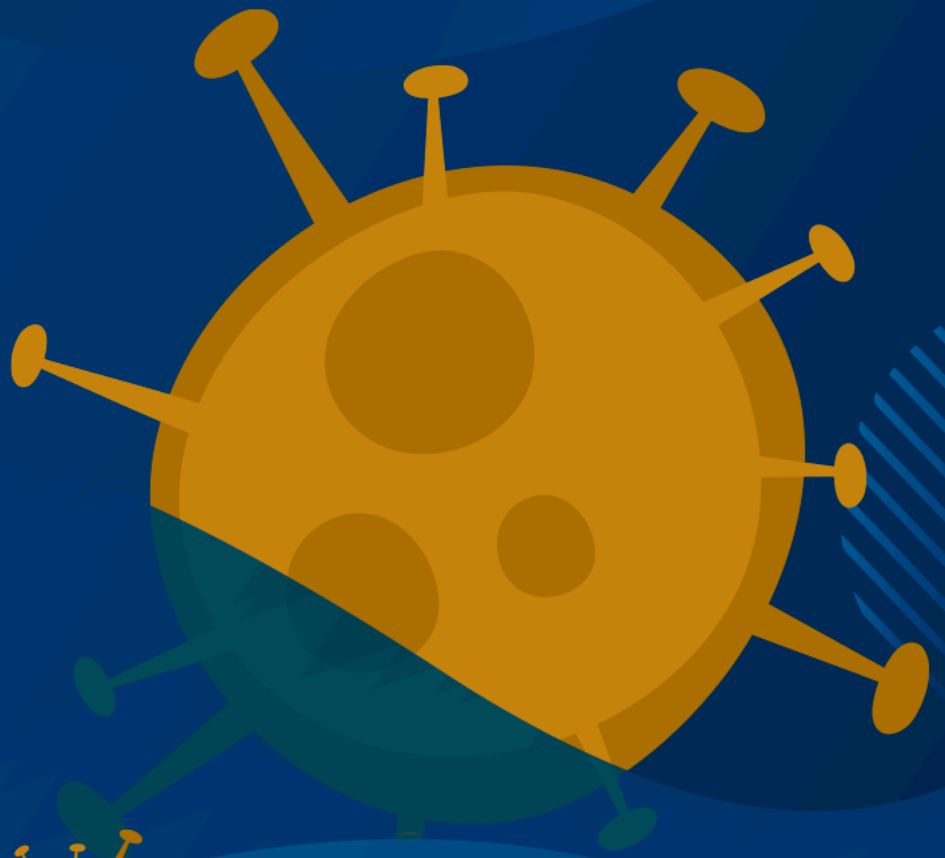
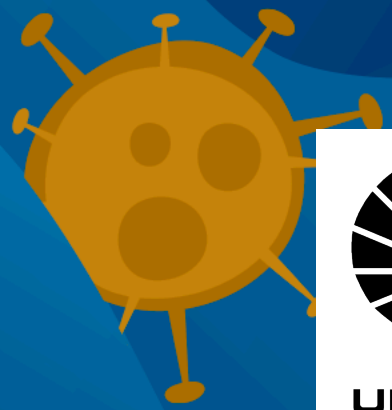
COVID-19 e CIVD

Erich de Paula





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Questões

- O que é CIVD e por que ela ocorre?
- CIVD na COVID-19: o que há de diferente?
- Qual a relevância clínica destas alterações?
- Qual a implicação no manejo destes pacientes?

O que é CIVD e por que ela ocorre?

CIVD (definições ISTH)

" Síndrome **clínico-laboratorial** adquirida"
Processo intermediário, e não uma doença

" Ativação intravascular da coagulação com **perda da localização**"
Disrupção de uma característica essencial da hemostasia

"Se suficientemente grave, **pode levar a lesões orgânicas**"
Mecanismo incerto

Taylor et al, T&H 2001

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Fisiopatologia

Resposta imune inata iniciada por patógeno ou lesão tecidual

↓

↑ Expressão fator tissular	↑ PAI-1 (hipofibrinólise)	↓ Anticoagulantes naturais

Desequilíbrio do balanço hemostático

- **Fase inicial:** hipercoagulabilidade
- **Fase tardia:** sangramento por consumo de fatores e plaquetas

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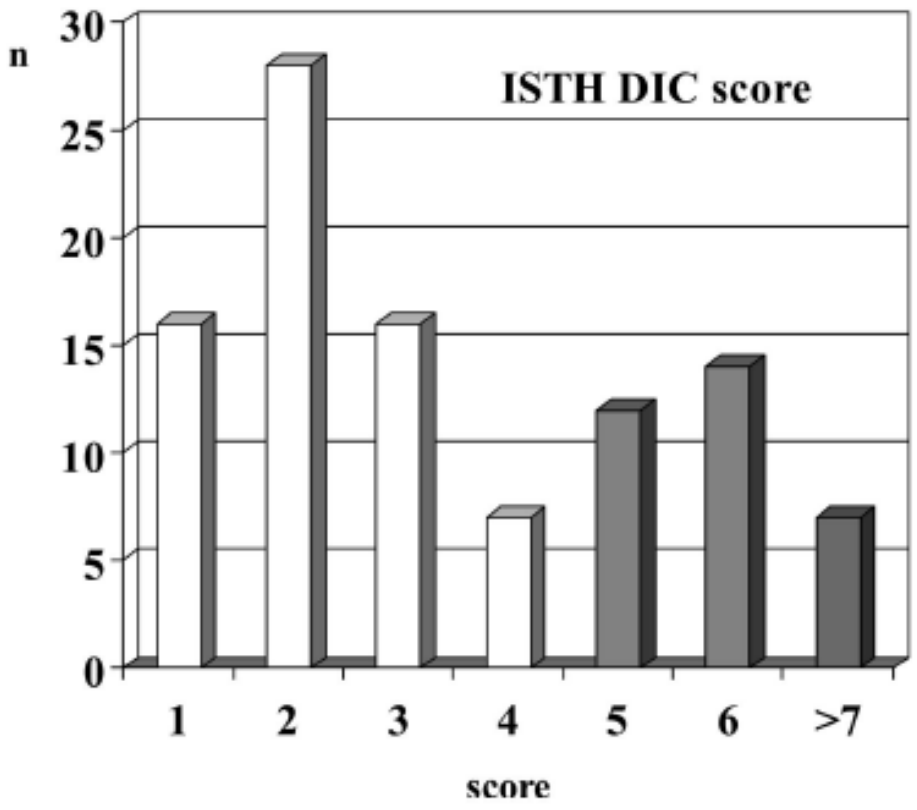
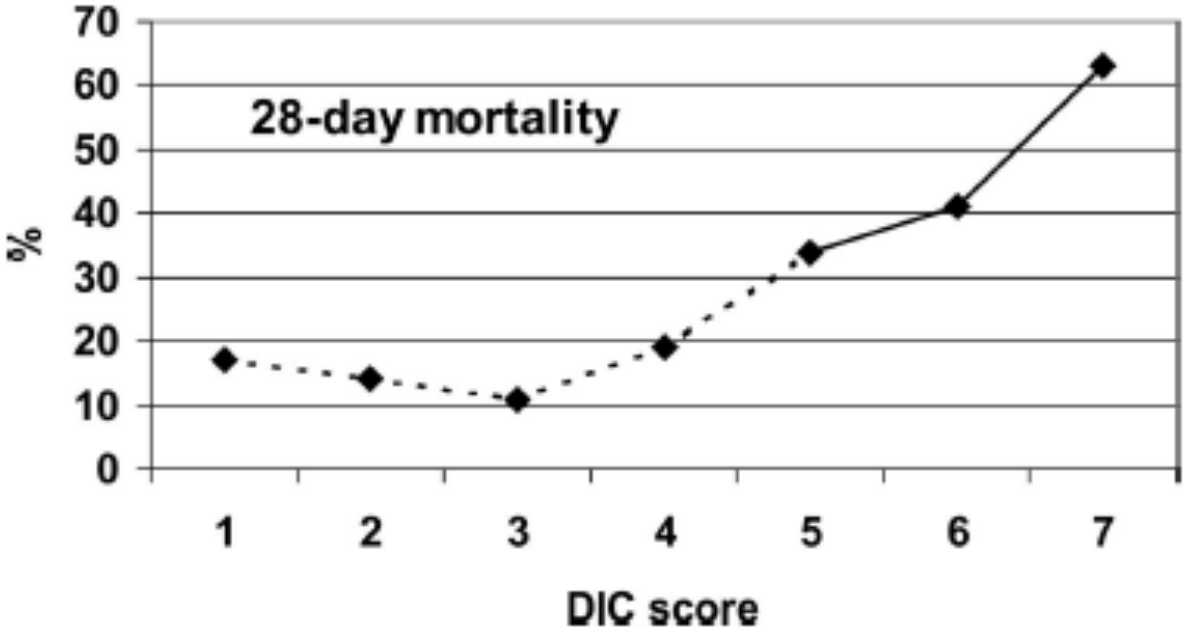
Relevância epidemiológica



CIVD associa-se a mortalidade em outros pacientes críticos



Bakhhtiari et al, CCM 2004

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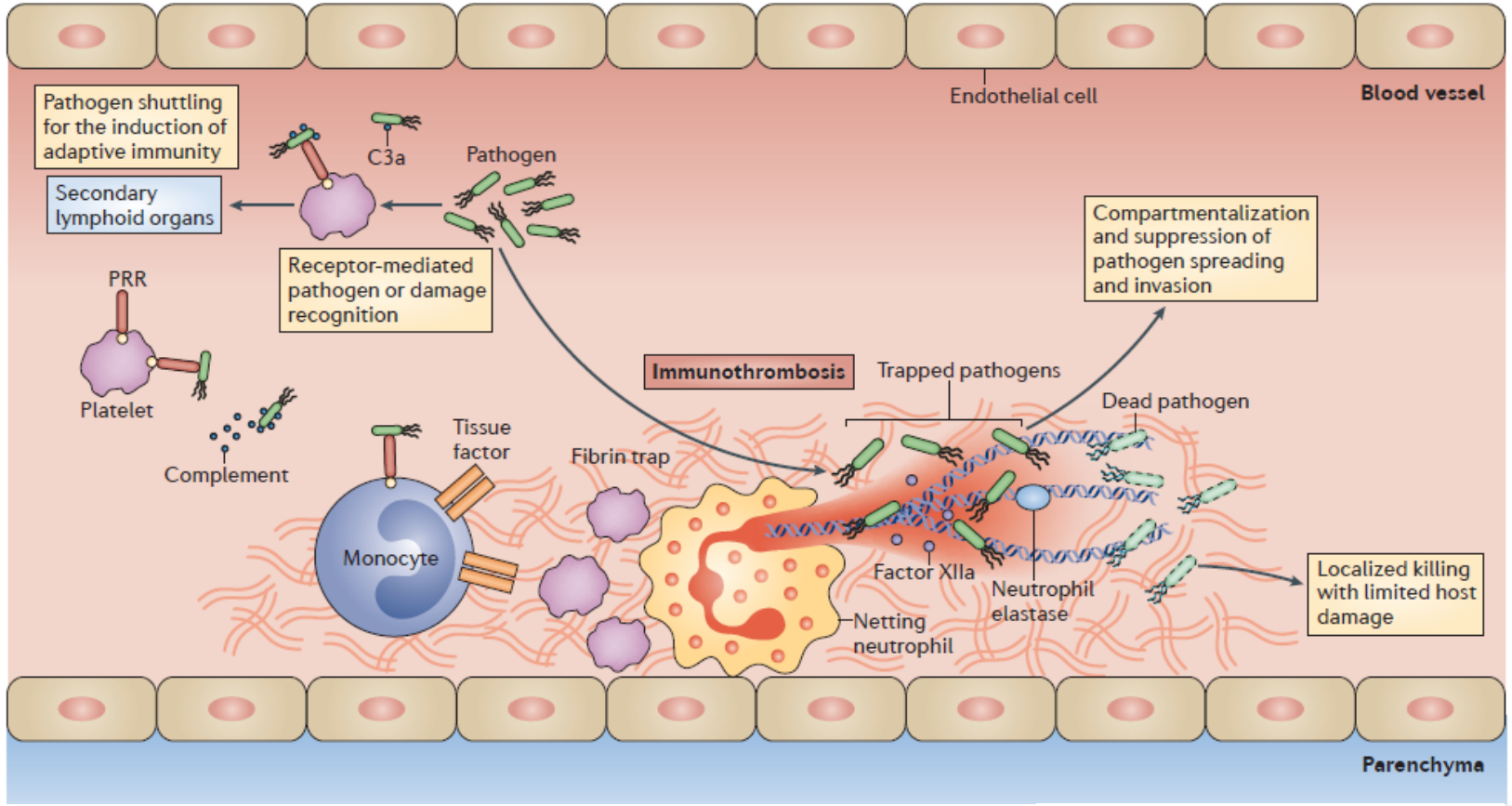
IMUNOTROMBOSE:
Ativação da coagulação como mecanismo efetor da resposta imune



Engelmann & Massberg, Nat Rev Immunol 2013

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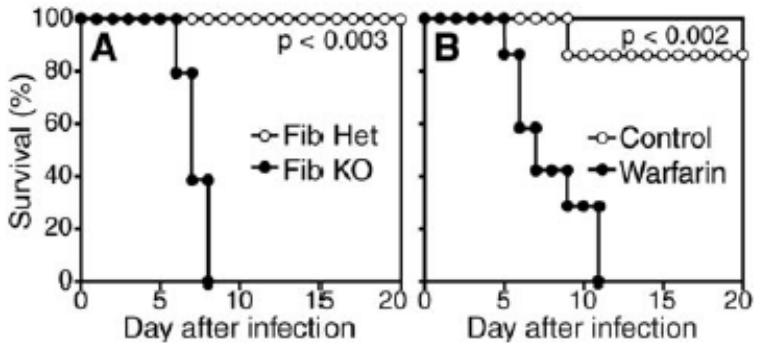
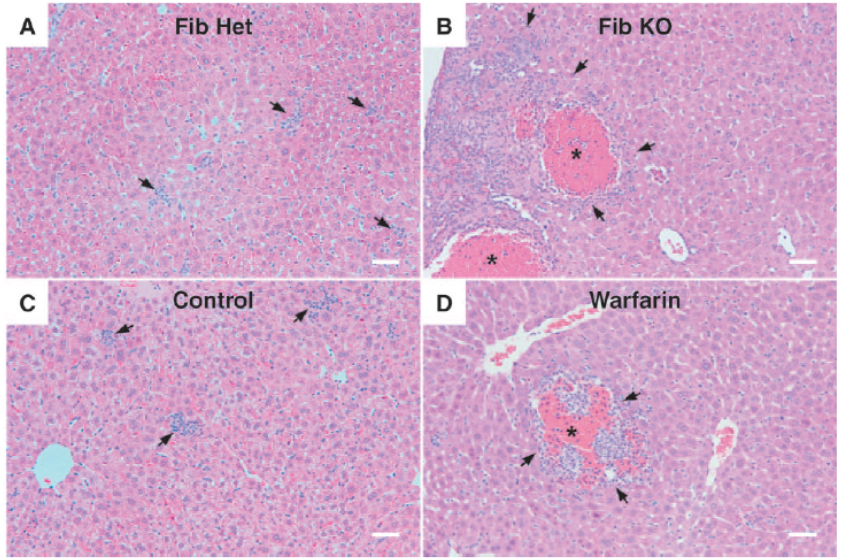
Infection and Immunity

Infection-Stimulated Fibrin Deposition Controls Hemorrhage and Limits Hepatic Bacterial Growth during Listeriosis

Isis K. Mullarky, Frank M. Szaba, Kiera N. Berggren, Michelle A. Parent, Lawrence W. Kummer, Wangxue Chen, Lawrence L. Johnson and Stephen T. Smiley

Infect. Immun. 2005, 73(7):3888. DOI: 10.1128/IAI.73.7.3888-3895.2005.





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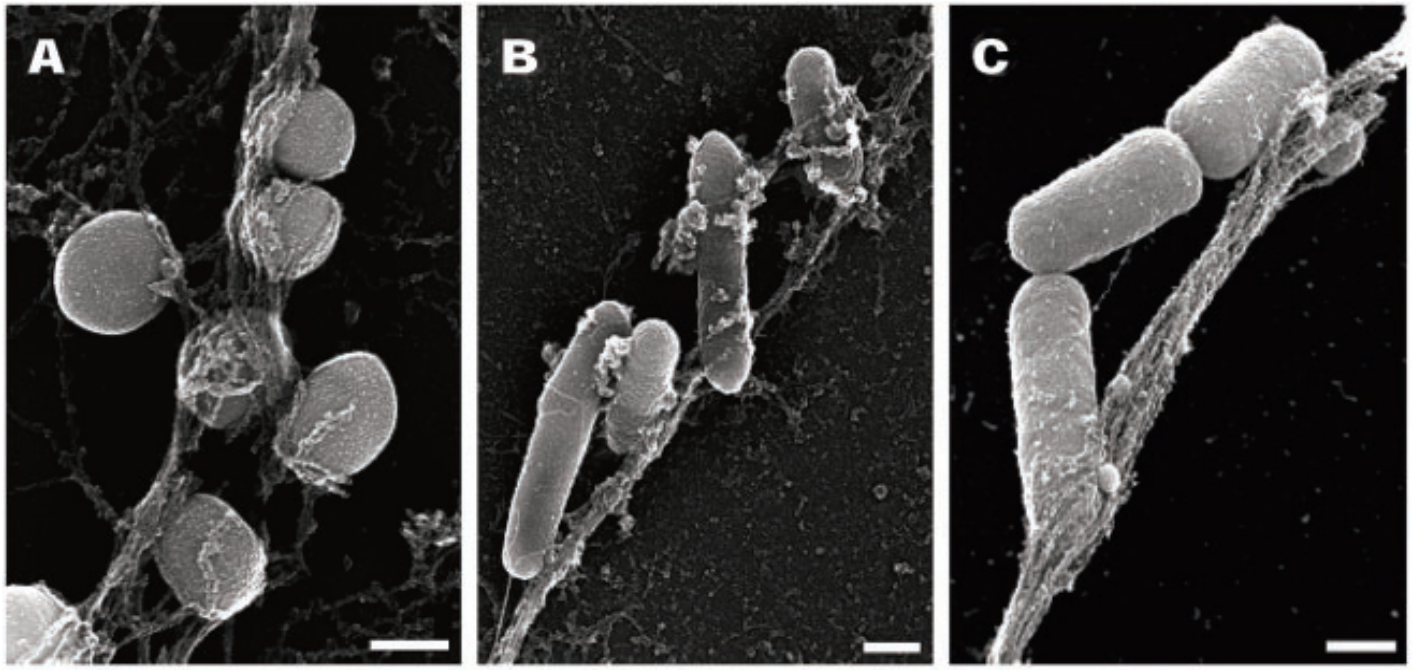
REPORTS

Neutrophil Extracellular Traps Kill Bacteria



Bactérias ligadas a NETs

Brinkmann et al, Science 2004

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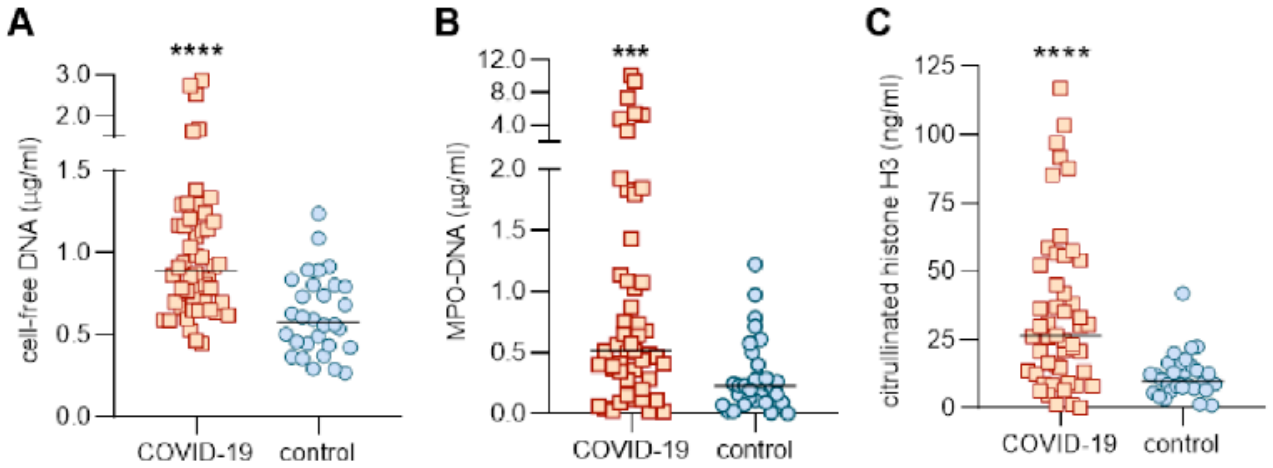

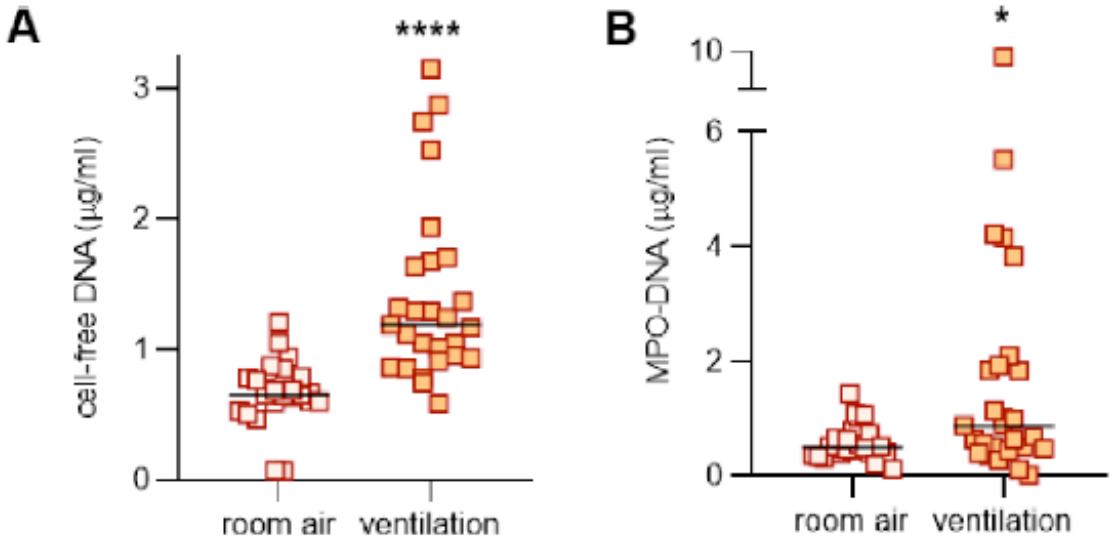

Aumento de marcadores de NETs em pacientes com COVID-19

Zuo et al, JCI Insight 2020

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CIVD na COVID-19: o que há de diferente ?

CIVD x CAHA

(COVID-19- associated hemostatic abnormalities)

- **Níveis elevados de dímeros D**
- Aumento importante do fibrinogênio
- Prolongamento do TP
- Plaquetopenia

} **Menos intensos que em outras formas de CIVD**

- Aumento de FVW e FVIII (ativação endotelial)

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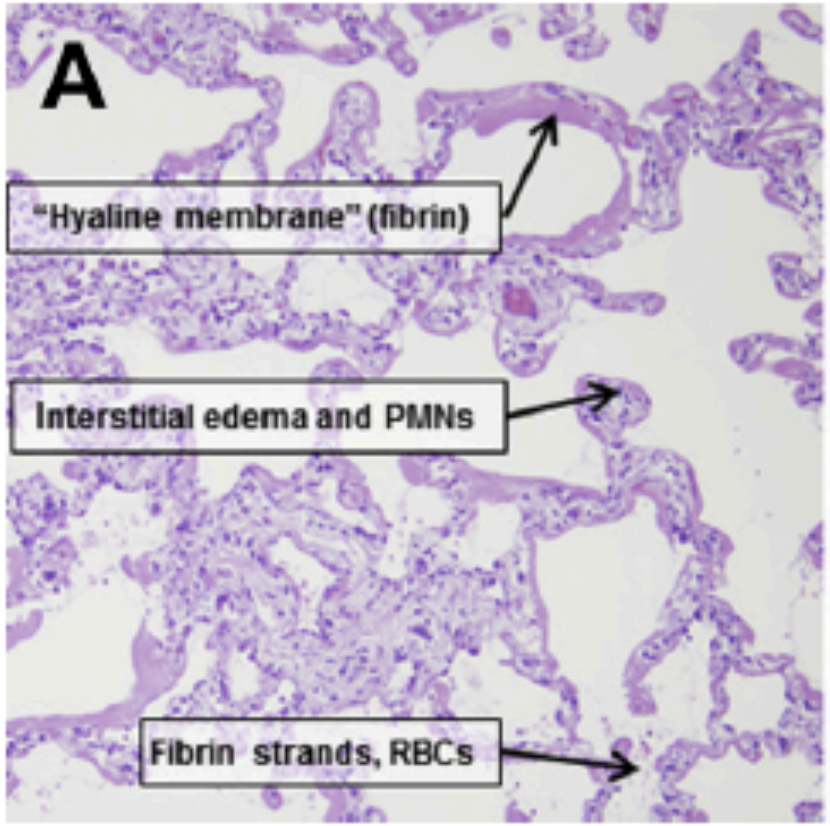
Fisiopatologia da SARA: papel de elementos da hemostasia

Fase exsudativa

- Infiltração de PMNs
- Destruição da barreira alvéolo-capilar
- Formação de membranas hialinas sobre epitélio
- Preenchimento alveolar com exsudato de fibrina
- Imigração de macrófagos

Fase fibroproliferativa (após 3 dias)

- Proliferação celular nos espaços alveolares
- Neoangiogênese
- Hipofibrinólise (aumento PAI-1)
- Microtrombos pulmonares



Standiford & Ward, Transl Res 2016

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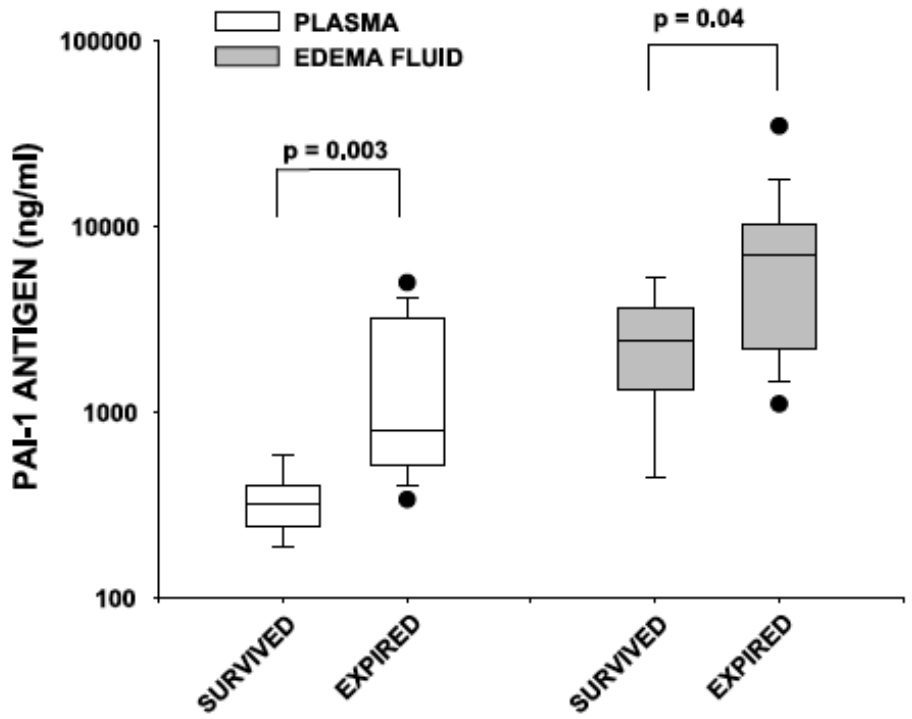
Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury



- Autores também observaram aumento da fibrinogenólise incompleta no espaço alveolar, com acúmulo de fibrina insolúvel
- **Hipótese**: fibrinogênio extravasa do plasma pelo dano alveolar difuso e não é eliminado completamente pela hipofibrinólise

Prabhakaran et al,
Am J Physiol Lung Cell Physiolo 2003

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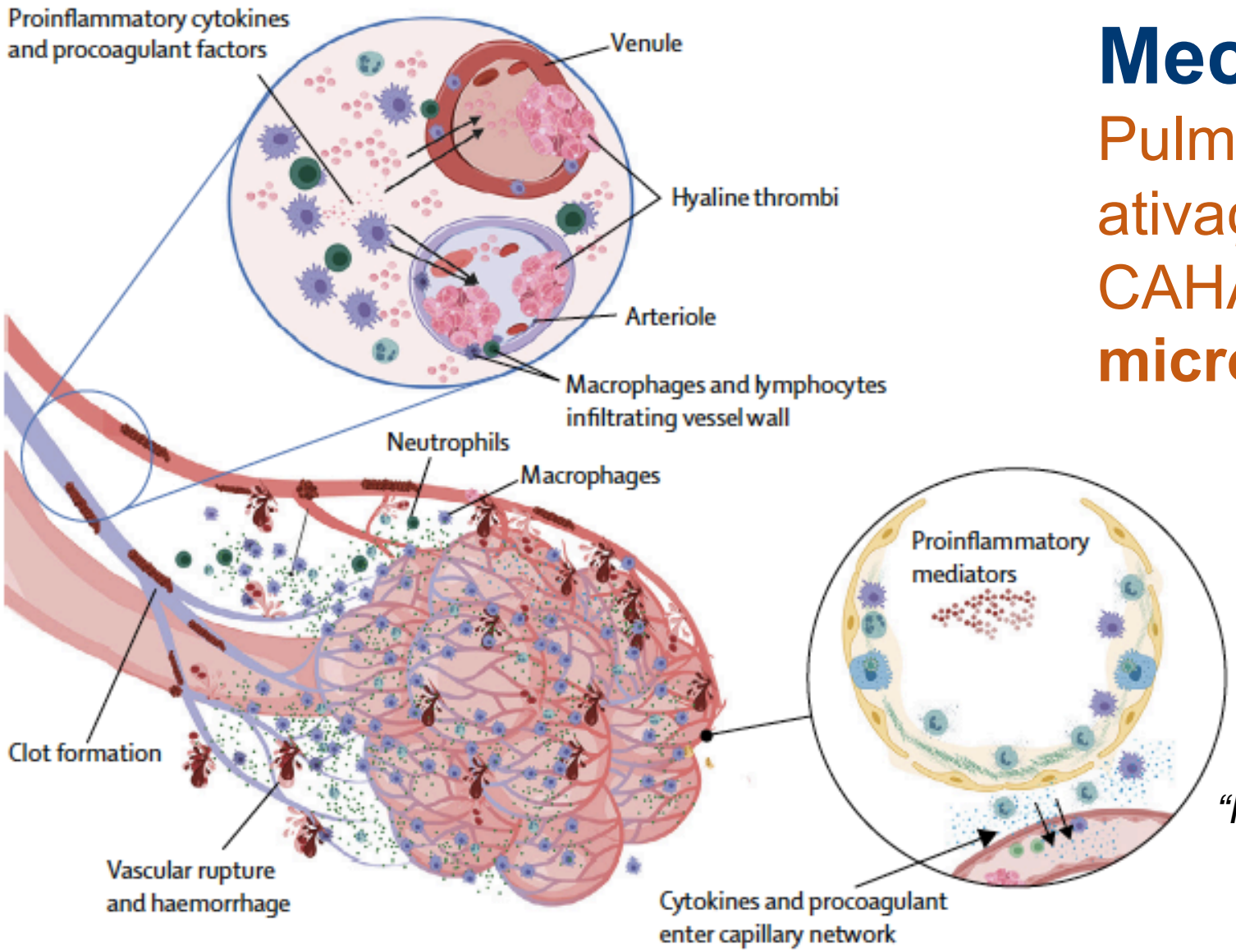
Mecanismo proposto:

Pulmão como órgão central da ativação e perpetuação da CAHA: **Imunotrombose na microcirculação pulmonar**



"Pulmonary intravascular coagulopathy"

McGonagle et al,
Lancet Rheumatol 2020

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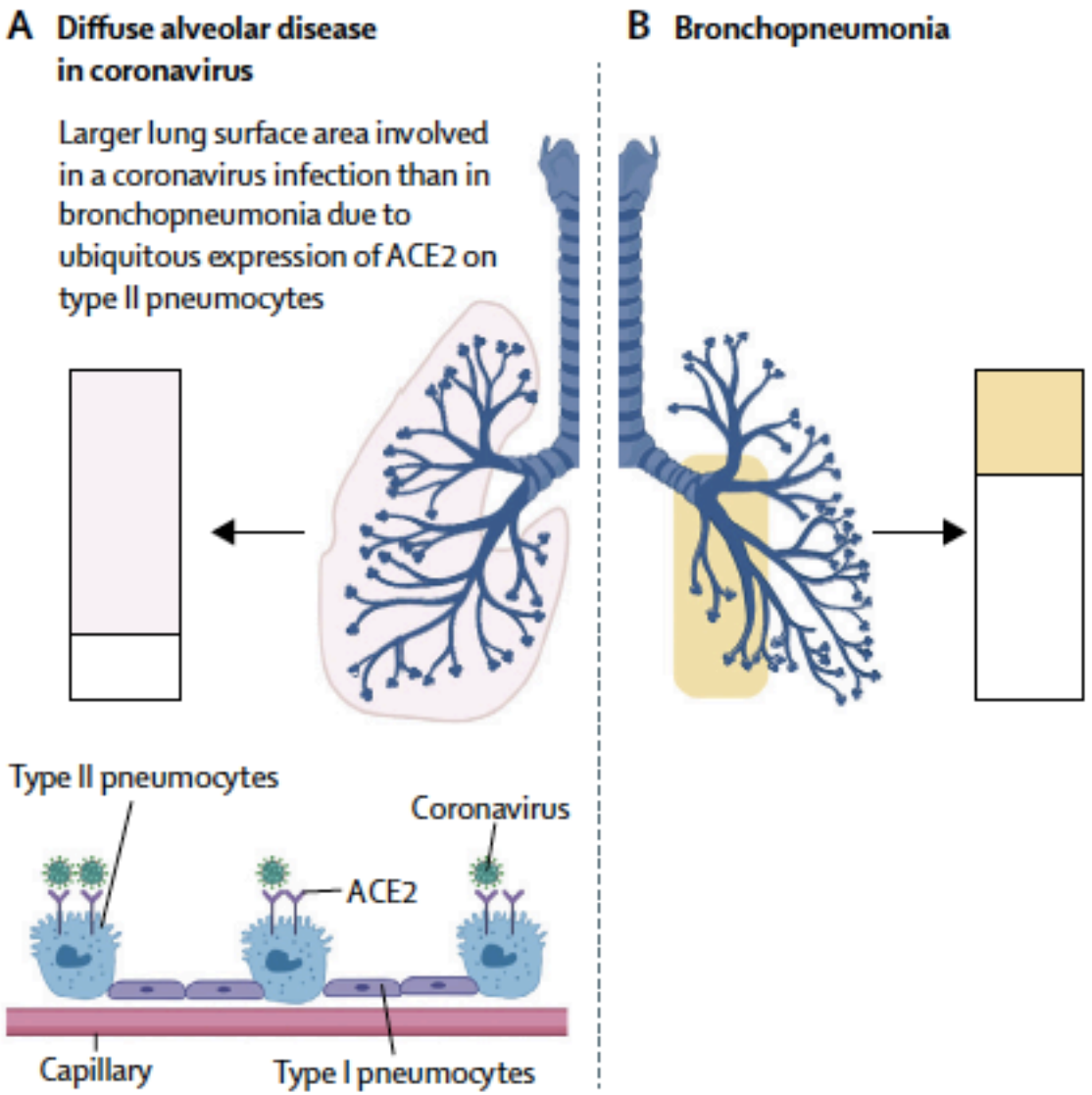

Quão diferente da SARA clássica?

- **Extensão do tecido acometido?**
- Viés de observação pela densidade de casos??

McGonagle et al,
Lancet Rheumatol 2020

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Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2

Parameters	Normal range	COVID (n = 449)	Non-COVID (n = 104)	*P* values
Age (years)		65.1 ± 12.0	58.4 ± 18.0	< 0.001
Sex ratio (male/female)		268/181	72/32	0.073
With underlying diseases		272 (60.6%)	64 (61.5%)	0.768
Receiving heparin		99 (22.0%)	22 (21.2%)	0.842
28-day mortality		134 (29.8%)	16 (15.4%)	0.003
Coagulation parameters				
PT (sec)	11.5–14.5	15.2 ± 5.0	16.2 ± 5.2	0.068
Platelet count (× 109/L)	125–350	215 ± 100	188 ± 98	0.015
D-dimer (μg/mL)	< 0.5	1.94 (0.90–9.44)	2.52 (1.40–5.81)	0.140

Yin et al, J Thromb Thrombol 2020

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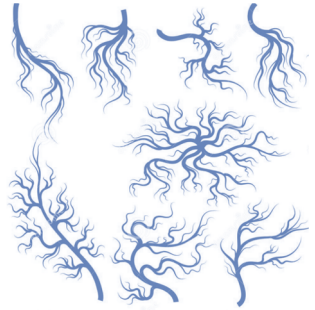
Qual a relevância clínica destas alterações ?

Aumento do risco de TEV

Informação prognóstica



Lesão pulmonar por tromboses microvasculares

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Informação prognóstica

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

Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

- Restrospectivo; 191 pacientes; 2 hospitais
  - 137 altas e 54 óbitos

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
(Continued from previous page)				
Anaemia	29 (15%)	14 (26%)	15 (11%)	0·0094
Platelet count, x 10^9 per L	206·0 (155·0–262·0)	165·5 (107·0–229·0)	220·0 (168·0–271·0)	<0·0001
<100	13 (7%)	11 (20%)	2 (1%)	<0·0001
Albumin, g/L	32·3 (29·1–35·8)	29·1 (26·5–31·3)	33·6 (30·6–36·4)	<0·0001
ALT, U/L	30·0 (17·0–46·0)	40·0 (24·0–51·0)	27·0 (15·0–40·0)	0·0050
>40	59/189 (31%)	26 (48%)	33/135 (24%)	0·0015
Creatinine >133 µmol/L	8/186 (4%)	5 (9%)	3/132 (2%)	0·045
Lactate dehydrogenase, U/L	300·0 (234·0–407·0)	521·0 (363·0–669·0)	253·5 (219·0–318·0)	<0·0001
>245	123/184 (67%)	53 (98%)	70/130(54%)	<0·0001
Creatine kinase, U/L	21·5 (13·0–72·4)	39·0 (19·5–151·0)	18·0 (12·5–52·1)	0·0010
>185	22/168 (13%)	11/52 (21%)	11/116 (9%)	0·038
High-sensitivity cardiac troponin I, pg/mL	4·1 (2·0–14·1)	22·2 (5·6–83·1)	3·0 (1·1–5·5)	<0·0001
>28	24/145 (17%)	23/50 (46%)	1/95 (1%)	<0·0001
Prothrombin time, s	11·6 (10·6–13·0)	12·1 (11·2–13·7)	11·4 (10·4–12·6)	0·0004
<16	171/182 (94%)	47 (87%)	124/128 (97%)	0·016*
≥16	11/182 (6%)	7 (13%)	4/128 (3%)	..

Zhou et al, Lancet 2020

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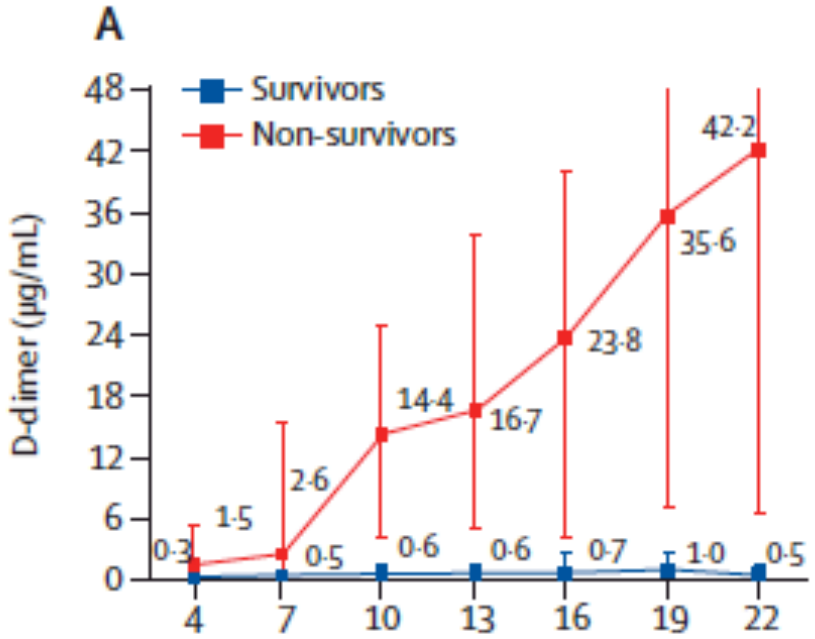
Informação prognóstica



	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
High-sensitivity cardiac troponin I, pg/mL				
≤28	1 (ref)	..	..	..
>28	80·07 (10·34–620·36)	<0·0001	..	..
D-dimer, µg/mL				
≤0·5	1 (ref)	..	1 (ref)	..
> 0·5	1·96 (0·52–7·43)	0·32	2·14 (0·21–21·39)	0·52
> 1	20·04 (6·52–61·56)	<0·0001	18·42 (2·64–128·55)	0·0033
Prothrombin time, s				
<16	1 (ref)	..	..	..
≥16	4·62 (1·29–16·50)	0·019	..	..

Zhou et al, Lancet 2020

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Dynamic evolution of coagulopathy in the first day of severe sepsis: Relationship with mortality and organ failure*

Table 2. Coagulation composite score components

Biomarker	Odds Ratio	95% CI	*p* Value[a]
AT <54% at baseline[b]	2.0	1.4–2.9	.002
AT decreased ≥20%[c]	2.2	1.4–3.4	.003
PT did not decrease by ≥2 secs[c]	1.6	1.1–2.5	.02
D-dimer did not decrease ≥20%[c]	1.7	1.1–2.6	.01

Dhainaut et al, CCM 2005

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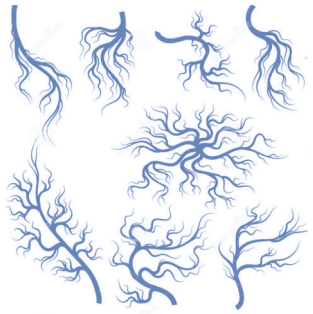
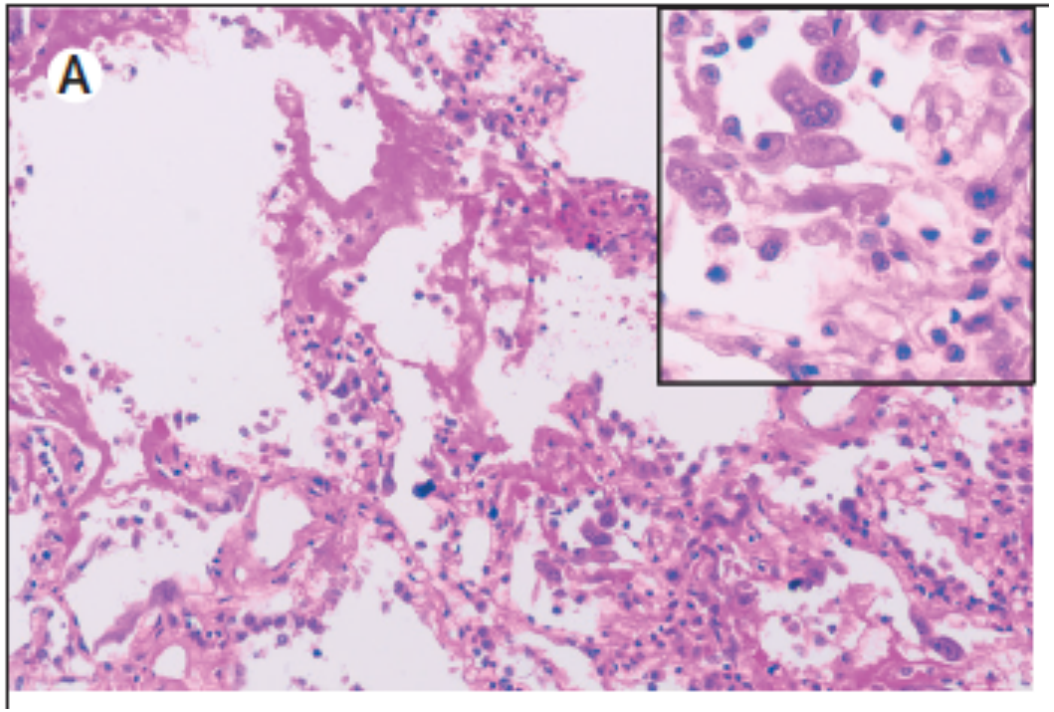


Lesão pulmonar por tromboses microvasculares

Pathological findings of COVID-19 associated with acute respiratory distress syndrome



DAD e formação de membranas hialinas;
Exsudato com fibrina

Xu et al, Lancet Resp Med 2020

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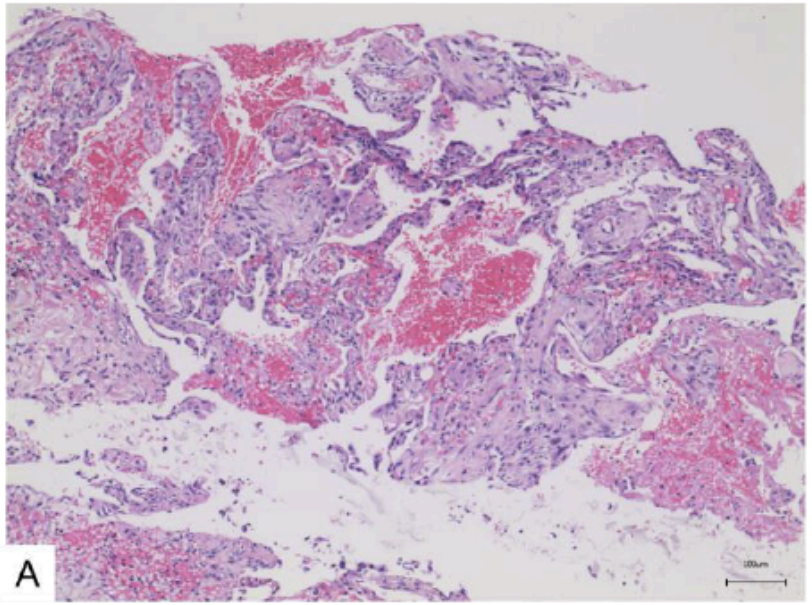
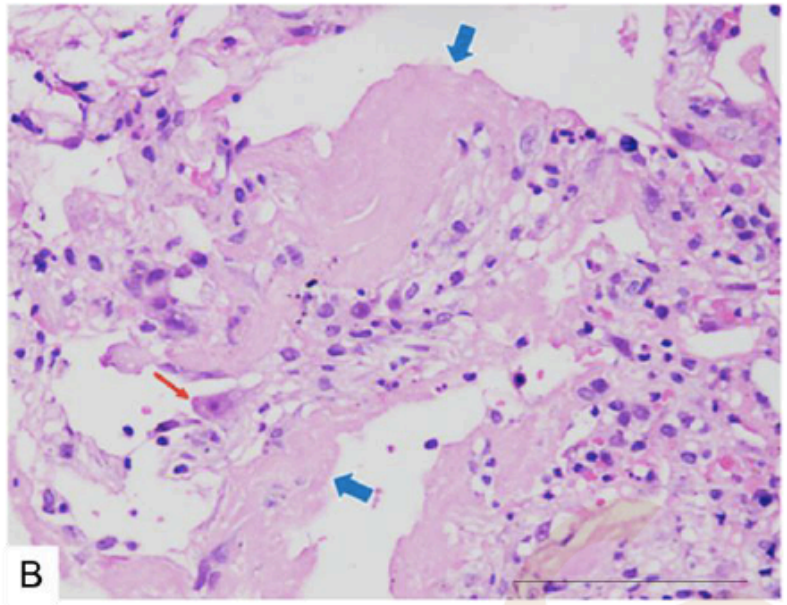
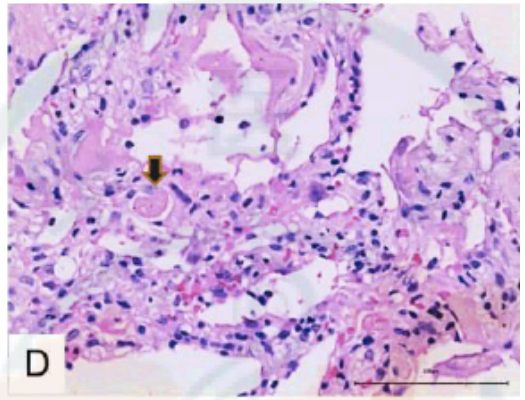
Destruição e exsudato alveolar com sangramento





Fluido seroso intra-alveolar

Dilatação dos capilares com congestão, infiltração mononuclear e **trombose** (seta)



Xiahong et al, 2020

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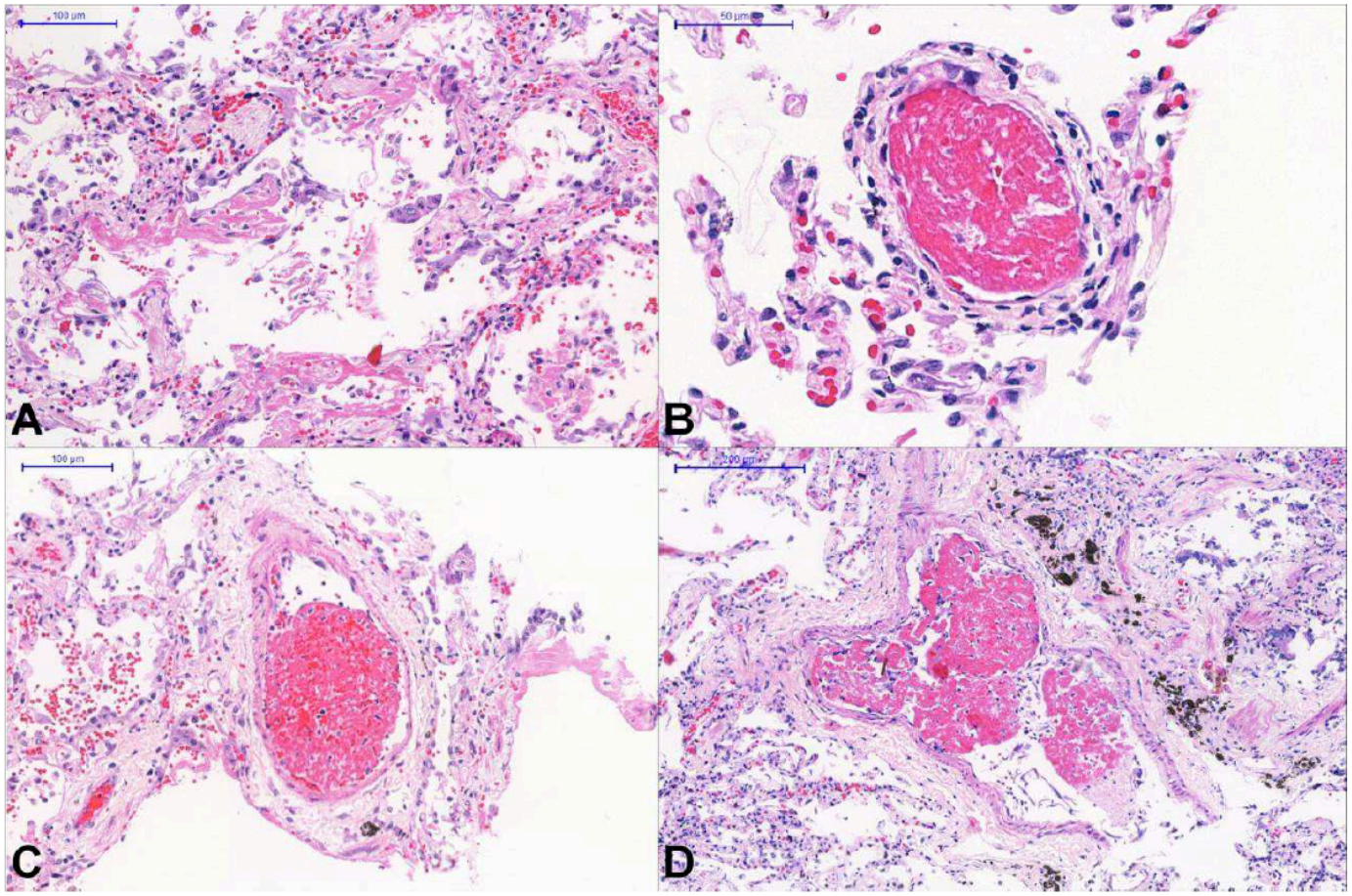
Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19



- Autópsia minimamente invasiva
- USP-SP
- Achados descritos em 8 de 10 pacientes

Microtrombos de fibrina em arteríolas pulmonares

Dolhnikoff, Duarte-Neto et al, JTH 2020

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Biological basis and pathological relevance of microvascular thrombosis

Participation of Microvascular Thrombosis in Diseases

Moreover, so far only in rare cases experimental evidence is available indicating a causal relevance of microvascular thrombosis for the development of the above mentioned pathologies. As one of the few

disease), and red blood cell lysis [11]. Several lines of evidence indicate that microvessel thrombosis is much more frequent than commonly assumed. Indeed, autopsy studies show a high prevalence of microvessel thrombi. For example in a third of patients with CAD, microvascular thrombosis was detected post mortem [3]. Furthermore, during

Pfeiler et al, Thromb Res 2014

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Quais as implicações para o manejo ?

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- **TROMBOPROFILAXIA**
- **ALTO ÍNDICE DE SUSPEIÇÃO PARA TEV**
- **TRATAMENTO ESPECÍFICO PARA CAHA?**
  - **Heparina**
  - **Trombolíticos**
  - **Outros anticoagulantes**

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Perspective

Coagulation Abnormalities in Acute Lung Injury and Sepsis

Edward Abraham

Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health Sciences Center, Denver, Colorado

Discussão antiga

How Important Are Coagulation Abnormalities in ALI?

Despite the fact that endotoxemia, hemorrhage, or exposure to proinflammatory cytokines such as TNF-α can lead to a procoagulant state, several important questions remain. Although tissue factor generation and widespread fibrin deposition accompany ALI, we still don't know how important these factors are in modulating the development and progression of ARDS. Accumulation of fibrin may enhance pulmonary inflammation or may simply be a result of the proinflammatory state that accompanies ALI and not substantially contribute to lung damage. As mentmost clinical situations. Similarly, it is presently unknown if interventions that affect coagulation will be beneficial when ALI is already present. We will have to wait for the results of ongoing clinical trials with TFPI, ATIII, or APC to know if modulation of coagulation with such agents can improve outcome from ARDS and sepsis.

Que como veremos, tiveram resultados frustrantes

Abraham, Am J Respir Cell Moll Biol, 200

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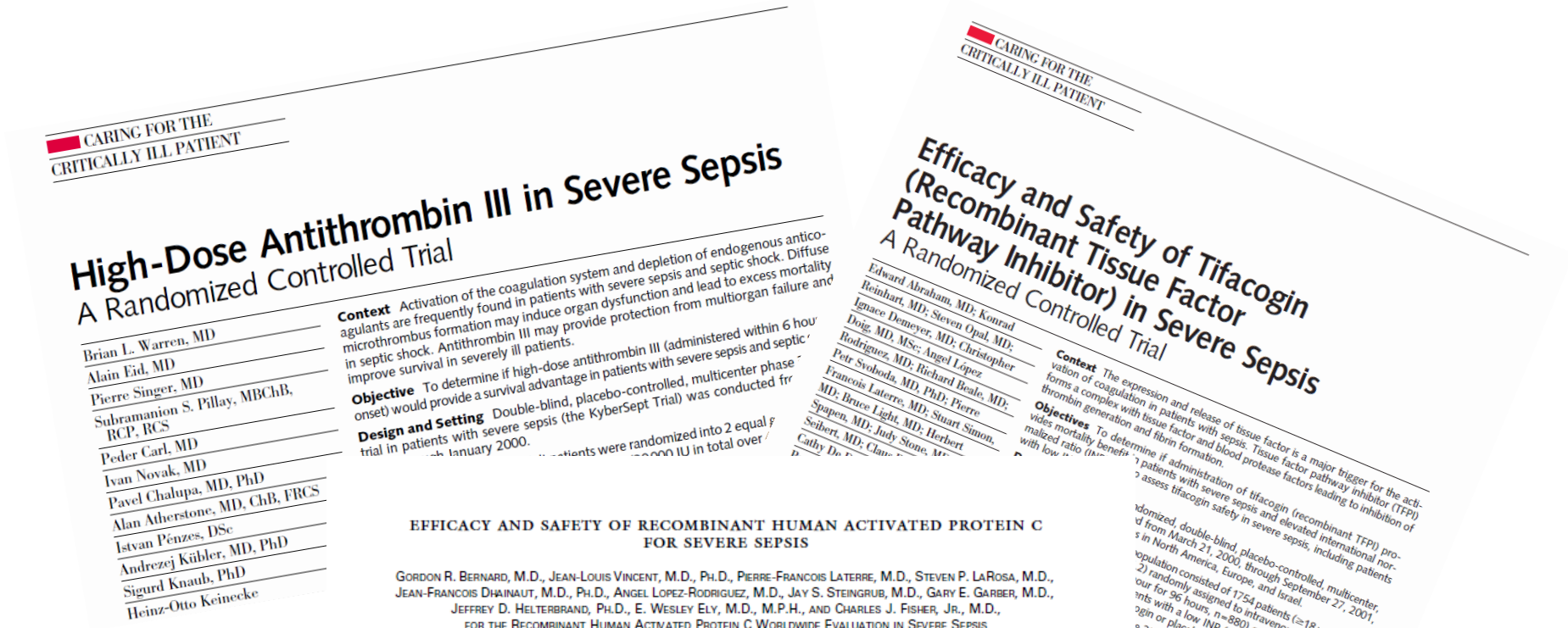
Anos 1990 e 2000

Grandes estudos clínicos com anticoagulantes na sepse



CARING FOR THE CRITICALLY ILL PATIENT

High-Dose Antithrombin III in Severe Sepsis
A Randomized Controlled Trial

Brian L. Warren, MD; Alain Eid, MD; Pierre Singer, MD; Subramanion S. Pillay, MBChB, RCP, RCS; Peder Carl, MD; Ivan Novak, MD; Pavel Chalupa, MD, PhD; Alan Atherstone, MD, ChB, FRCS; Istvan Pénzes, DSc; Andrezej Kübler, MD, PhD; Sigurd Knaub, PhD; Heinz-Otto Keinecke

Context Activation of the coagulation system and depletion of endogenous anticoagulants are frequently found in patients with severe sepsis and septic shock. Diffuse microthrombus formation may induce organ dysfunction and lead to excess mortality in septic shock. Antithrombin III may provide protection from multiorgan failure and improve survival in severely ill patients.

Objective To determine if high-dose antithrombin III (administered within 6 hou onset) would provide a survival advantage in patients with severe sepsis and septic

Design and Setting Double-blind, placebo-controlled, multicenter phase trial in patients with severe sepsis (the KyberSept Trial) was conducted fr

atients were randomized into 2 equal g 000 IU in total over

CARING FOR THE CRITICALLY ILL PATIENT

Efficacy and Safety of Tifacogin (Recombinant Tissue Factor Pathway Inhibitor) in Severe Sepsis
A Randomized Controlled Trial

Edward Abraham, MD; Konrad Reinhart, MD; Steven Opal, MD; Ignace Demeyer, MD; Christopher Doig, MD, MSc; Angel López Rodriguez, MD; Richard Beale, MD; Petr Svoboda, MD, PhD; Pierre Francois Laterre, MD; Stuart Simon, MD; Bruce Light, MD; Herbert Spapen, MD; Judy Stone, MD; Seibert, MD; Claus Cathy De

Context The expression and release of tissue factor is a major trigger for the activation of coagulation in patients with sepsis. Tissue factor pathway inhibitor (TFPI) forms a complex with tissue factor and blood protease factors leading to inhibition of thrombin generation and fibrin formation.

Objectives To determine if administration of tifacogin (recombinant TFPI) provides mortality benefi patients with severe sepsis and elevated international normalized ratio (IN with low assess tifacogin safety in severe sepsis, including patients

domized, double-blind, placebo-controlled, multicenter, d from March 21, 2000, through September 27, 2001, s in North America, Europe, and Israel.

opulation consisted of 1754 patients (≥18 years) with 2) randomly assigned to intravenous infusion of eiour for 96 hours, n=880) or placebo (arginine cints with a low INR (<1.2) randomly assigned to gin or placebo.

e 28-day mortality.

n the tifacogin-treated group (n=880) vs the 34.2% vs 33.9%, respectively (P=.88, Pearel). None of the protocol-specified second- tin vs placebo groups. An analysis on the

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

ABSTRACT

Background Drotrecogin alfa (activated), or recombinant human activated protein C, has antithrombotic, antiinflammatory, and profibrinolytic properties. In a previous study, drotrecogin alfa activated produced dose-dependent reductions in the levels of markers of coagulation and inflammation in patients with severe sepsis. In this phase 3 trial, we assessed whether treatment with drotrecogin alfa activated reduced the rate of death from any cause among patients with severe sepsis.

Methods We conducted a randomized, double-blind, placebo-controlled, multicenter trial. Patients with systemic inflammation and organ failure due to acute infection were enrolled and assigned to receive an intravenous infusion of either placebo or drotrecogin alfa activated (24 μg per kilogram of body weight per hour) for a total duration of 96 hours. The prospectively de-

SEVERE sepsis, defined as sepsis associated with acute organ dysfunction, results from a generalized inflammatory and procoagulant response to an infection.[1] The rate of death from severe sepsis ranges from 30 to 50 percent despite advances in critical care.[2-5] In the United States, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal.[6]

The inflammatory and procoagulant host responses to infection are closely related.[7] Inflamma tokines, including tumor necrosis factor α, i kin-1β, and interleukin-6, are capable of a coagulation and inhibiting fibrinolysis, whe procoagulant thrombin is capable of stimulati tiple inflammatory pathways.[7-11] The end re be diffuse endovascular injury, multiorgan dysf and death. Activated protein C, an endogen

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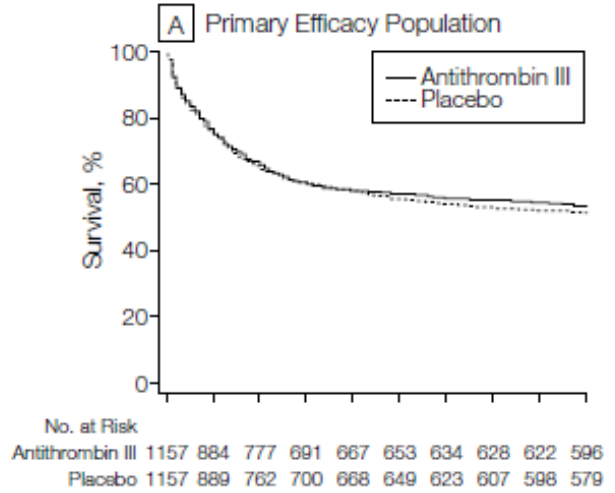
Antitrombina

Figure 3. Survival Rates for 90 Days

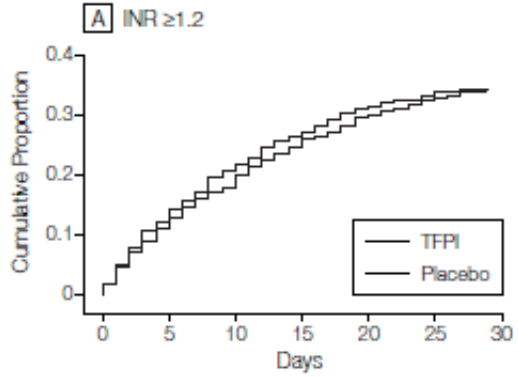


No. at Risk

Antithrombin III	1157	884	777	691	667	653	634	628	622	596
Placebo	1157	889	762	700	668	649	623	607	598	579

TFPI

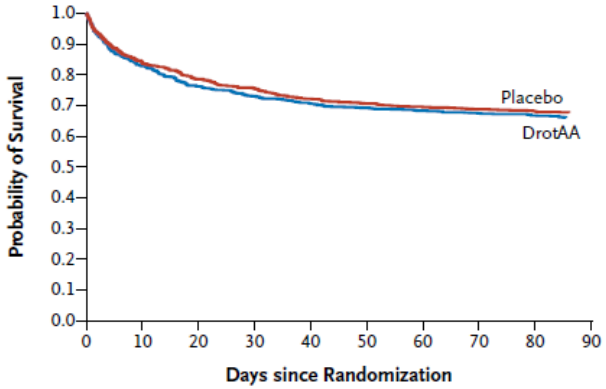
Figure 2. Cumulative Proportion of 28-Day All-Ca
Patients With High and Low INR



No. at Risk

TFPI	880	754	688	641	603	582
Placebo	874	764	701	646	612	588

Proteína C ativada



No. at Risk

Placebo	845	703	656	622	593	579	569	563	557	553
DrotAA	851	701	645	616	596	584	576	567	561	555

Abraham et al, JAMA 2001
Warren et al JAMA 2003
Ranieri et al, NEJM 2012

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Heparina

Study or Subgroup	Heparin Events	Heparin Total	Placebo/ Usual Care Events	Placebo/ Usual Care Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Placebo							
Levi 2007	275	1004	305	990	88.2%	0.89 [0.77, 1.02]	2007
Jaimes 2009	22	159	25	160	5.9%	0.89 [0.52, 1.50]	2009
Liu 2014	7	22	6	15	2.2%	0.80 [0.33, 1.90]	2014
Subtotal (95% CI)		**1185**		**1165**	**96.3%**	**0.89 [0.78, 1.01]**	
Total events	304		336				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%							
Test for overall effect: Z = 1.80 (P = 0.07)							
Usual Care							
Haneberg 1983	2	11	2	15	0.5%	1.36 [0.23, 8.24]	1983
Zhang 2006	3	11	3	11	0.9%	1.00 [0.26, 3.91]	2006
Zhao 2009	6	37	14	42	2.3%	0.49 [0.21, 1.14]	2009
Subtotal (95% CI)		**59**		**68**	**3.7%**	**0.67 [0.34, 1.30]**	
Total events	11		19				
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 2 (P = 0.48); I² = 0%							
Test for overall effect: Z = 1.19 (P = 0.24)							
Total (95% CI)		**1244**		**1233**	**100.0%**	**0.88 [0.77, 1.00]**	
Total events	315		355				
Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 5 (P = 0.82); I² = 0%							
Test for overall effect: Z = 1.99 (P = 0.05)							
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%							

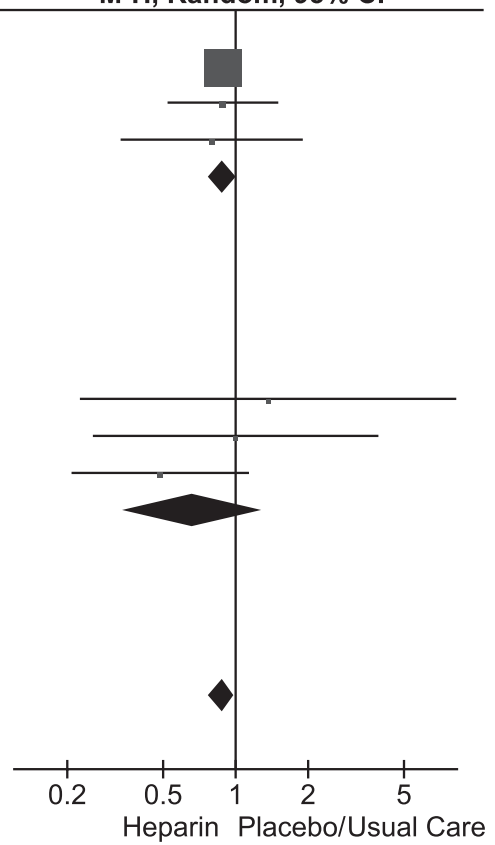

Figure 3. Mortality in patients randomized to heparin versus placebo or usual care. *Boxes* and *horizontal lines* represent point estimates, varying in size according to the weight in the analysis and 95% CIs. M-H = Mantel-Haenszel.

Zarychanski et al, CCM 2015

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