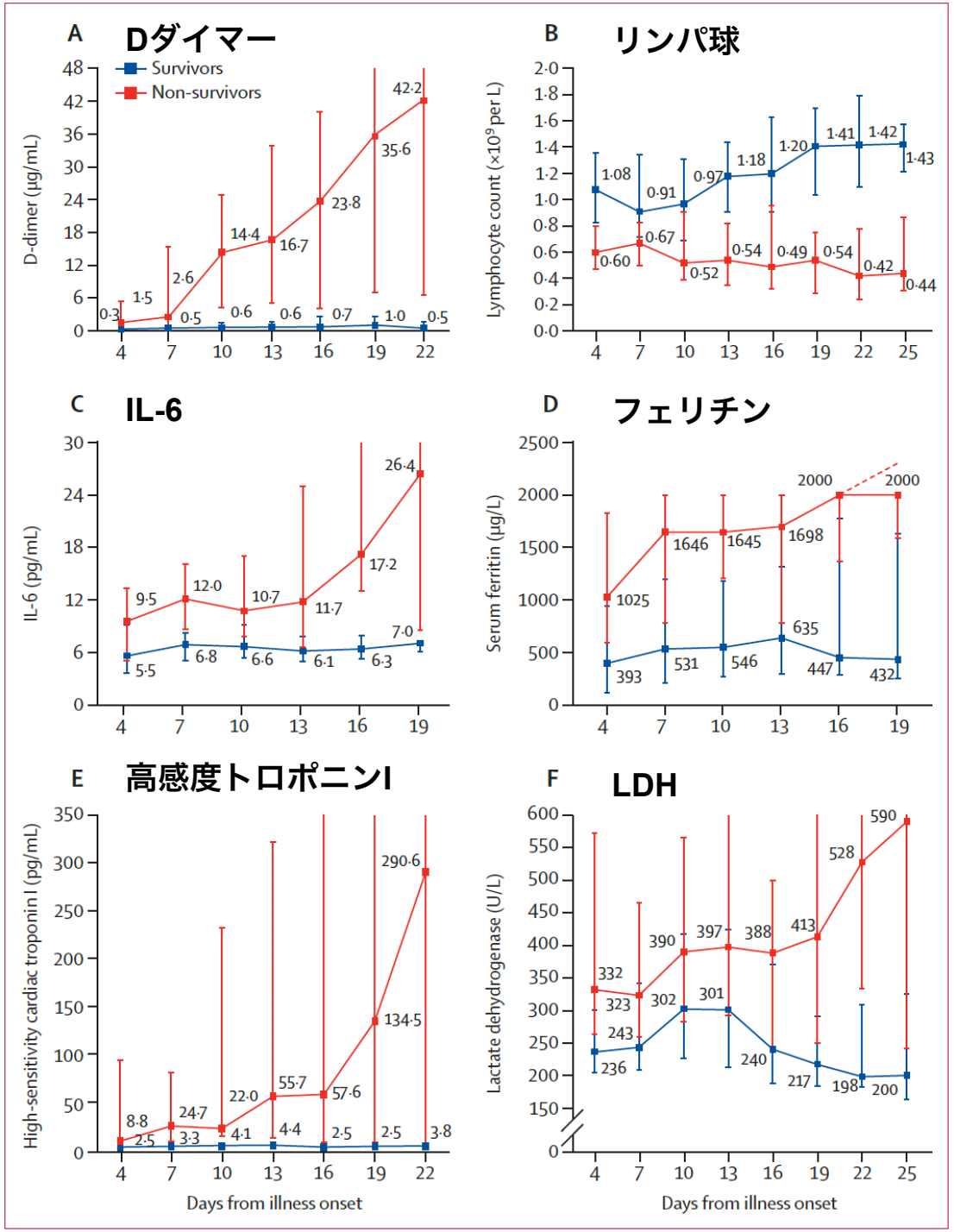
	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Demographics and clinical characteristics				
Age, years*	1·14 (1·09–1·18)	<0·0001	1·10 (1·03–1·17)	0·0043
Female sex (*vs* male)	0·61 (0·31–1·20)	0·15	..	..
Current smoker (*vs* non-smoker)	2·23 (0·65–7·63)	0·20	..	..
Comorbidity present (*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, × 10⁹ per L				
<4	0·73 (0·26–2·10)	0·56	..	..
4–10	1 (ref)	..	..	..
>10	6·60 (3·02–14·41)	<0·0001	..	..
Lymphocyte count, × 10⁹ per L*	0·02 (0·01–0·08)	<0·0001	0·19 (0·02–1·62)	0·13
ALT, U/L				
≤40	1 (ref)	..	..	..
>40	2·87 (1·48–5·57)	0·0018	..	..

(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, pg/mL				
≤28	1 (ref)	..	..	..
>28	80·07 (10·34–620·36)	<0·0001	..	..
D-dimer, μg/mL				
≤0·5	1 (ref)	..	1 (ref)	..
> 0·5	1·96 (0·52–7·43)	0·32	2·14 (0·21–21·39)	0·52
> 1	20·04 (6·52–61·56)	<0·0001	18·42 (2·64–128·55)	0·0033
Prothrombin time, s				
<16	1 (ref)	..	..	..
≥16	4·62 (1·29–16·50)	0·019	..	..
Serum ferritin, μg/L				
≤300	1 (ref)	..	..	..
>300	9·10 (2·04–40·58)	0·0038	..	..
IL-6, pg/mL*	1·12 (1·03–1·23)	0·0080	..	..
Procalcitonin, ng/mL*	13·75 (1·81–104·40)	0·011	..	..

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**



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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, × 10⁹ per L				
<4	0·73 (0·26–2·10)	0·56	..	..
4–10	1 (ref)	..	..	..
>10	6·60 (3·02–14·41)	<0·0001	..	..
Lymphocyte count, × 10⁹ per L	0·02 (0·01–0·08)	<0·0001	0·19 (0·02–1·62)	0·13
ALT, U/L				
≤40	1 (ref)	..	..	..
>40	2·57 (1·37–4·57)	0·0027	..	..

(Table 3 continues in next column)

(Continued from previous column)

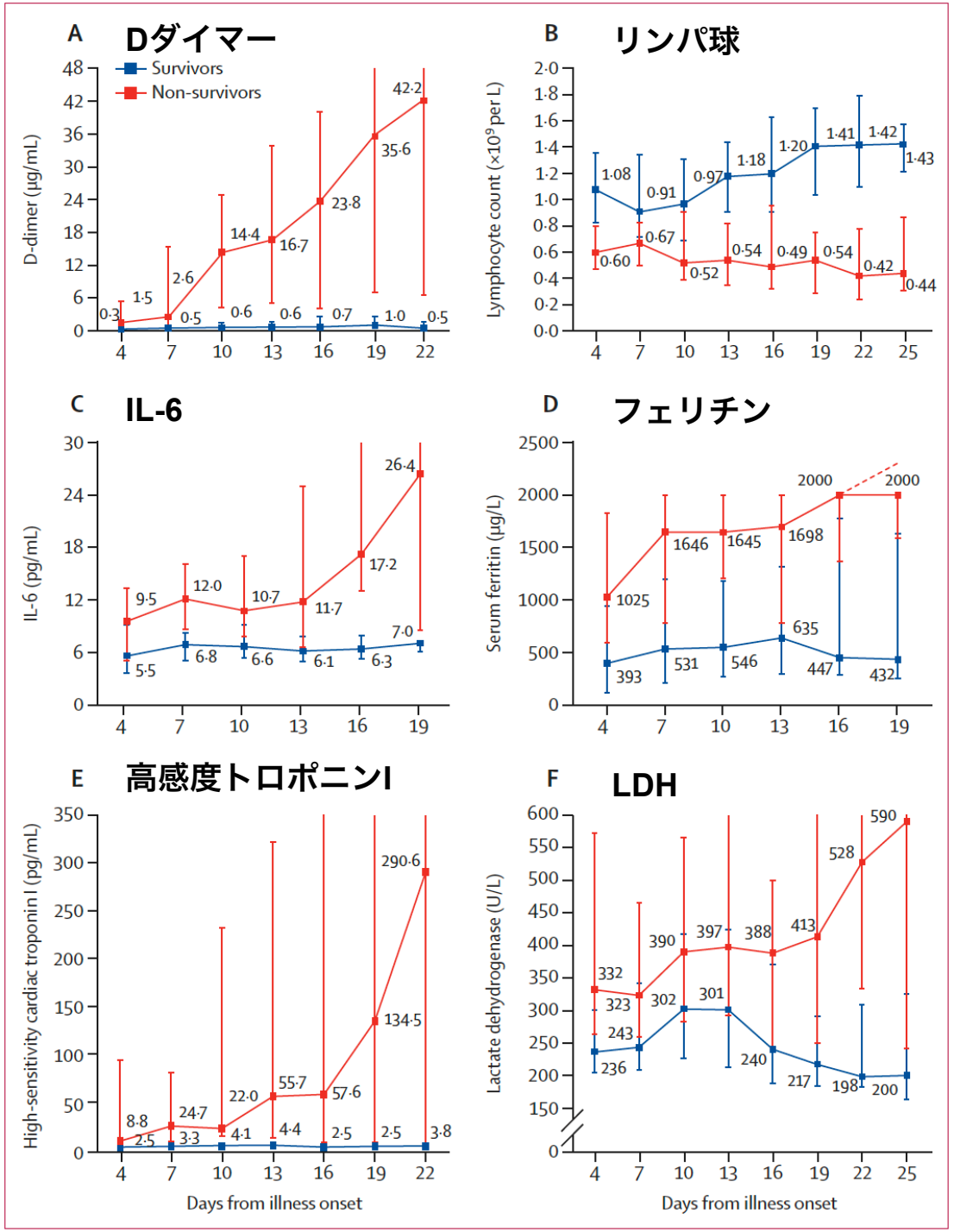
	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Creatinine, μmol/L				
≤133	1 (ref)	..	..	..
>133	4·39 (1·01–19·06)	0·048	..	..
Lactate dehydrogenase, U/L				
≤245	1 (ref)	..	..	..
>245	45·43 (6·10–338·44)	0·0002	..	..
Creatine kinase, U/L				
≤185	1 (ref)	..	..	..
>185	2·56 (1·03–6·36)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

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

予後不良因子

- 年齢
- SOFAスコア
- 心疾患（OR2.14）
- **Dダイマー上昇（OR18.42）**



JAMA Internal Medicine | Original Investigation

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China

PMID: 32167524

JAMA Intern Med. 2020 Mar 13;e200994.

201症例@Wuhan Jinyintan Hospital in China

2019年12月25日～2016年1月26日

最終follow-up 2020年1月13日

ARDSに進展・死亡の2点について検討

合計**201**症例（128症例が男性）

年齢の中央値は**51**歳

84症例（41.8%）がARDSに進展

44症例/84症例（52.4% ）が死亡

Table 1. Demographic Characteristics of Patients With Coronavirus Disease 2019 Pneumonia

Study population	No. (%)
No. of patients	201
Age, median (IQR), y	51 (43-60)
≥65	40 (19.9)
<65	161 (80.1)
Highest patient temperature, median (IQR), °C	38.8 (38.3-39.0)
≥39 (high fever)	77 (38.3)
<39	93 (46.3)
Gender	
Male	128 (63.7)
Female	73 (36.3)
Study population	**No. (%)**
Clinical outcomes	
ARDS	84 (41.8)
ICU admission	53 (26.4)
Death	44 (21.9)

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JAMA Intern Med. 2020 Mar 13;e200994.

全患者

ARDSなし　ARDSあり

ARDS患者

生存　死亡

Table 3. Clinical Characteristics and Initial Laboratory Indices Among Patients With and Without ARDS (continued)

Clinical characteristics	All patients				Patients with ARDS			
	Without ARDS, No. (%) (n = 117)	With ARDS, No. (%) (n = 84)	Difference (95% CI)[a]	*P* value[b]	Alive, No. (%) (n = 40)	Died, No. (%) (n = 44)	Difference (95% CI)[a]	*P* value[b]
Infection-related indices								
hs-CRP, mg/L	23.40 (6.65 to 57.80)	83.00 (39.45 to 152.40)	46.70 (32.50 to 64.00)	<.001	69.20 (26.60 to 120.80)	90.85 (44.55 to >160)	17.92 (−8.60 to 45.00)	.17
IL-6, pg/mL	6.29 (5.36 to 7.83)	7.39 (5.63 to 10.89)	0.93 (0.07 to 1.98)	.03	6.05 (5.12 to 6.99)	10.07 (7.36 to 14.80)	3.88 (2.20 to 6.13)	<.001
ESR, mm/h	47.70 (40.00 to 64.30)	52.40 (40.00 to 71.00)	4.00 (−2.00 to 11.60)	.20	51.60 (40.00 to 70.00)	59.50 (39.50 to 72.50)	1.80 (−9.00 to 14.51)	.74
Serum ferritin, ng/mL	457.66 (223.73 to 702.65)	1029.28 (546.26 to >2000)	545.50 (332.15 to 754.44)	<.001	853.00 (330.33 to 1968.57)	1096.21 (559.41 to >2000)	102.55 (−185.63 to 412.71)	.34
Coagulation function								
PT, s	10.60 (10.10 to 11.50)	11.70 (11.10 to 12.45)	1.00 (0.70 to 1.30)	<.001	11.75 (10.95 to 12.45)	11.60 (11.10 to 12.45)	0.00 (−0.50 to 0.60)	.87
APTT, s	29.75 (25.55 to 32.85)	26.00 (22.55 to 35.00)	−1.70 (−3.90 to 0.60)	.13	29.60 (24.00 to 35.75)	24.10 (22.25 to 28.35)	−3.10 (−7.00 to −0.20)	.04
D-dimer, μg/mL	0.52 (0.33 to 0.93)	1.16 (0.46 to 5.37)	0.52 (0.21 to 0.94)	<.001	0.49 (0.31 to 1.18)	3.95 (1.15 to 10.96)	2.10 (0.89 to 5.27)	.001

Abbreviations: α-HBDH, α-hydroxybutyric dehydrogenase; ARDS, acute respiratory distress syndrome; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK-MB, creatine kinase muscle-brain isoform; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IMV, invasive mechanical ventilation; IQR, interquartile range; NMV, noninvasive mechanical ventilation (including high flow supply and face mask); LDH, lactate dehydrogenase; LDL, low-density lipoprotein; PT, prothrombin time.

[a] Difference in location for continuous variables (by Hodges-Lehmann method) and in percentage for categorical variables (With ARDS vs Without ARDS or Died vs Alive).

[b] Mann-Whitney-Wilcoxon was used for continuous variables, and χ^2 test was used for categorical variables, if not specified.

[c] Fisher exact test.

IL-6とDダイマーは

ARDSに進展した患者で高く、その中では死亡者も多い

Table 4. Bivariate Cox Regression of Factors Associated With ARDS Development or Progression From ARDS to Death

Patient characteristics and findings	ARDS		Death	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical characteristics				
Age (≥65 vs <65), y	3.26 (2.08-5.11)	<.001	6.17 (3.26-11.67)	<.001
Gender (male vs female)	1.47 (0.92-2.36)	.11	0.56 (0.30-1.05)	.07
Highest patient temperature (≥39 °C vs <39 °C)	1.77 (1.11-2.84)	.02	0.41 (0.21-0.82)	.01
Comorbidities				
Hypertension (yes vs no)	1.82 (1.13-2.95)	.01	1.70 (0.92-3.14)	.09
Diabetes (yes vs no)	2.34 (1.35-4.05)	.002	1.58 (0.80-3.13)	.19
Laboratory findings				
Hematologic				
Neutrophils, 10^9/L	1.14 (1.09-1.19)	<.001	1.08 (1.01-1.17)	.03
Lymphocytes,10^9/L	0.37 (0.21-0.63)	<.001	0.51 (0.22-1.17)	.11
CD3, 100/μL	0.83 (0.72-0.96)	.01	0.81 (0.59-1.11)	.19
CD4, 100/μL	0.74 (0.59-0.93)	.01	0.83 (0.51-1.35)	.45
CD8, 100/μL	0.74 (0.53-1.04)	.08	0.51 (0.24-1.09)	.08
Biochemical				
Total bilirubin, μM	1.05 (1.02-1.08)	.001	1.07 (1.02-1.12)	.003
AST, U/L	1.02 (1.01-1.03)	<.001	0.99 (0.98-1.01)	.45
ALT, U/L	1.00 (1.00-1.01)	.09	1.00 (0.98-1.01)	.43
Albumin, 10 g/L	0.49 (0.37-0.66)	<.001	0.19 (0.07-0.49)	.001
Globulin, 10 g/L	2.32 (1.45-3.71)	<.001	1.91 (1.01-3.61)	.05
Prealbumin, mg/L	0.99 (0.98-0.99)	<.001	1.00 (0.99-1.00)	.31
Urea, mM	1.13 (1.09-1.18)	<.001	1.13 (1.06-1.20)	<.001
Creatinine, 10 μM	1.05 (1.01-1.10)	.02	1.04 (0.97-1.11)	.31
Glucose, mM	1.13 (1.08-1.19)	<.001	1.00 (0.92-1.08)	.92
CK-MB, U/L	1.01 (1.00-1.02)	.12	0.99 (0.97-1.01)	.46
Cholinesterase, $\times 10^3$U/L	0.81 (0.73-0.90)	<.001	0.84 (0.73-0.97)	.02
Cystatin C, mg/L	1.69 (1.31-2.19)	<.001	1.80 (1.28-2.53)	.001
LDH, 100 U/L	1.61 (1.44-1.79)	<.001	1.30 (1.11-1.52)	.001
α-HBDH, 100 U/L	1.74 (1.52-1.99)	<.001	1.34 (1.13-1.60)	.001
LDL, mM	0.63 (0.44-0.88)	.008	0.84 (0.54-1.31)	.45
Infection-related indices				
hs-CRP, mg/L (>5 vs ≤5)	4.81 (1.52-15.27)	.008	NA	NA
IL-6, pg/mL	1.02 (1.00-1.05)	.09	1.03 (1.01-1.05)	.01
ESR, mm/h	1.01 (1.00-1.02)	.19	1.01 (0.99-1.02)	.32
Serum ferritin, ng/mL (>300 vs ≤300)	3.53 (1.52-8.16)	.003	5.28 (0.72-38.48)	.10
Coagulation function				
PT, s	1.56 (1.32-1.83)	<.001	1.08 (0.84-1.38)	.54
APTT, s	0.97 (0.94-1.01)	.13	0.96 (0.91-1.00)	.06
D-dimer, μg/mL	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.04)	.002

Menu

凝固検査の異常所見

凝固関連の合併症

病態生理

抗凝固療法

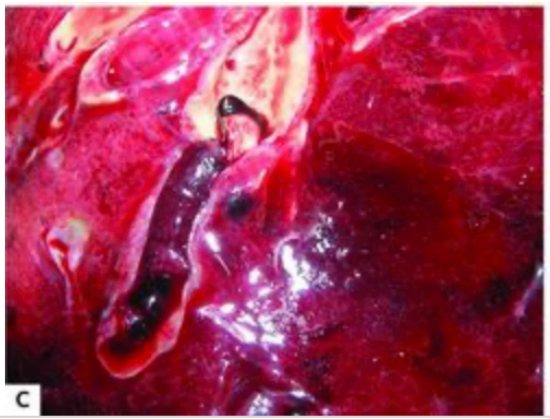
Annals of Internal Medicine

ORIGINAL RESEARCH

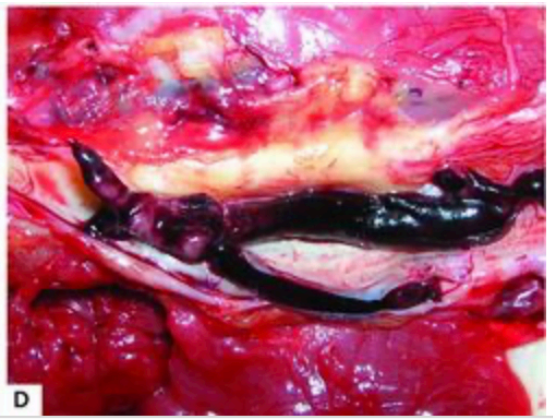
Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

A Prospective Cohort Study

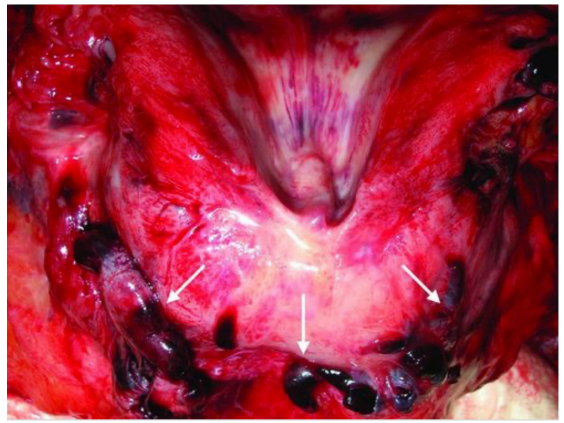
Dominic Wichmann, MD*; Jan-Peter Sperhake, MD*; Marc Lütgehetmann, MD; Stefan Steurer, MD; Carolin Edler, MD; Axel Heinemann, MD; Fabian Heinrich; Herbert Mushumba, MD; Inga Kniep, MD; Ann Sophie Schröder, MD; Christoph Burdelski, MD; Geraldine de Heer, MD; Axel Nierhaus, MD; Daniel Frings, MD; Susanne Pfefferle, MD; Heinrich Becker, MD; Hanns Bredereke-Wiedling, MD; Andreas de Weerth, MD; Hans-Richard Paschen, MD; Sara Sheikhzadeh-Eggers, MD; Axel Stang, MD; Stefan Schmiedel, MD; Carsten Bokemeyer, MD; Marylyn M. Addo, MD, PhD; Martin Aepfelbacher, MD; Klaus Püschel, MD†; and Stefan Kluge, MD†



肺塞栓



下肢静脈血栓症



前立腺静脈の血栓

Ann Intern Med. 2020 May 6.　PMID: 32374815

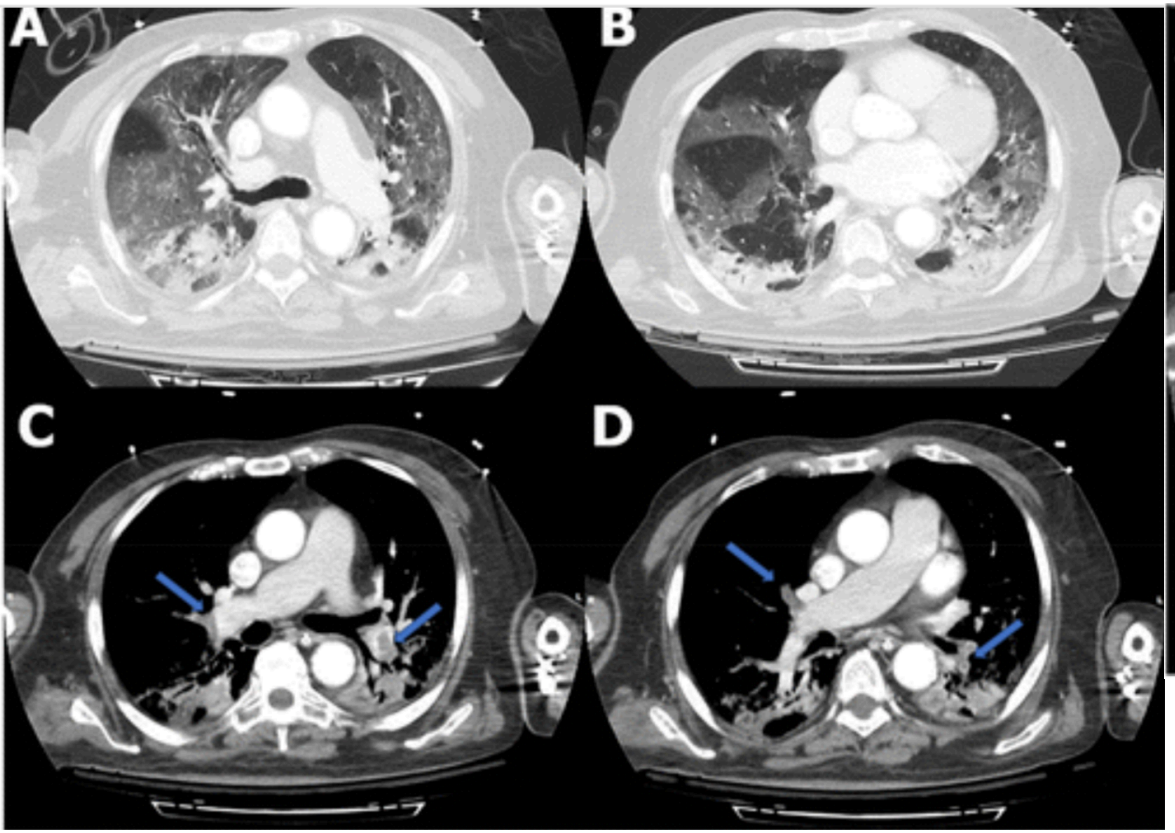
Images in *Radiology*

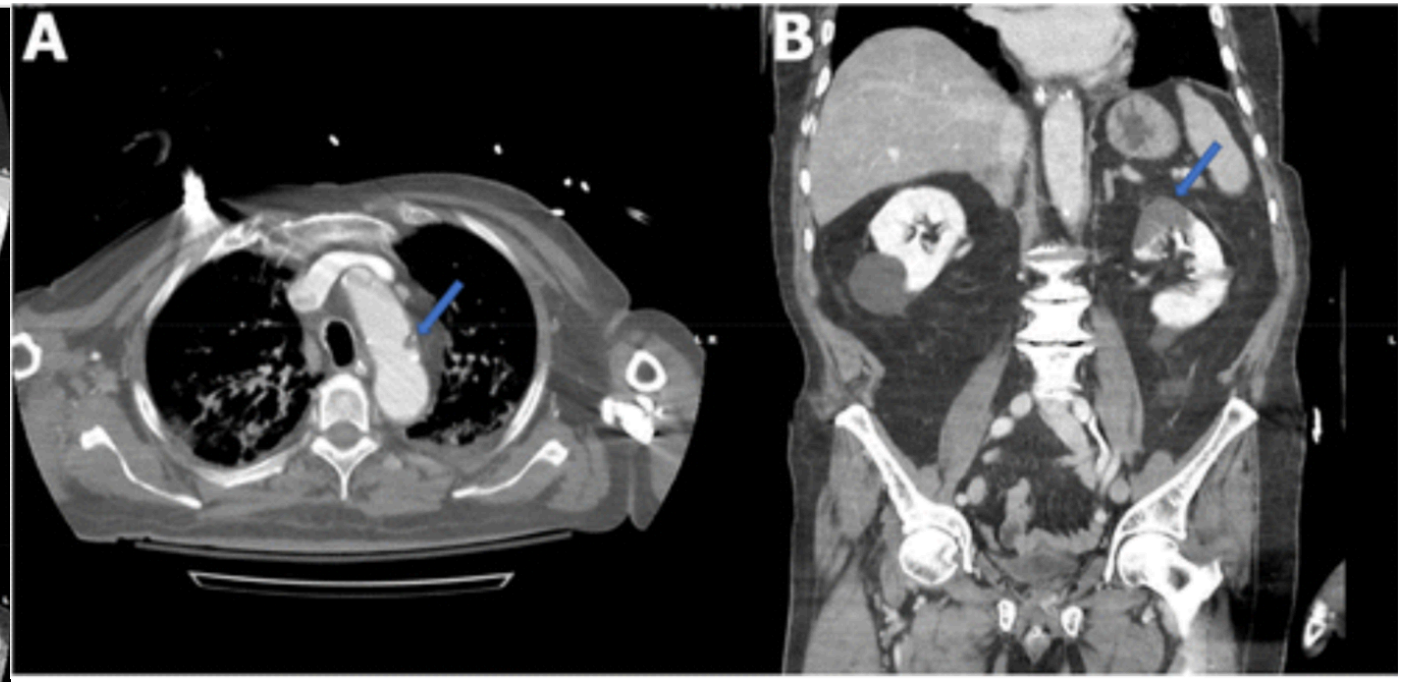
Pulmonary, Cerebral, and Renal Thromboembolic Disease Associated with COVID-19 Infection

Nadia Lushina, John S. Kuo, Hamza A. Shaikh

Author Affiliations

Published Online: Apr 23 2020 | https://doi.org/10.1148/radiol.2020201623





肺塞栓、大動脈に血栓、腎梗塞

ORIGINAL

Received: 8 April 2020 Accepted: 17 April 2020
Published online: 04 May 2020

PMID: 32367170

High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

組入基準：

- 2020年3月3日～31日
- フランスの3次病院で2つの病院、4つのICU
- **SARS-CoV-2陽性**で**ARDS**の患者と**Non-Covid-19**のARDS

除外基準：なし

4月7日にデータ解析(最短の症例で7日間のフォローアップ)

- ICUにいる間は毎日血小板と凝固の検査
- PT、AT活性、フィブリノーゲン、Dダイマー、APTT
- 第5因子(Factor V：FV)、von Willebrand factor(vWF)抗原、vWF活性、第8因子(FactorVIII：FVIII)
- ループスアンチコアグラントは凝固異常が疑われたときに調べた
- →APTT延長や血栓症のイベントがおきたとき

Primary Outcome

すべての血栓症イベント

深部静脈血栓症、肺塞栓、心筋梗塞、腸管虚血、下肢虚血、脳梗塞

Secondary Outcome

血栓症の発生率、RRT フィルターの凝固の発生率、出血の合併症
RRT回路のLifespanの中央値、ECMO回路の凝固、凝固検査の結果

Results

Baseline characteristics

データ解析時は100人は挿管中

ICU滞在9.6±4.2日

死亡率8.7%

36人はICU退室

ロピナビル＋リトナビル
84症例（60%）

レムデシビル
8症例（5.3%）

ヒドロクロロキン
49症例（32.7%）

処方なし
9症例（7.5%）

Table 1 Characteristics of COVID-19 ARDS and non-COVID-19 ARDS

	Population before matching ($n=383$)			Population after matching ($n=222$)		
	Non-COVID-19 ARDS ($n=233$)	COVID-19 ARDS ($n=150$)	*p*-value	Non-COVID-19 ARDS ($n=145$)	COVID-19 ARDS ($n=77$)	*p*-value
年齢 Age—median, IQR	74 [63; 81]	63 [53; 71]	< 0.001	72 [61; 80]	68 [61; 75]	0.593
男性 Male—*n* (%)	164 (70.4)	122 (81.3)	0.02	112 (77.2)	63 (81.8)	0.426
既往歴 Medical history—*n* (%)						
悪性腫瘍/ 血液疾患 Malignancies/hemopathies	31 (13.4)	9 (6.0)	0.02	14 (9.7)	6 (7.8)	0.678
心血管疾患 Cardiovascular diseases	143 (61.4)	72 (48)	0.01	85 (58.6)	42 (55.6)	0.753
血栓イベント Thrombo-embolic event	13 (5.6)	8 (5.3)	0.92	9 (6.2)	7 (9.1)	0.42
脳血管疾患 Cerebrovascular diseases	23 (10)	7 (4.7)	0.06	8 (5.5)	5 (6.5)	0.788
免疫疾患 Immune diseases	13 (5.6)	4 (2.7)	0.17	7 (4.8)	4 (5.2)	0.951
糖尿病 Diabetes	51 (21.9)	30 (20)	0.66	29 (20)	17 (22.1)	0.589
慢性肝疾患 Chronic liver disease	21 (9)	4 (2.7)	0.01	7 (4.8)	3 (3.9)	0.816
慢性腎臓病 Chronic renal disease	38 (16.3)	6 (4.0)	< 0.001	14 (9.7)	5 (6.5)	0.438
呼吸不全 Respiratory disease	49 (21.2)	21 (14)	0.07	36 (24.8)	11 (14.3)	0.207
SAPSII Baseline SAPS II—median, IQR	61 [49; 76]	49 [37; 64]	< 0.001	54 [45; 69]	53 [46; 67]	0.560
SOFA Baseline SOFA—median, IQR	11 [9, 13]	8 [5, 10]	< 0.001	10 [8, 13]	9 [7, 12]	0.204
ICU入室時のP/F PaO_2/FiO_2 on ICU admission (mmHg)—median, IQR	142 [93; 195]	125 [97; 170]	< 0.02	118 [89; 174]	135 [99; 181]	0.520
人工呼吸器管理 Invasive mechanical ventilation—*n* (%)	233 (100)	150 (100)	1	145 (100)	77 (100)	1
ヘパリン治療 Baseline heparin treatment—*n* (%)						
予防量 Prophylactic dosing[a]	188 (80.7)	105 (70)	0.27	110 (75.9)	60 (77.9)	0.768
治療量 Therapeutic dosing	45 (19.3)	45 (30)	0.02	35 (24.1)	17 (22.1)	0.697
ECMO ECMO—*n* (%)	10 (4.3)	12 (8.1)	0.124	7 (4.8)	4 (5.2)	0.952
ECMOの期間 ECMO duration (days)—median, IQR	8 [5.3; 10.8]	7 [4.3; 11]	0.642	10 [7.0; 11.5]	6.5 [4.5; 9]	0.527

SOFA, sequential organ failure assessment; SAPSII, simplified acute physiology score II

[a] Prophylactic dosing was 4000 UI/day for low molecular weight heparin or if contra-indicated, unfractioned heparin at 5–8 U/kg/h

Table 3 Outcomes of COVID-19 ARDS and non-COVID-19 ARDS

	Population before matching ($n=383$)				Population after matching ($n=222$)			
	Non-COVID-19-ARDS ($n=233$)	COVID-19-ARDS ($n=150$)	OR [95% IC]	*p*-value	Non-COVID-19-ARDS ($n=145$)	COVID-19-ARDS ($n=77$)	OR [95% IC]	*p*-value
Thrombo-embolic complications—*n* (%)	14 (6)	27 (18)	3.4 [1.7–7.3]	< 0.001	7 (4.8)	9 (11.7)	2.6 [1.1–6.1]	0.04
Pulmonary embolisms—*n* (%)	3 (1.3)	25 (16.7)	15.2 [4.5–80.4]	< 0.001	3 (2.1)	9 (11.7)	6.2 [1.6–23.4]	0.01
Deep vein thrombosis—*n* (%)	3 (1.3)	3 (2)	1 [0.1–9.2]	1	2 (1.4)	0 (0)		
Myocardial infarction—*n* (%)	6 (2			0.09	2 (1.4)	0 (0)		
Cerebral ischemic attack—*n* (%)	1 (0		185.5]	0.68	0 (0.0)	0 (0)	–	–
Limb ischemia—*n* (%)	0 (0)	1 (0.7)	Inf [0.0–Inf]	0.78	0 (0.0)	0 (0)	–	–
Mesenteric ischemia—*n* (%)	3 (1.3)	1 (0.7)	0.5 [0.0–6.5]	0.98	2 (1.4)	1 (1.3)	0.96 [0.09–9.8]	0.97
Nb of RRT filter per dialyzed patient—median, IQR	1 [2–1]	3 [2–7]	–	< 0.001	2.0 [1.0–2.5]	3.0 [2.0–6]	–	0.03
Nb of RRT filter per day of RRT—median, IQR	0.3 [0.3; 0.5]	0.7 [0.5; 1]	–	< 0.001	0.3 [0.3; 0.4]	0.7 [0.5; 1]	–	< 0.001
ECMO oxygenator thrombosis—*n* (%)	1/10 (10)	2/12 (16.7)	–	0.59	1/7 (14.3)	0/4 (0)	–	–
Hemorrhagic complications—*n* (%)	1 (1.8)	4 (2.7)	2.4 [0.27–28.5]	0.6	2 (1.4)	0 (0)	–	–

予防的／治療的ヘパリン投与していても**16.7%**で肺塞栓！

肺塞栓がOR**6.2**！！

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy

- 敗血症性ショック患者の30〜40%がDICを発症

それに対してCOVID19の患者では

- ISTH overtスコアを用いた場合：0人
- JAAM-DICスコアを用いた場合：6人のみ

COVID-19患者のDIC発症メカニズム

≠

通常ICU患者で報告されているDIC

Table 2 Coagulation parameters of COVID-19 patients

	All patients ($n = 150$)
Baseline coagulation parameters	
Platelet count (10^9/L)—normal range: 150–400.10^9/L	200 [152; 267]
aPTT—normal range: 0.7–1.2	1.2 [1.1; 1.3]
PT (%)—normal range: > 70%	84 [73; 91]
INR—normal range: 1.00–1.15	1.12 [1.05; 1.25]
D-dimers (mg/L)—normal range: < 0.5 mg/L	2.27 [1.16; 20]
Fibrinogen (g/L)—normal range: 2–4 g/L	6.99 [6.08; 7.73]
Antithrombin activity (%)—normal range: 50–150%	91 [78; 102]
Factor V (%)—normal range: > 70%	136 [115; 150]
Factor VIII (%)—normal range: 60–150%	341 [258; 416]
vWF activity (%)	328 [212; 342]
vWF antigen (%)—normal range: 50–150%	455 [350; 521]
Lupus anticoagulant[a]—*n* (%)	50/57 (87.7)
Screen patient (s)	68.6 [59.5; 85.4]
Screen ratio—normal range: < 1.2	1.63 [1.43; 2.04]
Confirm patient (s)	43.9 [40.9; 48.4]
Confirm ratio—normal range: < 1.2	1.25 [1.13; 1.46]
Screen/confirm ratio—normal range: < 1.2	1.4 [1.25; 1.48]

All results are given in median [IQR], except if specified otherwise

aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; vWF, von Willebrand factor

[a] Measured during ICU stay

Discussion

- このprospective cohortの結果、**高い確率で血栓症が起きる**のが結論
- 特にICUに低酸素で入るCOVID19で**肺塞栓が16.7%**も起きた。
- これは**予防的/治療的な抗凝固をしていても起こった**

Thrombosis Research 191 (2020) 145–147

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Thrombosis Research
Volume 191, July 2020, Pages 145-147

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c], M.S. Arbous[d], D.A.M.P.J. Gommers[e], K.M. Kant[f], F.H.J. Kaptein[a], J. van Paassen[d], M.A.M. Stals[a], M.V. Huisman[a,1], H. Endeman[e,1]

184症例のICU入室患者@オランダ

2つの大学病院＋1つの教育病院

184症例のCOVID-19でICU入室患者

死亡：23症例（13%）

生存退院：22症例（12%）

入院中：139症例（76%）（2020/4/5）

すべての患者で最低限の予防的抗凝固

Table 2
Local protocol for thromboprophylaxis in participating centres for patients admitted to the intensive care unit during the study period.

Site	3つの病院	予防的抗凝固プロトコル
Leiden University Medical Center		nadroparin 2850 IU sc per day or 5700 IU per day if body weight > 100 kg
Erasmus University Medical Center		Nadroparin 5700 IU per day; nadroparin 5700 IU sc twice daily from April 4th 2020 and onwards
Amphia Hospital Breda		Nadroparin 2850 IU sc per day or 5700 IU per day if body weight > 100 kg; nadroparin 5700 IU sc per day from March 30th 2020 and onwards

ナドロパリン：低分子ヘパリン

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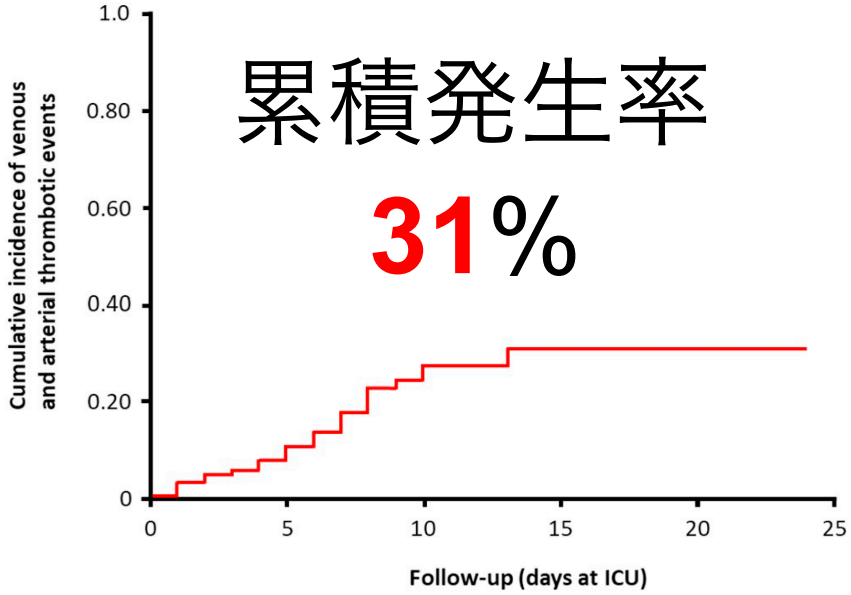


Composite outcome：**急性肺塞栓、深部静脈血栓症、虚血性脳卒中、心筋梗塞、動脈塞栓**

累積composite outcome発生率**31**%：VTE27%、動脈塞栓3.7%、**肺塞栓が最も多く25症例**で起きた。

Table 3
Description of thrombotic complications.

Type of event	Number of cases	Relevant details
Pulmonary embolism 肺塞栓	25	– 18 cases with at least PE in segmental arteries, 7 cases PE limited to subsegmental arteries
Other venous thromboembolic events	3	– 1 proximal deep-vein thrombosis of the leg – 2 catheter related upper extremity thrombosis
Arterial thrombotic events	3	– All ischemic strokes

Note: acute pulmonary embolism was diagnosed with CT-pulmonary angiography, deep vein thrombosis/upper extremity vein thrombosis was diagnosed with ultrasonography, strokes were diagnosed with CT.

Menu

凝固検査の異常所見

凝固関連の合併症

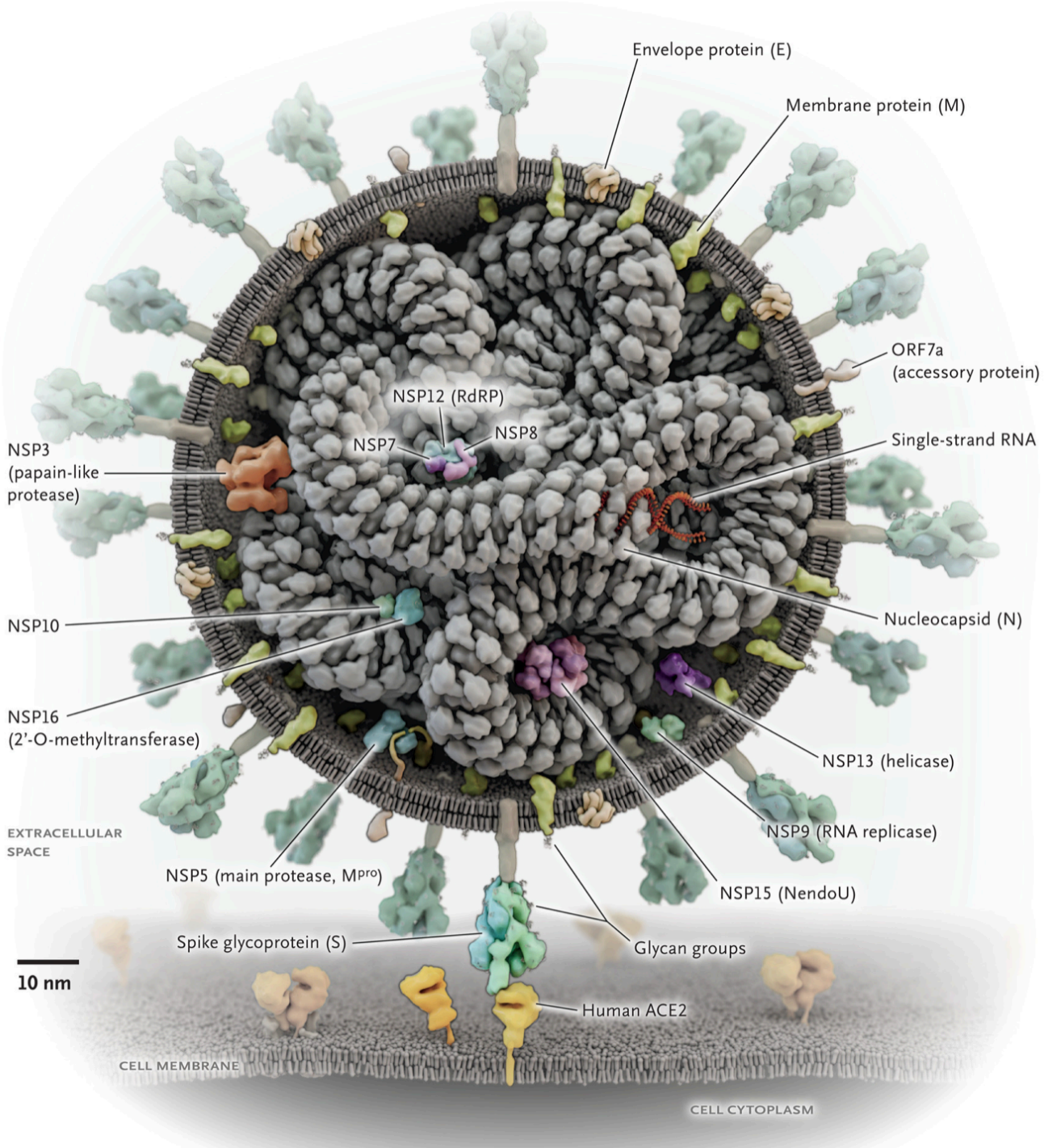
病態生理

抗凝固療法

The NEW ENGLAND JOURNAL of MEDICINE

王冠（コロナ）様の
突起物（Spike）を持つ

ACE2受容体
に結合

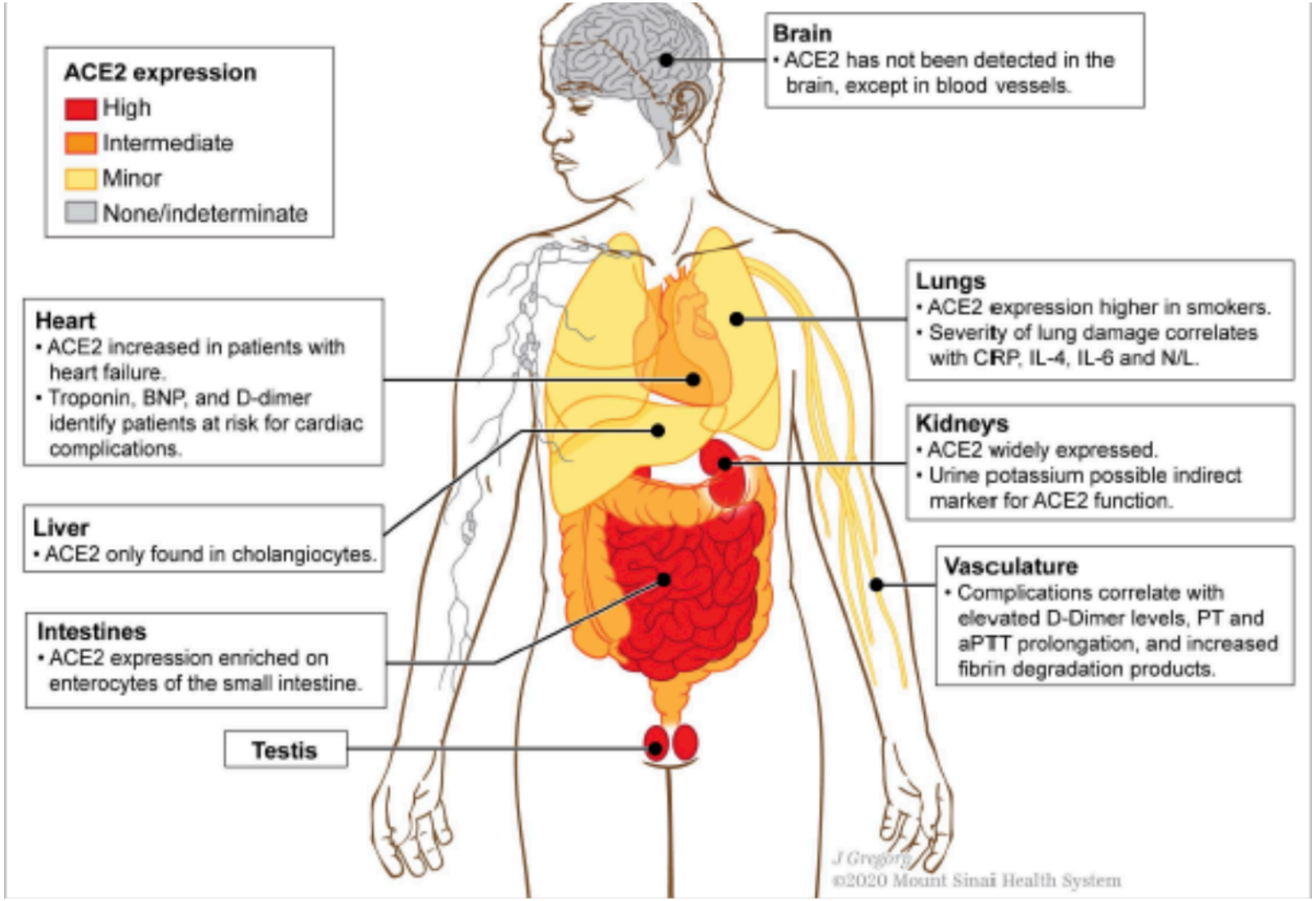


CLINICAL IMPLICATIONS OF BASIC RESEARCH

How to Discover Antiviral Drugs Quickly

Jerry M. Parks, Ph.D., and Jeremy C. Smith, Ph.D.

May 20, 2020
DOI: 10.1056/NEJMcibr2007042


ACE2 expression
High
Intermediate
Minor
None/indeterminate
Brain
• ACE2 has not been detected in the brain, except in blood vessels.
Lungs
• ACE2 expression higher in smokers.
• Severity of lung damage correlates with CRP, IL-4, IL-6 and N/L.
Heart
• ACE2 increased in patients with heart failure.
• Troponin, BNP, and D-dimer identify patients at risk for cardiac complications.
Kidneys
• ACE2 widely expressed.
• Urine potassium possible indirect marker for ACE2 function.
Liver
• ACE2 only found in cholangiocytes.
Vasculature
• Complications correlate with elevated D-Dimer levels, PT and aPTT prolongation, and increased fibrin degradation products.
Intestines
• ACE2 expression enriched on enterocytes of the small intestine.
Testis
J Gregory
©2020 Mount Sinai Health System

ACE2受容体

発現

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.

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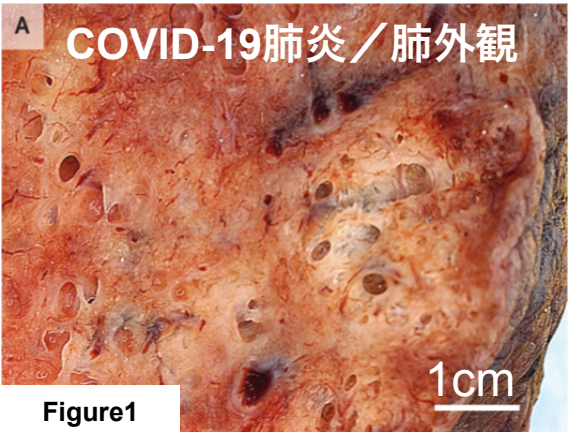

Figure1

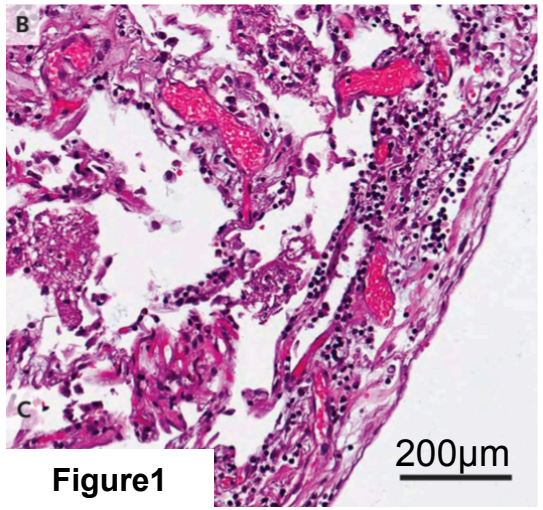

Figure1

COVID-19肺炎／HE染色
間質と血管周囲にリンパ球浸潤
multifocalな血管内皮の炎症

7人のCOVID-19＋7人のインフルエンザA＋10人の正常肺の剖検で得た肺

免疫組織化学的解析、マイクロコンピュータ断層撮影
走査型電子顕微鏡、腐食鋳造、遺伝子発現の直接多重測定

Covid-19またはインフルエンザ関連呼吸不全で死亡した患者では、
末梢肺の組織学的パターンは、**血管周囲T細胞浸潤を伴うびまん性肺胞損傷**であった。

Covid-19の患者：
細胞内ウイルスの存在と**重度の内皮損傷からなる特徴的な血管の特徴**を示した。
肺血管の組織学的解析：微小血管症を伴う**広範な血栓症**が認められた

肺胞毛細血管微小血栓症はCovid-19患者ではインフルエンザ患者の9倍の有病率（P<0.001）

Covid-19患者：主に内服受容性血管新生のメカニズムを介した新しい血管の成長の量は
インフルエンザ患者からの肺のそれの2.7倍の高さ（P<0.001）。

COVID-19は肺胞の微小血管にダメージを与える

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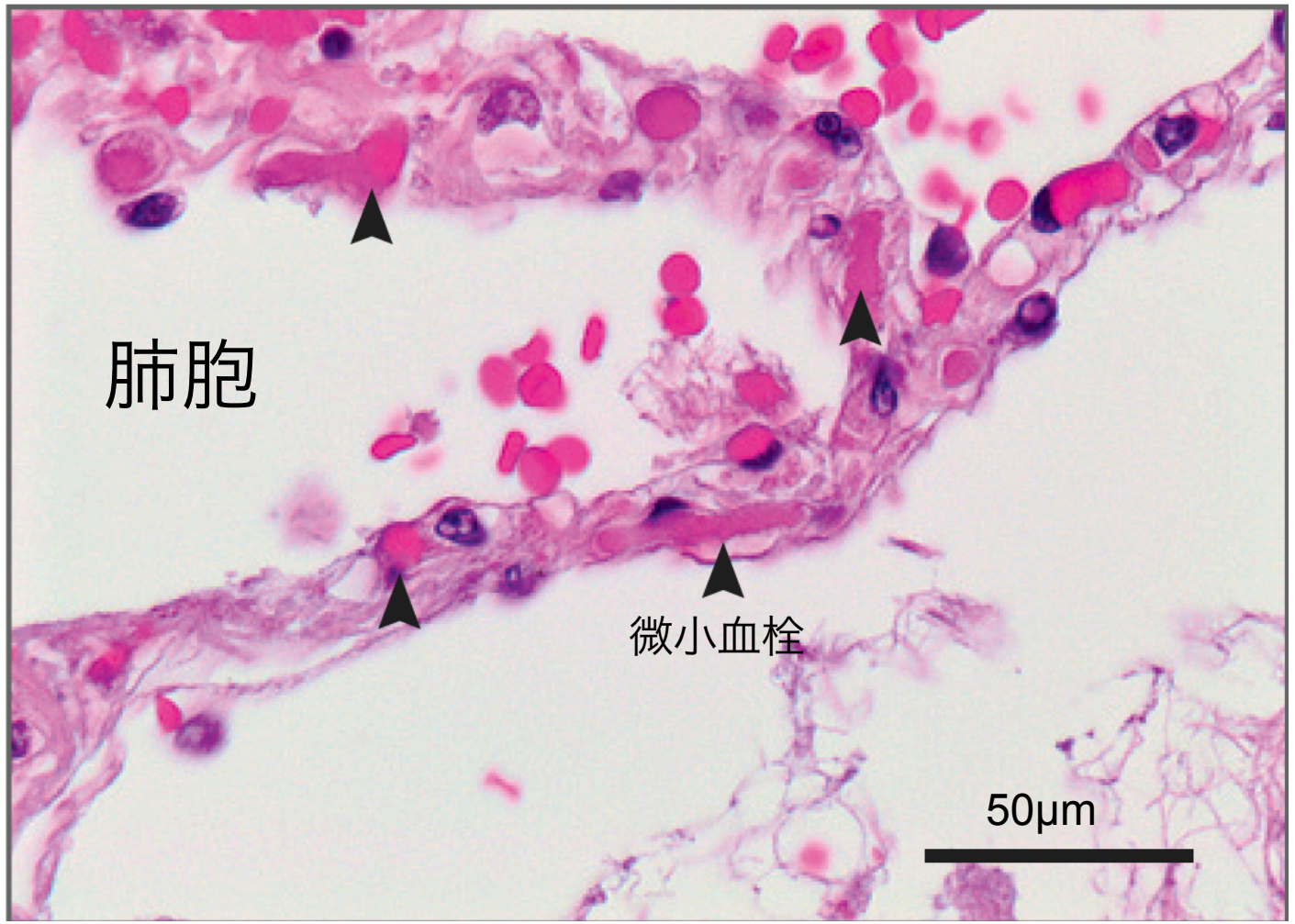

肺胞と間質

間質の血管内や肺胞に

微小血栓が見られる

Figure 2. Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.

The interalveolar septum of this patient (Patient 4 in Table S1A in the Supplementary Appendix) shows slightly expanded alveolar walls with multiple fibrinous microthrombi (arrowheads) in the alveolar capillaries. Extravasated erythrocytes and a loose network of fibrin can be seen in the intraalveolar space (hematoxylin–eosin staining; the scale bar corresponds to 50 μm).

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COVID-19患者の肺

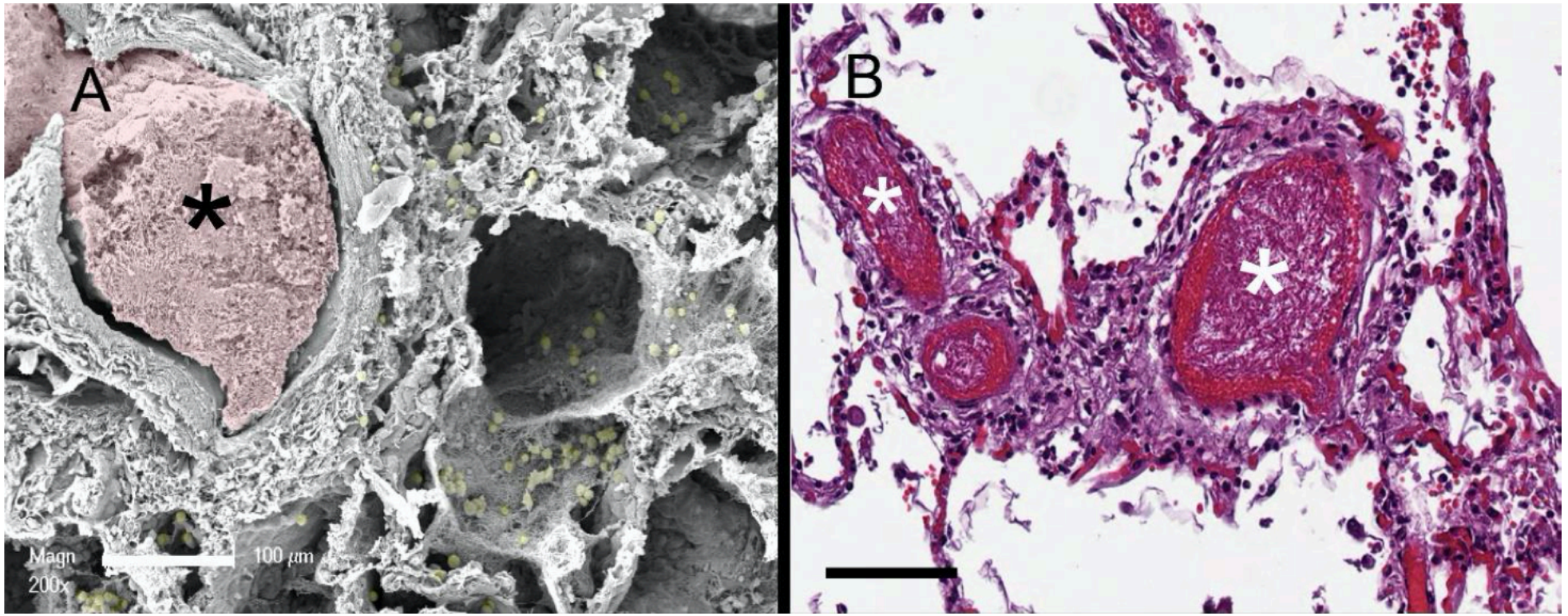
電子顕微鏡

病理組織

薄ピンク：血栓

淡黄色：リンパ球

＊ 血栓



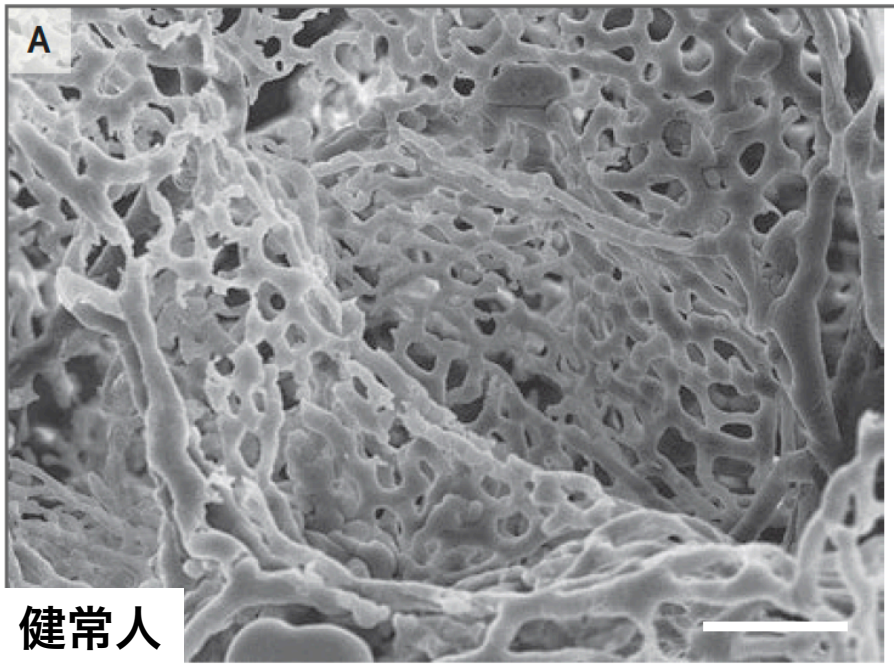
＊ 血栓

肺毛細血管の微小血栓はインフルエンザと比べてCOVID-19は9倍

A：電子顕微鏡

正常の肺胞の
毛細血管

スムーズ
口径不同なし



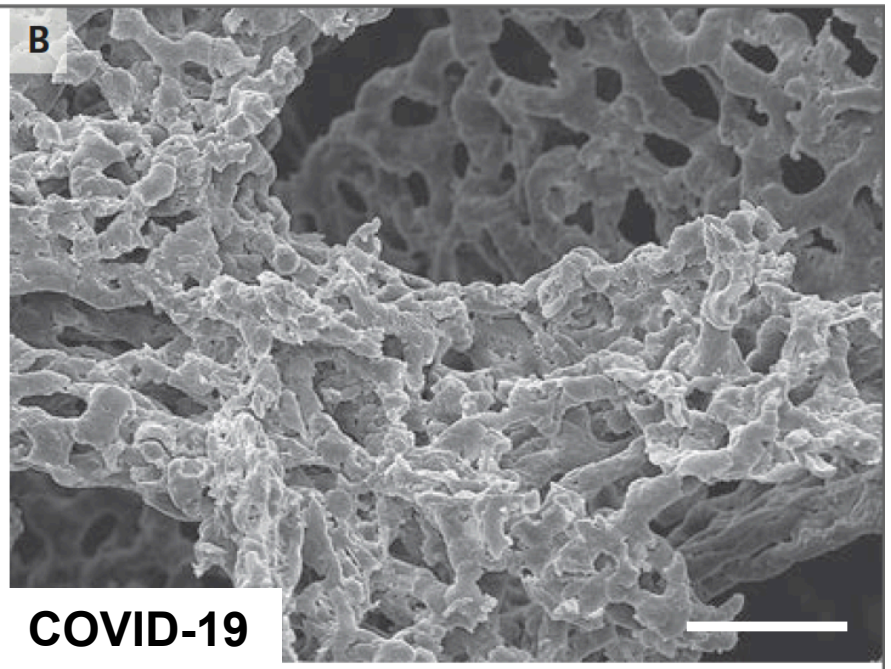
健常人

B：電子顕微鏡

COVID-19

傷害あり
口径不同あり
ゆがみあり

血管新生

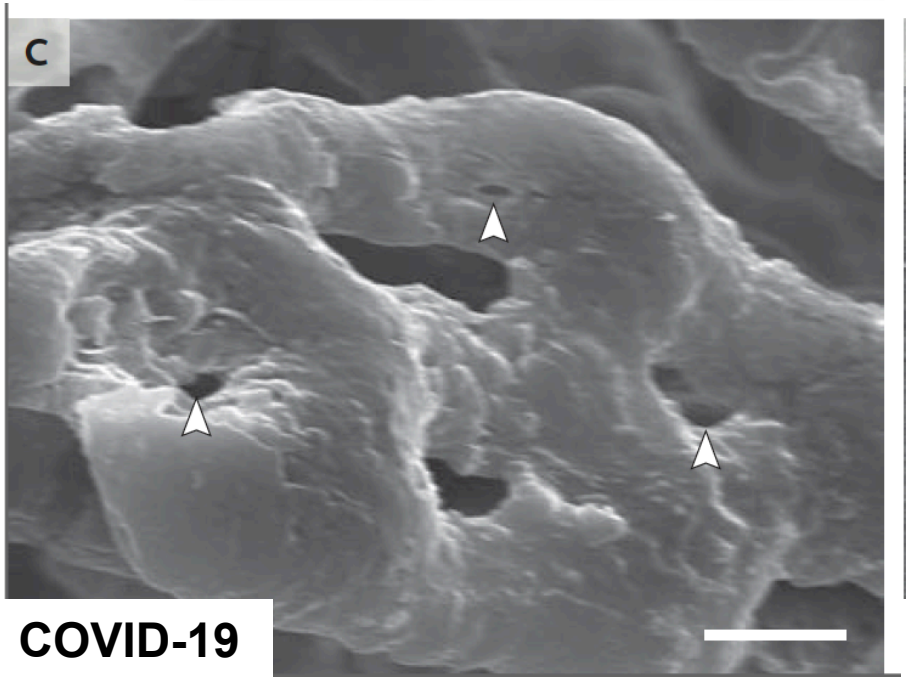


COVID-19

C：

毛細血管の
口径不同

矢印：
血管新生の柱

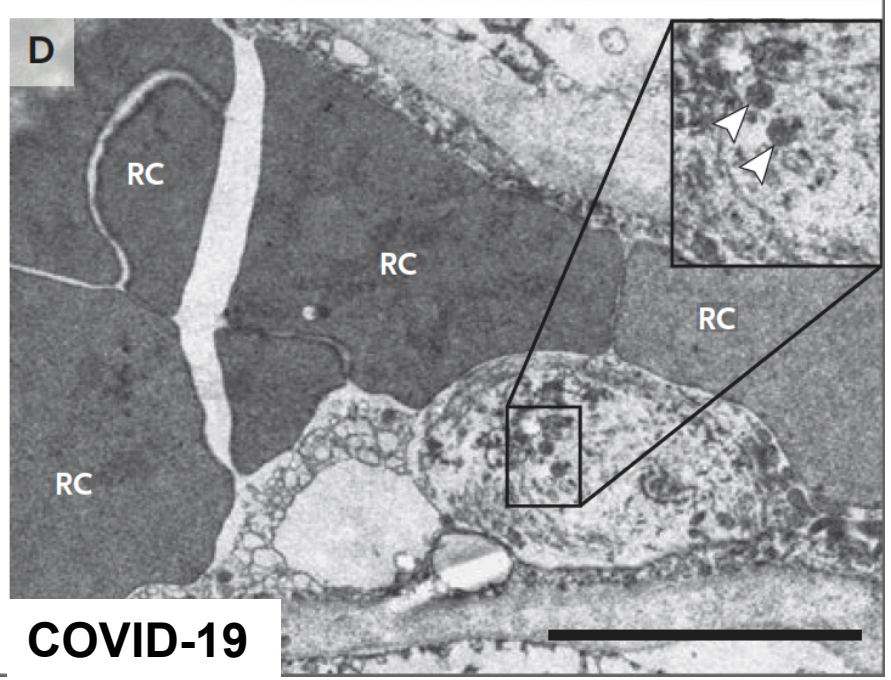


COVID-19

D：
透過型電子顕微鏡

内皮細胞の破壊

内皮細胞内（矢印）
にSARS-CoV-2



COVID-19

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３つのCOVID-19の血管の特徴

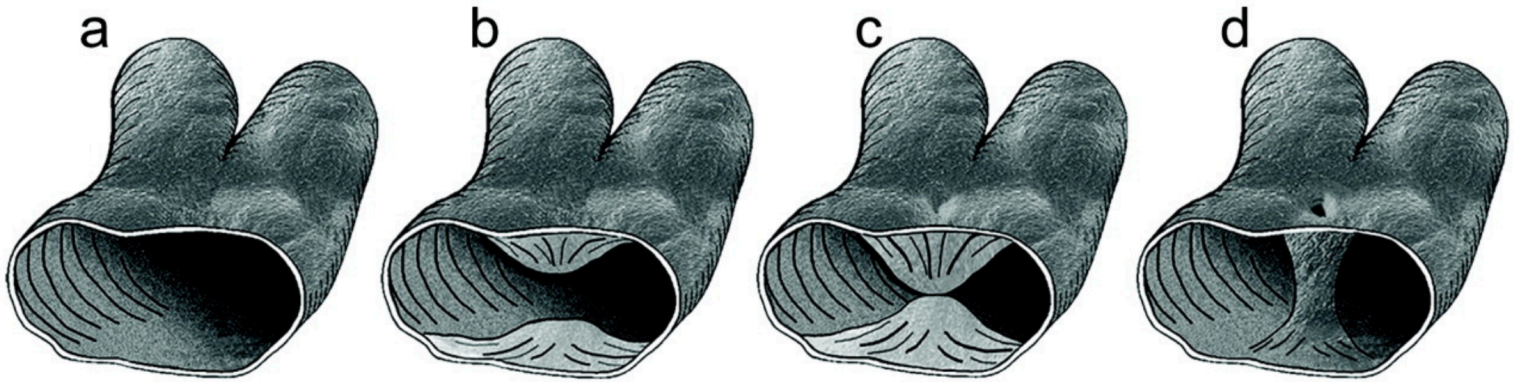
①重度の**血管内皮細胞の傷害**と内皮細胞の**細胞膜の破壊**

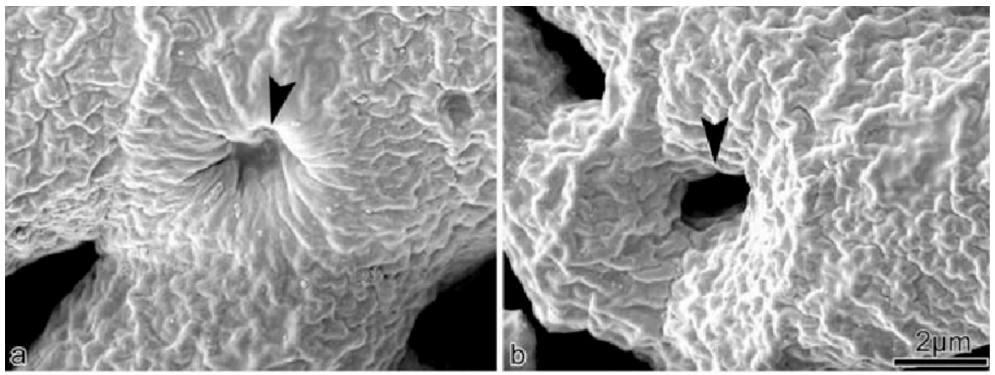
②微小血管症による**血栓形成**と**肺胞毛細血管の閉塞**

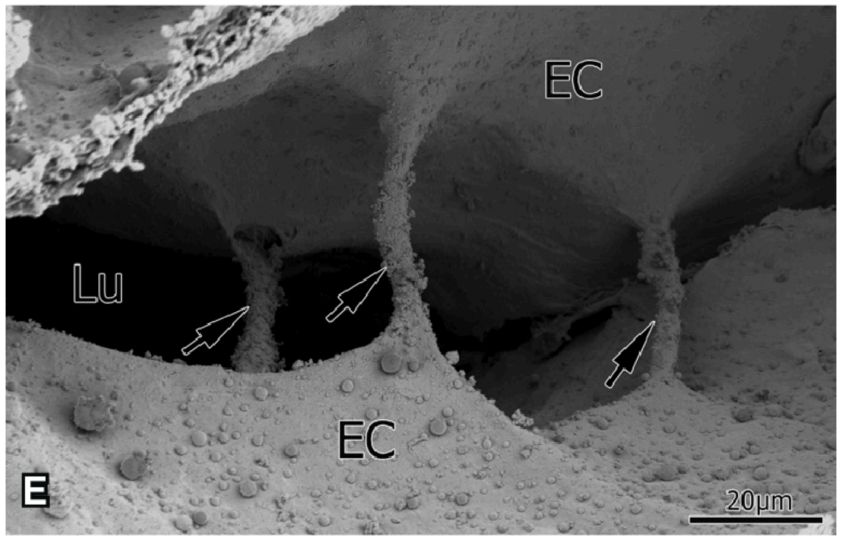
③intussusceptive angiogenesisの**血管新生**

補足：intussusceptive angiogenesisとは？

血管新生の一つの形式







Intussusceptive angiogenesis: Its emergence, its characteristics, and its significance

Peter H. Burri ✉, Ruslan Hlushchuk, Valentin Djonov

First published:16 September 2004 | https://doi.org/10.1002/dvdy.20184 | Citations: 171

https://www.researchgate.net/figure/Demonstration-of-the-mechanisms-involved-in-pillar-formation-A-D-Three-dimensional_fig1_51587576

https://www.semanticscholar.org/paper/New-insights-into-intussusceptive-angiogenesis.-Djonov-Makanya/0900f4ea1ebe74b79d4d7e8f3cac372352b8d1fe

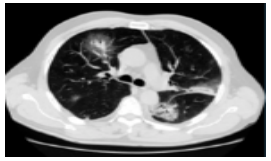
肺の微小血栓による死腔換気が、低酸素血症や吸気努力増大の大きな原因？

COVID-19肺炎による
低酸素血症

肺循環制御の
障害

- Low elastance
- Low V/Q
- Low lung weight
- Low lung recruitability

Phenotype L

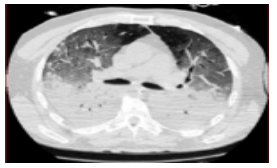


肺動脈
微小血栓
↓
死腔換気

肺水腫
ARDS like

- High elastance
- High R-L shunt
- High lung weight
- High lung recruitability

Phenotype H



> Lancet. 2020 Mar 28;395(10229):1033-1034. doi: 10.1016/S0140-6736(20)30628-0.
Epub 2020 Mar 16.

COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression

Puja Mehta [1], Daniel F McAuley [2], Michael Brown [3], Emilie Sanchez [4], Rachel S Tattersall [5], Jessica J Manson [6], HLH Across Speciality Collaboration, UK

Affiliations + expand

PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0

重症のCOVID-19では**サイトカインストームが関与**していると考えられる。

sHLHとCOVID-19はサイトカイン（IL-2、IL-7、GCSF、INF-γ、TNFαなど）が類似している。

フェリチンが上昇することやIL-6が上昇していることからも**高炎症状態**であると考えられる。

Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia

Dennis McGonagle, James S O'Donnell, Kassem Sharif, Paul Emery, Charles Bridgewood

Lancet Rheumatol 2020
Published Online
May 7, 2020
https://doi.org/10.1016/
S2665-9913(20)30121-1

- COVID-19患者肺の病態像は，**肺胞や間質の著明な炎症と結びつく著明な微小血管血栓と出血**である
- これは**マクロファージ活性化症候群（MAS: macrophage activation syndrome）と病態が類似**する.
- 早期には播種性血管内凝固症候群（DIC: disseminated intravascular coagulation）と様相が異なる.
- 早期の段階でCOVID-19ウイルス血症は起きずに、**広範な肺血管領域に著明な免疫学的血栓形成**
- びまん性に肺胞や肺間質に起こる炎症を背景とした免疫学的メカニズムがMAS様病態を引き起こし，免疫学的血栓形成を惹起する.

Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia

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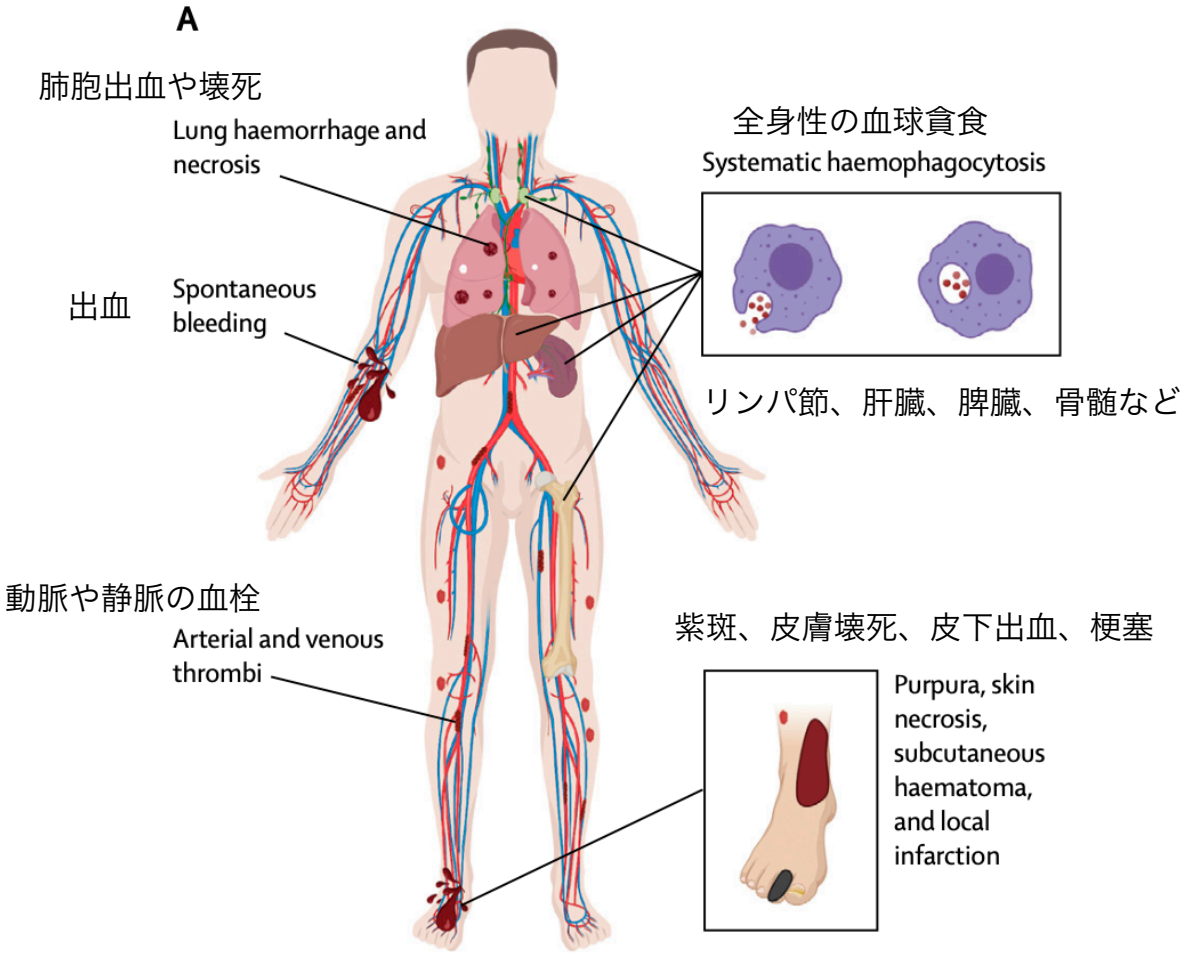
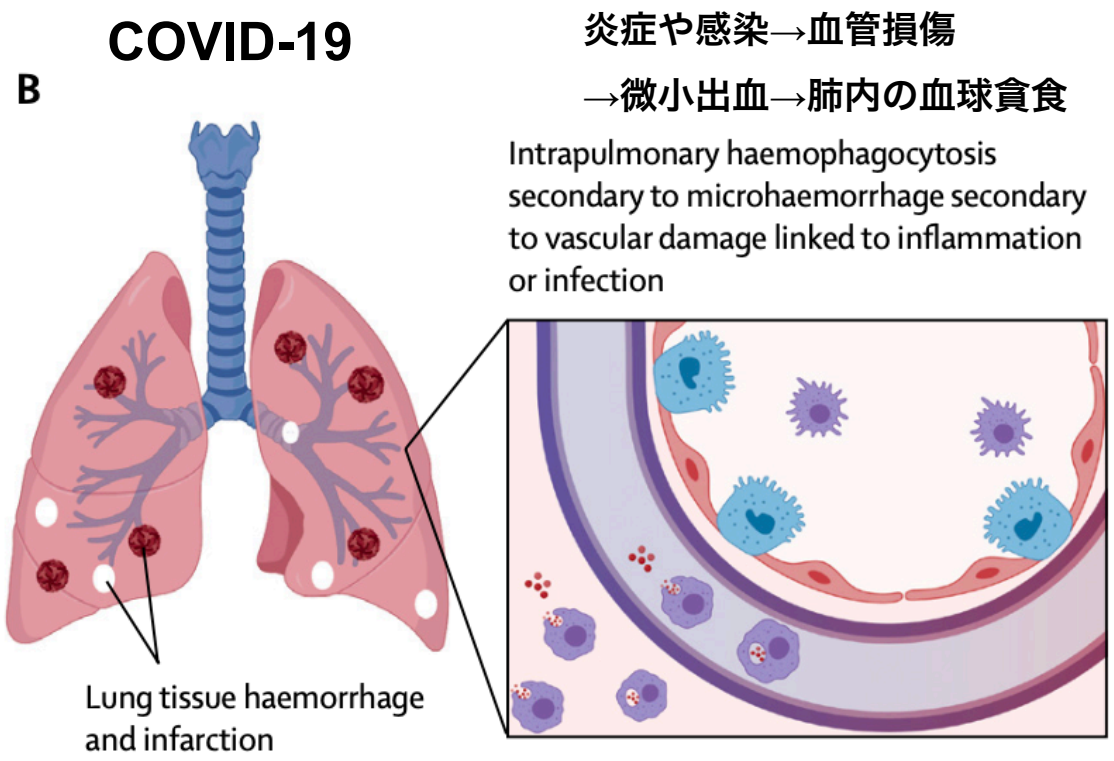
二次性血球貪食細胞性リンパ組織球症
またはマクロファージ活性化症候群





マクロファージ活性化症候群（MAS）

- 疾患名ではなく，“**過剰な炎症状態**”をさす病態名。外因子や内因子が影響。
- 外因子：ウイルス，細菌，真菌などの感染因子や薬剤
- 内因子：自己細胞のapoptosis/necrosisにより生じる破砕物など
- 炎症は外因子や内因子により活性化された樹状細胞，マクロファージから産出される炎症性サイトカインにより生じる病態
- この**炎症性サイトカインの過剰状態（cytokine storm）**による致死的な病態がMAS
- MASにかかわる炎症性サイトカインはinterferon（IFN）-γ，interleukin（IL）-1β，IL-6，IL-18，TNF-αなど

	DIC linked to HLH or MAS	PIC linked to COVID-19
Clinical features		
発症形式 Onset	Acute	Subacute
肝脾腫 Hepatosplenomegaly	+++	..
リンパ節腫脹 Adenopathy	++	..
肺への進展 Pulmonary involvement (%)	50%	100%
血栓症 Thrombosis	Multi-organ clotting	Mainly lung (occasional CNS and peripheral thrombosis reported; related to DIC evolution?)
出血 Bleeding	Generalised	Intrapulmonary microhaemorrhage
感染 Active infection considerations	Yes usually for primary HLH; secondary HLH might not have driving infection	Thought to be ongoing alveolar infection
Laboratory parameters		
肝機能 Liver function	Decreased synthetic function including fibrinogen and other clotting factors; raised transaminase +++	Preservation of liver synthetic function; +/-
貧血 Anaemia	+++	-
血小板減少 Thrombocytopenia	+++	Normal or low
免疫細胞減少 Immune cell cytopenia	++	No but lymphopenia is a feature of COVID-19 in general
CK Creatine kinase	+ (skeletal and cardiac origin)	+ (worse prognosis)
トロポニンT Troponin T	+	++ with high levels associated with worse outcome
血球貪食 Haemophagocytosis	Generalised to marrow, liver, and other sites detectable in >80%	Occasional intrapulmonary and regional lymph node haemophagocytosis reported
進展 Evolution	DIC secondary to MAS	PIC might evolve into DIC; PIC might occur without MAS
Coagulation and immunology markers		
PT,APTT延長 Elevated prothrombin time or activated partial thromboplastin time	+++/+++	+ or normal
フィブリノーゲン Fibrinogen levels	Decreased	Normal or slight increase
FDP or Dダイマー Fibrin degradation products or D-dimer	Increased	Increased
CRP C-reactive protein	Elevated	Elevated
フェリチン上昇 Ferritin elevation	+++	Elevated
高サイトカイン血症 Hypercytokinaemia	+++	++

MAS sHLH

COVID-19

多臓器

主に肺

全身性

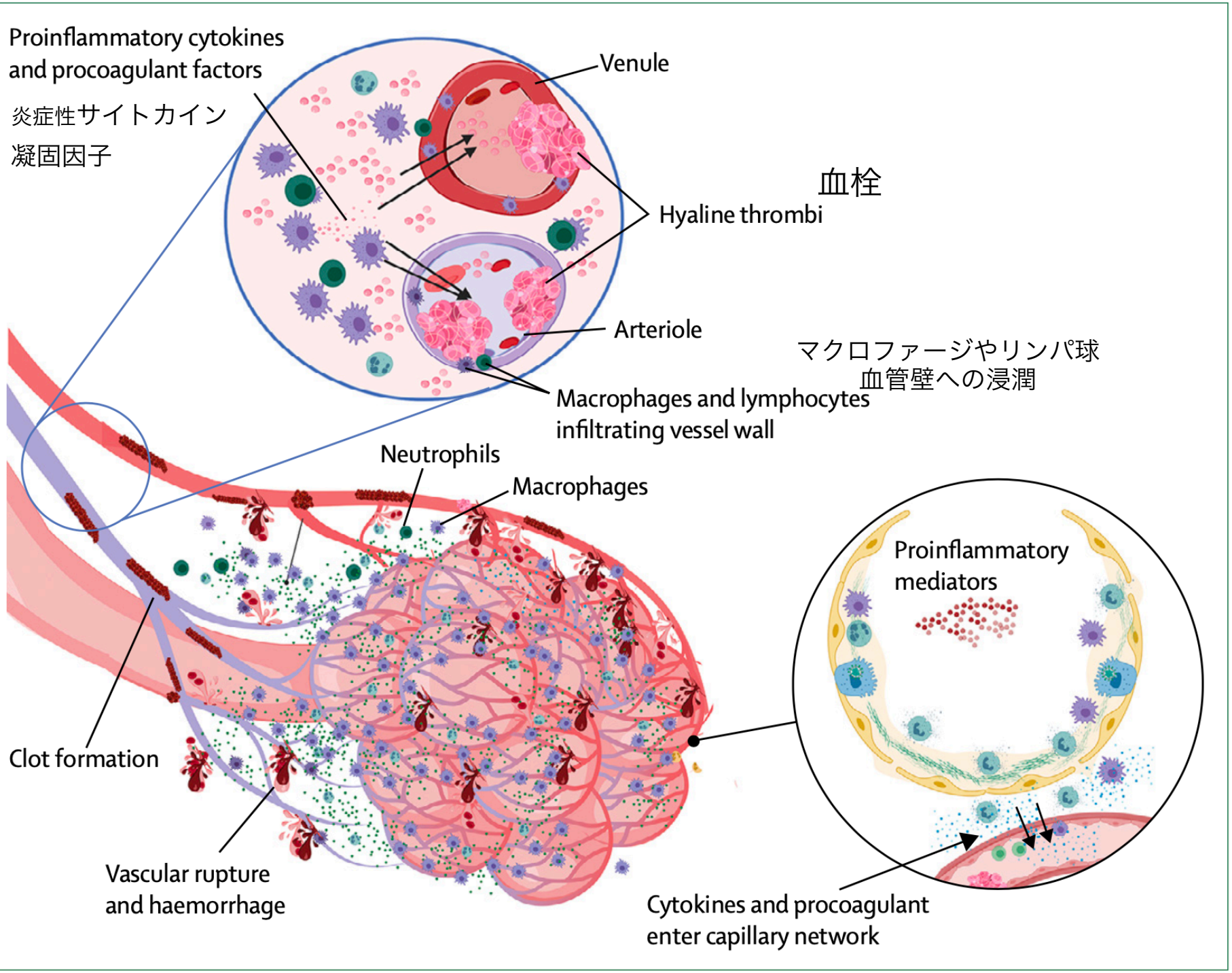
肺内出血

Present (+), usually present (++), frequently present (+++), or abser
DIC=disseminated intravascular coagulation. HLH=haemophagocy
coagulopathy. COVID-19=coronavirus disease 2019.

Table 1: **Differences and similarities between DIC and PIC**

COVID19とMAS or HLHと似ているが

古典的な二次性の血球貪食性リンパ組織球症（sHLH）とは異なる



炎症性サイトカイン
IL-1、IL-6、TNFαなど

↓

血管内皮細胞を傷害

↓

血管内皮細胞
機能不全

↓

凝固カスケード
活性化

活性酸素などの発現

Figure3

肺血管内の凝固に関与する免疫因子

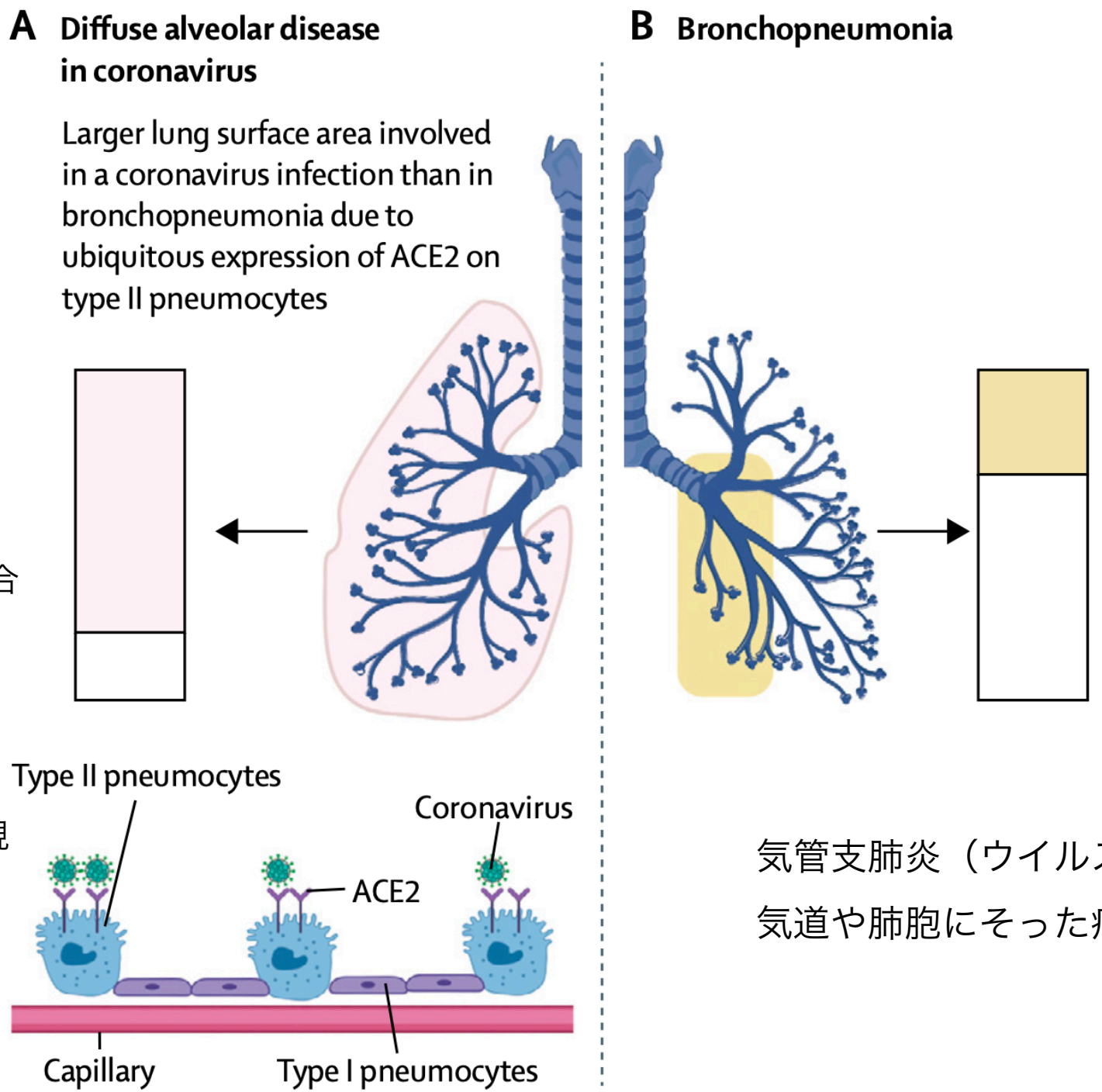
Panel: Immune factors contributing to pulmonary intravascular coagulopathy

- Diffuse alveolar damage and inflammation
- Diffuse interstitial inflammation
- Extensive pulmonary macrophage activation (MAS-like)
- Dysregulation of pulmonary innate immune responses (eg, ACE2 receptor expression downregulation)
- Adaptive immune responses to COVID-19
- Activation of innate immunity with older age
- Age-related coagulation cascade changes
- Mechanical ventilation forcing viral immunostimulatory molecules into microvasculature, increasing the propensity towards immunothrombosis

MAS=macrophage activation syndrome. ACE2=angiotensin-converting enzyme 2. COVID-19=coronavirus disease 2019.

Panel：

- びまん性肺胞損傷と炎症
- びまん性間質性炎症
- 広範囲肺マクロファージ活性化（MAS様）
- 肺の自然免疫反応の調節障害
- (例：ACE2受容体の発現ダウンレギュレーション)
- COVID-19に対する適応免疫応答
- 加齢に伴う自然免疫の活性化
- 加齢による凝固カスケードの変化
- ウイルス性免疫刺激分子を微小血管内に強制的に送り込む機械的換気により、免疫血栓症の傾向が強まる。



CoronavirusがACE2と結合

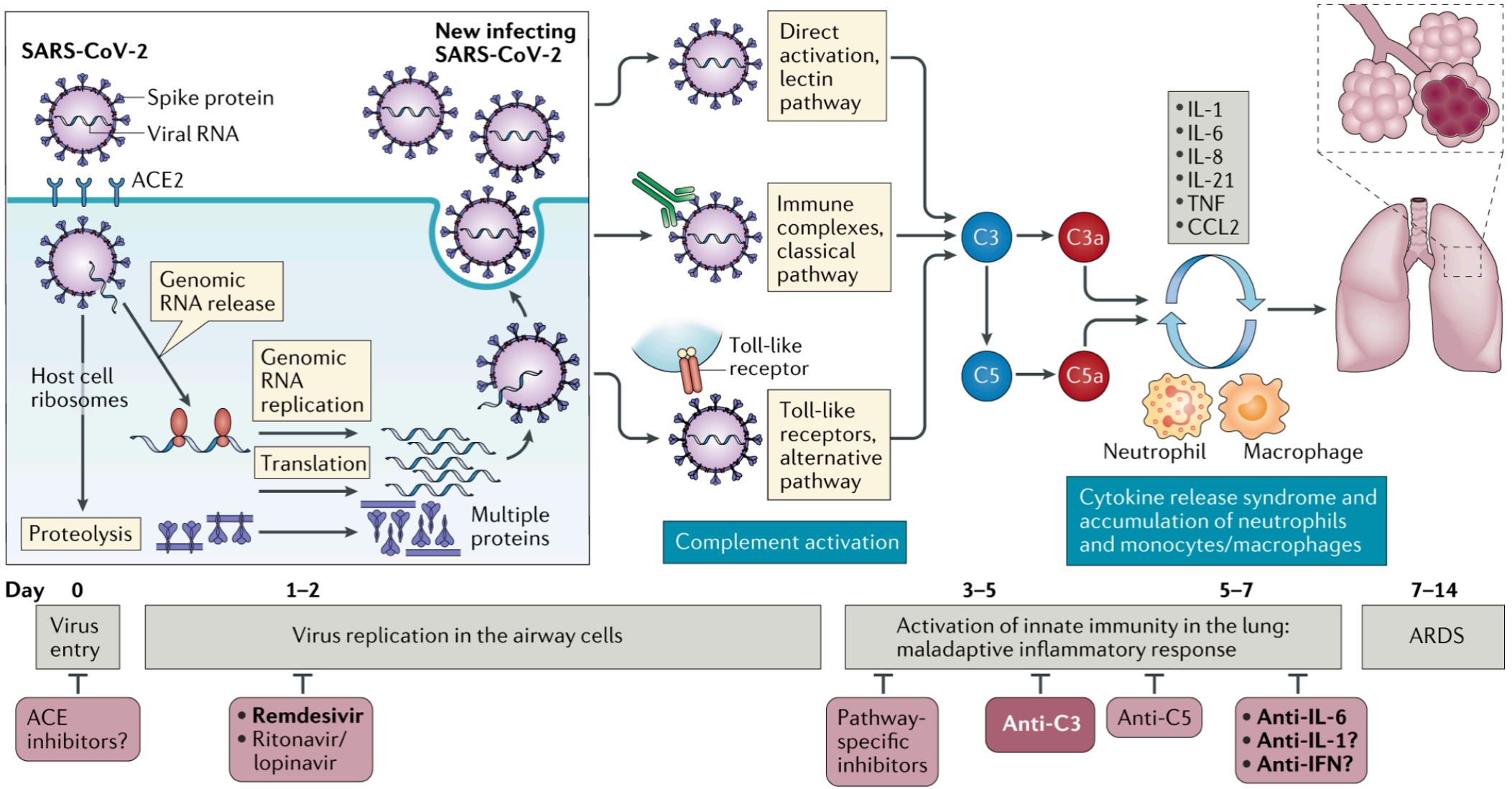
ACE2がII型肺胞細胞に発現
→広範囲に影響

気管支肺炎（ウイルス性や細菌性）

気道や肺胞にそった病変になる。

Fig. 1: Targeting complement in SARS-CoV-2-associated lung injury.

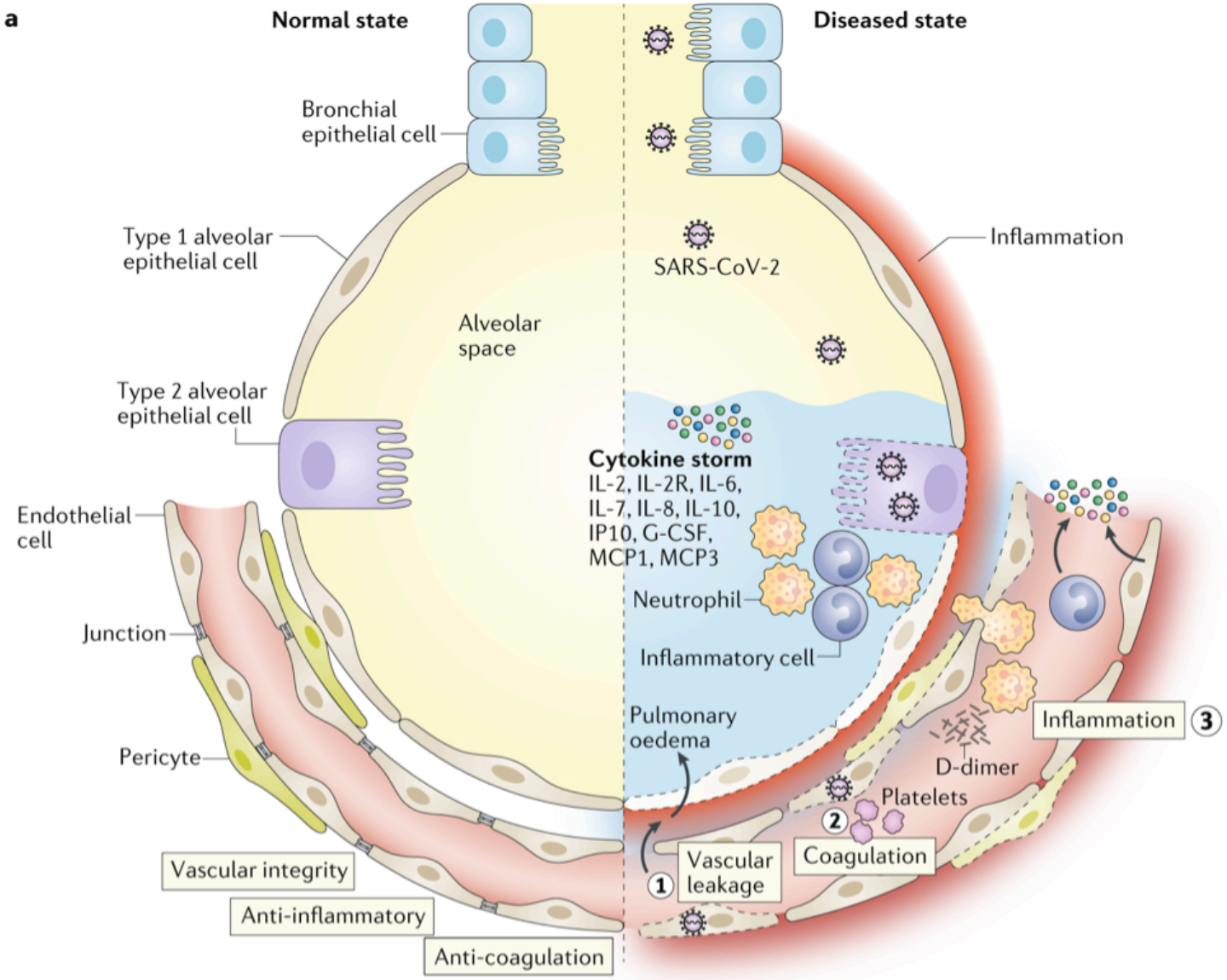
From: Complement as a target in COVID-19?



23 April 2020 Complement as a target in COVID-19? Nature Reviews Immunology (2020)

正常

COVID-19



ウイルスが内皮細胞に感染する

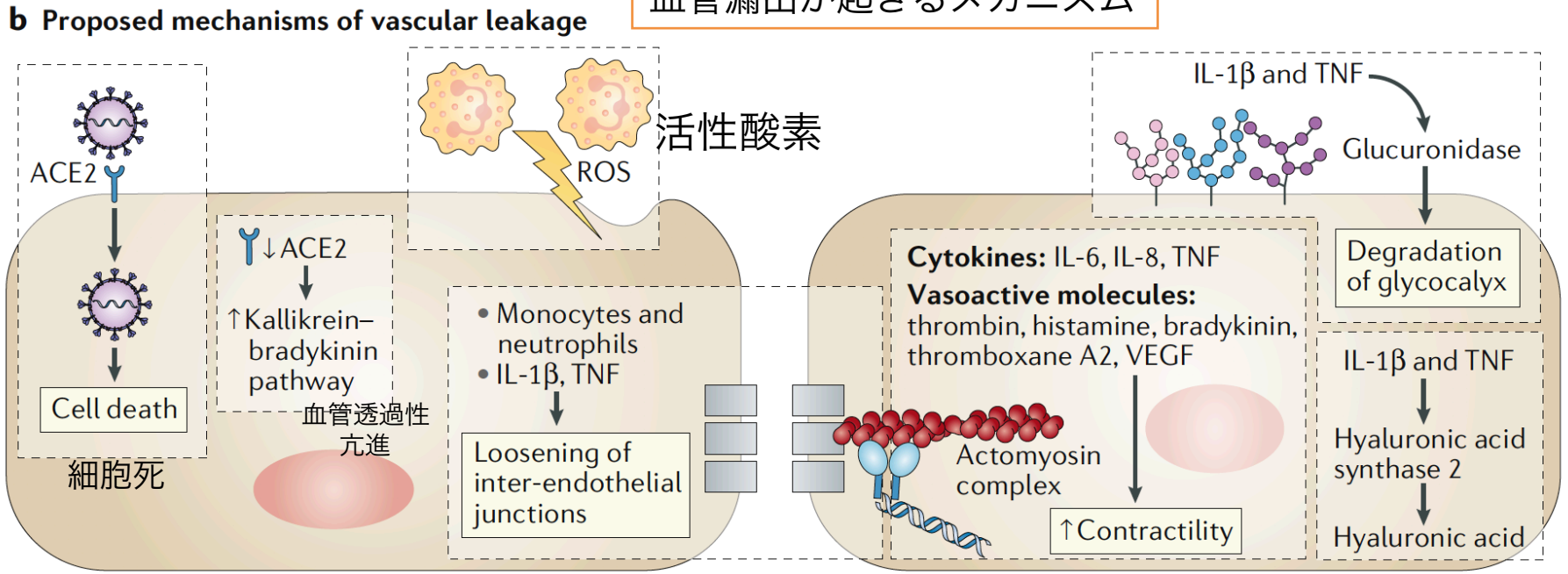
①内皮細胞の結合が崩れる

②凝固経路が活性化する

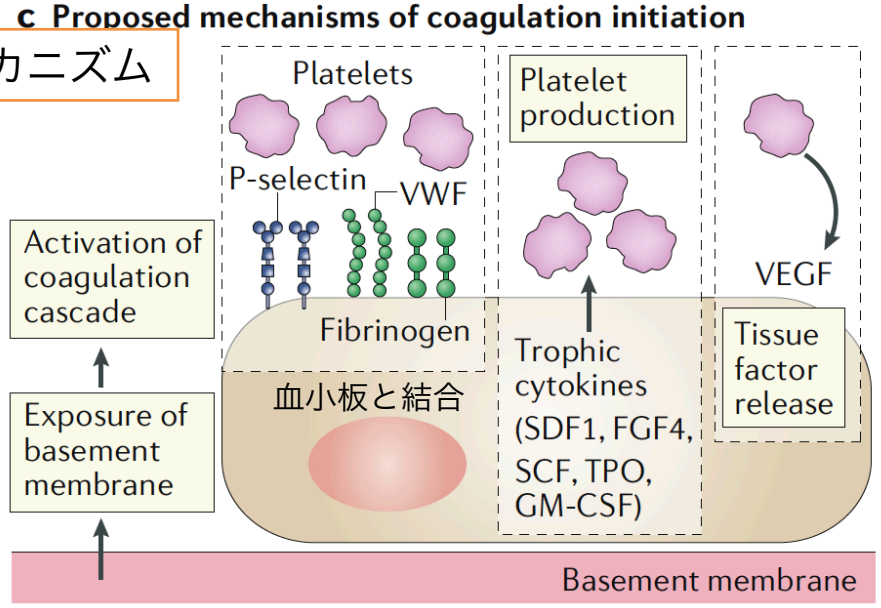
③炎症が起きる

COVID-19: the vasculature unleashed　Teuwen, L., Geldhof, V., Pasut, A. *et al.* *Nat Rev Immunol* (2020).　https://doi.org/10.1038/s41577-020-0343-0

血管漏出が起きるメカニズム



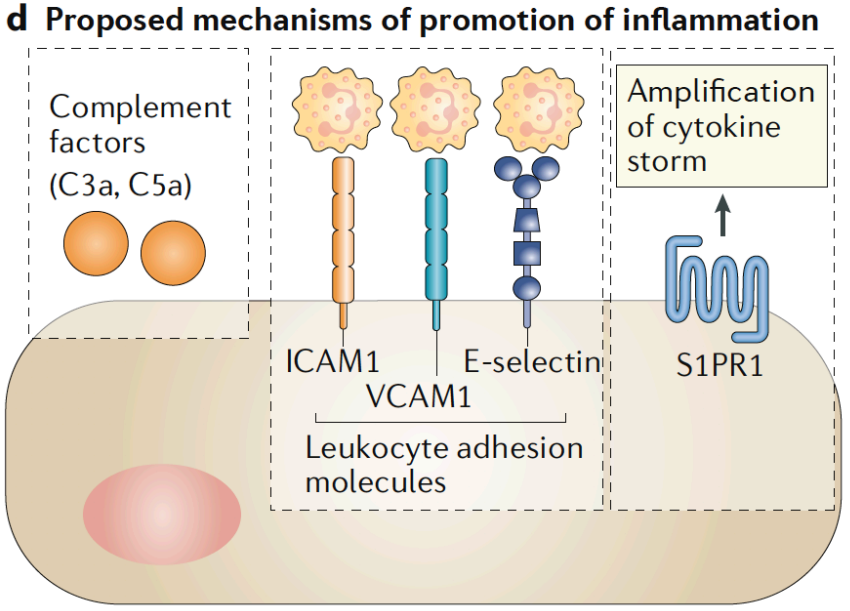
凝固が起きるメカニズム



凝固系カスケード活性化

基底膜が露出

炎症が促進するメカニズム

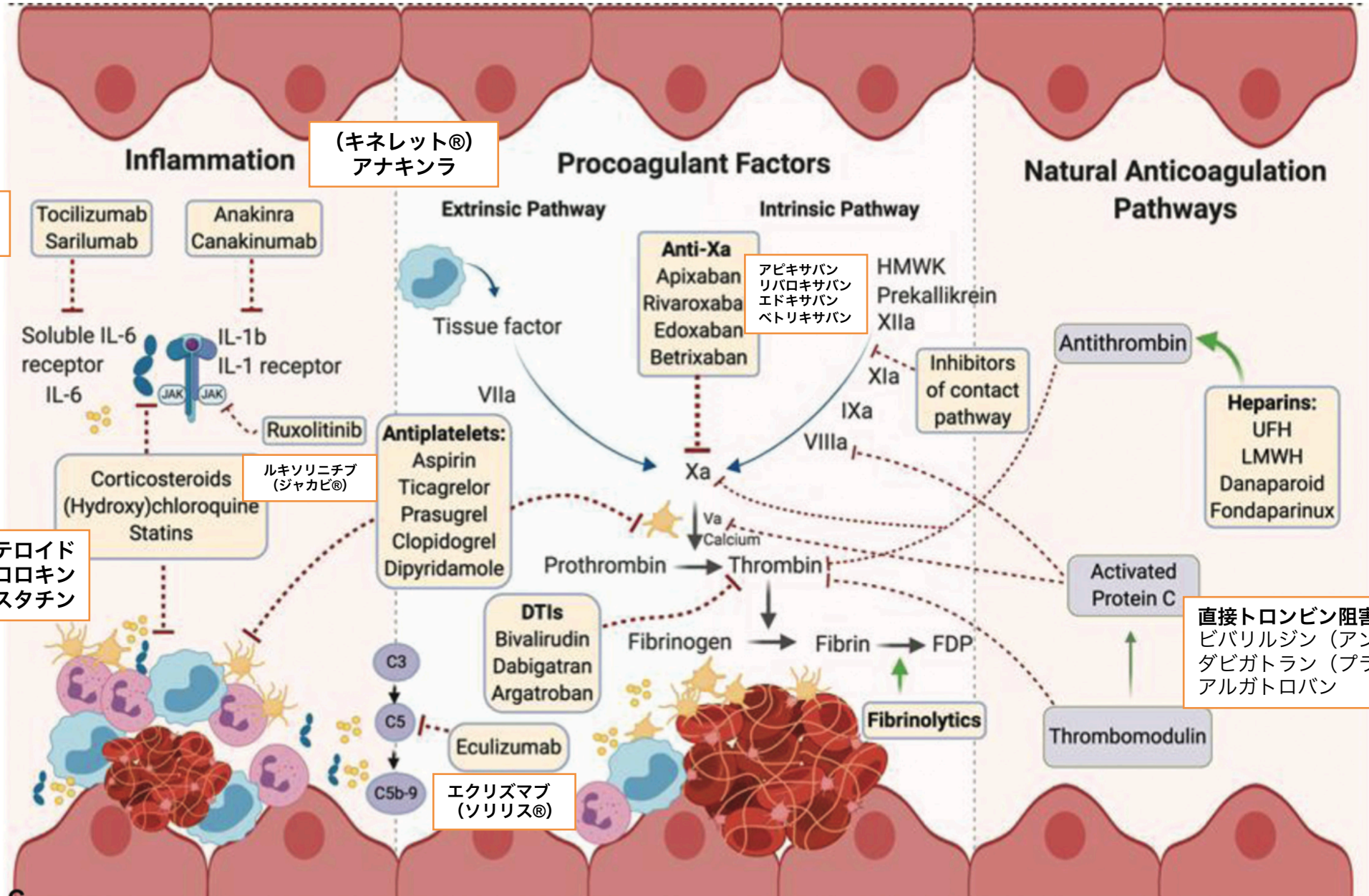


サイトカインストーム

COVID-19: the vasculature unleashed Teuwen, L., Geldhof, V., Pasut, A. *et al.* *Nat Rev Immunol* (2020). https://doi.org/10.1038/s41577-020-0343-0

Pharmacological Agents Targeting Thromboinflammation in COVID-19: Review and Implications for Future Research

Thromb Haemost. 2020 May 30.
doi: 10.1055/s-0040-1713152. Online ahead of print.



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Menu

凝固検査の異常所見

凝固関連の合併症

病態生理

抗凝固療法

Received: 20 March 2020 | Accepted: 24 March 2020

DOI: 10.1111/jth.14817

ORIGINAL ARTICLE

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Ning Tang[1] | Huan Bai[1] | Xing Chen[1] | Jiale Gong[1] | Dengju Li[2] | Ziyong Sun[1]

Tongji Hospitalに入院した449症例

2020年1月1日～2月13日

医療記録を参考に後ろ向きに調査

除外基準：

- 出血素因がある
- 入院期間＜7日間
- 凝固因子や内服薬の情報がない
- 18歳未満

抗凝固療法が死亡率に影響を与えるか調べた

重症COVID-19は以下のように定義
呼吸数≧30回/分、動脈血酸素飽和度≦93%（安静時）、P/F≦300mmHg

SICスコア：

敗血症を想定した作られたスコア

TABLE 1 ISTH SIC scoring system

Item	Score	Range
Platelet count (×10^9/L)	1	100-150
	2	<100
PT-INR	1	1.2-1.4
	2	>1.4
SOFA score	1	1
	2	≥2
Total score for SIC	≥4	

Abbreviations: INR, International Normalized Ratio; SOFA, sequential organ failure assessment.

血小板

PT-INR

SOFA

Received: 20 March 2020 | Accepted: 24 March 2020
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ORIGINAL ARTICLE

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

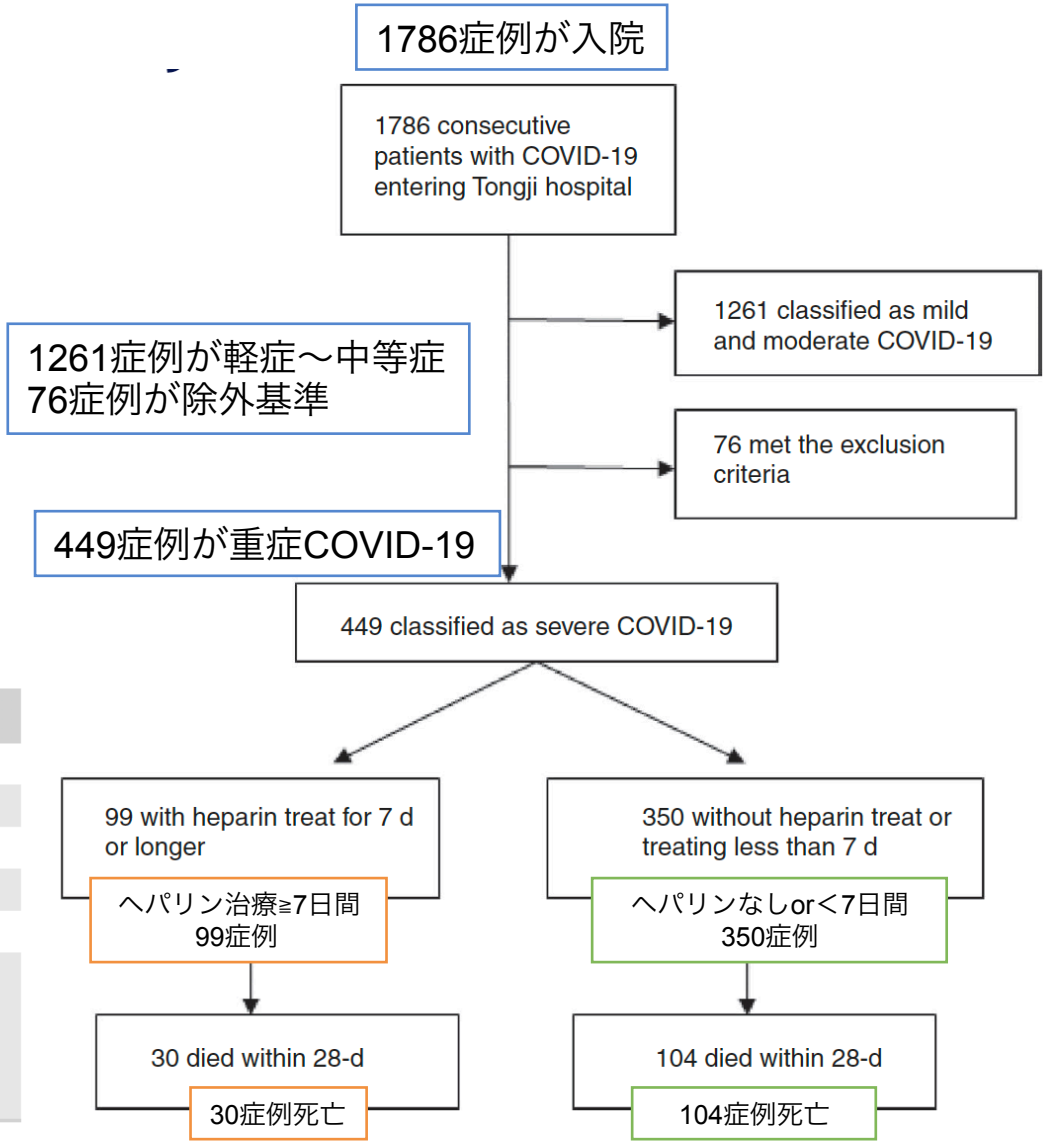
Ning Tang[1] | Huan Bai[1] | Xing Chen[1] | Jiale Gong[1] | Dengju Li[2] | Ziyong Sun[1]

ヘパリン治療：未分画ヘパリンor低分子ヘパリン≧7日間以上

生存者　非生存者

TABLE 2 Clinical and coagulation characteristics of patients being classified as severe COVID-19

Parameters	Normal range	Total (n = 449)	Survivors (n = 315)	Nonsurvivors (n = 134)	*P* values
Age (years)		65.1 ± 12.0	63.7 ± 12.2	68.7 ± 11.4	<.001
Sex ratio (male/female)		268/181	178/137	90/44	.036
With underlying diseases		272 (60.6%)	181 (57.5%)	91 (67.9%)	.136
Receiving heparin		99 (22.0%)	69 (21.9%)	30 (22.4%)	.910
Meeting SIC criteria		97 (21.6%)	42 (13.3%)	55 (41.0%)	<.001
Coagulation parameters					
PT (s)	11.5-14.5	15.2 ± 5.0	14.6 ± 2.1	16.5 ± 8.4	<.001
Platelet count ($\times 10^9$/L)	125-350	215 ± 100	231 ± 99	178 ± 92	<.001
D-dimer (μg/mL)	<0.5	1.94 (0.90-9.44)	1.47 (0.78-4.16)	4.70 (1.42-21.00)	<.001



全体の死亡率は30.3% vs 29.7%で有意差なし（p=0.917）

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Patients with	28-day mortality		Univariate analysis	
	Treating with heparin, %	Nontreating with heparin, %	Odds ratio (95% CI)	*P* value
SIC score ≥ 4 (n = 97)	40.0	64.2	0.372 (0.154-0.901)	.029
SIC score ≤ 4 (n = 352)	29.0	22.6	1.284 (0.700-2.358)	.419
D-dimer ≤ 1 ULN (n = 34)	33.3	9.7	4.667 (0.320-68.03)	.260
D-dimer > 1 ULN (n = 415)	30.2	32.7	0.934 (0.569-1.533)	.788
D-dimer > 2 ULN (n = 317)	32.1	36.9	0.810 (0.477-1.375)	.435
D-dimer > 3 ULN (n = 253)	31.1	42.5	0.611 (0.344-1.086)	.093
D-dimer > 4 ULN (n = 224)	33.3	44.5	0.623 (0.345-1.127)	.118
D-dimer > 5 ULN (n = 190)	34.9	48.8	0.563 (0.301-1.050)	.071
D-dimer > 6 ULN (n = 161)	32.8	52.4	0.442 (0.226-0.865)	.017
D-dimer > 8 ULN (n = 150)	33.3	54.8	0.412 (0.207-0.817)	.011

Abbreviation: ULN, upper limit of normal (0.5 μg/mL for D-dimer).

28日死亡率の多変量解析

TABLE 3 Multivariate correlative factors of 28-day mortality in severe COVID-19

	Multivariate analysis	
	Odds ratio (95% CI)	*P* value
Age	1.033 (1.013-1.055)	.002
Sex ratio	0.677 (0.425-1.078)	.100
With underlying diseases	0.861 (0.538-1.379)	.534
Treating with heparin	1.647 (0.929-2.921)	.088
Prothrombin time	1.107 (1.008-1.215)	.033
Platelet count	0.996 (0.993-0.998)	.001
D-dimer	1.058 (1.028-1.090)	<.001

Dダイマー、PT、年齢は28日死亡率と相関

SICスコア≧4、Dダイマー＞6ULNでは
ヘパリン治療群で死亡率低下

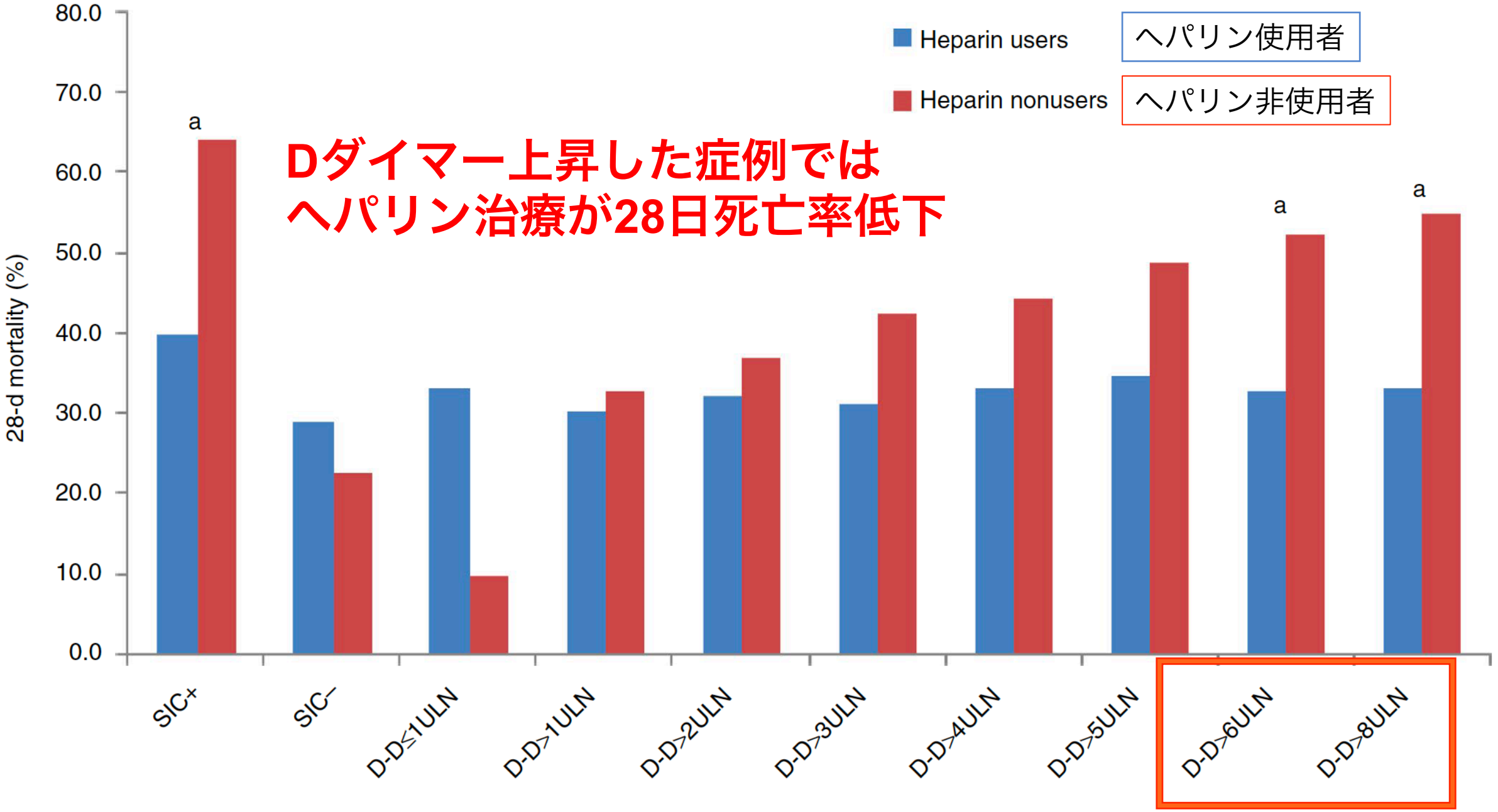


FIGURE 2 A paired bar chart showing the mortality between heparin users and nonusers in stratified patients. D-D, D-dimer; SIC+, SIC score ≥ 4; SIC−, SIC score < 4; ULN, upper limit of normal (0.5 μg/mL); a, *P* < .05 between heparin users and nonusers

入会のご案内
お問い合わせ

診療情報 新型コロナウイルス感染症に対する集中治療における臨床工学技士業務実態調査結果 NEW
2020/05/15

診療情報 ICUにおけるCOVID-19患者に対するリハビリテーション医療Q&A（Ver1.01） NEW
2020/05/15

診療情報 国内の病院における人工呼吸器等の取扱台数推計値 NEW
2020/05/14

お知らせ 特例承認に係る医薬品に関する特例について【厚生労働省／5月8日付】 NEW
2020/05/14

お知らせ レムデシビル製剤の使用に当たっての留意事項について【厚生労働省／5月7日付】 NEW
2020/05/14

お知らせ レムデシビルの必要量等の把握のための厚労省からの通知 【5月7日付】 NEW
2020/05/08

診療情報 COVID-19における抗凝固療法に関しての提言 NEW
2020/05/08

お知らせ レムデシビルの必要量等の把握のための厚労省からの通知【5月4日付】 NEW
2020/05/06

診療情報 ICU/HCUにおけるCOVID-19患者受け入れ体制準備チェックリスト：看護師版 NEW
2020/05/05

診療情報 都道府県別ICUならびにハイケアユニット等病床数 NEW
2020/04/30

2020 年 5 月 7 日

COVID-19 における抗凝固療法に関して

国際血栓止血学会 DIC 標準化委員会委員長 射場敏明
Chairman/DIC SSC of the International Society on Thrombosis and Haemostasis

COVID-19 では凝固異常や血栓症の合併頻度が高いことが認知され、そのリスクは重症にしたがって増加することが知られています[1]。また凝固異常の合併や血栓症の発症はそれ自体が突然死の原因となったり、病態の増悪因子となったりすることから注意が喚起されてきました。そして国際的なガイダンスにおいても積極的な抗凝固療法の実施が推奨されています[2]。しかしその臨床的な有用性ついては、これまで少数例における検討での効果が報告されているのみでした[3]。今回米国における比較的大規模のコホート研究結果が報告されたのでここで紹介しておきます。

https://www.sciencedirect.com/science/article/abs/pii/S0735109720352189?via%3Dihub

Paranjpe らは[4]、Mt. Sinai 病院に入院した 2,773 例の COVID-19 症例において何らかの抗凝固療法が実施されていた実施例(28%)と非実施例の間で院内死亡と生存期間の比較を行いました。その結果、実施例における死亡率と生存日数の中央値はそれぞれ 22.5%, 21 日であったのに対し、非実施例では 22.8%, 14 日という結果でした。検討症例の重症度については抗凝固治療実施例で重症例が多い傾向があり、侵襲的呼吸補助の実施率は実施例で 29.8%、非実施例では 8.1% (P< 0.01)でした。そして人工換気を実施した 395 例における検討では、実施例の死亡率と生存日数は 29.1%と 21 日、一方非実施例においてはそれぞれ 62.7%と 9 日という結果でした。出血性の有害事象に関しては前者で 3%、後者で 1.9% (P= 0.2)と差は認められませんでした。以上、とくに人工換気を要する重症例では抗凝固療法が転帰の改善をもたらすことが示唆されました。

有効性に関しては引き続き無作為比較試験で確認する必要がありますが、COVID-19 の重症化には凝固異常や血栓形成が関わっていることが予想され、積極的な介入を考慮する必要があると考えます。

Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19

Home JACC JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Ishan Paranjpe, BS[1], Valentin Fuster, MD, PhD [2], Anuradha Lala, MD [2,3], Adam Russak, MD[1,4], Benjamin S Glicksberg, PhD[1,5], Matthew A Levin, MD[3,7,8,9], Alexander W Charney, MD, PhD[5,6,8,10], Jagat Narula, MD, PhD[2], Zahi A Fayad, PhD[2,11,12], Emilia Bagiella, PhD[2,3], Shan Zhao, MD, PhD[1,9], Girish N Nadkarni, MD, MPH[1,4,13,14]

2020年3月14日～4月11日　2773症例

Mount Sinai Health System @NY

COVID19 2773症例	抗凝固群	非抗凝固群
症例数	786人（28%）	1987人（72%）
入院期間中央値	5日（3-8日）	—
抗凝固開始日までの中央値	2日（0-5日）	—
抗凝固治療期間の中央値	3日（2-7日）	—
入院中の死亡率	22.5%	22.8%
生存日数の中央値	21日	14日
人工呼吸器が必要（p<0.001）	29.8%	8.1%
出血イベント（p=0.2）	24人（3%）	38人（1.9%）

人工呼吸器患者（395症例）	抗凝固群	非凝固群
症例数	234人	161人
入院中の死亡率	**29.1%**	**62.7%**
生存の中央値	21日	9日

出血イベント（2773症例）	人工呼吸器群	非人工呼吸器群
症例数	395人	2378人
出血イベントの人数	30人	32人
出血イベント率	7.5%	1.35%

人工呼吸器を要する重症例では抗凝固治療により転帰改善！

No in-hospital anticoagulation

抗凝固なし

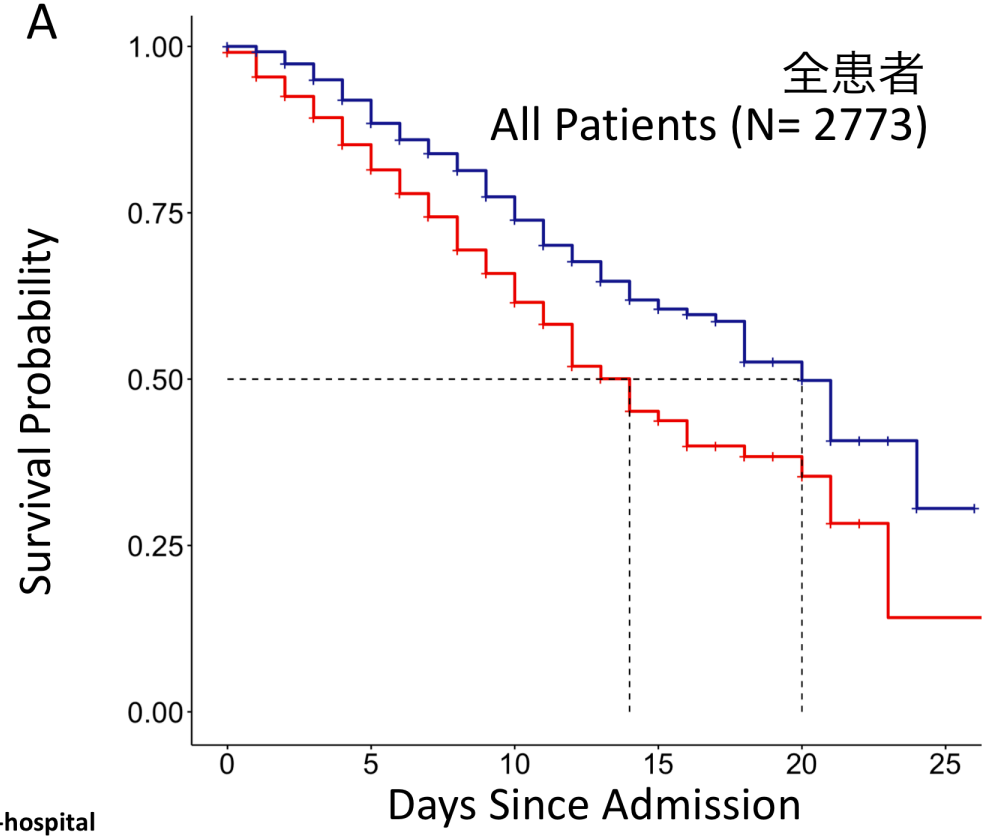
Received treatment-dose anticoagulation during hospitalization

抗凝固あり

A

全患者

All Patients (N= 2773)

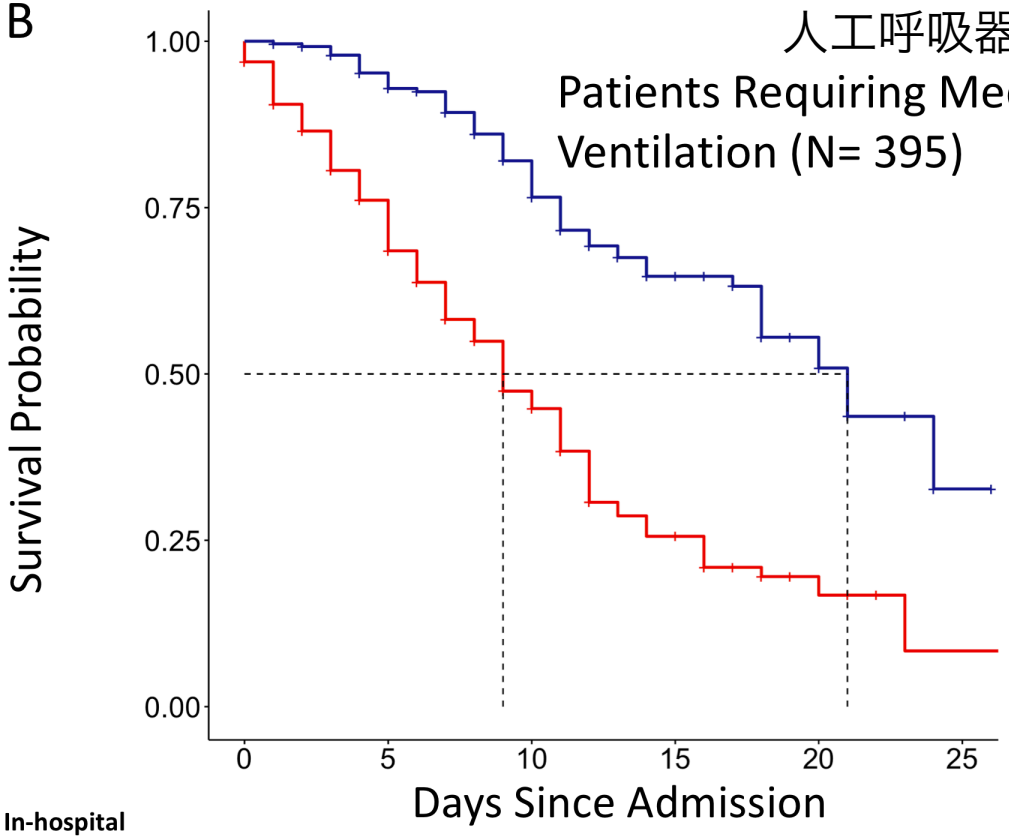


In-hospital Anticoagulation	Number at Risk					
Yes	786	538	266	90	19	3
No	1987	977	296	71	13	1

B

人工呼吸器装着患者

Patients Requiring Mechanical Ventilation (N= 395)



In-hospital Anticoagulation	Number at Risk					
Yes	234	197	137	65	14	3
No	161	100	54	25	7	1

multivariate proportional hazards model

AC治療の期間の長さが死亡率減少に関係(adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89, p<0.001)

新型コロナウイルス感染症

COVID-19

診療の手引き 第2版

6．血栓症対策

・重症感染症および呼吸不全は，深部静脈血栓症の中等度リスク因子である．

・さらに，COVID-19 患者においては，サイトカインストームや血管内皮障害などにより線溶亢進および線溶抑制が合併していると推定される．

・D ダイマーが正常上限を超えるような場合には，ヘパリンなどの抗凝固療法を実施することが推奨される．

ISTHガイドライン

Received: 20 March 2020 | Accepted: 21 March 2020

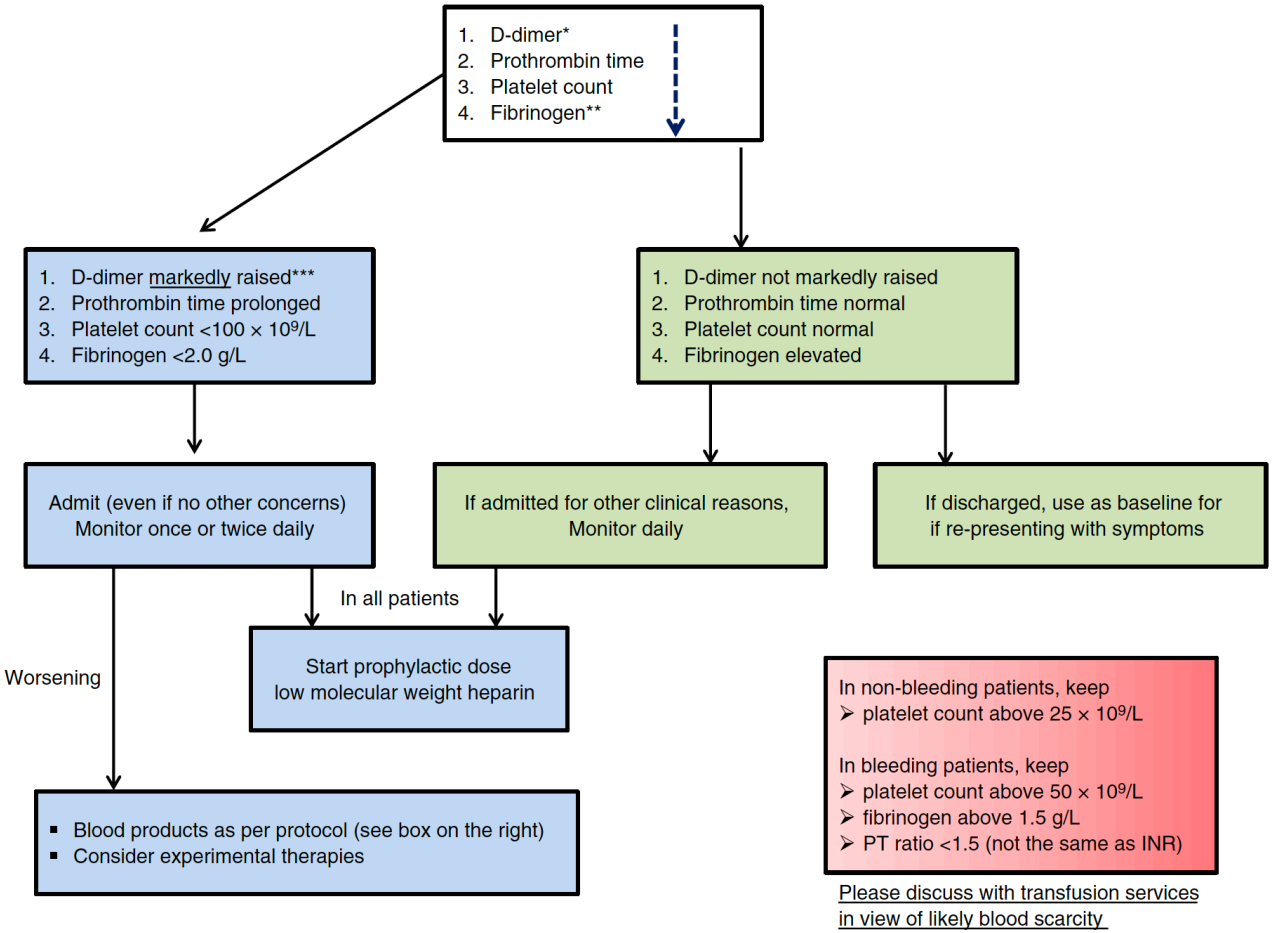
DOI: 10.1111/jth.14810

RECOMMENDATIONS AND GUIDELINES

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

Jecko Thachil[1] | Ning Tang[2] | Satoshi Gando[3] | Anna Falanga[4,5] | Marco Cattaneo[6] | Marcel Levi[7] | Cary Clark[8] | Toshiaki Iba[9]

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



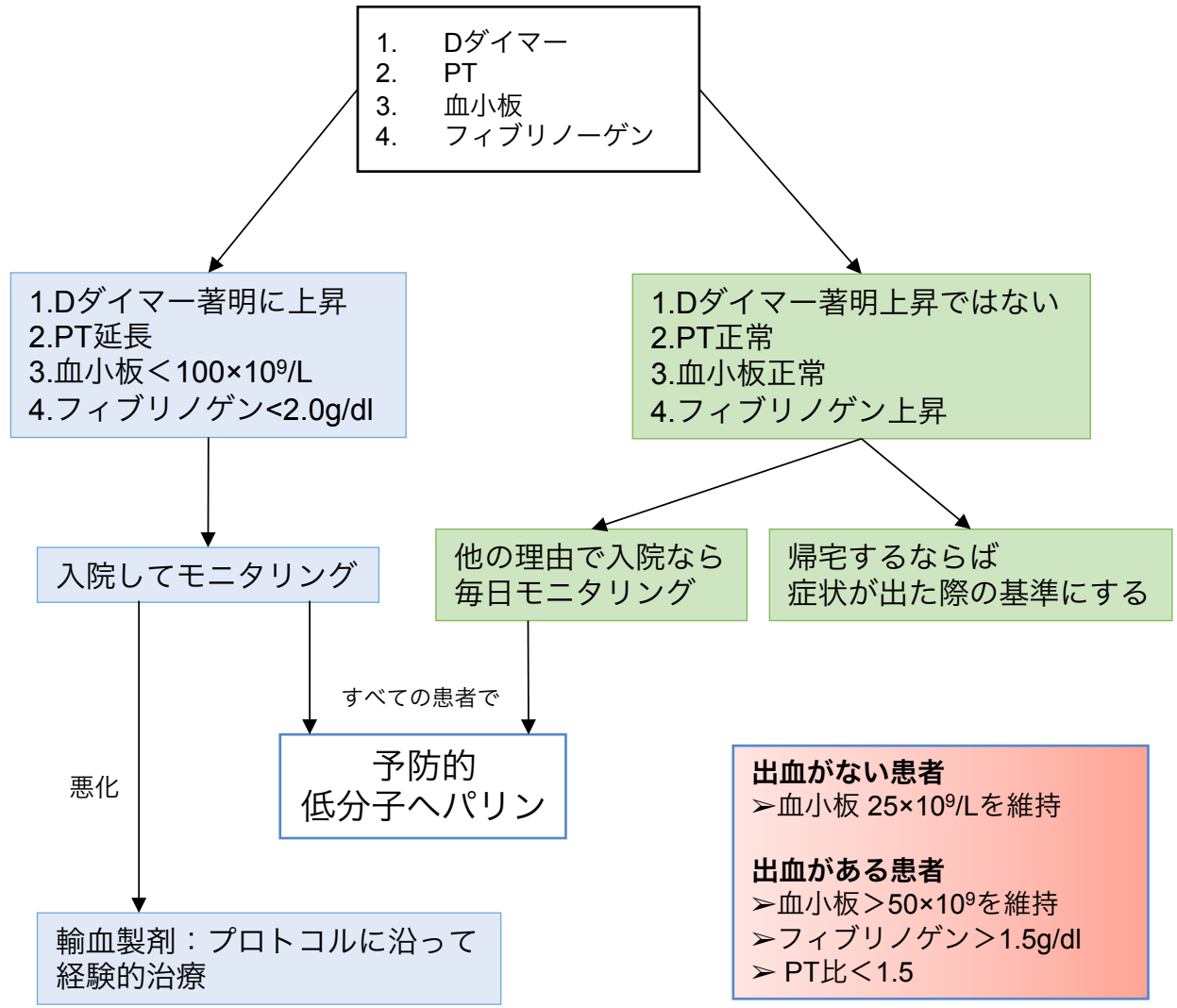


FIGURE 1 Algorithm for the management of coagulopathy in COVID-19 based on simple laboratory markers. * The list of markers is given in decreasing order of importance. ** Performing fibrinogen assays may not be feasible in many laboratories but monitoring the levels can be helpful after patient admission. *** Although a specific cut-off cannot be defined, a three- to four-fold increase in D-dimer values may be considered significant. Any one of the values in this table may be considered significant

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy
doi:10.1093/ehjcvp/pvaa036

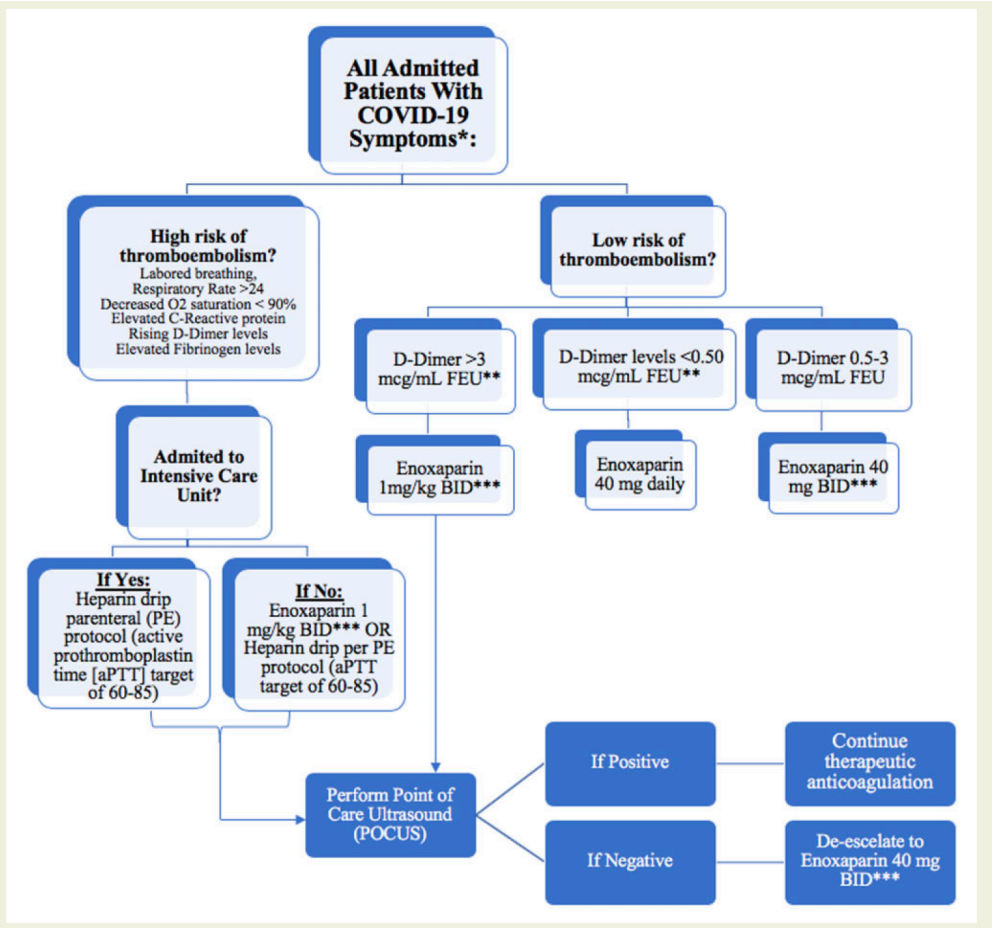


Figure 1 Tailored algorithm/protocol for the management of coagulopathy in COVID-19 patients. *High bleeding risk patients are excluded. Also exclude patients with platelet count <50 000; INR >2. **FEU, fibrinogen equivalent unit. ***Adjust enoxaparin dose for renal failure.

COVID-19
すべての入院患者

血栓症ハイリスク？
Labored breathing
呼吸数＞24回/分
酸素化低下SpO2＜90%
CRP上昇
Dダイマー上昇
フィブリノゲン上昇

ICU入院？

YES
ヘパリン投与
（肺塞栓プロトコル）
APTTターゲット
60~85秒

NO
エノキサパリン
1mg/kg　2回/日
or
ヘパリン投与
（肺塞栓プロトコル）
APTTターゲット60~85秒

血栓症ローリスク？

Dダイマー
＞3μg/ml
エノキサパリン
1mg/kg 2回/日

Dダイマー
＜0.5μg/ml
エノキサパリン
40mg/kg

Dダイマー
0.5～3μg/ml
エノキサパリン
40mg 2回/日

POCUS

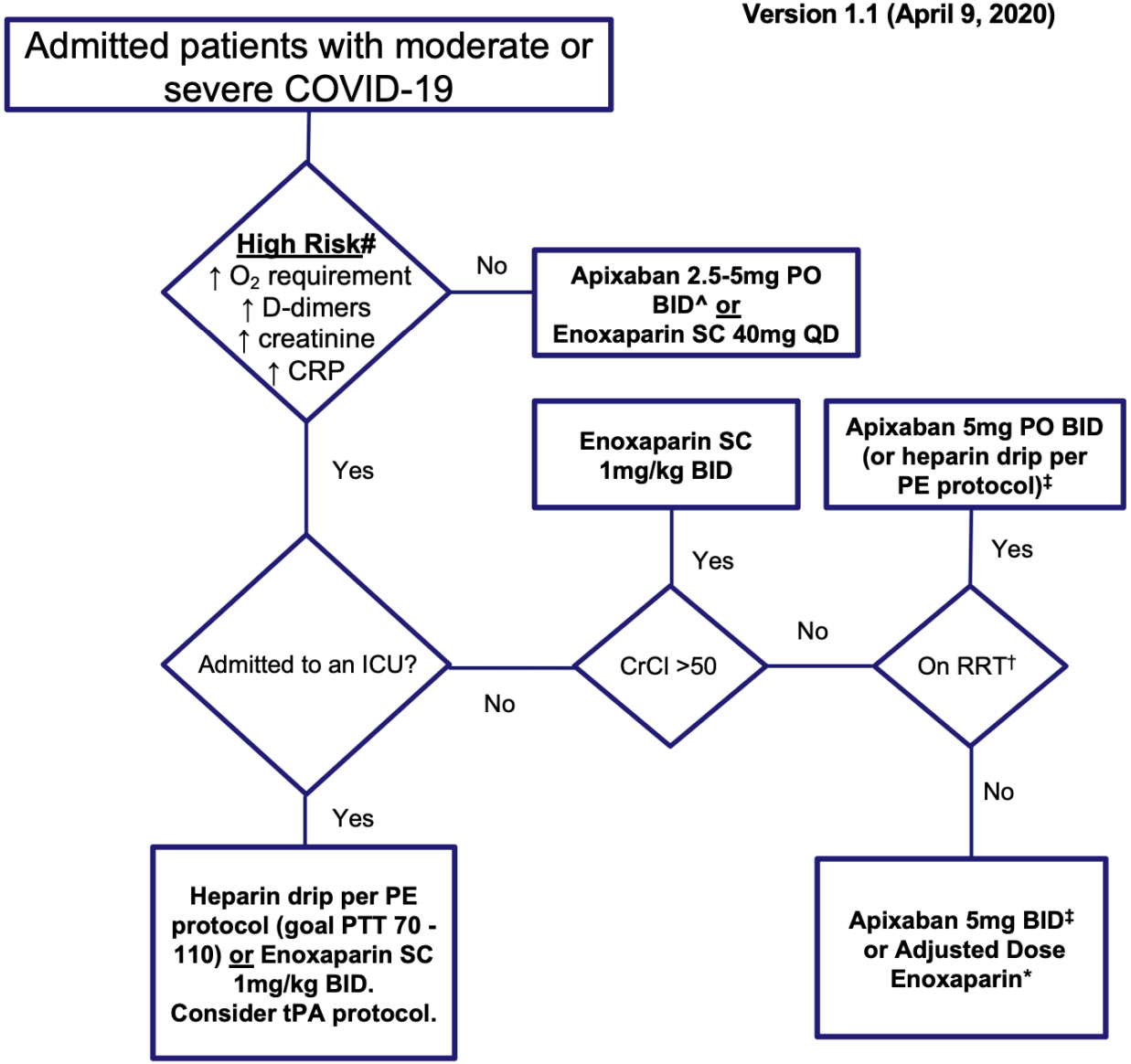
陽性
抗凝固治療
継続

陰性
エノキサパリン
40mg 1日2回
にDe-escalate

出血High Riskは除外
血小板＜5万、INR＞2は除外
エノキサパリンは腎機能により調節が必要

Mount Sinai COVID-19 Anticoagulation Algorithm

Version 1.1 (April 9, 2020)



Inclusion: All admitted patients with moderate or severe COVID-19
Exclusion: High risk of bleeding as judged by treating physician

Obtain at baseline and daily:
- CBC, PT/PTT, D-dimer

Hold anticoagulation if:
- Platelet count <50,000; INR>1.5
- Evidence of current or recent bleeding

If patients take AC at home:
- May switch to therapeutic enoxaparin or heparin (as per algorithm) for the duration of hospitalization, unless contraindicated

Rivaroxaban may be used in place of Apixaban at any indication

Discharged COVID-19 patient on therapeutic anticoagulation while hospitalized

Consider Prophylactic AC for 2 weeks post discharge (Apixaban 5mg PO BID for 2 wks)

#High Risk: No precise metrics exist. Consider exam (eg O_2 sat<90%, RR >24), ↑O_2 requirement (eg, ≥4L NC), labs (eg, ↑d-dimers, C-reactive protein)
^Efficacy and dose not established; prophylactic or treatment doses acceptable

†RRT – Renal Replacement Therapy
‡ If ≥80 years of age or weight ≤60 kg, reduce apixaban to 2.5 mg BID
* If CrCl <30: enoxaparin 0.5mg/kg BID with anti-Xa level after 3rd dose

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Definition of high risk for progression to ICU

- There is insufficient evidence to precisely define “high-risk” or provide specific cut-off values for individual factors
- Clinicians should consider a combination of exam findings (e.g, labored breathing, RR >24, decreased O_2 sat<90%), increased O_2 requirement (eg, ≥4L NC), and lab biomarkers (eg, elevated CRP, elevated creatinine, rising d-dimer >1.0).

Rationale for early anticoagulation

- Pathophysiology of COVID-19 associated respiratory disease is consistent with pulmonary vascular thromboemboli with increased dead space ventilation
- Autopsy studies have demonstrated venous thromboembolism in deceased coronavirus patients[1]
- Early anticoagulation is necessary to prevent propagation of microthrombi at disease presentation
- Anticoagulation may be associated with decreased mortality[2]

Rationale for choice of anticoagulant

- Heparins bind tightly to COVID-19 spike proteins[3,4]
- Heparins also downregulate IL-6 and directly dampen immune activation[5]
- DOACs do not appear to have these anti-inflammatory properties
- Rivaroxaban can be used in place of Apixaban in this algorithm

References

1. Xiang-Hua et al. Am J Respir Crit Care Med, 182 (3), 436-7. PMID: 20675682
2. Tang et al. J Thromb Haemost 2020 Mar 27. PMID: 32220112
3. Belouzard et al. Proc Natl Acad Sci, 2009 106 (14), 5871-6. PMID: 19321428
4. de Haan et al. J Virol. 2005 Nov; 79(22): 14451–14456. PMID: 16254381
5. Mummery et al. J Immunol, 2000. 165 (10), 5671-9. PMID: 1106792

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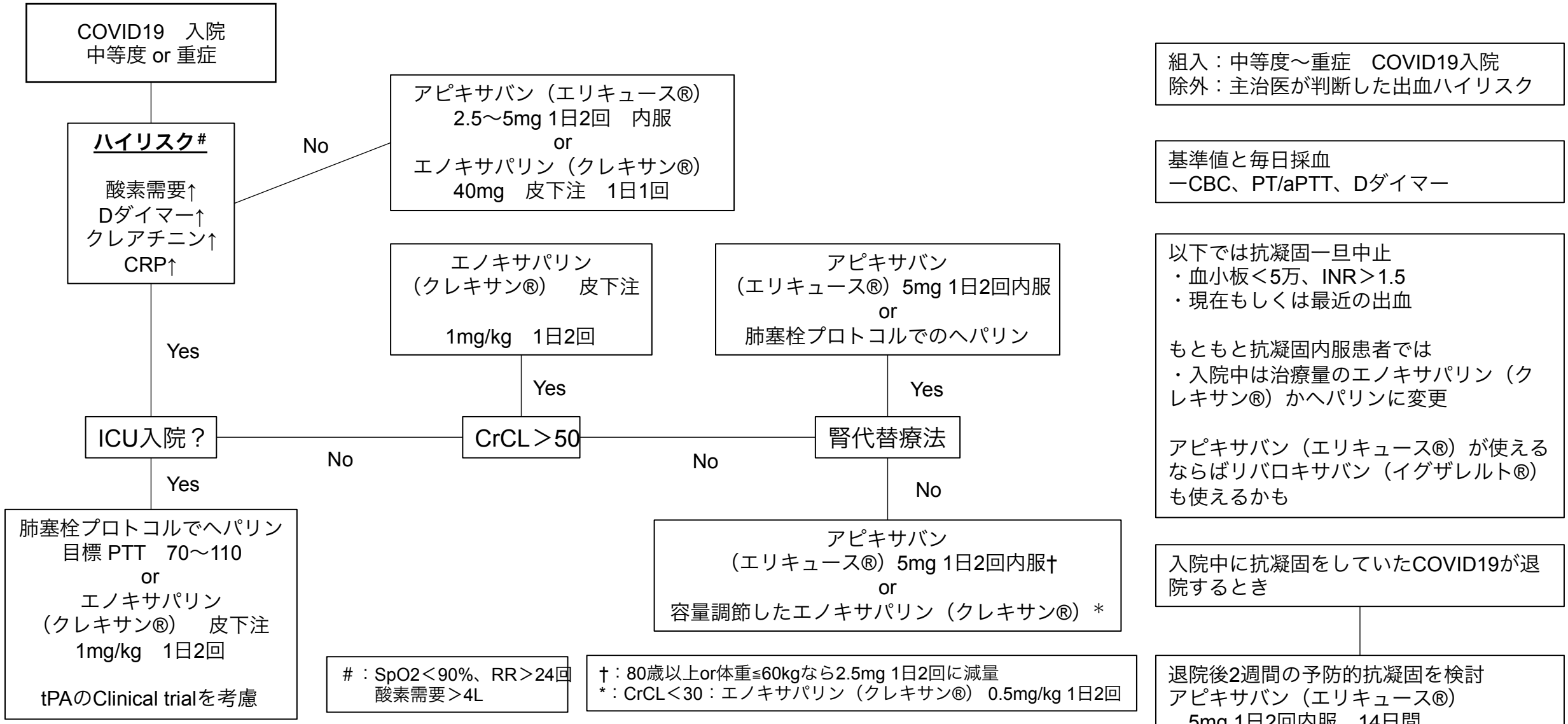
Mount Sinai COVID-19　抗凝固アルゴリズム



組入：中等度〜重症　COVID19入院
除外：主治医が判断した出血ハイリスク

基準値と毎日採血
ーCBC、PT/aPTT、Dダイマー

以下では抗凝固一旦中止
・血小板＜5万、INR＞1.5
・現在もしくは最近の出血

もともと抗凝固内服患者では
・入院中は治療量のエノキサパリン（クレキサン®）かヘパリンに変更

アピキサバン（エリキュース®）が使えるならばリバロキサバン（イグザレルト®）も使えるかも

入院中に抗凝固をしていたCOVID19が退院するとき

退院後2週間の予防的抗凝固を検討
アピキサバン（エリキュース®）
5mg 1日2回内服　14日間

エノキサパリン（クレキサン®）1mg＝100IU

Mount Sinai COVID-19　抗凝固アルゴリズム

ICUへの進行リスクの高さの定義

- 高リスクを正確に定義したり、個々の要因に具体的なカットオフ値を提示するためのエビデンスは不十分

- 検査所見（ex.呼吸困難、RR>24、O2減少<90％）、O2必要量増加（ex. ≥4L NC）、および検査所見（ex.CRP上昇、クレアチニン上昇、Dダイマー上昇>1.0）の組み合わせを考慮する必要あり

早期抗凝固療法の根拠

- COVID-19に関連する呼吸器疾患の病態生理は死腔換気の増加を伴う肺血管血栓塞栓と一致

- 剖検研究では、死亡したコロナウイルス患者の静脈血栓塞栓症が証明されている

- 疾患発現時の微小血栓の増殖を防ぐためには早期の抗凝固療法が必要である

- 抗凝固療法は死亡率の低下と関連している可能性がある

抗凝固剤選択の根拠

- ヘパリンはCOVID-19スパイク蛋白質に強固に結合する

- ヘパリンはまた、IL-6を減少させ、免疫活性化を直接減衰させる

- DOACはこのような抗炎症作用を持っていないよう

- このアルゴリズムではアピキサバンの代わりにリバロキサバンを使用することができる。

Coagulation abnormalities and thrombosis in patients with COVID-19

Marcel Levi • Jecko Thachil • Toshiaki Iba • Jerrold H Levy

Published: May 11, 2020 • DOI: https://doi.org/10.1016/S2352-3026(20)30145-9 • Check for updates

THE LANCET
Haematology

Panel: **Management of coagulopathy in patients with severe COVID-19**

Diagnostic approach

- Repeated (every 2–3 days) assessment of:
  - D-dimer
  - Prothrombin time
  - Platelet counts

Therapeutic management

- Subcutaneous low molecular weight heparin for all patients hospitalised
- Consider venous thromboembolism in patients with rapid respiratory deterioration and high D-dimer concentrations
  - Do CT angiography or ultrasound of the venous system of the lower extremities
  - If diagnostic testing is not possible and there are no bleeding risk factors, consider therapeutic anticoagulation
- Other interventions (such as plasma exchange, or administration of other anticoagulants or anti-inflammatory drugs) are experimental and should be considered in a clinical trial setting only

診断アプローチ

以下を繰り返し（2〜3日に1回）評価

- Dダイマー
- プロトロンビン時間
- 血小板数

治療管理

- 低分子ヘパリンの皮下注射（入院患者の全例）
- 急速な呼吸状態の悪化とDダイマーの上昇があれば静脈血栓を検討
- 静脈のCT血管造影や下肢静脈の超音波検査を行う
- 診断テストができない場合や出血の危険因子がな場合抗凝固治療を検討
- その他の介入（血漿交換など。他の抗凝固剤や抗炎症剤の投与）は実験的なものであり臨床試験のみを考慮

今後の展望

- 現在計画されている臨床試験

NCT	Study Type	Estimated Enrollment	Allocation	Intervention Model	Masking	Primary Purpose	Estimated（Actual） Study Start Date	Estimated Primary Completion Date	Estimated Study Completion Date
NCT04372589	**Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC)**								
	Interventional（Clinical trial）	3000	Randomized	Parallel Assignment	None（Open Label）	Treatment	May 2020	January2021	January 2021
NCT04367831	**Intermediate or Prophylactic-Dose Anticoagulation for Venous or Arterial Thromboembolism in Severe COVID-19: A Cluster Based Randomized Selection Trial (IMPROVE-COVID)**								
	Interventional（Clinical trial）	100	Randomized	Parallel Assignment	Single（Outcomes Assessor）	Treatment	May 2, 2020	November 2020	April 2021
NCT04345848	**Preventing COVID-19-associated Thrombosis, Coagulopathy and Mortality With Low- and High-dose Anticoagulation: a Randomized, Open-label Clinical Trial**								
	Interventional（Clinical trial）	200	Randomized	Parallel Assignment	Single（Outcomes Assessor）	Treatment	April 28, 2020	November 30, 2020	November 30, 2020
NCT04366960	**Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients: Comparison of 40 mg o.d. Versus 40 mg b.i.d. A Randomized Clinical Trial**								
	Interventional（Clinical trial）	2712	Randomized	Parallel Assignment	None（Open label）	Treatment	May 14, 2020	August 2020	November 2020

NIH U.S. National Library of Medicine

ClinicalTrials.gov

”COVID-19” “anticoagulation”＋ study type＝”Clinical Trial”で検索（2020/5/31）

Showing: 1-14 of **14** studies 25 studies per page Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Coagulopathy of **COVID-19**: A Pragmatic Randomized Controlled Trial of Therapeutic **Anticoagulation** Versus Standard Care	• **COVID-19**	• Drug: Therapeutic **Anticoagulation**	• St. Michael's Hospital Toronto, Ontario, Canada
2	☐	Not yet recruiting NEW	**Anticoagulation** in Critically Ill Patients With **COVID-19** (The IMPACT Trial)	• **COVID-19**	• Drug: Enoxaparin sodium • Drug: Unfractionated heparin • Drug: Fondaparinux • Drug: Argatroban	• Weill Cornell Medicine New York, New York, United States
3	☐	Recruiting	A Randomized Trial of **Anticoagulation** Strategies in **COVID-19**	• **COVID-19**	• Drug: Enoxaparin Higher Dose • Drug: Lower-dose prophylactic **anticoagulation**	• NYU Langone Health New York, New York, United States
4	☐	Not yet recruiting NEW	Safety and Efficacy of Therapeutic **Anticoagulation** on Clinical Outcomes in Hospitalized Patients With **COVID-19**	• Cardiovascular Diseases • **COVID-19**	• Drug: Enoxaparin	
5	☐	Recruiting NEW	Intermediate or Prophylactic-Dose **Anticoagulation** for Venous or Arterial Thromboembolism in Severe **COVID-19**	• **COVID-19** • Venous Thromboses • Arterial Thrombosis	• Drug: Enoxaparin Prophylactic Dose • Drug: Heparin Infusion • Drug: Heparin SC • Drug: Enoxaparin/Lovenox Intermediate Dose	• Columbia University Medical Center New York, New York, United States
6	☐	Recruiting	Preventing **COVID-19** Complications With Low- and High-dose **Anticoagulation**	• COVID • **Sars-CoV2**	• Drug: Enoxaparin	• Geneva University Hospitals Geneva, Switzerland
7	☐	Not yet recruiting	Trial Evaluating Efficacy and Safety of **Anticoagulation** in Patients With **COVID-19** Infection, Nested in the Corimmuno-19 Cohort	• **COVID19** Pneumonia	• Drug: Tinzaparin or unfractionated heparin	• Réanimation hôpital Louis Mourier Colombes, Hauts De Seine, France • réanimation hôpital Cochin Paris, France

Take home message

- COVID-19の患者は**血栓イベントのHigh Risk**であり、かつ

  ミクロな肺の毛細血管血栓症が、呼吸不全の病態生理の一つかもしれない

- 状態の変化があれば**血栓塞栓イベントを閾値低く**考えるべき

- その効果についてはRCTの結果を待つ必要があるが、

  重症COVID-19の場合は、出血リスクが高くなければ

  治療量としての抗凝固を行ってもいいのかもしれない