
# TERAPIA CON «TOCILIZUMAB» IN CORSO DI COVID-19: ESPERIENZA DI MILANO OSPEDALE SAN RAFFAELE

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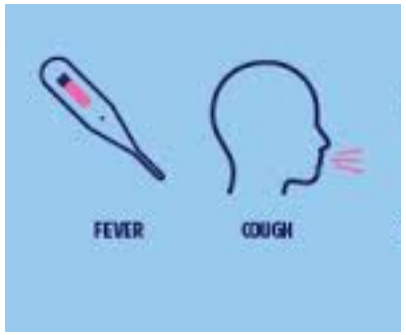
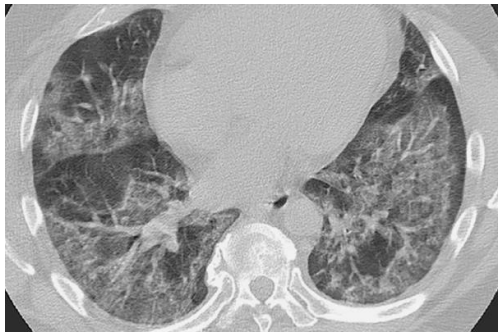
OSPEDALE SAN RAFFAELE

# COVID-19 and hyper-inflammation

**Cytokine storm**
**IL-1, IL-6, TNF, GM-CSF**



7-10 days

10-15 days

Late during hospitalization

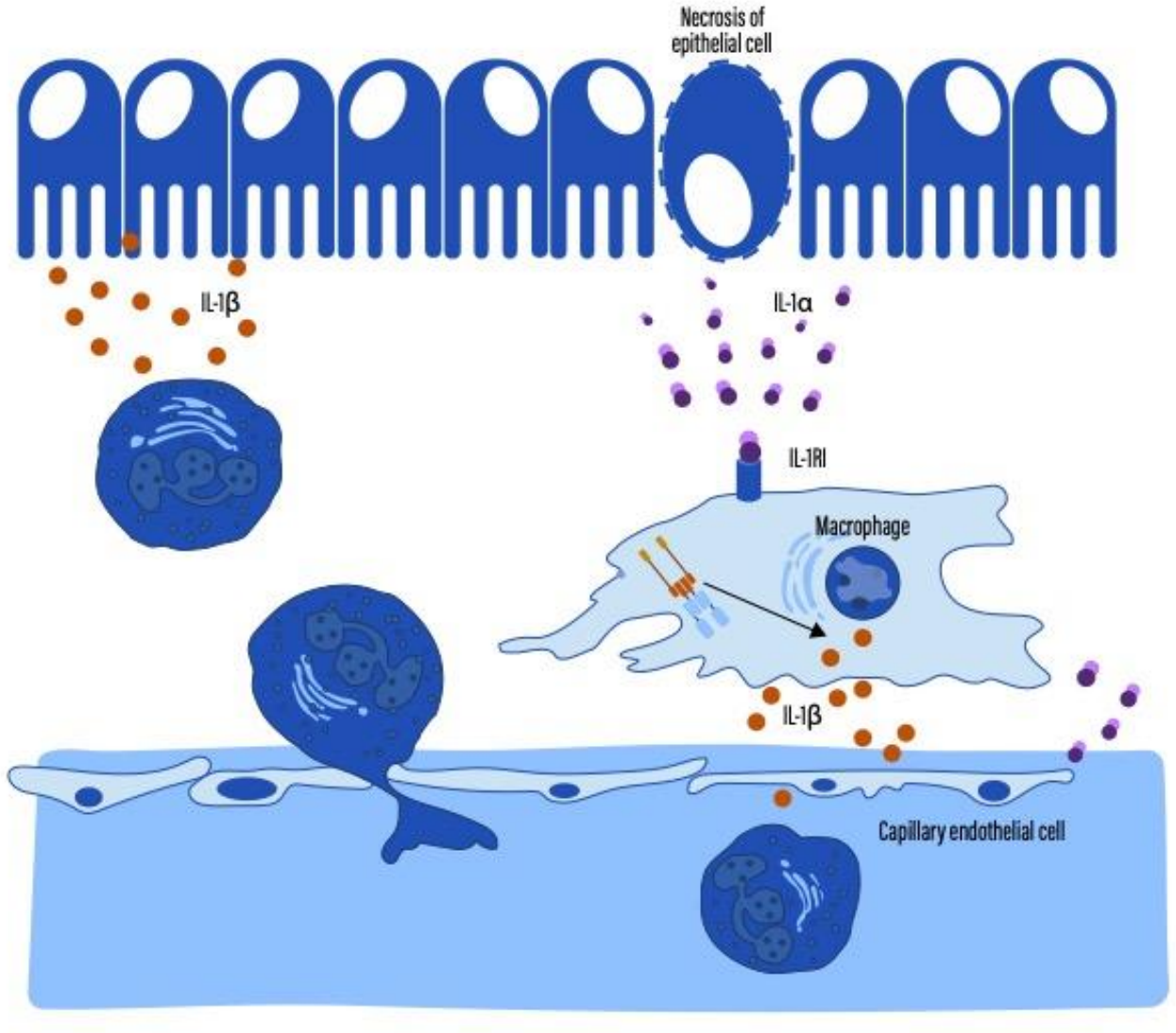
Anti-viral response
Fever
Cough
Anosmia
Myalgia

**Hyper-inflammation**
High fever, CRP, ferritin
Severe pneumonia, ARDS
Respiratory insufficiency
NIV, mechanical ventilation

Hyper-coagulation
Pulmonary thromboembolism
Limb ischemia

Courtesy of G. Cavalli

# The right place for IL-1 inhibition in Covid- 19




**Release of IL-1° as an alarming by epithelial cells is followed by sensing by inflammatory myeloid cell activation of the inflammasome, which results in amplification of the inflammatory cascade .**

**At the same time expression of IL-1 a by endothelial cells results in granulocye recruitment and inflammatory trombosis**

G. Cavalli, Autoimmunity Reviews 2020

# IL-1 and IL-6 inhibition in COVID-19

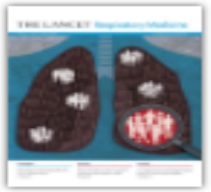
## Real-life evidence: IL- 1 inhibition might be effective in severe COVID-19 pneumonia

**Interleukin-1** blockade with high-dose **anakinra** in patients with **COVID-19**, **acute respiratory** distress **syndrome**, and hyperinflammation: a retrospective cohort study.

Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, Tomelleri A, Farina N, Ruggeri A, Rovere-Querini P, Di Lucca G, Martinenghi S, Scotti R, Tresoldi M, Ciceri F, Landoni G, Zangrillo A, Scarpellini P, Dagna L.

Lancet Rheumatol. 2020 Jun;2(6):e325-e331. doi: 10.1016/S2665-9913(20)30127-2. Epub

## Controlled evidence: IL-1 inhibition did not improve outcomes in patients with mild–to-moderate Covid-19 pneumonia



Effect of **anakinra** versus usual care in adults in hospital with **COVID-19** and mild-to-moderate pneumonia (CORIMUNO-ANA-**1**): a randomised controlled trial.

CORIMUNO-19 Collaborative group.

Lancet Respir Med. 2021 Jan 22:S2213-2600(20)30556-7. doi: 10.1016/S2213-

## No evidence: comparative effectiveness of IL-6 and IL-1 inhibition

# Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial

Lancet Respir Med 2021

*The CORIMUNO-19 Collaborative group*†*

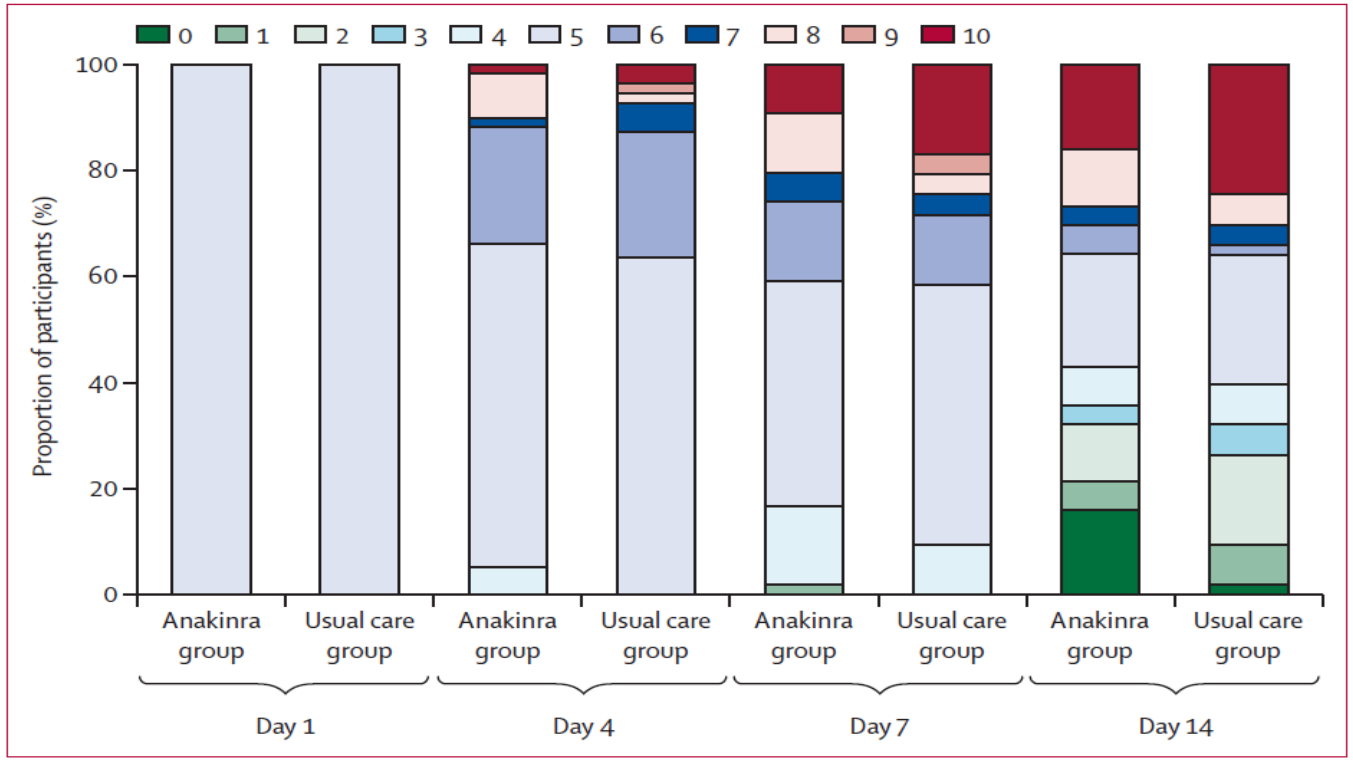



***Figure 3:*** **WHO Clinical Progression Scale score during 14-day follow up**
The WHO Clinical Progression Scale is a 10-point scale, from 0 (uninfected and no symptoms) to 10 (death).

**Interpretation** Anakinra did not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia. Furthe studies are needed to assess the efficacy of anakinra in other selected groups of patients with more severe COVID-19

# Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study

*Giulio Cavalli*, Alessandro Larcher*, Alessandro Tomelleri*, Corrado Campochiaro, Emanuel Della-Torre, Giacomo De Luca, Nicola Farina, Nicola Boffini, Annalisa Ruggeri, Andrea Poli, Paolo Scarpellini, Patrizia Rovere-Querini, Moreno Tresoldi, Andrea Salonia, Francesco Montorsi, Giovanni Landoni, Antonella Castagna, Fabio Ciceri, Alberto Zangrillo, Lorenzo Dagna*

Lancet Reumathol 2021

# Gap of knowledge and study aims

**Evidence of IL-6 and IL-1 inhibitors  to treat COVID-19 controversial**

**Study aims**

- **whether IL-1 inhibition confers an advantage over standard management;**
- **whether IL-1 inhibition is more effective than IL-6 inhibition;**
- **how to identify patients who are most likely to benefit from treatment.**

# Methods

**Retrospective study of a large cohort of COVID-19 patients (OSR, Milan)**

**Inclusion Criteria**
**Respiratory insufficiency**
**Hyperinflammation (CRP ≥100 mg/L, ferritin ≥900 ng/mL, or both)**

**Treatment**
1. **Standard treatment (200 mg HCQ BID and 400 mg lopinavir/ritonavir BID)**

2. **IL-1 inhibition with anakinra 5 mg/kg BID intravenously**
3. **IL-6 inhibition with Tocilizumab or Sarilumab 400 mg intravenously**

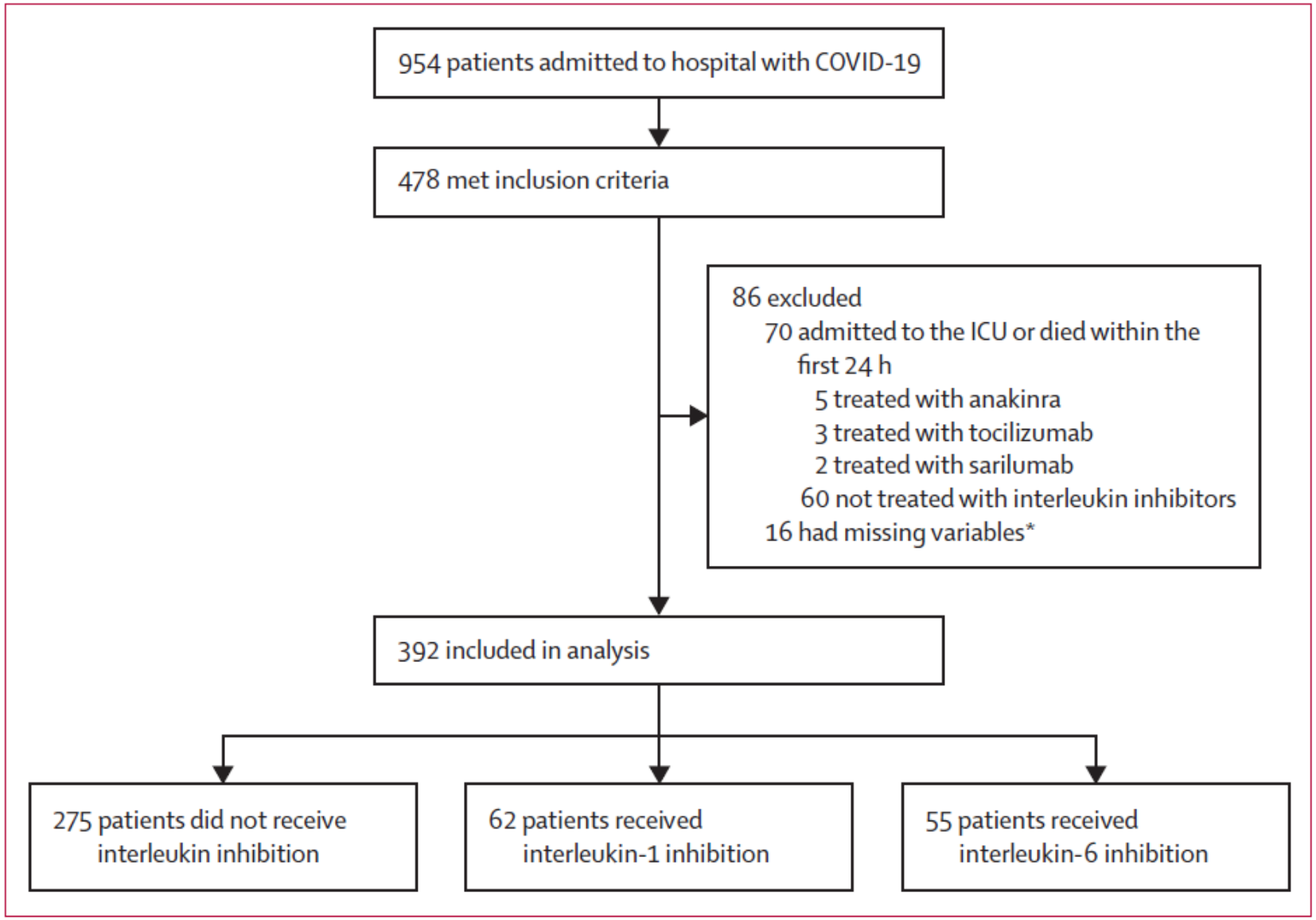
**Outcomes**
**Survival**

**Multivariable Cox regression analysis**
**To compare clinical outcomes of patients receiving IL-1 inhibition or IL-6 inhibition relative to patients who did not receive cytokine inhibitors, after accounting for baseline differences.**

**Interaction tests**
**Probability of survival according to CRP or LDH levels.**

G. Cavalli, LR 2021

# Study Overview




G. Cavalli, LR 2021

| | Overall population (n=392) | No interleukin inhibitors (n=275) | IL-1 inhibitor (n=62) | IL-6 inhibitor (n=55) |
|---|---|---|---|---|
| Age, years | 67 (56–77) | 68 (58–79) | 63 (52–73) | 58 (52–74) |
| Sex | | | | |
| Male | 301 (77%) | 201 (73%) | 52 (84%) | 48 (87%) |
| Female | 91 (23%) | 74 (27%) | 10 (16%) | 7 (13%) |
| Ethnicity | | | | |
| White | 375 (96%) | 265 (96%) | 57 (92%) | 53 (96%) |
| Non-white | 17 (4%) | 10 (4%) | 5 (8%) | 2 (4%) |
| C-reactive protein, mg/L | 129 (100–171) | 127 (91–169) | 143 (105–172) | 130 (100–195) |
| Ferritin*, ng/mL | 1295 (943–2359) | 1239 (841–1887) | 1459 (946–2761) | 1727 (1151–2757) |
| Lymphocytes, $10^3$ cells per L | 0·9 (0·6–1·2) | 0·9 (0·6–1·1) | 0·9 (0·7–1·3) | 0·8 (0·6–1·1) |
| Platelets, $10^3$ cells per L | 228 (170–297) | 228 (165–297) | 238 (190–296) | 219 (176–299) |
| Creatinine, mg/dL | 1·01 (0·8–1·31) | 1·03 (0·85–1·36) | 0·96 (0·83–1·34) | 1·00 (0·86–1·14) |
| Alanine aminotransferase, U/L | 40 (25–61) | 37 (23–59) | 45 (27–64) | 45 (30–62) |
| Lactate dehydrogenase, U/L | 396 (314–515) | 369 (300–479) | 430 (329–532) | 458 (414–542) |
| Respiratory support | | | | |
| Oxygen | 307 (78%) | 242 (88%) | 36 (58%) | 29 (53%) |
| Non-invasive mechanical ventilation | 85 (22%) | 33 (12%) | 26 (42%) | 26 (47%) |
| Cardiovascular disease | | | | |
| No | 273 (70%) | 175 (64%) | 52 (84%) | 46 (84%) |
| Yes | 119 (30%) | 100 (36%) | 10 (16%) | 9 (16%) |
| History of neoplasia | | | | |
| No | 326 (83%) | 218 (79%) | 57 (92%) | 51 (93%) |
| Yes | 66 (17%) | 57 (21%) | 5 (8%) | 4 (7%) |
| Diabetes | | | | |
| No | 320 (82%) | 219 (80%) | 50 (81%) | 51 (93%) |
| Yes | 72 (18%) | 56 (20%) | 12 (19%) | 4 (7%) |
| Month of admission | | | | |
| February | 9 (2%) | 9 (3%) | 0 | 0 |
| March | 323 (82%) | 223 (81%) | 46 (74%) | 54 (98%) |
| April | 56 (14%) | 39 (14%) | 16 (26%) | 1 (2%) |
| May | 4 (1%) | 4 (2%) | 0 | 0 |

Data are median (IQR) or n (%). IL=interleukin. *Data missing for 96 patients in the no interleukin inhibitor group, five patients in the IL-1 inhibitor group, and 11 patients in the IL-6 inhibitor group.

Baseline characteristics of patients with Covid-19, respiratory failure, hyperinflammation

G. Cavalli, Lancet Reum 2021

# Predicting outcomes of patients with Covid-19, respiratory failure, hyperinflammation

| | Mortality (Cox regression analysis) | | Adverse clinical outcome* (Cox regression analysis) | |
|---|---|---|---|---|
| | HR (95%CI) | p value | HR (95%CI) | p value |
| Treatment | | | | |
| No interleukin inhibitors | 1 (ref) | .. | 1 (ref) | .. |
| IL-1 inhibitor | 0·450 (0·204–0·990) | 0·047 | 0·866 (0·482–1·553) | 0·63 |
| IL-6 inhibitor | 0·900 (0·412–1·966) | 0·79 | 0·882 (0·452–1·722) | 0·71 |
| Age | 1·081 (1·054–1·109) | <0·0001 | 1·031 (1·013–1·050) | 0·0007 |
| Sex | | | | |
| Female | 1 (ref) | .. | 1 (ref) | .. |
| Male | 1·029 (0·608–1·739) | 0·92 | 1·176 (0·726–1·905) | 0·51 |
| Respiratory support | | | | |
| Oxygen | 1 (ref) | .. | 1 (ref) | .. |
| Non-invasive mechanical ventilation | 0·908 (0·459–1·799) | 0·78 | 0·771 (0·443–1·344) | 0·36 |
| C-reactive protein, mg/L | 1·003 (1·001–1·006) | 0·020 | 1·005 (1·002–1·007) | 0·0002 |
| Alanine aminotransferase, U/L | 0·995 (0·992–0·997) | <0·0001 | 0·995 (0·993–0·997) | <0·0001 |
| Creatinine, mg/dL | 1·212 (1·085–1·355) | 0·0007 | 1·101 (0·991–1·223) | 0·074 |
| Lactate dehydrogenase, U/L | 1·002 (1·001–1·003) | <0·0001 | 1·002 (1·001–1·003) | <0·0001 |
| Diabetes | | | | |
| No | 1 (ref) | .. | 1 (ref) | .. |
| Yes | 1·657 (1·025–2·680) | 0·039 | 1·836 (1·182–2·852) | 0·0068 |
| Treatment with glucocorticoids | | | | |
| No | 1 (ref) | .. | 1 (ref) | .. |
| Yes | 0·687 (0·377–1·253) | 0·22 | 0·634 (0·368–1·093) | 0·10 |
| ICU admission† | | | | |
| No | 1 (ref) | .. | .. | .. |
| Yes | 1·864 (0·872–3·988) | 0·11 | .. | .. |
| Days after admission of the first patient‡ | 0·984 (0·966–1·002) | 0·074 | 0·990 (0·973–1·007) | 0·24 |

G. Cavalli, Lancet Reum 2021

# Subgroup analysis in patients with Covid-19, respiratory failure, hyperinflammation

| | Mortality (Cox regression analysis*) | | Adverse clinical outcome (Cox regression analysis*) | |
|---|---|---|---|---|
| | HR (95% CI) | p value | HR (95% CI) | p value |
| **Treatment and C-reactive protein** | | | | |
| No interleukin inhibitors | 1 (ref) | .. | 1 (ref) | .. |
| IL-1 inhibitor by C-reactive protein | 0·994 (0·985–1·004) | 0·23 | 0·997 (0·991–1·003) | 0·31 |
| IL-6 inhibitor by C-reactive protein | 0·990 (0·981–0·999) | 0·031 | 0·987 (0·979–0·995) | 0·0021 |
| **Treatment and lactate dehydrogenase** | | | | |
| No interleukin inhibitors | 1 (ref) | .. | 1 (ref) | .. |
| IL-1 inhibitor by lactate dehydrogenase | 1·009 (1·003–1·014) | 0·0011 | 1·006 (1·002–1·010) | 0·0031 |
| IL-6 inhibitor by lactate dehydrogenase | 1·006 (1·001–1·011) | 0·028 | 1·005 (1·001–1·010) | 0·016 |

HR=hazard ratio. IL=interleukin. *Model adjusted for age, C-reactive protein, and lactate dehydrogenase.

G. Cavalli Lancet Reum 2021

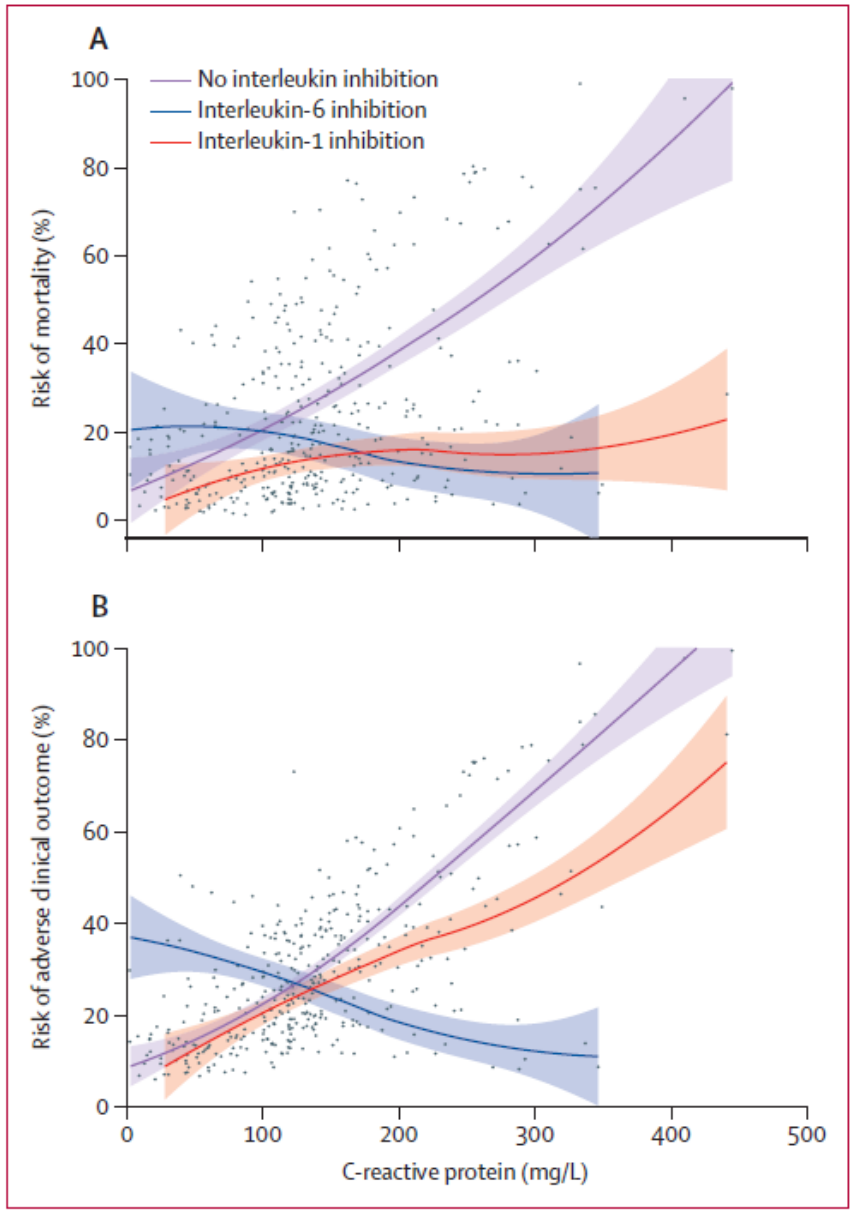



*Figure 2:* **Risk of mortality (A) and adverse clinical outcome (B) according to baseline C-reactive protein in patients diagnosed with COVID-19 and hyperinflammation**

Dots represent individual observations, solid lines represent multivariable model-derived probabilities, and shaded areas represent 95% CIs.

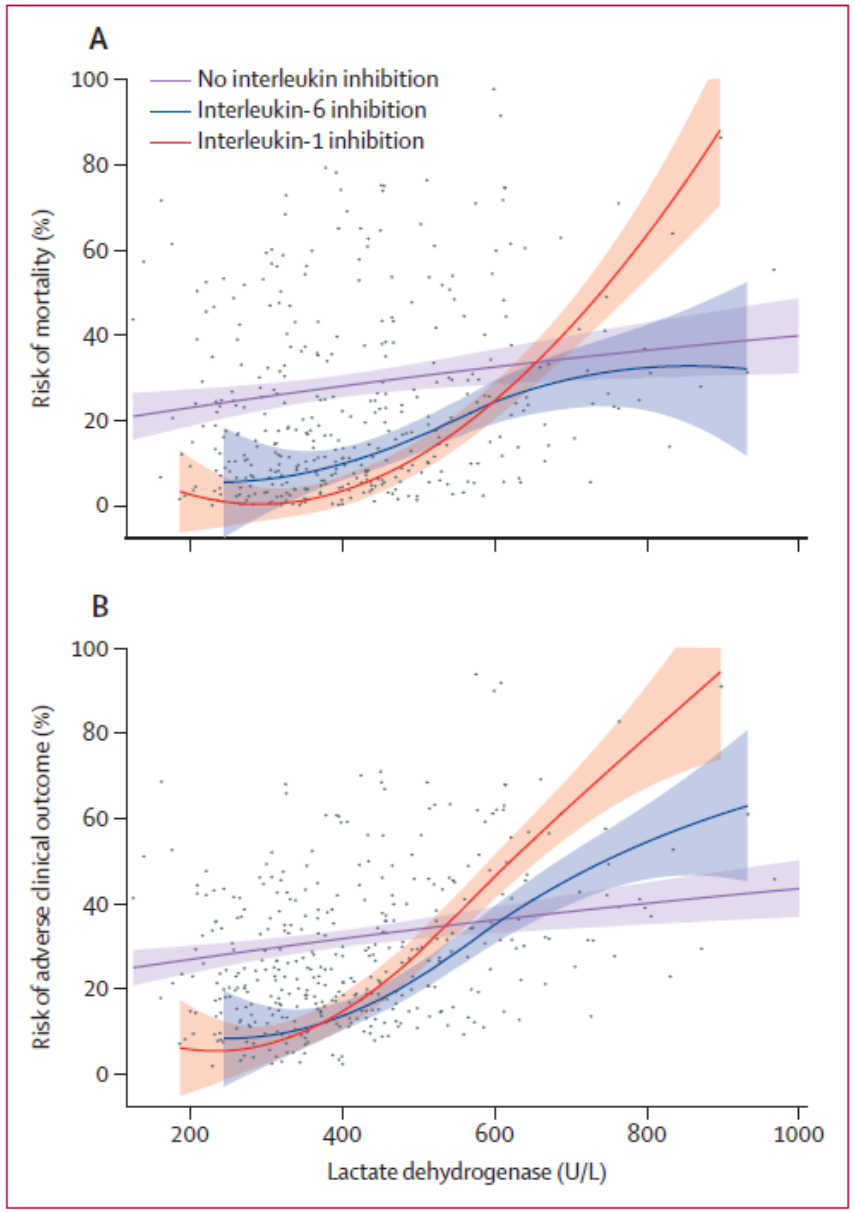



*Figure 3:* **Risk of mortality (A) and adverse clinical outcome (B) according to baseline lactate dehydrogenase in patients diagnosed with COVID-19 and hyperinflammation**

Dots represent individual observations, solid lines represent multivariable model-derived probabilities, and shaded areas represent 95% CIs.

G. Cavalli, Lancet Reum 2021

## Limitations

Inherent to retrospective investigations (i.e. indication bias and immortal time bias).

## Strengths

Timeliness and the uniqueness (i.e. real-life comparison of the effectiveness of IL-1 and IL-6 inhibition in the same cohort).

# Conclusions

**First study evaluating the effectiveness of IL-1 inhibition and IL-6 inhibition compared to standard management in patients with COVID-19, respiratory insufficiency, and hyper-inflammation.**

**IL-1 inhibition with anakinra, but not IL-6 inhibition with monoclonal antibodies, significantly reduced mortality in COVID-19 patients.**

**Protective effects of IL-6 inhibition were only observed in patients with very high CRP at baseline**

**Both IL-1 and IL-6 inhibition were more effective in patients with low LDH at baseline**

# COVID-19: TABELLA SINOTTICA TERAPIA FARMACOLOGICA

**COVID 019 rev. 0**
16 novembre 2020

## OSSIGENO TERAPIA

| | |
|---|---|
| $SatO_2$ **<94%**<br>no NIMV<br>no MV/ECMO | • $O_2$ e posture<br>• Enoxaparina<br>• Desametasone[2]<br>• Remdesivir[1] |
| $SatO_2$ **<94%**<br>NIMV, MV/ECMO | • O2 e posture<br>• Enoxaparina<br>• Desametasone |

**$O_2$ terapia**
- Applicare FiO2 minore possibile x ottenere o mantenere ***$SpO_2$ ≥94% (se BPCO ≥88%)***
- Se necessità di $FiO_2$ ≥50% o reservoir: EGA e valutazione rianimatoria

**Monitoraggio NIV**
Preferire $FiO_2$ iniziale 60%
Controllare durante il primo ciclo:
- 15 min dopo inizio NIMV: SpO2
- 1 h dopo inizio NIMV: $SpO_2$; EGA; FR; meccanica resp.
- 15 min prima di stop CPAP: SpO2; FR; meccanica resp.
- Subito prima del ciclo successivo: SpO2; FR; mecc. resp.

Controllare durante i cicli successivi:
- EGA a fine ciclo (durante NIMV o RS)

## TERAPIA E DIAGNOSTICA STANDARD

**Corticosteroidi**
- Se $FiO_2$<50% → desametasone per 10 giorni (o fino a dimissione; no decalage) o metilprenisolone
- ***Desametasone:*** *6 mg die ev*
- ***Metilprednisolone:*** *0.5 mg/kg BID ev per 5 giorni (decalage 0.5 mg/kg die ev dal giorno 6 al giorno 10 o in base ad andamento clinico). Non superare 10 giorni totali di terapia*

**Enoxaparina[5]**
- *4000 UI (40 mg)/die sc[6]*
- *4000 UI (40 mg) BID sc* se: BMI > 35 <40
- ***Considerare*** *4000 UI (40 mg) BID sc* se elevato rischio di malattia tromboembolica (pregressa TVP/EP, neoplasia attiva, XDP >3xULN);
- Peggioramento *in assenza di TVP/EP o malattia grave (grado 5)
- ***Raccomandato*** *4000 UI BID* per pazienti in UTI/MV
- Proseguire terapia in corso fino alla dimissione

**Remdesivir**
- *200 mg ev in 60 min (giorno 1), poi 100 mg ev die* per 4 gg

***Esami ematochimici (standard):***
→ *All'ingresso e successivamente in base a indicazione clinica*
→ *Pre e post terapia (remdesivir, corticosteroidi, anakinra): con PCR, ferritina, LDH, XDP*

***Rx torace, TC torace:***
→ *Rx all'ingresso*
→ *TC fortemente consigliata per pazienti in NIMV o MV o in peggioramento**
→ *Successivi controlli (Rx e TC) in base a indicazione clinica*

## INDICAZIONI ACCESSORIE/NOTE

**Anakinra *(Terapia di rescue - se studi controllati non accessibili e peggioramento a 48 h da desametasone):***
- *5 mg/kg BID ev fino a miglioramento *(rivalutare a 3-5 giorni) poi 100 mg BID per 3 giorni (durata massima totale terapia : 10 giorni)*

** Miglioramento dei parametri respiratori per almeno 48 ore*

**Terapia antibiotica empirica se**:
- infezione batterica fortemente sospetta[3] o accertata
- Elevato rischio individuale[4]

**** Definizione di peggioramento***
*Incremento fabbisogno $O_2$:*
*a) Switch da $FiO_2$<50% a $FiO_2$ ≥50%,*
*b) Switch da $FiO_2$ 50% a reservoir,*
*c) Switch a NIMV (da qualunque $FiO_2$)*
*d) Incremento NIMV o switch da NIMV a MV*
*Indicatori di iper-infiammazione:*
*a) Ferritina>2000 o*
*b) Ferritina>1000 + almeno 1 dei seguenti: Linfociti<800/µL, PCR>70, LDH>1.5xULN , XDP >3xULN*

***Note***
1. *Se esordio dei sintomi da <10 giorni*
2. *Preferibilmente se inizio dei sintomi da ≥ 7 giorni*
3. *In base a quadro radiologico polmonare ed indici infiammatori compatibili con co-infezione batterica*
4. *Immunocompromissione; malattie croniche gravi*
5. *Considerare alternative se Enoxaparina controidicata*
6. *BMI < 18 3000 UI q 24 h; BMI > 40 6000 UI q 12 h*

***(E' fortemente raccomandato l'uso di terapie sperimentali nell'ambito di studi clinici controllati)***

Con il contributo di P. Cinque, G. Di Lucca e i collaboratori delle aree COVID- 19 OSR