The so-called COVID-19 coagulopathy, from understanding to treatment: *facts and uncertainties*

Prof. Jean-Christophe Gris, *M.D., Ph.D.,*

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University of Montpellier, France;
I.M. Sechenov First Moscow state medical university, Moscow, Russian Federation

Athens, November the 12th, 2020

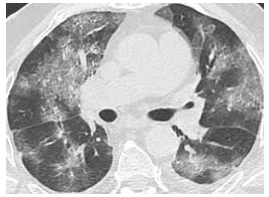
Disclosures

- Grants:
  - Bayer Healthcare SAS, Sanofi SA, Stago
- Scientific Advisory Boards:
  - Sanofi SA, LFB, Novo Nordisk,
    Coagulant Therapeutics
- Speaker / speaker bureau member, supports:
  - Alexion Pharma France, Amgen, Astra-Zeneca, Bayer,
    Bristol-Myers-Squibb, Boehringer-Ingelheim, Daïchi-Sankyo,
    Fumouze diagnostics-Sofibel, Glaxo-Smith-Kline,
    Horiba ABX SAS, Laboratoire Français des Biotechnologies (LFB),
    Léo Pharma, Novo Nordisk, Oséus, Pfizer, Sanofi SA, Shire, Stago

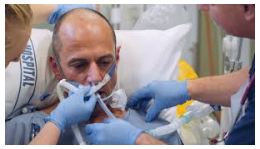
National Health Commission, People's Republic of China

– **Mild**
  - Mild clinical manifestations, no pulmonary imaging

– **Common**
  - Fever, respiratory symptoms, pneumonia evidence on X-ray or CT scan



– **Severe:** ***meet any of the followings***



  – respiratory distress syndrome (ARDS), respiratory rate > 30/min.
  – SaO_2 < 93% at rest state
  – O2 arterial partial pressure (PaO_2) / O_2 inspired fraction (FiO2) ≤ 300 mm Hg, 1 mmHg = 0.133 kPa

– **Critically severe:** ***meet any of the followings***

  – Mechanical ventilation
  – Shock
  – Combined with other organ failure, patient needing ICU support-monitoring-treatment.

COVID-19: basic clinical classification

8-category ordinal scale score

1	no hospitalisation, no limitations of activities
2	not hospitalised, limitation of activities, home O_2 requirement or both
3	hospitalised, not requiring supplemental O_2, no longer requiring care *(for infection control or other non-medical reasons)*
4	hospitalised, not requiring supplemental O_2, but requiring care *(CIVID-related or not)*
5	hospitalised, requiring any supplemental O_2
6	hospitalised, requiring non-invasive ventilation or use of high-flow O_2 devices
7	hospitalised, invasive mechanical ventilation or extracorporeal membrane oxygenation
8	death

(Remdesivir RCT, ACTT-1)

First-level laboratory data

… and the D-dimer historical sketch

Thrombosis and coagulopathy in COVID-19: An illustrated review

Marcel Levi MD, PhD[1] | Beverley J. Hunt MD, FRCP, FRCPath OBE[2]

Res Pract Thromb Haemost 2020;4(5):744-751.

Normal or high platelet count

*Mildly to moderately reduced in the **most severe** patients*

Normal prothrombin time PT

*Mild prolongation of the PT in a **minority** of patients*

High fibrinogen in virtually all patients

Elevated D-dimer levels

in particular in non-survivors

Normal antithrombin levels

Coagulation laboratory characteristics of COVID-19 infection

	Survivors	Non-survivors
Platelet count <150x10⁹/L	30-70%	45-80%
Platelet count <100x10⁹/L	0-1%	3-5%
Prothrombin time > 3 sec. prolonged	0-5%	15-25%
Fibrinogen < 1.0 g/L	0%	5-10%
Fibrinogen > 4.0 g/L	80-100%	80-100%
D-dimer > 1 mg/L (2x ULN)	15-25%	80-90%
D-dimer > 3 mg/L (6x ULN)	1-5%	50-70%
Antithrombin < 80%	0%	0-2%

Prevalence and Impact of Coagulation Dysfunction in COVID-19 in China: A Meta-Analysis

Shanen Jin[1,*] Yiyang Jin[2,*] Bai Xu[3] Jun Hong[4] Xianghong Yang[4]

Thromb Haemost 2020; Jul 17. doi: 10.1055/s-0040-1714369

22 Chinese studies
4,889 confirmed COVID-19 inpatients

Average D-dimer value: 0.67 μg/ml (0.56-0.78)
Elevated D-dimer value: 29% (20-39)

Severe patients *vs.* nonsevere patients:
higher D-dimer levels
prolonged prothrombin time (PT)

Non-survivors *vs.* survivors:
Higher D-dimer levels
Prolonged PT
Decreased platelet count

« DIC »: 6% (3-10)
log risk ratio in survivors *vs.* non survivors
3.3 (2.2-4.3)

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

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†

Lancet 2020; 395: 497–506

Published Online
January 24, 2020

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
D-dimer, mg/L	0·5 (0·3–1·3)	2·4 (0·6–14·4)	0·5 (0·3–0·8)	0·0042

Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study

Nanshan Chen*, Min Zhou*, Xuan Dong*, Jieming Qu*, Fengyun Gong, Yang Han, Yang Qiu, Jingli Wang, Ying Liu, Yuan Wei, Jia'an Xia, Ting Yu, Xinxin Zhang, Li Zhang

Lancet 2020; 395: 507–13

Published Online
January 29, 2020

	Patients (n=99)
D-dimer (μg/L; normal range 0·0–1·5)	0·9 (0·5–2·8)
Increased	36 (36%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Characteristics of Coronavirus Disease 2019 in China

W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, Jin-lin Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Ya-hua Hu, P. Peng, Jian-ming Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, and N. Zhong, for the China Medical Treatment Expert Group for Covid-19*

This article was published on February 28, 2020, and last updated on March 6,

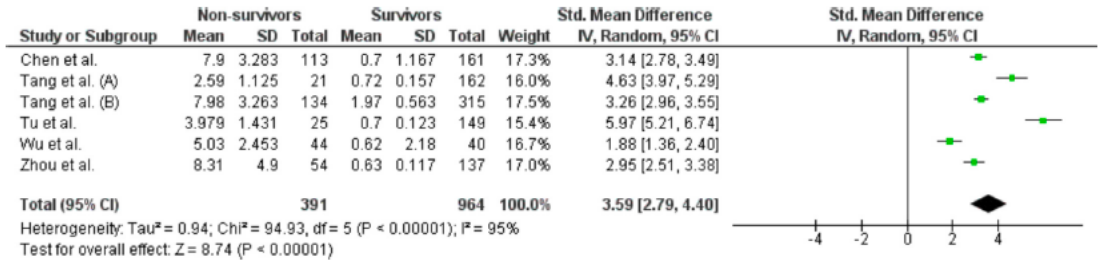
Characteristic	All Patients (N=1099)	Disease Severity	
		Nonsevere (N=926)	Severe (N=173)
D-dimer ≥0.5 mg/liter	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)

REVIEW

Association between D-Dimer levels and mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and pooled analysis

M. Sakka[a], J.M. Connors[b,c], G. Hékimian[d], I. Martin-Toutain[e], B. Crichi[f], I. Colmegna[g], D. Bonnefont-Rousselot[a,h], D. Farge[f,g,i,1], C. Frere[e,j,1,*]

JMV—Journal de Médecine Vasculaire (2020) 45, 268—274



Study or Subgroup	Non-survivors Mean	SD	Total	Survivors Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chen et al.	7.9	3.283	113	0.7	1.167	161	17.3%	3.14 [2.78, 3.49]
Tang et al. (A)	2.59	1.125	21	0.72	0.157	162	16.0%	4.63 [3.97, 5.29]
Tang et al. (B)	7.98	3.263	134	1.97	0.563	315	17.5%	3.26 [2.96, 3.55]
Tu et al.	3.979	1.431	25	0.7	0.123	149	15.4%	5.97 [5.21, 6.74]
Wu et al.	5.03	2.453	44	0.62	2.18	40	16.7%	1.88 [1.36, 2.40]
Zhou et al.	8.31	4.9	54	0.63	0.117	137	17.0%	2.95 [2.51, 3.38]
Total (95% CI)			**391**			**964**	**100.0%**	**3.59 [2.79, 4.40]**

Heterogeneity: Tau² = 0.94; Chi² = 94.93, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 8.74 (P < 0.00001)

Std. Mean Difference
IV, Random, 95% CI

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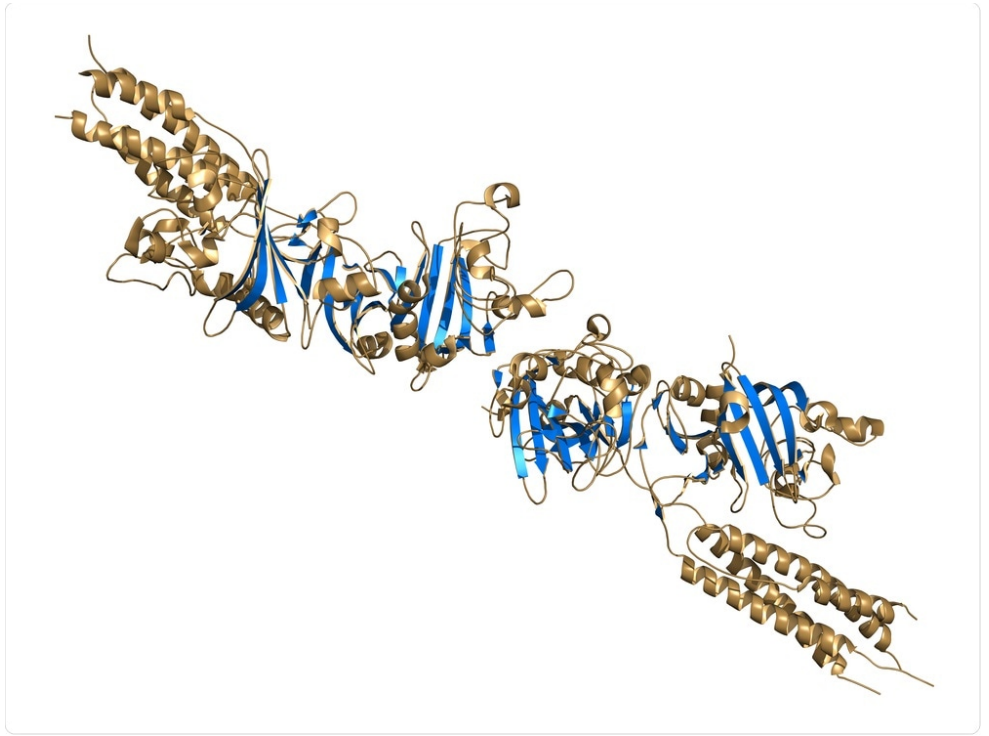

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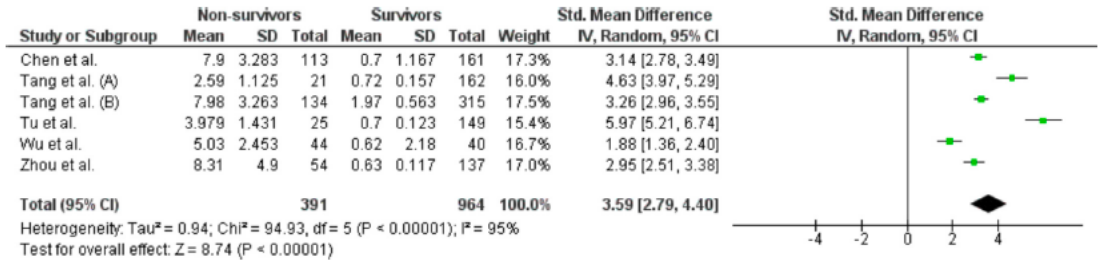

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Significant,

but very high heterogeneity across studies (I^2=95%)

RECOMMENDATIONS AND GUIDELINES

jth

The need for accurate D-dimer reporting in COVID-19: Communication from the ISTH SSC on fibrinolysis

Jecko Thachil[1] | Colin Longstaff[2] | Emmanuel J. Favaloro[3] | Giuseppe Lippi[4] | Tetsumei Urano[5] | Paul Y. Kim[6] | on behalf of the SSC Subcommittee on Fibrinolysis of the International Society on Thrombosis and Haemostasis

J Thromb Haemost. 2020;18:2408–2411.

Received: 10 May 2020 | Accepted: 1 June 2020

Two dozen puplished papers; *problems on:*

- Manufacturer or type of D-dimer assay?
- Analytical performances of the assay?
- D-dimer units or fibrinogen-equivalent units (2/1)?
- Magnitude of units chosen?
- Normal or disease cut-off, age-related cut-offs?
- Distinction between thromboembolism and DIC?
- Consistency of statistical analysis?

Received: 13 February 2020 | Accepted: 18 February 2020
DOI: 10.1111/jth.14768

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]

Received: 13 February 2020 | Accepted: 18 February 2020

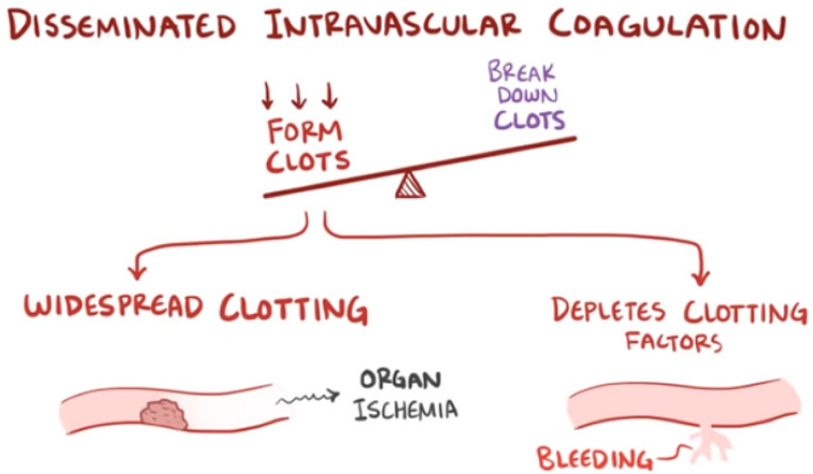
J Thromb Haemost. 2020;18:844–847.

- **Abnormal coagulation results: poor prognosis**
- **DIC: common in deaths**

Retrospective, 183 patients

Abnormal coagulation results,
especially markedly elevated D-dimer values
(> 3 μg/ml: 86%)
are common in deaths.

71% of non-survivors and 0.6% of survivors
met the criteria for DIC (ISTH score)
during their hospital stay



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Received: 24 February 2020 | Accepted: 24 February 2020
DOI: 10.1111/jth.14781

COMMENTARY

Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia

David Lillicrap

Evidence of DIC, especially elevated D-dimer levels, may be used in therapy considerations.

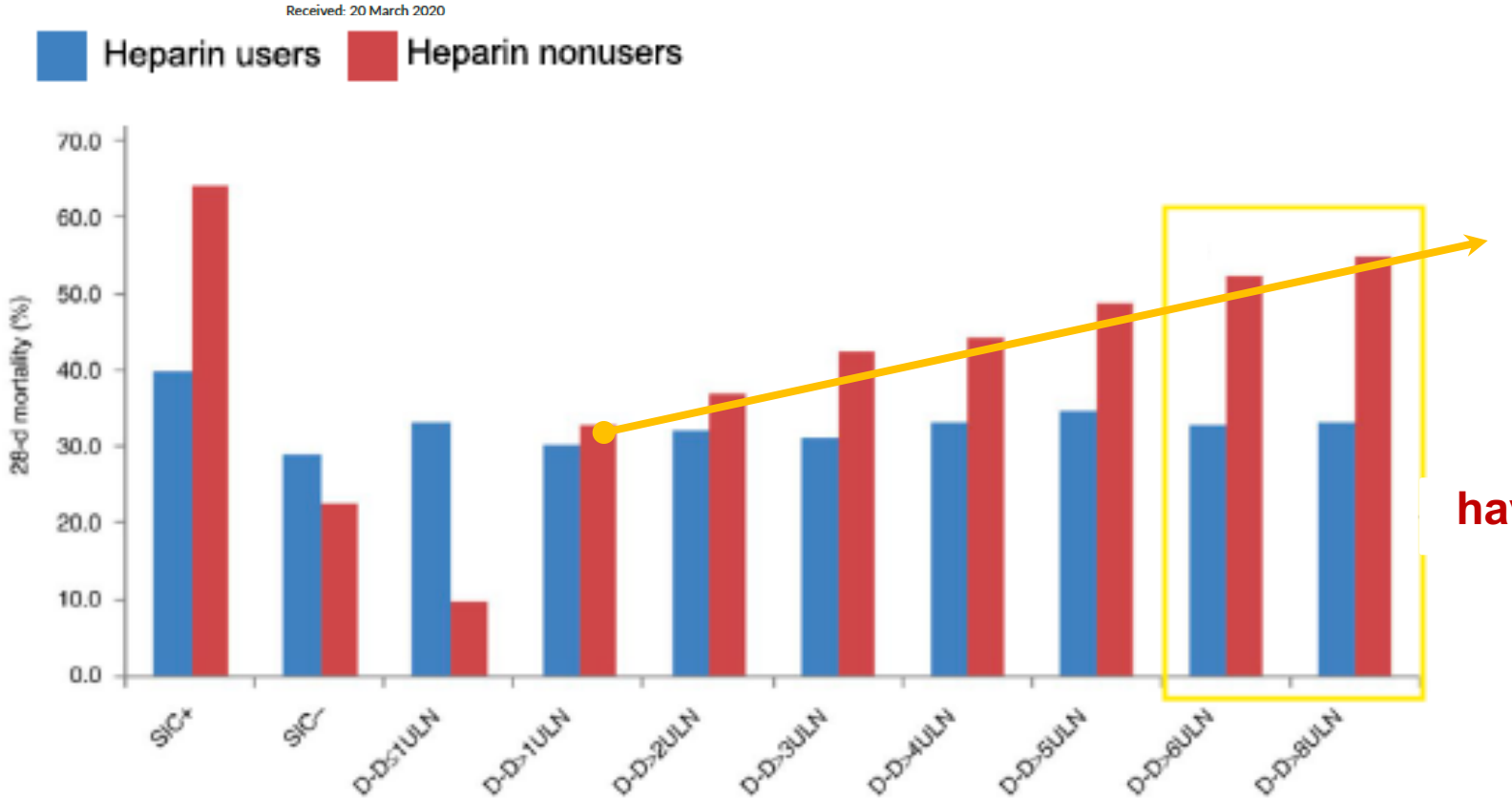
The observations of Tang and colleagues provide early evidence that enhanced vigilance is required to identify the emergence of DIC in 2019-nCoV pneumonia patients.

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]

J Thromb Haemost. 2020;18:1094–1099.

Received: 20 March 2020



Patients with (very) high D-dimers levels have a concentration-dependent higher 28-day mortality

SIC: sepsis-induced Coagulopathy; D-D: D-dimer; ULN: Upper Limit of Normal

Discrepancies in fibrin-generation markers…

Something is rotten in the state of D…IC

N= 170 COVID-19 patients
entering our University Hospital

D-dimers « Ddi »: VIDAS®; FEU
soluble Fibrin monomers: « sFM », Stago; FEU

Discrepancies in fibrin-generation markers…

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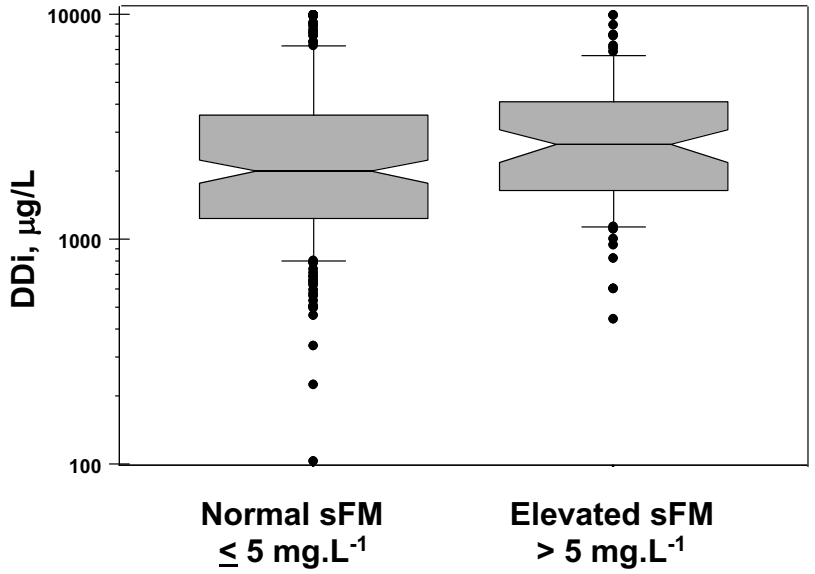

Very strong overlap of the distributions

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Impact of DDi and sFM values on the ISTH DIC score.

DDi: \ sFM:	0	2	3	
0	3	1	0	4
2	96	15	16	127
3	28	4	7	39
	127	20	23	170

Discrepancies in fibrin-generation markers…

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N= 170 COVID-19 patients
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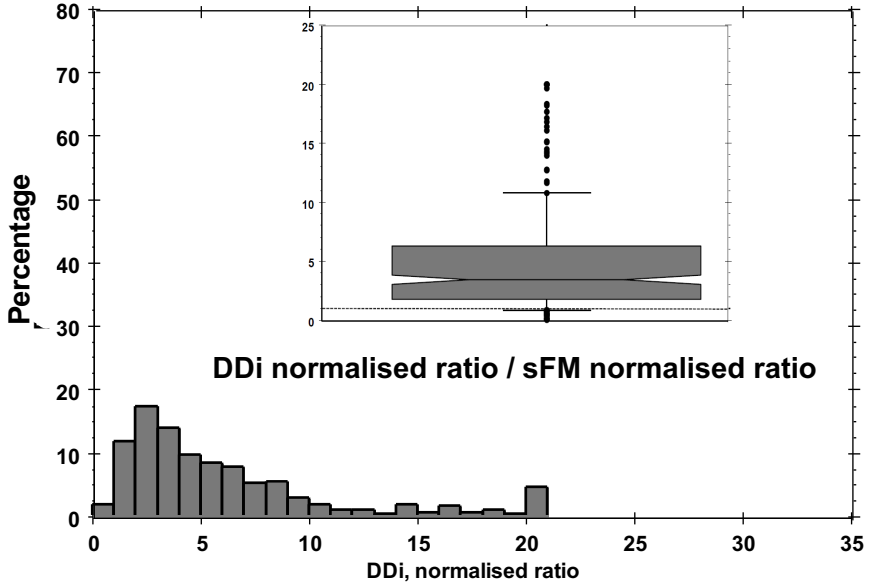
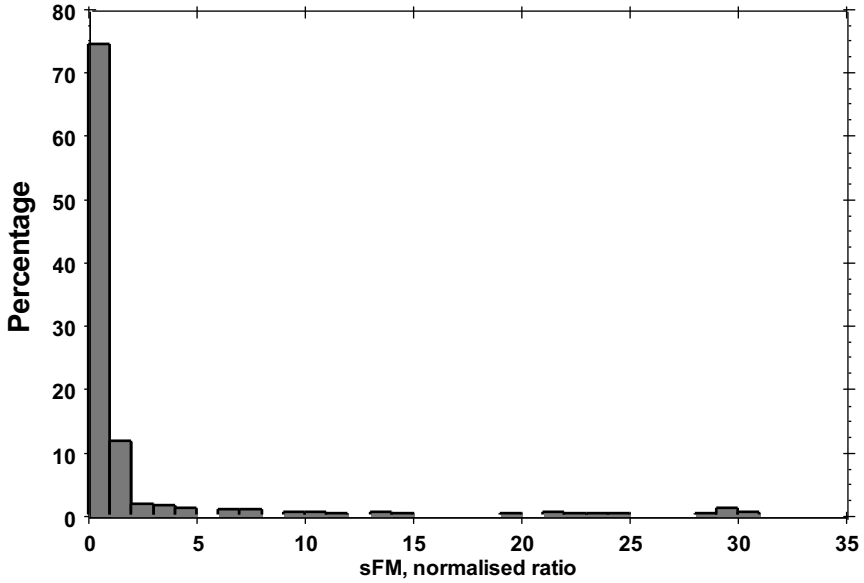
Results given as « **normalised ratios** »:
DDi patient / age-adjusted upper threshold
sFM patient / upper threshold

Normalised ratio	≤1	≤ 2	≤5	≤10	≤15	≤20
DDi, %	1.8	13.5	54.7	84.7	91.2	97.1
sFM, %	74.7	86.5	91.2	94.7	95.9	96.0





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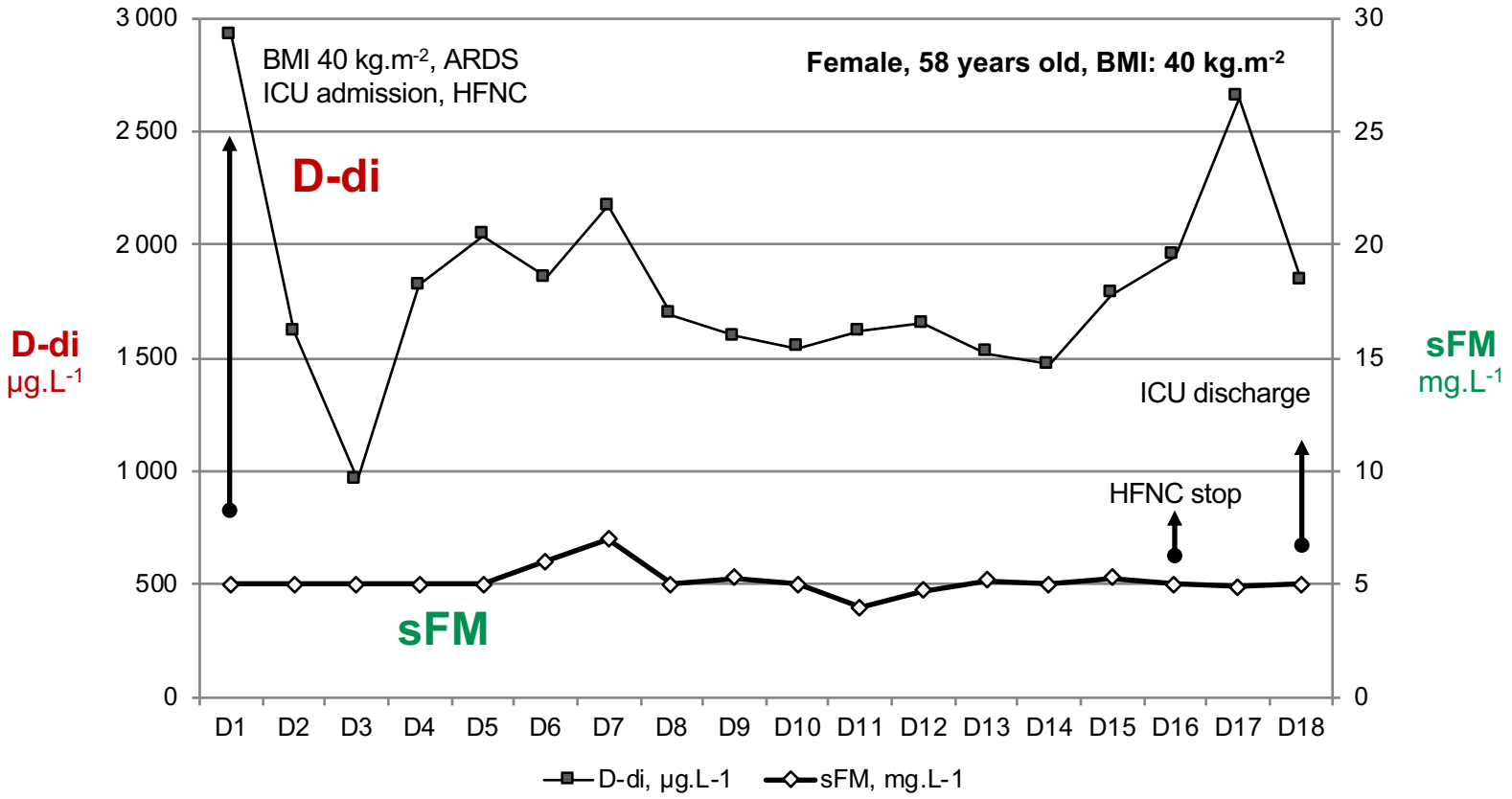

ICU: intensive care unit; BMI: body mass index;
ARDS: acute respiratory distress syndrome; HFNC: high-flow nasal canula oxygen therapy

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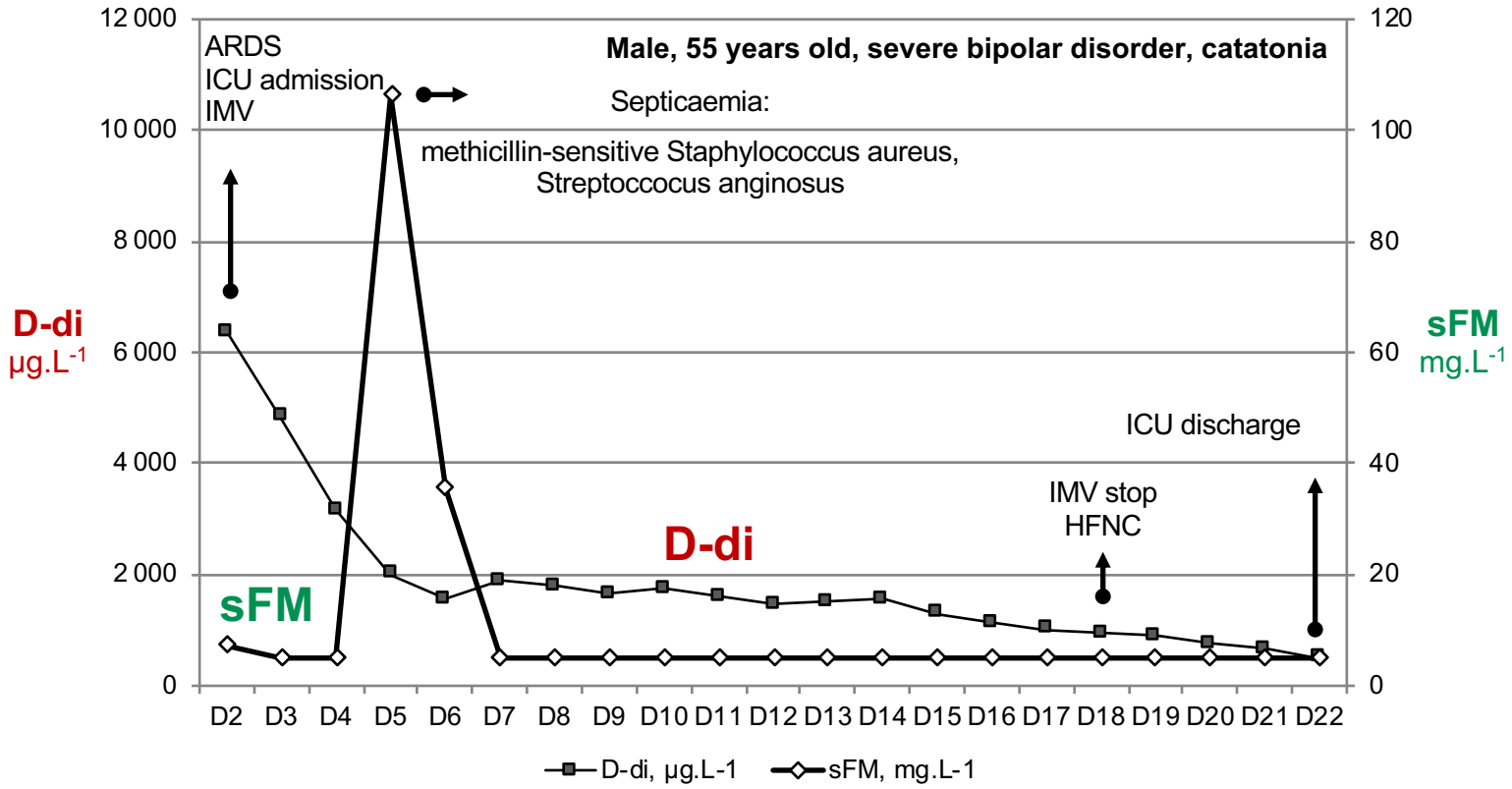

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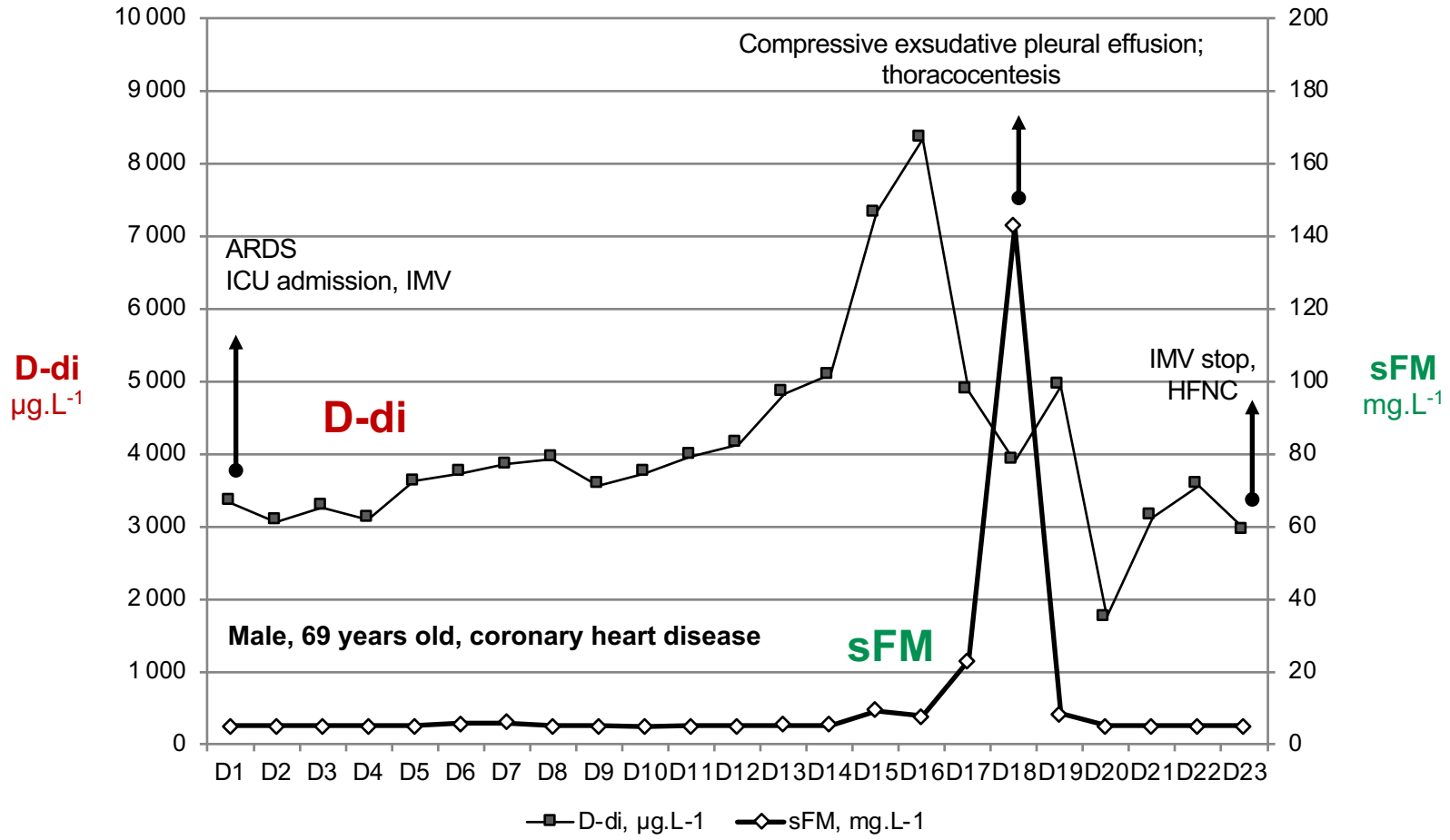

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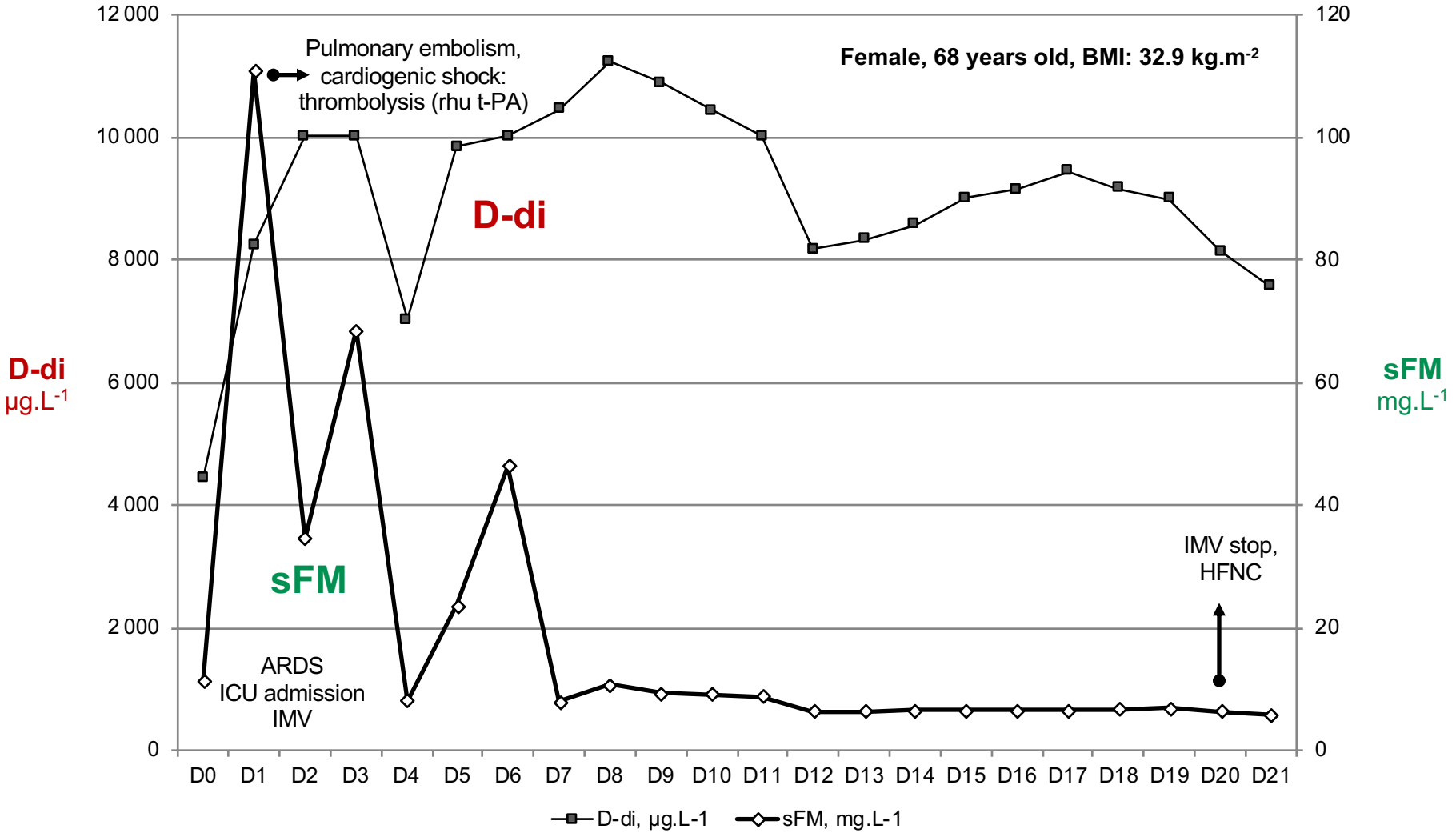

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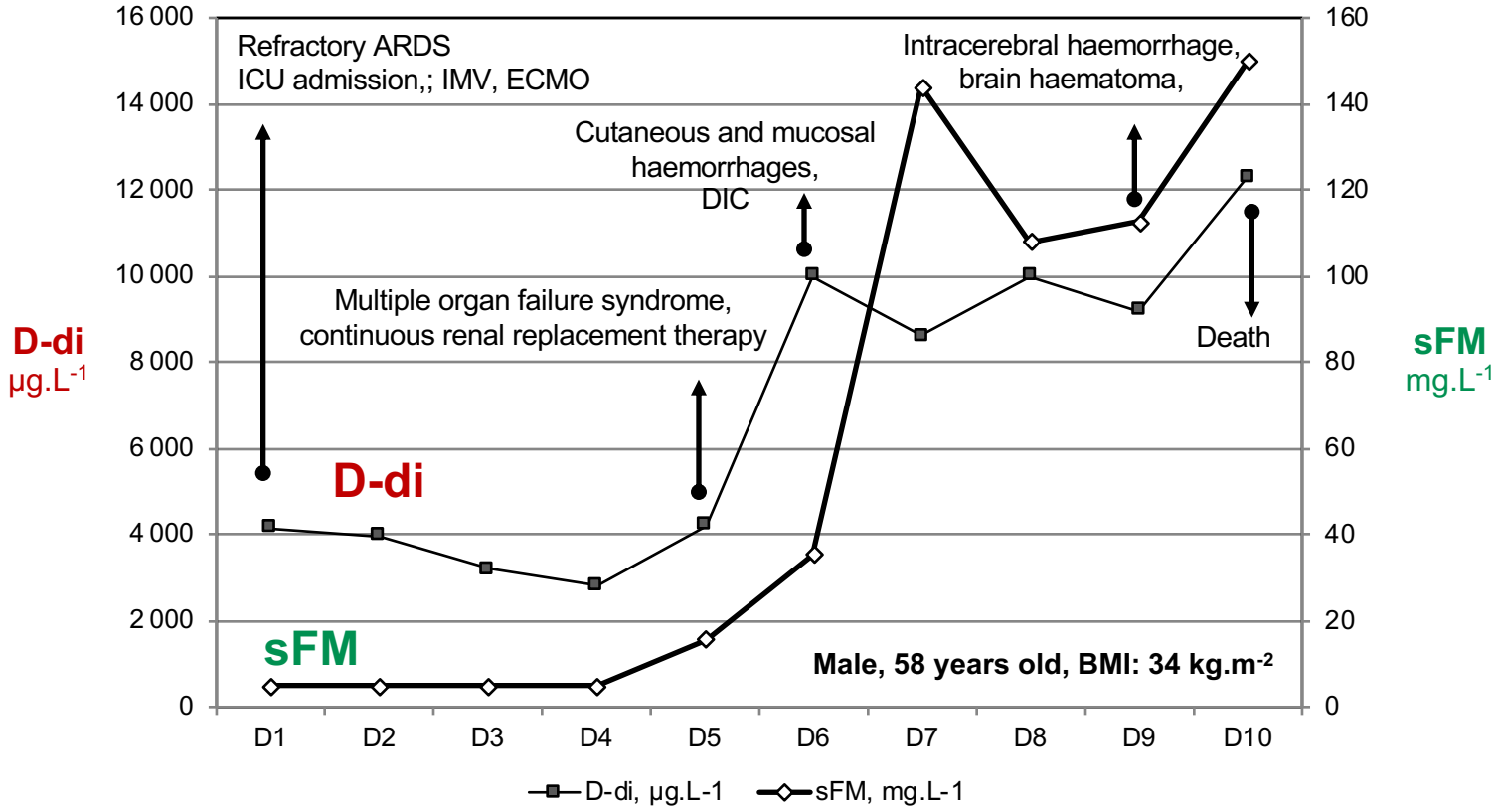

ICU: intensive care unit
ARDS: acute respiratory distress syndrome; IMV: invasive mechanical ventilation ;
ECMO: extra-corporeal membrane oxygenation; DIC: disseminated intravascular coagulation

Discrepancies in fibrin-generation markers…

Something is rotten in the state of D…IC

- Elevated D-dimer levels
- Normal sFM levels
  - sFM increase
    - in case of an intercurrent transient complication
    - or when death is coming

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.

N Engl J Med 2020;383:120-8.

May 21, 2020

Autopsy;

7 lungs from COVID-19 patients

vs.

7 lungs from ARDS secondary to influenza A H1N1 infection

10 uninfected control lungs

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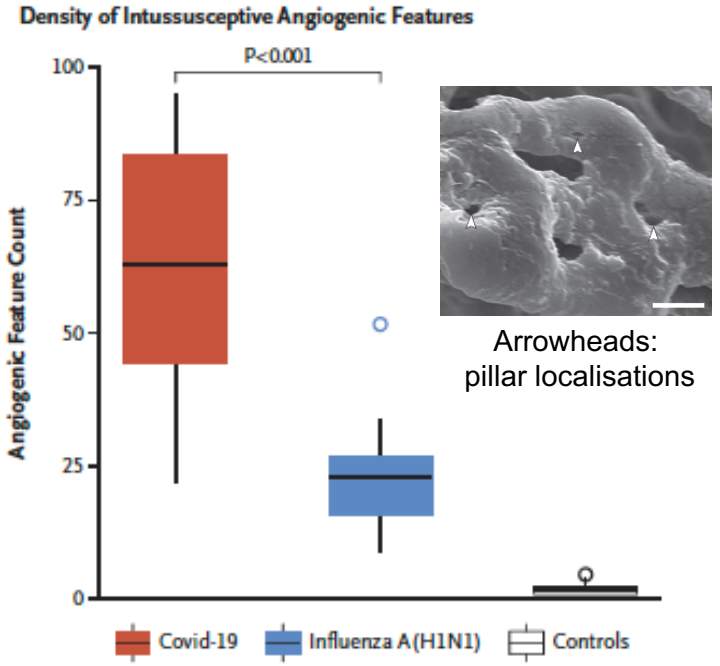
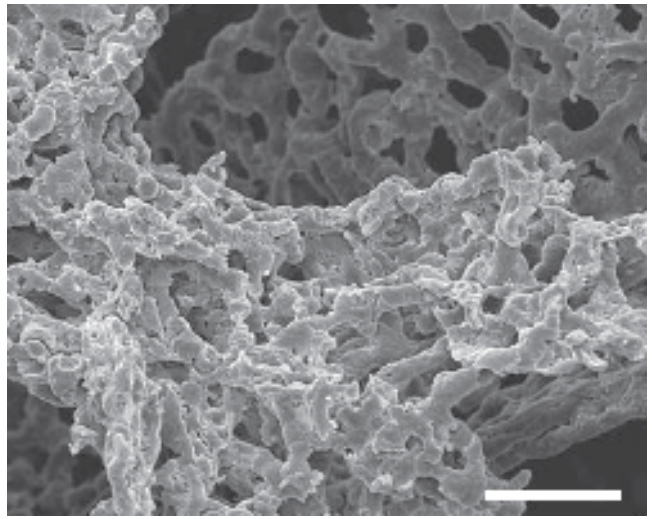
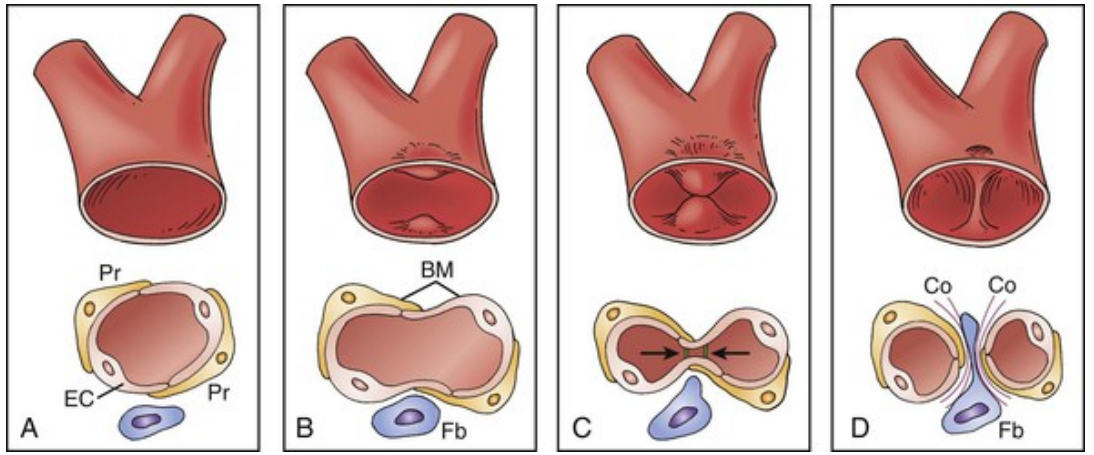


Arrowheads:
pillar localisations

The difference: vascular angiogenesis;
severe intussusceptive angiogenesis



Architectural distortion of the thin wall alveolar plexus



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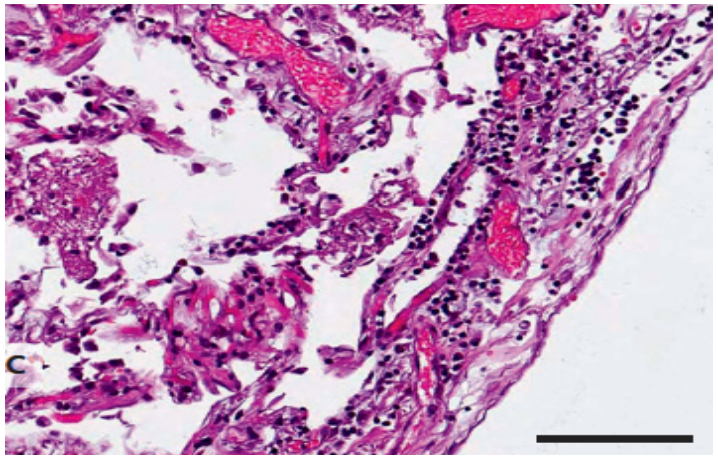

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7 lungs from COVID-19 patients
7 lungs from ARDS secondary to influenza A H1N1 infection
10 uninfected control liungs

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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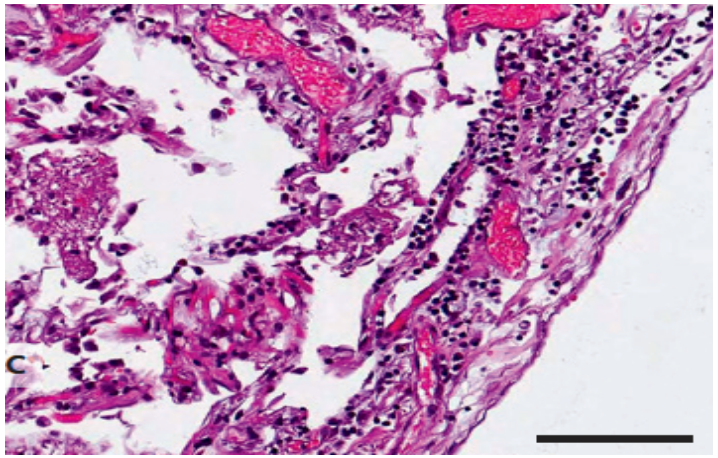

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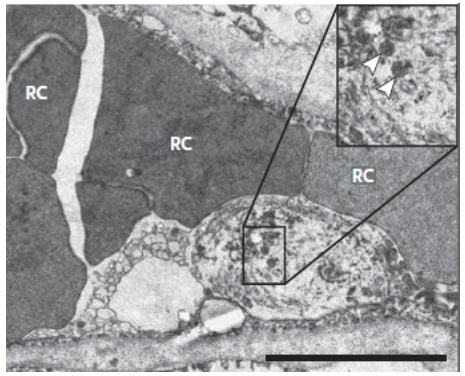
Endothelial cell destruction,
detectable **SARS-COV-2**



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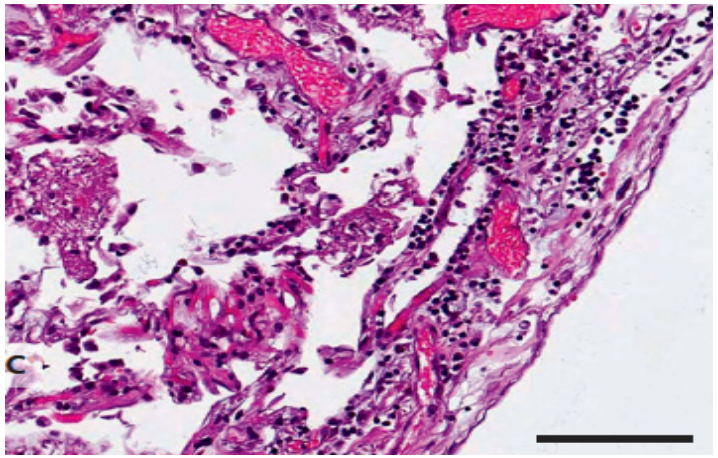

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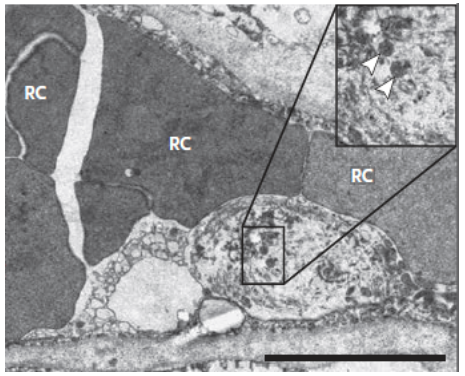
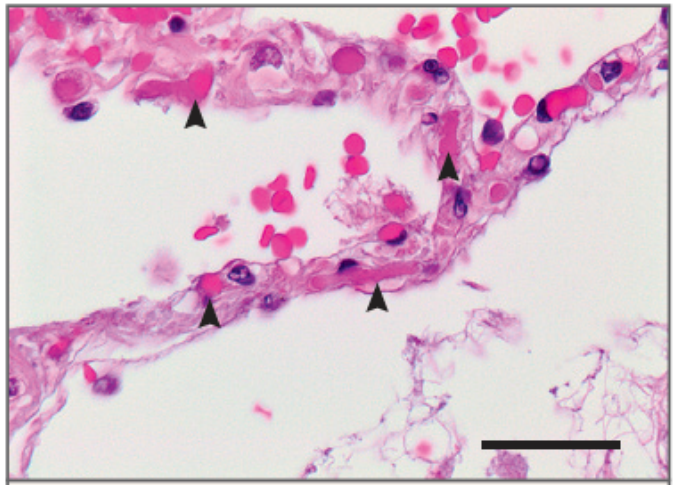




Fibrinous microthrombi in the alveolar septa;
extravasated erythrocytes
and **loose network of fibrin in the alveolar space**

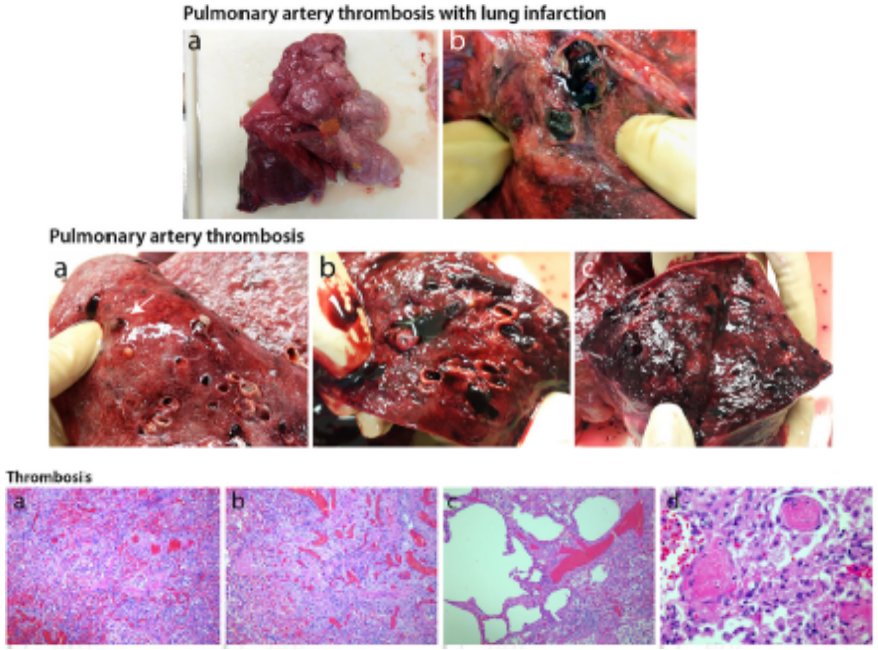
Persistence of viral RNA, pneumocyte syncytia and thrombosis are hallmarks of advanced COVID-19 pathology

Rossana Bussani[a,1], Edoardo Schneider[b], Lorena Zentilin[b], Chiara Collesi[a,b], Hashim Ali[c], Luca Braga[b,c], Maria Concetta Volpe[b], Andrea Colliva[b], Fabrizio Zanconati[a], Giorgio Berlot[a], Furio Silvestri[a], Serena Zacchigna[a,b,1,*], Mauro Giacca[a,b,c,1,*]

EBioMedicine 2020; Oct 30:103104.

41 consecutive post-mortem samples

Extensive alveolar damage and thrombosis of the lung micro- and macro-vasculature



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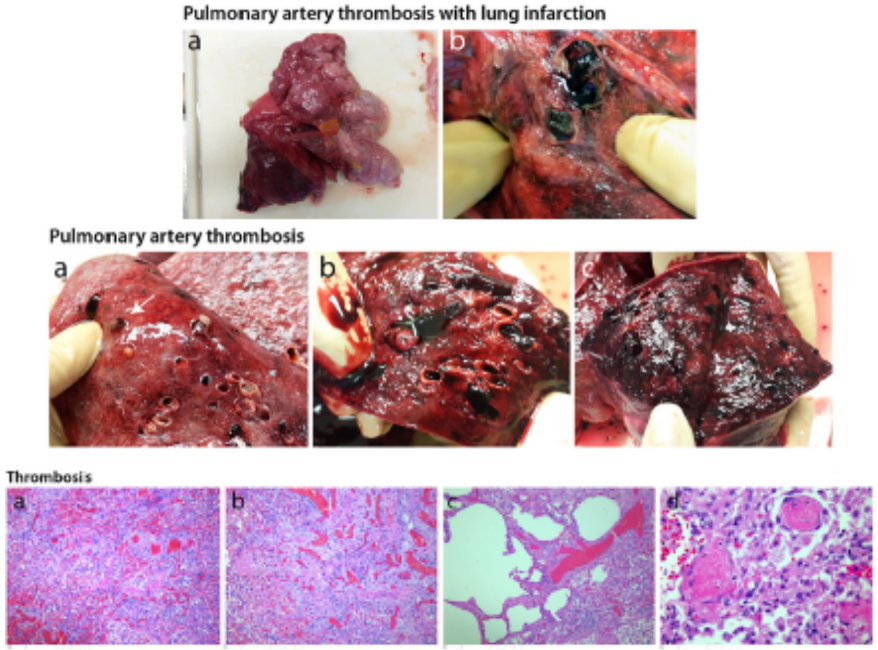
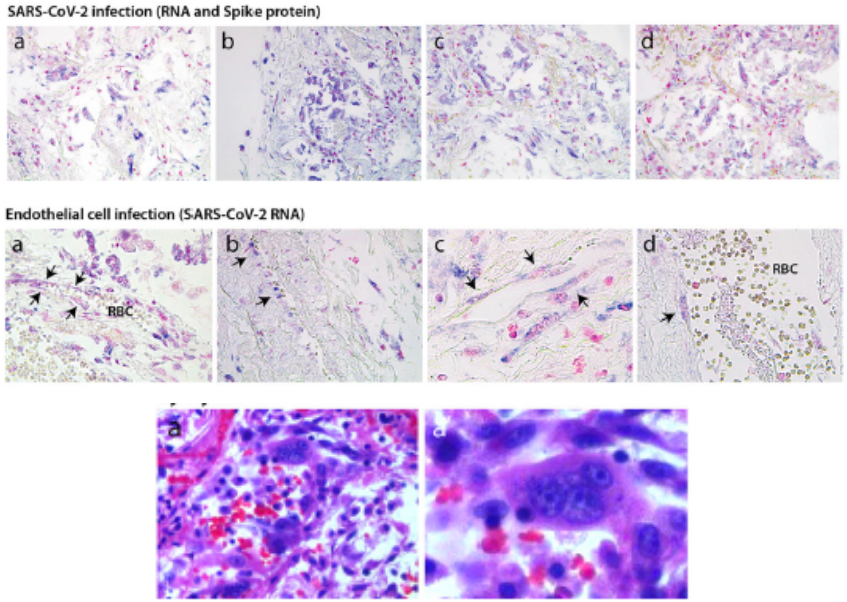


Long-term persistence of viral RNA in pneumocytes and in endothelial cells, with infected cell syncytia



Contrary to other interstitial pneumonias
several of the COVID-19 features
are not attributable to pneumocyte death
as a consequence of viral replication,
but to the persistence of virus-infected, Spike-expressing cells
in the lungs of the infected individuals

REVIEW

Autopsy findings in COVID-19-related deaths: a literature review

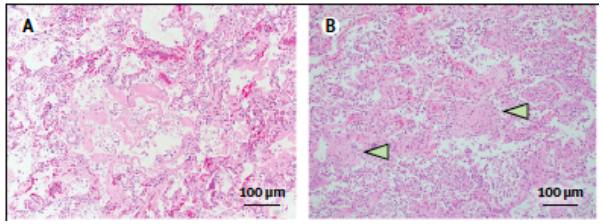
Aniello Maiese[1] · Alice Chiara Manetti[1] · Raffaele La Russa[2] · Marco Di Paolo[1] · Emanuela Turillazzi[1] · Paola Frati[2] · Vittorio Fineschi[2]

Forensic Sci Med Pathol 2020; Oct 7:1-18.

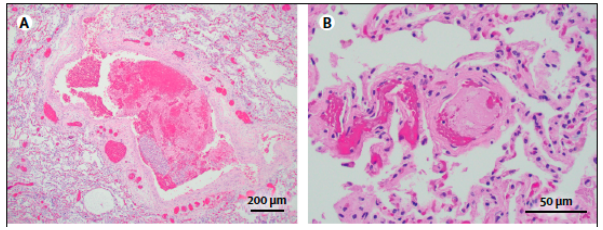
28 papers, 341 cases.

Major histological feature in the lung:

diffuse alveolar damage, hyaline membrane formation



microthrombi in small pulmonary vessels



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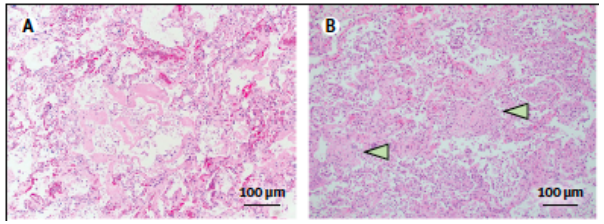

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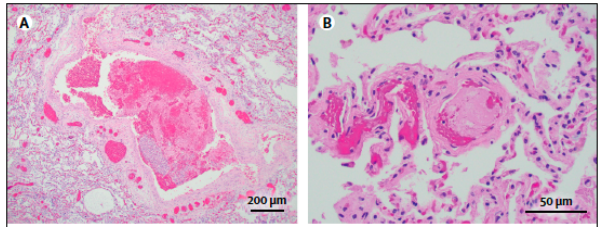

High incidence of

deep vein thrombosis *and* pulmonary embolism

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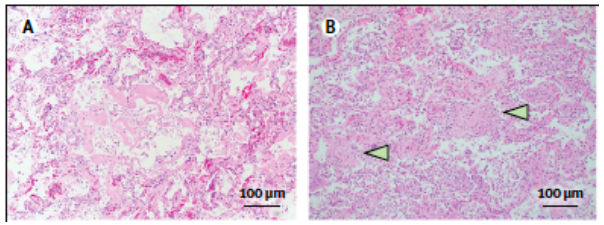

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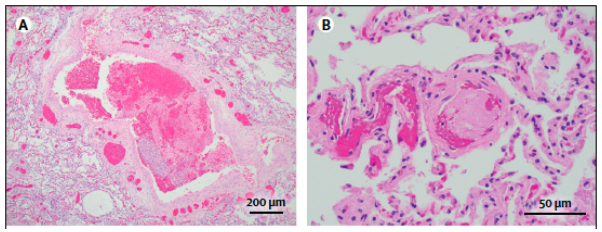

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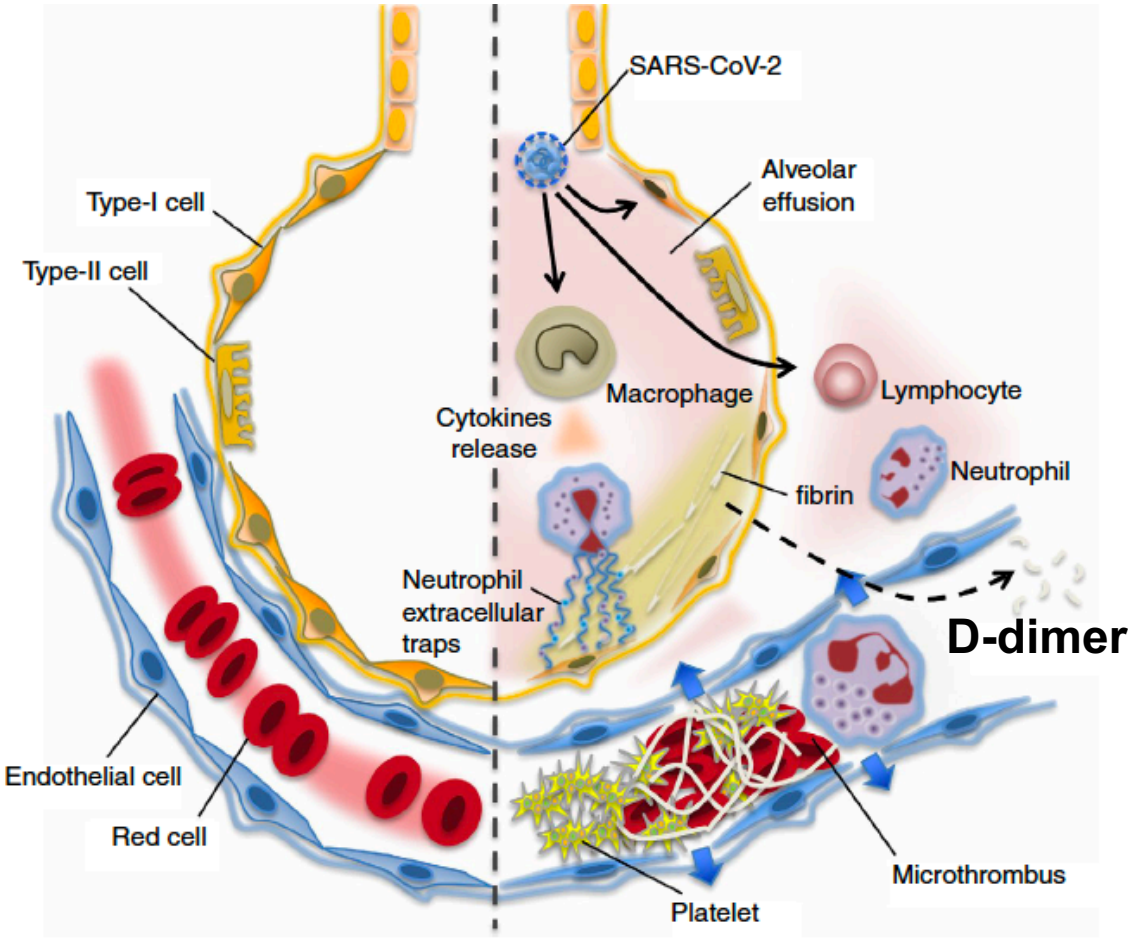

COVID19 coagulopathy in Caucasian patients

Helen Fogarty,[1,2,3] Liam Townsend,[4] Cliona Ni Cheallaigh,[4] Colm Bergin,[4] Ignacio Martin-Loeches,[1,5] Paul Browne,[6] Christopher L. Bacon,[6] Richard Gaule,[6] Alexander Gillett,[6] Mary Byrne,[2] Kevin Ryan,[2] Niamh O'Connell,[2] Jamie M. O'Sullivan,[1] Niall Conlon[7] and James S. O'Donnell[1,2,3,6]

British Journal of Haematology, 2020, **189**, 1044–1049

Received 22 April 2020

83 COVID19 patients, survivors *vs.* non-survivors, Dublin, Ireland

	Survivors and non-ICU $n = 50$	Non-survivors and/or ICU $n = 33$	P value
On admission			
PT (s)	12·6 (11·7–14·5)	12·9 (12·2–14·5)	0·11
APTT (s)	31.3 (29.3-33.1)	30.4 (28.2-32.2)	0.52
Fibrinogen (g/l)	4·5 (3·7–6·2)	5·6 (4·4–6·6)	0·045*
D-dimer (nanogram/ml)	804 (513–1290)	1003 (536·5–1782)	0·018*
Platelets ($\times 10^9$/l)	201 (161–251)	196 (153–289)	0·47
C-reactive protein (mg/l)	37·9 (7·9–92·1)	94·8 (35–158·5)	0·0005***

D-dimers levels:

consistent with progressive activation of coagulation and fibrinolysis ***within the lungs.***

Do not typically develop overt DIC; **rare** DIC cases: ***late-stage disease***.

The diffuse bilateral pulmonary inflammation is associated with a **novel pulmonary-specific vasculopathy**

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The source of elevated plasma D-dimer levels in COVID-19 infection

Beverley J. Hunt[1] Marcel Levi[2]

Br J Haematol. 2020 Aug;190(3):e133-e134.

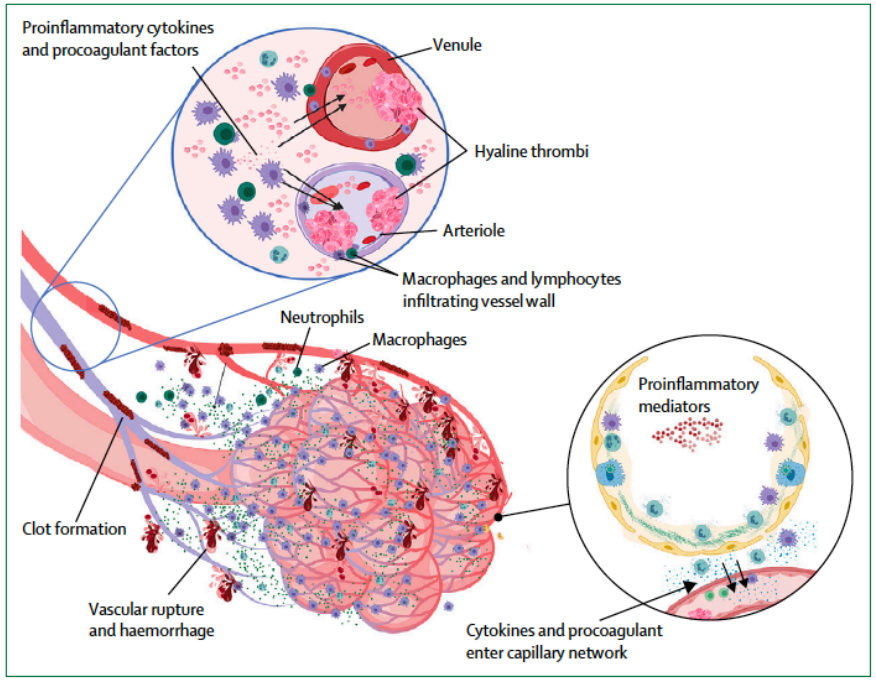
We suggest that **D-dimer** levels **represent the degree/extent of lung inflammation** present within the lungs in COVID-19 infection. This would explain why they relate to outcome.

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;
2: e437–45

Published Online
May 7, 2020



Extensive alveolar and interstitial inflammation
sharing features with macrophage activation syndrome

Lung-restrictive vascular immunothrombosis
associated with COVID-19
as diffuse **pulmonary intravascular coagulopathy**,
distinct from DIC,
distinct from macrophage activation syndrome.

Increased circulating D-dimers
(reflecting pulmonary vascular bed thrombosis with fibrinolysis)
with normal platelet and fibrinogen levels
are the key early features

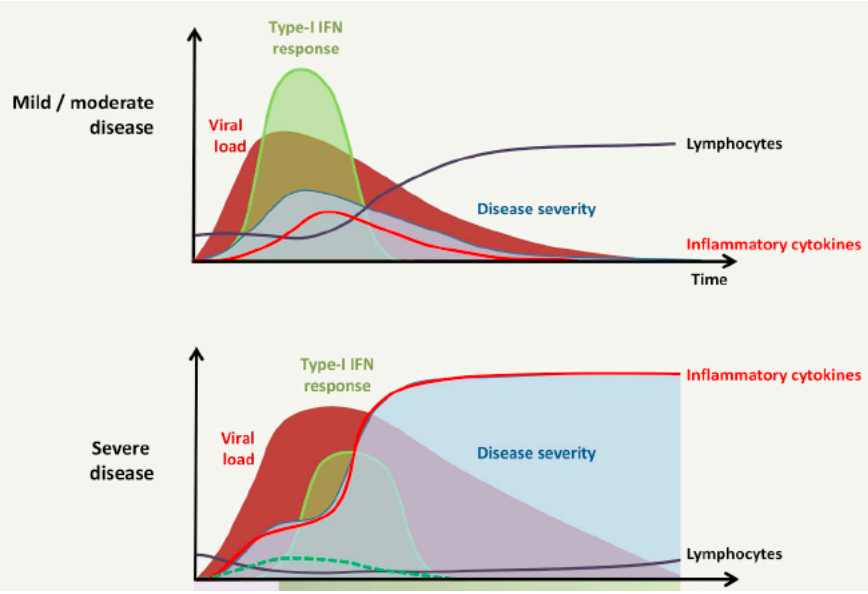
Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

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†

Lancet 2020; 395: 497–506

Published Online
January 24, 2020

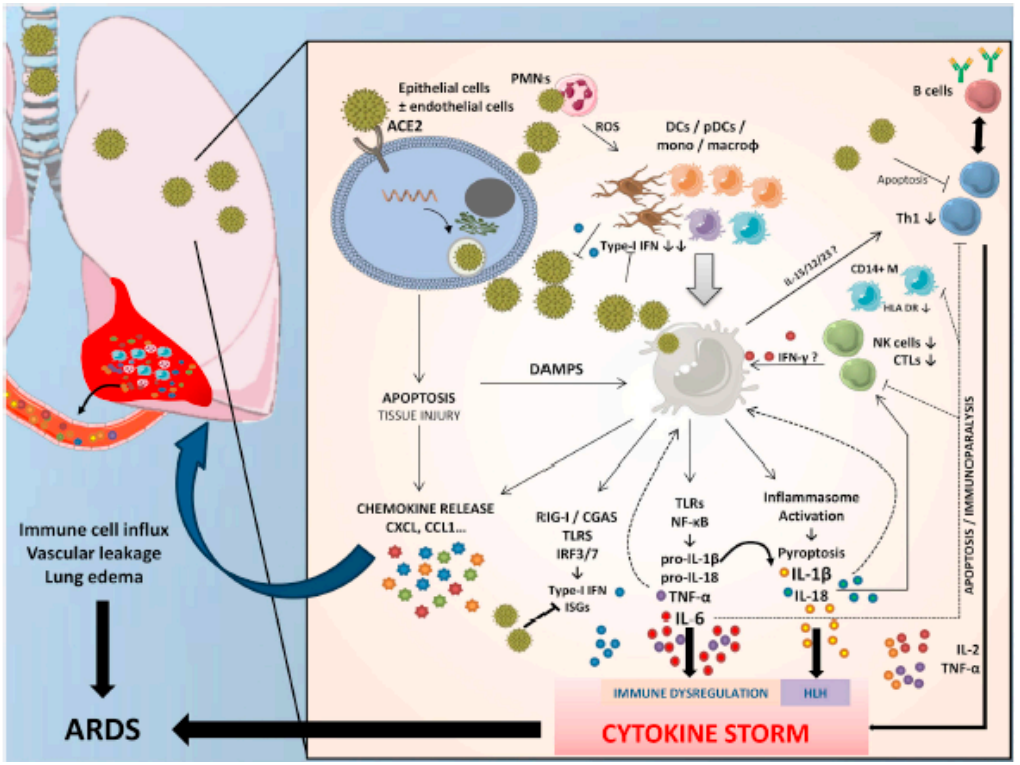
The COVID-19 « cytokine storm »



In-hospital COVID-19 patients:

high values of
IL1β, IL1RA, IFNγ, TNFα;
IL7, IL8, IL10, GCSF, GMCSF, PDFG, and VEGF;

ICU patients: higher values of
TNFα, IL2, IL7, IL10, GCSF, MCP1, MIP1A



Clinical and Translational Report

Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure

Evangelos J. Giamarellos-Bourboulis,[1,10,*] Mihai G. Netea,[2,3] Nikoletta Rovina,[4] Karolina Akinosoglou,[5] Anastasia Antoniadou,[1] Nikolaos Antonakos,[1] Georgia Damoraki,[1] Theologia Gkavogianni,[1] Maria-Evangelia Adami,[1] Paraskevi Katsaounou,[6] Maria Ntaganou,[4] Magdalini Kyriakopoulou,[4] George Dimopoulos,[7] Ioannis Koutsodimitropoulos,[8] Dimitrios Velissaris,[5] Panagiotis Koufargyris,[1] Athanassios Karageorgos,[1] Konstantina Katrini,[1] Vasileios Lekakis,[1] Mihaela Lupse,[9] Antigone Kotsaki,[1] George Renieris,[1] Danai Theodoulou,[4] Vassiliki Panou,[4] Evangelia Koukaki,[4] Nikolaos Koulouris,[4] Charalambos Gogos,[5] and Antonia Koutsoukou[4]

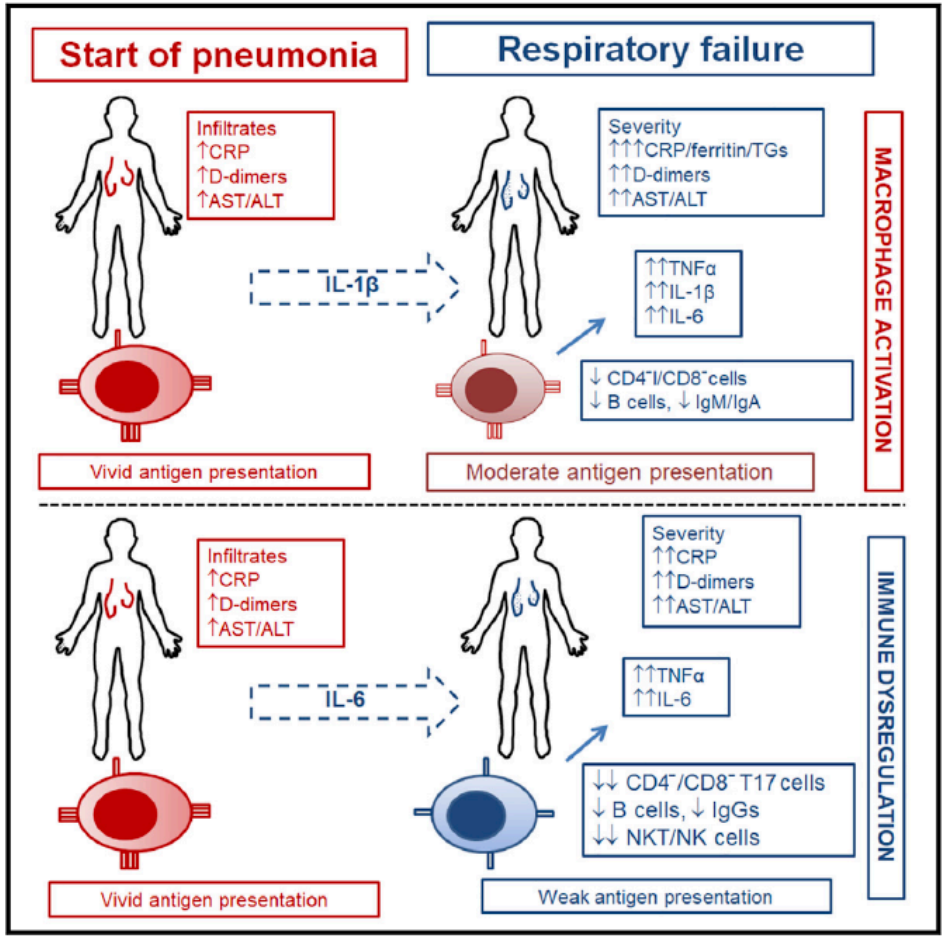
Cell Host & Microbe 27, 992–1000, June 10, 2020

Severe COVID-19 patients:
macrophage activation syndrome *OR* immune dysregulation.

Severe respiratory failure:
major decrease of HLA-DR on CD14 monocytes.

CD14 and NK cells cytopenia characteristics of severe COVID-19.

IL-6 blocker Tocilizumab *only partially recues*
SARS-CoV-2-associated immune dysregulation

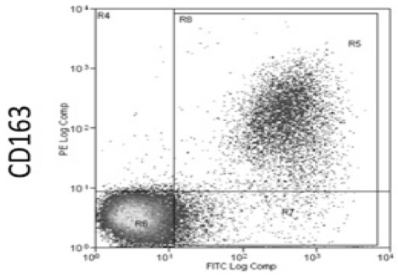


Unique pattern of immune dysregulation in severe COVID-19:
IL-6-mediated low HLA-DR expression and lymphocytopenia
associated with sustained cytokine production and hyper-inflammation

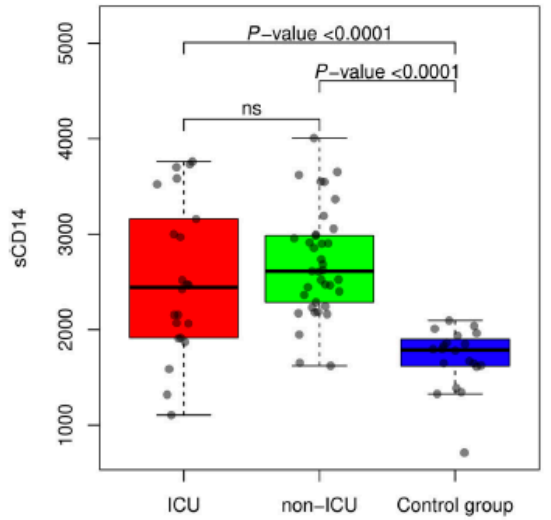
Increased Serum Levels of sCD14 and sCD163 Indicate a Preponderant Role for Monocytes in COVID-19 Immunopathology

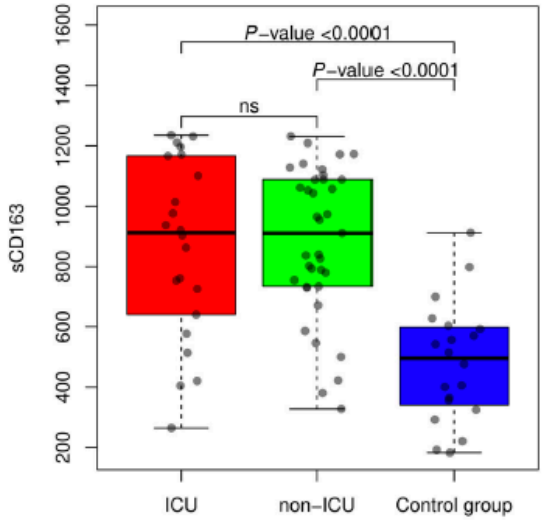
Jose Gómez-Rial[1,2†], Maria José Currás-Tuala[1†], Irene Rivero-Calle[1,3], Alberto Gómez-Carballa[1,4], Miriam Cebey-López[1], Carmen Rodríguez-Tenreiro[1], Ana Dacosta-Urbieta[1,3], Carmen Rivero-Velasco[5], Nuria Rodríguez-Núñez[6], Rocio Trastoy-Pena[7], Javier Rodríguez-García[8], Antonio Salas[1,4] and Federico Martinón-Torres[1,3*]*

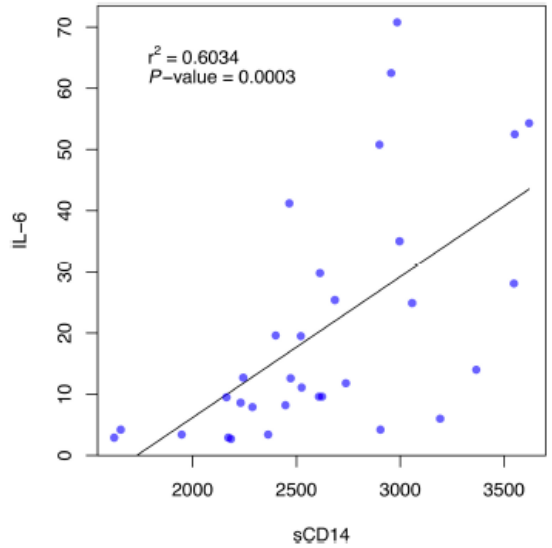
Front Immunol 2020; 11:560381 (Sept. 23).



Data suggesting a preponderant role for monocyte-macrophage activation in the development of immunopathology of COVID-19 in patients







nature medicine

An inflammatory cytokine signature predicts COVID-19 severity and survival

Diane Marie Del Valle[1,2,3,14], Seunghee Kim-Schulze[1,2,3,4,14], Hsin-Hui Huang[5,6,7,14], Noam D. Beckmann[8], Sharon Nirenberg[8,9], Bo Wang[10], Yonit Lavin[10], Talia H. Swartz[10], Deepu Madduri[10], Aryeh Stock[11], Thomas U. Marron[2,3,10], Hui Xie[1], Manishkumar Patel[1], Kevin Tuballes[1], Oliver Van Oekelen[8], Adeeb Rahman[1,2,3,8], Patricia Kovatch[8,9], Judith A. Aberg[10], Eric Schadt[8], Sundar Jagannath[10], Madhu Mazumdar[5,6,7], Alexander W. Charney[8], Adolfo Firpo-Betancourt[11], Damodara Rao Mendu[11], Jeffrey Jhang[11], David Reich[12], Keith Sigel[10], Carlos Cordon-Cardo[11], Marc Feldmann[13], Samir Parekh[3,4,10], Miriam Merad[1,2,3,4,10] and Sacha Gnjatic[1,2,3,4,10,11] ✉

Nat Med 2020;26(10):1636-1643.

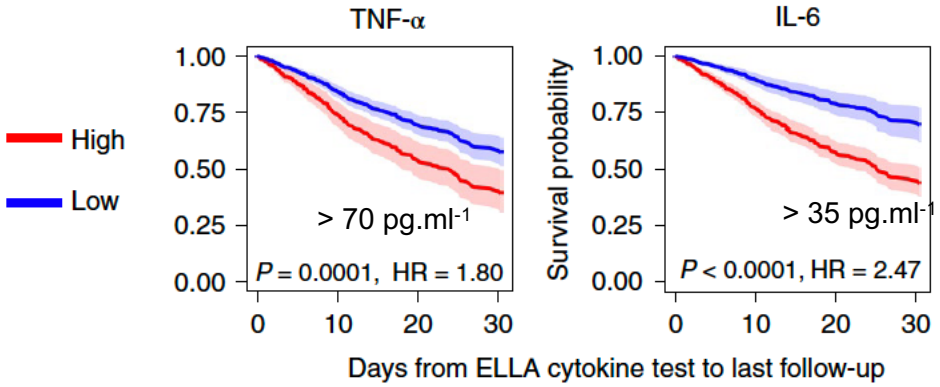
1,484 patients,
Mount Sinai Health System in New York city,
March 21 – April 28 2020.

SARS-CoV-2:
similarities to cytokine-release syndrome
in patients with cancer
treated with CAR-T cells

▼

Quantification of IL-6, IL-8, TNFα, IL1β
using the ELLA rapid ELISA microfluidic system

TNFα and **IL-6** serum levels:
independent* and significant predictors
of disease severity and death



- adjusted on multiple parameters,

D-dimer levels being not independent predictors

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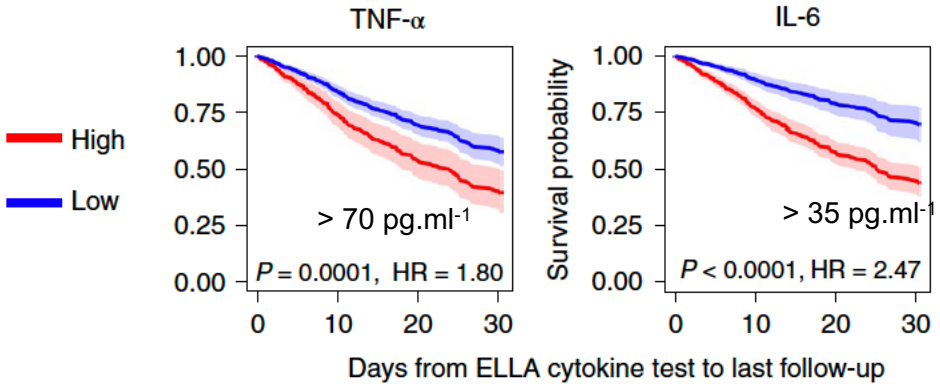


- adjusted on multiple parameters,

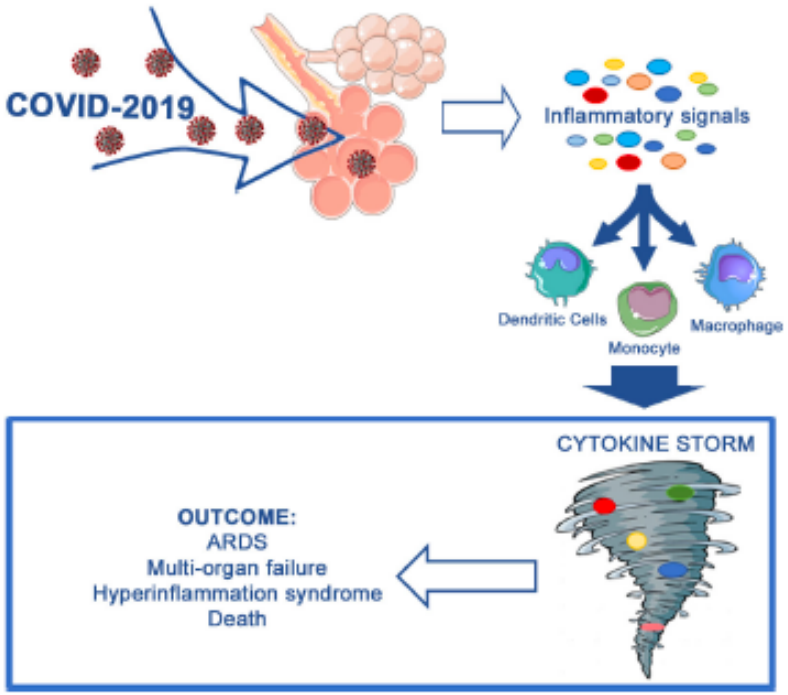
D-dimer levels being not independent predictors

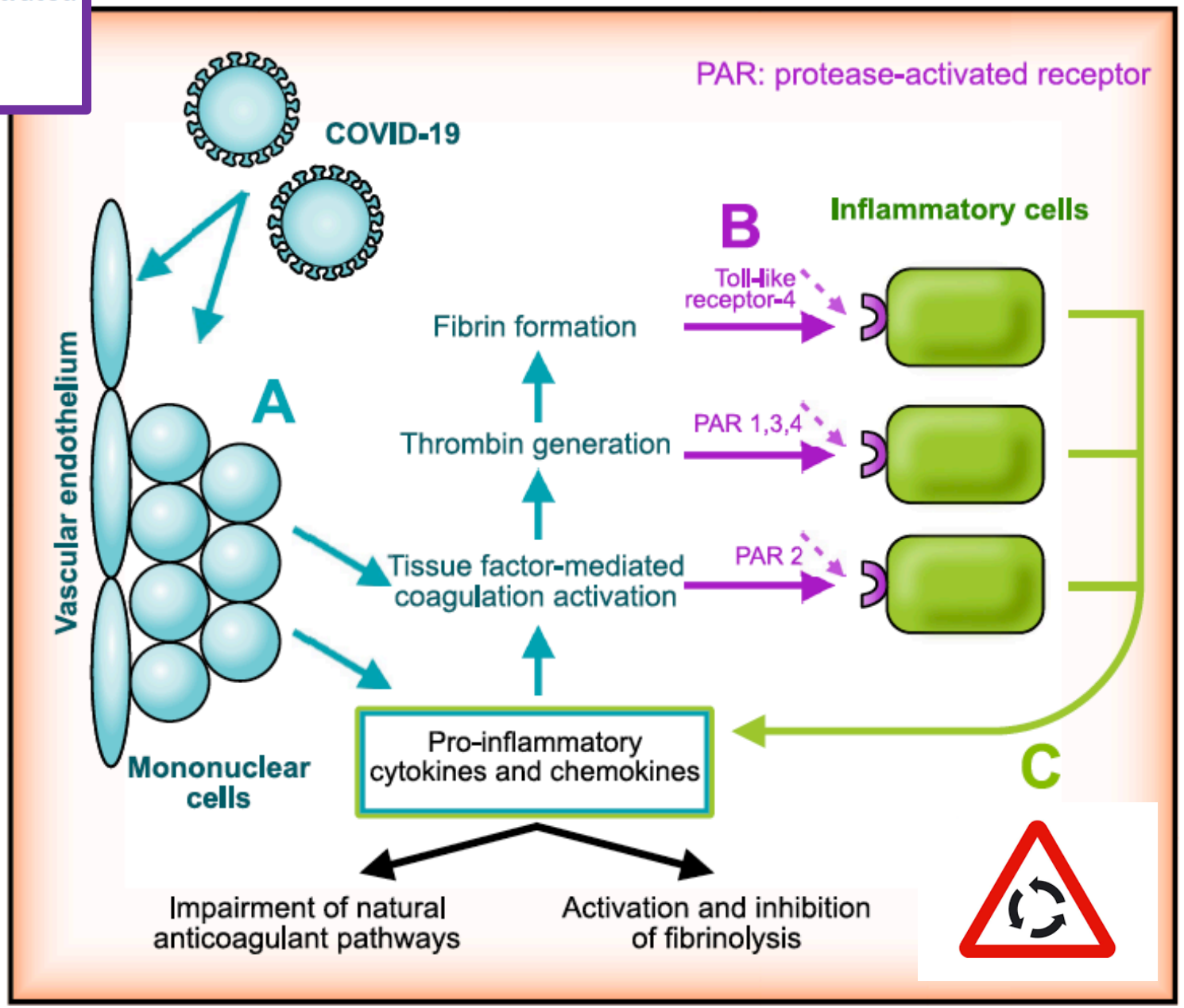
SARS-CoV-2 infection lungs ▶ Immune cells ▶ Coagulation & fibrinolysis activation ▶ D-dimers

Thrombosis and coagulopathy in COVID-19: An illustrated review

Marcel Levi MD, PhD[1] | Beverley J. Hunt MD, FRCP, FRCPath OBE[2]

Res Pract Thromb Haemost 2020;4(5):744-751.





CORONAVIRUS

Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients

Jérôme Hadjadj[1,2*], Nader Yatim[2,3*], Laura Barnabei[1], Aurélien Corneau[4], Jeremy Boussier[3], Nikaïa Smith[3], Hélène Péré[5,6], Bruno Charbit[7], Vincent Bondet[3], Camille Chenevier-Gobeaux[8], Paul Breillat[2], Nicolas Carlier[9], Rémy Gauzit[10], Caroline Morbieu[2], Frédéric Pène[11,12], Nathalie Marin[12], Nicolas Roche[9,11], Tali-Anne Szwebel[2], Sarah H. Merkling[13], Jean-Marc Treluyer[14,15], David Veyer[6,16], Luc Mouthon[2,11], Catherine Blanc[4], Pierre-Louis Tharaux[5], Flore Rozenberg[11,17], Alain Fischer[1,18,19], Darragh Duffy[3,7]†, Frédéric Rieux-Laucat[1]†, Solen Kernéis[10,20,21]†, Benjamin Terrier[2,5]†‡

Science **369**, 718–724 (2020) 7 August 2020

Severe and critical patients:

Highly impaired interferon (IFN) type 1 response

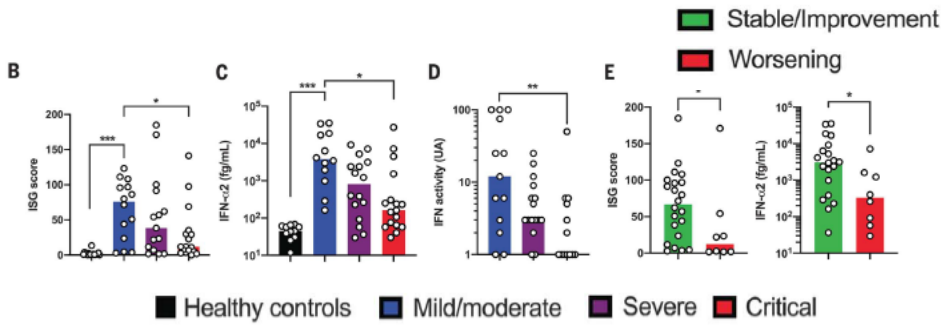
no IFN-β, low IFN-α,

associated with:

persistent blood viral load

exacerbated inflammatory response.

increased TNF-α and IL-6 production and signalling



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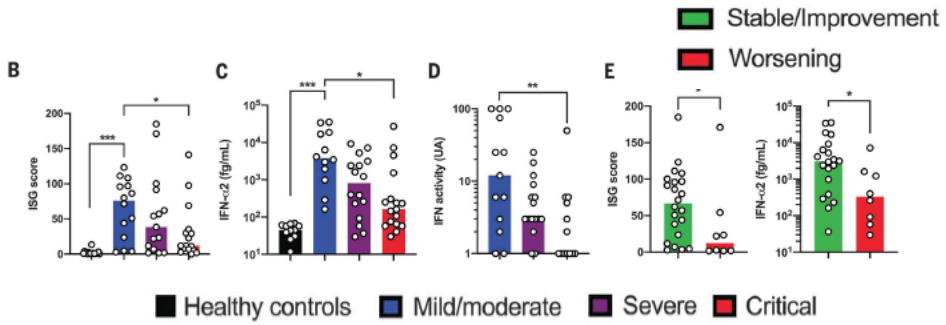


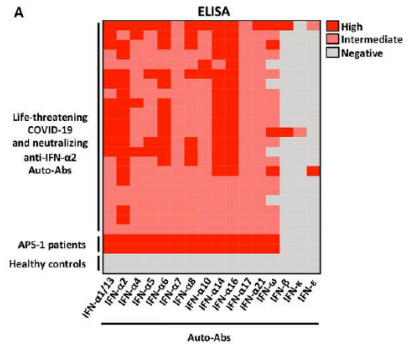
Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard[1,2,3*†], Lindsey B. Rosen[4†], Qian Zhang[3‡], Eleftherios Michailidis[5‡], Hans-Heinrich Hoffmann[5‡], Yu Zhang[4‡], Karim Dorgham[6‡], Quentin Philippot[1,2‡], Jérémie Rosain[1,2‡], Vivien Béziat[1,2,3‡], Jérémy Manry[1,2], Elana Shaw[4], Liis Haljasmägi[7], Pärt Peterson[7], Lazaro Lorenzo[1,2], Lucy Bizien[1,2], Sophie Trouillet-Assant[8,9], Kerry Dobbs[4], Adriana Almeida de Jesus[4], Alexandre Belot[10,11,12], Anne Kallaste[13], Emilie Catherinot[14], Yacine Tandjaoui-Lambiotte[15], Jeremie Le Pen[5], Gaspard Kerner[1,2], Benedetta Bigio[3], Yoann Seeleuthner[1,2], Rui Yang[3], Alexandre Bolze[16], András N. Spaan[3,17], Ottavia M. Delmonte[4], Michael S. Abers[4], Alessandro Aiuti[18], Giorgio Casari[18], Vito Lampasona[18], Lorenzo Piemonti[18], Fabio Ciceri[18], Kaya Bilguvar[19], Richard P. Lifton[19,20,21], Marc Vasse[22], David M. Smadja[23], Mélanie Migaud[1,2], Jérome Hadjadj[24], Benjamin Terrier[25], Darragh Duffy[26], Lluis Quintana-Murci[27,28], Diederik van de Beek[29], Lucie Roussel[30,31], Donald C. Vinh[30,31], Stuart G. Tangye[32,33], Filomeen Haerynck[34], David Dalmau[35], Javier Martinez-Picado[36,37,38], Petter Brodin[39,40], Michel C. Nussenzweig[41,42], Stéphanie Boisson-Dupuis[1,2,3], Carlos Rodríguez-Gallego[43,44], Guillaume Vogt[45], Trine H. Mogensen[46,47], Andrew J. Oler[48], Jingwen Gu[48], Peter D. Burbelo[49], Jeffrey Cohen[50], Andrea Biondi[51], Laura Rachele Bettini[51], Mariella D'Angio[51], Paolo Bonfanti[52], Patrick Rossignol[53], Julien Mayaux[54], Frédéric Rieux-Laucat[24], Eystein S. Husebye[55,56,57], Francesca Fusco[58], Matilde Valeria Ursini[59], Luisa Imberti[59], Alessandra Sottini[59], Simone Paghera[59], Eugenia Quiros-Roldan[60], Camillo Rossi[61], Riccardo Castagnoli[62], Daniela Montagna[63,64], Amelia Licari[62], Gian Luigi Marseglia[62], Xavier Duval[65,66,67,68,69], Jade Ghosn[68,69], HGID Lab§, NIAID-USUHS Immune Response to COVID Group§, COVID Clinicians§, COVID-STORM Clinicians§, Imagine COVID Group§, French COVID Cohort Study Group§, The Milieu Intérieur Consortium§, CoV-Contact Cohort§, Amsterdam UMC Covid-19 Biobank§, COVID Human Genetic Effort§, John S. Tsang[70,71], Raphaela Goldbach-Mansky[4], Kai Kisand[7], Michail S. Lionakis[4], Anne Puel[1,2,3], Shen-Ying Zhang[1,2,3], Steven M. Holland[4]¶, Guy Gorochov[6,72]¶, Emmanuelle Jouanguy[1,2,3]¶, Charles M. Rice[5]¶, Aurélie Cobat[1,2,3]¶, Luigi D. Notarangelo[4]¶, Laurent Abel[1,2,3]¶, Helen C. Su[4]#, Jean-Laurent Casanova[1,2,3,42,73]*#

Science. 2020 Sep 24:eabd4585.

At least 101/987 patients (10%)
with life-threatening COVID-19 pneumonia:
neutralising IgG auto-Abs
against IFN-α or the 13 types of IFN-α.

The auto-Abs neutralise
the ability of the corresponding type I IFN-α
to block SARS-CoV-2 infection in vitro.

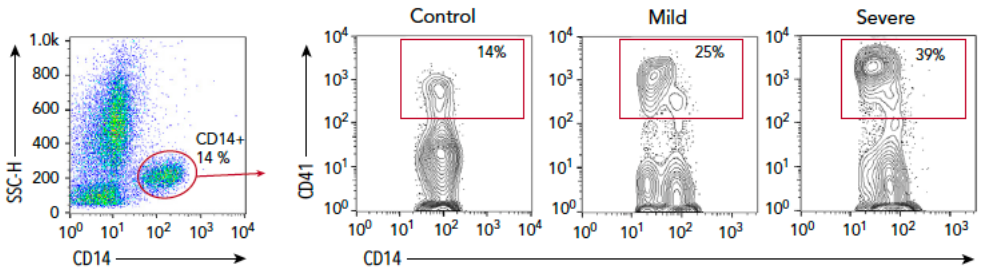


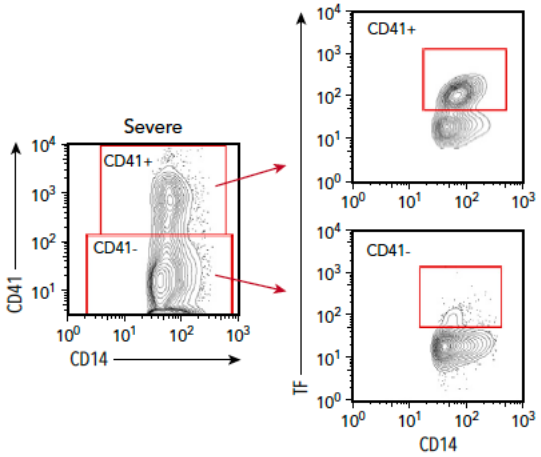
Apart from D-dimers…

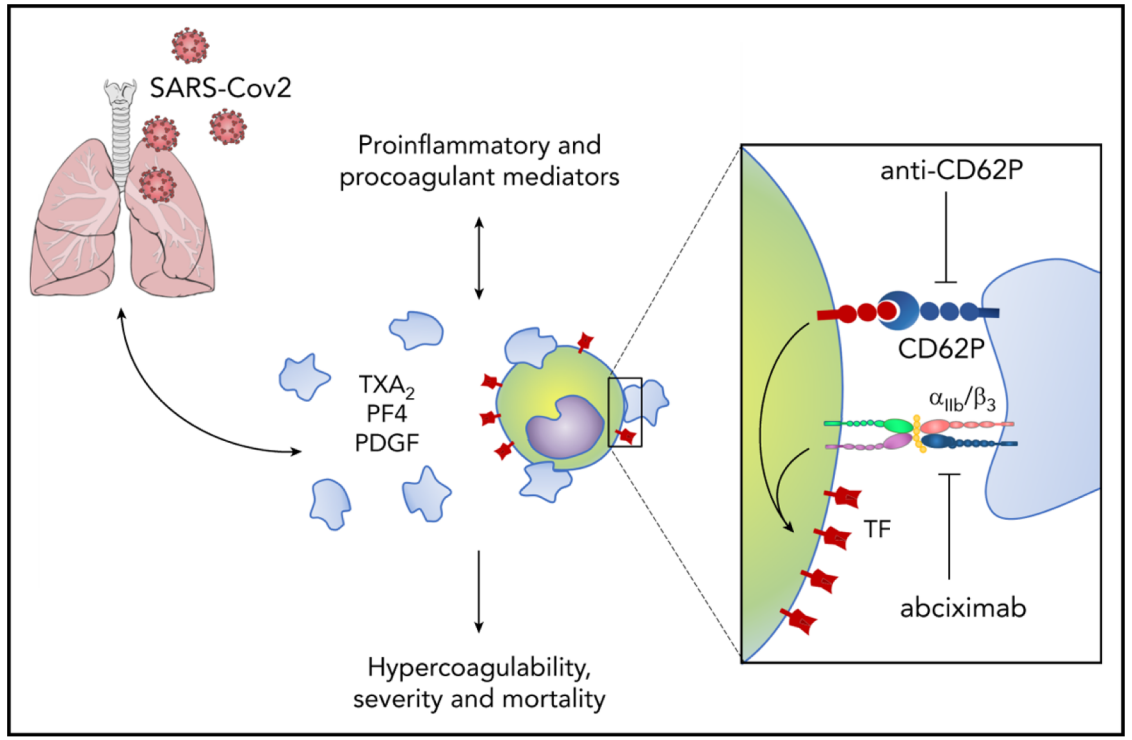
Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19

Eugenio D. Hottz,[1,2] Isaclaudia G. Azevedo-Quintanilha,[1] Lohanna Palhinha,[1] Lívia Teixeira,[1] Ester A. Barreto,[1] Camila R. R. Pão,[1] Cassia Righy,[3,4] Sérgio Franco,[3] Thiago M. L. Souza,[1,5] Pedro Kurtz,[3,6] Fernando A. Bozza,[4,6] and Patrícia T. Bozza[1]

Blood 2020;136:1330-41.







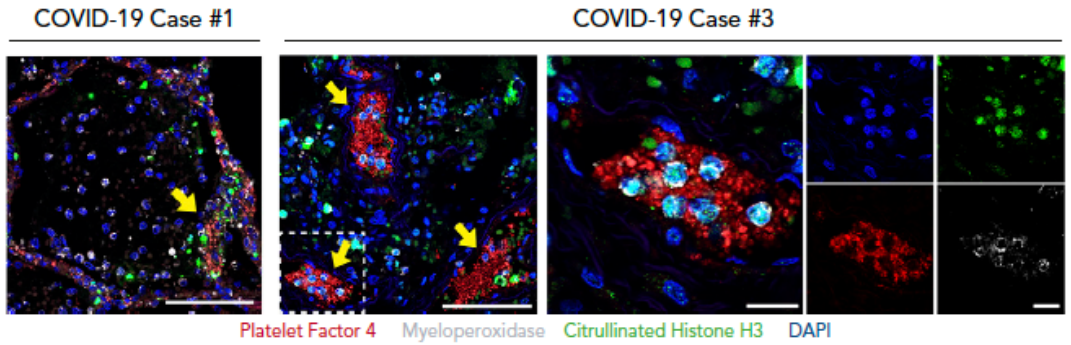
Increased platelet activation and platelet-monocyte aggregate formation associated with poor outcome in severe COVID-19 patients

Platelets from severe COVID-19 patients induce monocyte TF expression through P-selectin and integrin α_{IIb}/β_3 signaling

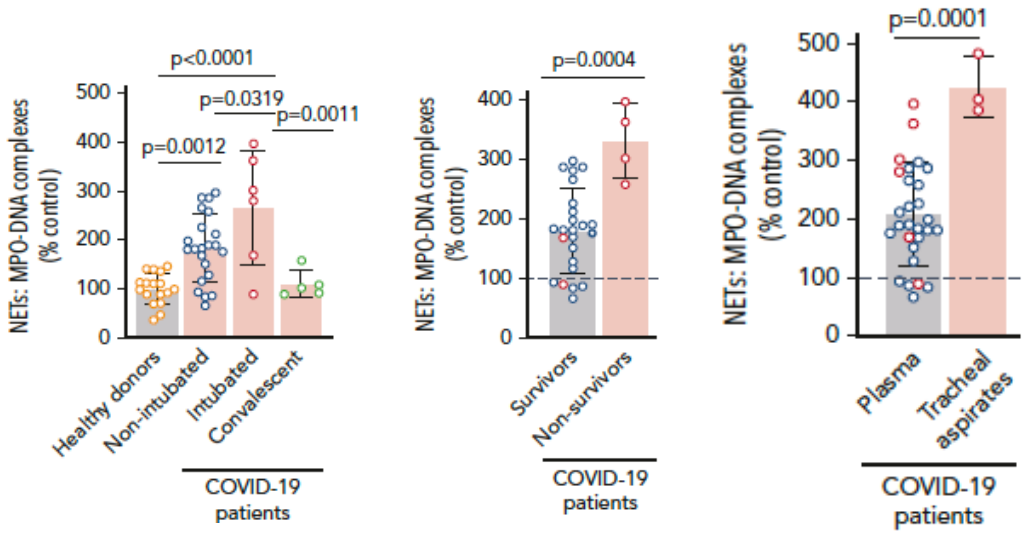
Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome

Elizabeth A. Middleton,[1,2] Xue-Yan He,[3] Frederik Denorme,[1] Robert A. Campbell,[1,2] David Ng,[3] Steven P. Salvatore,[4,5] Maria Mostyka,[4] Amelia Baxter-Stoltzfus,[4] Alain C. Borczuk,[4,5] Massimo Loda,[4,5] Mark J. Cody,[1,6] Bhanu Kanth Manne,[1] Irina Portier,[1] Estelle S. Harris,[2] Aaron C. Petrey,[1,7] Ellen J. Beswick,[2] Aleah F. Caulin,[8] Anthony Iovino,[6,8] Lisa M. Abegglen,[6,8] Andrew S. Weyrich,[1,2] Matthew T. Rondina,[1,2,9,10] Mikala Egeblad,[3] Joshua D. Schiffman,[1,6,8,*] and Christian Con Yost[1,6,*]

***Blood*. 2020;136(10):1169-1179**



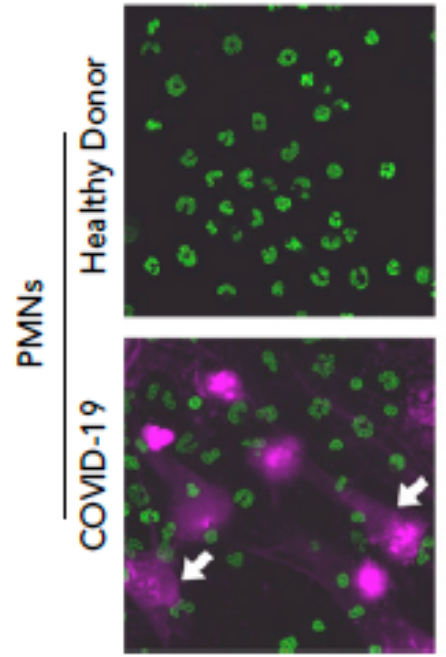
COVID-19 autopsies



Plasma myeloperoxydase-DNA complexes

NETs contribute
to **microthrombi**
through platelet-neutrophil
interactions
in COVID-19 ARDS

NET formation *ex vivo*
in COVID-19 neutrophils



A component of thrombotic microangiopathy

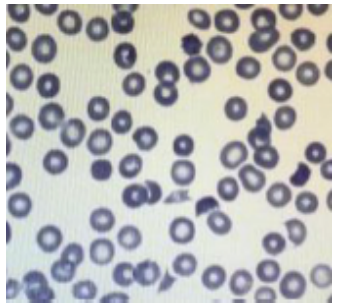
*low **ADAMTS-13***

A relative ADAMTS13 deficiency supports the presence of a secondary microangiopathy in COVID 19

Nicola Martinelli[a], Martina Montagnana[b], Francesca Pizzolo[a], Simonetta Friso[a], Gian Luca Salvagno[b], Gian Luca Forni[c], Barbara Gianesin[c], Matteo Morandi[a], Claudio Lunardi[a], Giuseppe Lippi[b], Enrico Polati[d], Oliviero Olivieri[a], Lucia De Franceschi[a,*]

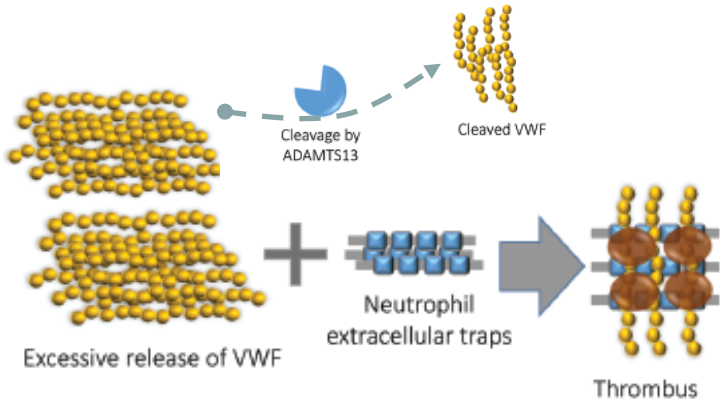
Thrombosis Research 193 (2020) 170–172

	COVID-19 pts (*n*=50)	Normal range values
ADAMTS 13 activity (%) *	47 (40-55)	60-130



Schistocytes

Endothelitis



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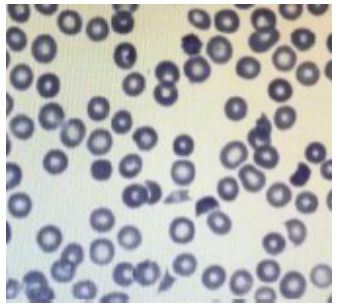

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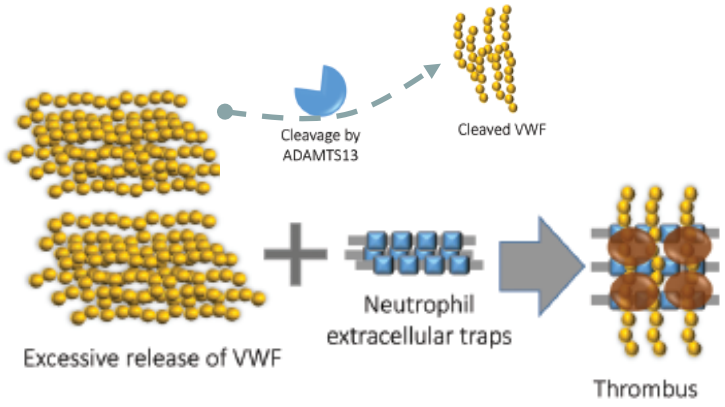
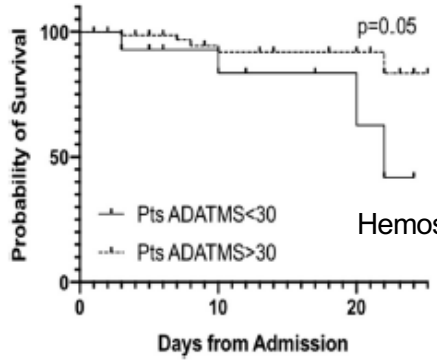


Low ADAMTS 13 plasma levels are predictors of mortality in COVID-19 patients

Internal and Emergency Medicine (2020) 15:861–863

Mario Bazzan[1] · Barbara Montaruli[2] · Savino Sciascia[3] · Domenico Cosseddu[2] · Claudio Norbiato[4] · Dario Roccatello[3]

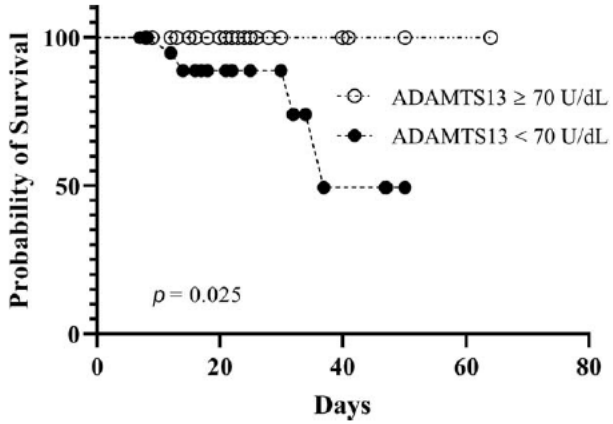


HemosIL Acustar ADAMTS13 activity

Reduction of ADAMTS13 Levels Predicts Mortality in SARS-CoV-2 Patients

Giovanni L. Tiscia[1] Giovanni Favuzzi[1] Antonio De Laurenzo[1] Filomena Cappucci[1] Lucia Fischetti[1] Lazzaro di Mauro[2] Giuseppe Miscio[2] Antonio Mirijello[3] Elena Chinni[1] Elvira Grandone[1] on behalf of CSS COVID-19 Group*

TH Open 2020;4(3):e203-e206



Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study

George Goshua*, Alexander B Pine*, Matthew L Meizlish*, C-Hong Chang, Hanming Zhang, Parveen Bahel, Audrey Baluha, Noffar Bar, Robert D Bona, Adrienne J Burns, Charles S Dela Cruz, Anne Dumont, Stephanie Halene, John Hwa, Jonathan Koff, Hope Menninger, Natalia Neparidze, Christina Price, Jonathan M Siner, Christopher Tormey, Henry M Rinder, Hyung J Chun*, Alfred I Lee*

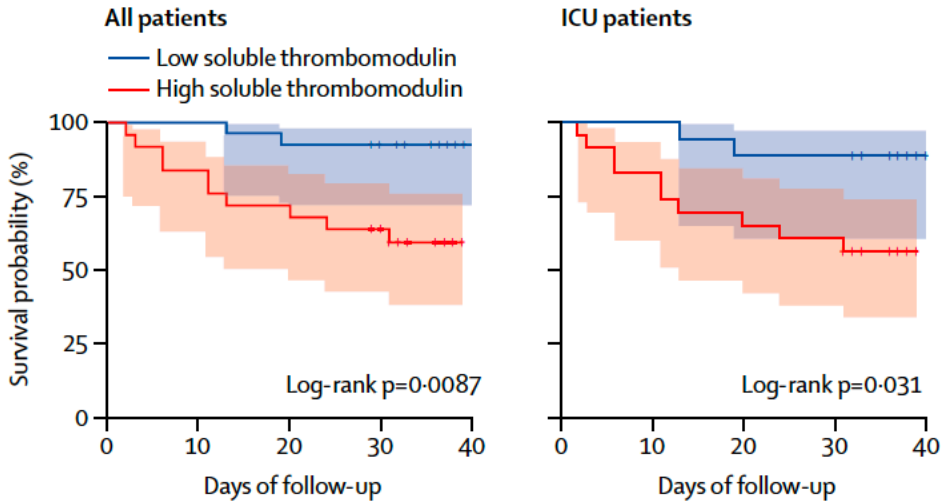
Lancet Haematol 2020; 7: e575–82

Single-center cross-sectional study
COVID-19 patients: 48 in ICU
20 non-ICU
13 non-hospitalised controls

Markers of endothelial cells and platelet activation

Preserved endogenous anticoagulant activity
Preserved antifibrinolytic activity

Increased:
VWF, sP-selectin, sCD40L
s-thrombomodulin (sTM)

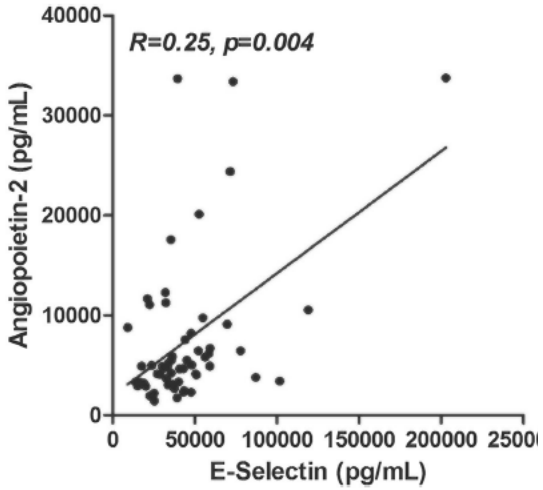


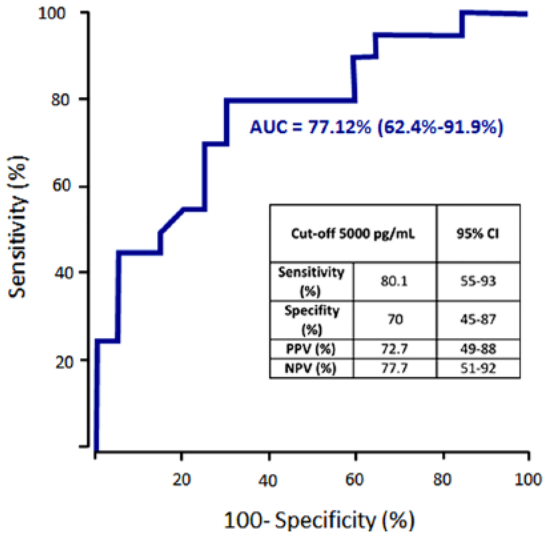
High s-TM blood concentrations (>3.26 ng.ml^{-1})
associated with impaired survival

Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients

David M. Smadja[1,2] · Coralie L. Guerin[1,3] · Richard Chocron[4,5] · Nader Yatim[6,7] · Jeremy Boussier[6,7] · Nicolas Gendron[1,2] · Lina Khider[8] · Jérôme Hadjadj[7,9] · Guillaume Goudot[8] · Benjamin Debuc[10] · Philippe Juvin[11] · Caroline Hauw-Berlemont[12] · Jean-Loup Augy[12] · Nicolas Peron[12] · Emmanuel Messas[4,13] · Benjamin Planquette[1,14] · Olivier Sanchez[1,14] · Bruno Charbit[15] · Pascale Gaussem[1,16] · Darragh Duffy[6,7] · Benjamin Terrier[17,18] · Tristan Mirault[4,13] · Jean-Luc Diehl[1,19]

Angiogenesis (2020) 23:611–620





Angiogenesis

Angiopoietin 2,

a marker of endothelial activation,

is a relevant predictive factor for ICU admission.

Reinforces the hypothesis of

COVID-19-associated microvascular dysfunction

Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients

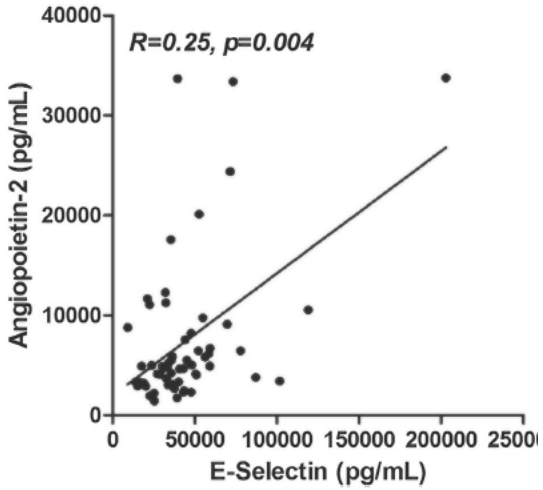
David M. Smadja[1,2] · Coralie L. Guerin[1,3] · Richard Chocron[4,5] · Nader Yatim[6,7] · Jeremy Boussier[6,7] · Nicolas Gendron[1,2] · Lina Khider[8] · Jérôme Hadjadj[7,9] · Guillaume Goudot[8] · Benjamin Debuc[10] · Philippe Juvin[11] · Caroline Hauw-Berlemont[12] · Jean-Loup Augy[12] · Nicolas Peron[12] · Emmanuel Messas[4,13] · Benjamin Planquette[1,14] · Olivier Sanchez[1,14] · Bruno Charbit[15] · Pascale Gaussem[1,16] · Darragh Duffy[6,7] · Benjamin Terrier[17,18] · Tristan Mirault[4,13] · Jean-Luc Diehl[1,19]

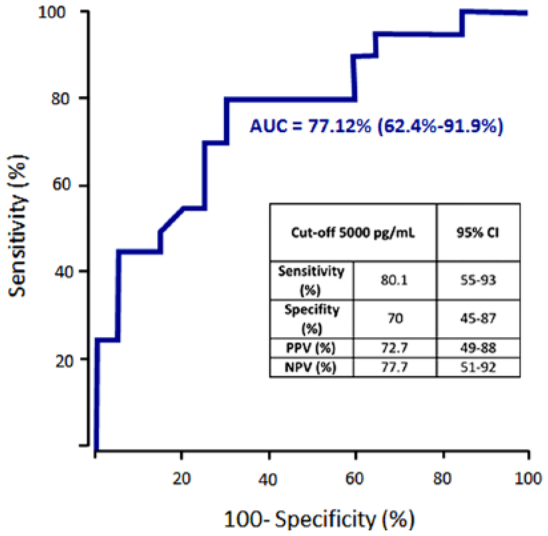
Angiogenesis (2020) 23:611–620

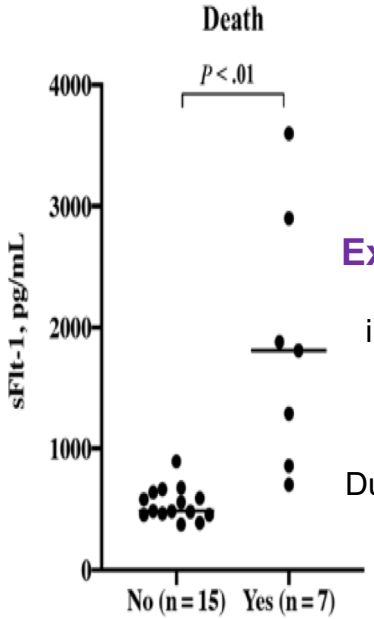
Angiogenesis:

Angiopoietin 2, sFlt1

Reinforces the hypothesis of **COVID-19-associated microvascular dysfunction**







Excess sFlt1

in critically ill COVID-19 patients.

Dupont V. *et al.*

Clin Infect Dis 2020; Jul 16:ciaa1007

Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients

David M. Smadja[1,2] · Coralie L. Guerin[1,3] · Richard Chocron[4,5] · Nader Yatim[6,7] · Jeremy Boussier[6,7] · Nicolas Gendron[1,2] · Lina Khider[8] · Jérôme Hadjadj[7,9] · Guillaume Goudot[8] · Benjamin Debuc[10] · Philippe Juvin[11] · Caroline Hauw-Berlemont[12] · Jean-Loup Augy[12] · Nicolas Peron[12] · Emmanuel Messas[4,13] · Benjamin Planquette[1,14] · Olivier Sanchez[1,14] · Bruno Charbit[15] · Pascale Gaussem[1,16] · Darragh Duffy[6,7] · Benjamin Terrier[17,18] · Tristan Mirault[4,13] · Jean-Luc Diehl[1,19]

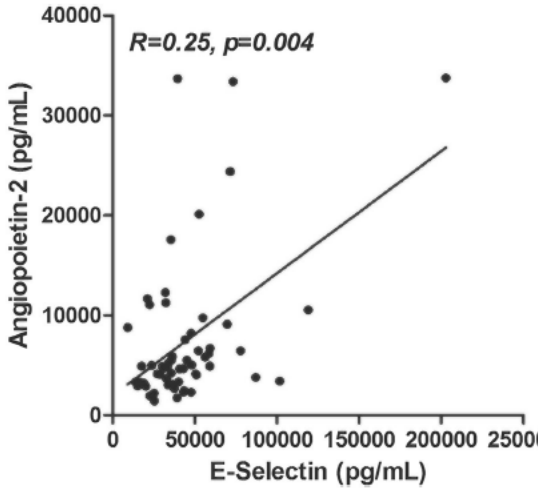
Angiogenesis (2020) 23:611–620

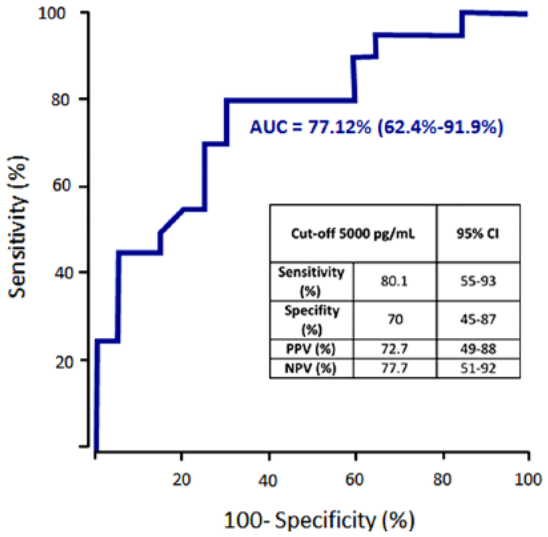
Angiogenesis:

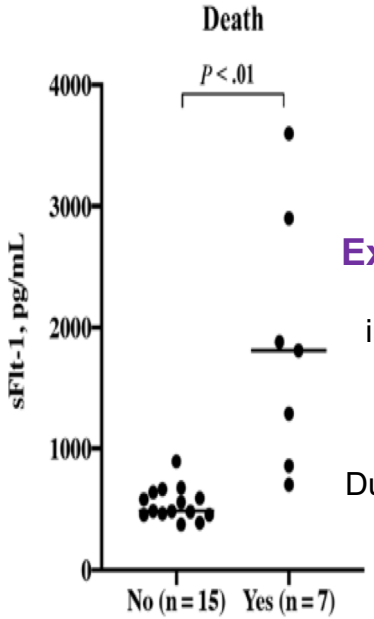
Angiopoietin 2, sFlt1

Endothelial cells

Reinforces the hypothesis of **COVID-19-associated microvascular dysfunction**







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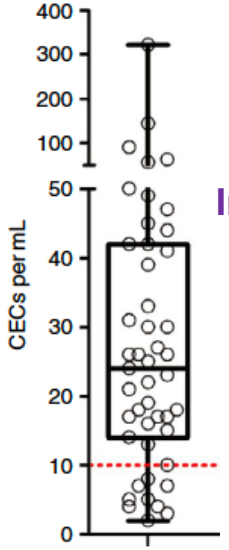
Dupont V. *et al.*

Clin Infect Dis 2020; Jul 16:ciaa1007



Increased number of circulating endothelial cells

in COVID-19 patients.

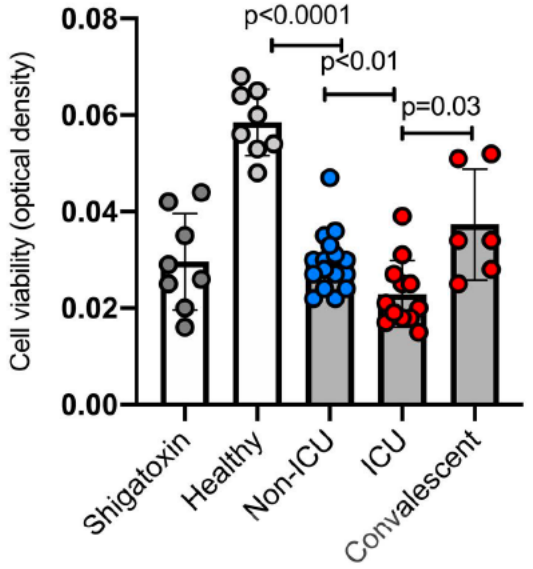
Khider L. *et al.*

J Thromb Haemost 2020; 18:2391-9

Endotheliopathy is induced by plasma from critically-ill patients and associated with organ failure in severe COVID-19

Rauch A, Dupont A, Goutay J, Caplan M, Staessens S, Moussa M, Jeanpierre E, Corseaux D, Lefevre G, Lassalle F, Faure K, Lambert M, Duhamel A, Labreuche J, Garrigue D, De Meyer SF, Staels B, Van Belle E, Vincent F, Kipnis E, Lenting P, Poissy J, Susen S; Lille Covid Research Network(LICORNE)

Circulation. 2020 Sep 24. doi: 10.1161/CIRCULATIONAHA.120.050907



Direct and rapid cytotoxic effect of plasma on pulmonary microvascular **endothelial cells**

Cultured human pulmonary microvascular endothelial cells
+
patient's platelet poor, plasma;

Incubation: 1 hour;
Assessment of mitochondrial activity.

Endotheliopathy is induced by plasma from critically-ill patients and associated with organ failure in severe COVID-19

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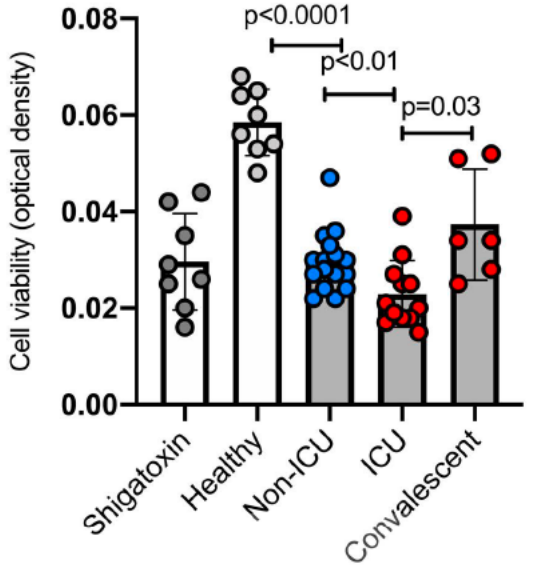

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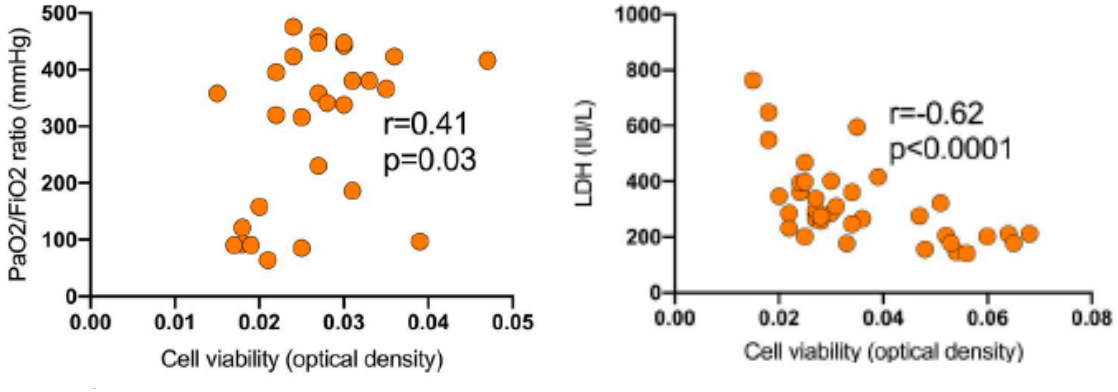
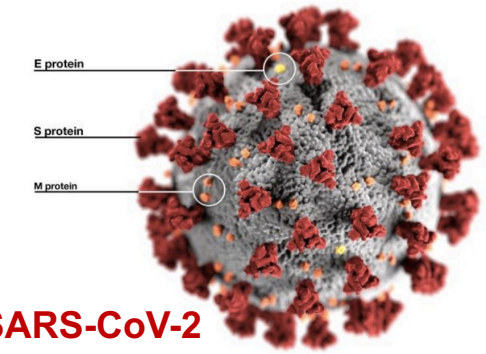
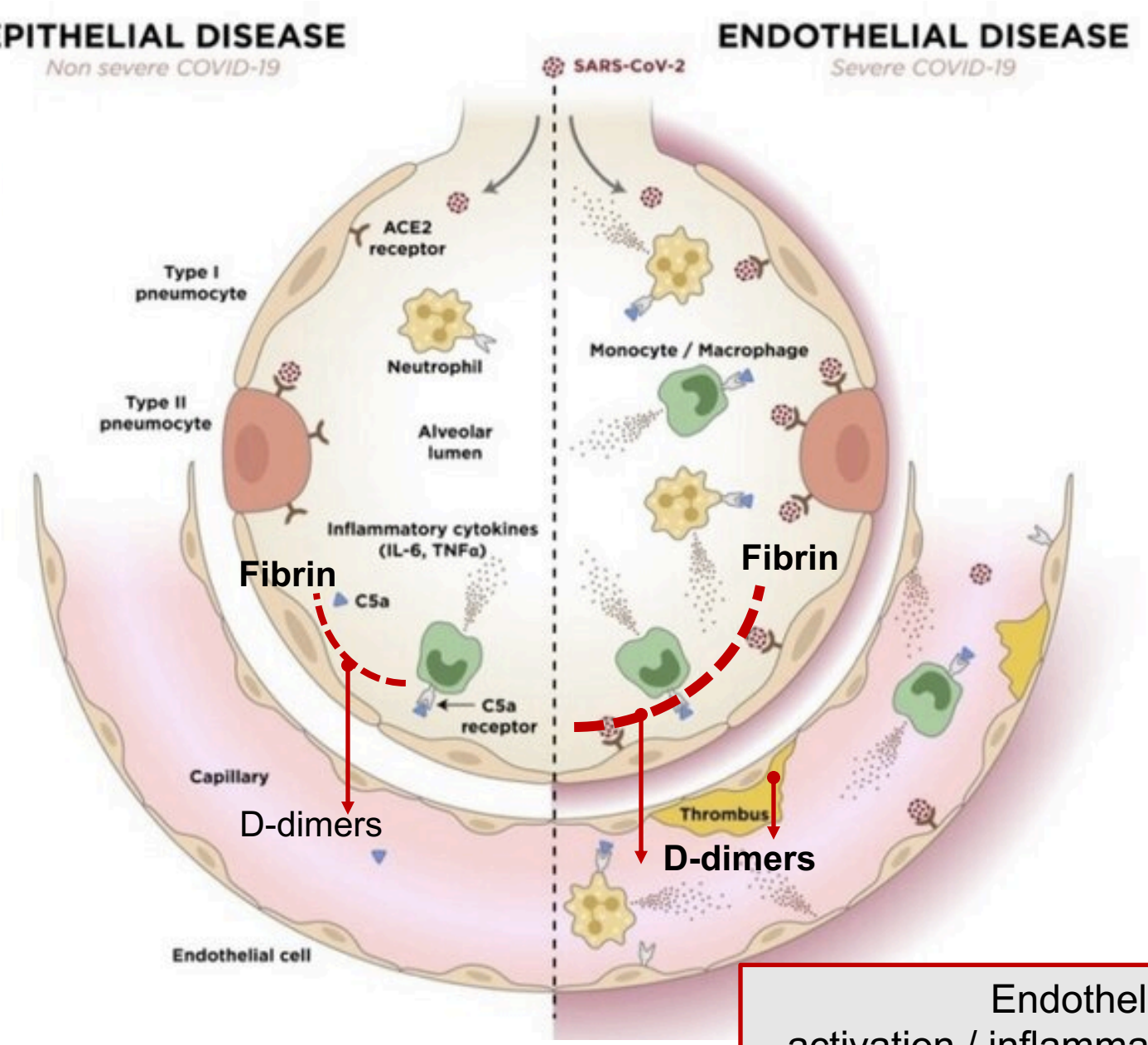


Higher cytotoxic effect of plasma associated with a more pronounced hypoxaemia and organ dysfunction



SARS-CoV-2



Endothelial
activation / inflammation / damage

Antiphospholipid antibodies

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

COVID-19 CASES

Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19

N Engl J Med 2020;382(17):e38.

Characteristic	Patient 1	Patient 2	Patient 3
Demographic characteristics			
Age — yr	69	65	70
Sex	Male	Female	Male
Antiphospholipid antibodies	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG	Anticardiolipin IgA, anti–β_2-glycoprotein I IgA and IgG
Imaging features	Multiple cerebral infarctions in bilateral frontal parietal occipital lobe and bilateral basal ganglia, brain stem, and bilateral cerebellar hemispheres	Multiple cerebral infarctions in right frontal and bilateral parietal lobe	Multiple cerebral infarctions in frontal lobe, right frontal parietal temporal occipital lobe, and bilateral cerebellar hemispheres

First,
a cartoonish paving stone thrown into the pond

Very severely compromised patients
Multiple arterial thrombosis

Solid-phase aPL Ab, IgA isotype
LA not detected

No idea of aPL Ab titers;
No idea of aPL Ab persistence

JAMA Network | Open

Research Letter | Pathology and Laboratory Medicine

Assessment of Lupus Anticoagulant Positivity in Patients With Coronavirus Disease 2019 (COVID-19)

Morayma Reyes Gil, MD, PhD; Mohammad Barouqa, MD; James Szymanski, MD; Jesus D. Gonzalez-Lugo, MD; Shafia Rahman, MD; Henny H. Billett, MD

JAMA Network Open. 2020;3(8):e2017539.

COVID-19:
high prevalence of a positive LA

Retrospective
187 patients with LA testing, March 1 - April 30, 2020; Montefiore hospital, Bronx, NY City

LA-positive rate (dRVVT):

COVID-19 negative: 22% (27/119)
thrombosis in 34%
COVID-19 positive: 44% (30/68)
thrombosis in 63%
higher CRP levels

Adjustement for CRP levels: ***LA*** *associated with* ***thrombosis****,* OR 4.39 (1.45-14.6)

Presence of antiphospholipid antibodies in COVID-19: case series study

Luis M Amezcua-Guerra ,[1] Gustavo Rojas-Velasco,[2]
Malinalli Brianza-Padilla,[1] Armando Vázquez-Rangel,[2]
Ricardo Márquez-Velasco,[1] Francisco Baranda-Tovar,[2] Rashidi Springall,[1]
Hector Gonzalez-Pacheco,[2] Yaneli Juárez-Vicuña,[1] Claudia Tavera-Alonso,[2]
Fausto Sanchez-Muñoz,[1] Marisol Hernández-Salas[2]

[1]Immunology, Instituto Nacional de Cardiología Ignacio Chavez, Mexico City, Mexico
[2]Intensive Care Unit, Instituto Nacional de Cardiología Ignacio Chavez, Mexico City, Mexico

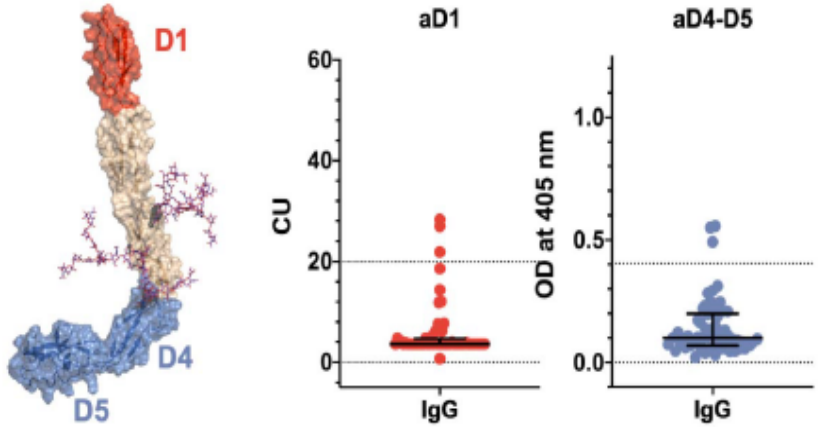
Ann Rheum Dis 2020; Aug 4. doi: annrheumdis-2020-218100.

As high as 57%
of both « criteria *and* non-criteria » positive aPL Abs
in patients with severe and critical COVID-19!

Prevalence, specificity, and clinical association of anti-phospholipid antibodies in COVID-19 patients: *are the antibodies really guilty?*

Maria Orietta Borghi[*,†], Asmaa Beltagy[*,‡], Emirena Garrafa[§,¶], Daniele Curreli[*], Germana Cecchini[**], Caterina Bodio[*], Claudia Grossi[*], Simonetta Blengino[††], Angela Tincani[‡‡], Franco Franceschini[‡‡], Laura Andreoli[‡‡], Maria Grazia Lazzaroni[‡‡], Silvia Piantoni[‡‡], Stefania Masneri[‡‡], Francesca Crisafulli[‡‡], Duilio Brugnoni[¶], Maria Lorenza Muiesan[§§], Massimo Salvetti[§§], Gianfranco Parati[††], Erminio Torresani[**], Michael Mahler[¶¶], Francesca Heilbron[††], Francesca Pregnolato[*], Martino Pengo[††], Francesco Tedesco[*], Nicola Pozzi[***,#], Pier Luigi Meroni[*,#]

medRxiv 2020; Jun 19. doi: 2020.06.17.20134114.



Differences and doubts

122 patients, Lombardia, Italy

anti-β2GP1 IgG/IgA/IgM: *the most frequent*
15.6% / 6.6% / 9.0%

No association of aPL Abs with thrombosis

Anti-β2GPI-D1 and anti-β2GPI-D4-D5: **rare;**
only 5.3% aPL Ab positive sera.

COVID-19: aPLAbs mainly directed against β2GP1,
but display epitope specificity different from aPL Abs in APS

jth

Antiphospholipid antibodies in patients with COVID-19: A relevant observation?

Katrien M. J. Devreese[1,2] | Eleni A. Linskens[1] | Dominique Benoit[3] | Harlinde Peperstraete[3]

J Thromb Haemost 2020; Jul 3. doi:10.1111/jth.14994.

Differences and doubts

Prospective

COVID-19 patients admitted to the ICU
Ghent university hospital, Blegium

Patients were **mainly single LA-positive**

No clear relation with thrombosis

Triple positivity and high aCL/ab2GP1 titers: *very rare*

aPL Abs are mostly transient

(LA: 9/10 negative on a second occasion)

LETTER TO THE EDITOR

jth

Coagulopathy of COVID-19 and antiphospholipid antibodies

Nathan T. Connell[1,2]
Elisabeth M. Battinelli[1,2]
Jean M. Connors[1,2]

J Thromb Haemost. 2020 May 7:10.1111/jth.14893.

Strong doubts…

Letter to the Editors-in-Chief

Lupus Anticoagulant (LAC) testing in patients with inflammatory status: Does C-reactive protein interfere with LAC test results?

Sofie M.E. Schouwers
Katrien M.J. Devreese*

Thrombosis Research 125 (2010) 102–104

« False-positive LA testing might be expected in patients with COVID-19 given the marked elevation of CRP. Many assays to detect LA are sensitive to CRP, resulting in false positive results. »

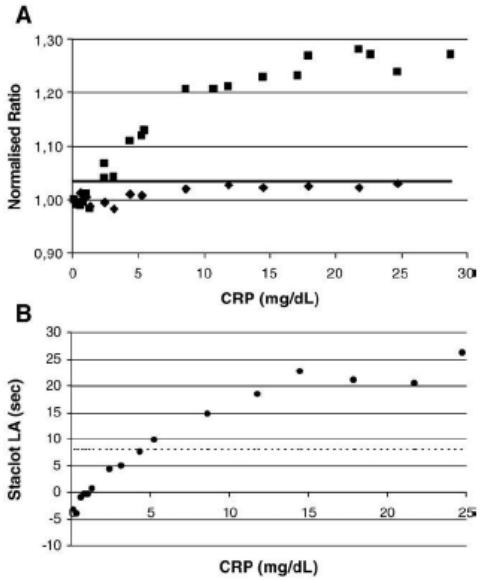


Fig. 1. Influence of CRP on LA-screen, PTT-LA and Staclot-LA. (A) LA-Screen and PTT-LA expressed as normalised ratios; (B) Staclot-LA in seconds. ■ PTT-LA; ♦ LA-Screen; ● Staclot-LA. The full line indicates the cut-off values for PTT-LA (1.035) and dRVVT (1.034). The dashed line indicates the cut-off value for Staclot-LA (8 sec).

COVID-19 and aPL Abs:

apart from striking case reports,
no methodologically correct prospective work
allowing to support
a direct link between a SARS-CoV-2-mediated aPL Ab induction
and thrombotic events.

Treatment: antithrombotics

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]

J Thromb Haemost. 2020;18:1094–1099.

Received: 20 March 2020

28-days mortality, multivariate analysis, ***all patients:***
heparin use 1.65 (0.93-2.92) p=0.088, **NS**…

Tongji hospital, China
Reprospective study
449 patients with severe COVID-19
at least one of:
respiratory rate > 30/min
$SaO_2 \leq 93\%$;
$PaO_2/FiO_2 \leq 300$ mm Hg
99 received heparin, for at least 7 days
criteria???
« prophylactic LMWH dose in most of the users »

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criteria???
« prophylactic LMWH dose in most of the users »

« Heparin treatment appears to be associated with better prognosis in severe COVID-19 patients with coagulopathy »

28-days mortality, sub-group analysis:

Patients with	28-day mortality: Treating with heparin, %	28-day mortality: Nontreating with heparin, %	Univariate analysis: Odds ratio (95% CI)	Univariate analysis: *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 > 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).

SIC: sepsis-induced coagulopathy, ISTH'score

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	

The association between treatment with heparin and survival in patients with Covid-19

Luis Ayerbe[1,2] · Carlos Risco[3] · Salma Ayis[4,5]

Journal of Thrombosis and Thrombolysis (2020) 50:298–301

Published online: 31 May 2020

17 Spanish hospitals
Retrospective study

2,075 patients admitted with COVID-19
March 1st- April 20th 2020

Heparin use in 1,734

Criteria?
Dose? Duration?

Heparin use: lower in-hospital mortality

aOR* 0.42 (0.26-0.66) p<0.001

**adjusted for age, gender, SaO_2<90%, temperature > 37°C, and other treatments.*

Mortality in heparin-treated patients: 14%.

In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation

Annabel Blasi[1] | Fien A. von Meijenfeldt[2] | Jelle Adelmeijer[2] | Andrea Calvo[1] | Cristina Ibañez[1] | Juan Perdomo[1] | Juan C. Reverter[3] | Ton Lisman[2]

J Thromb Haemost. 2020;18:2646–2653.

Received: 11 June 2020

Hospital Clinic Barcelona, Spain
23 COVID-19 patients (11:ward, 12: ICU)
LMWH enoxaparin

No	10%
< 0.5 mg/kg/d	30%
0.5-1.5 mg/kg/d	40%
≥ 1.5 mg/kg/d	20%

Despite LMWH treatments:

Thrombin Generation Test, rTF 5pmol/L: **N°**
Deficient in ICU patients
(but much higher anti-Xa activities…)

ROTEM: largely **within the normal r**ange

Clot Lysis Time: **higher values**
No difference ward *vs.* ICU

High values of
D-dimers, thrombin-antithrombin TAT
and plasmin-antiplasmin PAP complexes

Persistent in vivo activation of coagulation and fibrinolysis despite anticoagulant therapy;
low therapeutic anticoagulant regimens are often insufficient to downregulate coagulation activation

Heparin resistance in COVID-19 patients in the intensive care unit

D. White[1] · S. MacDonald[1] · T. Bull[1] · M. Hayman[1] · R. de Monteverde-Robb[2] · D. Sapsford[2] · A. Lavinio[3] · J. Varley[3] · A. Johnston[3] · M. Besser[1] · W. Thomas[1]

Journal of Thrombosis and Thrombolysis (2020) 50:287–291

Retrospective study
15 patients, ICU, Cambridge, UK

In vitro recovery: ratio of observed increase in anti-Xa activity
of patient sample from baseline
on
normal supplemented pooled plasma from baseline

Patient number	In-vitro percentage recovery of anti-Xa
Normal pooled plasma	100
1	73
2	61
3	70
4	58
5	82
6	72
7	69
8	68
9	83
10	82
11	72
12	79

Evidence of heparin resistance in critically unwell COVID-19 patients;
***optimal thromboprophylaxis*?**

Inadequate prophylactic effect of low-molecular weight heparin in critically ill COVID-19 patients

K. Stattin [a,*], M. Lipcsey [a,b], H. Andersson [a], E. Pontén [a], S. Bülow Anderberg [a], A. Gradin [a], A. Larsson [c], N. Lubenow [d], M. von Seth [a], S. Rubertsson [a], M. Hultström [a,e], R. Frithiof [a]

Journal of Critical Care 60 (2020) 249–252

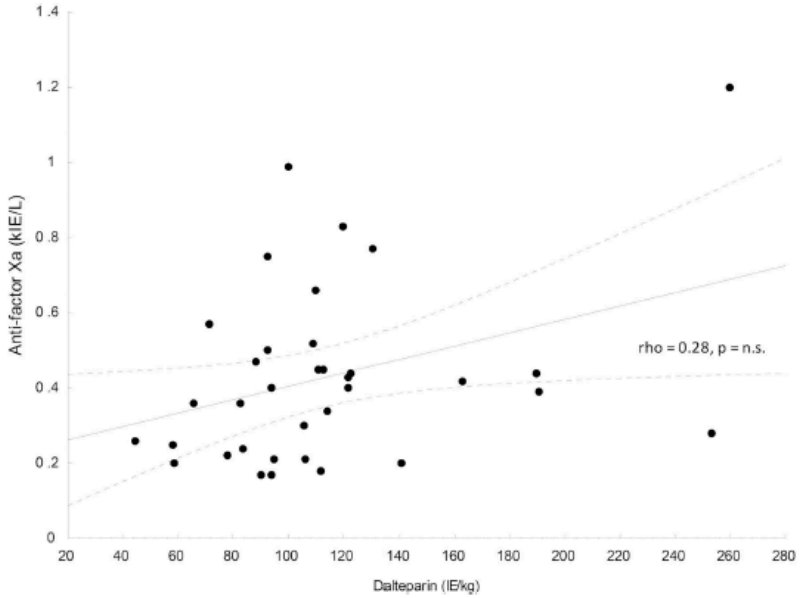
Uppsala, Sweden
31 COVID-19 patients, ICU

Dalteparin (Fragmin®) sc
< 70kg: 5,000 IU
70-90 kg: 7,500 IU
> 90kg: 10,000 IU

Anti-FXa activity target range: 0.2-0.4 IU/ml

5 patients had a symptomatic VTE event

No significant correlation between LMWH dose and anti-FXa activity



Anti-Xa **below** the target range: **23%** of the patients
Anti-Xa **above** the target range: **46%** of the patients

Standard prophylactic doses of LMWH may be insufficient
Monitoring LMWH effect? Interpreting in relation to risk is difficult…

Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis

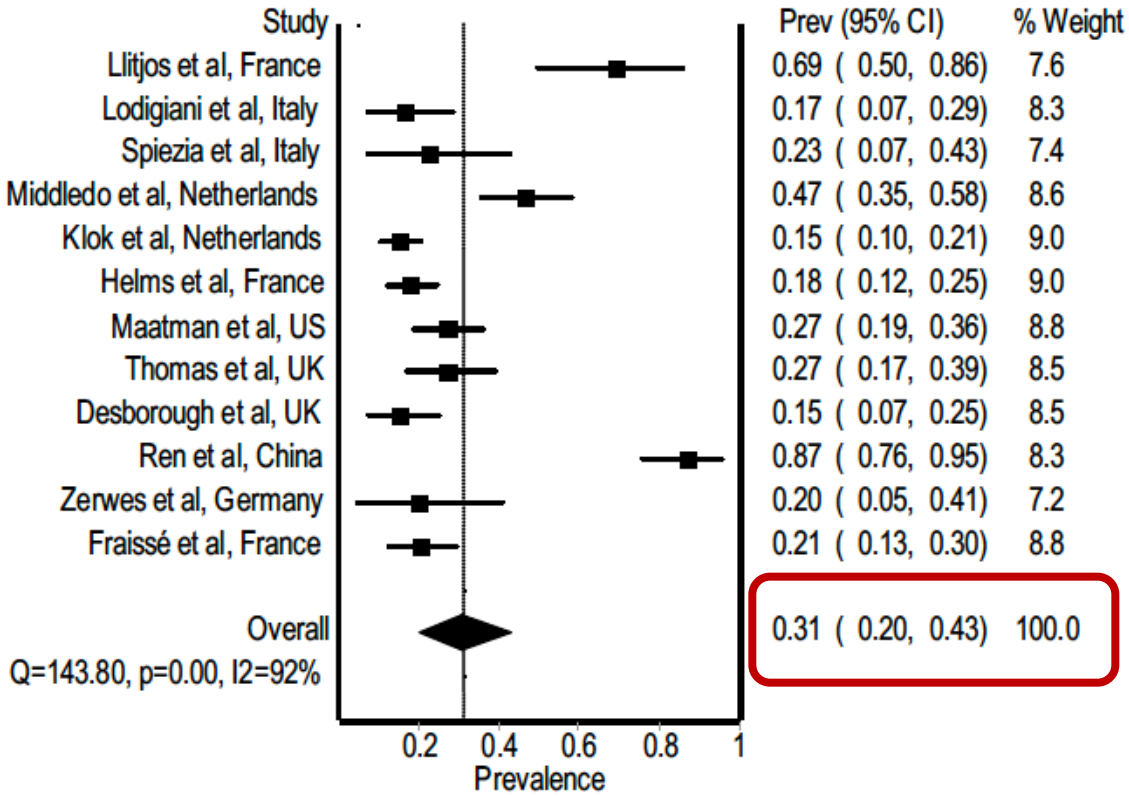
Syed Shahzad Hasan[1] · Sam Radford[2,3] · Chia Siang Kow[4] · Syed Tabish Razi Zaidi[5,6]

J Thromb Thrombolysis 2020; Aug 3:1-8.

Published online: 03 August 2020

High prevalence of thromboprophylaxis failure among COVID-19 patients admitted to ICU.

Individualised rather than protocolised VTE thromboprophylaxis would appear prudent at interim.



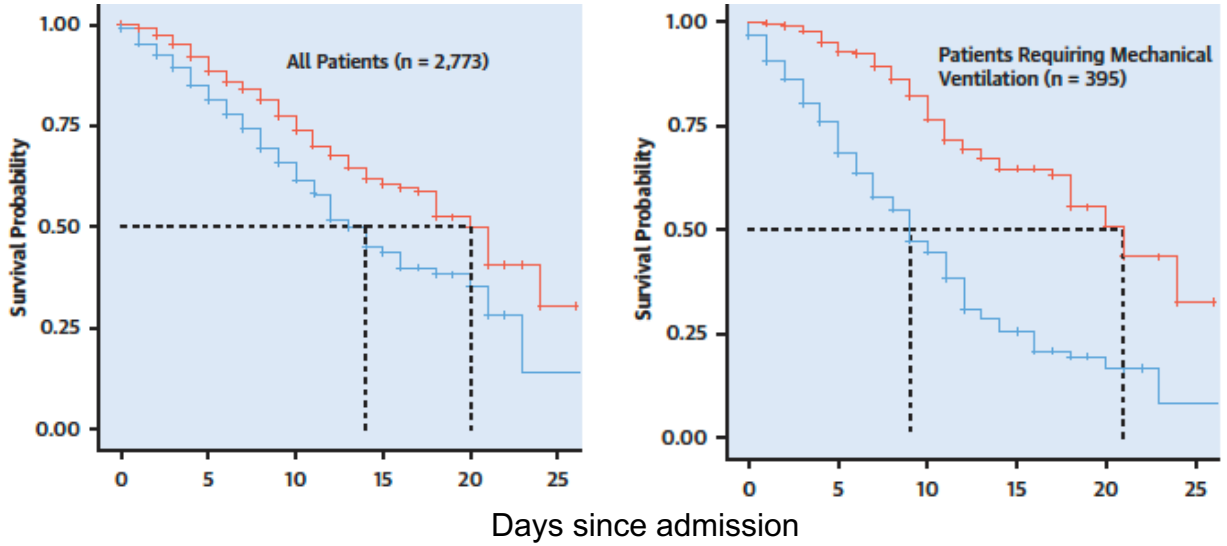
Subgroup pooled prevalence of VTE:

prophylactic:	38% (10%-70%)
prophylactic + therapeutic:	27% (17%-40%)

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

Ishan Paranjpe, BS
*Valentin Fuster, MD, PhD
Anuradha Lala, MD
Adam J. Russak, MD
Benjamin S. Glicksberg, PhD
Matthew A. Levin, MD
Alexander W. Charney, MD, PhD
Jagat Narula, MD, PhD
Zahi A. Fayad, PhD
Emilia Bagiella, PhD
Shan Zhao, MD, PhD
†Girish N. Nadkarni, MD, MPH

J Am Coll Cardiol. 2020 Jul 7;76(1):122-124.



Observational, retrospective
March 14 – April 11, 2020
2,773 patients, COVID-19,
Mount Sinai Health System in New York, USA.
786 (28%) received systemic treatment-dose anticoagulation (AC)

Multivariate proportional hazards model:
longer duration of AC treatments
associated with a reduced risk of mortality;
aHR 0.86 per day (0.82-0.89)

Major bleeding:
AC neg: 1.9%, AC+: 3%, p=0.2

***Suggest* systemic treatment-dose anticoagulation may be associated with improved outcomes**

Intensity of anticoagulation and survival in patients hospitalized with COVID-19 pneumonia

Andrew Hsu[a,*], Yuchen Liu[b], Adam S. Zayac[a], Adam J. Olszewski[a], John L. Reagan[a]

Thrombosis Research 196 (2020) 375–378

Retrospective, observational
February 27 – April 24 2020
468 hospitalised patients, Providence, USA

Standard prophylaxis SP:
Enoxaparin 40mg, UFH 5,000 IUx3, apixaban 2.5 mgx2

High intensity prophylaxis HIP
Enoxaparin 40mgx2, UFH 7,500 IUx3

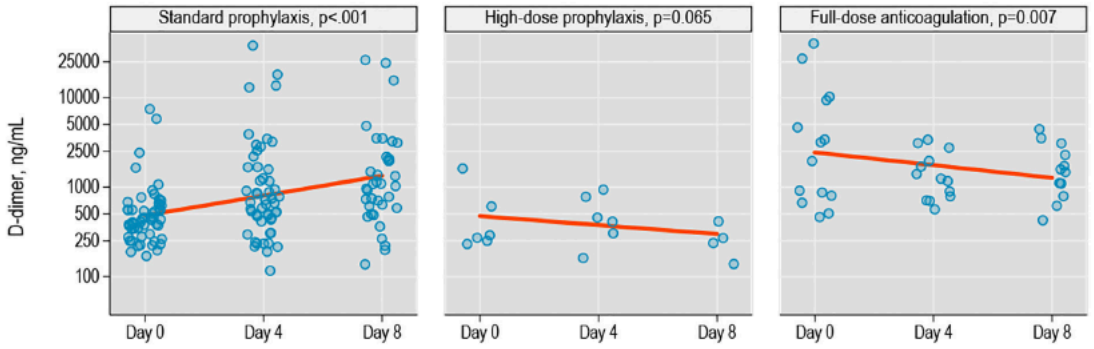
Therapeutic anticoagulation AC:
Enoxaparin 1 mg/kgx2; warfarin INR 2-3;
apixaban 5 mgx2; rivaroxaban 20 mg

Choice: *let to the discretion of the admitting provider.*

Initial use of HIP:

Improved 30-days mortality
aRR 0.26 (0.07-0.97), p=0.045

No increased rate of bleeding (p=0.11)



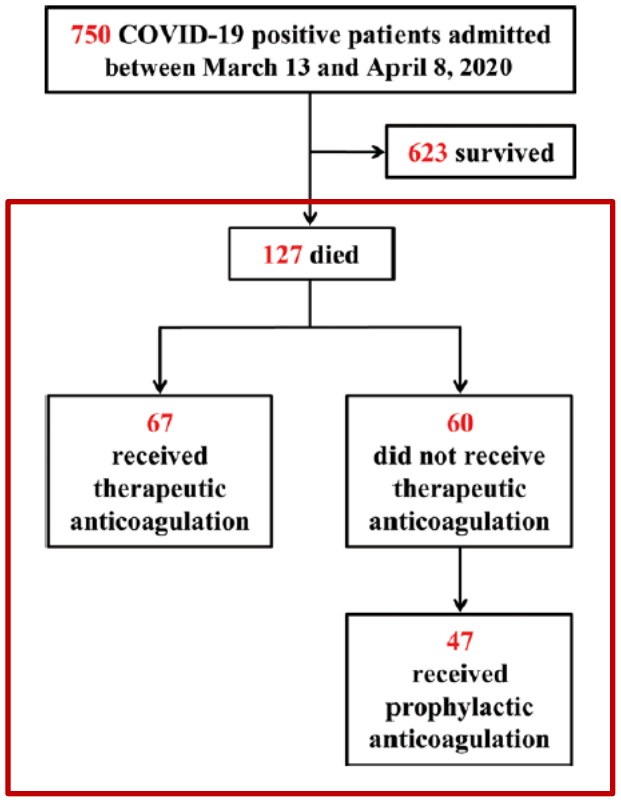
Severe COVID-19 cases:
D-dimers stable or decreased with HIP or AC

Suggests a role of anticoagulation in mitigating adverse outcomes associated with COVID-19

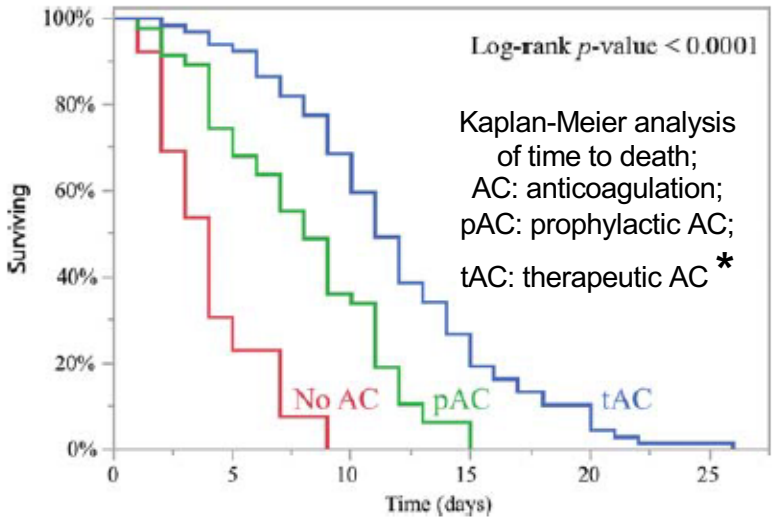
Therapeutic Anticoagulation Delays Death in COVID-19 Patients: Cross-Sectional Analysis of a Prospective Cohort

Filip Ionescu[1] Giovi Grasso-Knight[2] Edward Castillo[3,4] Ehsun Naeem[1] Ioana Petrescu[1]
Zaid Imam[1] Vishal K. Patel[2] Mangala Narasimhan[5] Girish B. Nair[2]

TH Open 2020;4:e263–e270.



Single-center,
cross-sectional analysis
of deceased patients
in a prospective cohort,
first 4 weeks
of COVID-19 pandemic in Michigan,
March13- April 8
William Beamont Hospital,
Royal Oak, USA



Kaplan-Meier analysis
of time to death;
AC: anticoagulation;
pAC: prophylactic AC;
tAC: therapeutic AC *

* Intravenous UFH, aPTT > 45 sec.
enoxaparin 1mg/kg twice daily or 1.5 mg/kg once daily
warfarin INR 2-4
DOAC rivaroxaban and apixaban

Multivariate Cox proportional hazards model

	Hazard ratio	Confidence interval	Significance
Ever smoker	1.86	1.25–2.8	0.002
CKD grade 3 or above	0.70	0.46–1.05	0.085
ICU stay	0.92	0.60–1.43	0.738
Prophylactic anticoagulation[a]	0.29	0.15–0.58	<0.001
Therapeutic anticoagulation[a]	0.15	0.07–0.32	<0.001
CS treatment duration (day)	0.89[b]	0.84–0.93	<0.001

In deceased COVID-19 patients,
anticoagulation was associated
with a delay of death
in a dose-dependent manner

Association of Anticoagulation Dose and Survival in Hospitalized COVID-19 Patients:

A Retrospective Propensity Score Weighted Analysis

Filip Ionescu[1], M.D.; Ishmael Jaiyesimi[2], D.O., M.S.; Ioana Petrescu[1], M.D.; Patrick R Lawler[3], M.D., M.P.H.; Edward Castillo[4,5], PhD; Yolanda Munoz-Maldonado[2,6], PhD; Zaid Imam[1], M.D.; Mangala Narasimhan[7], D.O.; Amr E Abbas[8], M.D., M.S.; Anish Konde[2], M.D.; Girish B Nair[9], M.D., M.S.

Eur J Haematol 2020; Oct 11. doi: 10.1111/ejh.13533

Retrospective analysis of a large cohort
3,480 consecutive COVID-19 patients,
tested positive between March 13th, 2020 and May 5th,
hospitalised within 8 hospitals in Southern Michigan, USA.

Propensity score-weighted multivariate Cox proportional hazards model

	Hazard ratio	Confidence interval	Significance
Age (years)	1.6 [a]	1.4-1.8	**<0.001**
BMI (kg/m²) [b]			
<18.5 kg/m²	3.0	1.5-6.0	**0.001**
30-40 kg/m²	0.8	0.6-1.1	0.214
≥40 kg/m²	1.1	0.7-1.6	0.779
ICU stay	5.2	3.5-7.8	**<0.001**
Prophylactic anticoagulation [c]	0.35	0.22-0.54	**<0.001**
Therapeutic anticoagulation [c]	0.14	0.08-0.23	**<0.001**
AKI requiring dialysis	1.3	0.96-1.8	0.095

[a] Per 10-year increase [b] Reference: BMI 18.5-30 kg.m^{-2}
[c] Reference is no anticoagulation
ICU: intensive care unit; AKI: acute kydney injury

	All patients (n=3480)	No AC (n=361)	pAC (n=2121)	tAC (n=998)	Significance
Major bleeding	147 (4.2%)	20 (5.5%)	46 (2.2%)	81 (8.1%)	**<0.001**
No major bleeding	3333 (95.8%)	341 (94.5%)	2075 (97.8%)	917 (91.9%)	
≥ 5 units PRBC in 48 hours	70 (2.0%)	9 (2.5%)	18 (0.9%)	43 (4.3%)	**<0.001**
< 5 units PRBC in 48 hours	3410 (98.0%)	352 (97.5%)	2103 (99.1%)	955 (95.7%)	

Higher doses of anticoagulation were associated with prolonged survival, especially in critically ill patients,
but this larger effect size came at the cost of excess of non-disabling bleeding

COVID-19: opening a new paradigm in thromboprophylaxis for critically ill patients?

Raquel Ferrandis[1], Juan V. Llau[2*], Manuel Quintana[3], Pilar Sierra[4], Francisco Hidalgo[5], Concepción Cassinello[6] and Aurelio Gómez-Luque[7]

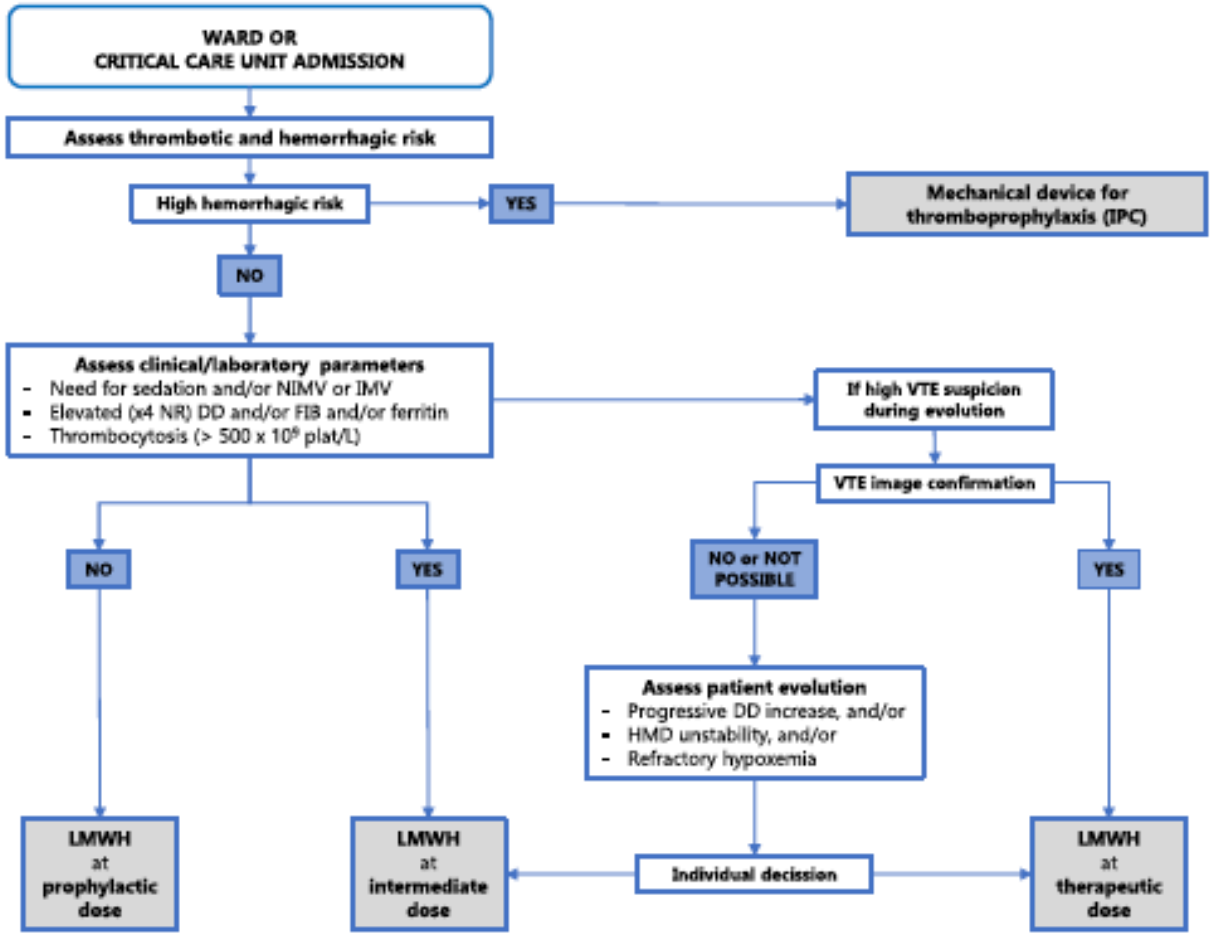
Critical Care (2020) 24:332

1- COVID-19 patients admitted to the hospital:
assessment for their thrombotic and haemorrhagic risk.

2- Unless contraindicated, **prophylactic LMWH**
must be administered.

3- When a procoagulant profile is confirmed:
extended or intermediate-dose LMWH
should be considered,
mainly in patients admitted to ICU

4- In case of severe disease progression,
the increase of LMWH dose up to therapeutic one
should be considered



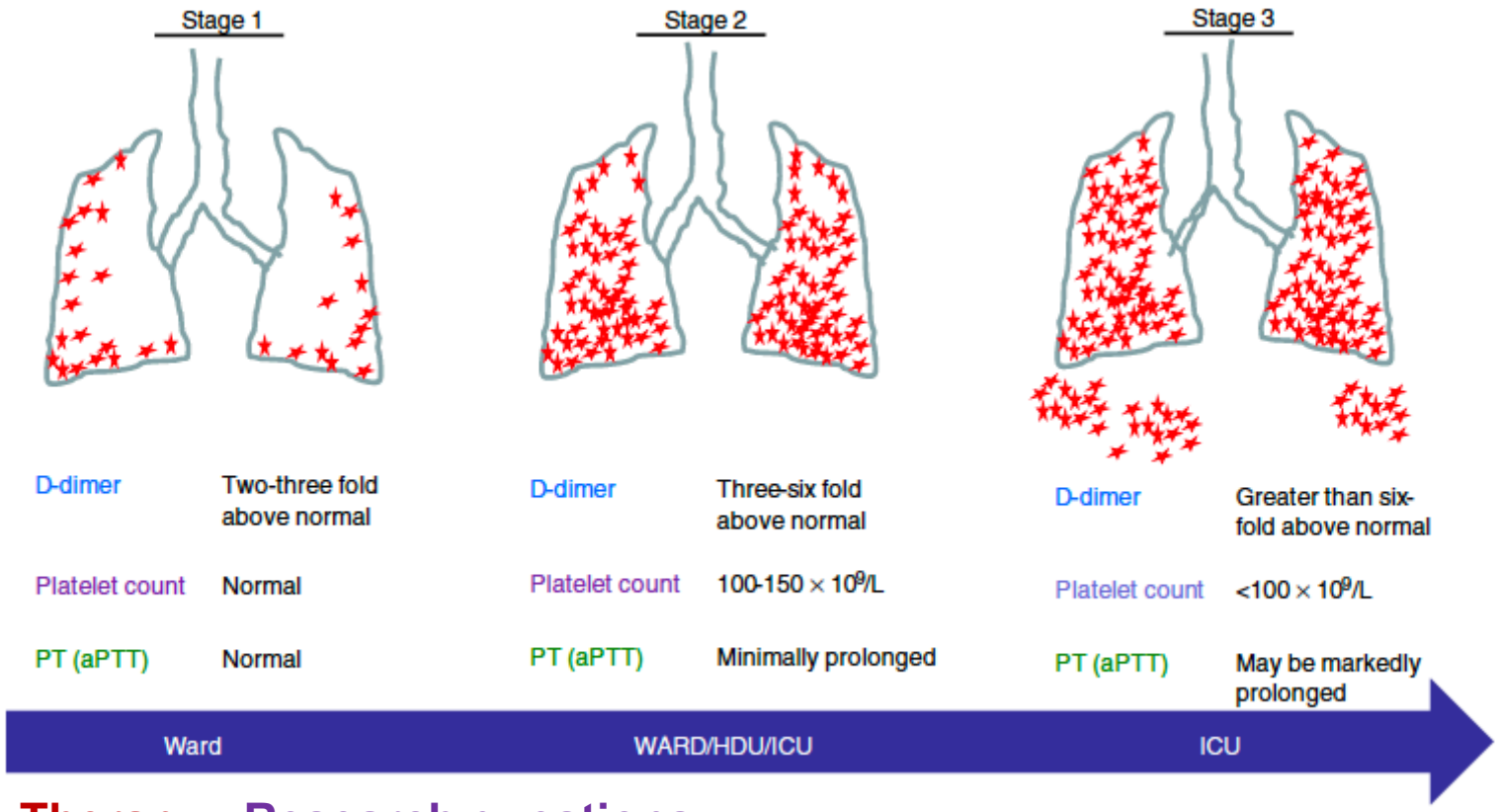
rpth
research & practice in thrombosis & haemostasis

A proposal for staging COVID-19 coagulopathy

Jecko Thachil MD, FRCPath[1] | Mary Cushman MD, MSc[2] |
Alok Srivastava MD, FRACP, FRCPA, FRCP[3]

Res Pract Thromb Haemost 2020; 4:731-6.

Received: 30 April 2020



Therapy Research questions

- Fixed dose LMWH prophylaxis vs weight based LMWH prophylaxis vs full dose LMWH
- Experimental Drugs

- Regular vs double dose LMWH prophylaxis vs full dose LMWH
- Experimental drugs

- Double dose LMWH prophylaxis vs full dose LMWH
- Thrombolysis
- Experimental drugs

REVIEW

Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring

Sophie Susen[1,2*], Charles Ambroise Tacquard[3], Alexandre Godon[4], Alexandre Mansour[5], Delphine Garrigue[1], Philippe Nguyen[6], Anne Godier[7], Sophie Testa[8], Jerrold H. Levy[9], Pierre Albaladejo[4], Yves Gruel

Critical Care (2020) 24:364

Thrombotic risk levels in patients with COVID-19

according to BMI,
need of O2 or mechanical assistance,
and other risk factors for thrombosis

LOW RISK

- Non-hospitalised patients,
  BMI < 30 $kg.m^{-2}$,
  no added risk factor for VTE
  (such as active cancer,
  recent history of VTE,…)

No thromboprophylaxis

REVIEW

Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring

Sophie Susen[1,2*], Charles Ambroise Tacquard[3], Alexandre Godon[4], Alexandre Mansour[5], Delphine Garrigue[1], Philippe Nguyen[6], Anne Godier[7], Sophie Testa[8], Jerrold H. Levy[9], Pierre Albaladejo[4], Yves Gruel

Critical Care (2020) 24:364

Thrombotic risk levels in patients with COVID-19

according to BMI,
need of O2 or mechanical assistance,
and other risk factors for thrombosis

INTERMEDIATE RISK

- BMI < 30 kg.m^{-2},
  no need for high-flow nasal O_2 therapy
  or mechanical ventilation,

LMWH, standard prophylactic dose *or* fondaparinux

LMWH: enoxaparin 4,000 IU/24h
enoxaparin 2,000 IU/24h if ClCr 15-30 ml/min
tinzaparin 3,500 IU/24h if ClCr > 20 ml/min
dalteparin 5,000 IU/24h if ClCr > 30 ml/min

Fondaparinux: 2.5 mg. /24h if ClCr > 50 ml/min.

REVIEW

Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring

Sophie Susen[1,2*], Charles Ambroise Tacquard[3], Alexandre Godon[4], Alexandre Mansour[5], Delphine Garrigue[1], Philippe Nguyen[6], Anne Godier[7], Sophie Testa[8], Jerrold H. Levy[9], Pierre Albaladejo[4], Yves Gruel

Critical Care (2020) 24:364

Thrombotic risk levels in patients with COVID-19

according to BMI,
need of O2 or mechanical assistance,
and other risk factors for thrombosis

HIGH RISK

- BMI < 30 kg.m^{-2} under high-flow nasal O_2 therapy or mechanical ventilation
- BMI > 30 kg.m^{-2} without high-flow nasal O_2 therapy or mechanical ventilation, with added risk factors for VTE
- BMI > 30 kg.m^{-2} with high-flow nasal O_2 therapy or mechanical ventilation, without added risk factors for VTE

LMWH, intermediate dose prophylaxy
UFH if renal insufficiency

Enoxaparin 4,000 IU/12h
Enoxaparin 6,000 IU/12h if weight > 120 kg
UFH 200 IU/kg/24h if ClCr <30 ml/min

Monitoring anti-FXa activity:

LMWH: avoid overdose,
maintain < 1.2 IU/ml for enoxaparin

UFH: target 0.3-0.5 IU/ml
and platelet count every 48 hours

REVIEW

Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring

Sophie Susen[1,2*], Charles Ambroise Tacquard[3], Alexandre Godon[4], Alexandre Mansour[5], Delphine Garrigue[1], Philippe Nguyen[6], Anne Godier[7], Sophie Testa[8], Jerrold H. Levy[9], Pierre Albaladejo[4], Yves Gruel

Critical Care (2020) 24:364

VERY HIGH RISK

- BMI > 30 kg.m^{-2} with high-flow nasal O_2 therapy or mechanical ventilation, with added risk factors for VTE
- ECMO (venovenous or veno arterial)
- Unexplained catheter thrombosis
- Dialysis filter thrombosis
- Marked inflammatory syndrome and/or hypercoagulability (e.g. fibrinogen > 8 g/L and/or D-dimers > 3 µg/ml

Thrombotic risk levels in patients with COVID-19

according to BMI,
need of O2 or mechanical assistance,
and other risk factors for thrombosis

LMWH at curative dose, UFH if renal insufficiency

Enoxaparin	100 IU/kg/12h without exeeding 10,000 IU/12h
UFH	500 IU/kg/24h if ClCr < 30 ml/min

Reevaluatre the dose in case of multiorgan failure or consumption coagulopathy

Monitoring anti-FXa activity:

LMWH: avoid overdose,
maintain < 1.2 IU/ml for enoxaparin

UFH: target 0.5-0.7 IU/ml
and platelet count every 48 hours

The hazard of fondaparinux in non-critically ill patients with COVID-19: Retrospective controlled study versus enoxaparin

Paolo Prandoni[a,*], Anna Maria Cattelan[b], Laura Carrozzi[c], Lucia Leone[d], Lucia Filippi[e], Egidio De Gaudenzi[f], Sabina Villalta[g], Raffaele Pesavento[h], for the FONDACOVIT Investigators [all in Italy][1],

Thrombosis Research 196 (2020) 395–397

Retrospective, observational
7 medical departments in Northern Italy
Non-critically ill COVID-19 patients

Enoxaparin 4,000 UI (2,000 if severe renal failure)
Fondaparinux 2.5 mg (1.5 mg if severe renal failure)

Clinically syptomatic thrombotic events:

Fondaparinux:	4/148, 2.7%	
Enoxaparin:	5/160, 3.1%	p=0.83

Rate of major or clinically significant bleeding

Fondaparinux:	**7/148, 4.7%**	
Enoxaparin:	1/160, 0.6%	p=0.03

The use of fondaparinux in place of LMWH in patients with non-critically ill COVID-19 infectious disease *should be discouraged.*

Coagulopathy in COVID-19: Manifestations and management

Mucha SR, Dugar S, McCrae K, Joseph D,
Bartholomew J, Sacha GL, Militello M.

Cleve Clin J Med 2020; 87(8):461-468.

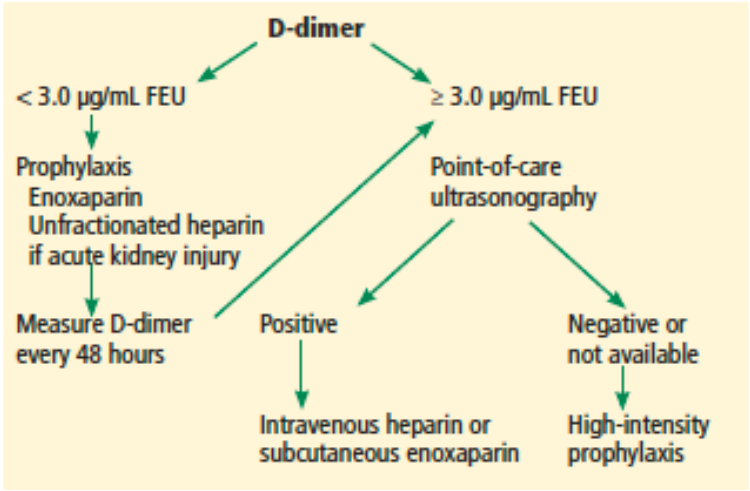
Systematic monitoring, every 48 hours:
D-dimers
Fibrinogen
PT/INR
aPTT

High risk D-dimer level:
at least 6 times the upper limit,
3.0 μg/ml (3,000 ng) FEU

Tang N. et al., J Thromb Haemost 2020; 18(4):844-7
Cui S. et al., J Thromb Haemost 2020; 18(6):1421-4

Use of point-of-care ultrasonography:
« POCUS »

Category 1: D-di < 3.0, no evidence of VTE
Category 2: D-di ≥ 3, POCUS negative.
Category 3: Confirmed thrombosis



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Cui S. et al., J Thromb Haemost 2020; 18(6):1421-4

	Category 1 D-dimer < 3.0 μg/mL FEU Standard prophylaxis
Standard	Enoxaparin 40 mg subcutaneously every 24 hours
Renal failure	**CrCl 10–30 mL/min:** Enoxaparin 30 mg subcutaneously every 24 hours
	CrCl < 10 mL/min or AKI[a]: Unfractionated heparin 5,000 U subcutaneously every 12 hours
	CRRT: Unfractionated heparin 500 U/hour through circuit
	Circuit clotting: IV heparin per ACS nomogram[a]
Obesity	
Standard	**> 100 kg:** Enoxaparin 40 mg subcutaneously every 12 hours
	> 120 kg: Enoxaparin 60 mg subcutaneously every 12 hours
Renal failure CrCl < 30 mL/min or AKI[b]	**≤ 120 kg:** 7,500 U every 12 hours
	> 120 kg: 10,000 U every 12 hours
	CRRT: 500 U/h through circuit
	Circuit clotting: IV heparin per ACS nomogram[a]

Coagulopathy in COVID-19: Manifestations and management

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Systematic monitoring, every 48 hours:
D-dimers
Fibrinogen
PT/INR
aPTT

High risk D-dimer level:
at least 6 times the upper limit,
3.0 μg/ml (3,000 ng) FEU

Tang N. et al., J Thromb Haemost 2020; 18(4):844-7
Cui S. et al., J Thromb Haemost 2020; 18(6):1421-4

	Category 2 D-dimer ≥ 3.0 μg/mL FEU High-intensity prophylaxis
Standard	Enoxaparin 40 mg subcutaneously every 12 hours
Renal failure	**CrCl < 30 mL/min or AKI:** Enoxaparin 40 mg subcutaneously every 24 hours **CrCl < 10 mL/min or AKI[a]:** Unfractionated heparin 7,500 U subcutaneously every 12 hours **CRRT:** Unfractionated heparin 500 U/hour through circuit **Circuit clotting:** IV heparin per ACS nomogram[3]
Obesity	
Standard	**> 100 kg:** Enoxaparin 60 mg subcutaneously every 12 hours **> 120 kg:** Enoxaparin 80 mg subcutaneously every 12 hours
Renal failure CrCl < 30 mL/min or AKI[b]	**≤ 120 kg:** 7,500 U every 8 hours **> 120 kg:** 10,000 U every 8 hours **CRRT:** 500 U/h through circuit **Circuit clotting:** IV heparin per ACS nomogram[3]

Coagulopathy in COVID-19: Manifestations and management

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D-dimers
Fibrinogen
PT/INR
aPTT

High risk D-dimer level:
at least 6 times the upper limit,
3.0 μg/ml (3,000 ng) FEU

Tang N. et al., J Thromb Haemost 2020; 18(4):844-7
Cui S. et al., J Thromb Haemost 2020; 18(6):1421-4

	Category 3 Confirmed VTE Full anticoagulation
Standard	IV heparin per DVT/PE nomogram or enoxaparin 1 mg/kg subcutaneously every 12 hours
Renal failure	IV heparin per DVT/VTE nomogram
Obesity	
Standard	IV heparin per DVT/PE nomogram or Enoxaparin 1 mg/kg subcutaneously every 12 hours, up to 150 mg Above 150 kg use unfractionated heparin
Renal failure CrCl < 30 mL/min or AKI[b]	IV heparin per DVT/PE nomogram

COMPARISON OF PUBLISHED GUIDELINES FOR MANAGEMENT OF COAGULOPATHY IN CRITICALLY ILL COVID-19 PATIENTS

- International society for Thombosis and Haemostasis' interim guidance (ISTH-IG)
  - J Thromb Haemost 2020; 18:1023-6.
  - J Thromb Haemost 2020; 18:2057-8.
- Scientific and Standardisation Committee of the ISTH (ISTH-SCC)
  - J Thromb Haemost 2020; 18:1859-65
- American Society of Hematology (ASH)
  - https://www.hematology;org/covid-19/covid-19-and-vte-antocoagulation
  - https://www.hematology;org/covid-19/covid-19-and-coagulopathy
- American College of Chest Physicians (ACCP)
  - Chest 2020; 158(3):1143-63
- American College of Cardiology (ACC)
  - J Am Col Cardiol 2020; 75(23):2950-73
- Center for Disease Control and Prevention (CDC) guidelines
  - https://www.covid19treatmentguidelines.nih.gov/

Laboratory testing for risk stratification and triage?

ISTH-IG	**D-dimer, PTT, platelet count and fibrinogen: all patients, helpful for risk stratification** (D-di raised 3 to 4 fold, prolonged PT, platelets < 100 G/L, fibrinogen < 2 g/L) **Monitoring of patients after admission: helpful** (more aggressive treatments, experimental treatment to consider if parameters worsen)
ISTH-SCC	**States further study is required**. *Very elevated D-di > 6 times upper limit of normal is consistent predictor of thrombotic events and poor overall prognosis.*
ACCP	**Not mentioned**
ACC	**Similar to other acutely ill medical patients without COVID-19**, *regular monitoring of platelet count, PT, D-di and fibrinogen important to diagnose worsening coagulopathy. Treatment of underlying conditions of DIC and bacterial superinfections important.*
ASH	**D-di, PTT, platelet count and fibrinogen.** *Worsening of the parameters may predict more aggressive critical care and experimental therapies might be considered.*
CDC	**Lack of prospective data** demonstrating laboratory testing in risk stratification of patients with asymptomatic or mild infection. Insufficient data to recommend for or against using laboratory values to guide management.

Biomarkers to guide anticoagulation?	
ISTH-IG	**Not mentioned**
ISTH-SCC	**D-dimers should not be used solely to guide anticoagulation regimens**
ACCP	**Not mentioned**
ACC	**D-dimer > 2 times the upper limit: may suggest** *that patient is at high risk of VTE and consideration of extended prophylaxis (up to 45 days) in patients at low risk of bleeding.* Further investigation needed to determine the role of APLAs in pathophysiology of COVID-19-associated thrombosis.
ASH	No particular change to regimen recommended for patients with lupus-like inhibitors. **TEG and ROTEM should not be used routinely to guide management**.
CDC	**Insufficient data to recommend for or against** using haematological and coagulation parameters to guide management decisions

VTE prophylaxis regimen and preferred medications

ISTH-IG	**LMWH (standard dosing)**
ISTH-SCC	**LMWH or UFH.** **Intermediate intensity LMWH: can be considered** *in high-risk critically ill patients (50% of responders*) **and may be considered** *in non-critically hill hospitalised patients (30%)*. Several advantages of LMWH over UFH. Regimens may be modified based on extremes of body weight (50% increase if obese), severe thrombocytopenia (?), or worsening renal function.
ACCP	**LMWH (standard dosing)**
ACC	**Enoxaparin 40 mg or similar LMWH regimen.** **SC Heparin** (5000 U twice or three times a day) **if renal dysfunction** (CrCl<30 ml/min). **Insufficient data to consider routine therapeutic or intermediate dose anticoagulation** (only a minority of the panellists considered intermediate -32%- to therapeutic –5%- intensity reasonable)
ASH	**LMWH over UFH (standard dosing)** to reduce exposure unless risk of bleeding outweighs risk of thrombosis
CDC	**LMWH or UFH. insufficient data to recommend for or against** the increase of anticoagulation outside of a clinical trial.

Therapeutic regimens and preferred medications	
ISTH-IG	**Not mentioned**
ISTH-SCC	**Not mentioned**
ACCP	**LMWH or fondaparinux over UFH.** UFH preferred if high bleeding risk and in renal failure or needing imminent procedures. Recommend increasing dose of LMWH by 25-30% if recurrent VTE on therapeutic LMWH
ACC	Medication regimen can change depending on comorbidities (renal, hepatic, gut, platelets) **Prefer parenteral anticoagulation (UFH) given it may be withheld temporarily** **LMWH in patients unlikely to need procedures** DOACS may have risks in settings of organ dysfunction related to clinical deterioration
ASH	**LMWH or UFH over DOACs** due to reduced drug-drug interactions and shorter half-life.
CDC	**Standard regimens for non-COVID-19 patients**

When hold anticoagulation	
ISTH-IG	Signs of **active bleeding** or **platelets < 25 G/L**. Abnormal APTT or PT not a contraindication to thromboprophylaxis.
ISTH-SCC	**No specific recommendations**. 50% of respondents report holding if **platelets < 25 G/**L.
ACCP	**Not mentioned**.
ACC	Patients with moderate or severe COVID-19 on chronic therapeutic anticoagulation, with **DIC without overt ble**eding: consider the indication and the risk, **adjust dose or discontinue**. Reduce the intensity of anticoagulation unless there is an exceeding risk of thrombosis.
ASH	**Thromboprophylaxis is recommended in the absence of active bleeding even if abnormal coagulation tests, held only if platelets < 25 G/L or fibrinogen < 0.5 g/L**. Abnormal PT or APTT not a contraindication. Therapeutic anticoagulation: to be held if platelets < 30-50 G/L or fibrinogen < 1.0 g/L.
CDC	**Active haemorrhage** or **severe thrombocyto**penia (?)

When to use mechanical thromboprophylaxis	
ISTH-IG	**Not mentioned**
ISTH-SCC	Mechanical thromboprophylaxis, *pneumatic compression devices being preferred*, **when pharmacological prophylaxis is contraindicated**. Multimodal thromboprophylaxis with mechanical methods considered by 60% of the respondents.
ACCP	Suggest critically ill who have a **contraindication to pharmacological thromboprophylaxi**s. Suggest **against adding if receiving pharmacological thrombo**prophylaxis
ACC	Pneumatic compression devices **when pharmacological prophylaxis is contraindicated** **Use of both** (pharmacological + mechanical) **reasonabl**e for 55% of the panellists even if lack of high-quality evidence
ASH	Pneumatic compression devices **when pharmacological prophylaxis is contraindicated**
CDC	**Not mentioned**

When to consider therapeutic anticoagulation	
ISTH-IG	**No specific recommendations**.
ISTH-SCC	**Not for primary prevention, no RCT**. Consider increased intensity of anticoagulation regimen (from prophylactic to intermediate, or intermediate to therapeutic) in **patients without confirmed VTE but deteriorating pulmonary status or ARDS.**
ACCP	**Patients with PE or proximal DVT**.
ACC	**Key to VTE treatment.** No distinction between confirmed and suspected VTE.
ASH	Consider increased intensity of anticoagulation regimen (from prophylactic to intermediate, or intermediate to therapeutic) or change anticoagulant in **patients with recurrent thrombosis of catheters and extracorporeal circuits on prophylactic anticoagulation regimens.**
CDC	When a clinically suspected **VT**E is present or highly suspected. **Insufficient data to recommend for or against the increase** of anticoagulation intensity .

When to consider thrombolytics	
ISTH-IG	**Not mentioned**
ISTH-SCC	**Not mentioned**
ACCP	**PE with hemodynamic instability or signs of obstructive shock** not at high bleeding risk Peripheral thrombolysis recommended over catheter-directed thrombolysis
ACC	Multidisciplinary evaluation for intermediate and high risk patients with VTE. **Haemodynamically high risk PE**: systemic fibrinolysis; catheter-based therapies for situations not amenable to systemic fibrinolysis
ASH	**Not mentioned**
CDC	**Insufficient data to recommend for or against**. **Pregnant women**: only if life-threatening haemodynamic instability, due to risk for maternal haemorrhage.

Duration of therapeutic anticoagulation	
ISTH-IG	Not mentioned
ISTH-SCC	Minimum of 3 months
ACCP	Minimum of 3 months
ACC	Not mentioned
ASH	Not mentioned
CDC	Not mentioned

Monitoring of patients receiving LMWH	
ISTH-IG	**Advised in patients with severe renal impairment**
ISTH-SCC	**No specific recommendations.**
ACCP	**Body weight adjusted doses for LMWH do not require laboratory monitoring** in majority of patients
ACC	**Not mentioned**
ASH	**Not mentioned**
CDC	**Not mentioned**

Monitoring of patients with elevated PTT receiving therapeutic anticoagulation	
ISTH-IG	**Not mentioned**
ISTH-SCC	**Not mentioned**
ACCP	**Not mentioned**
ACC	**Not mentioned**
ASH	May necessitate **anti-Xa monitoring of UFH** given artefactual increases in PTT
CDC	**Not mentioned**

Monitoring of patients receiving therapeutic anticoagulation	
ISTH-IG	**Not mentioned**
ISTH-SCC	**No specific recommendations.** Expert clinical guidance statements target an anti-factor Xa level of 0.3-0.7 IU/ml for UFH.
ACCP	**Monitor anti-Xa levels in all patients receiving UFH given potential of heparin resistance**
ACC	**Not mentioned**
ASH	**May necessitate anti-Xa monitoring of UFH** given artefactual increases in PTT
CDC	**Per standard of care for patients without COVID-19**

Recommendations on anticoagulation on discharge	
ISTH-IG	**No specific recommendations**
ISTH-SCC	**Either LMWH or approved post-discharge prophylactic anticoagulation regimens (DOACs) should be considered in patients with high VTE risk criteria**. Duration: 14 days at least, up to 30 days. Aspirin not recommended.
ACCP	**Can be considered in patients at low risk of bleeding** if a clinical benefit is suggested
ACC	**Reasonable to consider extended prophylaxis with LMWH or DOACs for up to 45 days in patients at high risk of VTE** (D-di > 2 times the upper limit, reduced mobility, active cancer) and low risk of bleeding.
ASH	**Reasonable to consider approved post-discharge prophylactic** anticoagulation regimens, or aspirin if criteria from trials for post-discharge thromboprophylaxis are met.
CDC	**Routine venous thromboprophylaxis post-discharge is not recommended**. Approved prophylactic regimens if high risk for VTE and low risk of bleeding using criteria from clinical trials.

Correction of active bleeding	
ISTH-IG	**Transfuse** to keep platelet count > 50 G/L, fibrinogen > 1.5 g/L, PT ratio < 1.5.
ISTH-SCC	**Not mentioned.**
ACCP	**Not mentioned.**
ACC	**Transfuse platelets** to maintain > 50 G/L in patients with DIC and active bleeding, or if platelets < 20 G/L in patient at high risk of bleeding or requiring invasive procedures. **FFP** (15-25 ml/kg) if active bleeding with either prolonged PT or PTT ratios (> 1.5) or decreased fibrinogen < 1.5 g/L. **Fibrinogen** if persistent hypo fibrinogenaemia < 1.5 g/L. **Prothrombin complex concentrates** if FFP not possible. **Tranexamic acid not to be used routinely.**
ASH	**Transfuse** one adult unit of **platelets** if < 50 G/L, give 4 units of plasma if INR > 1.8, and **fibrinogen concentrate** (4g) if fibrinogen < 1.5 g/L. Patients with severe coagulopathy and bleeding: consider 4 **prothrombin complex concentrates** (25 U/kg) instead of plasma.
CDC	**Not mentioned.**

Variability in Institutional Guidance for COVID-19-Associated Coagulopathy in the United States

Rushad Patell[1,*] Shonali Midha[2,*] Stephen Kimani[3] Richard Martin[4] Natalia Neparidze[5]
Michael Jaglal[2] Jason Freed[1] Nigel S. Key[3]

Thromb Haemost 2020; Aug 22. doi: 10.1055/s-0040-1715837.

University of Michigan, Ann Arbor, MI

Loyola University Medical Center, Chicago, IL

Emory University, Atlanta, GA

New York Presbyterian Hospital/ Weil Cornell/, Columbia NY, NY

Moffitt Cancer Center/ University of South Florida, Tampa, FL

Vanderbilt University Medical Center, Nashville, TN

Johns Hopkins University Hospital, Baltimore, MD

Mount Sinai Hospital, NY, NY

University of Alabama at Birmingham Hospital, Birmingham, AL

University of North Carolina, Chapel Hill, NC

Yale New Haven Health System, New Haven, CT

University of Pennsylvania, Philadelphia, PA

Massachusetts General Hospital, Boston, MA

Beth Israel Deaconess Medical Center, Boston, MA

Cleveland Clinic Medical Center, Cleveland, OH

4/15: thromboprophylaxis using enoxaparin 40 mg daily
8/15: D-di thresholds to risk-stratify patients
8/15: higher risk patients: intermediate-dose LMWH
4/15: higher risk patients: full-dose LMWH (3), apixaban (1)
1/15: clinical prediction rules, Wells' + VTE-BLEED scores
1/15: empiric fibrinolysis for salvage therapy in severe hypoxia
8/15: postdischage outpatients thromboprophylaxis

*« The **wide disparity** in institutional recommendations highlight the existing equipoise regarding antithrombotic management in patients with COVID-19, **the lack of true standard of care**, **the need for data from robust, prospective RCTs** to guide clinical practice »*

Other treatments

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

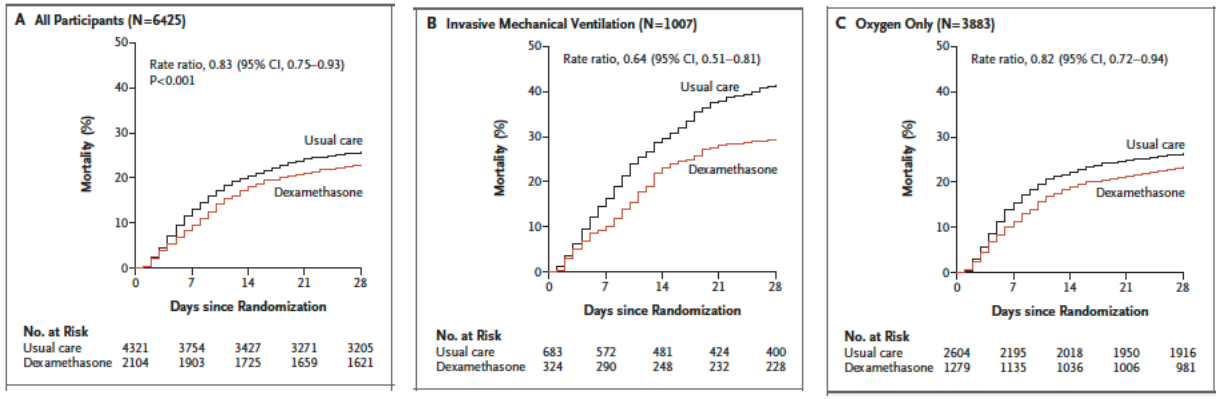
Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ

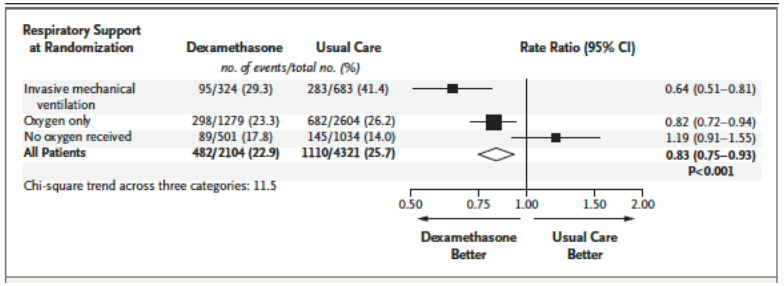
N Engl J Med 2020; Jul 17:NEJMoa2021436. doi: 10.1056/NEJMoa2021436.

Controlled, open-label trial
oral or intravenous dexamethasone 6 mg once daily
for up to 10 days (N=2,104)
vs. usual care alone (N=4,321)

Randomisation: March 19 - June 8, 2020

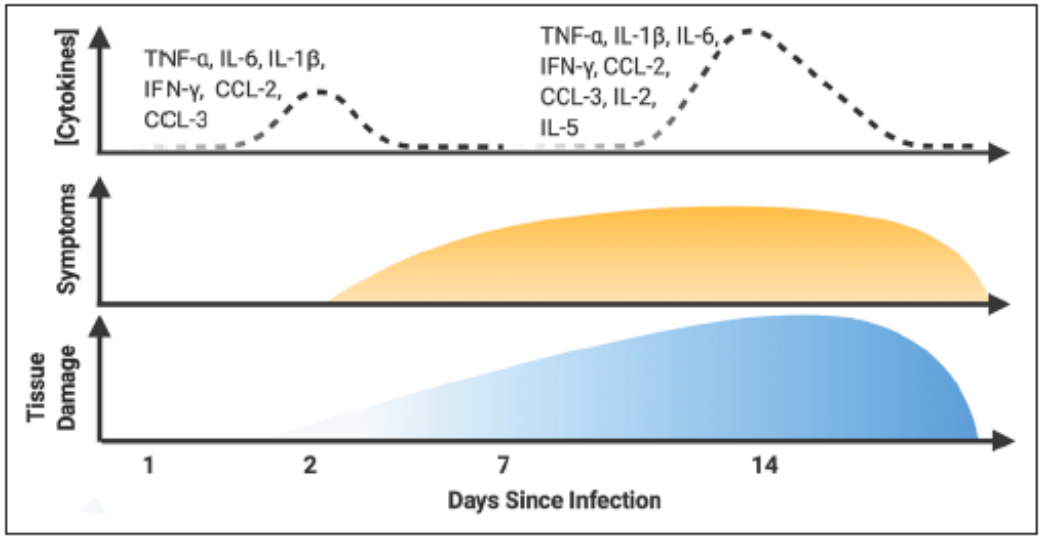
Primary outcome: 28-day mortality
22.9% vs. 25.7%, p<0.001.





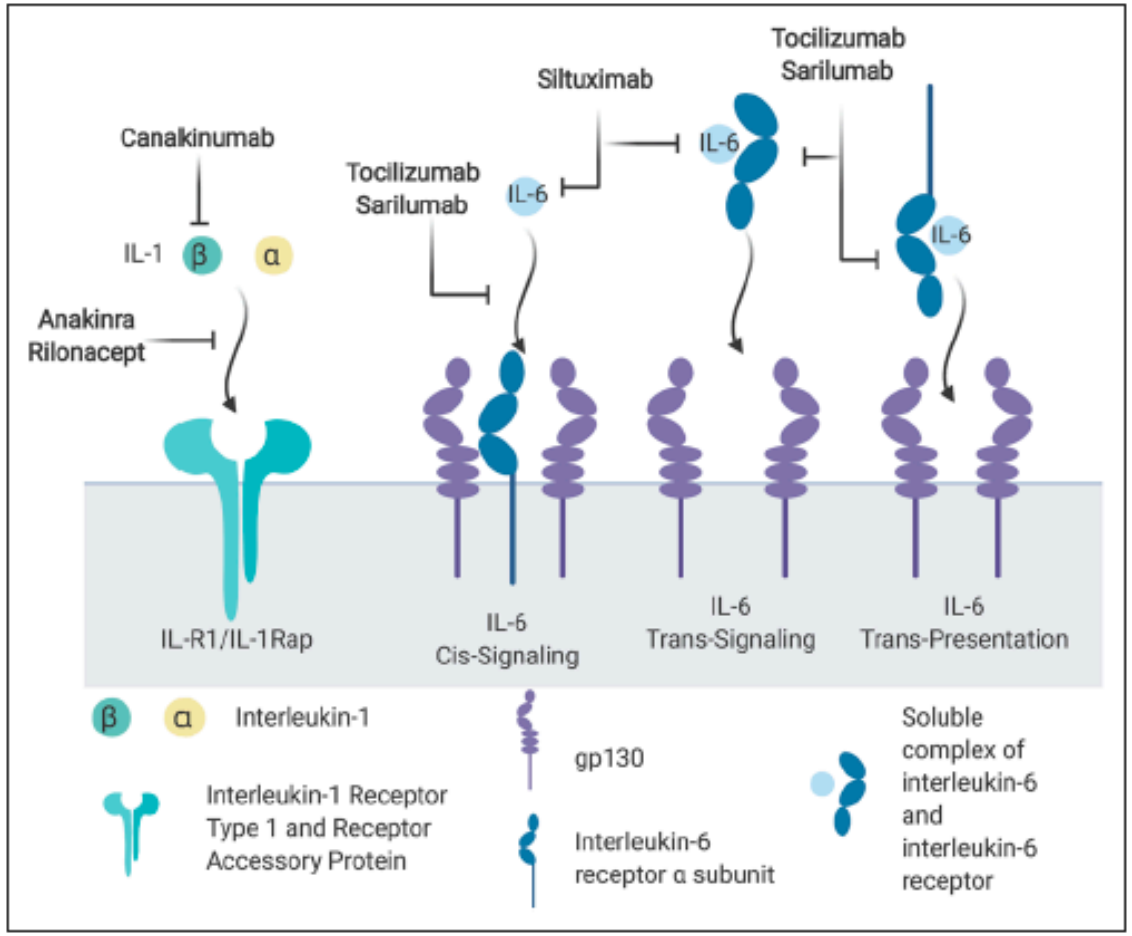
Dexamethasone 6 mg: lower 28-day mortality
if either invasive mechanical ventilation
or oxygen support alone
at randomisation

Anti-cytokine therapies in severe COVID-19?



Second wave of disease:
major determinant of outcomes;
both innate and adaptative cytokines

Waiting for results of RCTs



JAMA Internal Medicine | Original Investigation

Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19

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Observational retrospective

JAMA Intern Med 2020; Oct 20. doi: 10.1001/jamainternmed.2020.6252

Reduced time to death and risk of death at 30 days
but important differences in treatment groups at baseline and risk of residual confounding despite adjustments

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Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia
A Randomized Clinical Trial

Olivier Hermine, MD, PhD; Xavier Mariette, MD, PhD; Pierre-Louis Tharaux, MD, PhD; Matthieu Resche-Rigon, MD, PhD; Raphaël Porcher, PhD; Philippe Ravaud, MD, PhD; for the CORIMUNO-19 Collaborative Group

Randomized prospective

JAMA Intern Med 2020; Oct 20. doi: 10.1001/jamainternmed.2020.6820

Lack of blinding and placebo control
Very different study populations

Hospitalised patients in France, moderate to severe COVID-19, only requiring low-flow O_2
Tocilizumab may improve outcomes at 14 days,
(non-invasive ventilation+mechanical ventilation+death)
but unclear significance of this finding
(similar death rates at day 28).

Hospitalised patients in Italy, severe COVID-19, high-flow O_2 nasal canula, not yet ICU-level care
Stopped early for futility

JAMA Internal Medicine | Original Investigation

Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia
A Randomized Clinical Trial

Carlo Salvarani, MD; Giovanni Dolci, MD; Marco Massari, MD; Domenico Franco Merlo, PhD; Silvio Cavuto, BSc; Luisa Savoldi, BSc; Paolo Bruzzi, MD, PhD; Fabrizio Boni, MD; Luca Braglia, BSc; Caterina Turrà, MSc; Pier Ferruccio Ballerini, MD; Roberto Sciascia, MD; Lorenzo Zammarchi, MD; Ombretta Para, MD; Pier Giorgio Scotton, MD; Walter Omar Inojosa, MD; Viviana Ravagnani, MD; Nicola Duccio Salerno, MD; Pier Paolo Sainaghi, MD; Alessandro Brignone, MD; Mauro Codeluppi, MD; Elisabetta Toopompi, MD, PhD; Maurizio Milesi, MD; Perla Bertomoro, MD; Norbisato Claudio, MD; Mario Sallo, MD; Marco Falcone, MD; Giovanni Cenderello, MD; Lorenzo Donghi, MD; Valerio Del Bono, MD; Paolo Luigi Colombelli, MD; Andrea Anghoben, MD; Angelina Passaro, MD; Giovanni Secondo, MD; Renato Pascale, MD; Ilaria Piazza, MD; Nicola Facciolongo, MD; Massimo Costantini, MD, PhD; for the RCT-TCZ-COVID-19 Study Group

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Stopped early for futility

EDITORIAL

Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia

Jonathan B. Parr, MD, MPH

JAMA Intern Med 2020; Oct 20. doi: 10.1001/jamainternmed.2020.6557.

« Newly released randomised trials *suggest* a potential role for tocilizumab but not show clear evidence of efficacy, in contrast to observational studies. Do not support the routine use.
Reconsider tocilizumab use only if more compelling data from ongoing RCTs emerges.

ORIGINAL ARTICLE

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

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This article was published on October 21, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2028836

Randomised, double-blind, placebo-controlled trial

SARS-CoV-2-mediated severe acute respiratory syndrome
plus hyperinflammation state
CRP > 50 mg/L, ferritin > 500 ng/ml, or D-di > 1000 ng/ml
and at least two of:
fever > 38°C
pulmonary infiltrate
need for supplementary O2 to maintain SaO_2 > 92%

2(161):1 (82), a single dose 8 mg/kg
Primary outcome: intubation or death
Secondary efficacy outcomes:
clinical woersening
discontinuation of supplemental O_2

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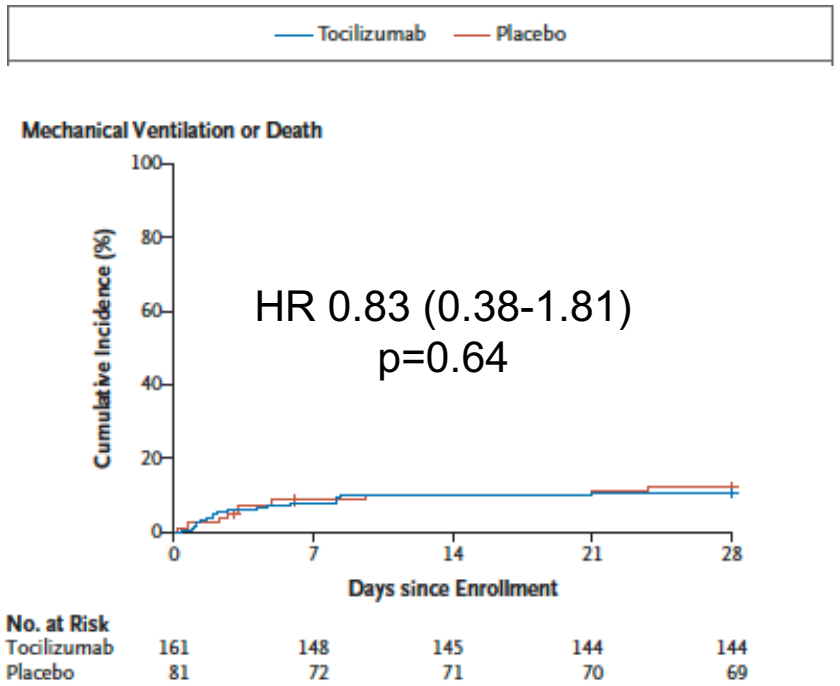

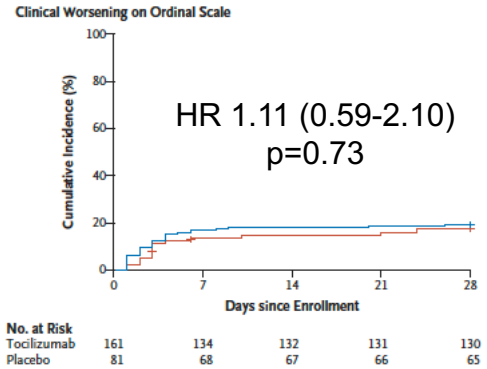

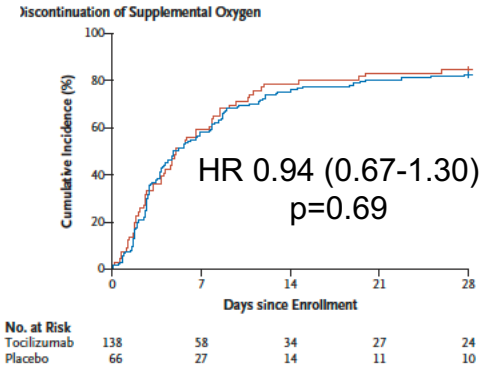

Adverse events: neutropenia < 1 G/L (13% vs. 1%, p=0.0002)

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

Giulio Cavalli, Giacomo De Luca, Corrado Campochiaro, Emanuel Della-Torre, Marco Ripa, Diana Canetti, Chiara Oltolini, Barbara Castiglioni, Chiara Tassan Din, Nicola Boffini, Alessandro Tomelleri, Nicola Farina, Annalisa Ruggeri, Patrizia Rovere-Querini, Giuseppe Di Lucca, Sabina Martinenghi, Raffaella Scotti, Moreno Tresoldi, Fabio Ciceri, Giovanni Landoni, Alberto Zangrillo, Paolo Scarpellini, Lorenzo Dagna

Lancet Rheumatol 2020;
2: e325-31
Published Online
May 7, 2020

Retrospective cohort study

San Raffaele Hospital in Milan, Italy

Moderate-to-severe ARDS,
Non-invasive ventilation outside the ICU,
Hyperinflammation (CRP > 100 mg/L, ferritin > 900 ng/ml)

Anakinra:
high dose IV: 5 mg/kg x2, N=29
vs.
retrospective cohort (!), N=16

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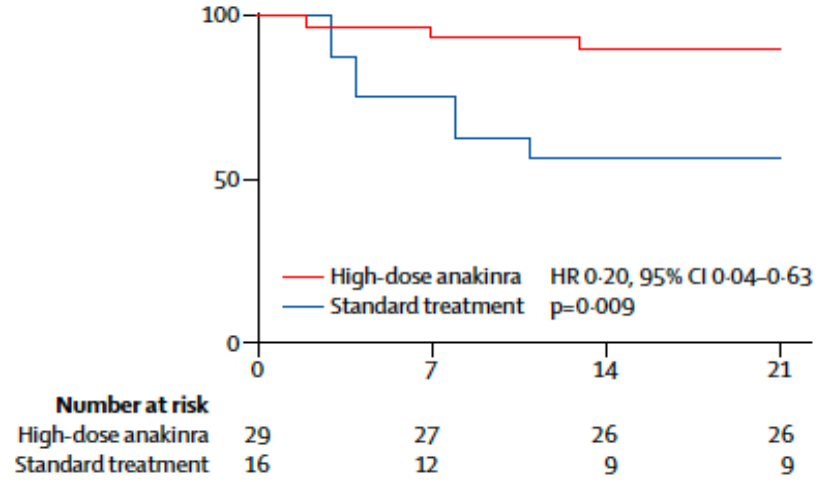
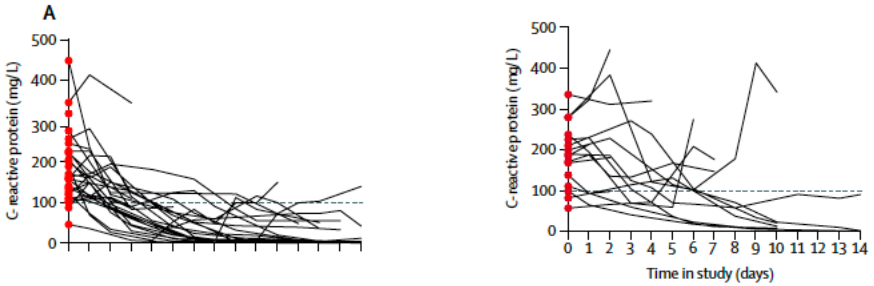
Survival (%)



CRP levels



Anakinra | No- Anakinra

Retrospective cohort study
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vs.
retrospective cohort (!), N=16

"Treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients"

No adjustment for confounders

Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19

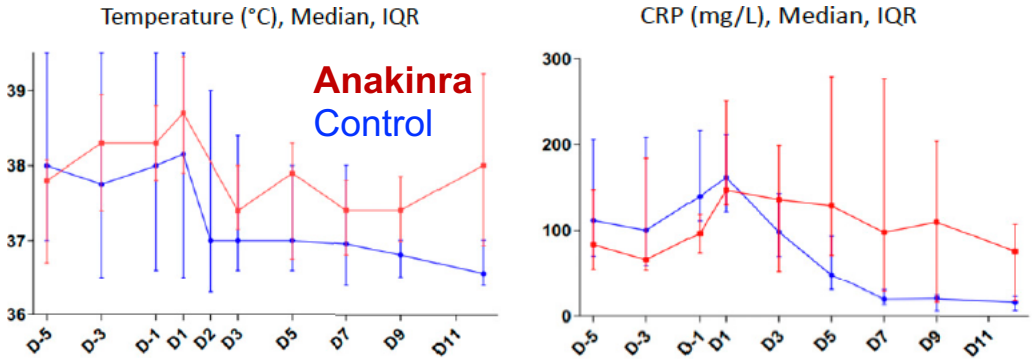
Raphaël Cauchois[a,1], Marie Koubi[a,1], David Delarbre[b], Cécile Manet[c], Julien Carvelli[d], Valery Benjamin Blasco[e], Rodolphe Jean[a], Louis Fouche[f], Charleric Bornet[g], Vanessa Pauly[h], Karin Mazodier[a], Vincent Pestre[c], Pierre-André Jarrot[a], Charles A. Dinarello[i,2], and Gilles Kaplanski[a,2]

PNAS | August 11, 2020 | vol. 117 | no. 32 | 18951–18953

(received for review May 11, 2020)

Retropective, 22 patients, 3 centers
acute severe respiratory failure + systemic inflammation
O_2 requirement > 4l/min, CRP > 110 mg/L

12 treated *vs.* 10 non treated
Anakinra IV, 300 mg per day, 5 days, then tapering over 3 days



No death, best clinical improvement,
more days without invasive mechanical ventilation.
Rapid effect:
decrease of fever and CRP at day 3

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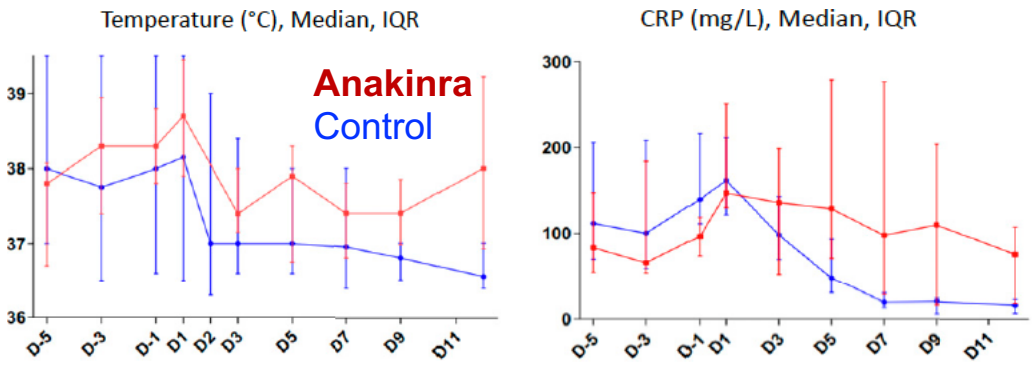

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Anakinra for severe forms of COVID-19: a cohort study

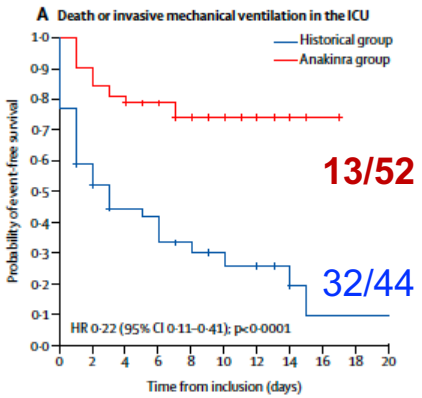
Thomas Huet, Hélène Beaussier, Olivier Voisin, Stéphane Jouveshomme, Gaëlle Dauriat, Isabelle Lazareth, Emmanuelle Sacco, Jean-Marc Naccache, Yvonnick Bézie, Sophie Laplanche, Alice Le Berre, Jérôme Le Pavec, Sergio Salmeron, Joseph Emmerich, Jean-Jacques Mourad, Gilles Chatellier, Gilles Hayem

Lancet Rheumatol 2020; 2: e393-400
Published Online May 29, 2020

Hospital Paris St Joseph
Patients: 52 prospectivelly treated *vs.* 44 historical, non-treated
$SaO_2 \leq 93\%$ under oxygen 6 L/min.
or aggravation: $SaO_2 \leq 93\%$ under 3L/min
and loss of 3% of SaO_2 in ambiant air over 24h.

Anakinra 100 g SC twice a day 72 h then 100 mg per day, 7 days

Main outcome:
admision to the ICU for invasive mechanical ventilation, or death.



Multivariate analysis:
aHR=0.22 (0.10-0.49) p=0.0002

Waiting for double-blind RCTs.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

7 RCTs with at least one interventional arm containing an anakinra-based treatment

ANACONDA study: French multicentre, open-label, randomized, controlled superiority trial
standard of care and Anakinra *vs.* standard of care
hospitalised patients with COVID-19 infection and worsening respiratory symptoms
primary outcome: patient alive and free of mechanical ventilation
71 included patients

Anakinra, 100mg IV every 6 hours, day 1, 2 and 3.
Day 4 to day 10: Anakinra 100mg every 12 hours.

Has been suspended on October 30, 2020:
the interim review of data shows an ***unexplained early excess mortality in the intervention arm****.*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Double-blind, RCT

Patients hospitalised with COVID-19, lower respiratory tract infection
Remdesivir: 200 mg D1, then 100 g daily up to 10 days, vs. placebo
541 vs. 521

Primary outcome:
Initially: comparison of the 8-category ordinal scale scores on D15
Then… **time to recovery up to day 29**
i.e. *discharge or hospitalisation for infection-control purposes only*

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Median recovery time:
10 days (9-11) *vs.* 15 days (13-18)

Mortality:
D_{29}: 11.4% vs. 15.2%, *NS*

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Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

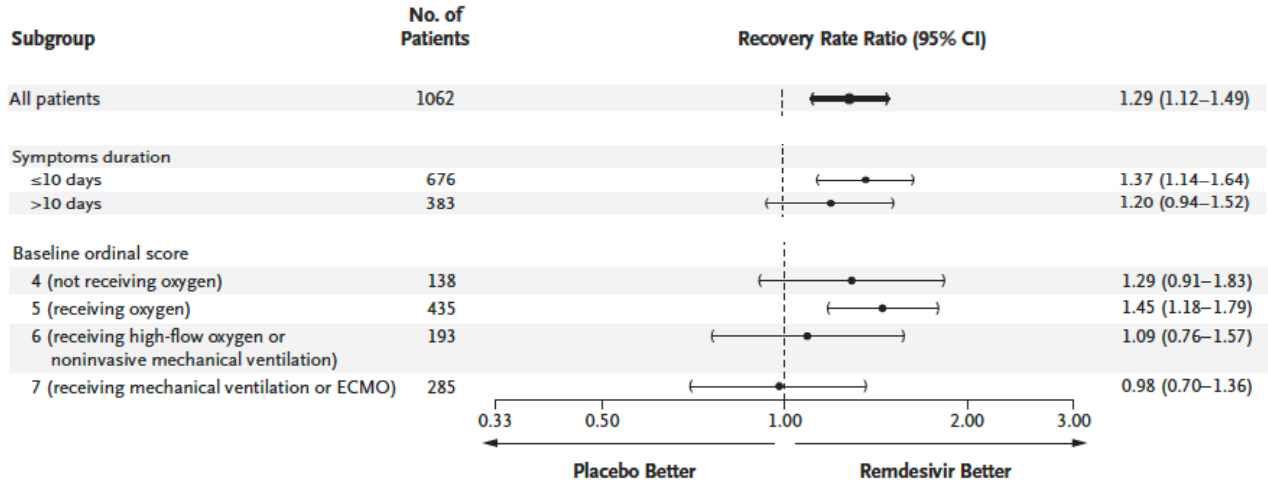
Median recovery time:
10 days (9-11) *vs.* 15 days (13-18)

Mortality:
D_{29}: 11.4% vs. 15.2%, *NS*

Double-blind, RCT

Patients hospitalised with COVID-19, lower respiratory tract infection
Remdesivir: 200 mg D1, then 100 g daily up to 10 days, vs. placebo
541 vs. 521

Primary outcome:
Initially: comparison of the 8-category ordinal scale scores on D15
Then… **time to recovery up to day 29**
i.e. *discharge or hospitalisation for infection-control purposes only*



Benefit: most apparent in patients receiving low-flow O_2 (ordinal score 5)
Interaction tests:
greater benefit with respect to mortality and recovery in lower ordinal score categories

Conclusion

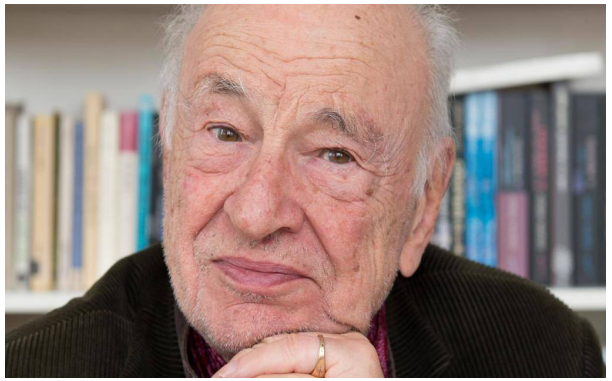
- **A new coagulopathy model**
  - initial focalised coagulopathy with systemic shadows
  - secondary endotheliopathy
  - terminal systemic dissemination
- **The crowning glory of the thrombo-inflammation concept**
  - the era of clinical applications for cytokine assays
- **Uncertainties on anticoagulation**
  - what we have learned over time shows its limits
  - benefit / risk ratios of prophylactic modalities to be specified
  - the pitfalls and limitations of observational studies
  - the temptation of pragmatic individual adaptation, the pioneer syndrome
- **More than ever, blinded RCTs are an absolute necessity**

Still a lot of uncertainties

Knowledge *is a navigation* in a sea of uncertainty, through archipelagos of certainty.

Knowledge *progresses* by integrating uncertainty into it, not by exorcising it.

Edgard Morin,
French philosopher and sociologist



- Haematology
- Gynaecology - Obstetrics
- Intensive Care Unit
- Internal & Vascular Medicine
- Diagnostic Imaging
- Clinical Research Unit

- ***The NOHA network***

Mario KON, placenta