



PLANTÃO CORONAVÍRUS

20/05 | 17h30*

QUARTA-FEIRA

Uso profilático da heparina nos distúrbios de coagulação da Covid-19 - novos achados e possibilidades de tratamento.

*A sala estará aberta, para ajustes, às 17h00 (horário de Salvador)

Palestrante:

Dr^a. Elnara Marcia Negri

Pneumologista e médica intensivista do Hospital Sírio Libanês.

Mediador:

Dr. Miguel Nicolelis

Neurocientista e coordenador do Comitê Científico do Consórcio Nordeste.

EVIDÊNCIAS DA
COAGULOPATIA
COMO CAUSA DA
DISFUNÇÃO DE
ÓRGÃOS NA COVID-19



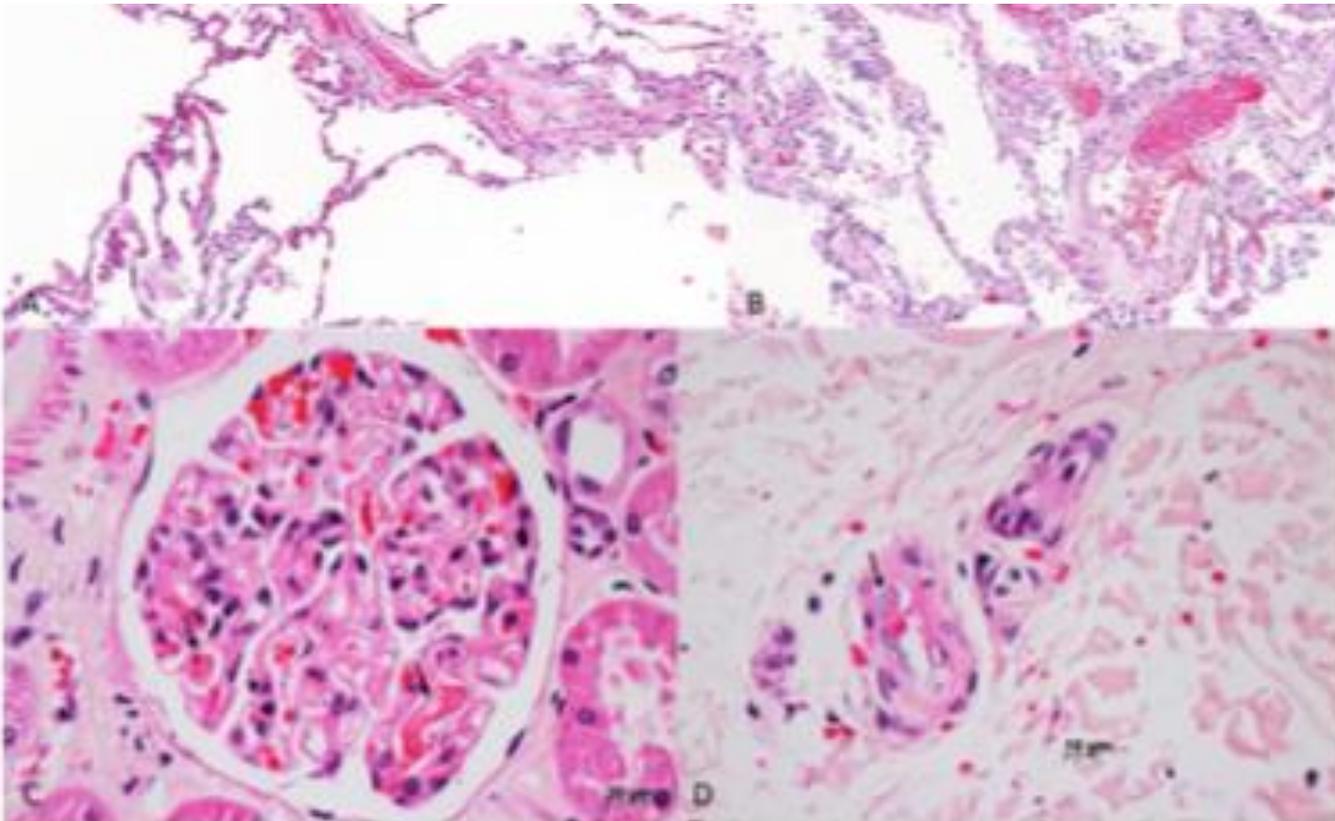
Hipoxemia grave em
pulmões com
complacência normal

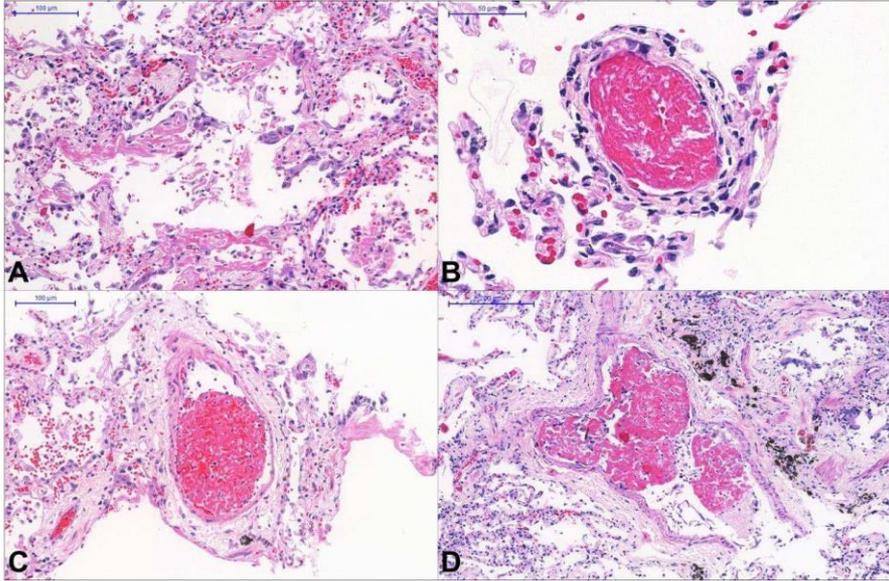
Fenômenos
trombóticos
frequentes

Alterações
laboratorias
(Ddimero, plaquetas,
fibrinogenio)

Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19

Marisa Dolhnikoff^{1*}, Amaro Nunes Duarte-Neto^{1*}, Renata Aparecida de Almeida Monteiro¹, Luiz Fernando Ferraz da Silva^{1,2}, Ellen Pierre de Oliveira³, Paulo Hilário Nascimento Saldiva¹, Thais Mauad¹, Elnara Marcia Negri⁴

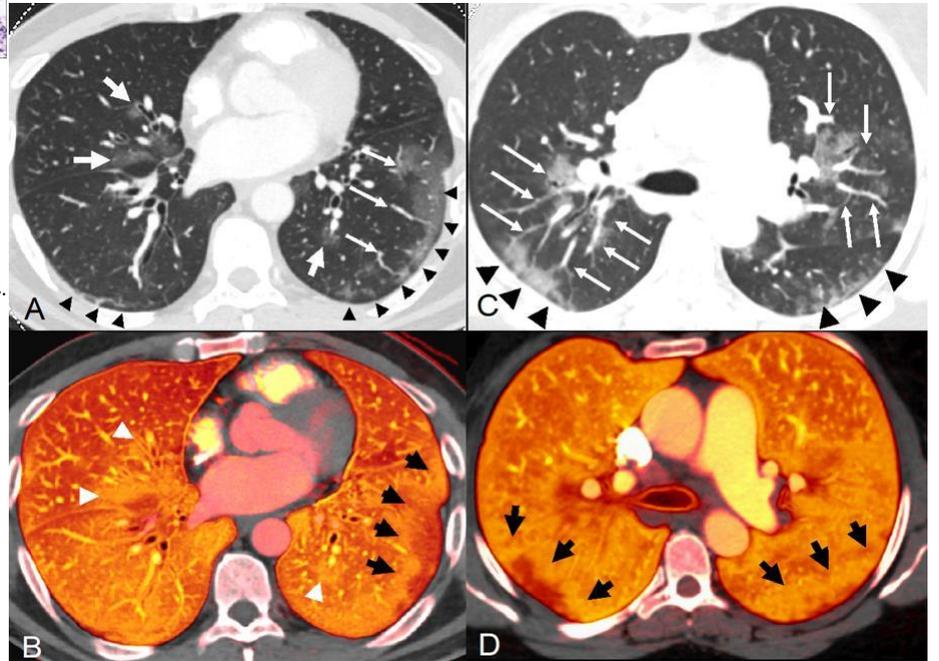




JTH, abril 2020

April 30. [https://doi.org/10.1016/S1473-3099\(20\)30367-4](https://doi.org/10.1016/S1473-3099(20)30367-4).

Lancet



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COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome.

[Gattinoni L](#)¹, [Coppola S](#)², [Cressoni M](#)³, [Busana M](#)¹, [Rossi S](#)⁴, [Chiumello D](#)².

[Am J Respir Crit Care Med](#). 2020 May 15;201(10):1299-1300. doi:

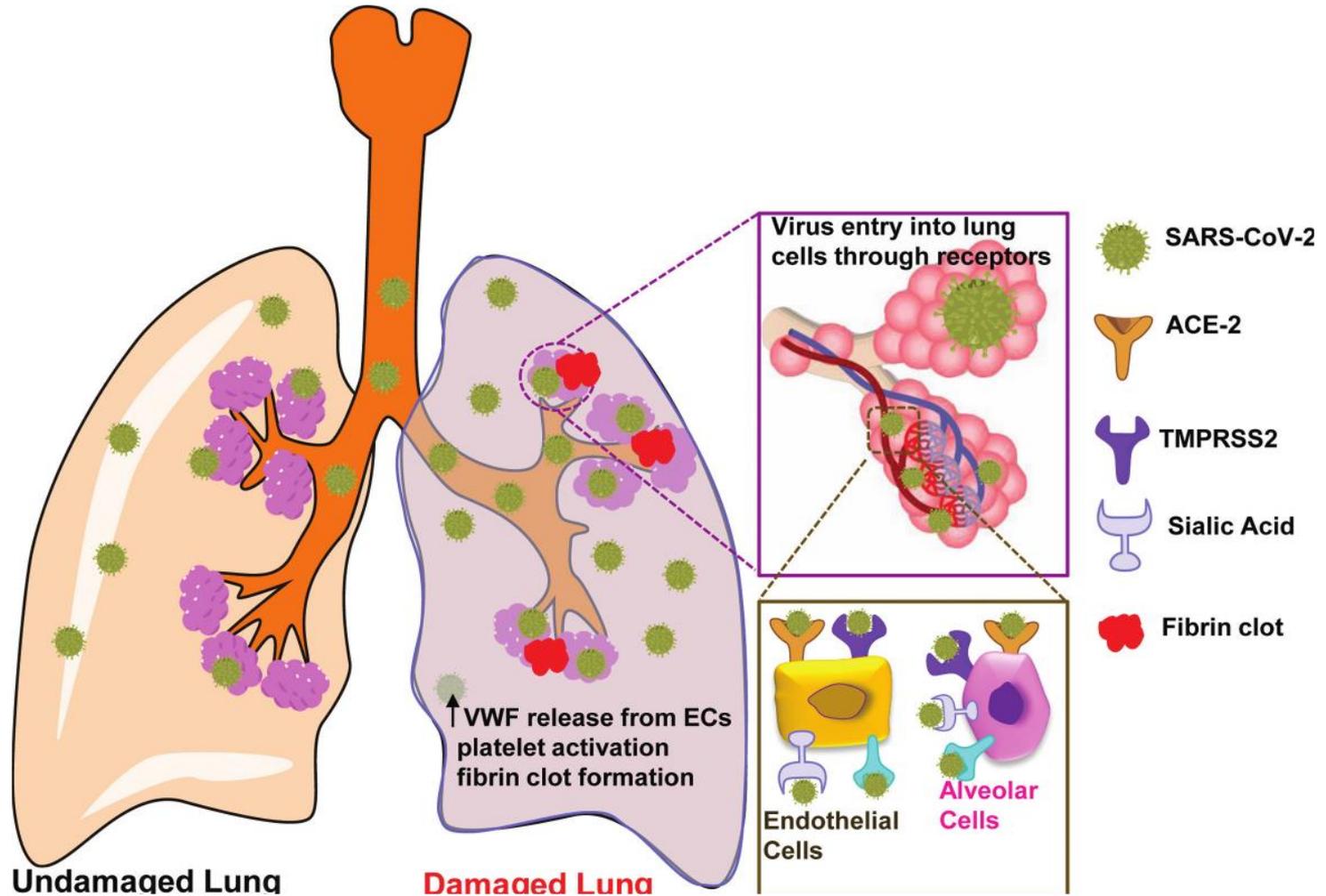
10.1164/rccm.202003-0817LE

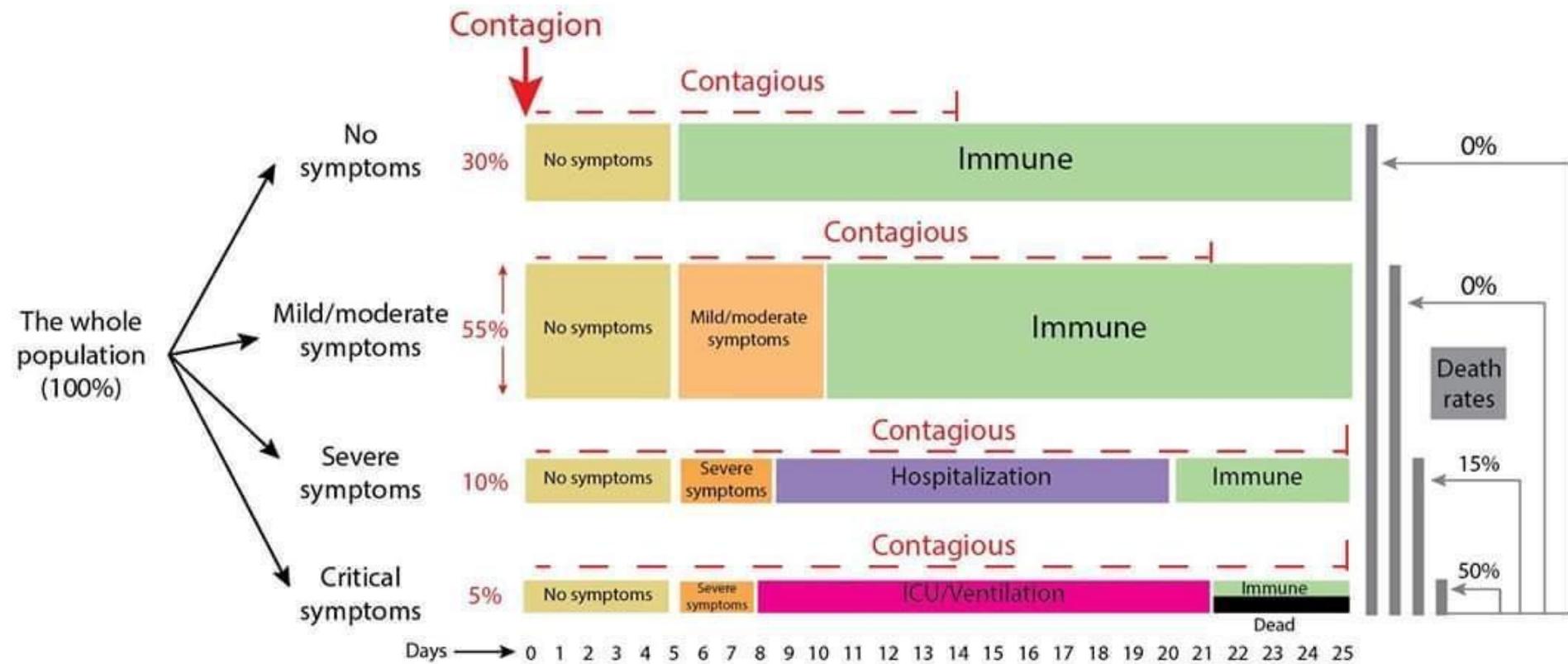
Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis.

[Ciceri, Fabio](#); [Beretta, Luigi](#); [Scandroglio, Anna Mara](#); [Colombo, Sergio](#); [Landoni, Giovanni](#); [Ruggeri, Annalisa](#); [Peccatori, Jacopo](#); [D'Angelo, Armando](#); [De Cobelli, Francesco](#); [Rovere-Querini, Patrizia](#); [Tresoldi, Moreno](#); [Dagna, Lorenzo](#); [Zangrillo, Alberto](#).

[***Crit Care Resusc***](#); 2020 Apr 15.

Hemostatic Lung Abnormality in COVID-19: Pulmonary Thrombosis or Pulmonary Embolism? Thachil et al.





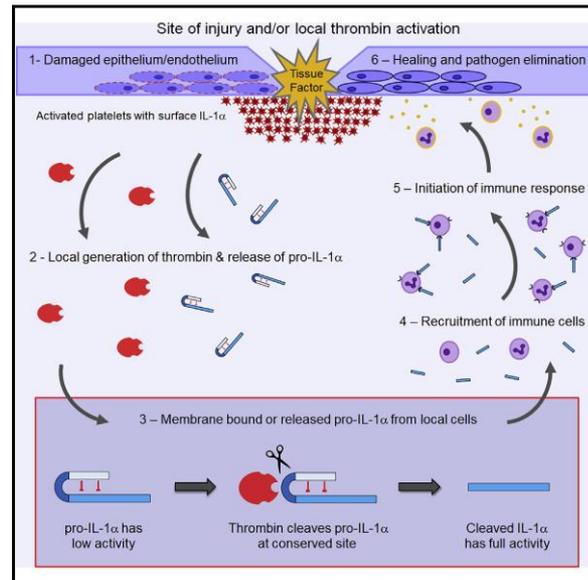
References:

1. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Lauer SA et al. Ann Intern Med. 2020 Mar 10.
2. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. Neil M Ferguson et al. Imperial College COVID-19 Response Team. 16 March 2020.
3. Viral dynamics in mild and severe cases of Covid-19. Yang Liu et al. The Lancet, March 19, 2020.

Immunity

The Coagulation and Immune Systems Are Directly Linked through the Activation of Interleukin-1 α by Thrombin

Graphical Abstract



Authors

Laura C. Burzynski, Melanie Humphry, Katerina Pyrillou, ..., Paul B. Martin, Martin R. Bennett, Murray C.H. Clarke

Correspondence

mchc2@cam.ac.uk

In Brief

Burzynski et al. reveal that the coagulation protease thrombin directly cleaves pro-interleukin (IL)-1 α , rapidly activating the downstream inflammatory cascade. This cleavage site in IL-1 α is conserved throughout mammals, suggesting that this link between coagulation and inflammation may be relevant in multiple disease settings.

SEPSIS INDUCED COAGULATION (SIC)

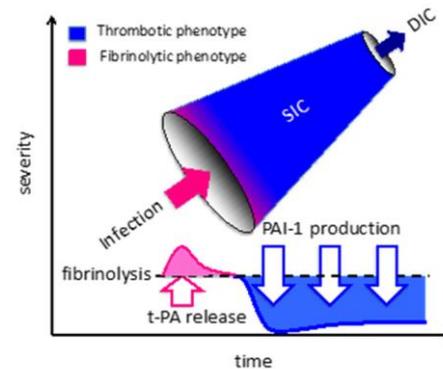


Figure 3. The sequential change from sepsis-induced coagulopathy to disseminated intravascular coagulation. Sepsis-induced coagulopathy progresses to disseminated intravascular coagulation (DIC) if the infection/inflammation is severe enough. Transient activation of fibrinolysis is observed initially, due to the release of tissue-type plasminogen activator (t-PA) from the vascular endothelial cells. Subsequently, the fibrinolytic system is suppressed by the production of plasminogen activator inhibitor-1. The imbalance between coagulation and fibrinolysis leads to a hypercoagulable state and organ dysfunction in sepsis.

TIPOS DE CIVD

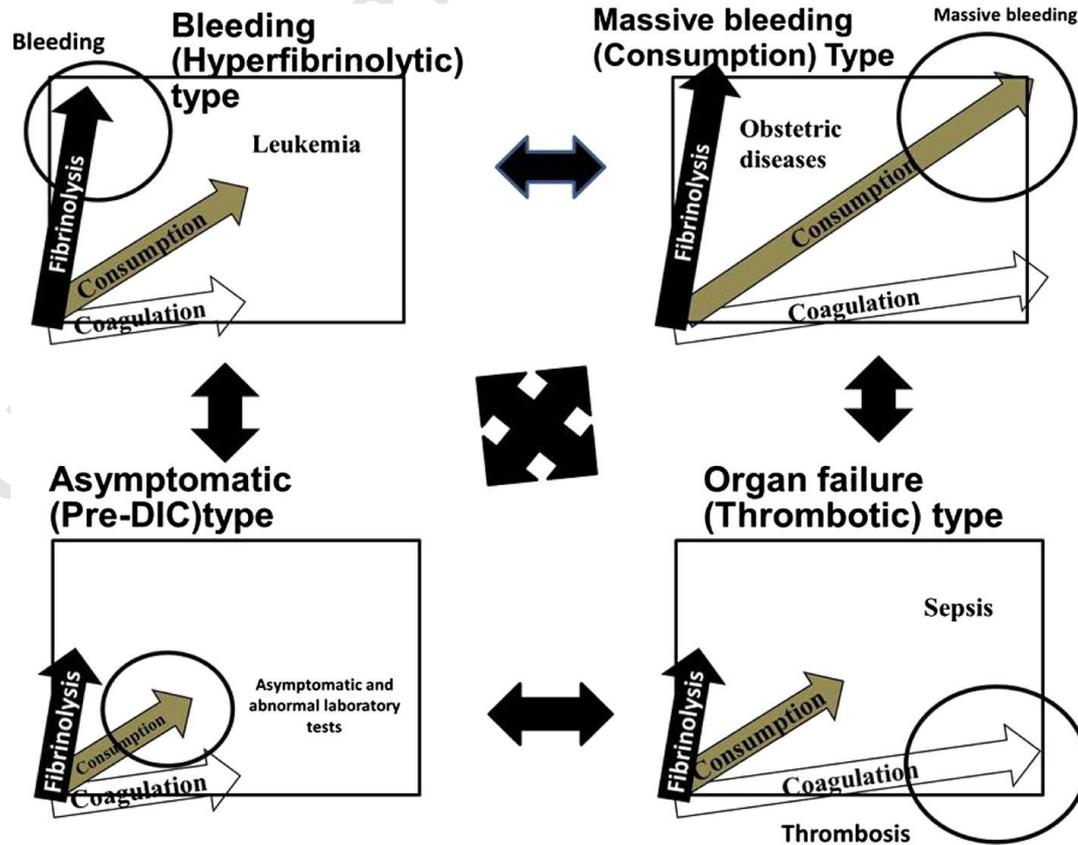


Fig. 1. Four types of DIC.

GLICOALY X ENDOTHELIAL

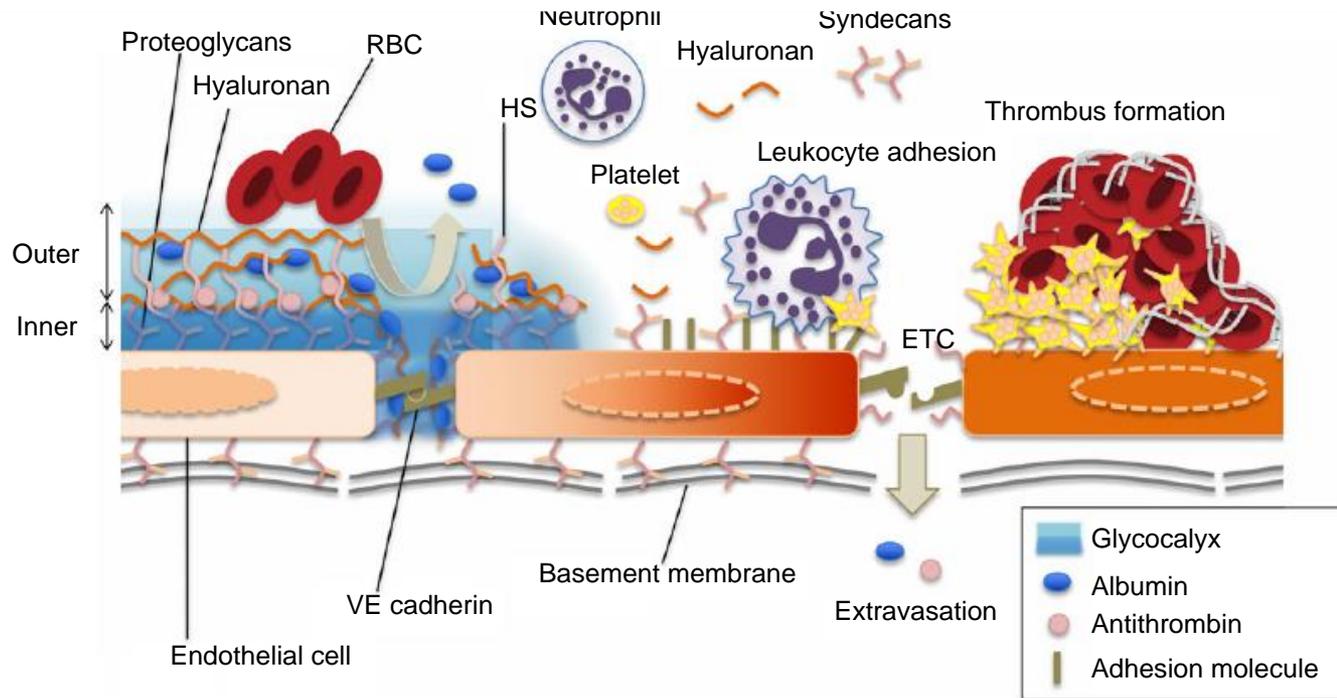
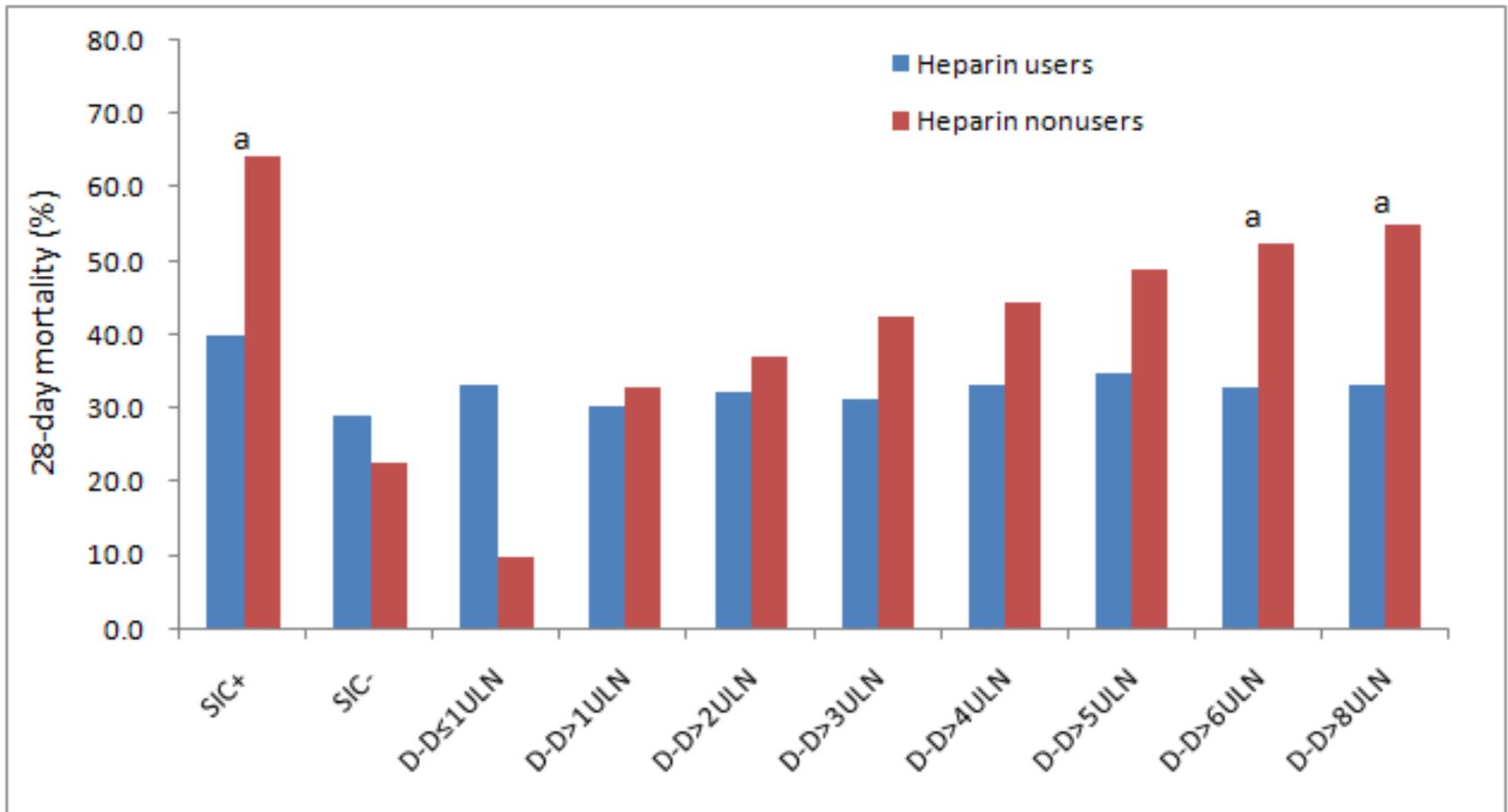


Fig. 1. Vascular endothelial damage and the glycocalyx. The glycocalyx has a two-layer structure. The inner layer is composed of a membrane-binding domain containing proteoglycan (e.g., syndecan) and conjugated oligosaccharides. The outer thicker layer is composed mainly of hyaluronan and plasma proteins (e.g. albumin). Antithrombin binds to its specific binding site, heparan sulphate. The glycocalyx contributes to various vascular functions such as antithrombogenicity, the suppression of cellular adhesion and selective permeability. The glycocalyx is easily destroyed, beginning at an early stage during sepsis, allowing leukocyte adhesion and thrombus formation. RBC, red blood cell; HS, heparan sulphate; ETC, endothelial cleft.



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

Ning Tang¹, Huan Bai¹, Xing Chen¹, Jiale Gong¹, Dengju Li², Ziyong Sun^{1*}

EFEITOS DE HEPARINA ALÉM DA ANTICOAGULAÇÃO?

*J Extra Corpor Technol. 2017;49:192-197
The Journal of ExtraCorporal Technology*

Heparin: Effects upon the Glycocalyx and Endothelial Cells

Bruce D. Spiess, MD, FAHA

Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida

Presented at the Perfusion Downunder Meeting, The Barossa Valley, South Australia, Australia, August 6-8, 2015.

The 2019 coronavirus (SARS-CoV-2) surface protein (Spike) S1 Receptor Binding Domain undergoes conformational change upon heparin binding.

Courtney Mycroft-West #1, Dunhao Su#2, Stefano Elli #3, Scott Guimond 4, Gavin Miller 5, Jeremy Turnbull 2, Edwin Yates 2, Marco Guerrini *3, David Fernig *2, Marcelo Lima *1 and Mark Skidmore *1§.

Human Coronavirus NL63 Utilizes Heparan Sulfate Proteoglycans for Attachment to Target Cells

Aleksandra Milewska,^a Miroslaw Zarebski,^b Paulina Nowak,^a Karol Stozek,^a Jan Potempa,^{a,c} Krzysztof Pyrc^{a,d}

Microbiology Department, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland^d; Division of Cell Biophysics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Krakow, Poland^d; Department of Oral Immunology and Infectious Diseases, School of Dentistry, University of Louisville, Louisville, Kentucky, USA^c; Laboratory of Virology, Malopolska Centre of Biotechnology, Jagiellonian University, Krakow, Poland^d

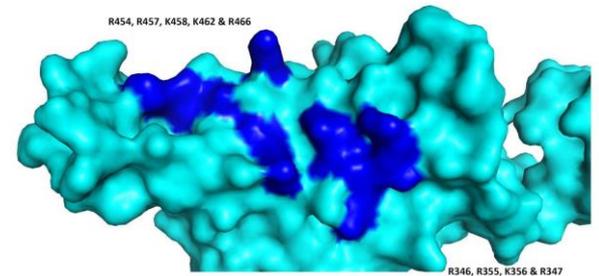
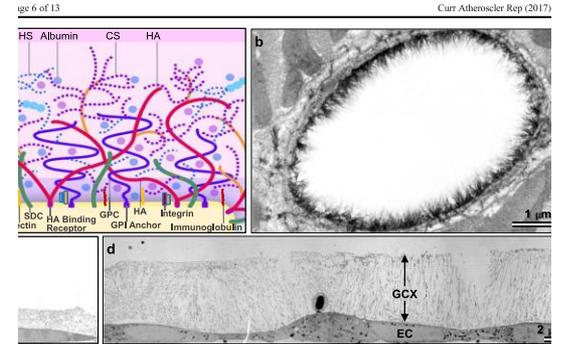
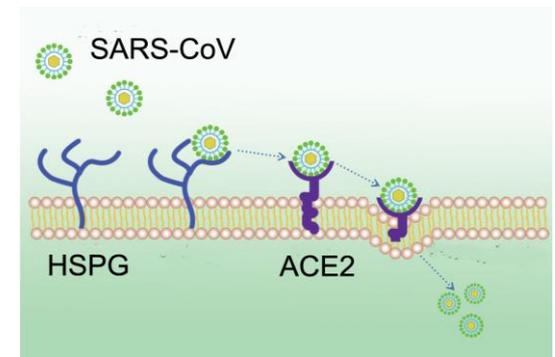


Figure 3. SARS-CoV-2 S1 RBD protein model. Basic amino acids that are solvent accessible on the surface are indicated (dark blue); these can be observed to form a continuous patch.



THE VERSATILE HEPARIN

THACHIL, ET AL - JTH

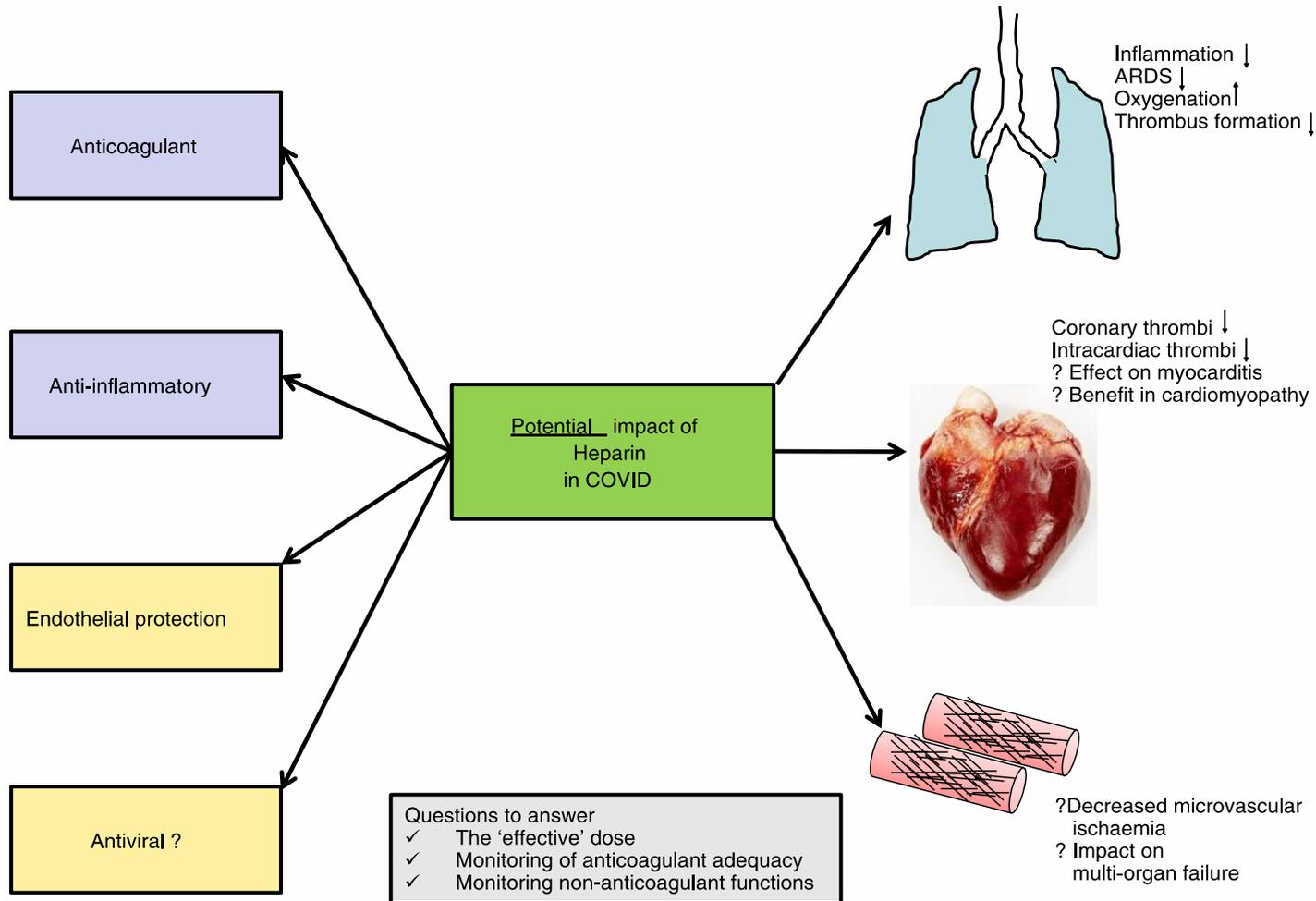


FIGURE 1 Possible impact of heparin in COVID-19

HEPARIN THERAPY IMPROVING HYPOXIA IN COVID-19 PATIENTS - A CASE SERIES

ELNARA MARCIA NEGRI, BRUNA PILOTO, LUCIANA KATO MORINAGA, CARLOS VIANA POYARES JARDIM, SHARI ANNE EL-DASH LAMY, MARCELO ALVES FERREIRA, ELBIO ANTONIO D'AMICO, DANIEL DEHEINZELIN
DOI: [HTTPS://DOI.ORG/10.1101/2020.04.15.20067017](https://doi.org/10.1101/2020.04.15.20067017)

KEY MESSAGES:

Key question:

Does therapeutical doses of heparin bring benefit in the management of respiratory failure in COVID 19 patients? And is it safe?

Bottom line:

Our results show a significant improvement of hypoxemia in COVID-19 patients treated with early heparin therapy.

Why read on?

DIC may play a major role in the development of respiratory failure in COVID-19 and anticoagulation could be incorporated in the standard-of-care for these patients

HEPARIN THERAPY IMPROVING HYPOXIA IN COVID-19 PATIENTS - A CASE SERIES - PROTOCOLO



Profilaxia de TEV para todos os infectados Enoxparina 0,5mg
Manter hidratação adequada em todos os estágios



IMPORTANTE - período da intervenção - Enoxparina 1mg kg dia dividida em 2 doses ou heparina 5000 UI SC 6;6 hs ou 10.000 UI SC 12;12 horas, INICIAR assim que o paciente mostrar os primeiros sinais de hipoxemia com necessidade de suplementação de oxigênio, SAT 93% OU MENOR EM AR AMBIENTE. Dímero D – errático, pode demorar para subir, não esperar para guiar aumento das doses e evolução. Atenção aos pacientes com IMC >35. (ajustar para peso) considerar heparina EV desde o início.

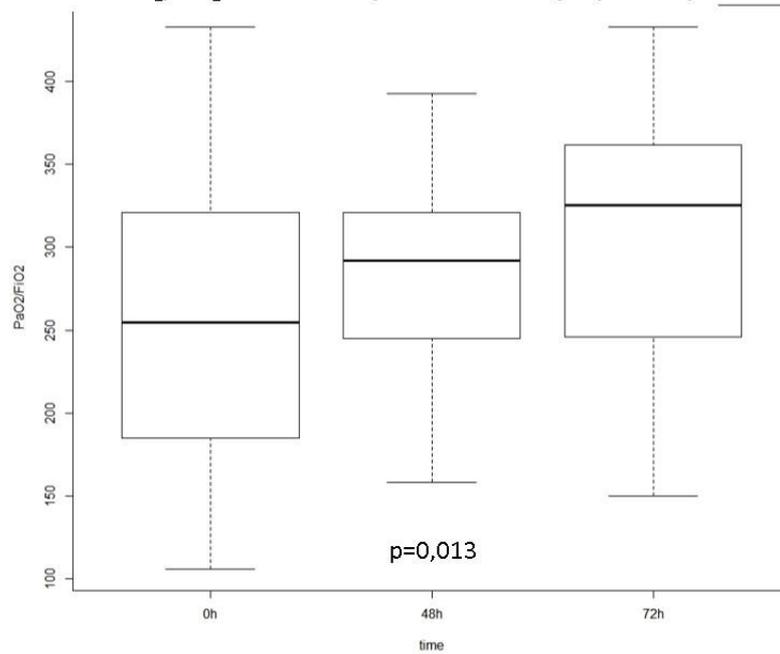


Se internados em Uti e sob VM e ou IMC >35 – consideramos manter heparina EV continua suficiente para manter o TTPA em torno de 2,0 junto com a terapêutica de suporte. Iniciar heparina plena TTPA 2,0 A 2,5 se identificado algum evento trombótico.

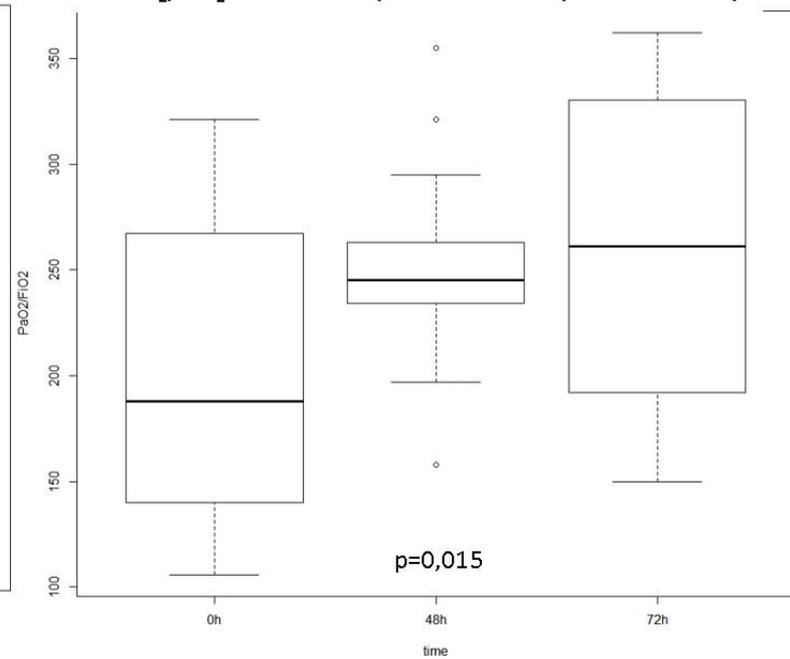


PIORA RADIOLÓGICA, sem elevação substancial do Dímero D, muitas vezes com elevação importante da PCR e ocasionalmente da DHL. Fibrogenese? Infecção bacteriana secundária? Metilprednisolona 0,5 a 1 mg kg dia 5 dias seguida de desmame em 7 a 10 dias, e escalonamento de antibióticos se apropriado.

A. PaO₂/FiO₂ ratio after heparin treatment (all patients)

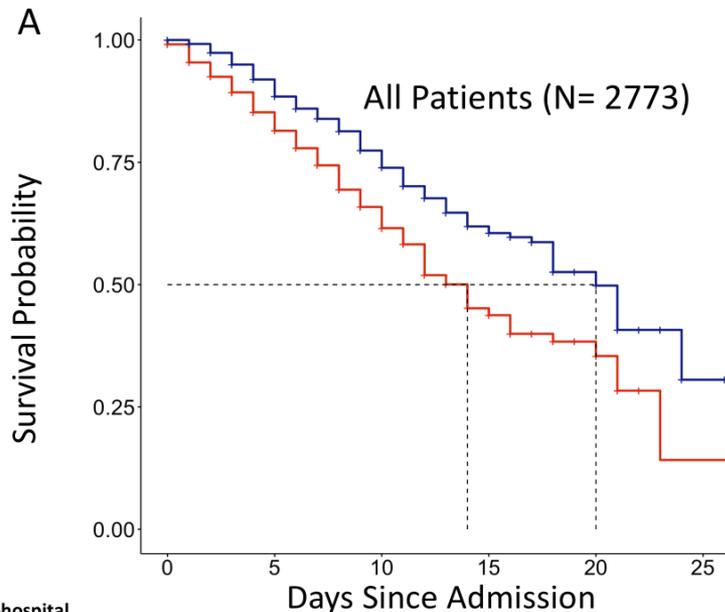


B. PaO₂/FiO₂ ratio after heparin treatment (WHO score ≥ 4)

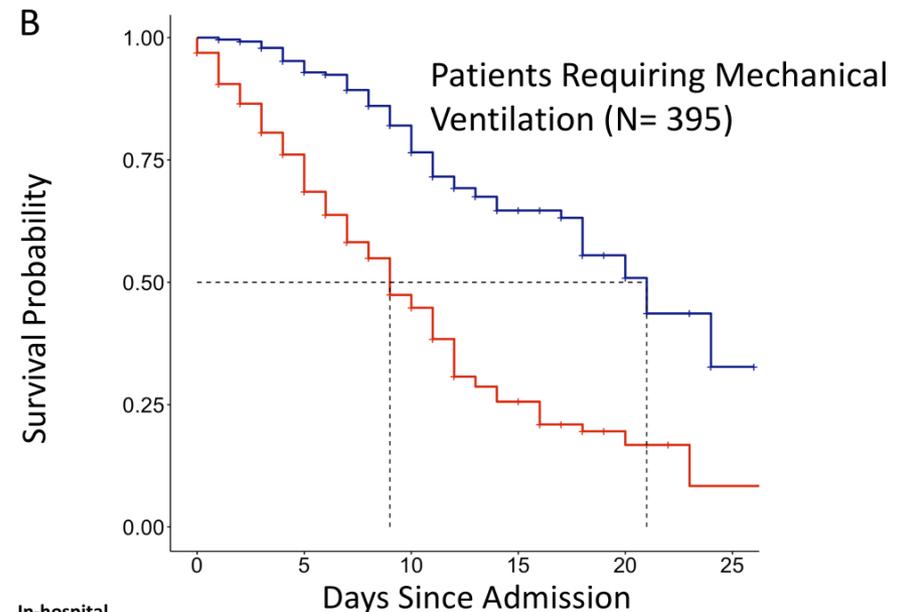


ASSOCIAÇÃO DE ANTICOAGULAÇÃO DE DOSE DE TRATAMENTO COM SOBREVIVÊNCIA HOSPITALAR ENTRE PACIENTES HOSPITALIZADOS COM COVID-19

■ No in-hospital anticoagulation
 ■ Received treatment-dose anticoagulation during hospitalization



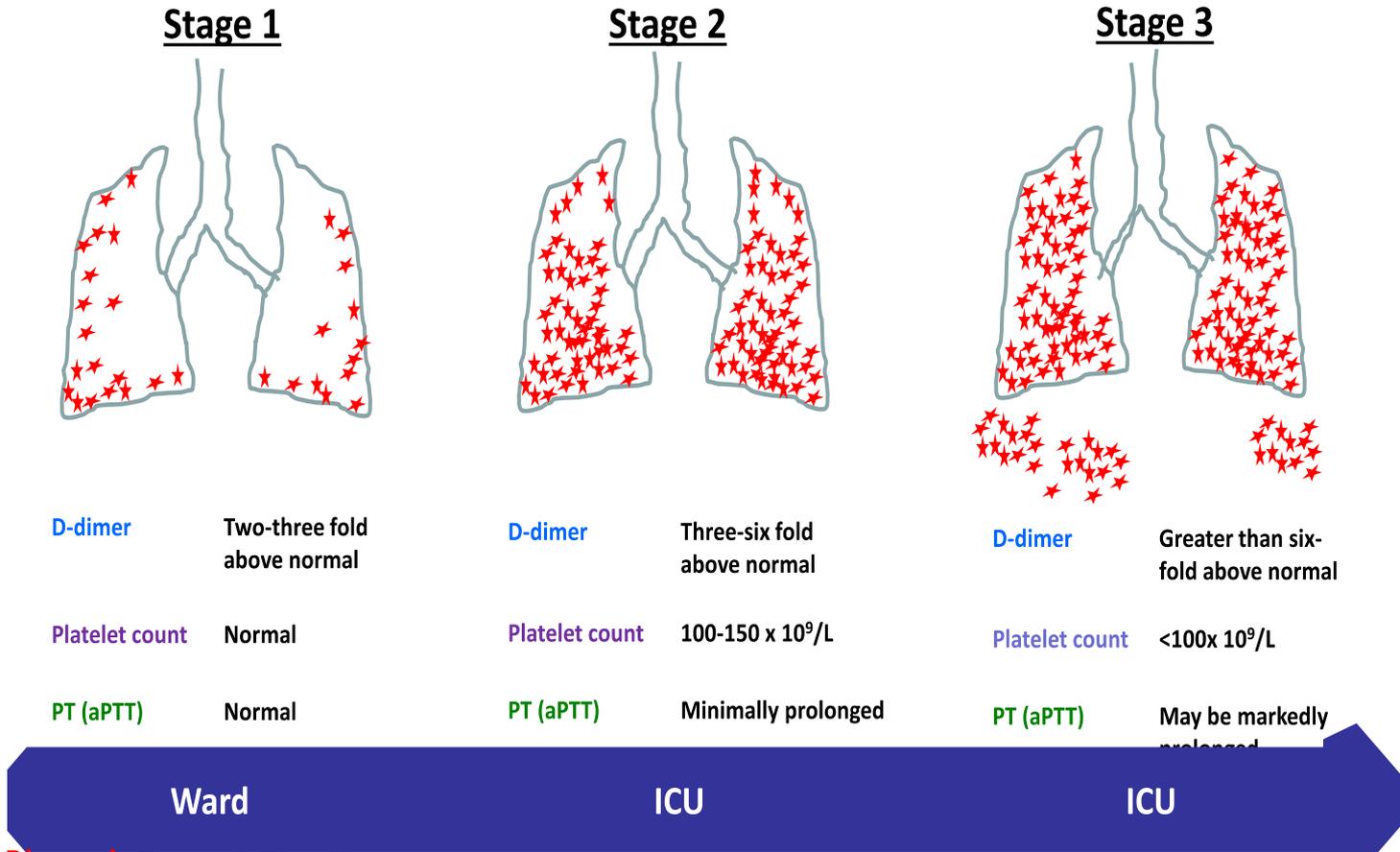
In-hospital Anticoagulation	Number at Risk					
Yes	786	538	266	90	19	3
No	1987	977	296	71	13	1



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

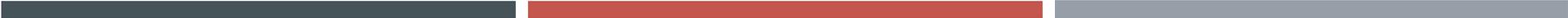
<https://doi.org/10.1016/j.jacc.2020.05.001>

COVID 19 – NÃO FENÓTIPOS DIFERENTES, MAS UMA DOENÇA ESPECTRAL



CONCLUSÕES E PERGUNTAS A SEREM RESPONDIDAS

- Risco trombótico em Covid-19 é real, ocorre em todas as fases da doença e se correlaciona com insuficiência respiratória;
- Trombose acontece apesar das doses profilática;
- Doses devem ser ajustadas na obesidade (maior risco)
- Anticoagulação plena precoce – pode prevenir VM? menos sequelas?
- Anticoagulação plena em UTI e MV – menos tempo em MV? Menor impacto renal e na IMOS?
- Duração da tromboprolifaxia após a alta?



OBRIGADA!