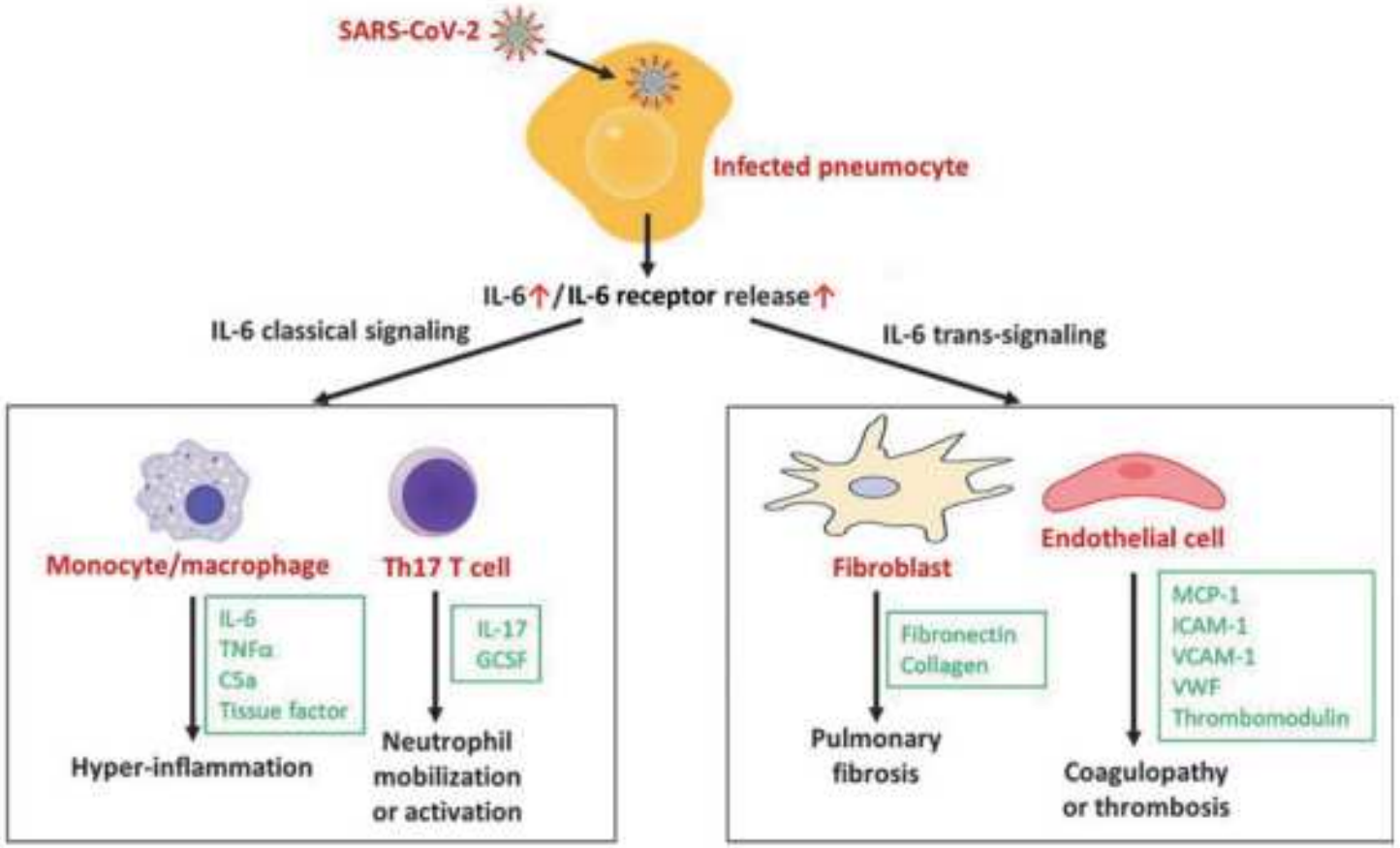
«IL-6R antagonist in hospitalized patients with COVID-19»

Matteo Sala

A multiphasic pathogenesis

- COVID-19 first phase is dominated by the immune response to the viral invasion, while the second is carried on by the systemic flogistic reaction[1];
- Flogistic phase as the principal responsibile of the organic damage, especially in the lungs[2];
- Correlation between seric IL-6 levels and severity of the clinical manifestation[3].



Patra T, Ray R. IL-6 Induction and Signaling: Horizons of COVID-19-Related Pathogenesis. *DNA Cell Biol*. 40(5):2021. doi:10.1089/dna.2021.0152

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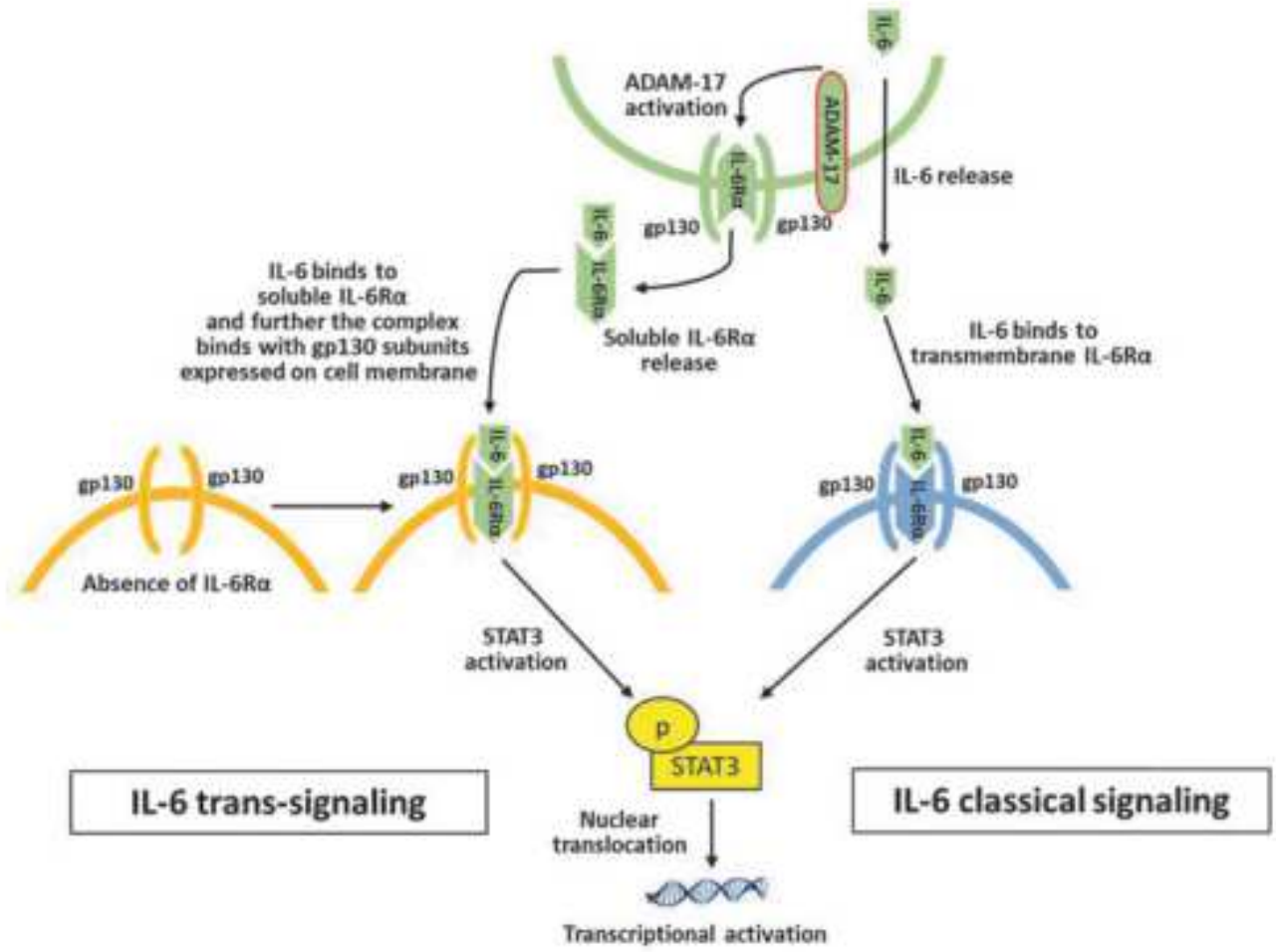
2. Chen R, Lan Z, Ye J, et al. Cytokine Storm: The Primary Determinant for the Pathophysiological Evolution of COVID-19 Deterioration. *Front Immunol*. 2021;12. doi:10.3389/fimmu.2021.589095
3. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. *J Med Virol*. 2020;92:2283-2285. doi:10.3389/fimmu.2021.589095

Blocking the cytokine-storm

- Possible therapeutic option: block the IL-6 pathway;
- Usefulness in the clinical practice of tocilizumab e sarilumab.



Patra T, Ray R. IL-6 Induction and Signaling: Horizons of COVID-19-Related Pathogenesis. *DNA Cell Biol*. 2021;40(5):639-642. doi:10.1089/dna.2021.0152

Conflicting evidence in literature


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

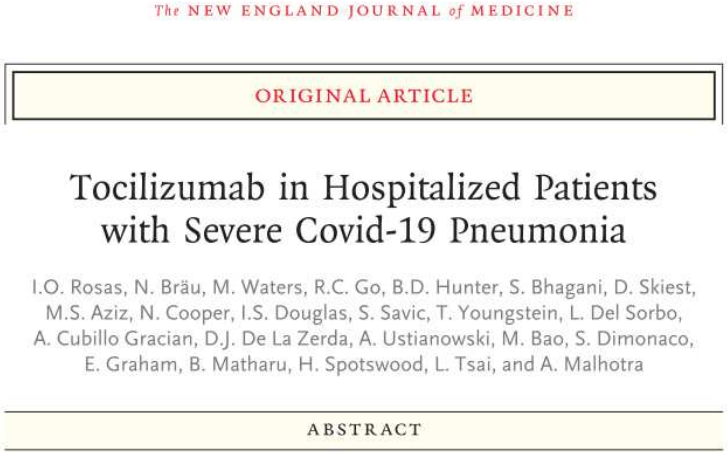
Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

ABSTRACT

- Randomized platform trial;
- 895 pts.: 366 to tocilizumab, 48 to sarilumab, 412 to control;
- IL-6R-antagonists effective in increasing the days free of respiratory/CV support

Group, The REMAP-CAP investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med*. February 2021. doi:10.1056/nejmoa2100433


The NEW ENGLAND JOURNAL of MEDICINE

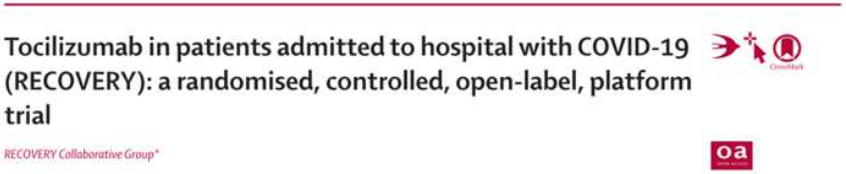
ORIGINAL ARTICLE

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M.S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, and A. Malhotra

ABSTRACT

Rosas IO, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *N Engl J Med*. 2021;384(16):1503-1516. doi:10.1056/nejmoa2028700


Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. doi:10.1016/S0140-6736(21)00676-0

- Randomized phase 3 trial;
- 452 pts. with severe COVID-19, 294 assigned to tocilizumab group, 144 assigned to placebo group
- Tocilizumab not effective in improving 7-categories clinical status when compared to standard of care.

- Randomized control trial;
- 2022 pts. asigned to tocilizumab group VS 2094 pts. assigned to SOF;
- Tocilizumab effective in reducing 28-day mortality, increasing the probability of discharge alive up to 28 days and

Restrospective data from the Modena cohort

Tocilizumab in patients with severe COVID-19: a retrospective cohort study

Giovanni Guaraldi, Marianna Meschiari*, Alessandro Cozzi-Lepri, Jovana Milic, Roberto Tonelli, Marianna Menozzi, Erica Franceschini, Gianluca Cuomo, Gabriella Orlando, Vanni Borghi, Antonella Santoro, Margherita Di Gaetano, Cinzia Puzzolante, Federica Carli, Andrea Bedini, Luca Corradi, Riccardo Fantini, Ivana Castaniere, Luca Tabbi, Massimo Girardis, Sara Tedeschi, Maddalena Giannella, Michele Bartoletti, Renato Pascale, Giovanni Dolci, Lucio Brugioni, Antonella Pietrangelo, Andrea Cossarizza, Federico Pea, Enrico Clini, Carlo Salvarani, Marco Massari, Pier Luigi Viale, Cristina Mussini*

Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(8):e474-e484. doi:10.1016/S2665-9913(20)30173-9

- Cohort study: eligible patients with SaO_2 < 93%; PaO_2/FiO_2 < 300 mmHg in RA o decrease > 30% of PaO_2 in the 24 h previous the hospitalization;
- Sample: 544 pts., 365 assigned to SOF, 179 to SOF + tocilizumab;
- Primary outcome: composite outcome of mortality and progression to invasive mechanical ventilation;
- Tocilizumab effective in reaching the primary outcome of reducing the risk of invasive mechanical ventilation or death.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

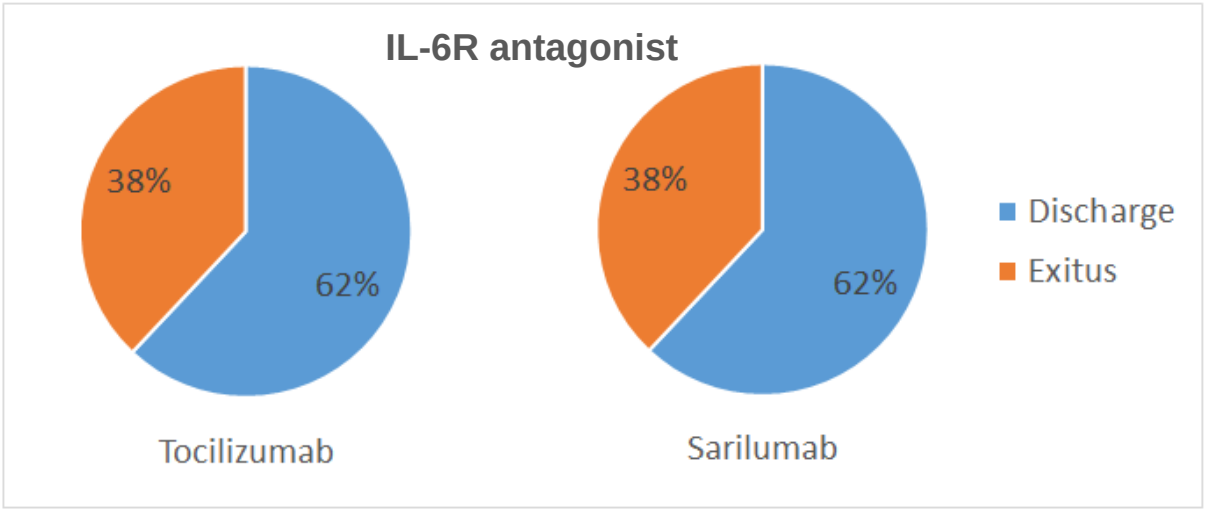
Interleukin-6 Receptor Inhibition in Covid-19 — Cooling the Inflammatory Soup

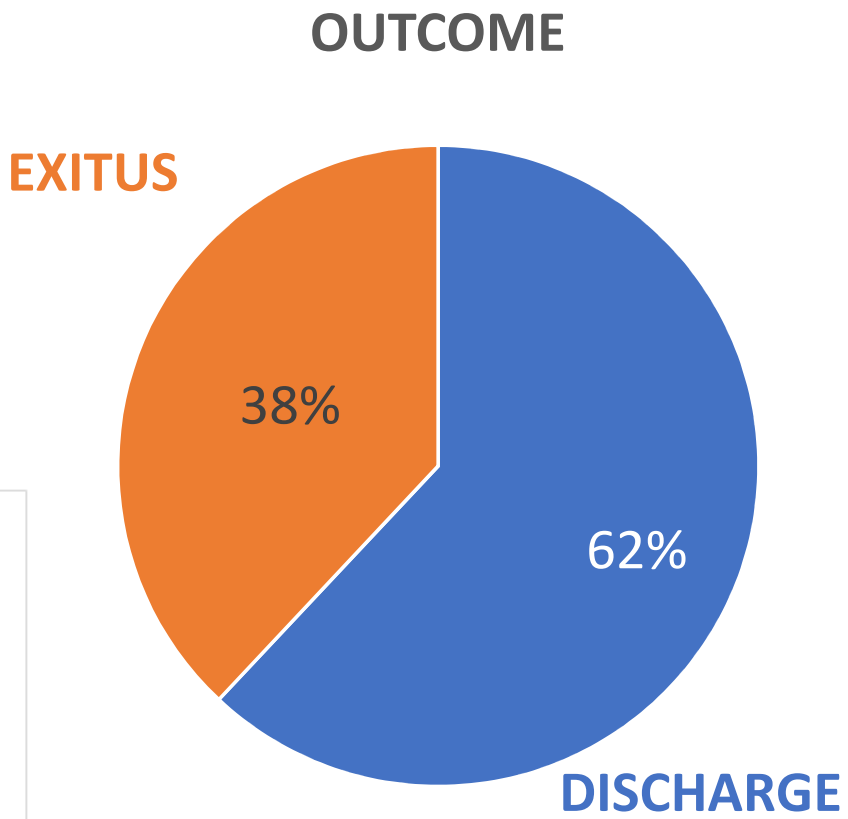
Eric J. Rubin, M.D., Ph.D., Dan L. Longo, M.D., and Lindsey R. Baden, M.D.

Preliminary data from ASST Santi Paolo e Carlo from March 2020 to December 2020

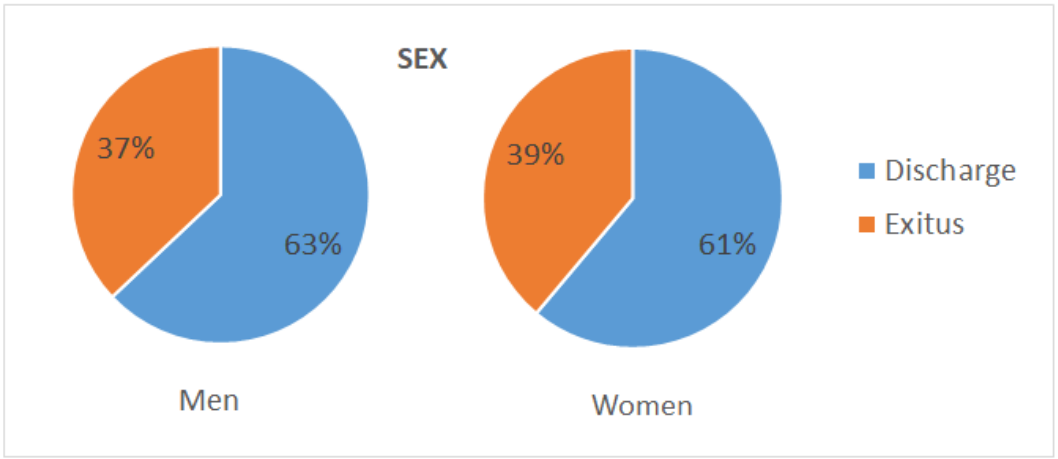
Introduction

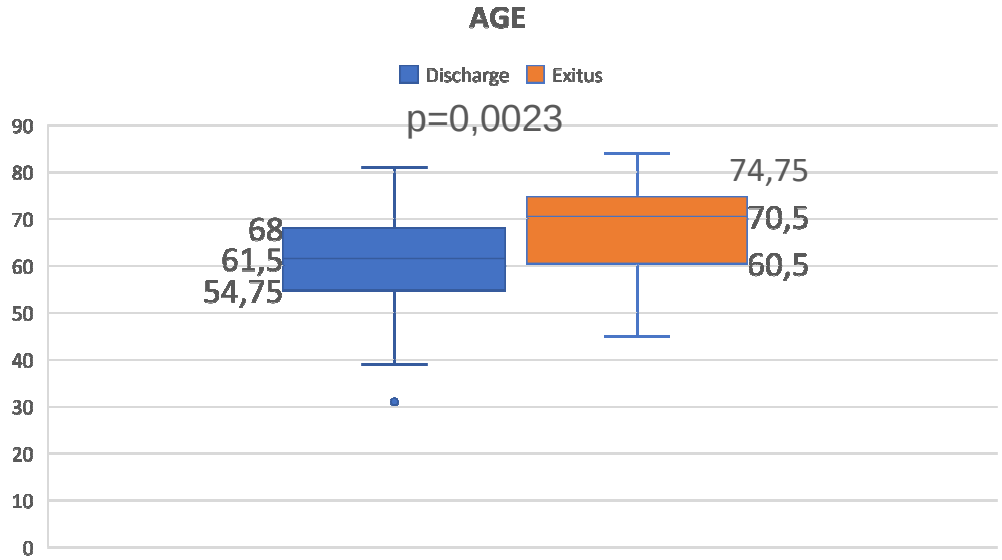
- Data recordered from the REDCAP platform: patients admitted to isolation department of Ospedale San Paolo and Ospedale San Carlo(ASST Santi Paolo e Carlo) from March 2020 to December 2020;
- Total of 72 patients treated with IL-6r antagonist tocilizumab or sarilumab

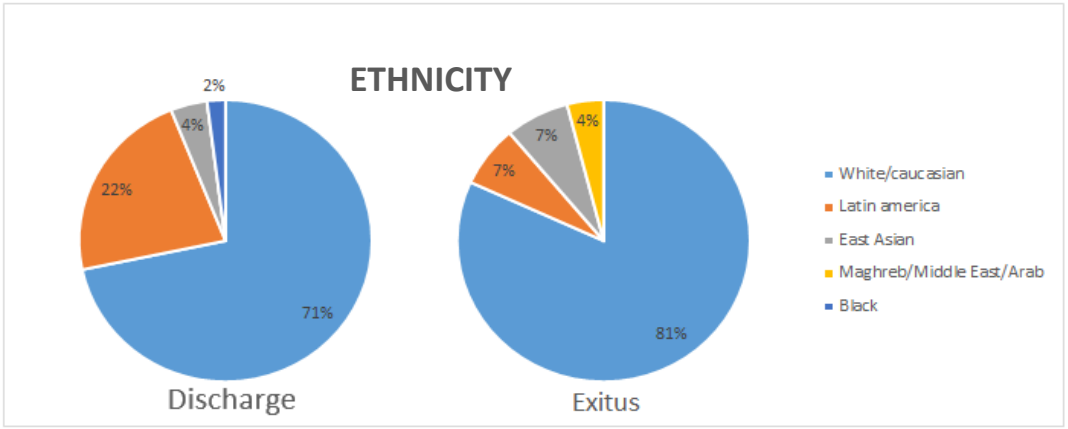


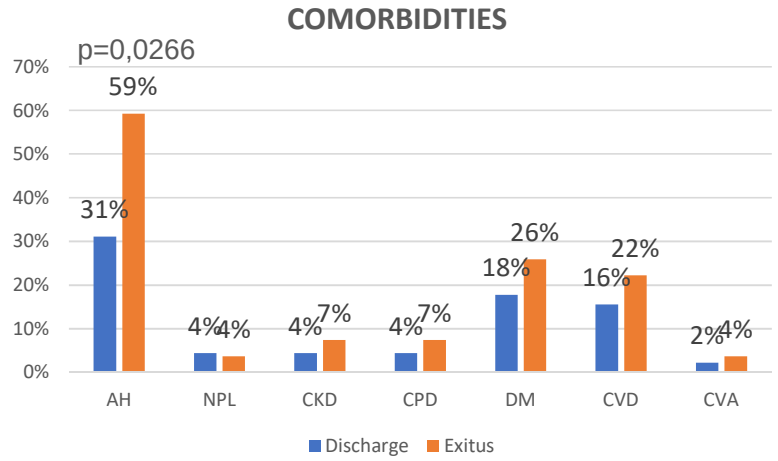


Older subjects and higher proportions of pts. with AH among those who died in course of IL-6R-antagonist therapy

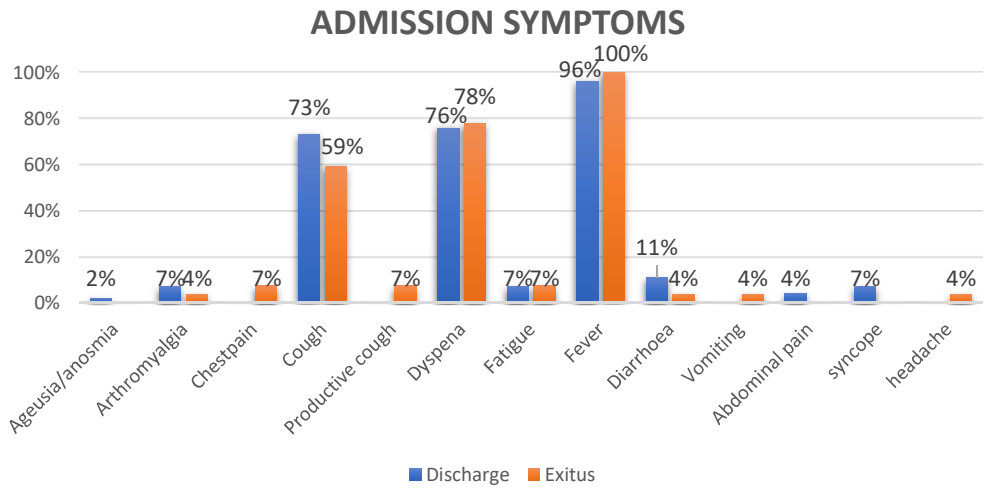


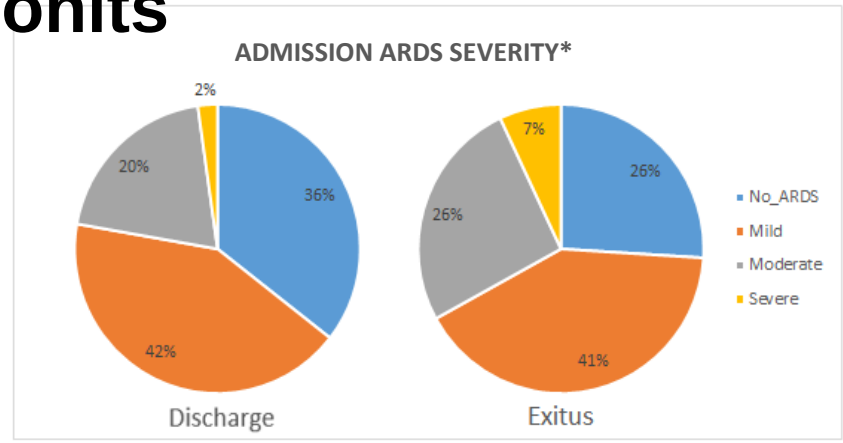






Comparable disease severity on admission in subjects with different outcome following IL-6R antagonits





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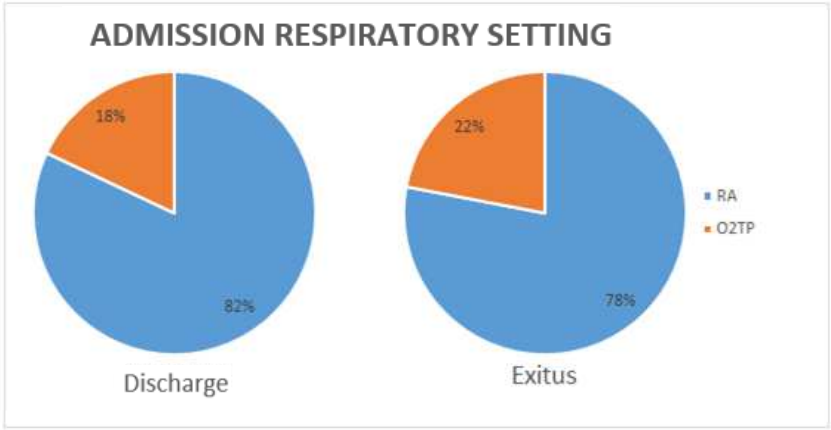
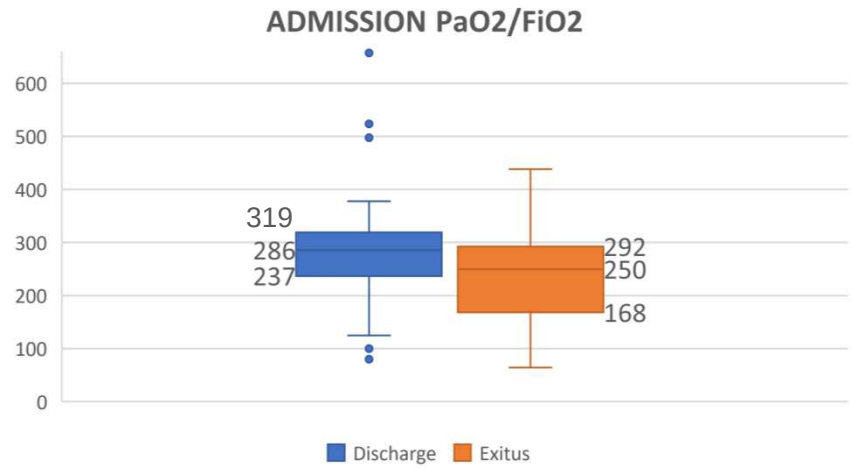
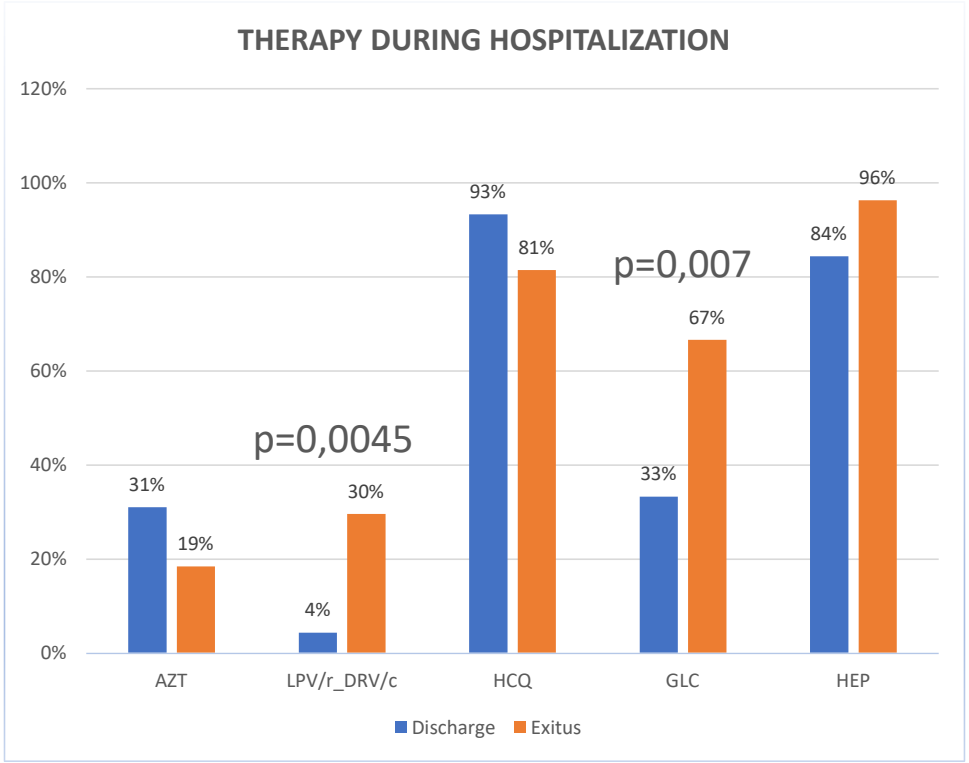


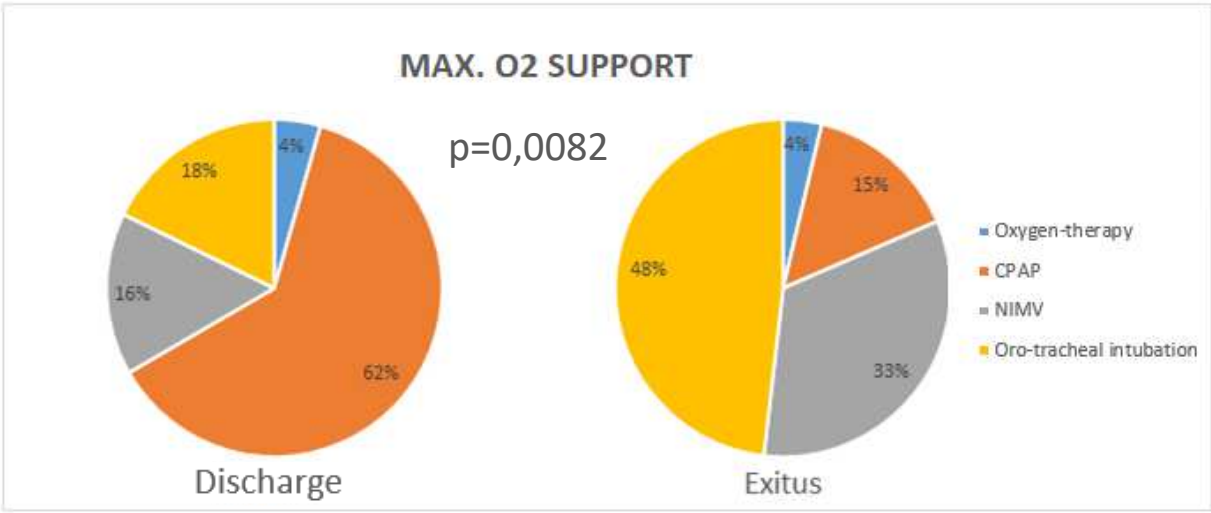


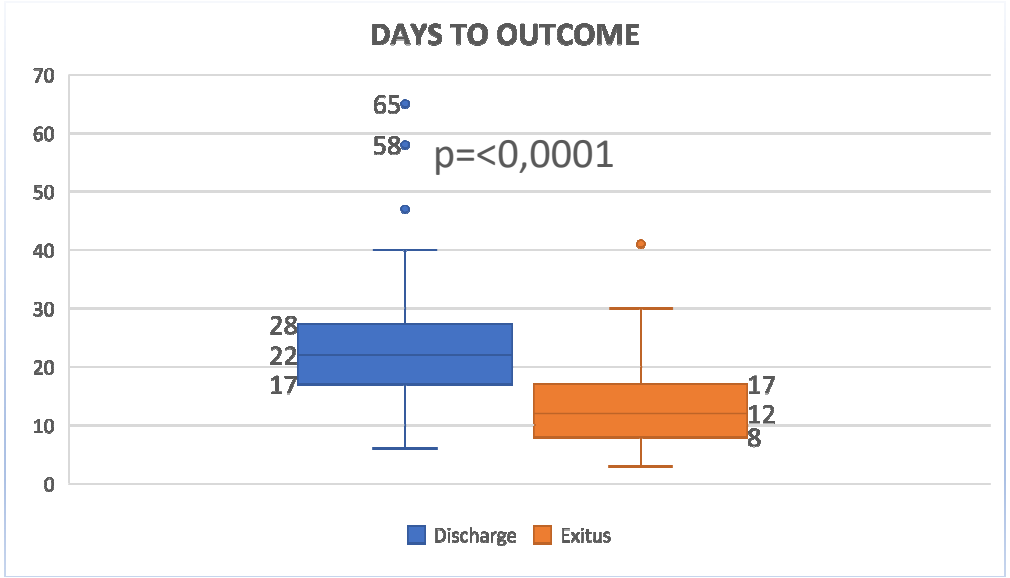
Lower lymphocytes and platelet count on admission, higher creatinine in patients who died

Laboratory examination	Survived	Exitus	P-value (< 0.05)
Complete Blood Cell Count, cell/µL (median, IQR)			
White blood cells	6840, 5500-9030	6680, 4265-8959	0.353
Neutrophils	5440, 3980-7040	5170, 3180-7215	0.500
Lymphocytes	890, 650-1210	690, 515-935	0.043
Monocytes	370, 310-490	360, 250-505	0.457
Platelet count, x 10^3	218, 185-263	175, 156-228	0.015
Biochemistry (median, IQR)			
Proteina C-Reattiva, mg/L	84.2, 60.1-121.5	98, 58-121	0.851
Ferritina, ng/mL	783, 425-1365	981, 585-1358	0.535
LDH, U/L	349, 286.5-382.5	431, 306-492	0.170
AST	47, 35-70	44, 37-59	0.543
ALT	41, 28-67	31, 21-35	0.074
Creatinine	0.9, 0.7-1.1	1, 0.8-1.2	0.033
Coagulation (median, IQR)			
D-dimero, ng/mL	375.5, 281.5-735	670, 356-1231	0.075

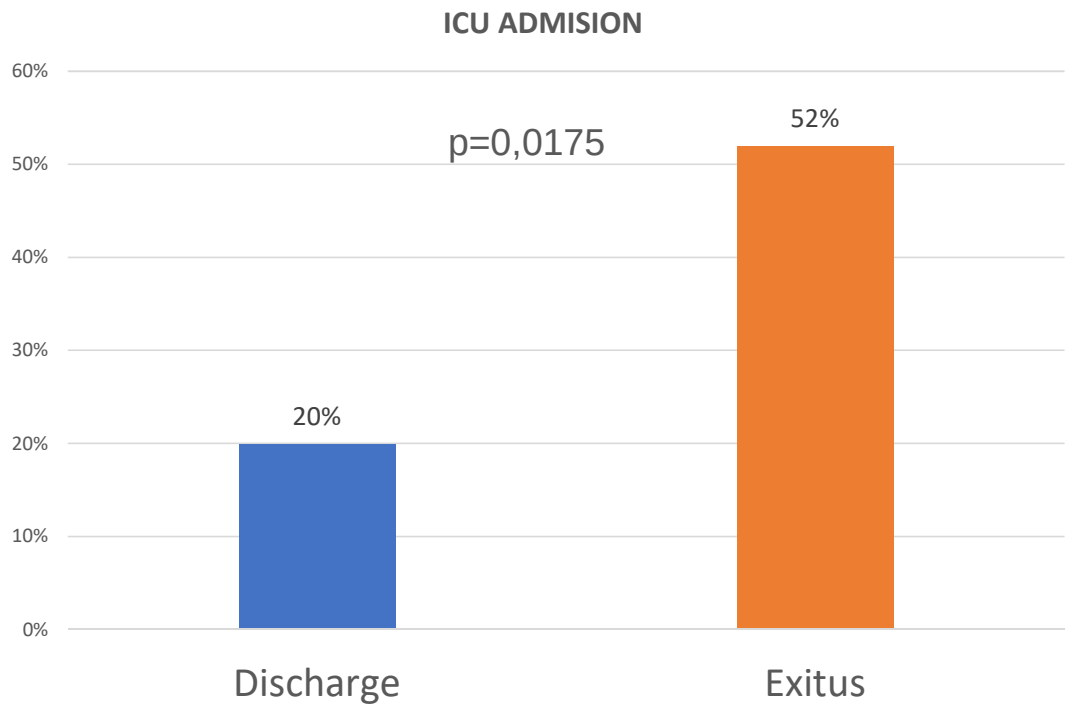
Similar admission features but different clinical course in the two groups and…

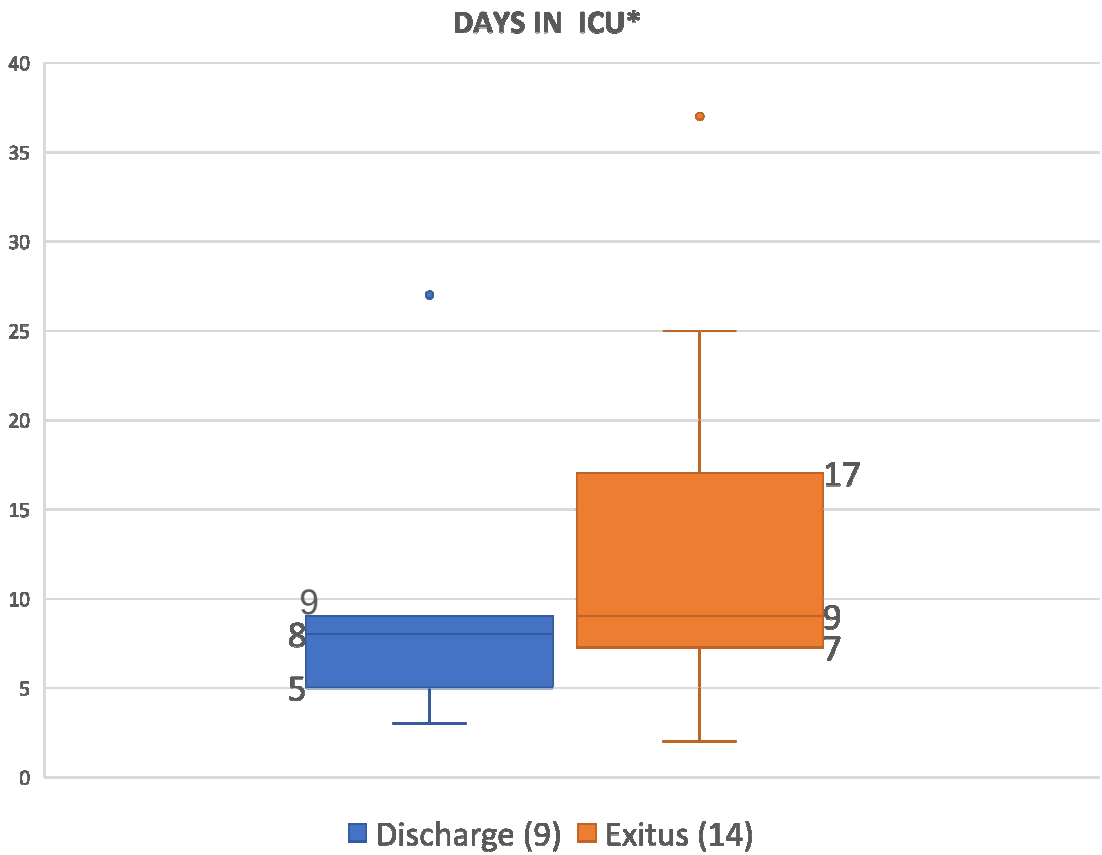






… different ICU course





*established on 23 patients admitted to ICU

Conclusions and future directions

- IL-6R-antagonist therapy in our cohort, negative outcome in 38% of the study population, in particular:

- Older subjects;
- Hypertension;
- Patients who underwent treatment with glucocorticoids, antiviral and IOT.

The higher percentage of death in our cohort, compared to other reports on anti-IL-6R, is probably due to a selection bias, as we assigned to this treatment the most seriously ill patients.

- Future perspectives:
  - Inclusion of data from 2021;
  - Elaborate a multivariate analysis to assess outcome-conditioning factors;
  - Immune analysis to examine the physiopathology of the divergence between the two groups.

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THANKS FOR YOUR ATTENTION