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HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

Host-response based endotyping and prognostication of patients with COVID19 – the Greek experience

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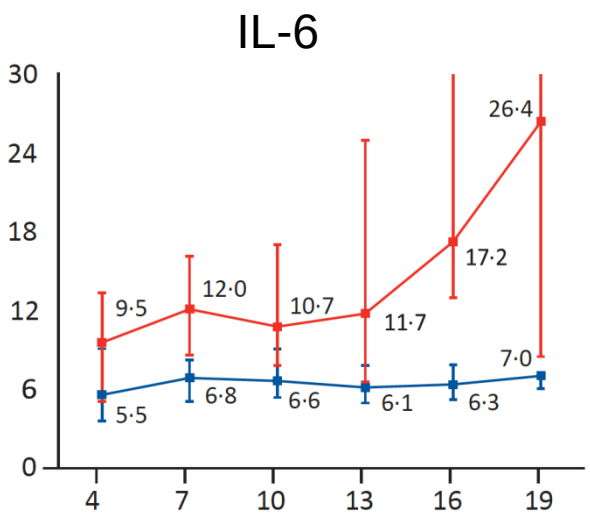
European Sepsis Alliance

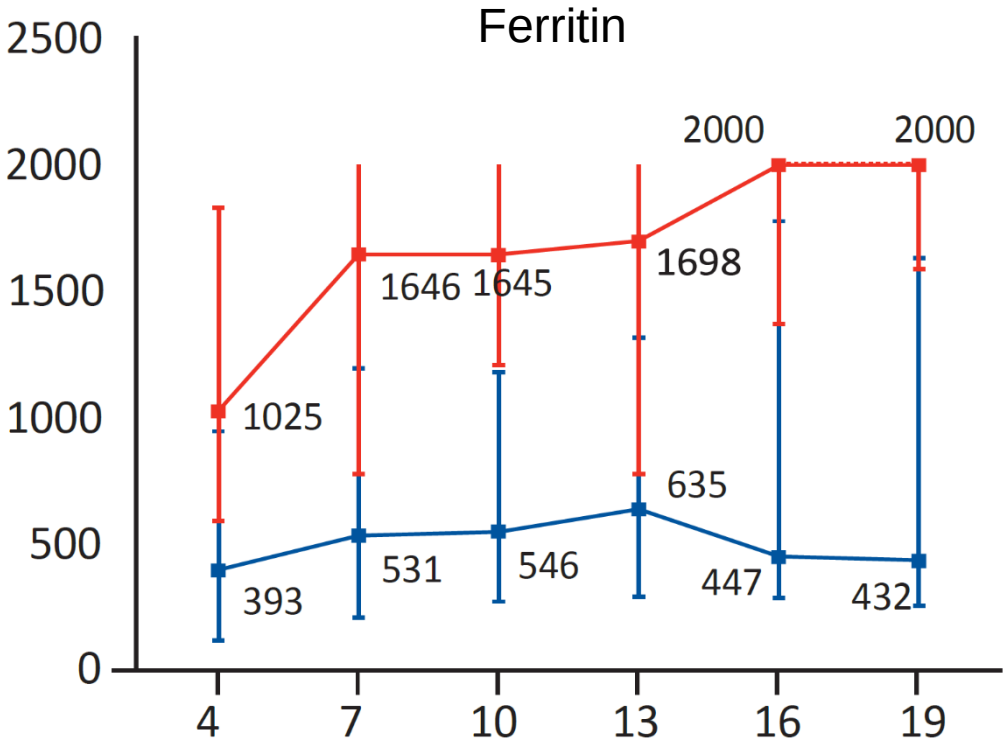
CONFLICT OF INTEREST DISCLOSURE

- Honoraria (paid to the University of Athens) from Abbott CH, Brahms ThermoFisher GmbH Germany, GSK, Inflammatix Inc and Sobi
- Consultant for Fab’nTech, InflaRx GmbH, UCB and Xbiotech Inc
- Independent educational grants (paid to the University of Athens) from AbbVie USA, InflaRx GmbH, Novartis, UCB
- Independent educational grants (paid to the Hellenic Institute for the Study of Sepsis) from Abbott CH, BioMérieux France, MSD, Inflammatix Inc Sobi, ThermoFisher Brahms GmbH, Xbiotech Inc
- Funding by the Horizon 2020 ITN European Sepsis Academy (granted to the University of Athens) and by the Horizon 2020 ImmunoSep and RISKinCOVID (granted to the Hellenic Institute for the Study of Sepsis)

IMMUNE RESPONSE IN COVID-19: TRAITS OF MACROPHAGE ACTIVATION

(Zhou F, et al. *Lancet* 2020; 395: 1-54-1062)





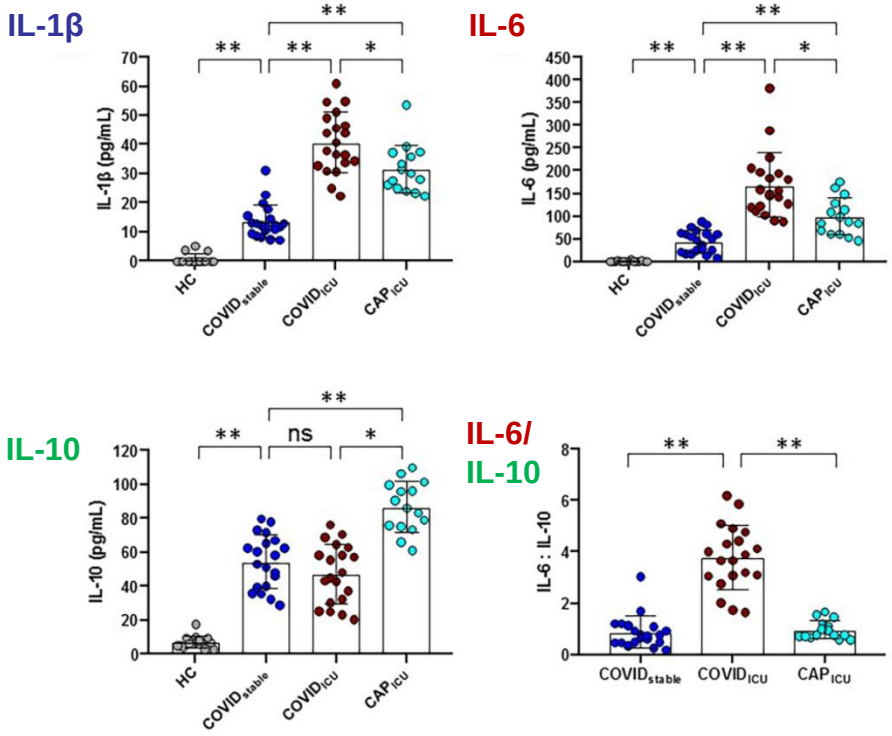
Survivors (n=137)

Non-survivors (n=54)

IMMUNE RESPONSES IN COVID-19: TH1 TO TH2 IMBALANCE

(McElvaney OJ, et al. *Am J Resp Crit Care Med* 2020; 202: 812-81)

- Healthy (HC, n=20)
- $COVID_{stable}$ (n=20)
- $COVID_{ICU}$ (n=20)
- CAP: community-acquired pneumonia (n=20)



*p<0.05
**p<0.01

THE SEPSIS PARARDIGM OF HETEROGENEITY

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Research Paper

A Transcriptomic Biomarker to Quantify Systemic Inflammation in Sepsis — A Prospective Multicenter Phase II Diagnostic Study

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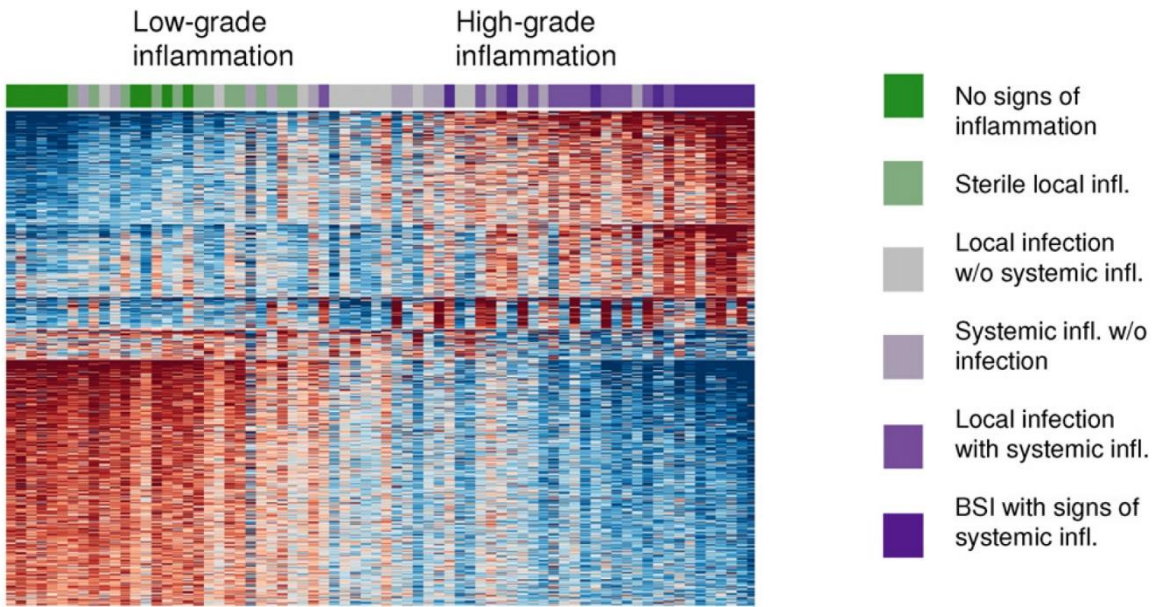

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01499-z

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OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

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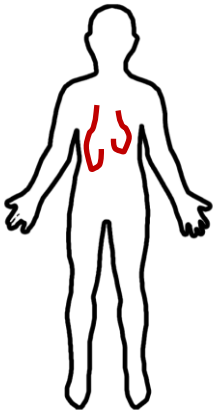
suPAR-GUIDED ANAKINRA TREATMENT FOR VALIDATION OF THE RISK AND EARLY MANAGEMENT OF SEVERE RESPIRATORY FAILURE BY COVID-19

THE SAVE STRATEGY



STOP
IL-1α
IL-1β

PREVENT
Unfavorable outcome

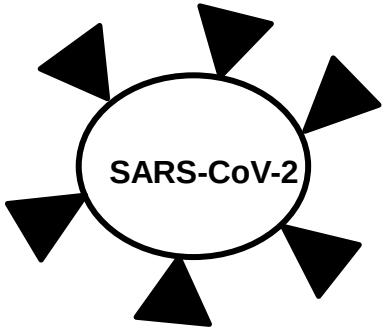
Early identification of risk

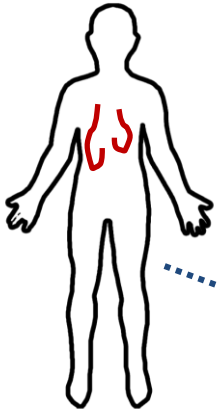
- COVID-19 pneumonia
- Hospitalization
- pO_2/FiO_2: 150-400
- Oxygen mask/nasal oxygen
- suPAR ≥6 ng/ml

Anakinra

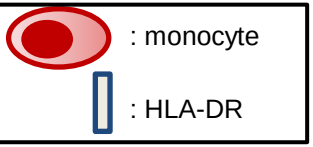
- Recombinant human receptor antagonist
- Block the action of IL-1α and IL-1β

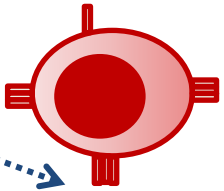
suPAR: soluble urokinase Plasminogen Activator Receptor





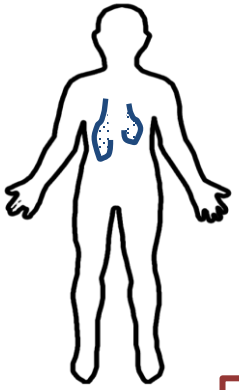
Infiltrates
↑CRP
↑D-dimers
↑AST/ALT

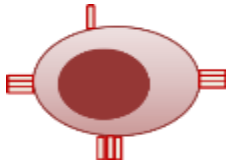




Vivid antigen-presentation

Macrophage activation: IL-1β (25%)



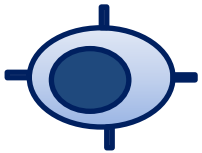


↑↑↑CRP/ferritin/TGs
↑↑D-dimers
↑↑AST/ALT

↑↑TNFα
↑↑IL-1β
↑↑IL-6

Moderate antigen-presentation

Immune dysregulation: IL-6 (75%)



↑↑CRP
↑↑D-dimers
↑↑AST/ALT

Weak antigen-presentation

↑↑TNFα
↑↑IL-6

↓↓ CD4-/CD8-/T17-lymphocytes
↓ B-lymphocytes,↓IgGs
↓↓ NKT-/NK-cells

Giamarellos-Bourboulis EJ, et al. *Cell Host Microbe* 2020; 27: 992

HOW COULD SEVERE COVID-19 BE CLASSIFIED?

Hyper-inflammation*	*ARG1, LCN2, LTF, OLFM4, HLA-DMB*
Adaptive immunity*	*YKT6, PDE4B, TWISTNB, BTN2A2, ZBTB33, PSMB9, CAMK4, TMEM19, SLC12A7, TP53BP1, PLEKHO1, SLC25A22, FRS2, GADD45A, CD24, S100A12, STX1A*
Hyper-coagulation*	*KCNMB4, CRISP2, HTRA1, PPL, RHBDF2, ZCCHC4, YKT6, DDX6, SENP5, RAPGEF1, DTX2, RELB*

*Sweeney TE, et al. *Crit Care Med* 2018; 46: 915-925

THE PATIENT POPULATION

	Survivors (n=81)	Non-survivors (n=16)	p
Age (years)	60.0 (50.8-70.3)	68.5 (62.8-84.3)	0.003
Male gender (%)	56 (69.1)	12 (75.0)	0.865
White blood cells	6,480 (5,145-9,622)	8,540 (5,542- 12,510)	0.275
Lymphocytes	1049.5 (759.7-1395.7)	613.8 (377.9-831.3)	<0.001
Platelets	214,000 (172,600- 260,800)	249,050 (180,750, 298,000)	0.176
D-dimers, ng/ml	850.0 (437.5-1947.5)	4480.0 (2440.0-13161.5)	<0.001
CRP, mg/l	79.1 (28.8-202.0	224.8 (142.9-260.8)	0.002
IL-6, pg/ml	10.0 (10.0-59.0)	22.5 (10.0-135.0)	0.355
suPAR, ng/ml	4.80 [3.00, 6.00]	7.80 [5.50, 9.65]	0.002
Ferritin, ng/ml	633.0 (362.5-1324.0)	1407.0 (302.5-5033.5)	0.195
SOFA score	2 (1-6)	5 (4-6.3)	0.006
APACHE II	7.0 (4.0-9.0)	11.0 (8.0-13.5)	0.001
Hospital stay (days)	13.0 (11.0-20.0)	13.0 (8.8-17.3)	0.41
Mechan. Ventil. (%)	34 (42.0)	16 (100.0)	<0.001

Values reported as medians and quartiles

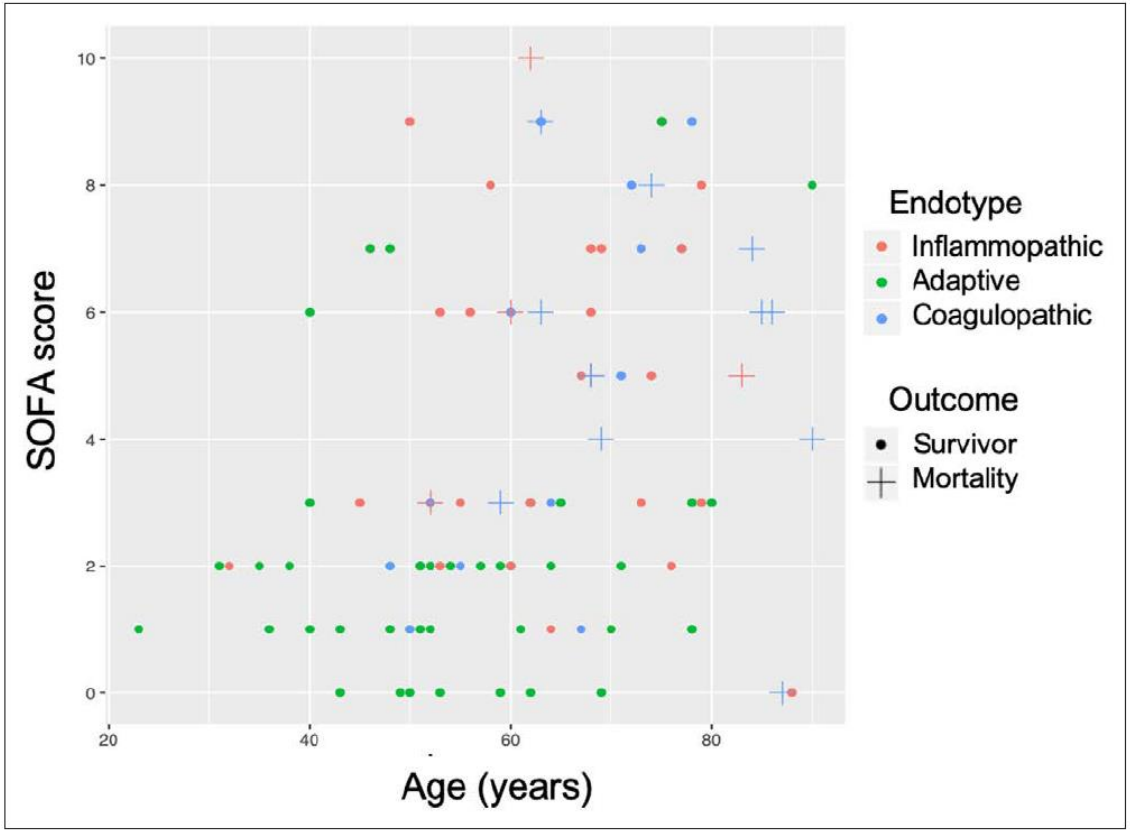
APACHE: acute physiology and chronic health evaluation score
CRP: C-reactive protein; IL: interleukin
SOFA; sequential organ failure assessment
suPAR: soluble urokinase plasminogen activator receptor

ENDOTYPE: MODERATOR OF PROGNOSIS (Sweeny T, et al. *Crit Care Med* 2021; 49: e170)

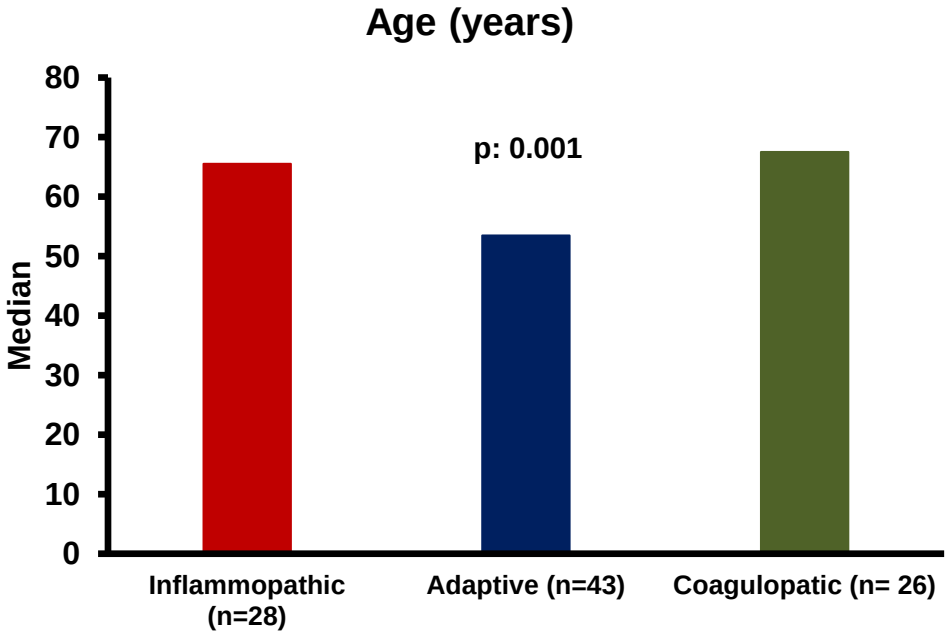
Inflammopathic: 29%

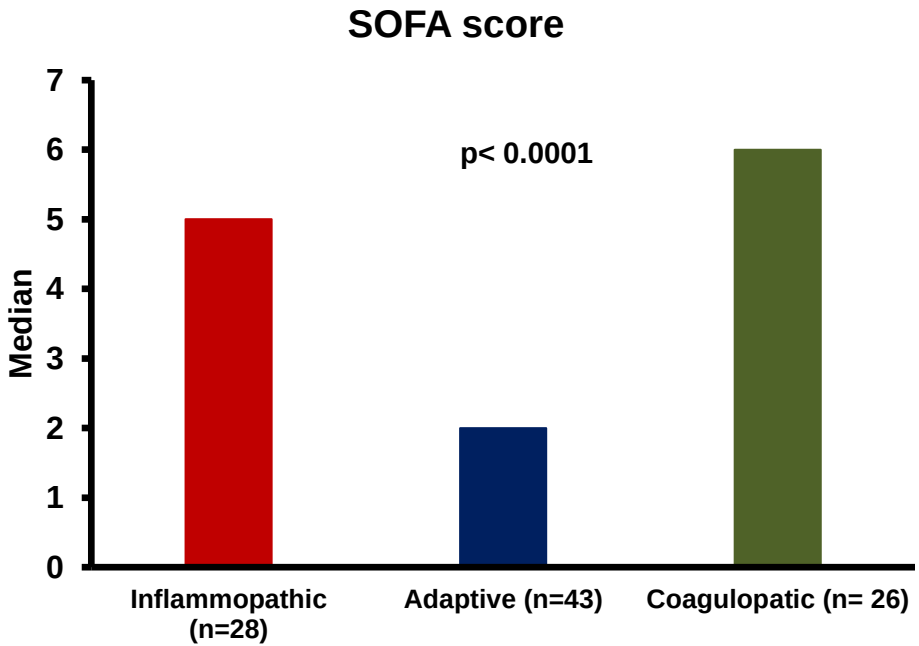
Adaptive: 44%

Coagulopathic 27%

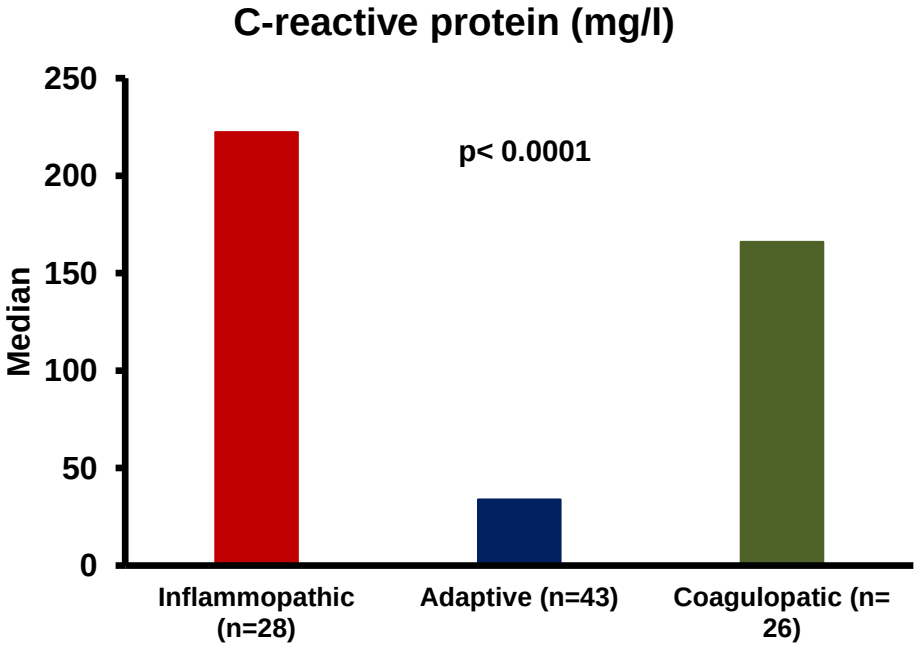


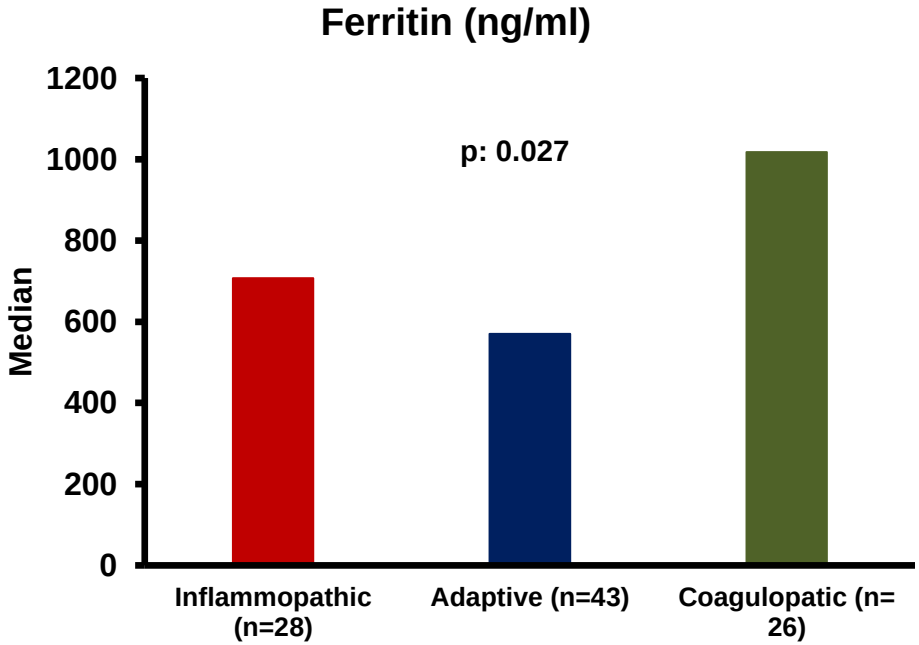
TRANSLATION INTO DAILY ROUTINE



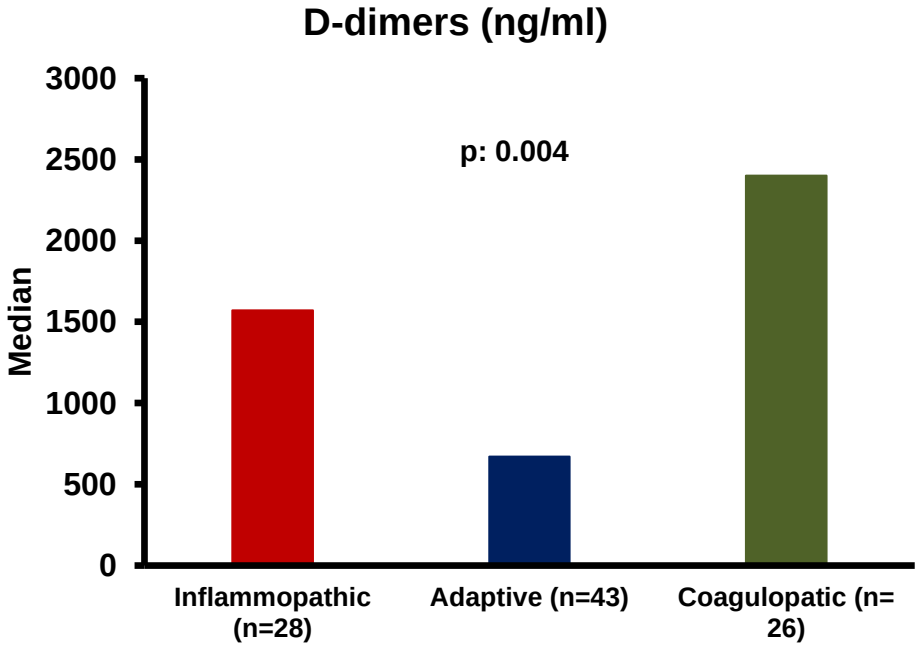


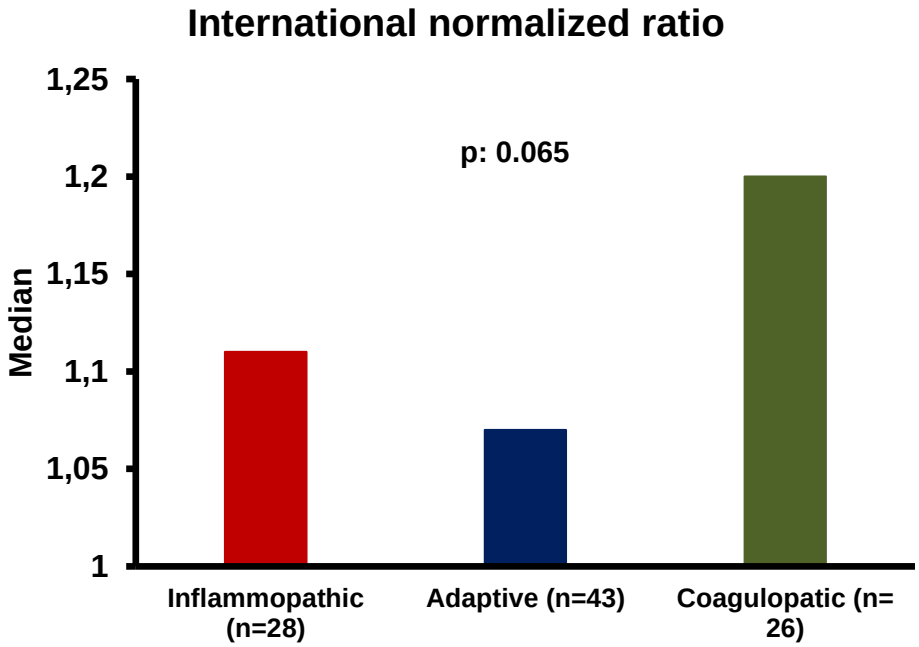
ASSOCIATION WITH INFLAMMATION



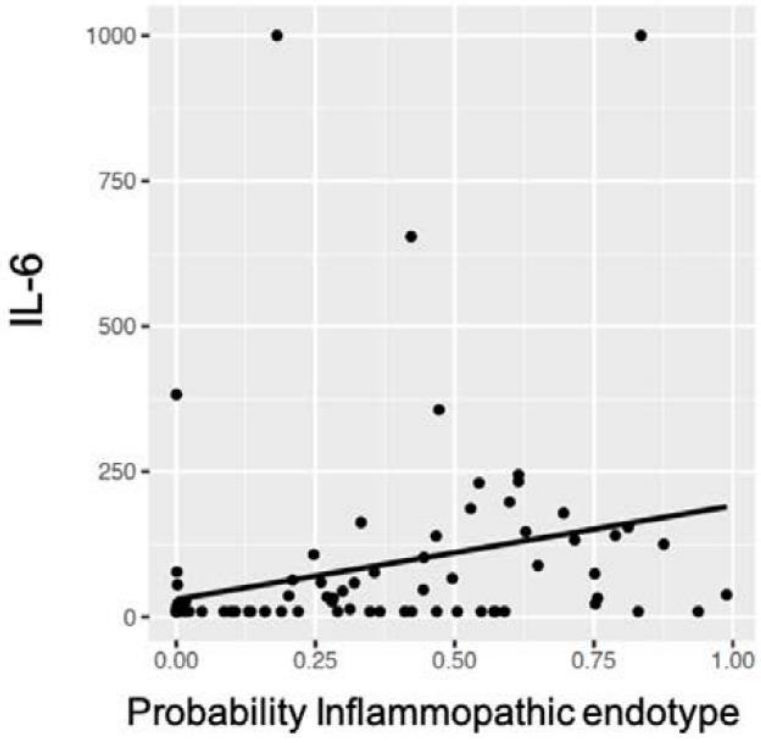


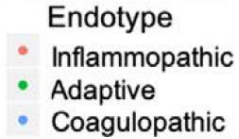
ASSOCIATION WITH COAGULATION

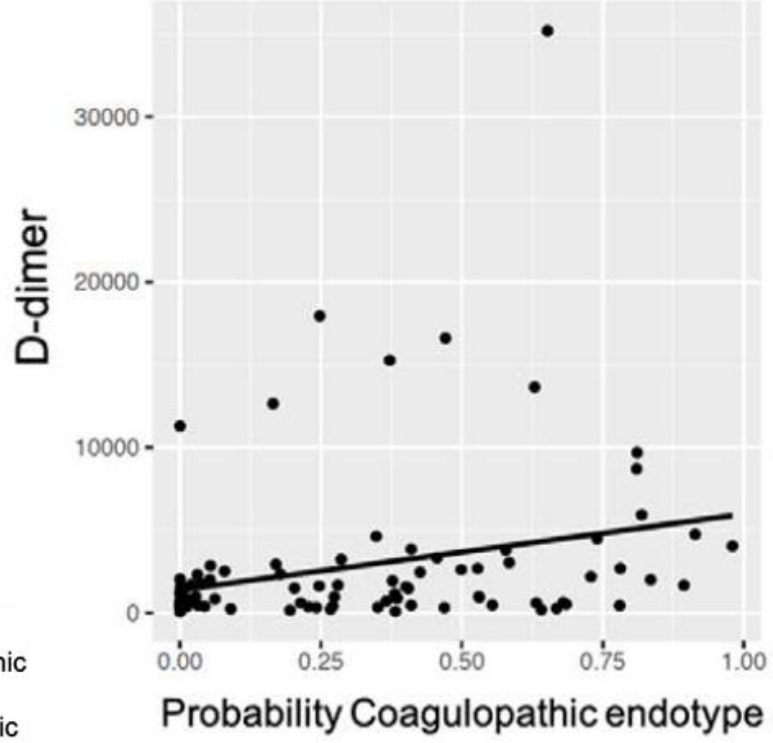




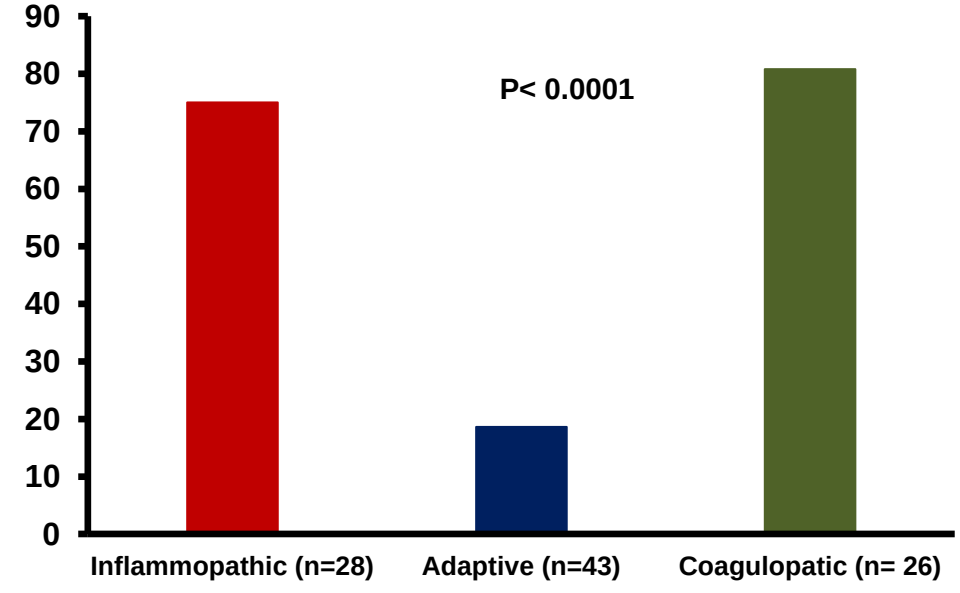
STATISTICAL PROBABILITY & BIOMARKERS

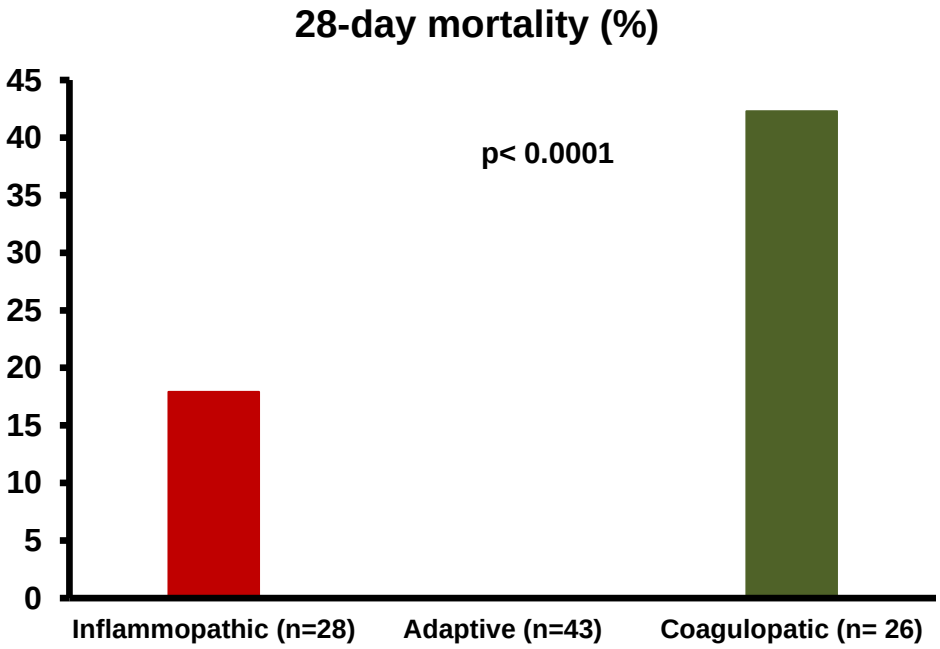






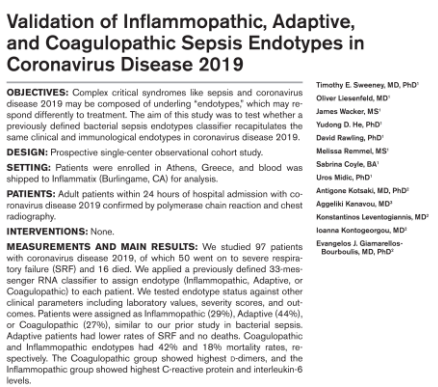
ASSOCIATION WITH OUTCOME





CONCLUSIONS

- Heterogeneity of severe COVID-19
- Use a 33-mRNA read-out of the host



Validation of Inflammopathic, Adaptive, and Coagulopathic Sepsis Endotypes in Coronavirus Disease 2019

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Yudong D. He, PhD[1]
David Rawling, PhD[1]
Melissa Remmel, MS[1]
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OBJECTIVES: Complex critical syndromes like sepsis and coronavirus disease 2019 may be composed of underling "endotypes," which may respond differently to treatment. The aim of this study was to test whether a previously defined bacterial sepsis endotypes classifier recapitulates the same clinical and immunological endotypes in coronavirus disease 2019.

DESIGN: Prospective single-center observational cohort study.

SETTING: Patients were enrolled in Athens, Greece, and blood was shipped to Inflammatix (Burlingame, CA) for analysis.

PATIENTS: Adult patients within 24 hours of hospital admission with coronavirus disease 2019 confirmed by polymerase chain reaction and chest radiography.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We studied 97 patients with coronavirus disease 2019, of which 50 went on to severe respiratory failure (SRF) and 16 died. We applied a previously defined 33-messenger RNA classifier to assign endotype (Inflammopathic, Adaptive, or Coagulopathic) to each patient. We tested endotype status against other clinical parameters including laboratory values, severity scores, and outcomes. Patients were assigned as Inflammopathic (29%), Adaptive (44%), or Coagulopathic (27%), similar to our prior study in bacterial sepsis. Adaptive patients had lower rates of SRF and no deaths. Coagulopathic and Inflammopathic endotypes had 42% and 18% mortality rates, respectively. The Coagulopathic group showed highest D-dimers, and the Inflammopathic group showed highest C-reactive protein and interleukin-6 levels.

Inflammopathic endotype

- 5 genes
- Mortality ~20%
- ↑ CRP, IL-6
- Macrophage activation?

Adaptive endotype

- 17 genes
- Mortality <10%
- T-cell activation?

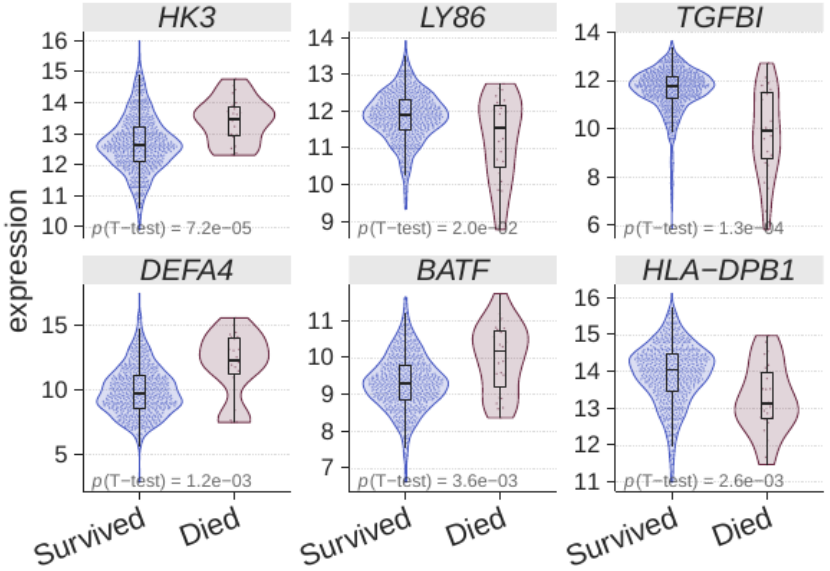
Coagulopathic endotype

- 11 genes
- Mortality >40%
- ↑ D-dimers
- Endothelial activation?

THE FUTURE:
HOST SIGNATURE FOR PROGNOSIS

(Buturovic L, et al. medRxiv doi.org/10.1101/2020.12.07.20230235)

- Signature from 6 gene copies generated in non-COVID-19 patients
- Application in the same cohort of 97 patients



THE NEW GENOMIC SCORE FOR PROGNOSIS

(Buturovic L, et al. medRxiv doi.org/10.1101/2020.12.07.20230235)