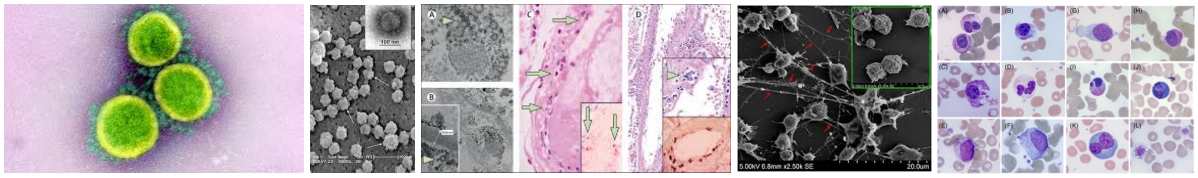

Impairment of the immune response in SARS-CoV-2 infection to the ICU patient: What's consequence in clinical practice ?

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Immunological consequences of severe COVID-19

- Severe **persistent lymphopenia** + leukocytosis
- Peripheral depletion, probably no recruitment to organs (Liao M, Nature Med 2020)
- Oligoclonal plasmablast expansion (Kuri-Cervantes L, Science Immunol 2020)
- Heterogeneous T cells activation – exhaustion (Diao B, Front Immunol 2020)
- Immunophenotypes (1 to 3) based on CD4, CD8, B cells (Mathew Science 2020)

Complex and heterogenous dependant on:
- Severity
- Age
- Immunologic status (eg. Pregnancy, systemic disease, cancer, ...)
- Time
- (multiplicity of published data)

Immunological consequences of severe COVID-19

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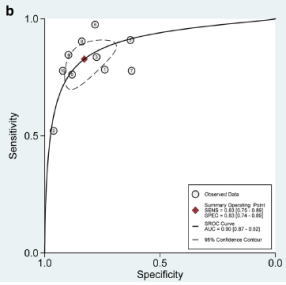


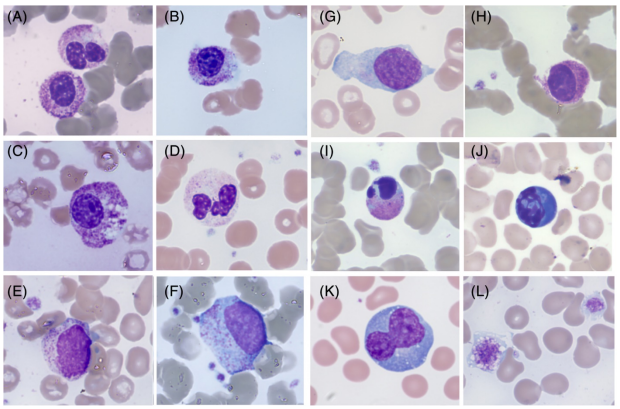
Neutrophils to lymphocytes ratio

AUC for mortality: 0,90 (95%CI 0,87-0,92)

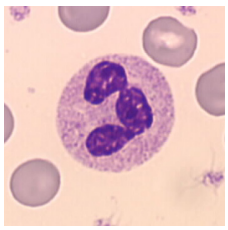
NLR>6,5 (Se 0,83; Sp 0,87), odd ratio 32 (95% CI 17-61), post-test prob 83%

(Li X Critical Care 24; 2020)

Marked alteration in neurtrophil morphology



- Hyper granularity
- **Increased N band form**
- Total absence of of nuclear segmentation (eg. Pseudo-Pelger anomaly)
- Apoptotic neutrophils
- Immature granulocytes



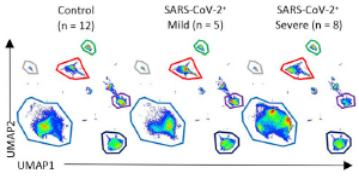
Zini G. Am J Hematol 2020

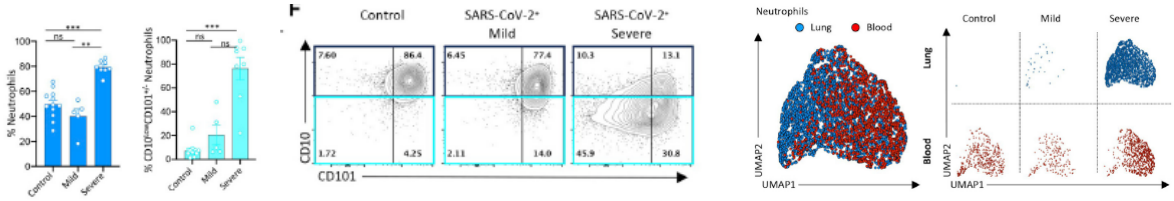
Neutrophils in severe COVID-19

Spectral cytometer/25 markers

1) Exagerated immature neutrophilia ($CD10^{Low}CD101^{-}CXCR4^{+/-}$)

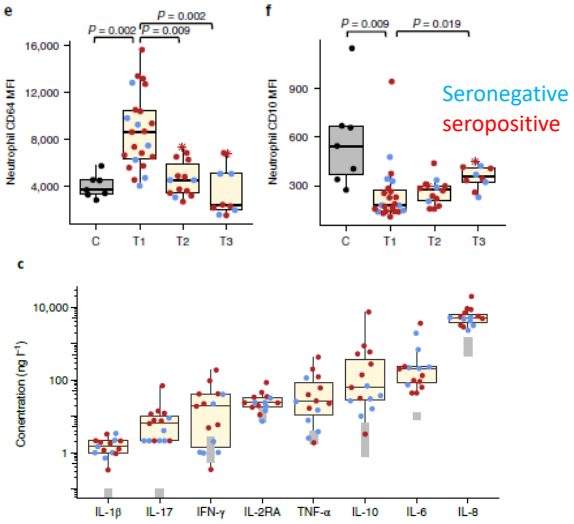
2) Emergent myelopoeisis





Silvin A. Cell 2020

Neutrophils in severe COVID-19 **and pediatric PIMS**



Initial and resolution phase

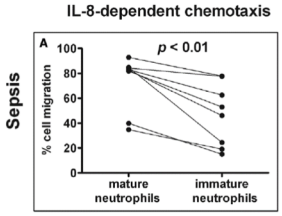
- Initially activated neutrophil
- But immature neutrophils ($CD10^{low}$)
- Cytokines profile different between sero-positive and – negative ?

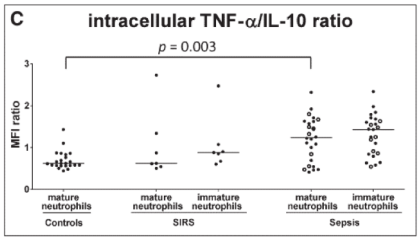
Carter M. Nature Med 2020

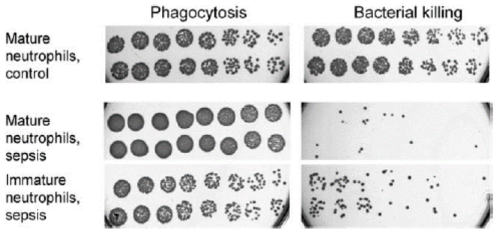
Consequences of exagerated immature neutrophilia

3) Altered neutrophils function:

- ⬇ Chemotaxism
- ⬇ Phagocytosis
- ⬇ Bactericidia
- But **increased proinflammatory balance**

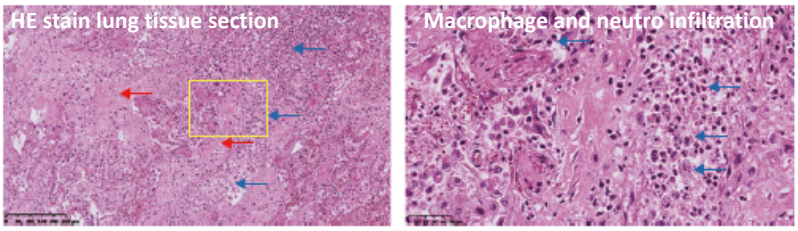


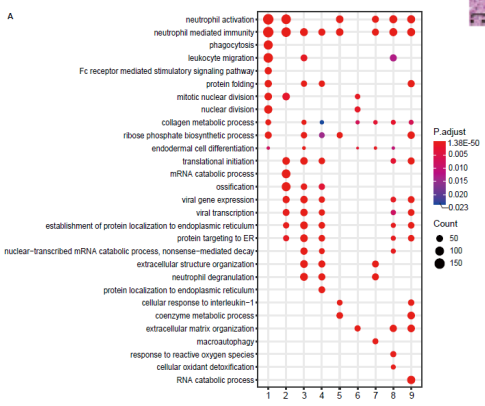


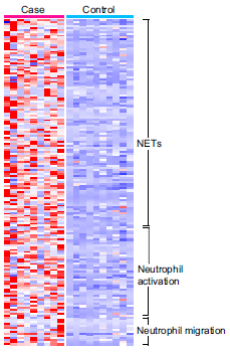


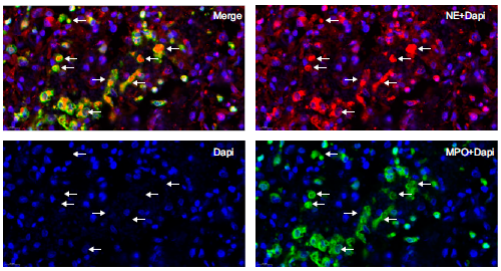
Drifte G Crit Care Med 2013

Where are mature neutrophils ????









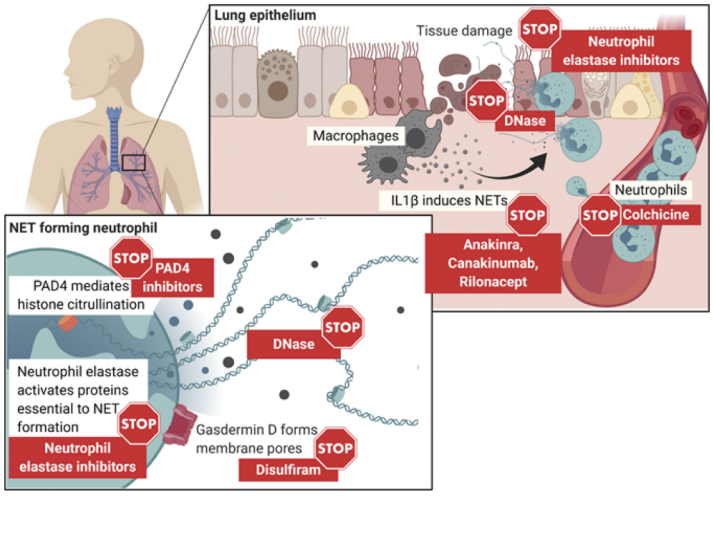
Wu M. PNAS 117; 2020

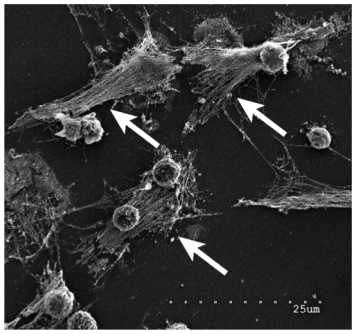
4) Neutrophils sewing in the lung / Lung NETosis

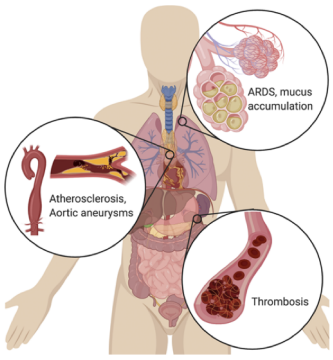
1- Upregulated NETosis genes
- myeloperoxidas, lactiferin, histones

2- co-local myeloperoxidase and neutrophil elastase

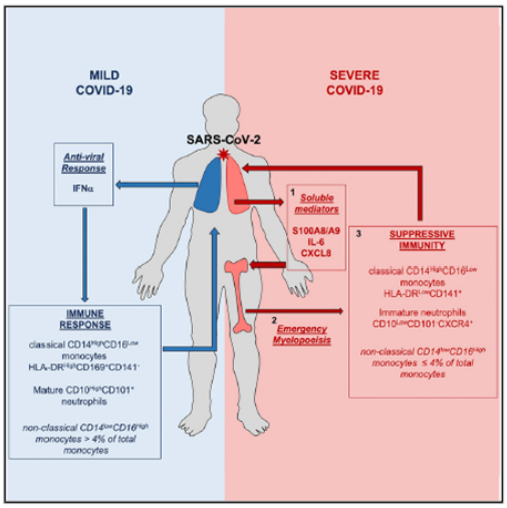
NETosis

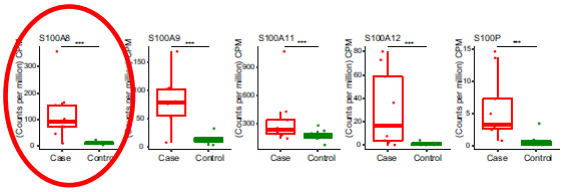






Massive proteins releases (incl. Cytokines, cathepsins, calprotectin)

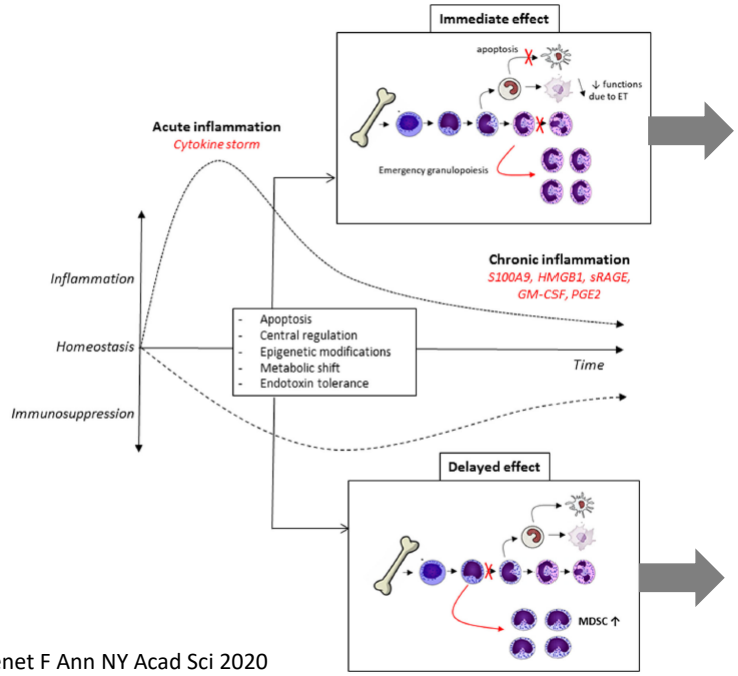




- ❖ Induction of emergency myelopoeisis
- ❖ Maturation blockage/ expansion of immature myeloid cells (eg. calprotectin, GM-CSF, CXCL)
- ❖ Activation of MDSC (eg. LPS, IL6, HMGB1)

5) Induction of myeloid immunosuppressive cells

Silvin A Cell 2020
Wu M. PNAS 117; 2020

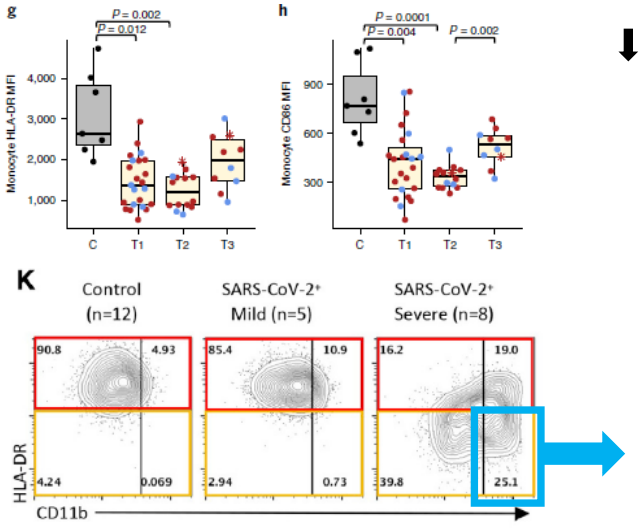


Immature neutrophils « N band »

Immature myeloid precurssors

Venet F Ann NY Acad Sci 2020

Induction of immature myeloid precurssors and deactivated monocytes



⬇ Non-classical CD14^{Low} CD16^{High} monocytes

Within classical CD14^{High} CD16^{Low} monocytes

→ **Increase in CD11b ^{High}**

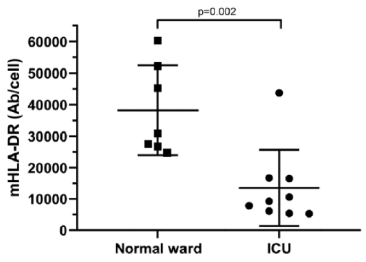
→ **Decrease in mHLA-DR**

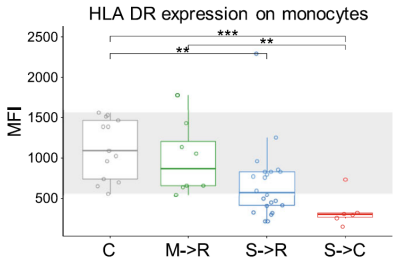
Monocytes Myeloid derived suppressor cells (M-MDSC)

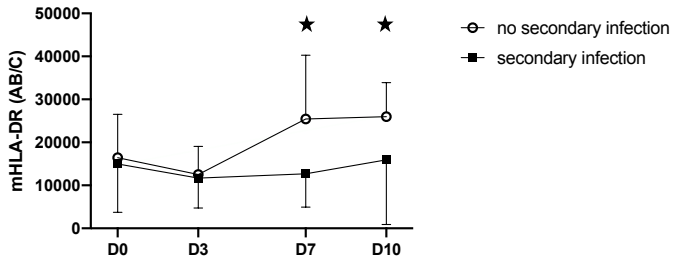
Silvin A Cell 2020

Carter M, Nature Med 2020

6) mHLA-DR is transiently decreased in severe COVID-19





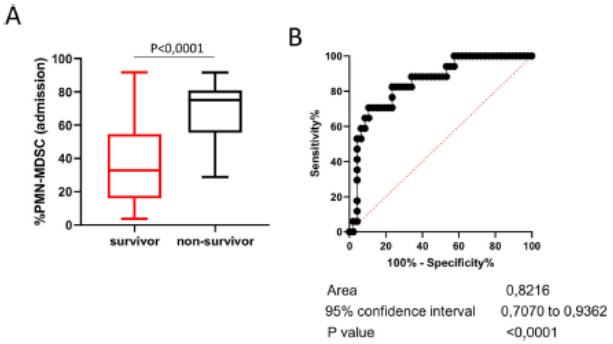


Spinetti T. Anest Analg 2020
Moratto D. J Clin Immunol 2020
Tissieres et al. unpublished

MDSC at admission has a prognostic value

PMN-MDSC

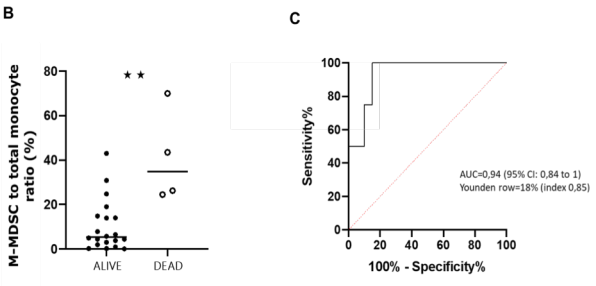
Cutt-off 53%



Sacchi A. Cell Death Dis 2020

M-MDSC

Cutt-off 18%



Tissieres et al. unpublished

How to modulate severe COVID 19 immune response ?

- Cytokines storm and massive release of circulating compounds are triggering altered myeloid phenotype (mHLA-DR depression, MDSC)
- Functional effect ?

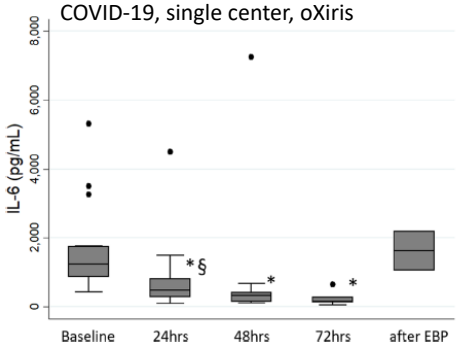
→ anti-IL6, IL-1 receptor antagonist, colchicine, ..?

→ **Extracorporeal blood purification/cytokines removal**

Rationale behind ECBP in COVID-19

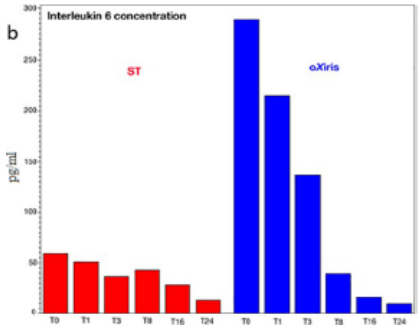
1) Reducing pro-inflammation (cytokines)

COVID-19, single center, oXiris



Villa G. Crit Care 2020

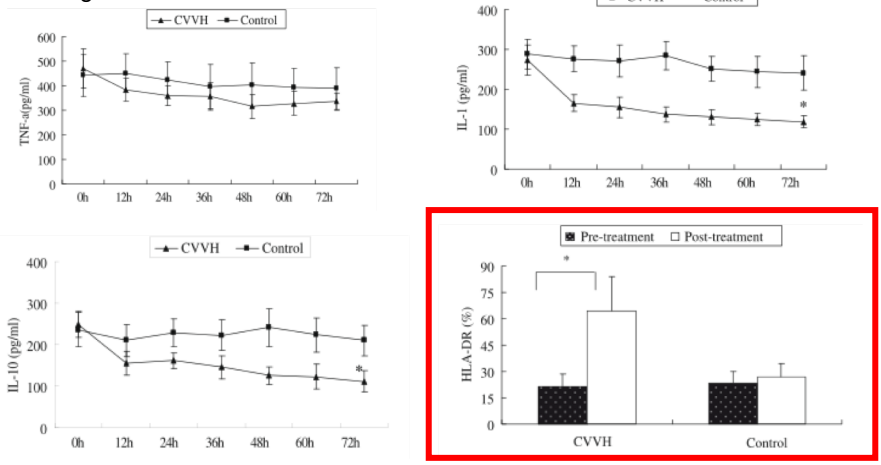
Septic shock, multicentre RCT, oXiris



Broman M. Plos One 2019

2) immuno-modulation (mHLA-DR)

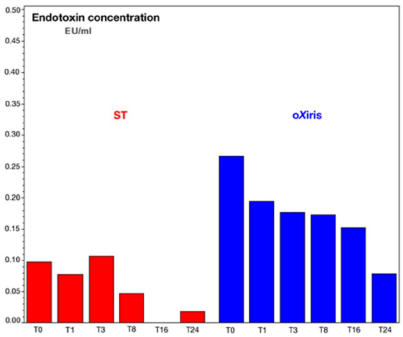
70 ml/kg/h



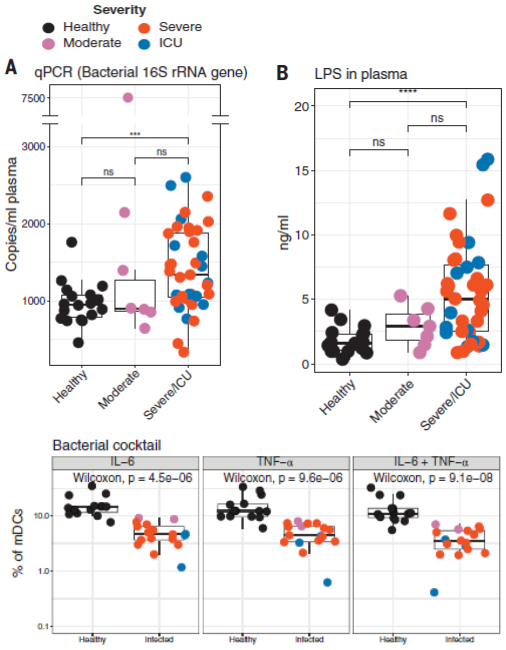
Peng Z et al, Cytokines 2010

Arunachalam PS. Science 2020

3) Capturing circulating endotoxins



Broman M. Plos One 2019



8) Increased circulating LPS and bacterial DNA in severe COVID-19 + altered response

Consequences of severe COVID-19 on myeloid cells

1) Exagerated immature neutrophilia

2) Emergent myelopoeisis

3) Altered neutrophils function

4) Neutrophils sewing in the lung / Lung NETosis

5) Induction of myeloid immunosuppressive cells

6) mHLA-DR is transiently decreased in severe COVID-19, correlates with severity and secondary infection

7) MDSC at admission has a prognostic value

8) Increased circulating LPS on severe COVID-9 and altered response