

COVID-19 ÉS A SZERVDISZFUNKCIÓ

CITOKIN VIHAR

Ruszkai Zoltán, Tánczos Krisztián, Fazakas János, Leiner Tamás, Rudas László, Molnár Zsolt



KORONAVÍRUS
ELLENI TRANSZLÁCIÓS
LAKOSSÁGTÁMOGATÓ
AKCIÓ- ÉS KUTATÓCSOPORT

Emlékeztető...

Critical Care Utilization for the COVID-19 Outbreak
in Lombardy, Italy
Early Experience and Forecast During an Emergency Response

Giacomo Grasselli, MD^{1,2}; Antonio Pesenti, MD^{1,2}; Maurizio Cecconi, MD³

JAMA. Published online March 13, 2020. doi:10.1001/jama.2020.4031

Characteristics of and Important Lessons From
the Coronavirus Disease 2019 (COVID-19) Outbreak in China
Summary of a Report of 72 314 Cases From
the Chinese Center for Disease Control and Prevention

Zunyou Wu, MD, PhD¹; Jennifer M. McGoogan, PhD¹

JAMA. Published online February 24, 2020. doi:10.1001/jama.2020.2648

- Enyhe, tünetmentes lefolyás - 80%
- Közepes- súlyos - 14-20.4 % - kórházi ellátást igényel
 - RR = 30/perc
 - SpO₂ 93 %
- ITO kezelést a kórházba felvett betegek 5-20 % igényel

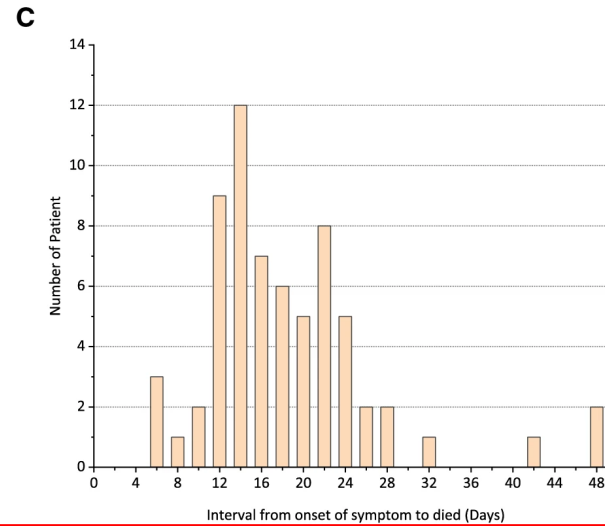
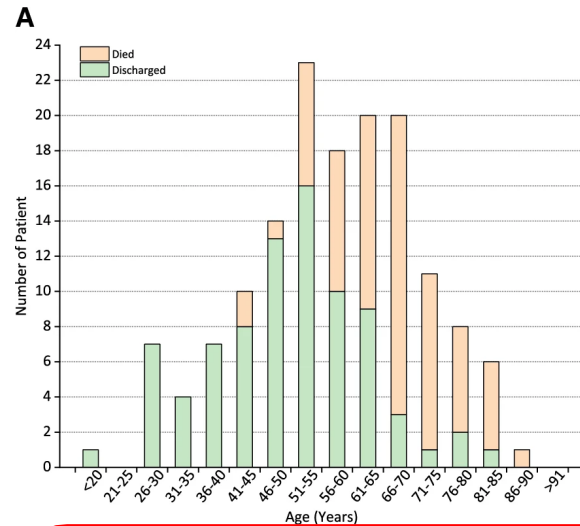
COVID-19 ITO mortalitás

Table 7 Outcome, length of stay and organ support* for patients admitted to critical care with confirmed COVID-19

Az elhunytak száma 3 hét alatt meghúszorozódott,
míg a mortalitás gyakorlatilag nem változott!

Alive	1437	(48.9)	4184	(78.0)
Dead	1499	(51.1)	1183	(22.0)

Mi okozza ezt a magas mortalitást?



Intensive Care Med
<https://doi.org/10.1007/s00134-020-05991-x>

LETTER

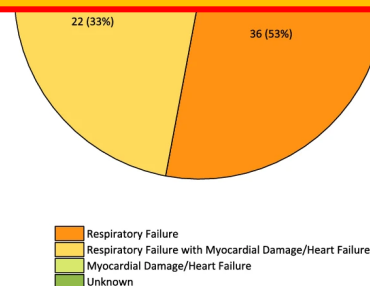
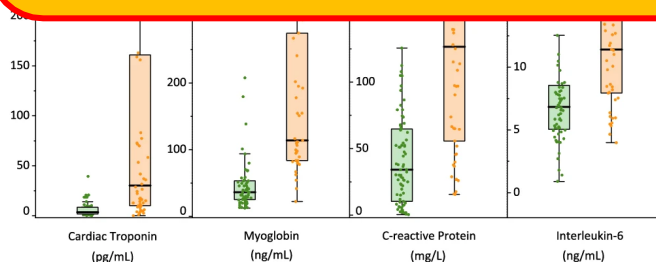
Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China

Qiorong Ruan^{1,2}, Kun Yang³, Wenxia Wang⁴, Lingyu Jiang⁵ and Jianxin Song^{4*}



In conclusion, predictors of a fatal outcome in COVID-19 are underlying disorders and elevated cytokine levels. The results of this study suggest that a cytokine storm is associated with a fatal outcome in COVID-19.

A citokin vihar proinflammatorikus túlsúlyú diszregulált immunválasz



Citokin vihar COVID-19-ben?

THE LANCET

CORRESPONDENCE | VOLUME 395, ISSUE 10229, P1033-1034, MARCH 28, 2020

COVID-19: consider cytokine storm syndromes and immunosuppression

Puja Mehta · Daniel F McAuley · Michael Brown · Emilie Sanchez · Rachel S Tattersall · Jessica J Manson  · et al.

Show all authors

Published: March 16, 2020 · DOI: [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)

Shimabukuro-Vornhagen et al. *Journal for ImmunoTherapy of Cancer* (2018) 6:56
<https://doi.org/10.1186/s40425-018-0343-9>

Journal for ImmunoTherapy
of Cancer

REVIEW

Open Access

Cytokine release syndrome



Alexander Shimabukuro-Vornhagen^{1,2,3,4*1}, Philipp Gödel^{1,2,3,1}, Marion Subklewe^{5,6,7,10}, Hans Joachim Stemmler^{5,10}, Hans Anton SchlöBer^{1,8}, Max Schlaak⁹, Matthias Kochanek^{2,3,4}, Boris Böll^{2,3,4} and Michael S. von Bergwelt-Baildon^{1,4,5,7,10}

Accumulating evidence suggests

that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. We recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.

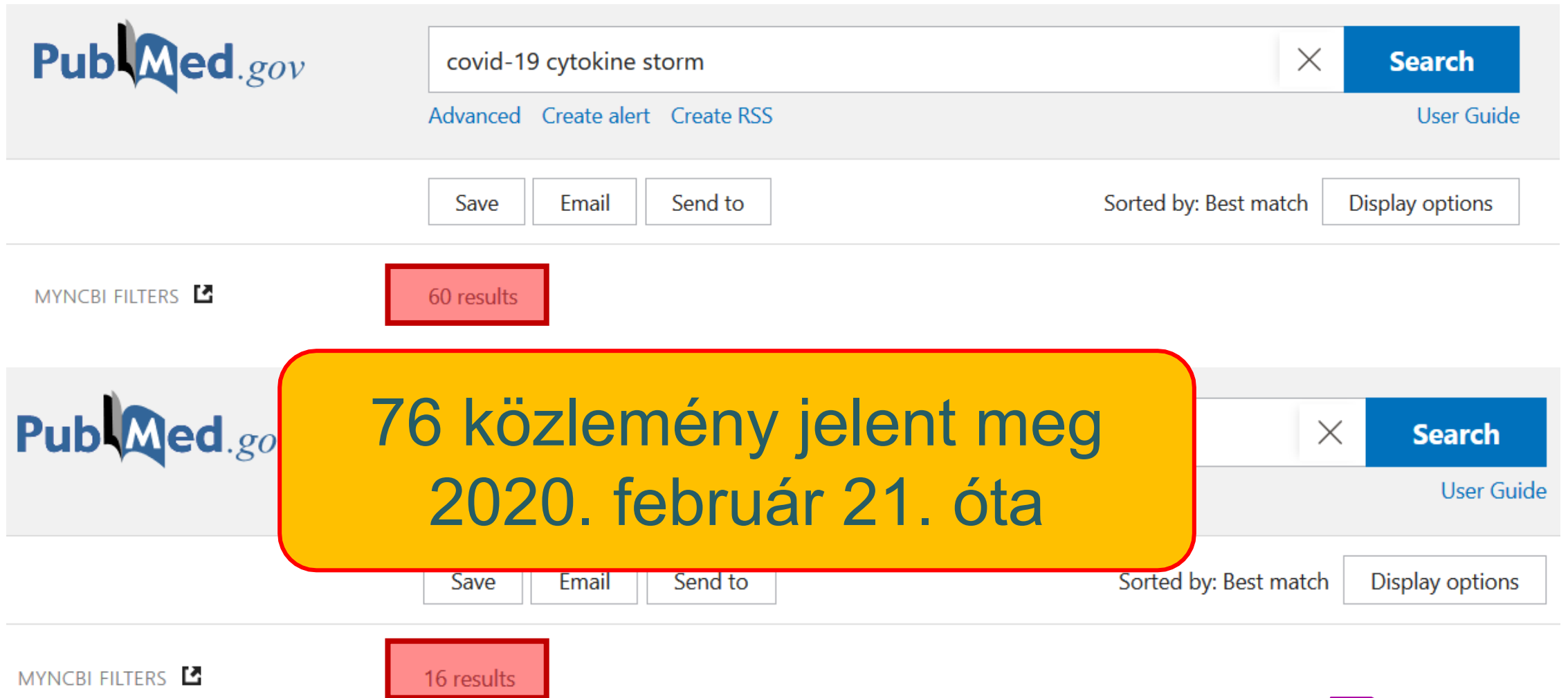
Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.² Secondary haemophagocytic lymphohistiocytosis (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, sHLH is most commonly triggered by viral infections³ and occurs in 3·7–4·3% of sepsis cases.⁴

Table 2 Differential diagnoses of CRS-related HLH/MAS

	Familial HLH	Secondary HLH/MAS	CRS-related HLH/MAS	Sepsis
Genetic Predisposition	Homozygous mutations	Heterozygous mutations in some patients	unknown	unknown
Age group	Young children	All ages	All ages	All ages
Biomarkers				
IL-10	↑↑↑	↑↑↑	↑	↑
IFN-γ	↑↑↑	↑↑↑	↑↑↑	↔
IL-6	↑	↑	↑↑↑	↑↑↑
Ferritin	↑↑↑	↑↑↑	↑↑↑	↑
CD163	↑↑↑	↑↑↑	NDA	↑

CRS cytokine release syndrome, HLH hemophagocytic lymphohistiocytosis, MAS macrophage activation syndrome, Sepsis. NDA no data available

Publikációk



The image shows a screenshot of the PubMed.gov search interface. The search query is "covid-19 cytokine storm". The results are sorted by "Best match". A yellow callout box with a red border is overlaid on the page, containing the text "76 közlemény jelent meg 2020. február 21. óta". Below the callout, the "60 results" count is highlighted in a red box. At the bottom of the page, the "16 results" count is also highlighted in a red box. The interface includes buttons for "Save", "Email", and "Send to", and a "User Guide" link.

PubMed.gov covid-19 cytokine storm Search

Advanced Create alert Create RSS User Guide

Save Email Send to Sorted by: Best match Display options

MYNCBI FILTERS 60 results

PubMed.gov Search

User Guide

Save Email Send to Sorted by: Best match Display options

MYNCBI FILTERS 16 results

76 közlemény jelent meg
2020. február 21. óta

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

Authors

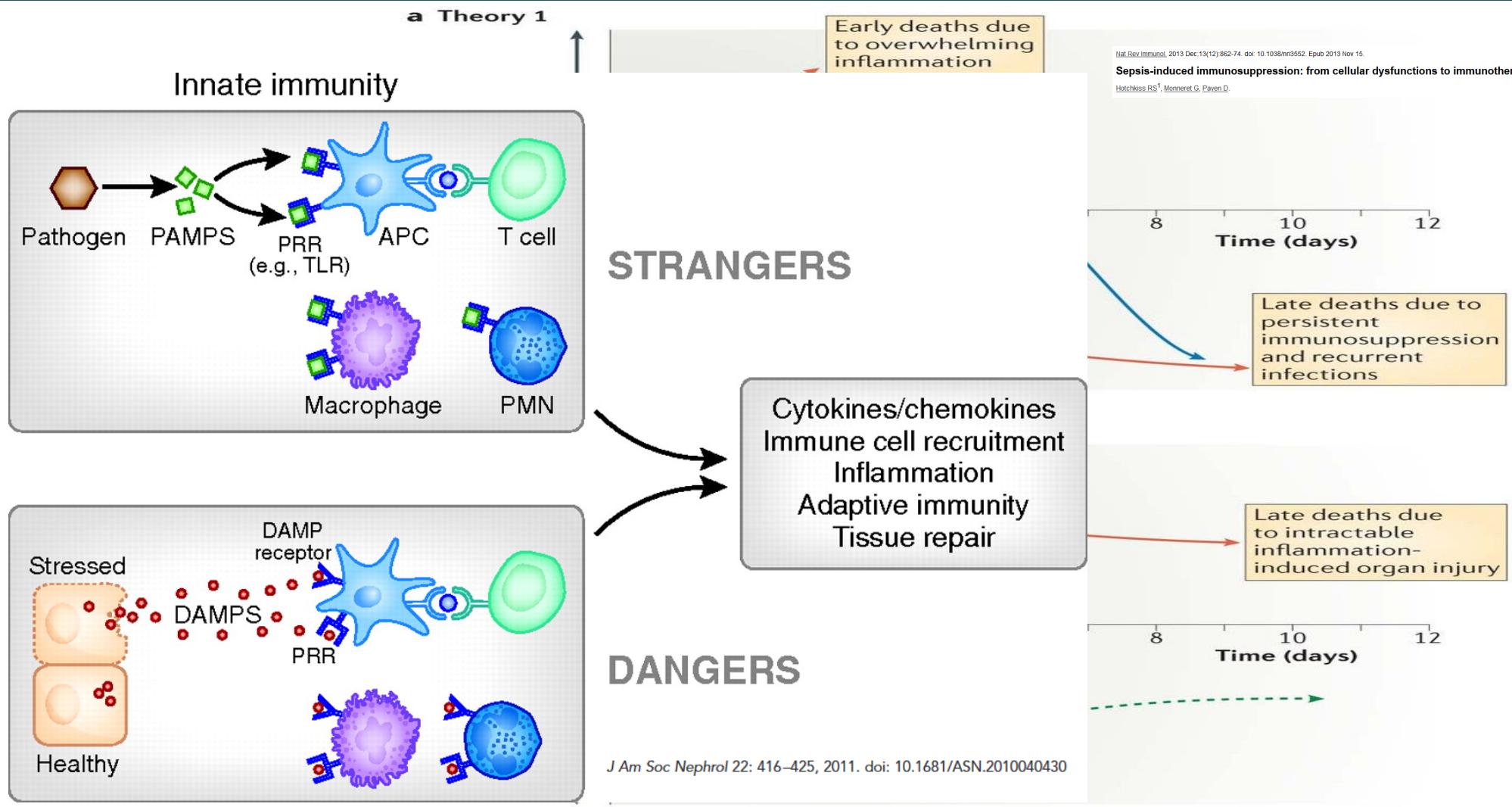
Waleed Alhazzani^{1,2}, Morten Hylander Møller^{3,4}, Yaseen M. Arabi⁵, Mark Loeb^{1,2}, Michelle Ng Gong⁶, Eddy Fan⁷, Simon Oczkowski^{1,2}, Mitchell M. Levy^{8,9}, Lennie Derde^{10,11}, Amy Dzierba¹², Bin Du¹³, Michael Aboodi⁶, Hannah Wunsch^{14,15}, Maurizio Cecconi^{16,17}, Younsuck Koh¹⁸, Daniel S. Chertow¹⁹, Kathryn Maitland²⁰, Fayez Alshamsi²¹, Emilie Belley-Cote^{1,22}, Massimiliano Greco^{16,17}, Matthew Laundry²³, Jill S. Morgan²⁴, Jozef Kesecioglu¹⁰, Allison McGeer²⁵, Leonard Mermel⁸, Manoj J. Mammen²⁶, Paul E. Alexander^{2,27}, Amy Arrington²⁸, John Centofanti²⁹, Giuseppe Citerio^{30,31}, Bandar Baw^{1,32}, Ziad A. Memish³³, Naomi Hammond^{34,35}, Frederick G. Hayden³⁶, Laura Evans³⁷, Andrew Rhodes³⁸

Citokin vihar szindróma

Cytokine Storm Syndrome

Cytokine storm syndrome is a hyperinflammatory state that is characterized by fulminant multi-organ failure and elevation of cytokine levels. A recent study from China showed that COVID-19 is associated with a cytokine elevation profile that is reminiscent of secondary hemophagocytic lymphohistiocytosis (HLH) [44]. Some authors even suggest that we screen critically ill COVID-19 patients for secondary HLH using the Hscore [140], and that corticosteroids and other immunosuppressive agents can be used in patients with a high likelihood of HLH [141]. More evidence is needed before we can make recommendations on the treatment options for cytokine storm.

Az immunválasz



A SARS-CoV-2 infekcióra adott immunválasz



TRANSLATIONAL
MEDICINE

Science

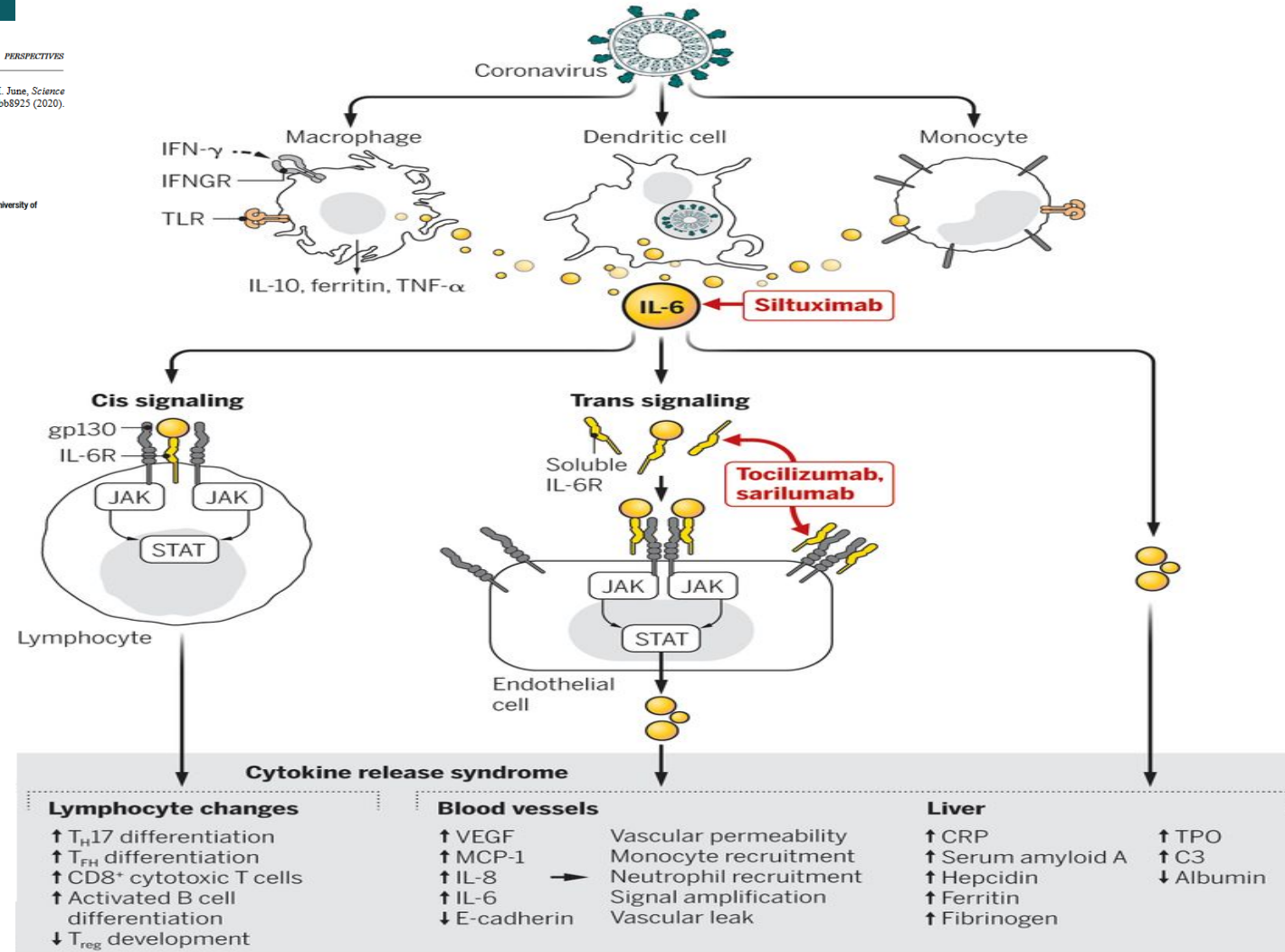
PERSPECTIVES

Cite as: J. B. Moore, C. H. June, *Science*
10.1126/science.abb8925 (2020).

Cytokine release syndrome in severe COVID-19

By John B. Moore¹ and Carl H. June²

¹Department of Hematology-Oncology, Walter Reed National Military Medical Center, Bethesda, MD, USA. ²Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, PA, USA. Email: john.b.moore74.mil@mail.mil; cjune@upenn.edu



C3, complement 3; CRP, C reactive protein; IFN- γ , interferon- γ ; IFNGR, IFN- γ receptor; IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; STAT3, signal transducer and activator of transcription 3; T_{FH}, T follicular helper cell; T_H17, T helper 17 cell; TNF- α , tumor necrosis factor- α ; TLR, Toll-like receptor; TPO, thrombopoietin; T_{reg}, T regulatory cell; VEGF, vascular endothelial growth factor.

GRAPHIC: V. ALTOUNIAN/SCIENCE

A SARS-CoV-2 és DAMPs

Critical Care



[Crit Care](#). 2011; 15(6): 235.

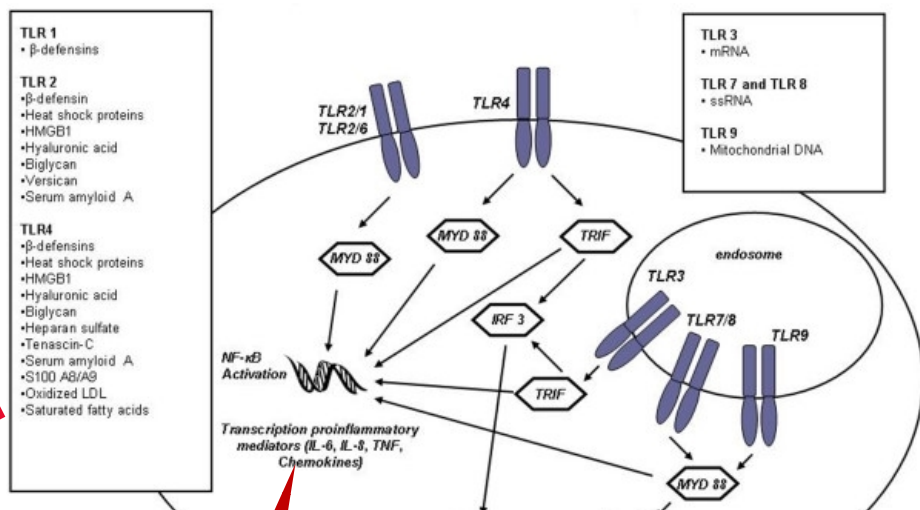
Published online 2011 Nov 30. doi: [10.1186/cc10437](#)

PMCID: PMC3388678

PMID: [22216838](#)

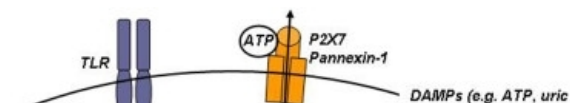
Bench-to-bedside review: Damage-associated molecular patterns in the onset of ventilator-induced lung injury

[Maria T Kuipers](#),^{1,2,3,4} [Tom van der Poll](#),^{3,4} [Marcus J Schultz](#),^{1,2} and [Catharina W Wieland](#)^{1,2}



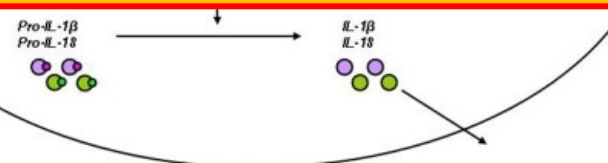
Signal 1
Activation of NFκB

Signal 2
Activation of NLRP3 by DAMPs



DAMPs = Ventilátor indukált tüdőkárosodás
(biotrauma)

TLR → NF-κβ, IL-6, IL-8,
TNF-α

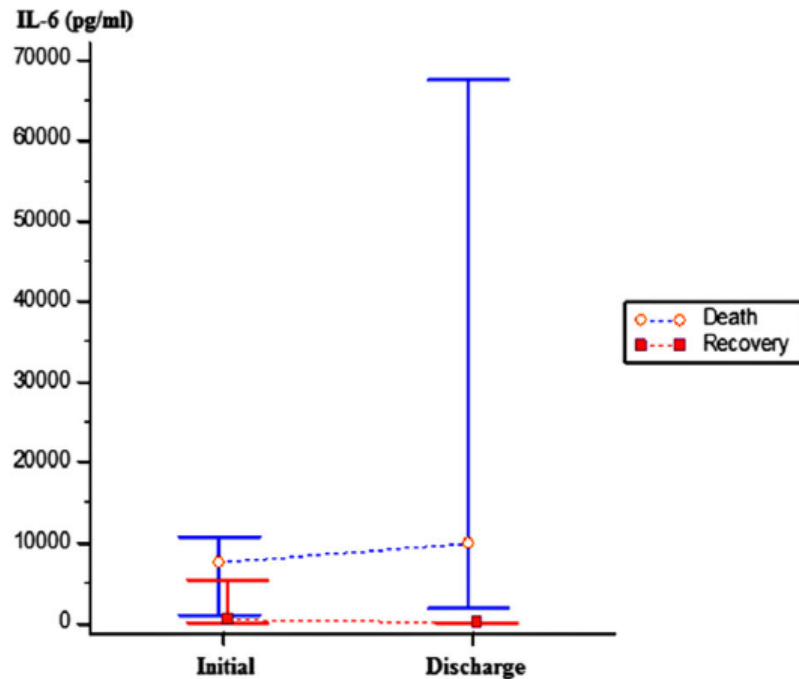


IL-6 diagnosztikus szerepe

RESEARCH ARTICLE

Open Access

Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions



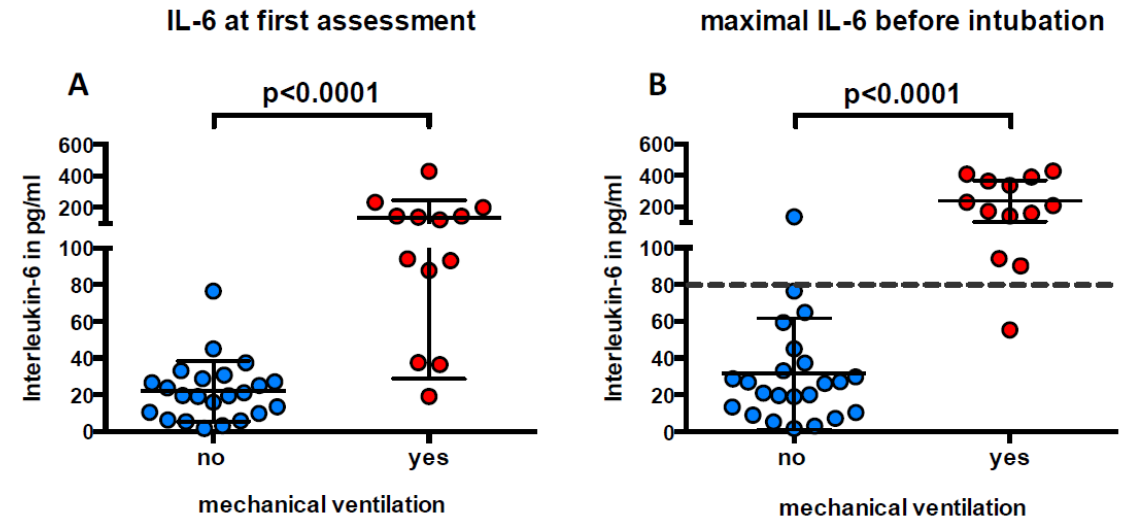
(a)

Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients

Tobias Herold, Vindi Jurinovic, Chiara Arnreich, Johannes C Hellmuth, Michael von Bergwelt-Baildon, Matthias Klein, Tobias Weinberger

doi: <https://doi.org/10.1101/2020.04.01.20047381>

Figure 1



Egy gyors kérdés, egy gyors válasz

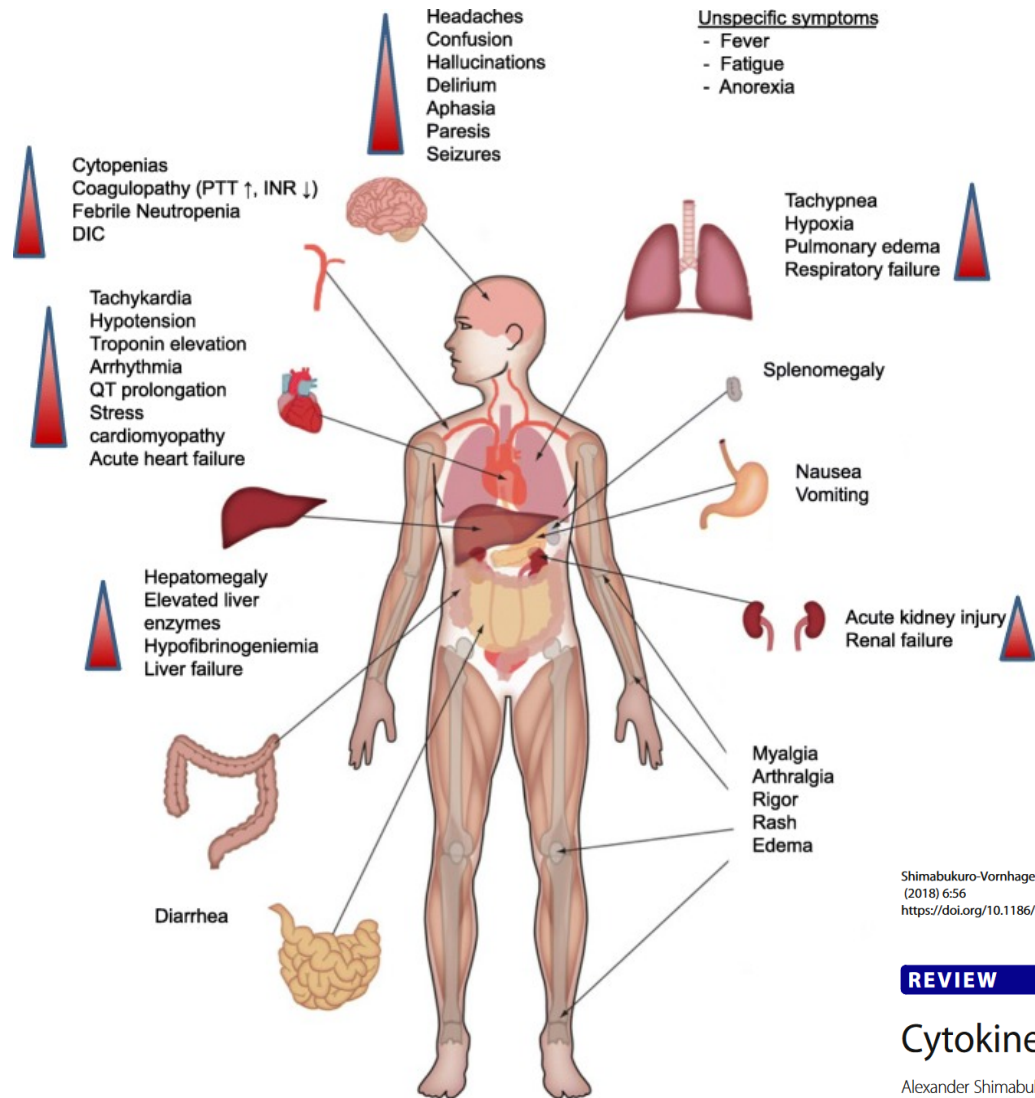
Van-e lehetőséged a mindennapi gyakorlatban az IL-6 szérumszintjének mérésére?

- Igen, meg tudom mérni
- Nem, nincs lehetőségem

Mit tudok használni a mindennapi gyakorlatban?



TRANSLATIONAL
MEDICINE



- Klinikai jelek
- Vitális paraméterek
- Labor eredmények

- HScore
- Plt/Lymph (PLR)

Shimabukuro-Vornhagen et al. *Journal for ImmunoTherapy of Cancer* (2018) 6:56
<https://doi.org/10.1186/s40425-018-0343-9>

Journal for ImmunoTherapy
of Cancer

REVIEW

Open Access



Cytokine release syndrome

Alexander Shimabukuro-Vornhagen^{1,2,3,4*}, Philipp Gödel^{1,2,3†}, Marion Subklewe^{5,6,7,10}, Hans Joachim Stemmler^{5,10}, Hans Anton Schlößer^{1,8}, Max Schlaak⁹, Matthias Kochanek^{2,3,4}, Boris Böhl^{2,3,4} and Michael S. von Bergwelt-Baildon^{1,4,5,7,10}

MAS/sHLH - HScore

	Number of points
Temperature	
<38.4°C	0
38.4–39.4°C	33
>39.4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1.5 mmol/L	0
1.5–4.0 mmol/L	44
>4.0 mmol/L	64
Fibrinogen (g/L)	
>2.5 g/L	0
≤2.5 g/L	30

Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The HScore¹¹ generates a probability for the presence of secondary HLH. HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator.¹¹ HLH=haemophagocytic lymphohistiocytosis. *Defined as either haemoglobin concentration of 9.2 g/dL or less (≤5.71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110 000 platelets per mm³ or less, or all of these criteria combined. †HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

Table: HScore for secondary HLH, by clinical parameter

Published Online
March 13, 2020
[https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)

<http://saintantoine.aphp.fr/score/>

Platelet / Lymphocyte Ratio (PLR)

Index	Nonsevere patients	Severe patients	Statistics	P value
Age	49.44 ± 14.86	60 ± 5.29	2.52 (t)	.041
<u>Time of hospitalization (mean ± standard deviation), d</u>	<u>15.33 ± 4.32</u>	<u>27 ± 1.41</u>	<u>3.745 (t)</u>	<u>.01</u>
Platelet value at admission (mean ± standard deviation), ×10 ⁹ /L	192.26 ± 58.12	169.67 ± 48.95	-0.645 (t)	.524
Lymphocyte value at admission (mean ± standard deviation), ×10 ⁹ /L	1.01 ± 0.45	1.16 ± 0.55	0.54 (t)	.593
PLR at admission (mean ± standard deviation)	242.75 ± 173.74	160.02 ± 51.99	30.00 (χ ²)	.414
Peak of platelet during treatment (mean ± standard deviation), ×10 ⁹ /L	301.22 ± 80.18	392 ± 123.38	1.776 (t)	.047
PLR at peak of platelet (mean ± standard deviation)	262.35 ± 97.78	626.27 ± 523.64	3.544 (t)	.001

JOURNAL OF

MEDICAL VIROLOGY

RESEARCH ARTICLE | [Free Access](#)

Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19

Rong Qu, Yun Ling, Yi-hui-zhi Zhang, Li-ya Wei, Xiao Chen, Xu-mian Li, Xuan-yong Liu, Han-mian Liu, Zhi Guo✉, Hua Ren✉, Qiang Wang✉

First published: 17 March 2020 | <https://doi.org/10.1002/jmv.25767> | Citations: 1

Potenciális kezelési lehetőségek

	Δ PLR statistics	P value
Time of hospitalization, d	0.413 ^a (R)	.023
Severe patients or nonsevere patients	4.122 (t)	.000

JOURNAL OF
MEDICAL VIROLOGY

RESEARCH ARTICLE | [Free Access](#)

Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19

Rong Qu, Yun Ling, Yi-hui-zhi Zhang, Li-ya Wei, Xiao Chen, Xu-mian Li, Xuan-yong Liu, Han-mian Liu, Zhi Guo✉, Hua Ren✉, Qiang Wang✉

First published: 17 March 2020 | <https://doi.org/10.1002/jmv.25767> | Citations: 1

Previous studies have shown that severe infections, immune-related factors, and other factors cause secondary thrombocytopenia, such as DIC, TTP, and HLH, which are characterized by rapid platelet decline.¹⁷ Through the observation of patients included, we found that platelets increased first and then decreased in severe patients during treatment and there were six patients with significantly increased platelets, who were generally older and had longer hospital stays. Therefore, we speculated that the changes in platelets in the treatment course may be correlated with the progression and prognosis of COVID-19.

CRS → PLT ↑↑
majd
PLT elhasználódás

- **Kortikoszteroidok**
 - IL-1R antagonistá (Anakinra)
 - IL-6 antagonistá (Tocilizumab)
 - TNF- α antagonistá (Infliximab)
-
- **Extrakorporális citokin eltávolítás**

Recommendations


41. In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we **suggest against the routine use of systemic corticosteroids** (weak recommendation, low quality evidence).
42. In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids, over not using corticosteroids (weak recommendation, low quality evidence).


Extrakorporális vértisztító eljárások

THE LANCET
Respiratory Medicine

SPOTLIGHT | VOLUME 8, ISSUE 3, P240-241, MARCH 01, 2020

Coronavirus epidemic: preparing for extracorporeal organ support in intensive care

Claudio Ronco  Paolo Navalesi • Jean Louis Vincent

Published: February 06, 2020 • DOI: [https://doi.org/10.1016/S2213-2600\(20\)30060-6](https://doi.org/10.1016/S2213-2600(20)30060-6) •  Check for updates

Finally, a sepsis-like syndrome might occur frequently due to the virus itself or to a superimposed bacterial infection and in this case, since pharmacological approaches have shown poor results, new extracorporeal organ support therapies including haemoadsorption and haemoperfusion, with new sorbent cartridges designed to remove cytokines and other circulating mediators, should be considered.

... azonban van egy kis bökkenő

Ebben a betegségben lassan az a meglepő,
ha valami nem meglepő

Már a kezdeti stádiumban
súlyos, akut hypoxiás légzési elégtelenség

Ez az ARDS nem az a „megszokott” ARDS

Miért lenne ez másként a citokin-szintekkel?

„A megszokott” citokin vihar

ANNALS OF SURGERY

A Monthly Review of Surgical Science Since 1885

Ann Surg. 1992 Apr; 215(4): 356–362.
doi: [10.1097/00000658-199204000-00009](https://doi.org/10.1097/00000658-199204000-00009)

PMCID: [PMC1242452](https://pubmed.ncbi.nlm.nih.gov/1242452/)
PMID: [1558416](https://pubmed.ncbi.nlm.nih.gov/1558416/)

Cytokine serum level during severe sepsis in human IL-6 as a marker of severity.

There was a direct correlation between IL-6 peak serum level and TNF alpha peak serum level during septic shock and between IL-6 serum level and temperature or C-reactive protein serum level. Moreover, IL-6 correlated well with APACHE II score, and the mortality rate increased significantly in the group of patients who presented with IL-6 serum level above 1000 pg/mL. Thus, IL-6 appears to be a good marker of severity during bacterial infection.

„A megszokott” citokin vihar

Song et al. *BMC Infectious Diseases* (2019) 19:968
<https://doi.org/10.1186/s12879-019-4618-7>

BMC Infectious Diseases

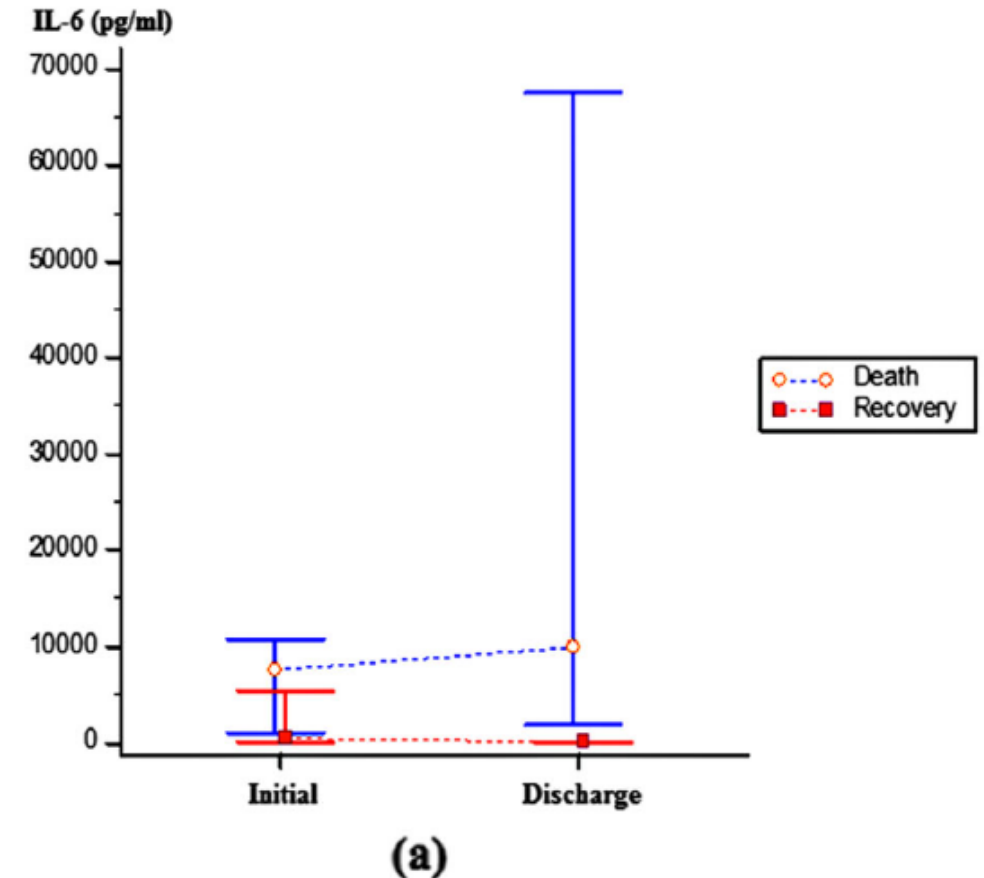
RESEARCH ARTICLE

Open Access

Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions



Among the patients with septic shock at presentation, initial IL-6 levels within 6 h of clinical diagnosis in the recovered survivors ($n = 15$) and non-survivors ($n = 13$) were 444.3 (261.2–5893.5) and 7609.5 (4526.0–12,208.4) pg/mL, respectively ($P = 0.05$), and follow-up IL-6 levels within 24 h of discharge were 21.5 (10.2–51.7) and 9976.5 (4651.2–71,048.3) pg/mL, respectively ($P < 0.001$).



Citokin szintek MERS-ben

Table 2

Comparison of the cytokines/chemokines expression levels between MERS-CoV infected patients and healthy non-infected group.

Cytokines/ chemokines	MERS-CoV infected patients (n = 39)	Healthy non-infected group (n = 30)	p-value
	Mean concentrations pg/ml (± SD)	Mean concentrations pg/ml (± SD)	
IL-1 α	1148.7 (688.2)	18.7 (3.8)	0.001
IL-1 β	1230.8 (580.4)	23.2 (4.4)	0.001
IL-2	20.7 (20.5)	20.5 (18.4)	0.9666
IL-4	13 (8.5)	12.5 (9.1)	0.8150
IL-6	20.2 (28.8)	11 (8.6)	0.0957
IL-8	1956.4 (695.8)	18.9 (1.1)	0.001
IL-10	9.2 (1.1)	8.5 (2.7)	0.1461
IL-12	13.7 (6.3)	11.2 (6.8)	0.1191
IL-17A	19.3 (15.5)	15.5 (15.9)	0.3217
IFN- γ	32.4 (53.9)	12.3 (11.1)	0.0488
TNF- α	20.7 (32.8)	11.5 (11.8)	0.1481
GM-CSF	23.3 (25.5)	20.1 (25.1)	0.6046



Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

MERS-CoV infection is associated with downregulation of genes encoding Th1 and Th2 cytokines/chemokines and elevated inflammatory innate immune response in the lower respiratory tract

Bandar Alosaimi^{a,b,*}, Maaweya E. Hamed^c, Asif Naeem^a, Ali A. Alsharif^d, Saeed Y. AlQahtani^d, Kamel M. AlDosari^e, Aref A. Alamri^e, Kholoud Al-Eisa^e, Taghreed Khojah^e, Abdullah M. Assiri^f, Mushira A. Enani^g

Citokin szintek COVID-19-ben

Figure 2. Meta-Analysis of Serum IL-6 Levels in COVID-19

Interleukin-6 in COVID-19: A Systematic Review and Meta-Analysis

Panel A. Patients with Complicated COVID-19 versus Non-Complicated

Eric Anthony Coomes,  Hourmazed Haghbayan

doi: <https://doi.org/10.1101/2020.03.30.20048058>

Study or Subgroup	log[Ratio of Means]	SE	Complicated		Non-Complicated		Ratio of Means	
			Total	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chen et al. 2020a	0.75030559	0.01700847	14	15	16.7%	2.12 [2.05, 2.19]		
Diao et al. 2020	1.2861085	0.01523892	20	479	16.7%	3.62 [3.51, 3.73]		
Huang et al. 2020a	1.03489647	0.08752466	13	28	16.6%	2.81 [2.37, 3.34]		
Liu 2020	2.69261639	0.00539448	69	11	16.7%	14.77 [14.61, 14.93]		

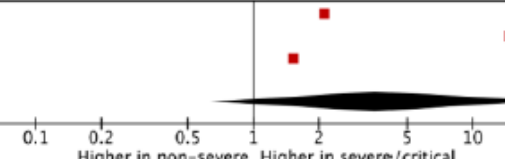
2.9-szeres IL-6 szint emelkedés a súlyos esetekben a nem súlyos esetekhez képest

Study or Subgroup	log[Ratio of Means]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Diao et al. 2020	1.2861085	0.01523892	20	479	55.9%	3.62 [3.51, 3.73]	

És a cut off érték is alacsonyabb


Study or Subgroup	log[Ratio of Means]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chen et al. 2020a	0.75030559	0.01700847	14	15	33.3%	2.12 [2.05, 2.19]	
Liu 2020	2.69261639	0.00539448	69	11	33.3%	14.77 [14.61, 14.93]	
Qin et al. 2020	0.42527895	0.0036103	286	166	33.3%	1.53 [1.52, 1.54]	
Total (95% CI)			369	192	100.0%	3.63 [0.65, 20.37]	

Heterogeneity: Tau² = 2.32; Chi² = 122484.25, df = 2 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.47 (P = 0.14)



Citokin szintek COVID-19-ben

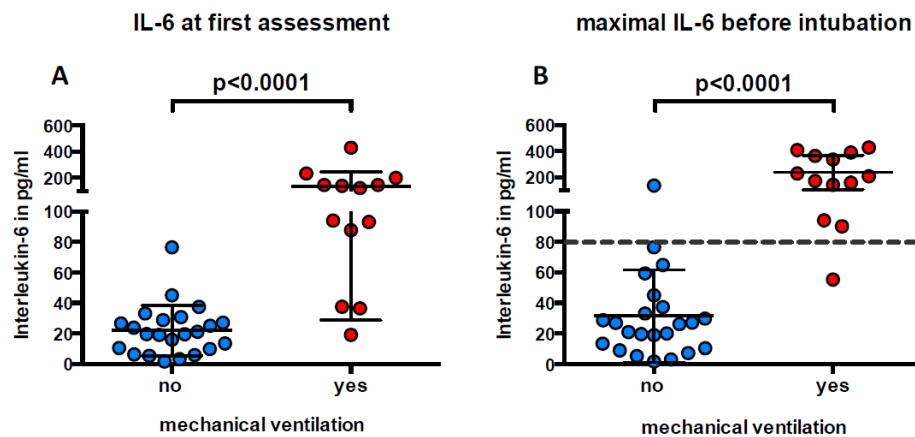
Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients

 Tobias Herold, Vindi Jurinovic, Chiara Arnreich, Johannes C Hellmuth, Michael von Bergwelt-Baildon, Matthias Klein, Tobias Weinberger

doi: <https://doi.org/10.1101/2020.04.01.20047381>

Elevated interleukin-6 (IL-6) was very strongly associated with mechanical ventilation (figure 1A, $p=1.2 \cdot 10^{-5}$, $q=0.00032$)


Figure 1



Laboratory parameters	Evaluable	Median (range)	Mechanical ventilation		p-value	q-value
			No (n = 27)	Yes (n = 13)		
Lymphocyte count (%)	36	19 (4 - 45)	21 (4 - 45)	15 (6 - 26)	0.050	0.11
CRP (mg/dl)	40	2.8 (0 - 31.5)	1.7 (0 - 31.5)	7.8 (1.6 - 17.1)	0.0019	0.012
Bilirubin (mg/dl)	36	0.5 (0.2 - 1.9)	0.5 (0.2 - 1.2)	0.5 (0.4 - 1.9)	0.93	>0.99
WBC (G/l)	40	5.295 (2.12 - 308)	4.75 (2.12 - 12.5)	6.64 (4.99 - 308)	0.0014	0.012
LDH (U/l)	38	292 (182 - 1078)	281 (182 - 619)	346 (252 - 1078)	0.0026	0.012
PCT (ng/ml)	37	0 (0 - 5)	0 (0 - 0.6)	0.1 (0 - 5)	0.011	0.041
IL6 (pg/ml)	37	27.1 (0 - 430)	19.6 (0 - 76.5)	121 (19.2 - 430)	0.000012	0.00032
Thrombocyte count (G/l)	40	165 (88 - 440)	186 (88 - 334)	160 (1 - 440)	0.59	0.80
Troponin T (ng/ml)	34	0 (0 - 0.032)	0 (0 - 0.022)	0 (0 - 0.032)	0.018	0.058
Creatinine (mg/dl)	40	0.9 (0.4 - 2.1)	0.9 (0.4 - 1.3)	1.0 (0.9 - 2.1)	0.00034	0.0044
D-Dimer	30	0.7 (0 - 2.9)	0.6 (0 - 2.2)	1.1 (0.6 - 2.9)	0.028	0.074
Ferritin (ng/ml)	27	644 (64 - 2153)	606 (64 - 1748)	810 (431 - 2153)	0.16	0.28

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Even though IL-6 levels were significantly elevated in patients requiring ventilation, they are relatively low compared to levels observed in patients with septic shock.⁵ Our data suggests that even moderately elevated IL-6 levels above 80pg/ml are sufficient to identify COVID-19 patients with a high risk of respiratory failure. Further studies and larger sample sizes will be needed to validate our findings and possibly determine a more accurate cutoff. To date, it is unclear whether IL-6 merely represents a biomarker or a central pathogenetic element of severe COVID-19 that should be used as a parameter for therapeutic intervention.

Citokin szintek COVID-19-ben

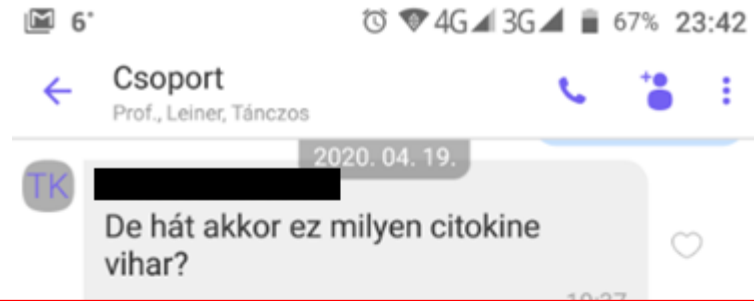
The reported inflammatory response in COVID-19 is also not consistent with either typical ARDS or with cytokine-release syndromes (CRS) or “cytokine storm”. Qin *et al.* report mean interleukin-6 levels were 25 (SD:10-55) pg/mL (normal-range: 7pg/mL).³ Other smaller COVID-19 reports have ranged from 7pg/mL to 125pg/mL. These findings contrast with interleukin-6 elevations seen in typical ARDS and in CRS. Sinha *et al.* report mean interleukin-6 levels of 282 (111-600) pg/mL in “hypo-inflammatory” ARDS⁹ and 1,618 (517-3,205) pg/mL in hyper-inflammatory ARDS,⁴ 10 to 60-fold higher than reported in the Wuhan data. Among CRS patients, mean interleukin-6 levels are frequently as high as 10,000 pg/mL.⁵ Other inflammatory cytokines (e.g., interleukin-8, interleukin-1 β) demonstrate similar patterns.

Citokin vihar vagy csak „citokin szellő”?

TRANSLATIONAL
MEDICINE



Akkor most hogy is van ez?



Lehet, hogy még valami más is van a háttérben?

Hypoinflammatios ARDSben meg
100 körül van
19:38

Akkor itt első körben nem az
inflammatio a hunyó
19:39

Hanem a vírus, na utána nézek ennek
19:39

Ezért más a coagulatio is, mint a
septic us coagulopathias dic
19:40