Biomarcadores de daño endotelial y activación inmune para clasificar la severidad de las infecciones pediátricas por SARS-CoV-2

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ISGlobal Barcelona Institute for Global Health

SJD Sant Joan de Déu Barcelona · Hospital

Grupo de Cooperación Internacional de la FEP-AEP

EXCELENCIA SEVERO OCHOA

ciberesp Centro de Investigación Biomédica en red Epidemiología y Salud Pública

Institució CERCA Centres de Recerca de Catalunya

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¿Qué nos hubiese gustado tener en urgencias en estos 2 últimos años?

Necesidades pediátricas para SARS-CoV-2

- EPIs adecuados
- Tests diagnósticos
- Tests diagnósticos rápidos
- Tests diagnósticos en saliva (menos invasivos para edad pediátrica)
- Tratamientos para evitar progresión a gravedad
- Tratamientos profilácticos post-contacto
- Asistencia vital para cuadros graves (incluyendo oxígeno)
- Vacunas avaladas para su uso en pediatría (en todas las edades)
- Circuitos eficientes de seguimiento post-infección para complicaciones tardías
- **Estrategias validadas de estratificación de riesgo en el niño que llega a urgencias**


TRIAGEM PEDIATRIA
DÊ SANGUE AGORA

El problema que queremos resolver no es solo relativo a COVID ni a los niños

Billions of febrile cases

- Severe infection
- Uncomplicated infection
- Non-infectious origin

Current triaging tools

CRP
PCT

SOFA
qSOFA
LODS

Inefficient	Slow (hours)
Expensive	High expertise
Misdirected	Infrastructure

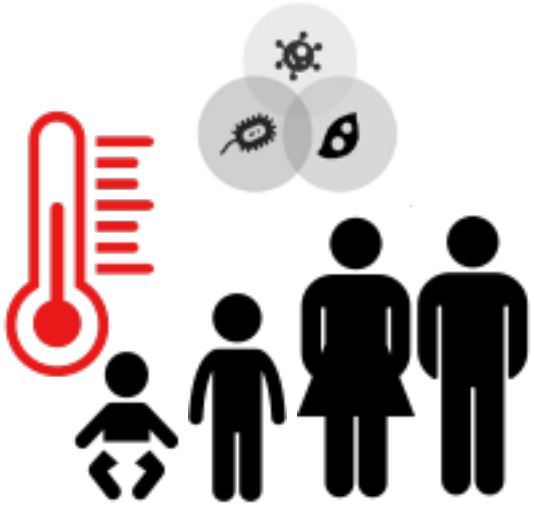
Deaths due to infections

>15 M

mostly in children

only from most common severe infections:
sepsis, pneumonia,
malaria and meningitis

¿No sería maravilloso tener esto?



Host biomarkers:
Ang-2, sTREM-1

High-risk

Middle-risk →

Low-risk

Clinical decisions:

ICU, Admission / referral

Observe and monitor

Discharge

Sick newborn, children or adult	Quantitative PoC	Objective risk stratification	Appropriate clinical decisions

- ✓ 1 drop of blood
- ✓ Battery-powered
- ✓ User-friendly
- ✓ Quantitative

10 min

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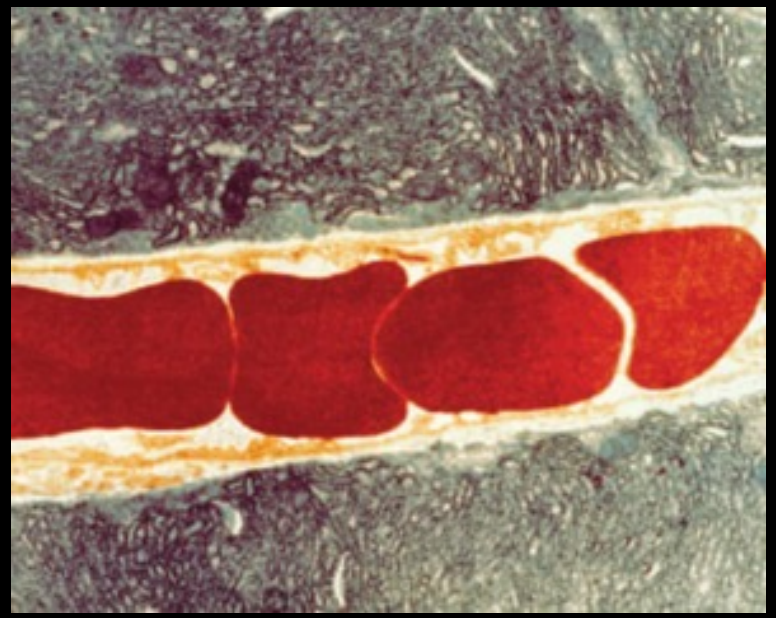
¿Qué ciencia avala la factibilidad de esta estrategia?

Why the endothelium?

Nature Immunol 2009;9:364

- Largest organ linking all others, 100,000 km
- >60 trillion cells ~4000 m^2
- Common pathway of injury in critical illness (sepsis, ARDS, CM, VHF, DSS, HUS, TSS etc.)



- Massive surface area & PRRs (TLR2,4,9)

  → essential surveillance organ

  → contributes to life-threatening response, progression to critical illness & MOD → death

Slide courtesy of Kevin Kain

Biomarcadores basados en la respuesta del huésped

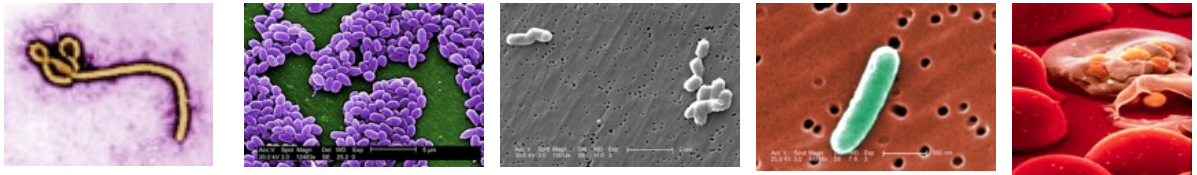
- Muchas infecciones potencialmente letales causan una **respuesta del huésped disregulada o exagerada** que al final puede llevar a un fallo multiorgánico

- Patógenos completamente diferentes pueden compartir un mecanismo común de "insulto" ("common pathways of injury) (**mecanismos de enfermedad "agnósticos de patógeno"**).

- **La activación inmune y endotelial** están en la base de la desestabilización endotelial, de la fuga microvascular, de la disfunción multi-orgánica y de la muerte. Estos mecanismos o "pathways" se han convertido en **fundamentales en la patogénesis de la infección grave o letal**, de forma **transversal y común** a muchas infecciones diferentes.

Hypothesis:

Multiple Biothreats → common pathway to death

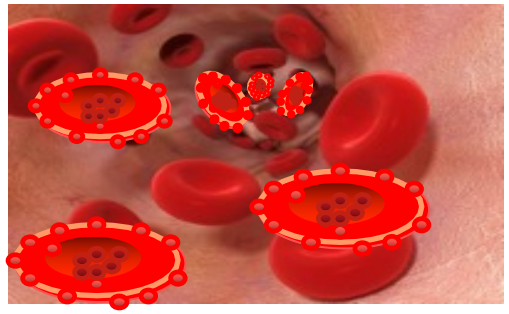


multiple natural and synthetic biothreats

- *Endothelial activation*
- *Vascular permeability*

→ ***Endothelial & Immune activation markers***

→ ***Identify those at risk of sepsis***



Multi-organ failure; death*

**Therapeutic intervention*

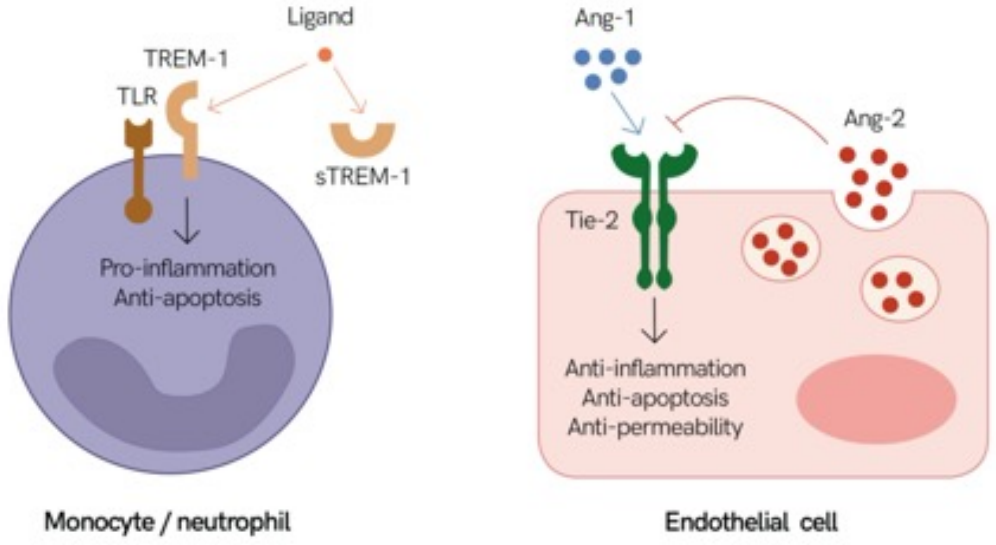
- ***preserve endothelium integrity***
- ***"agnostic" (pathogen independent) countermeasure***

*Despite antimicrobial treatment

Slide courtesy of Kevin Kain

Ejemplos de Biomarcadores basados en la respuesta del huésped

- Soluble triaggering receptor expressed on myeloid cells 1 (sTREM-1)
- Tumour necrosis factor (TNF)
- Soluble TNF receptor 1 (sTNFR-1)
- Interleukin-10 (IL-10)
- Interleukin-6 (IL-6)
- Interferon γ-induced protein 10 kDA (CXCL10)
- Soluble urokinase plasminogen activator receptor (suPAR)
- Angiopoietin-1 (Ang-1)
- Angiopoietin-2 (Ang-2)
- Soluble intercellular adhesion molecule-1 (sICAM-1)
- Soluble vascular cell adhesion molecule-1 (sVCAM-1)
- Soluble fms-like tyrosine kinase-1 (sFlt-1)

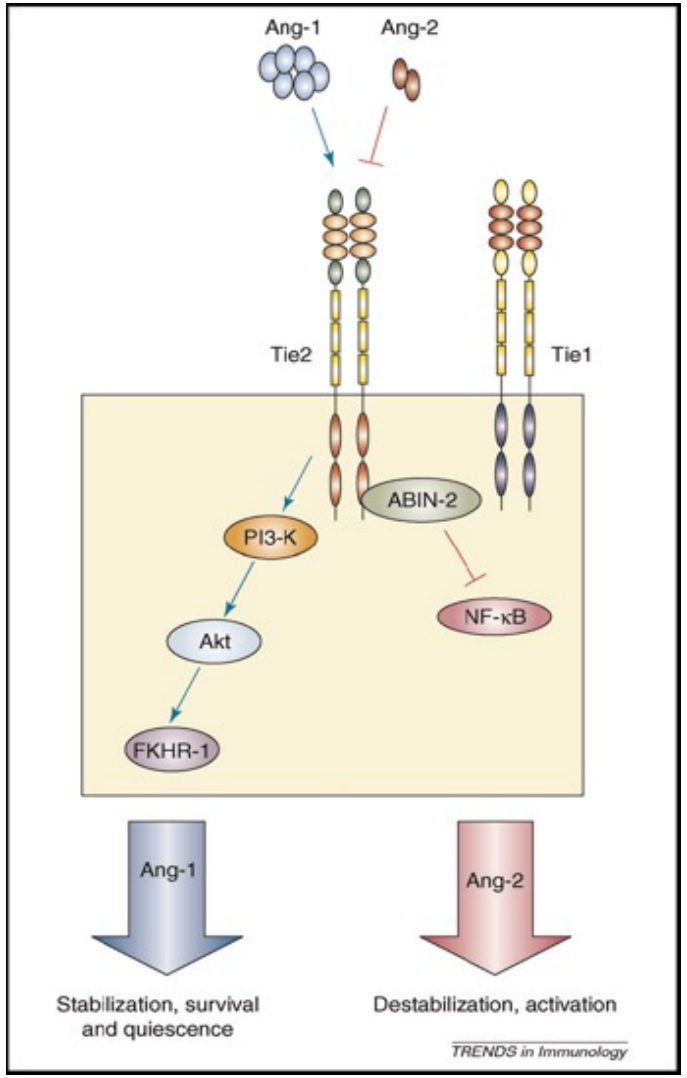


Balanza et al., Front Pediatr. 2020

Angiopoietin-Tie2

Angiopoietin-1

- **Good guy**
- Binds and activatesTie2
- Mediates endothelial quiescence and vascular integrity



Angiopoietin-2

- **Bad guy**
- Blocks Ang-1
- Leads to endothelial activation and leak

Slide courtesy of Kevin Kain

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Evidencia para COVID-19

STREM-1 – COVID-19

COVID-19 risk stratification algorithms based on sTREM-1 and IL-6 in emergency department

Mathias Van Singer, MD,[a*] Thomas Brahier, MD,[a*] Michelle Ngai, PhD,[b] Julie Wright, MD,[b] Andrea M. Weckman, MSc,[b] Clara Erice, PhD,[b] Jean-Yves Meuwly, MD,[c] Olivier Hugli, MPH,[d] Kevin C. Kain, PhD,[b*] and Noémie Boillat-Blanco, MD, PhD[a*] *Lausanne, Switzerland; and Toronto, Ontario, Canada*

Switzerland
N = 74, outpatient or inpatient adults
sTREM-1 had the best prognostic accuracy for 30-day intubation/mortality → AUROC: 0.86 (0.77-0.95)

Research Article

Increased sTREM-1 plasma concentrations are associated with poor clinical outcomes in patients with COVID-19

Aline H. de Nooijer[1,2], Inge Grondman[1,2], Simon Lambden[3], Emma J. Kooistra[2,4], Nico A.F. Janssen[1,2], Matthijs Kox[2,4], Peter Pickkers[2,4], Leo A.B. Joosten[1,2,5], Frank L. van de Veerdonk[1,2], Marc Derive[6], Sebastien Gibot[7] and Mihai G. Netea[1,2,8] on behalf of RCI-COVID-19 study group*

Netherlands
N = 218, inpatient adults
sTREM-1 associated with severe disease needing ICU admission, as well as with mortality ($p<0.001$)
Mortality discrimination → AUROC: 0.73

viruses MDPI

Article

sTREM-1 Predicts Disease Severity and Mortality in COVID-19 Patients: Involvement of Peripheral Blood Leukocytes and MMP-8 Activity

Pedro V. da Silva-Neto [1,2,†], Jonatan C. S. de Carvalho [1,3,†], Vinícius E. Pimentel [1,4,†], Malena M. Pérez [1,†], Diana M. Toro [1,2,†], Thais F. C. Fraga-Silva [4,†], Carlos A. Fuzo [1,†], Camilla N. S. Oliveira [1,4,†], Lilian C. Rodrigues [1], Jamille G. M. Argolo [5], Ingryd Carmona-Garcia [5], Nicola T. Neto [5], Camila O. S. Souza [1,4], Talita M. Fernandes [5], Victor A. F. Bastos [1], Augusto M. Degiovani [6], Leticia F. Constant [6], Fátima M. Ostini [6], Marley R. Feitosa [7], Rogerio S. Parra [7], Fernando C. Vilar [8], Gilberto G. Gaspar [8], José J. R. da Rocha [7], Omar Feres [7], Fabiani G. Frantz [1], Raquel F. Gerlach [9], Sandra R. Maruyama [10], Elisa M. S. Russo [1], Angelina L. Viana [5], Ana P. M. Fernandes [5], Isabel K. F. M. Santos [4], Vânia L. D. Bonato [4], Antonio L. Boechat [2], Adriana Malheiro [2], Ruxana T. Sadikot [11], Marcelo Dias-Baruffi [1,‡], Cristina R. B. Cardoso [1,‡], Lúcia H. Faccioli [1,*,‡], Carlos A. Sorgi [2,3,4,*,‡] and on behalf of the IMUNOCOVID Study Group [§]

Brazil
N = 237, Adults
sTREM-1 associated with severe disease and mortality
For hospitalized patients and in-hospital mortality → AUROC: 0.75

ANG/TIE AXIS – COVID-19

Angiogenesis
https://doi.org/10.1007/s10456-020-09730-0

ORIGINAL PAPER

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]

France
N = 40, inpatient adults
Ang-2 best predictor for patients requiring ICU admission →
AUROC: 0.77 (0.62-0.92)

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

The role of angiopoietin-2 and surfactant protein-D levels in SARS-CoV-2-related lung injury: A prospective, observational, cohort study

Handan Alay[1] | Esra Laloglu[2]

Turkey
N = 64, inpatient adults
Ang-2 was associated with severity

cells MDPI

Article

ICU Admission Levels of Endothelial Biomarkers as Predictors of Mortality in Critically Ill COVID-19 Patients

Alice G. Vassiliou [1], Chrysi Keskinidou [1], Edison Jahaj [2], Parisis Gallos [3], Ioanna Dimopoulou [1,2], Anastasia Kotanidou [1,2] and Stylianos E. Orfanos [1,2,4,*]

Greece
N = 38, inpatient adults admitted to ICU
Ang-2 was associated with severity ($p<0.001$)

suPAR – COVID-19

Ind J Clin Biochem
https://doi.org/10.1007/s12291-021-01008-6

REVIEW ARTICLE

Utility of P-SEP, sTREM-1 and suPAR as Novel Sepsis Biomarkers in SARS-CoV-2 Infection

Sagar Dholariya[1] · Deepak N. Parchwani[1] · Ragini Singh[1] · Madhuri Radadiya[2] · C. D. S. Katoch[1]

Review:

suPAR has been associated with severity, respiratory failure, other inflammatory markers, kidney dysfunction, mortality

Table 2 Summary of data extracted for suPAR in SARS-COv-2 infection from various studies

	suPAR in SARS-CoV-2 infection				
Author	Rovina N et al. [63]	Huang M et al. [64]	Kyriazopoul-ou E et al. [65]	Azam TQ et al. [66]	Chalkias A et al. [67]
Place of study	Chicago, USA	Fuijan, China	Athens, Greece	Ann Arber, MI	Larisa, Greece
Sample size	57	117	130	352	Not mentioned
Serum level in severe/critical type of SARS-CoV-2 infection	Increased > 6.0 ng/ml	Increased 5.51 ± 2.53 ng/ml	Increased > 6.0 ng/ml	Increased 5.61 ng/ml	Increased
Correlation with Severity/Respiratory failure/ Mortality	Positive correlation	Positive correlation	Positive correlation	Positive correlation	Positive correlation
Correlation with CRP/D-Dimer/PCT	Positive correlation	Positive correlation	Positive correlation	Positive correlation	No correlation
Increased in progressive kidney dysfunction	Yes	Not mentioned	Not mentioned	Yes	Not mentioned
Sensitivity for predicting respiratory failure/Mortality	85.7%	85.9%	Not mentioned	Not mentioned	> 80%

suPAR – COVID-19

ARTICLES
https://doi.org/10.1038/s41591-021-01499-z
nature medicine
Check for updates

OPEN

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

Selection of adults with COVID-19 at **high risk o progressing to respiratory failure (suPAR ≥ 6 ng/mL)**
N = 594; Italy and Greece

Anakinra:
IL-1α/β inhibitor

20.7% progressed to severe respiratory failure or death by D14

Placebo

31.7% progressed to severe respiratory failure or death by D14

If suPAR <6 ng/mL → Only 2.9% progressed to severe respiratory failure or death by D14

Treatment group (vs. placebo group):

- **Less odds of having a worse clinical status by day 28 → aOR: 0.36 (95% CI: 0.26-0.50), p<0.0001**

- Less odds of having a worse clinical status by day 14 → aOR: 0.58 (95% CI: 0.43-0.79), p=0.001
- Less persistent disease at day 28 → OR: 0.36 (95% CI 0.25.0.53), p<0.0001
- Less severe disease at day 28 → OR: 0.46 (95% CI 0.26–0.83), p=0.010
- Less progress to severe respiratory failure or death by day 14→ HR: 0.62 (95% CI 0.45–0.87), p=0.005
- Less 28-day mortality → HR: 0.45, 95%CI 0.21–0.98), p=0.045
- Shorter hospital stays
- By day 7: IL-6 and CRP decreased, lymphocyte count increased
- Treatment benefit also for the subset with altered high levels of inflammation markers

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Nuestros datos


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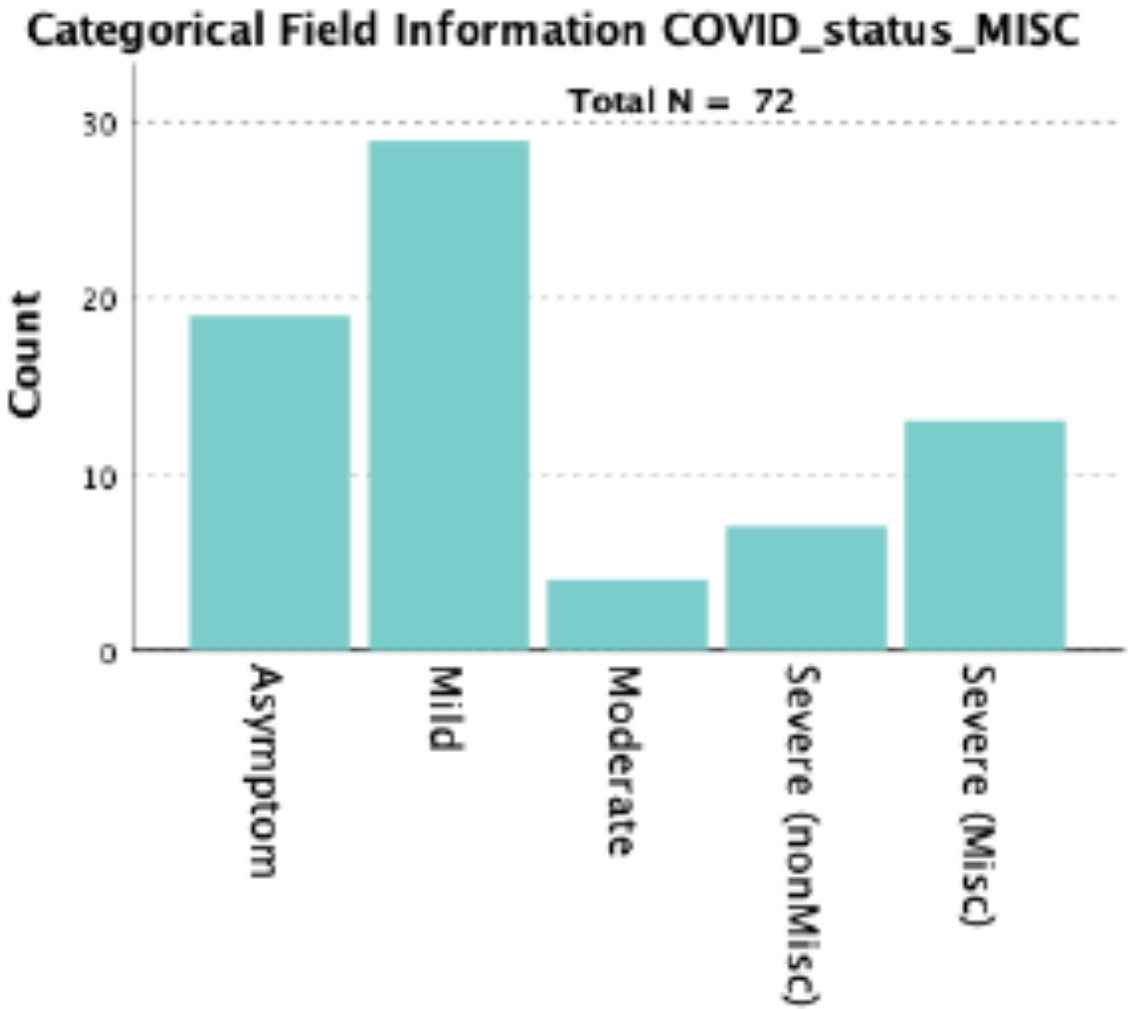
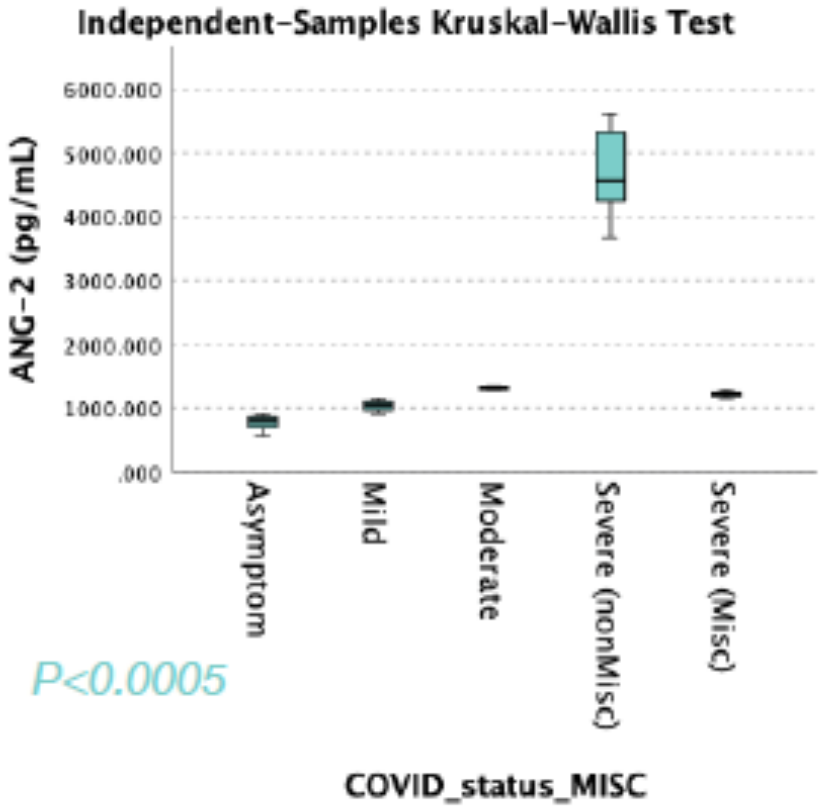
Children
Women
Healthcare professionals
We take care of you
Kids Corona
A platform to understand COVID-19 in children and pregnancy

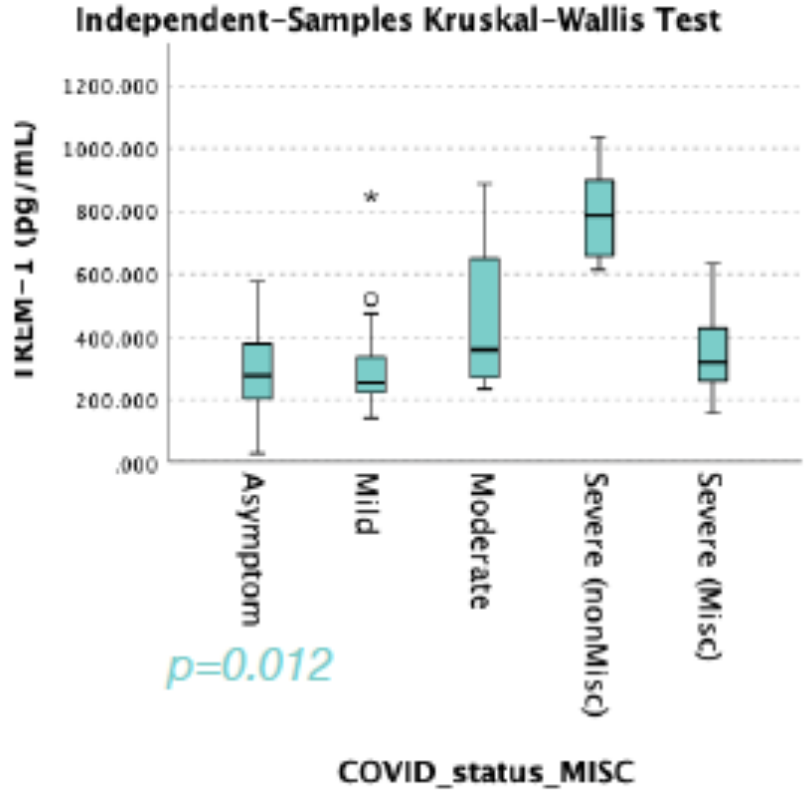

Categorical Field Information COVID_status_MISC
Total N = 72
Count
30
20
10
0
Asymptom
Mild
Moderate
Severe (nonMisc)
Severe (Misc)

ANG-2



P<0.0005

TREM-1



p=0.012

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Conclusiones

Conclusiones

- Una herramienta fiable de estratificación de riesgo para el COVID-19, que identifique a aquellos pacientes con **mayor riesgo de progresar hacia enfermedad grave y muerte**, hubiese salvado muchas vidas, sobre todo en la población adulta

- Una solución innovadora radica en el ENDOTELIO, un biosensor *in vivo* recientemente reconocido, que desempeña un papel fundamental en nuestra defensa contra los patógenos (muchos y de diferentes tipos).

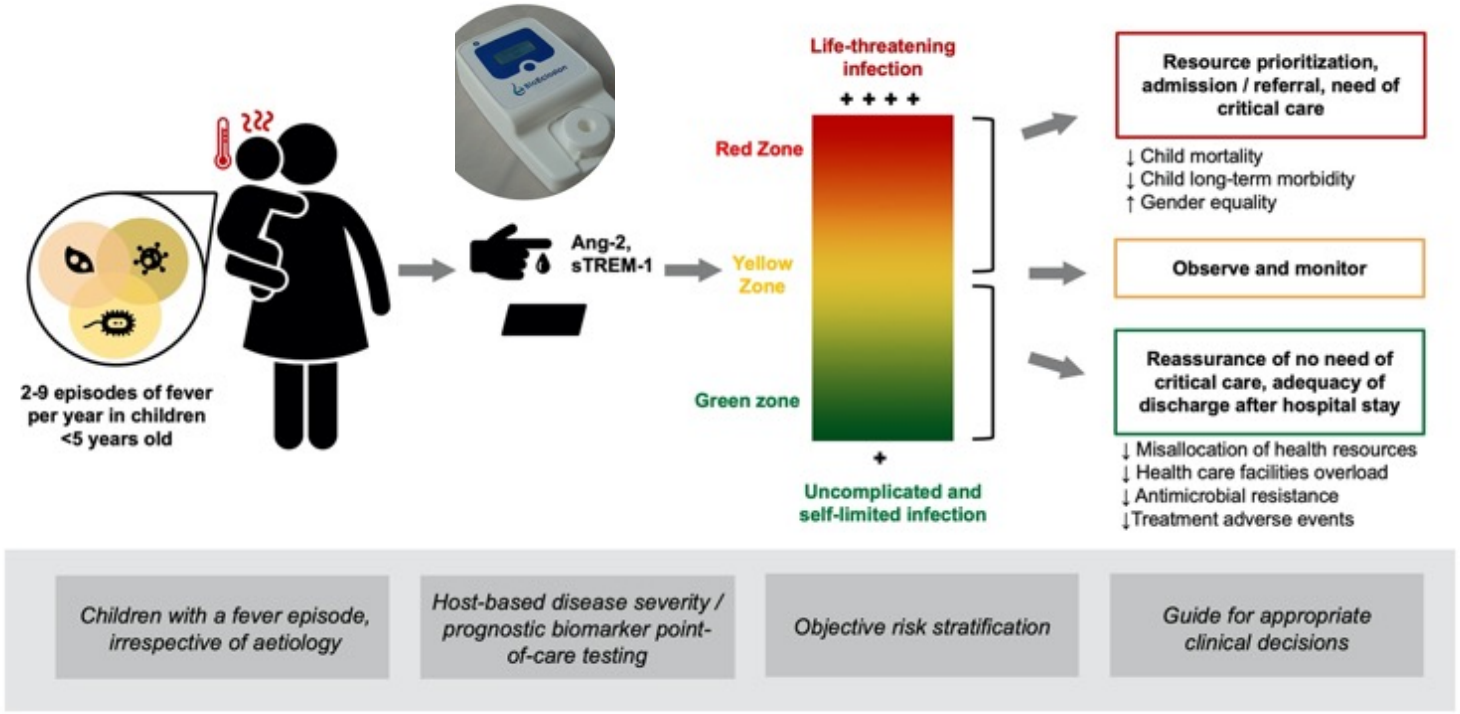
- Marcadores medibles en sangre del nivel de estabilidad endotelial pueden indicar de forma muy robusta un riesgo vital para el paciente, y su medición mediante tests PoC podría revolucionar el triaje, no sólo para COVID-19, sino que también para múltiples otras causas infecciosas (sistema de triaje "universal" en el paciente con fiebre)

- Nuestro grupo acaba de obtener un proyecto Europeo H2021 para desarrollar esta idea en un PoC, y validar mediante ensayos clínicos que su uso puede mejorar la supervivencia

ECHILBRIST

Enhancing CHildren's Lives with Biomarkers for Risk Stratification and triage)
HORIZON-HLTH-2021-DISEASE-04-03

Title: Development and validation of a quantitative point-of-care test for the measurement of severity biomarkers to improve risk stratification of fever syndromes and enhance child survival
Role of ISGlobal: Coordinators
Overall PI: Quique Bassat
Funding: 8M€
Start date: 01 June 2022
End Date: 31 May 2027
13 partners: 9 European (4 Spain, 2 UK, 1 Germany, 1 Italy), 3 African (Mozambique, Gabon, Ethiopia), 1 Canadian



Workstream 1: *Design and validation of the device and establishing the exploitation and regulatory pathways*

Workstream 2: *Clinical trials and sub-studies to assess the impact of the introduction of the device for risk stratification purposes, to enhance outcomes, guide management, and save costs.*