IL-6 is a pro-inflammatory marker (together with TNF and IL-1). Serum IL-6 levels are associated with conditions such as Crohn’s disease, Rheumatoid Arthritis, Osteoporosis, JCA, and SLE. Treatment with Tocilizumab (blocking anti-IL-6R Ab) by Tadamitsu Kishimoto, Japan.
IL-6

B cells  Macrophages

DC

endothelial cells

vascular smooth muscle cells

fibroblasts

Epithelial cells

Virus infection

Insults/damage stimuli
Influenza virus induces IL-6 production in mouse lung epithelial cells

SARS-CoV induces IL-6 production in human lung epithelial cells

Yoshikawa et al J. Virology 2009
Study on COVID-19 patients:

- Use of neutrophil to lymphocyte ratio (NLR): lymphopenia and neutrophilia

- Cytokine Analysis in Serum between non-severe and severe cases
  
  - increased IL-6 levels (normal TNF levels) in serum in severe relative to non-severe patients

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>NLR\textsuperscript{high}</th>
<th>NLR\textsuperscript{low}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-severe</td>
<td>Severe</td>
</tr>
<tr>
<td>IL-2, pg/ml</td>
<td>3.3 (3.0-4.1)</td>
<td>3.2 (3.1-3.5)</td>
</tr>
<tr>
<td>IL-4, pg/ml</td>
<td>3.2 (2.9-4.3)</td>
<td>3.3 (2.9-3.6)</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>5.7 (4.5-12.5)</td>
<td>24.4 (10.2-97.6)*#</td>
</tr>
<tr>
<td>IL-10, pg/ml</td>
<td>5.6 (4.2-7.6)</td>
<td>8.0 (5.7-25.0)</td>
</tr>
<tr>
<td>TNF-α, pg/ml</td>
<td>3.1 (2.9-3.3)</td>
<td>3.2 (2.9-3.2)</td>
</tr>
<tr>
<td>IFN-γ, pg/ml</td>
<td>3.6 (2.2-4.3)</td>
<td>3.4 (2.7-4.4)</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>29.4 (5/17)</td>
<td>100 (16/16)</td>
</tr>
</tbody>
</table>

Zhang et al. Cancer Center Renmin Hospital of Wuhan University
Study on COVID-19 patients:

- Analysis between non-severe and severe cases upon admission
  - Baseline CRP, ferritin and D-dimer elevated
  - Baseline immunological parameters were within normal range

Liu et al.  Cancer Center, Union Hospital Huazhong University of Science and Technology, Wuhan
Study on COVID-19 patients:

- Analysis between non-severe and severe cases upon admission
  - Baseline CRP, ferritin and D-dimer elevated
  - Baseline immunological parameters were within normal range
  - Baseline IL-6 levels in serum were higher in severe cases

Liu et al.  Cancer Center, Union Hospital Huazhong University of Science and Technology, Wuhan
Study on COVID-19 patients:

- Analysis between patients requiring mechanical ventilation or not after admission
  - No differences in baseline comorbidities, radiological findings, respiratory rate
  - Baseline IL-6 levels in serum were higher patients requiring mechanical ventilation

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Evaluable</th>
<th>Median (range)</th>
<th>Mechanical ventilation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No (n = 27)</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count (%)</td>
<td>36</td>
<td>19 (4 - 45)</td>
<td>21 (4 - 45)</td>
<td>0.050</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>40</td>
<td>2.8 (0 - 31.5)</td>
<td>1.7 (0 - 31.5)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>36</td>
<td>0.5 (0.2 - 1.9)</td>
<td>0.5 (0.2 - 1.2)</td>
<td>0.93</td>
</tr>
<tr>
<td>WBC (G/l)</td>
<td>40</td>
<td>5.295 (2.12 - 308)</td>
<td>4.75 (2.12 - 12.5)</td>
<td>0.0014</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>38</td>
<td>292 (182 - 1078)</td>
<td>281 (182 - 619)</td>
<td>0.0026</td>
</tr>
<tr>
<td>PCT (ng/ml)</td>
<td>37</td>
<td>0 (0 - 5)</td>
<td>0 (0 - 6)</td>
<td>0.011</td>
</tr>
<tr>
<td>IL6 (pg/ml)</td>
<td>37</td>
<td>27.1 (0 - 430)</td>
<td>19.6 (0 - 76.5)</td>
<td>0.000012</td>
</tr>
<tr>
<td>Thrombocyte count (G/l)</td>
<td>40</td>
<td>165 (88 - 440)</td>
<td>186 (88 - 334)</td>
<td>0.59</td>
</tr>
<tr>
<td>Troponin T (ng/ml)</td>
<td>34</td>
<td>0 (0 - 0.032)</td>
<td>0 (0 - 0.022)</td>
<td>0.018</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>40</td>
<td>0.9 (0.4 - 2.1)</td>
<td>0.9 (0.4 - 1.3)</td>
<td>0.00034</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>30</td>
<td>0.7 (0 - 2.9)</td>
<td>0.6 (0 - 2.2)</td>
<td>0.028</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>27</td>
<td>644 (64 - 2153)</td>
<td>606 (64 - 1748)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Study on COVID-19 patients:

- Analysis between patients requiring mechanical ventilation or not after admission
  - No differences in baseline comorbidities, radiological findings, respiratory rate
  - Baseline immunological parameters were within normal range
  - Baseline IL-6 levels in serum were higher in patients requiring mechanical ventilation
  - Maximal IL-6 level for each patient during disease predicts respiratory failure
  - Risk of respiratory failure for patients with IL-6 ≥80 pg/ml was 22 times higher compared with patients with lower IL-6 levels

Herold et al. Depart of Medicine, University Hospital, LMU Munich Munich,
Classical IL-6 signaling (use of transmembrane IL-6R)

Cells expressing IL-6R:
- hematopoietic cells (CD4 and CD8 T cells, macrophages, neutrophils…)
- hepatocytes
**IL-6 trans-signaling (use of soluble IL-6R)**

**Cells expressing IL-6R**
(macrophages, neutrophils, CD4 cells)

**Cells lacking IL-6R**
(epithelial cells, smooth muscle cells, endothelial cells etc)
SARS-CoV

Lung epithelial cells

mIL-6R

sIL-6R

mIL-6R

mblIL-6R

gp130

CD4+ T cell

Neutrophils

Macrophages

Fibroblasts
Smooth muscle cells
Endothelial cells

Epithelial cells

IL-6

gp130
Effects of IL-6 on multiple types of cells,

- promotes survival of neutrophils
- promotes proliferation and migration of vascular smooth muscle cells
- endothelial dysfunction
- induces fibrinogen synthesis (CVD)
- induces collagen production in fibroblasts
- induces acute phase response
- regulates CD4 and CD8 T cell function

Association of IL-6 with multiple diseases

- autoimmune disease (e.g. RA)
- diabetes
- pulmonary hypertension (poor survival)
- heart failure
- asthma, COPD, lung fibrosis
- Kidney diseases
- etc
Treatment of COVID-19 patients with a blocker of IL-6R (tocilizumab) in a single-arm trial:

Tocilizumab treatment outcomes:
- CRP levels decreased to normal levels in 84% of the patients after 5 days
- Fever returned to normal within 1 day
- Peripheral oxygen saturation improved rapidly
- 1 patient was taken off the ventilator after 1 day, 1 extubated patient regained consciousness after 5 days
- 15 patients lowered their oxygen intake

21 patients
Inhibiting IL-6/IL-6R signaling therapeutically in COVID-19

- **Tocilizumab.** Blocking IL-6R (membrane and sIL-6R) antibody
- **Sarilumab.** Blocking IL-6R (membrane and sIL-6R) antibody
- **Jak1/Jak2 inhibitors:** Baracitinib,
- **Blockers for IL-1.**
Is there any genetic component that could influence severity of COVID-19?

????????
**IL-6 gene polymorphisms:**

- **-174 G>C** in the *IL-6* gene promoter
- “C”, minor allele (CC about 20% of population but varies),
- **CC** is associated with lower IL-6 levels in plasma,
- **CC** associated with decrease risk of type 2 diabetes

**IL-6R gene polymorphisms:**

- Rs2228145 Asp^{358}Ala (A>C) in coding region (exon 9).
- “C” is the minor allele (10-15% population)
- “C” - increased production of sIL-6R (increased cleavage)
- “C” - association with risk of asthma and impaired lung function

**Levels of IL-6 in serum are lower in females versus males**
- both in mouse and human

**Elevated levels of IL-6 in serum with aging**
IL-6 in COVID-19, overall summary:

- High IL-6 levels correlate with severity of disease in COVID patients

- IL-6 levels do not necessarily represent an exaggerated immune response (no TNF increase)

- IL-6 most likely comes from lung epithelial cells (virus replication), vascular smooth muscle cells (IL-1) and other lung cells

- Blocking IL-6R in hospitalized severe patients is a promising therapy that could reduce the use time for ventilators and potentially save lives.