I Sessione

Moderatori: A. Ballestrero (Genova) - G. Icardi (Genova)

10:00 - 10:40 COVID-19: sono già due anni. Come si cura oggi in ospedale?
C. Dentone (Genova) | *Discussant*: L. Ball (Genova)

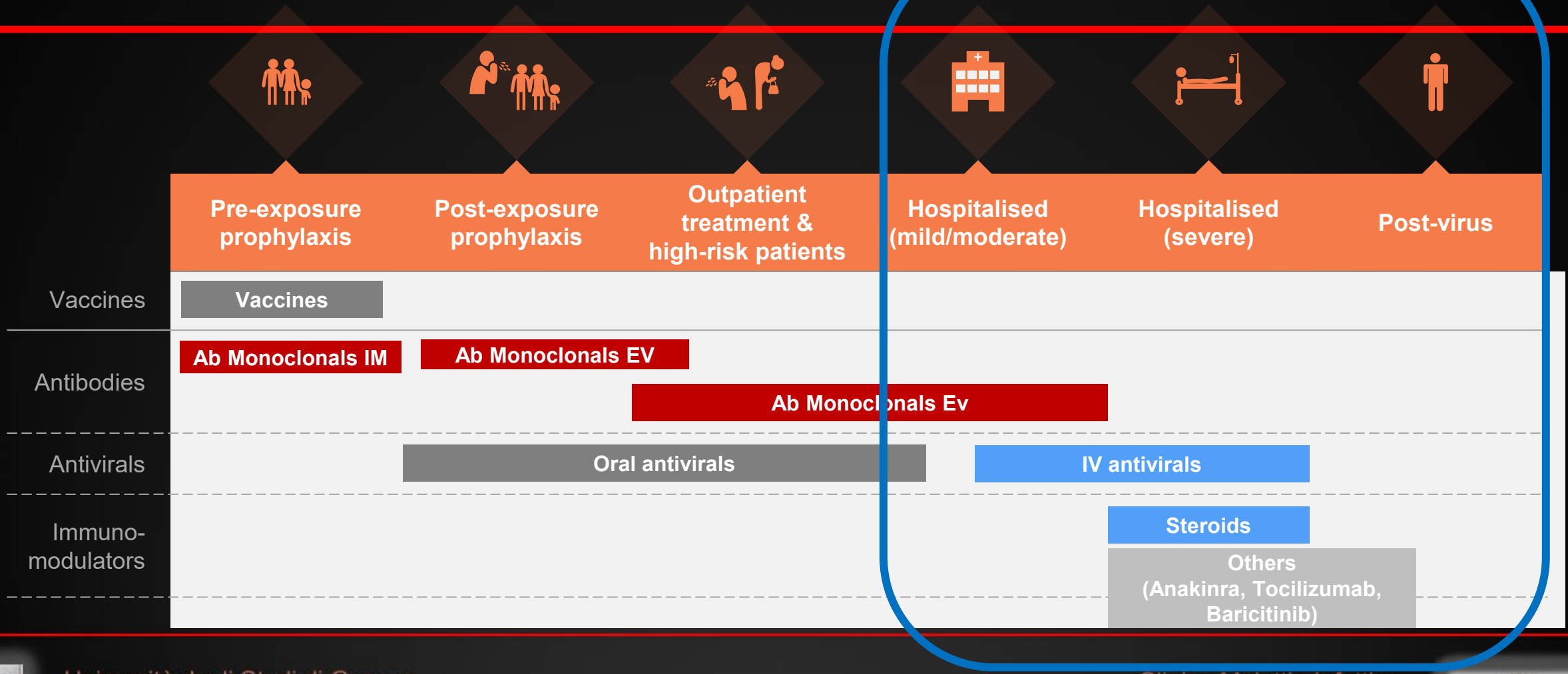
COVID-19: Sono già due anni. Come si cura oggi in Ospedale?

Chiara Dentone
Clinica Malattie Infettive
IRCCS Policlinico San Martino
Genova

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Potential role in the treatment of COVID-19 (based on available data)



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Song. Int J Antimicrob Agents 2020; Xu. Mil Med Res 2020; Pascarella. J Intern Med 2020

PNAS PERSPECTIVE OPEN ACCESS

COVID-19 therapeutics: Challenges and directions for the future

	Prophylaxis	Primary Care	Ambulatory care (not requiring supplementary oxygen)	Inpatient; General Ward (supplementary oxygen)	Inpatient High dependency Unit	Inpatient Intensive care	Post hospital	Long COVID
Example studies	PROTECT-CH	PRINCIPLE	COMET-ICE; BLAZE-1; COV-2067	RECOVERY ACTIV trials ACTT trials SOLIDARITY		RECOVERY REMAP-CAP	HEAL-COVID	
Treatments with strong evidence of benefit*	None	Budesonide ψ (duration of disease)	Monoclonal antibodies (Sotrovimab ΦδΨ; bamlanivimab and etesevimab ΦδΨ; casirivimab and imdevimab ΦδΨ; regdanvimab δ)	Dexamethasone δψ Tocilizumab Φψ Remdesivir Φδ Baricitanib (with Remdesivir) Φ REGEN-COV (Casirivimab and Imdevimab) ψ in those seronegative for SARS-CoV-2 at baseline Convalescent plasma Φ (note RECOVERY did not show mortality benefit)			None	None
Outstanding therapeutic questions	Strong evidence of an effective prophylaxis agent- both pre and post exposure	Treatments able to reduce hospitalisation		Optimal combination of available / forthcoming agents Prevention of long-term complications			Evidence of treatments able to impact high post discharge mortality	Which aspects of the syndrome are responsive to treatment

ΦFDA Emergency Use Authorisation
δEMA approved (remdesivir), endorsed (dexamethasone) or under rolling review (monoclonal antibodies)
Ψ Evidence from large clinical trial(s)

Università de
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy
tie Infettive
Ospedale Policlinico San Martino IRCCS

Robinson PC, et al. PNAS 2022

GUIDELINES

Clinical Management of Adult Patients with COVID-19 Outside Intensive Care Units: Guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

Matteo Bassetti · Daniele Roberto Giacobbe · Paolo Bruzzi · Emanuela Barisione · Stefano Centanni · Nadia Castaldo · Silvia Corcione · Francesco Giuseppe De Rosa · Fabiano Di Marco · Andrea Gori · Andrea Gramegna · Guido Granata · Angelo Gratarola · Alberto Enrico Maraolo · Malgorzata Mikulska · Andrea Lombardi · Federico Pea · Nicola Petrosillo · Dejan Radovanovic · Pierachille Santus · Alessio Signori · Emanuela Sozio · Elena Tagliabue · Carlo Tascini · Carlo Vancheri · Antonio Vena · Pierluigi Viale · Francesco Blasi on behalf of the Italian Society of Anti-infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

Key Summary Points

The use of neutralizing monoclonal antibodies may be considered for outpatients at risk of disease progression.

For inpatients, favorable recommendations are provided for anticoagulant prophylaxis and systemic steroids administration, although with low certainty of evidence.

Favorable recommendations, with very low/low certainty of evidence, are also provided for, in specific situations, remdesivir, alone or in combination with baricitinib, and tocilizumab.

The presence of many best practice recommendations testifies to the need for further investigations by means of randomized controlled trials.

Infect Dis Ther 2021

NIH, COVID-19 Guidelines, Feb 2022- Therapeutic Management of Adults Hospitalized for COVID-19 based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

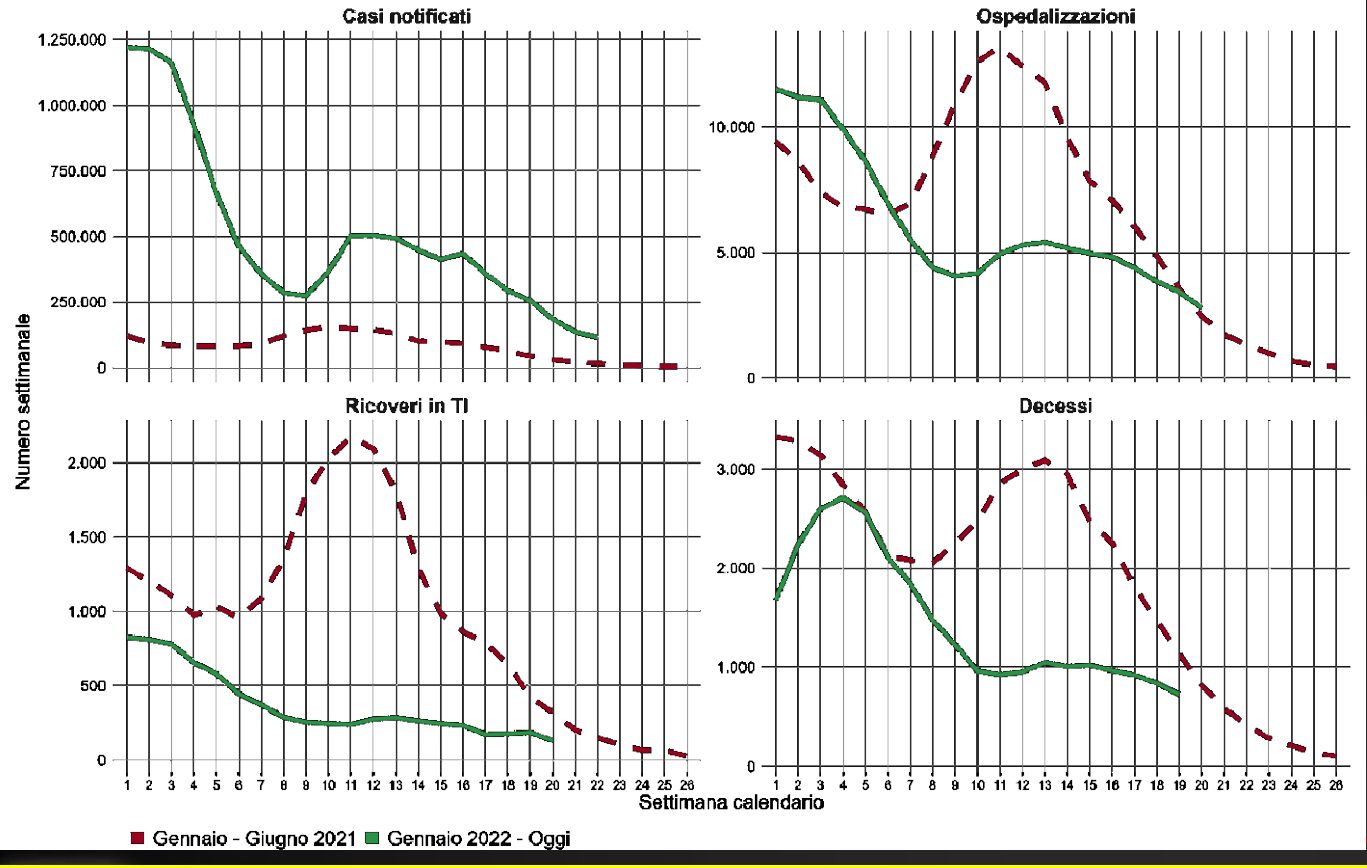
Cosa è cambiato in 2 anni???

Arrivo ed utilizzo del Vaccino

Ampia Conoscenza

DATA PUBBLICAZIONE: 10/06/2022

Efficacia della vaccinazione nel



Confronto per settimana dei casi notificati di COVID-19, ospedalizzazioni, ricoveri terapia intensiva e decessi (Gen-Giu 2021 e 2022)

- **prevenire casi di malattia severa è:**
  - pari a 70% nei vaccinati con ciclo completo da meno di 90 giorni, 68% nei vaccinati con ciclo completo da 91 e 120 giorni, e 71% nei vaccinati che hanno completato il ciclo vaccinale da oltre 120 giorni.
  - pari al 87% nei soggetti vaccinati con dose aggiuntiva/booster.

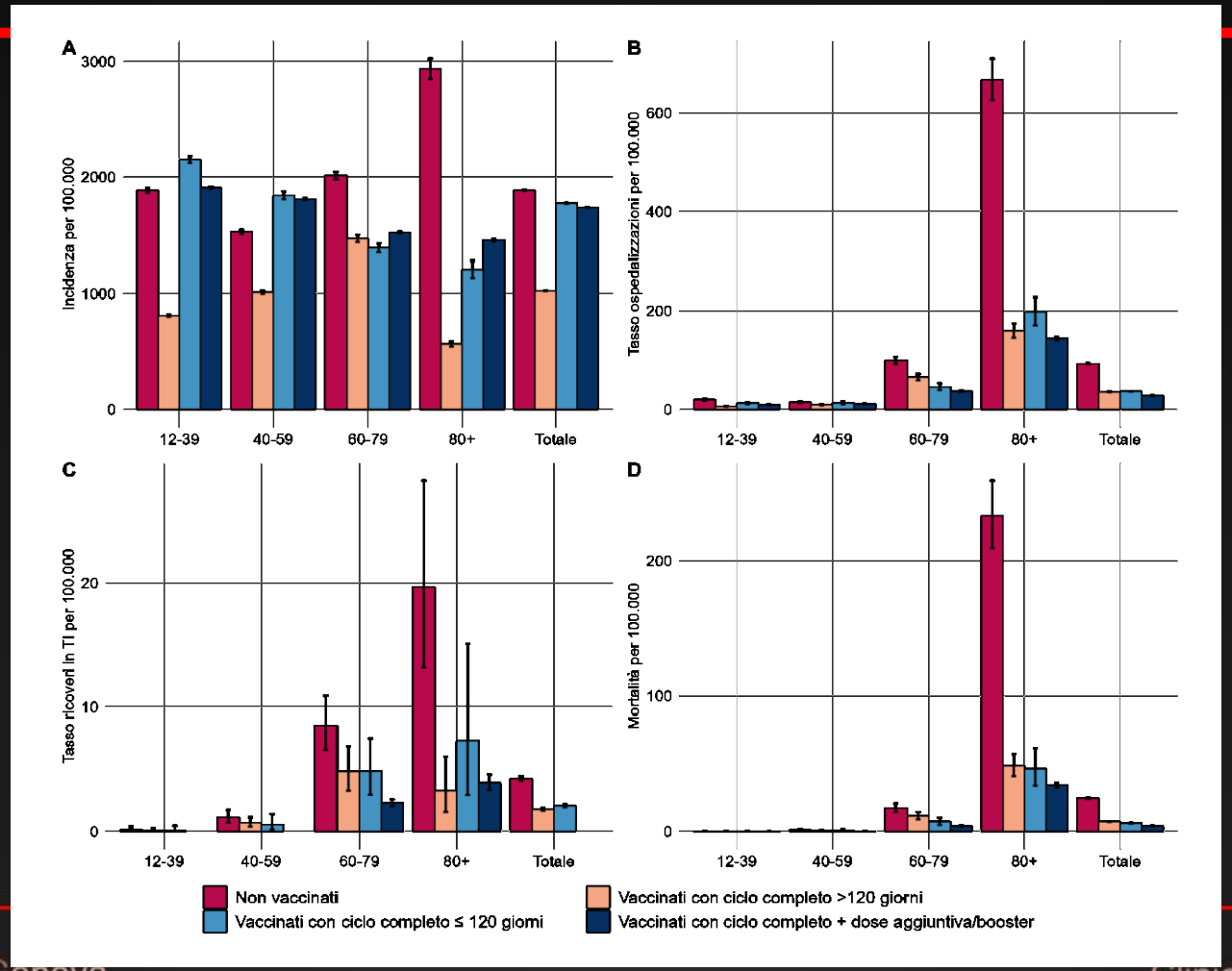
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

DATA PUBBLICAZIONE: 10/06/2022

Tasso di incidenza per 100000 per stato vaccinale e fascia di età

Casi COVID-19 segnalati

COVID-19 ospedalizzati



COVID-19 ICU

Decessi COVID-19

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Effect of SARS-CoV-2 vaccination in a frailty COVID-19 cohort: a real life experience in a Northern Italy Hospital

Retrospective, single-center study including patients ≥ 18 years hospitalized for COVID-19 in Infectious Disease and Emergency Units (San Martino Hospital) from 1st May to 31st December 2021.

Data collected: demographical data, multimorbidity and disability score,

vaccination time ("vaccinated" all patients hospitalized ≥ 14 days after first dose or ≥ 7 days after second/third dose)

therapy for COVID-19, mortality at 7 and 30 days, ICU admission, ventilation type.

	Not Vaccinated N=245 (62.03%)	Vaccinated N=150 (37.97%)	Std Diff
Baseline Characteristics			
Male sex, N(%)	150(61.22%)	84(56.00%)	**0.106**
Age, mean(SD)	63.94(16.02)	77.11(12.41)	**-0.919**
CIRS, median(IQR)	3(1-7)	8(4-11)	**-0.865**
Barthel, median(IQR)	100(68.5-100)	70(25.5-100)	**0.546**
BMI>= 30, N(%)	67(27.35 %)	20(13.33%)	**0.353**
Diabete Mellito, N(%)	35(14.29%)	32(21.33%)	**-0.184**

	Overlap-weighting [a]		Inverse weighting [b]	
	HR(95% CI)	p-value	HR(95% CI)	p-value
30-days death	0.83(0.49-1.40)	0.483	0.77(0.43-1.35)	0.360
7-days death*	0.78 (0.32-1.86)	0.579	0.66(0.25-1.72)	0.392
	OR(95% CI)	p-value	OR(95% CI)	p-value
ICU	0.23(0.05-0.97)	**0.046**	0.23(0.06-0.91)	**0.036**
Oxygen	0.33(0.14-0.75)	**0.008**	0.32(0.14-0.74)	**0.008**

Cox proportional hazards models for death at 30 days were performed
and logistic regression models were used
to assess the impact of vaccination on ICU admission and need of Oxygen
(adjusting for age, Cumulative Illness Rating Scale [CIRS], gender, Remdesivir, Monoclonal antibodies, Tocilizumab use)

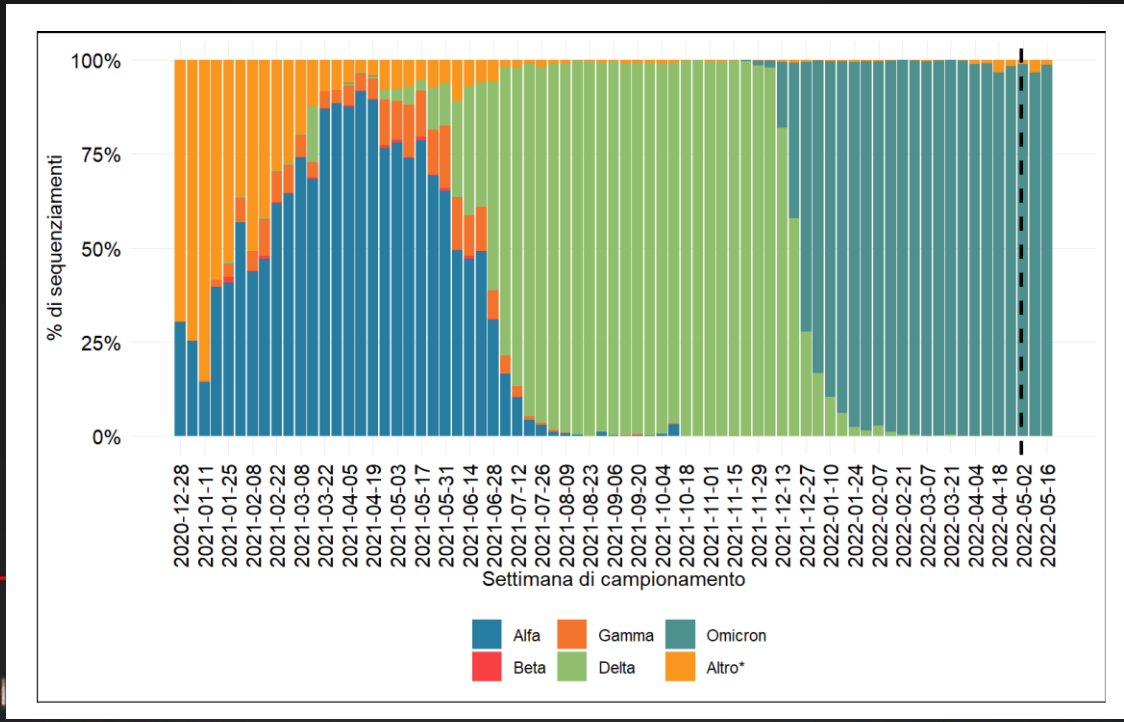
Università degli Studi di Genova

Under consideration ID Week. Russo C, Tagliafico L, Labate L, Ponzano M et al.

Remdesivir, 'Steroids', mAb, Tocilizumab, Anakinra

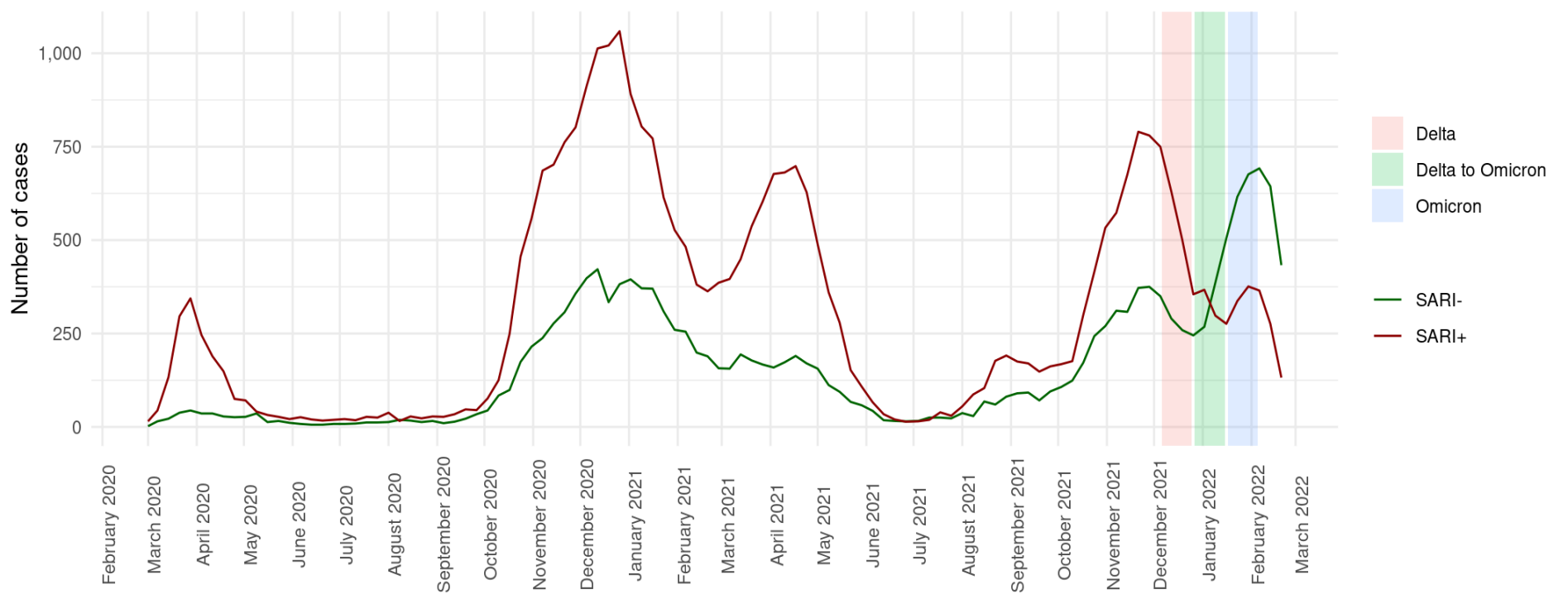
SARS-COV-2: Variabilità sincrona delle varianti

Vince il più efficiente e non il più forte



Cit. CFP

Figure 1: COVID-19 cases since beginning of 2020 stratified by encoded SARI



The coloured bars represent three phases with respect to the dominating SARS-CoV-2 variants. SARI = Severe Acute Respiratory Infection; SARI- = COVID-19 without SARI; SARI+ = COVID-19 with SARI

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedal
Genoa, Italy

Submitted BMC Infect Dis

Clinical outcomes associated with SARS-CoV-2 Omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in southern California

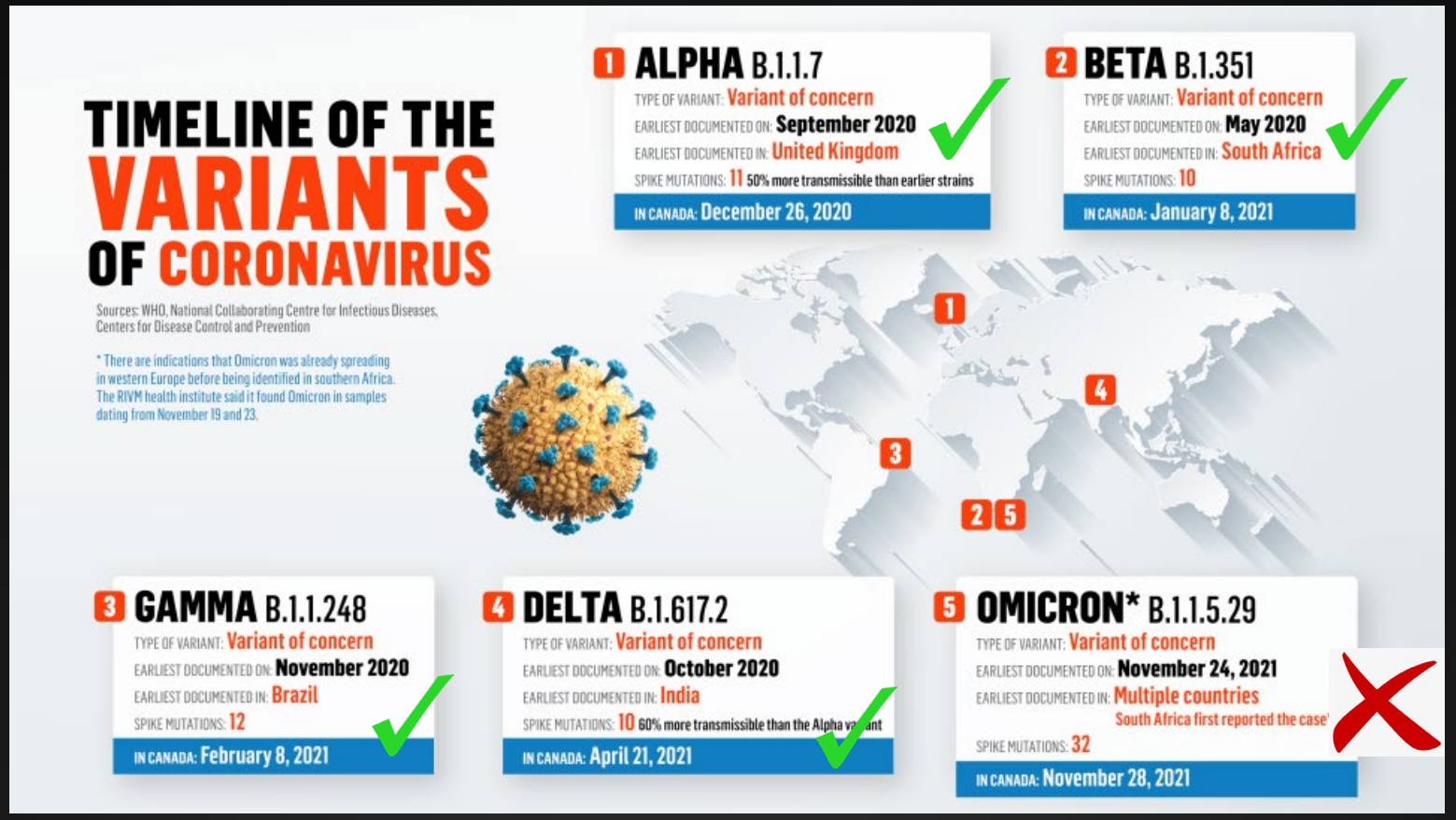
Lewnard J, Nature Medicine 2022

healthcare practices. Here we show that Omicron variant infections were associated with substantially reduced risk of progression to severe clinical outcomes relative to time-matched Delta (B.1.617.2) variant infections within a large, integrated healthcare system in southern California. Adjusted hazard ratios (aHRs) for any hospital admission, symptomatic hospital admission, intensive care unit admission, mechanical ventilation, and death comparing cases with Omicron versus Delta variant infection were 0.59 (95% confidence interval: 0.51-0.69), 0.59 (0.51-0.68), 0.50 (0.29-0.87), 0.36 (0.18-0.72), and 0.21 (0.10-0.44) respectively. This reduced severity could not be explained by differential history of prior infection among cases with Omicron or Delta variant infection, and was starkest among cases not previously vaccinated against COVID-19 (aHR=0.40 [0.33-0.49] for any hospital admission and 0.14 [0.07-0.28] for death). Infections with the Omicron BA.2 subvariant were not associated with differential risk of severe outcomes in comparison to BA.1/BA.1.1 subvariant infections. Lower risk of severe clinical outcomes among cases with Omicron variant infection should inform public health response amid establishment of the Omicron variant as the dominant SARS-CoV-2 lineage globally.

uary, 2022

16.12.2021:
C+I no retain neutralising activity against the Omicron variant

C+I & Variants of Concern



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

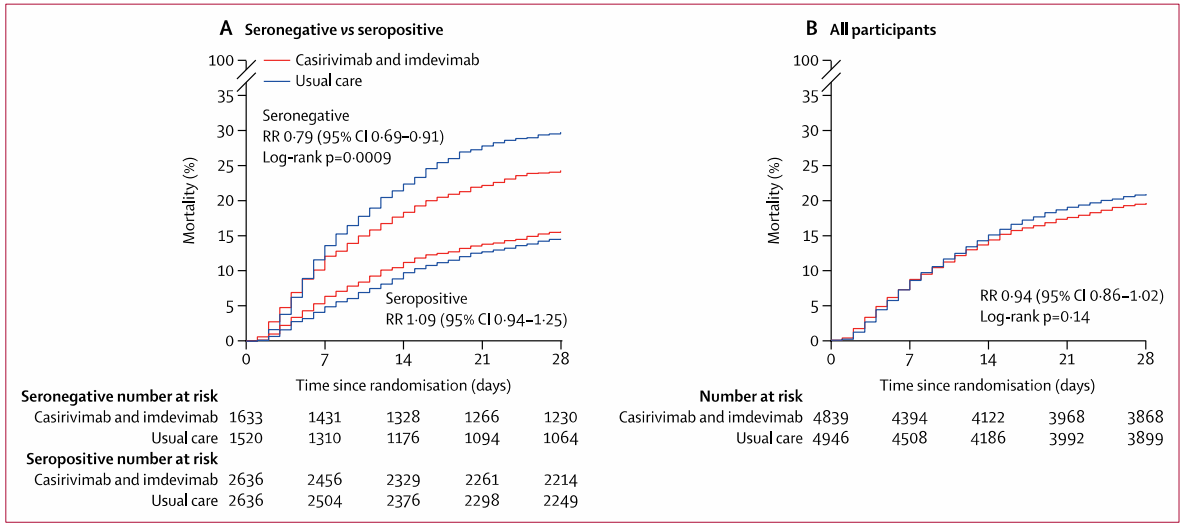
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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

*RECOVERY Collaborative Group**

Lancet Infect Dis 2021

Interpretation In patients admitted to hospital with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab reduced 28-day mortality in patients who were seronegative (and therefore had not mounted their own humoral immune response) at baseline but not in those who were seropositive at baseline.

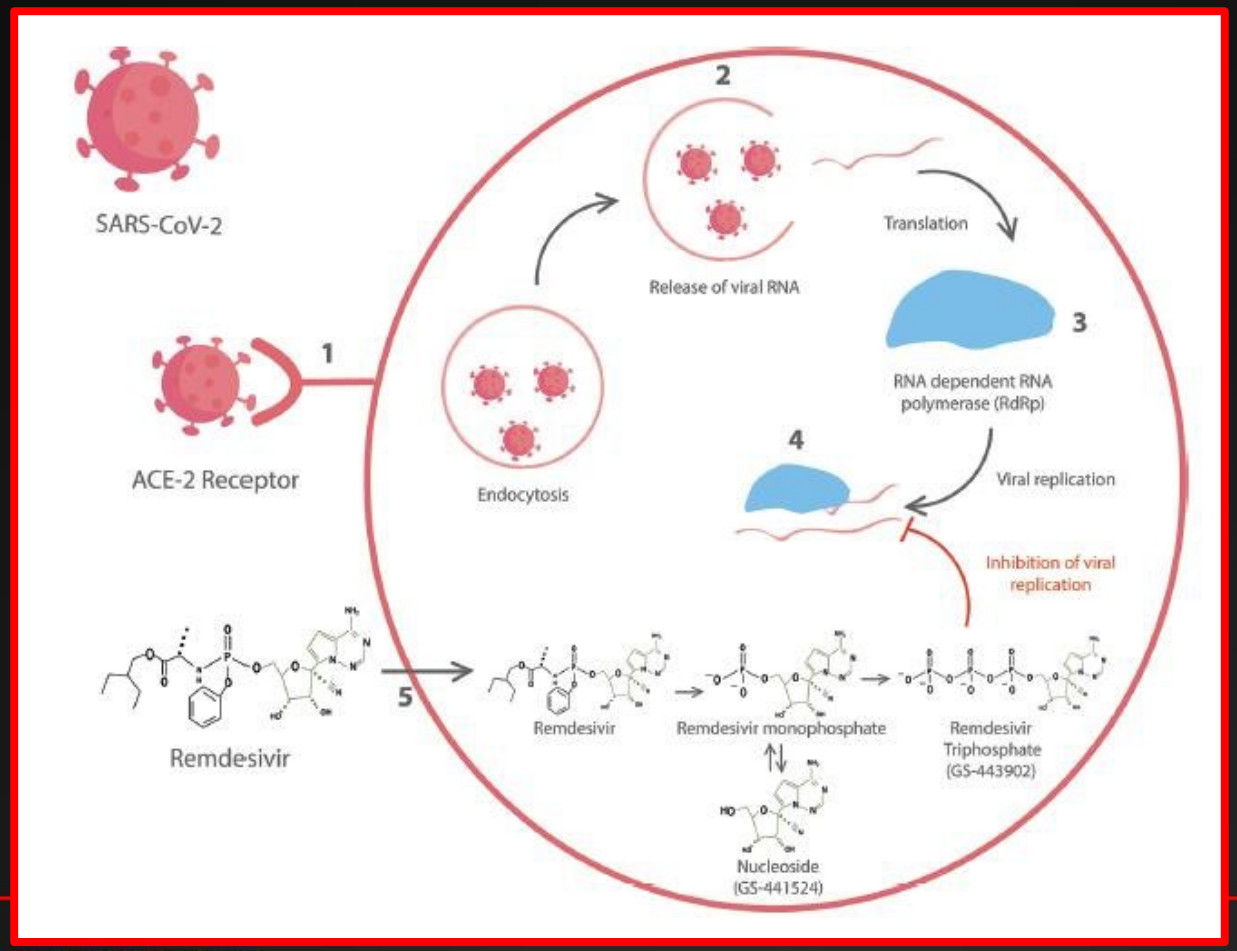


25% C+I and Remdesivir
15% C+I and tocilizumab or sarilumab

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Remdesivir: mantenuta efficacia su varianti



Martinot M et al CID 2020

Emerging RNA-Dependent RNA Polymerase Mutation in a Remdesivir-Treated B-cell Immunodeficient Patient With Protracted Coronavirus Disease 2019

Reported mutation in RdRP (D484Y) following remdesivir treatment

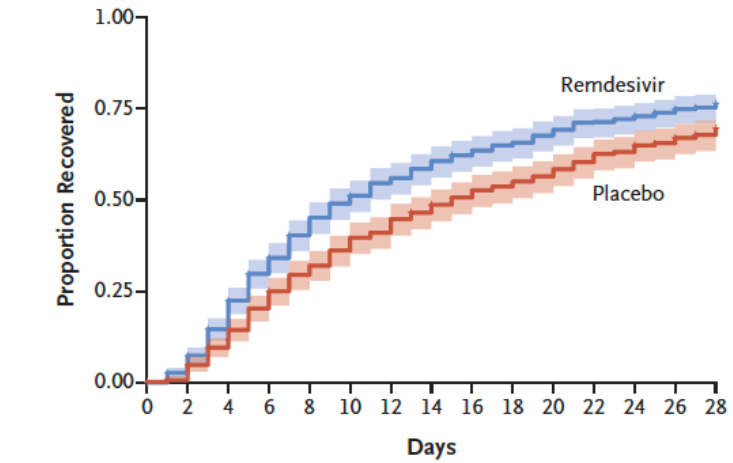
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

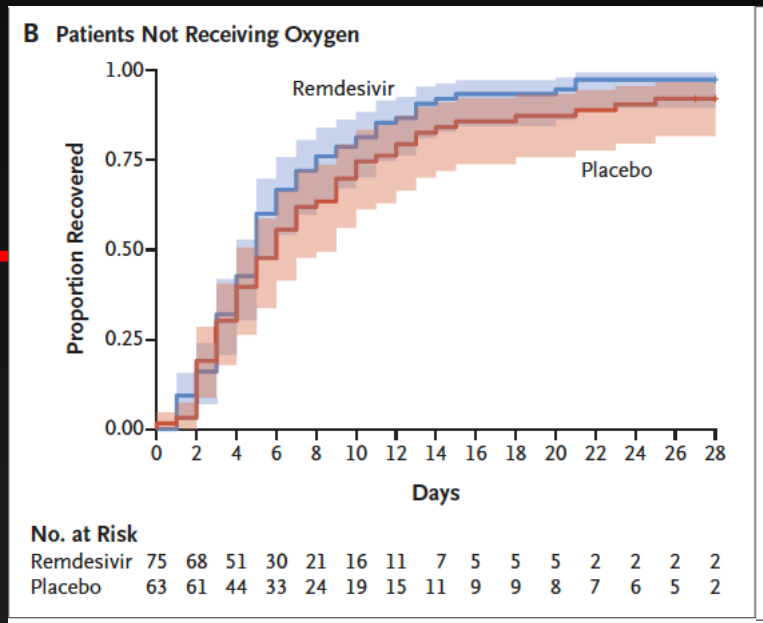
The NEW ENGLAND JOURNAL of MEDICINE

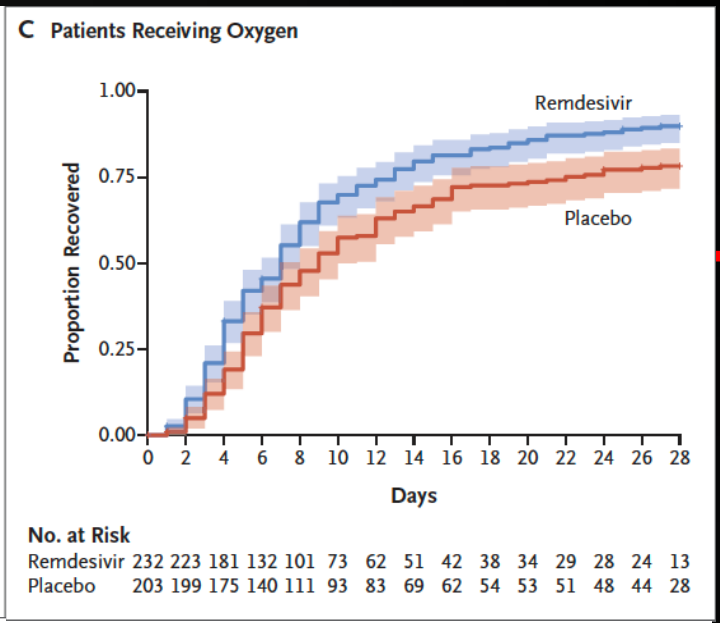
ORIGINAL ARTICLE

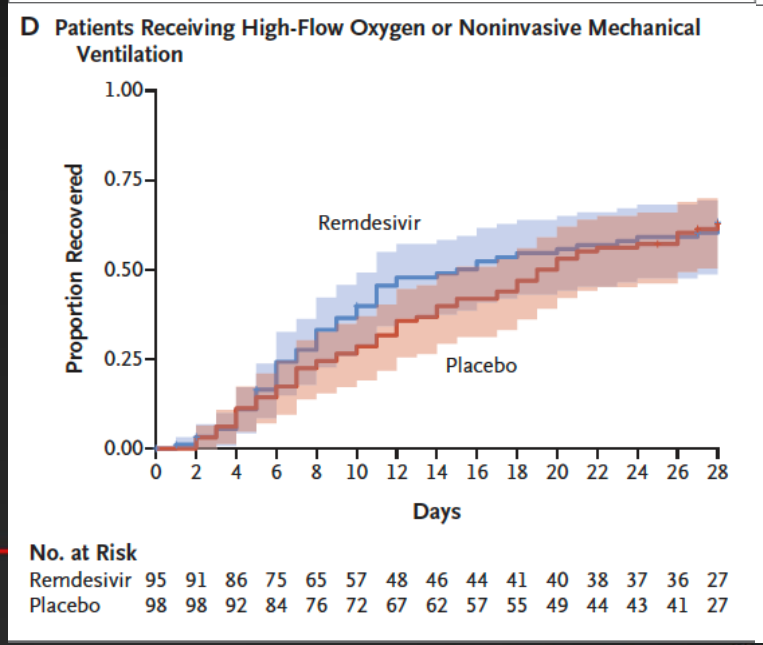
Remdesivir for the Treatment of Covid-19 — Final Report

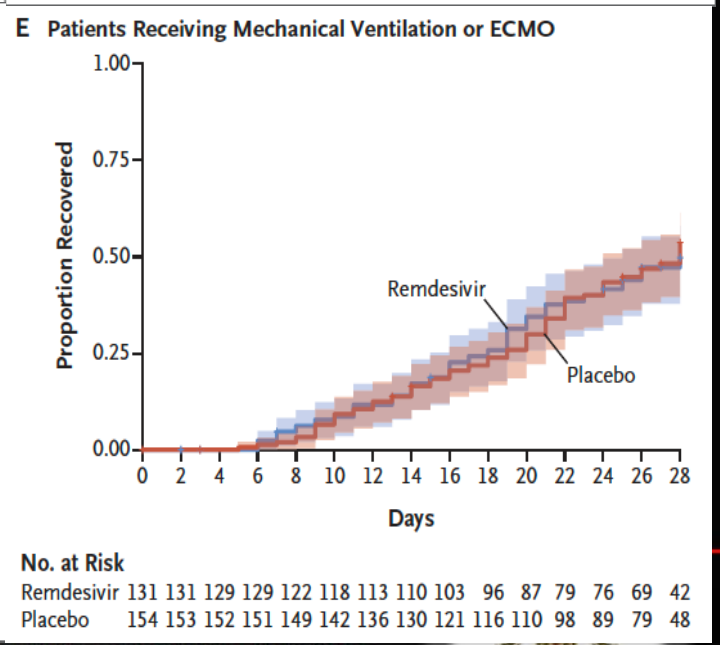


y, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-









Beigel JH *et al*. NEJM 2020

New Perspectives on Antimicrobial Agents: Remdesivir Treatment for COVID-19

Aleissa M M et al, AAC 2020

Study	Method(s)	Study population	Key results	Strengths/limitations	Interpretation
Spinner et al., JAMA 2020 (SIMPLE Moderate Trial) (40)	Randomized, open-label, phase 3 trial (group 1, 200 mg loading dose, 100 mg maintenance dose for up to 4 days; group 2, 200 mg loading dose, 100 mg maintenance dose for up to 9 days; group 3, standard care)	Age ≥12 yrs; positive SARS-CoV-2 PCR; radiographic evidence of pulmonary infiltrates; SpO2 > 94% and breathing on room air at screening; ALT or AST < 5× ULN; eGFR > 50 ml/min	Those randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard of care at day 11, but not those randomized to a 10-day group; this difference was of uncertain clinical importance	Strengths: first study to evaluate remdesivir in patients with moderate COVID-19 pneumonia, had adequate power; limitations: did not evaluate SARS-CoV-2 loads, did not stratify by sites, which could have influenced the results, given the differences in patient care and discharge practices	A 5-day course of remdesivir may be sufficient to treat patients with moderate COVID-19 pneumonia
Pan et al. (SOLIDARITY Trial) (41)	Randomized, open-label, phase 3 trial (remdesivir 200 mg loading dose, 100 mg maintenance dose for up to 9 days or standard of care)	Age ≥18 yrs; diagnosis of definitive COVID-19	Remdesivir was not associated with a reduction in in-hospital mortality compared to standard of care (11% vs 11.2%); remdesivir was not associated with reduced initiation of ventilation or hospital length of stay	Strengths: large sample size; limitations: open-label study, no definition of COVID-19 or definitive COVID-19, did not stratify by oxygen requirements or site, has not reported duration of symptoms prior to start of treatment, inclusion criteria not clearly defined, patients who were discharged were not followed, did not use WHO ordinal scale	Remdesivir was not associated with improved in-hospital mortality among patients hospitalized with COVID-19
Goldman et al., NEJM 2020 (SIMPLE Severe Trial) (39)	Randomized, open-label, phase 3 trial (group 1, 200 mg loading dose, 100 mg maintenance dose for up to 4 days; group 2, 200 mg loading dose, 100 mg maintenance dose for up to 9 days)	Age ≥12 yrs; positive SARS-CoV-2 PCR; radiographic evidence of pulmonary infiltrates; SpO2 ≤ 94% or requiring supplemental oxygen; ALT or AST < 5× ULN; eGFR > 50 ml/min	difference in incidence of serious adverse events There was no difference in clinical improvement of at least 2 points in the ordinal scale between 5-day and 10-day courses (65% vs 54%); among patients receiving noninvasive ventilation or high-flow oxygen on day 5, day 14 mortality was 10% in the 5-day group vs 15% in the 10-day group; among patients receiving mechanical ventilation or ECMO on day 5, day 14 mortality was 40% in the 5-day group vs 17% in the 10-day group	Strengths: first study to evaluate optimal duration of remdesivir in COVID-19, adequate power, high protocol adherence; limitations: did not evaluate SARS-CoV-2 loads, excluded patients on mechanical ventilation or ECMO	5 days of remdesivir is sufficient to treat COVID-19 patients who are not receiving mechanical ventilation/ECMO; patients who progress to mechanical ventilation or ECMO may benefit from a 10-day course

Febbraio 2020

1° utilizzo Roma Spallanzani per terapia coppia cinese

……

28 mesi di utilizzo

COVID Original Research

Early Use of Remdesivir and Risk of Disease Progression in Hospitalized Patients With Mild to Moderate COVID-19

Falcone M et al. Clin Therap 2022

Studio prospettico osservazionale 312 pts ospedalizzati con COVID-19 tra sett 2020- Gen 2021
N=90 < 5 gg, N=222 > 5 gg da inizio sintomi
Primary composite outcome: HFNC, NIV or IMV, or death

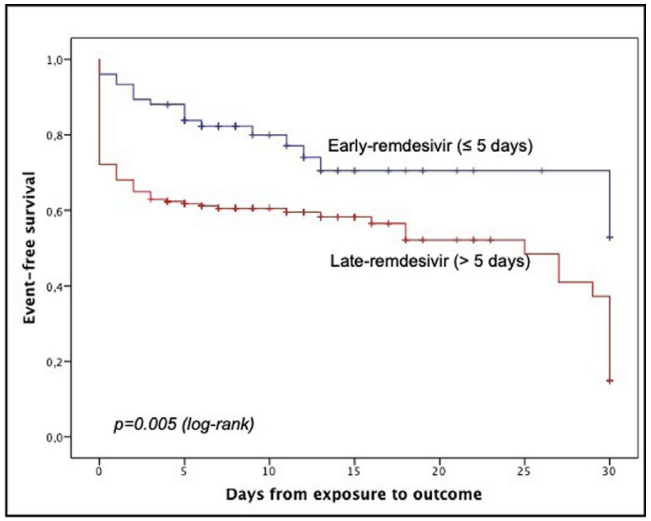


Figure. Kaplan-Meier analysis of disease progression between patients who received remdesivir within 5 days of symptoms onset and those who did not.

Table III. Multivariate logistic regression of factors independently associated with disease progression.*

Factor	OR (95% CI)	*P*
Early remdesivir (≤5 days from symptoms)	0.49 (0.27–0.87)	0.015
P/F ratio <300 on admission	2.22 (1.35–3.63)	0.002
History of dyspnea at home	2.53 (1.55–4.12)	<0.001
Age	1.02 (1.003–1.04)	0.025
C-reactive protein >5 mg/dL on admission	1.66 (1.01–2.72)	0.044

Real-life use of remdesivir in hospitalized patients with COVID-19

Garcia Vidal C, 2021

Studio osservazionale di coorte da lug-sett 2020

123/242 pts received Remdesivir and

Anti-inflammatory effect	
Tocilizumab (%)	33 (26.8%)
Anakinra (%)	7 (5.7%)
Methyl-prednisolone (%)	14 (11.4%)
Dexamethasone (%)	57 (46.3%)
Prednisone (%)	24 (19.5%)
Antibiotic treatment	
Ceftriaxone (%)	52 (42.8%)
Ceftaroline (%)	16 (13%)
Outcomes	
Median (IQR) of length of hospital stay	8 (6-12)
ICU admission (%)	24 (19.5%)
Need of mechanical ventilation (%)	9 (7.3%)
30-day mortality (%)	5 (4.1)

hospitalized patients with severe pneumonia due to SARS-CoV-2 documented by rRT-PCR, serology or antigen test, and all the following characteristics: 1) aged >12 years and >40 kg; 2) need of supplemental low-flow oxygen; 3) ≤7 days from symptom onset to remdesivir prescription; and 4) met at least two of these three criteria: respiratory rate ≥24 bpm, oxygen saturation at air ambient ≤94%, or PaO_2/FiO_2 <300 mmHg. Exclusion criteria included requirement of supplemental high-flow oxygen, mechanical ventilation, vasoactive drugs, extra-corporeal membrane oxygenation (ECMO), or meeting criteria

The most severe patients required co-administration of an anti-inflammatory therapy, and as expected they had the highest mortality rate. Interestingly, the concomitant use of remdesivir and tocilizumab was associated with the lowest mortality rate in this group (5.3%), in line with the recent report showing better outcomes among patients receiving remdesivir plus baricitinib [12]. Both inmune-modulators inhibit specific pathways of inflammatory cascade instead of the broad-spectrum inhibition induced by steroids with potential harmful consequences [13].

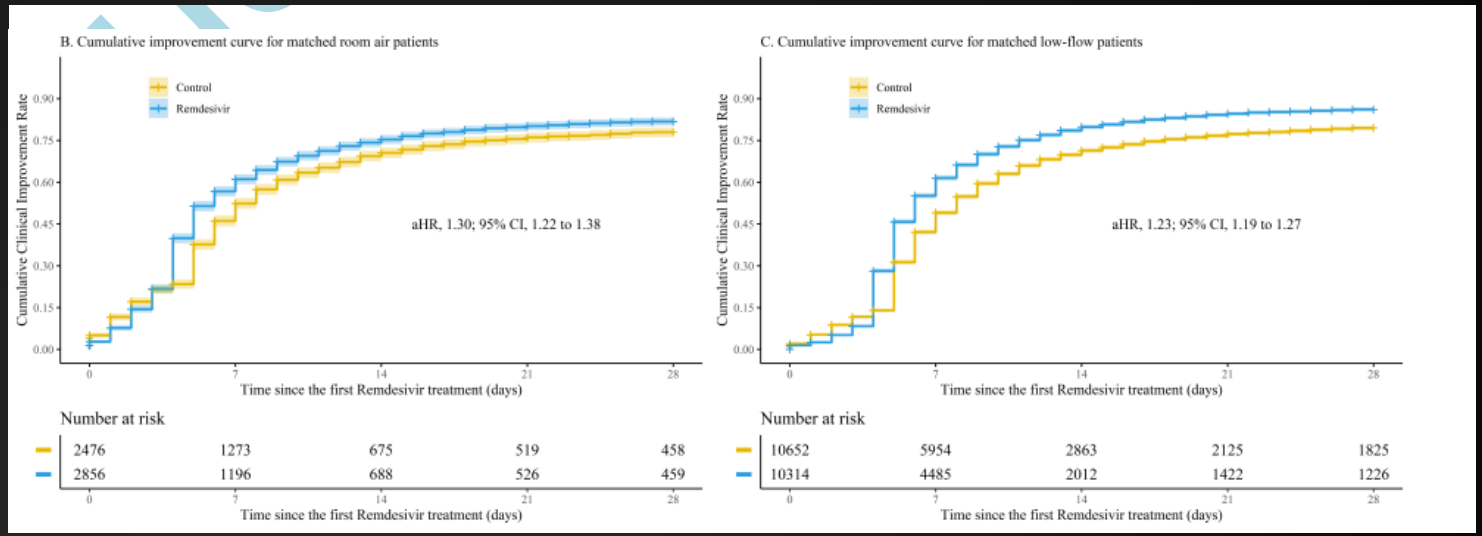
REAL-WORLD EFFECTIVENESS OF REMDESIVIR IN ADULTS HOSPITALIZED WITH COVID-19: A RETROSPECTIVE, MULTICENTER COMPARATIVE EFFECTIVENESS STUDY

Garibaldi BT, CID 2021

Studio retrospettivo, pts COVID-19 ospedalizzati Feb 20-Feb 21 US.
Remdesivir recipients matched to control using Time Dependent PS.
Primary outcome: time to improvement
Secondary outcome: time to death
42473 pts (44%) in Remdesivir

Remdesivir pts on:
no Oxygen (aHR 1.3 95%CI 1.22-1.38)
or low flow oxygen (aHR 1.23, 95% CI 1.19-1.27) were significantly more likely to achieve clinical improvement by 28 d and significantly reduced mortality in pts on low flow oxygen

Incidenza cumulativa per clinical improvement



…E survival probability

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2021 VOL. 384 NO. 9

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

Scala ordinale

1: Non ospedalizzato e nessuna limitazione di attività

2: Non ospedalizzato con limitazione di attività, ossigenoterapia domiciliare o entrambi

3: Ospedalizzato, senza ossigenoterapia supplementare ne ulteriore assistenza medica continuativa (usato se l'ospedalizzazione è stata estesa per il controllo dell'infezione)

4: Ospedalizzato, senza ossigenoterapia supplementare, ma con necessita di assistenza medica continuativa (condizione medica legata al COVID-19)

5: Ospedalizzato, in ossigenoterapia supplementare

6: Ospedalizzato, in ventilazione non invasiva o con ossigeno ad alto flusso

7: Ospedalizzato, in ventilazione meccanica invasiva o ECMO

8: Decesso

CONCLUSIONS

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. The combination was associated with fewer serious adverse events. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT04401579.)

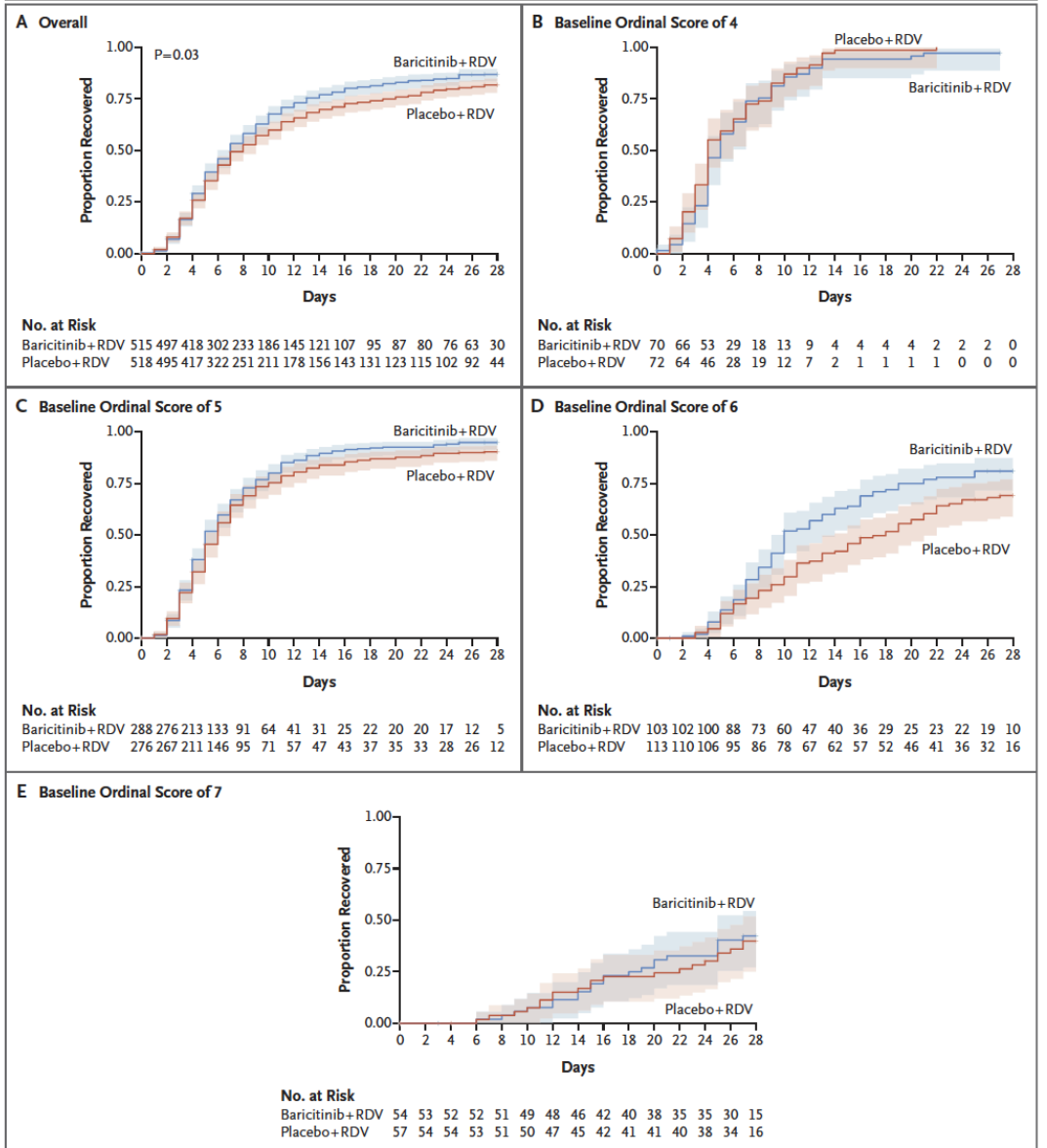


Figure 2. Kaplan–Meier Estimates of Cumulative Recoveries.

Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not requiring oxygen; Panel B), in those with a baseline score of 5 (requiring oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or extracorporeal membrane oxygenation [ECMO]; Panel E). Shaded areas indicate 95% confidence intervals.

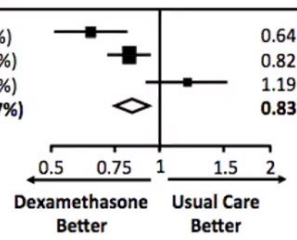
Dexamethasone

RECOVERY Trial: Mortality at Day 28

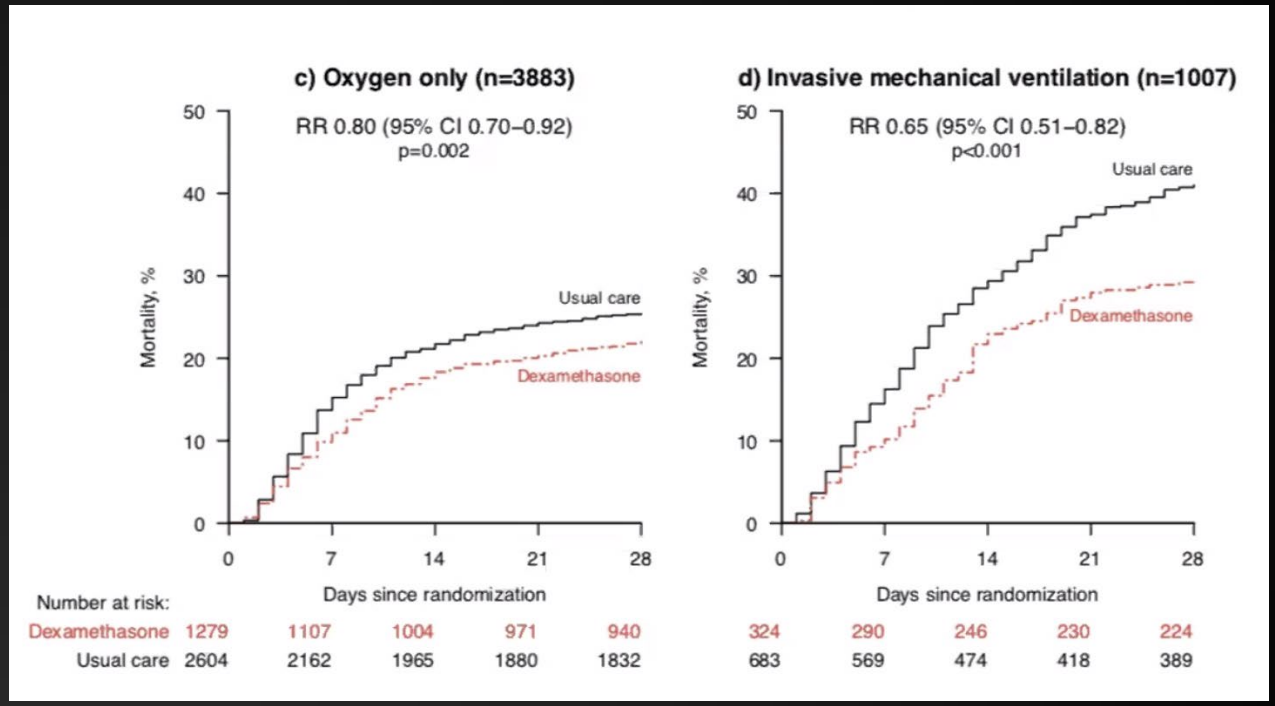
- Addition of dexamethasone to usual care associated with **lower mortality** among subsets receiving invasive mechanical ventilation or oxygen alone but not in those receiving no baseline respiratory support

Respiratory Support at Randomization	Dexamethasone + Usual Care	Usual Care Only	28-Day Mortality RR (95% CI)	*P* Value
Invasive mechanical ventilation	95/324 (29.3%)	283/683 (41.4%)	0.64 (0.51-0.81)	
Oxygen only	298/1279 (23.3%)	682/2604 (26.2%)	0.82 (0.72-0.94)	
No oxygen received	89/501 (17.8%)	145/1034 (14.0%)	1.19 (0.91-1.55)	
All patients	**482/2104 (22.9%)**	**1110/4321 (25.7%)**	**0.83 (0.75-0.93)**	**< .001**

Chi-square trend across 3 categories: 11.5



RECOVERY Collaborative Group. NEJM. 2021;384:693.



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Wagner C, et al 2021

Based on the current evidence, we are moderately certain that systemic corticosteroids probably reduce mortality slightly amongst
hospitalised, symptomatic COVID-19 patients.
Most of the participants in the studies
were treated with invasive mechanical ventilation and non-invasive ventilation/continuous positive airway pressure or high-flow oxygen.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial

Prado Jeronimo CM, MetCovid Team, CID 2021

MAJOR ARTICLE

Background. Steroid use for coronavirus disease 2019 (COVID-19) is based on the possible role of these drugs in mitigating the inflammatory response, mainly in the lungs, triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study aimed to evaluate the efficacy of methylprednisolone (MP) among hospitalized patients with suspected COVID-19.

Methods. A parallel, double-blind, placebo-controlled, randomized, Phase IIb clinical trial was performed with hospitalized patients aged ≥18 years with clinical, epidemiological, and/or radiological suspected COVID-19 at a tertiary care facility in Manaus, Brazil. Patients were randomly allocated (1:1 ratio) to receive either intravenous MP (0.5 mg/kg) or placebo (saline solution) twice daily for 5 days. A modified intention-to-treat (mITT) analysis was conducted. The primary outcome was 28-day mortality.

Results. From 18 April to 16 June 2020, 647 patients were screened, 416 were randomized, and 393 were analyzed as mITT, with 194 individuals assigned to MP and 199 to placebo. SARS-CoV-2 infection was confirmed by reverse transcriptase polymerase chain reaction in 81.3%. The mortality rates at Day 28 were not different between groups. A subgroup analysis showed that patients over 60 years old in the MP group had a lower mortality rate at Day 28. Patients in the MP arm tended to need more insulin therapy, and no difference was seen in virus clearance in respiratory secretion until Day 7.

Conclusions. The findings of this study suggest that a short course of MP in hospitalized patients with COVID-19 did not reduce mortality in the overall population.

A subgroup analysis:
patients > 60 y in the MP group had a lower mortality rate at Day 28

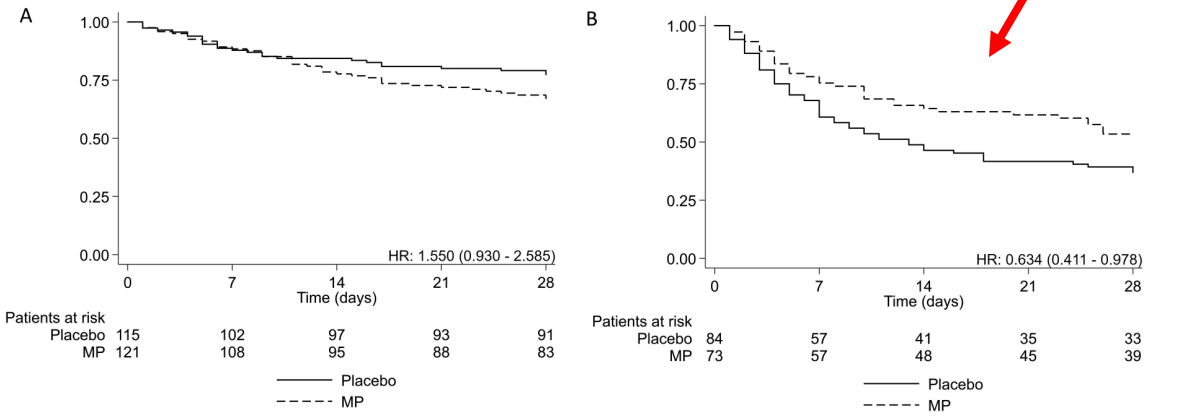


Figure 3. Time from randomization to death in subgroups of patients (*A*) ≤60 years old and (*B*) >60 years old. Survival analysis until Day 28. Abbreviations: HR, hazard ratio; MP, methylprednisolone.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

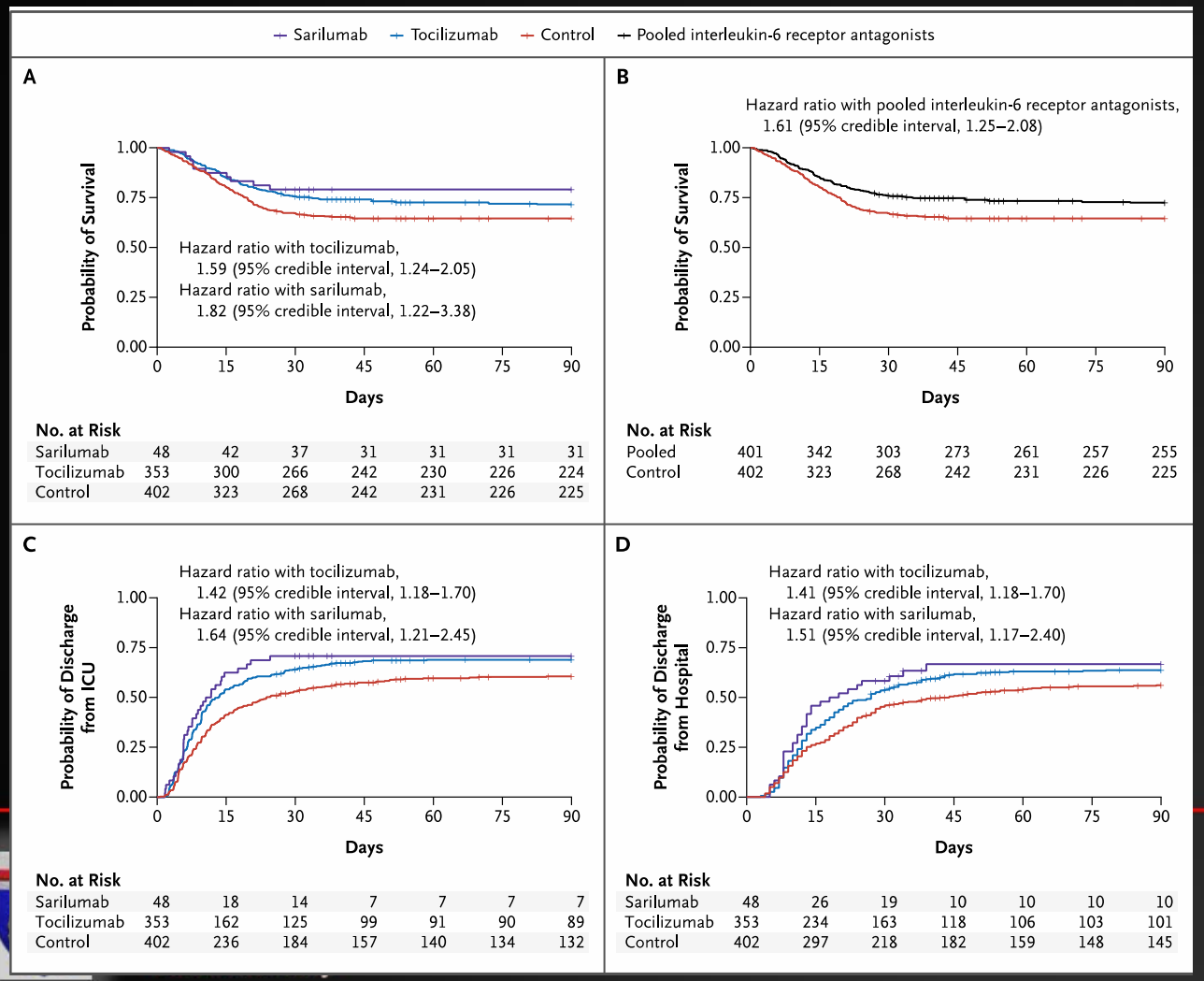
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The REMAP-CAP Investigators*



Critically ill patients in ICU: tocilizumab and sarilumab were effective as compared with SOC (glucocorticoids in > 80%)

CONCLUSIONS

In critically ill patients with Covid-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival. (REMAP-CAP ClinicalTrials.gov number, NCT02735707.)

NEJM, 2021

Clinica Malattie Infettiv
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Tocilizumab administration for the treatment of hospitalized patients with COVID-19: A systematic review and meta-analysis

Kyriakopoulos C, et al.
Respirology 2021

9 RCT, 43 Observational Studies

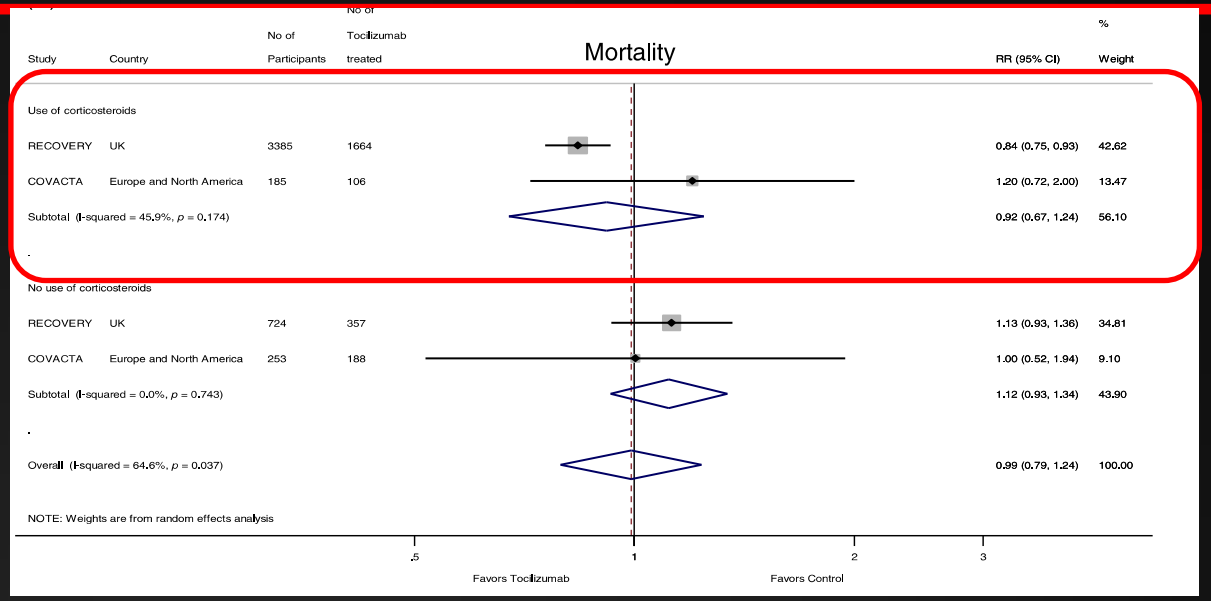
Primary objective

The primary objective was to determine whether treatment with tocilizumab reduces mortality in patients hospitalized with COVID-19.

Secondary objectives

Secondary objectives included the evaluation of differences between the tocilizumab and control groups in:

- The need for intubation or invasive mechanical ventilation (IMV).
- A composite endpoint of mortality or IMV.
- A composite endpoint of ICU admission or IMV.
- The length of hospitalization.
- Mortality in non-ICU and ICU-treated patients.
- Mortality in patients according to the concomitant use of systemic corticosteroids.



In conclusion, this systematic review and meta-analysis of nine RCTs and 43 observational studies provides the most up-to-date and complete evidence for the role of tocilizumab in the management of COVID-19. We demonstrated that the use of tocilizumab is associated with lower mortality and risk of intubation or need for mechanical ventilation in hospitalized COVID-19 patients, with its benefit magnified when administered concomitantly with systemic corticosteroids. The optimal timing of administration and the patients who will benefit the most need to be evaluated in future appropriately designed trials.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Infettive
IRCCS
Genoa, Italy

ARTICLES
https://doi.org/10.1038/s41591-021-01499-z
nature medicine
OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

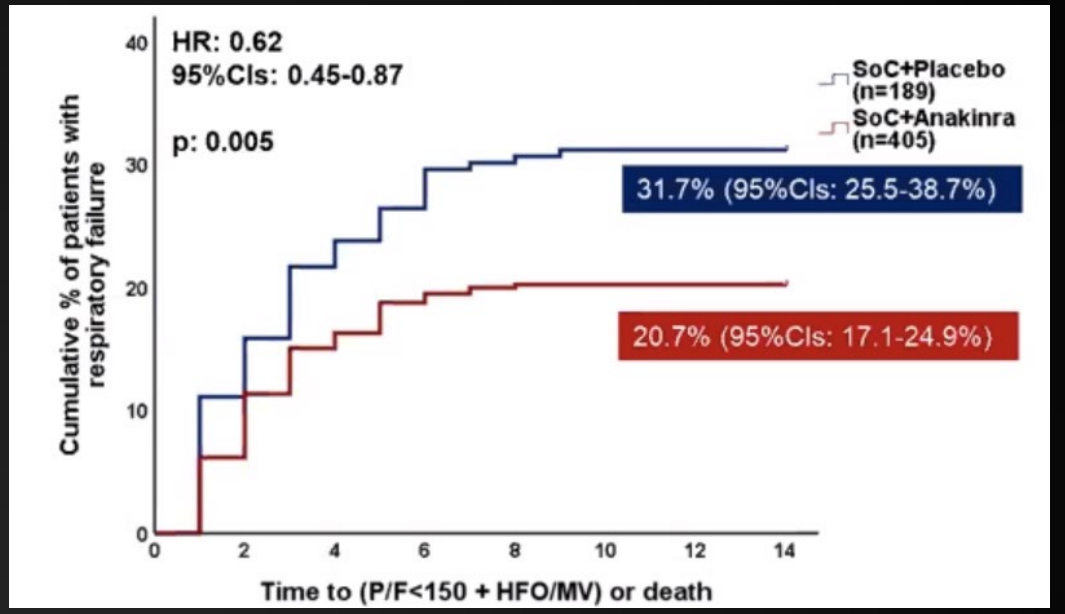
ANAKINRA and SAVE MORE Trial

Kyriazopoulos E et al, 2021

Sobi and Hellenic Institute for the Study of Sepsis report use of anakinra improved overall clinical outcomes by 64% in hospitalised patients with COVID-19 pneumonia

About SAVE-MORE

SAVE-MORE (NCT04680949); suPAR-Guided Anakinra Treatment for Management of Severe Respiratory Failure by COVID-19) is a pivotal, confirmatory, phase III randomized controlled trial (RCT). The trial aims to evaluate the efficacy and safety of early start of anakinra guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days, as measured by the ordinal scale of the 11-point World Health Organization (WHO) clinical progression scale (CPS). Anakinra was administered at a dose of 100mg/day SC for up to 10 days. Of 1,060 patients screened, 606 patients were randomised across 40 sites in Greece and Italy. SAVE-MORE is an investigator-sponsored study conducted independently by Professor Giamarellos-Bourboulis, with the Hellenic Institute for the Study of Sepsis being the regulatory sponsor. Sobi has supported the study with study drug and funding.



Analysis of the primary end point, the comparative 11-point WHO Clinical Progression ordinal Scale (CPS)[i], at day 28 demonstrated significant improvement in patients receiving standard-of-care treatment plus anakinra vs patients receiving standard-of-care plus placebo (Odds Ratio 0.36, p<0.001). There were reductions in the number of patients who died or who progressed to severe respiratory failure, as well as an increase in the number of patients who were discharged from hospital with no evidence of COVID-19 infection. These changes were apparent at day 14 (Odds Ratio 0.59, p=0.001).

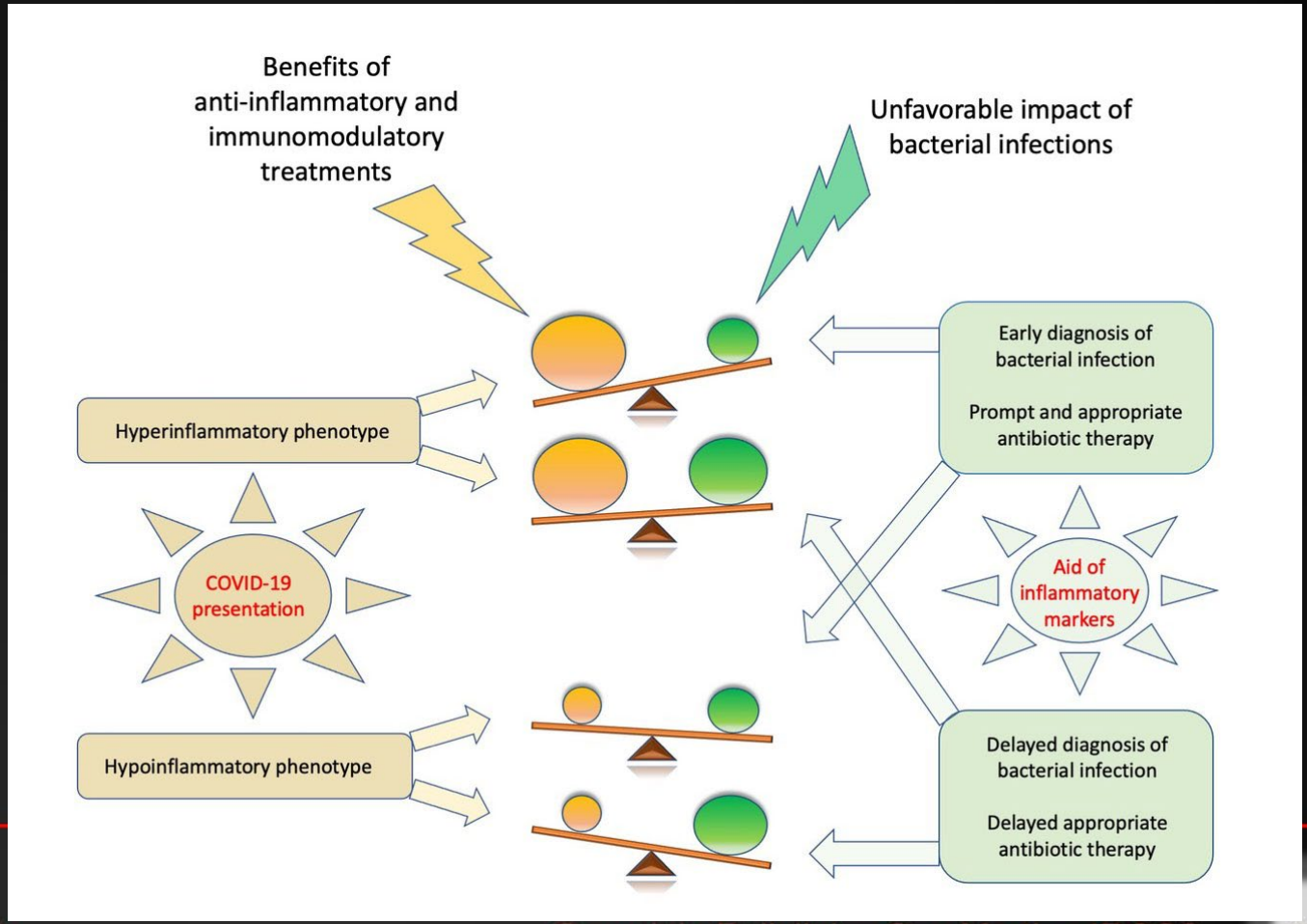
The SAVE-MORE trial showed that early start of treatment with anakinra guided by suPAR levels in patients hospitalized with moderate and severe COVID-19 significantly reduced the risk of worse clinical outcome at day 28.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinical significance of inflammatory markers of bacterial infection in critically ill patients with COVID-19 after treatment with anti-inflammatory and immunomodulatory drugs: a complex new scenario

Giacobbe DR et al, Front in Bio Land 2021

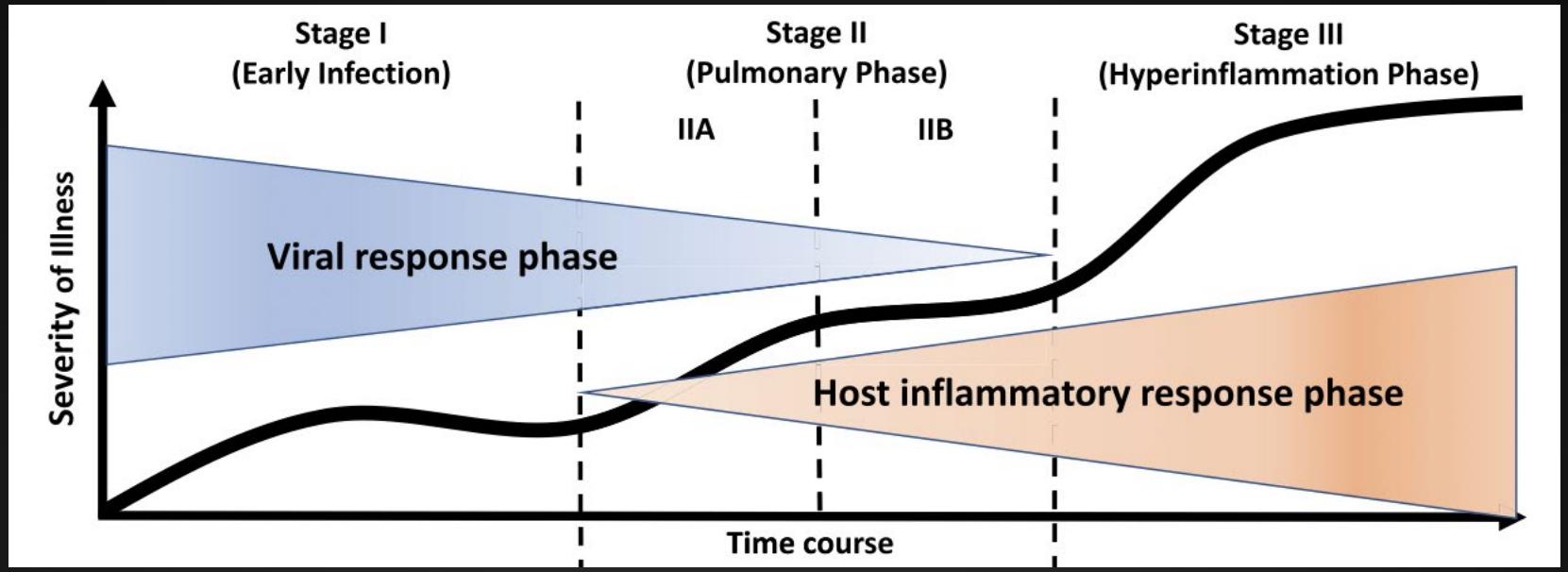
Complex balance between the effects of anti inflammatory/ immunomodulatory agents for the treatment of COVID-19 and possible unfavoreble impact of bacterial infections



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Ospedale Policlinico San Martino IRCCS
Genoa, Italy

I pazienti con COVID-19 dal pdv terapeutico possono essere gestiti in maniera simile?



Siddiki H, el al. 2020

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

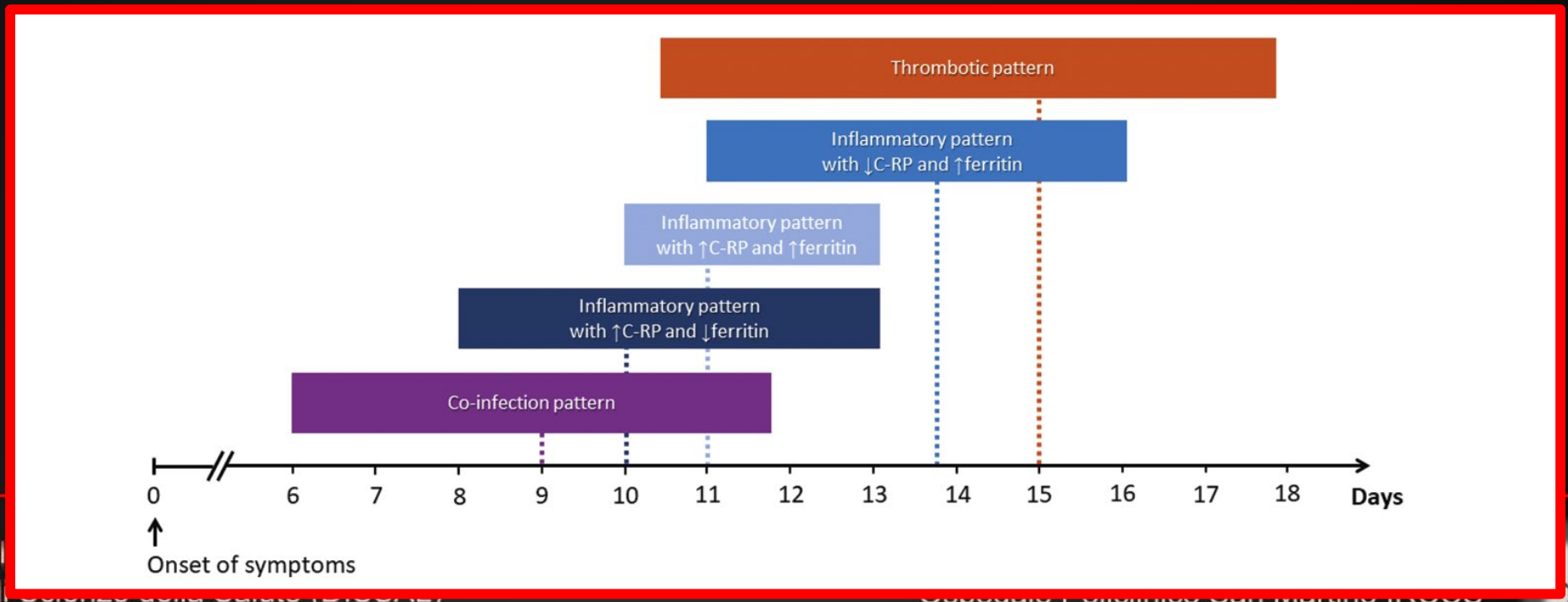
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Personalized Therapy Approach for Hospitalized Patients with Coronavirus Disease 2019

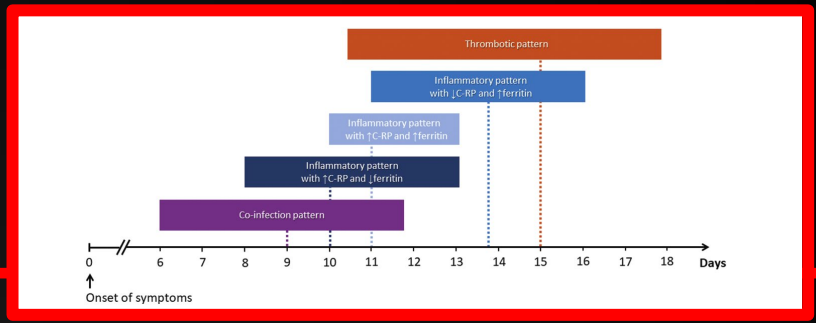
Garcia-Vidal C, et al. CID 2022

Studio retrospettivo osservazionale di coorte, 246 pts
99 (40%) personalized therapy
147 (60%) no

We aimed to describe the main clinical complications of hospitalized patients with COVID-19 through classification into 3 pattern groups (inflammatory, co-infection, and thrombotic), and demonstrate how personalized therapy for each pattern improves outcomes.



3 Clinical Patterns



1) Co-infection pattern:

Co-infection pattern comprised patients with plasma procalcitonin > 2 ng/mL with creatinine < 1.5 mg/dL. We considered a personalized therapy approach whenever infections

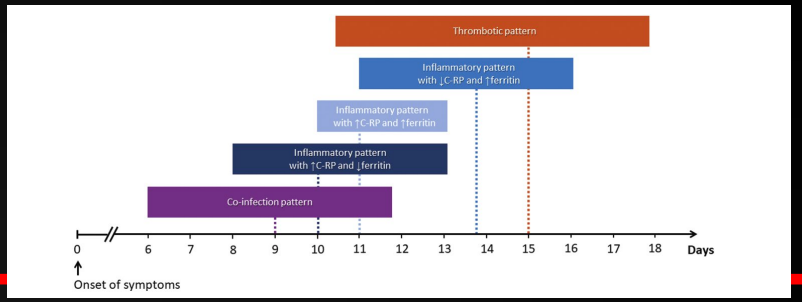
3) Thrombotic pattern: patients who were assumed to have coagulopathy events

The thrombotic pattern comprised patients who were assumed to have coagulopathy events. This pattern was identified with CRP < 10 mg/dL and ferritin < 3000 ng/mL, and D-dimer and high-sensitivity troponin higher than 5000 ng/mL and 45.2 ng/L, respectively. We considered those patients followed a personalized therapy approach whenever pulmonary embolism was ruled out by computed tomography (CT) scan and/or anticoagulation treatment was administered if CT scan was not performed.

1) Inflammatory pattern: excessive cytokine response
3 clinical-inflammatory subset patterns

a) CRP > 10 mg/dl, ferritine < 3000 ng/ml >>IL-6 profile
b) CRP > 10 mg/dl, ferritine > 3000 ng/ml >>Il-6 and IL-1 profile
c) CRP < 10 mg/dl, ferritine > 3000 ng/ml >>IL-1 profile

This patterns justified personalized therapy approaches



Outcomes at day 5 after identification:
Improvement (< 02 and > Sp02) >>> 93.9% in personalized therapy group
Death (early 5 d, 14d, 28d >> 2% vs 18%, 20% vs 40%, 20%vs 44%)

Multivariate analyses: personalized therapy was indipendently associated with decreased early mortality (OR 0.144 95%CI 1.003-1.121)

Analytics markers are a reflex of cytokine patterns

CRP reflects pro-inflammatory response mediated by IL-6

Hyperferritine reveals immune dysregulation mainly mediated by IL-1 and IFN gamma

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

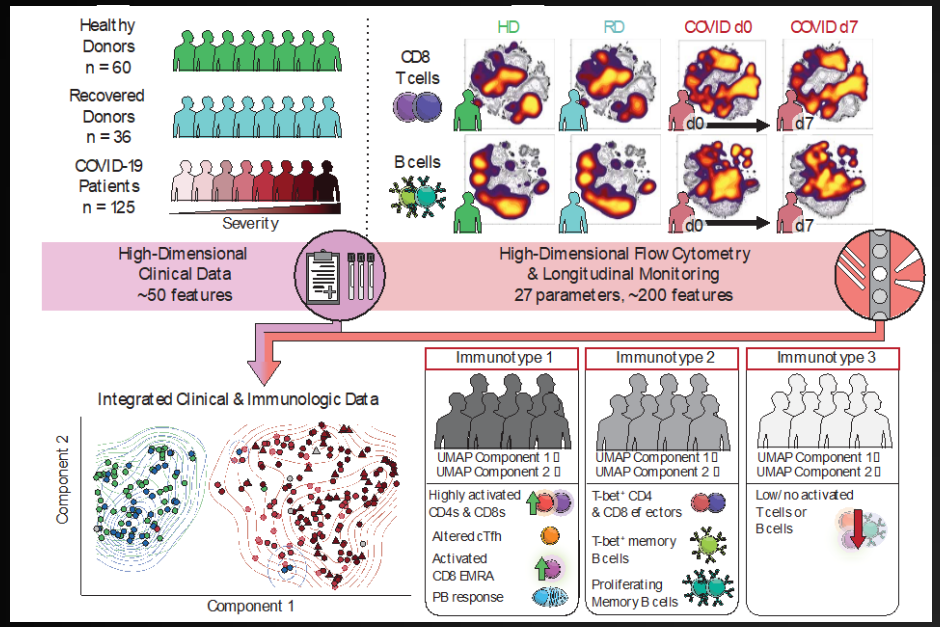
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

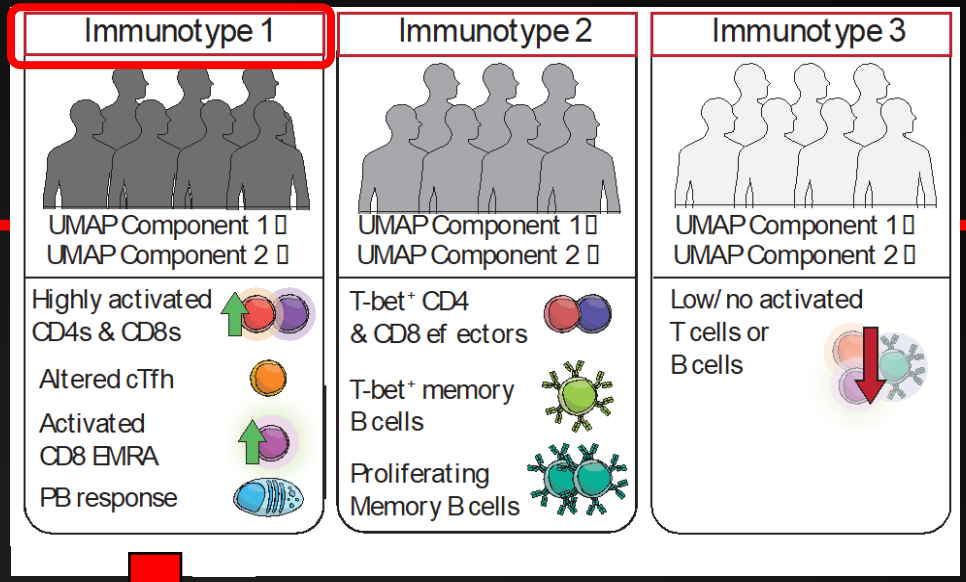
RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications

Matthew D et al. Science 2020





Immunotype 1: connected to more-severe disease

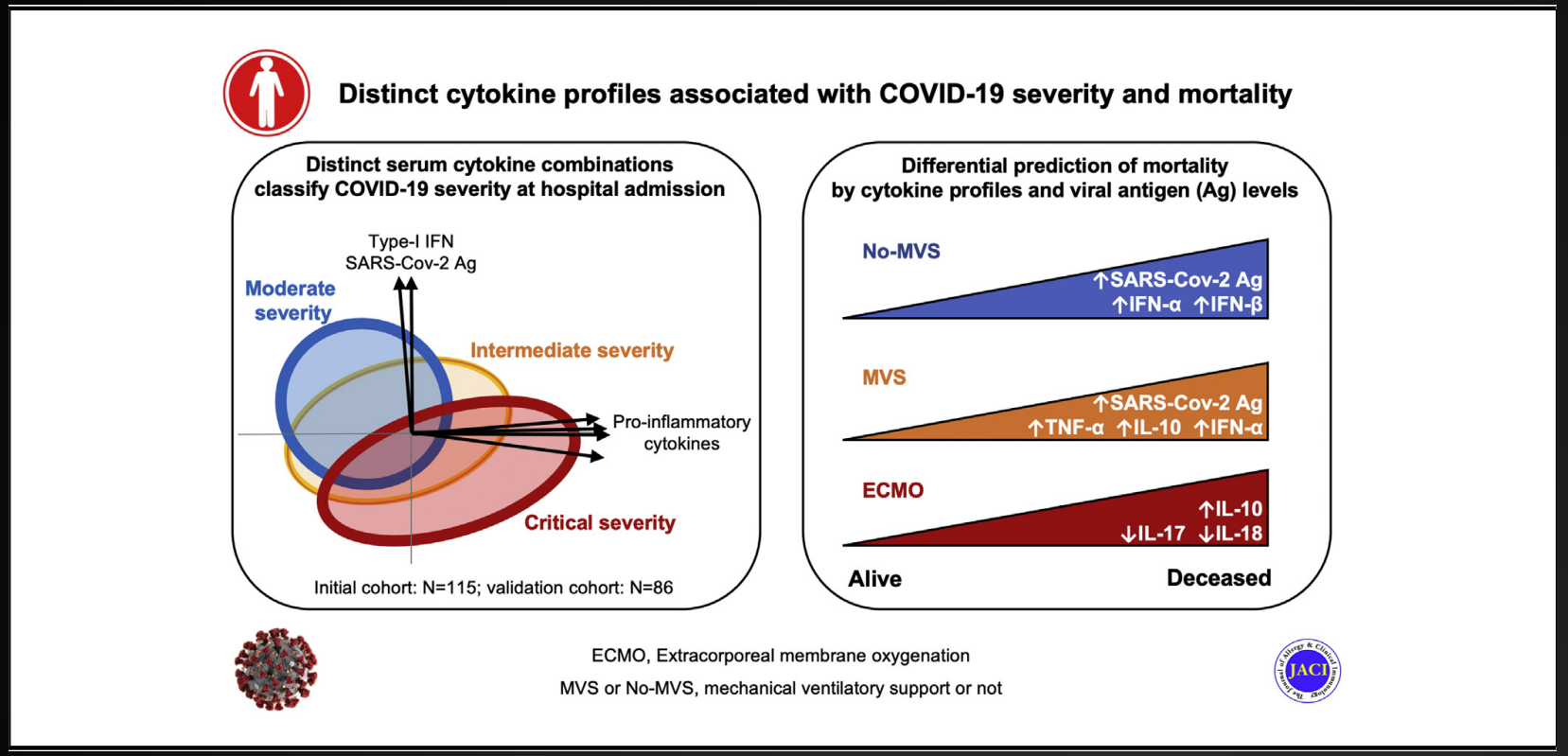
Tailoring clinical treatment

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Distinct cytokine profiles associated with COVID-19 severity and mortality

Dorgham K, et al. JACI 2021



Key messages

- COVID-19 severity is associated with distinct cytokine profiles, whereas measurement of 6 cytokines at hospital admission predicts mortality.
- SARS-CoV-2 antigenemia, associated with mortality in moderate severity patients, correlates with levels of type-I interferon, but not with other proinflammatory cytokines.
- These results call for personalized COVID-19 management based on a combined cytokine/viral load profiling.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

La durata ed il tipo di terapia Nel paziente con COVID-19 va individualizzata su ospite?

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

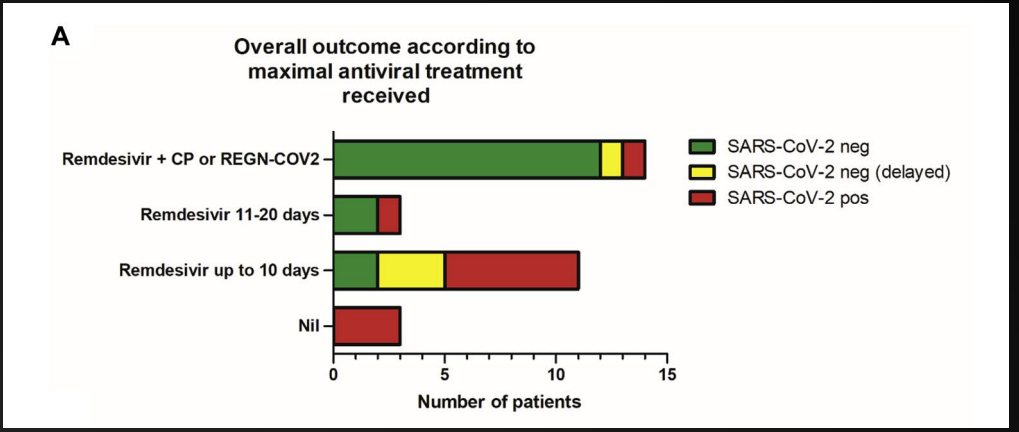
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Treatment of chronic or relapsing COVID-19 in immunodeficiency

Brown Li An K, et al JACI 2022

Results: We identified 31 patients (median age 49 years). Their underlying immunodeficiency was most commonly characterized by antibody deficiency with absent or profoundly reduced peripheral B-cell levels; prior anti-CD20 therapy, and X-linked agammaglobulinemia. Their clinical features of COVID-19 were similar to those of the general population, but their median duration of symptomatic disease was 64 days (maximum 300 days) and individual patients experienced up to 5 episodes of illness. Remdesivir monotherapy (including when given for prolonged courses of ≤20 days) was associated with sustained viral clearance in 7 of 23 clinical episodes (30.4%), whereas the combination of remdesivir with convalescent plasma or anti-SARS-CoV-2 mAbs resulted in viral clearance in

13 of 14 episodes (92.8%). Patients receiving no therapy did not clear SARS-CoV-2.
Conclusions: COVID-19 can present as a chronic or relapsing disease in patients with antibody deficiency. Remdesivir monotherapy is frequently associated with treatment failure, but the combination of remdesivir with antibody-based therapeutics holds promise. (J Allergy Clin Immunol 2022;149:557-61.)



Clinical implications: COVID-19 can become chronic in patients with immunodeficiency, and the optimal treatment for this situation remains unknown. Here, we have demonstrated that the combination of antivirals and antibody-based therapeutics is highly effective.

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

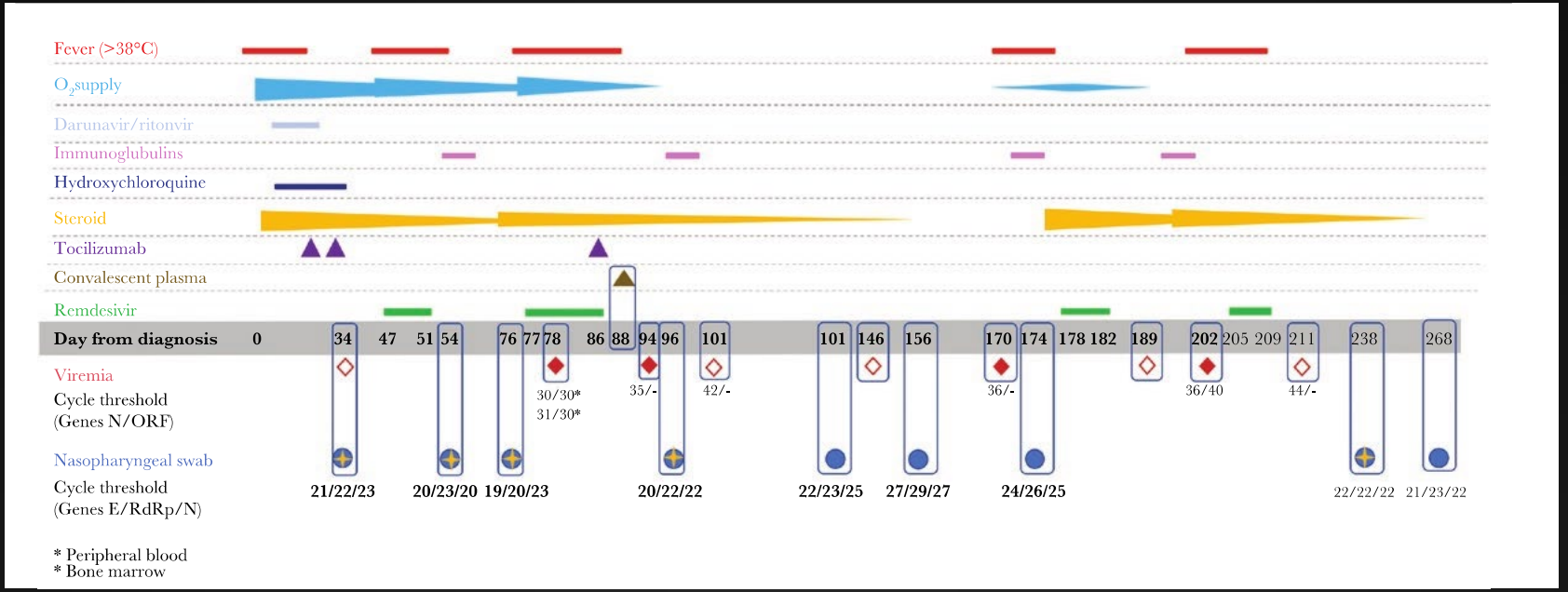
The Longest Persistence of Viable SARS-CoV-2 With Recurrence of Viremia and Relapsing Symptomatic COVID-19 in an Immunocompromised Patient—A Case Study

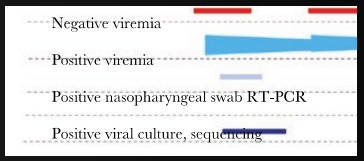
Chiara Sepulcri,[1,a] Chiara Dentone,[2,a] Malgorzata Mikulska,[1,2] Bianca Bruzzone,[3] Alessia Lai,[4] Daniela Fenoglio,[5,6] Federica Bozzano,[2] Annalisa Bergna,[4] Alessia Parodi,[6] Tiziana Altosole,[5] Emanuele Delfino,[2] Giulia Bartalucci,[7] Andrea Orsi,[3,8] Antonio Di Biagio,[1,2] Gianguglielmo Zehender,[9] Filippo Ballerini,[10] Stefano Bonora,[11] Alessandro Sette,[15,16] Raffaele De Palma,[6,12] Guido Silvestri,[13,14] Andrea De Maria,[1,2] and Matteo Bassetti[1,2]

Open Forum Infectious Diseases

MAJOR ARTICLE

2021



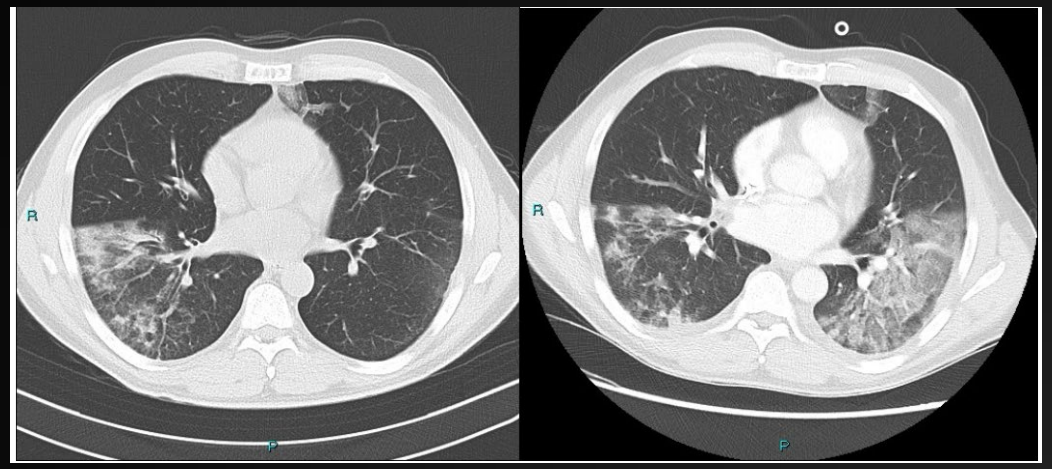


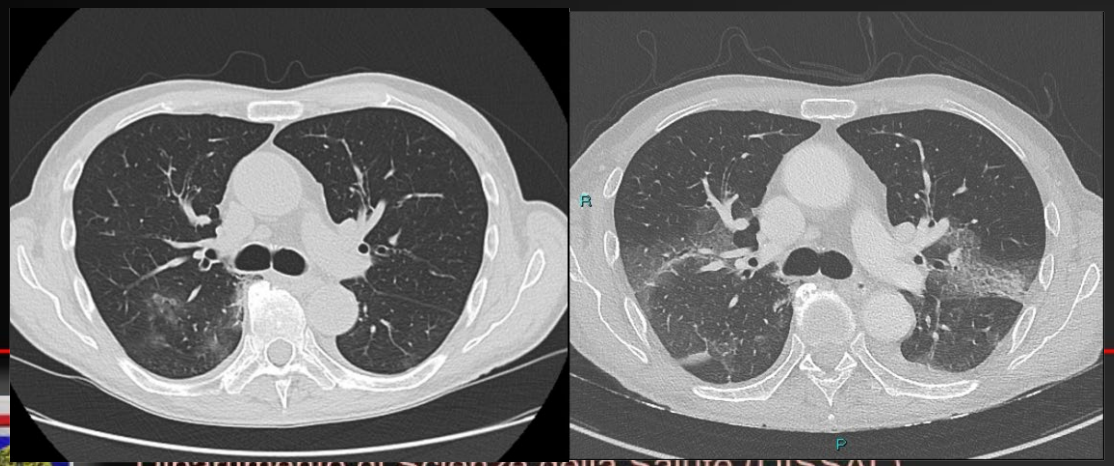
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Sotrovimab, remdesivir and nirmatrelvir/ritonavir combination as salvage treatment option in immunocompromised patients hospitalized for COVID-19

Baldi F et al Submitted





2 Pts trattati con rituximab (LNH e Wegener)
BAL SARS-COV-2 pos e viremia positiva

Pattern cellulare differente vs pt trattato solo con remdesivir o solo con monoclonale

Therefore, the analysis of the CD4+ and CD8+ T cell maps analyzed before and after combination therapy (sotrovimab, remdesivir, nirmatrelvir/ritonavir) and steroids in viremic and aviremic samples, respectively, would seem to highlight immunological patterns indicative of a resolution of the infection in the samples derived after therapies, such as the decrease of EOMES expression, the activation status and the reduction of granzyme level.

Peer Re

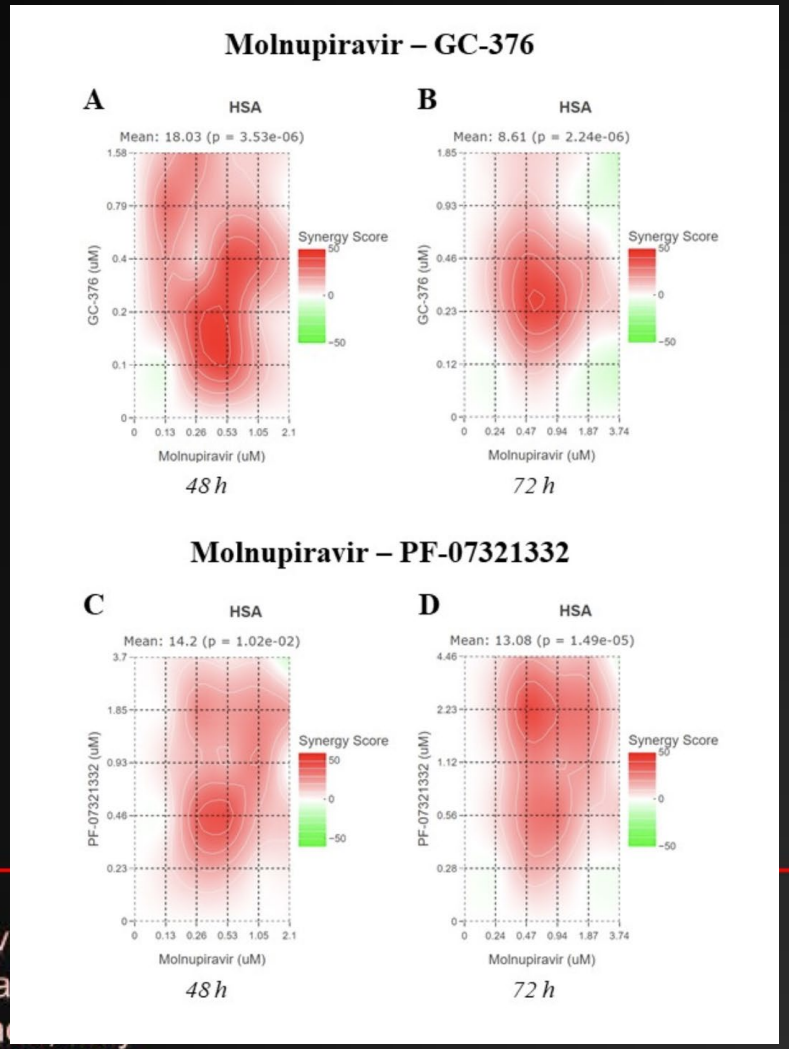
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

OC 25 In vitro activity of molnupiravir in combination with GC-376 or PF-07321332 against SARS-CoV-2

Authors: A. Gidari[1], S. Bastianelli[1], S. Pierucci[1], C. Busti[1], S. Sabbatini[2], G. Genga[1], E. Svizzeretto[1], A. Tommasi[1], E. Schiaroli[1], D. Francisci[1]

Affiliation: [1]Department of Medicine and Surgery, Clinic of Infectious Diseases, "Santa Maria della Misericordia" Hospital, University of Perugia, Perugia, Italy, [2]Department of Medicine and Surgery, Medical Microbiology Section, University of Perugia, Perugia, Italy



In vitro Effetto sinergico molnupiravir e nirmatrelvir a 48 h e a 72 ore

Nuova combinazione sinergica anti SARS-COV-2
Next step: studi preclinici e trials su popolazioni a rischio

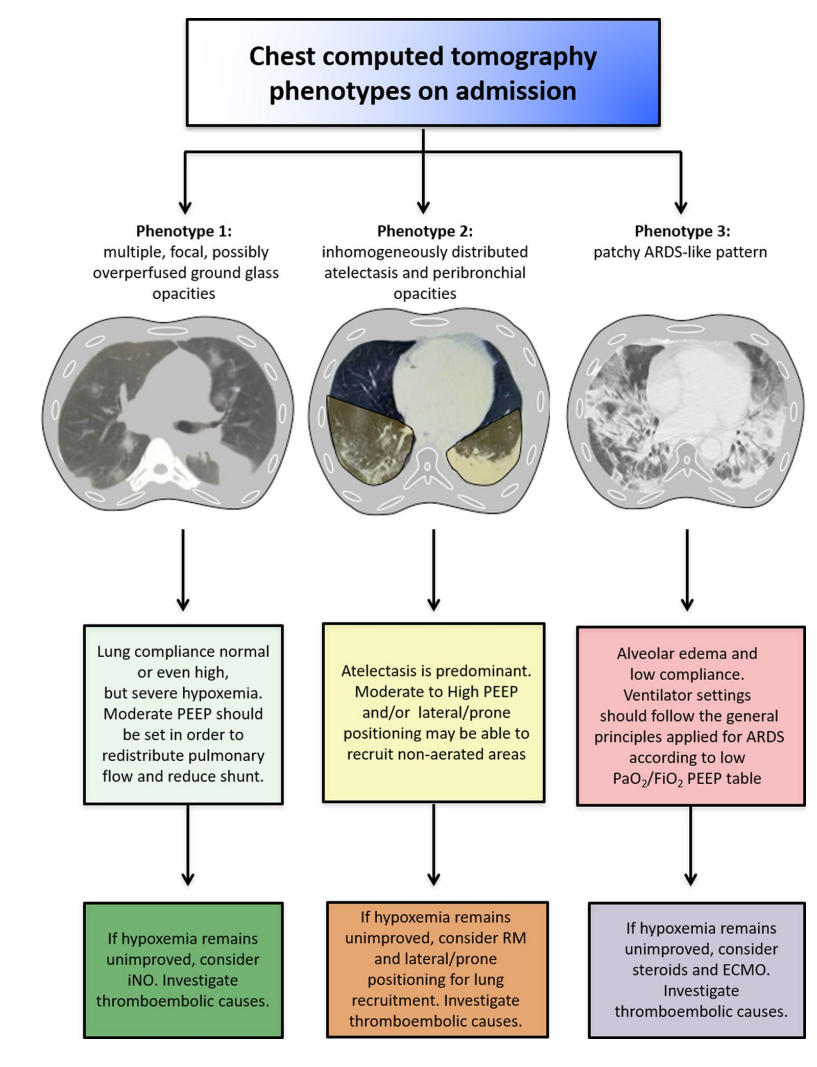
Nel paziente con severe e/o critical COVID-19 il Respiratory management (tecnica e timing) va individualizzato su paziente?

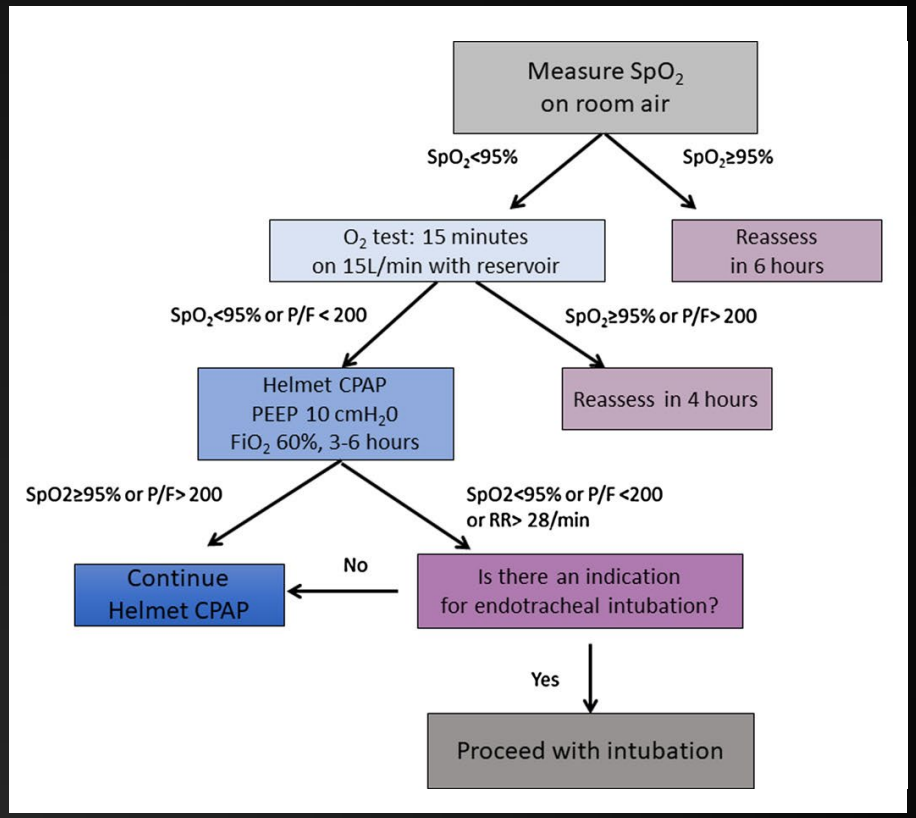
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Distinct phenotypes require distinct respiratory management strategies in severe COVID-19

Chiara Robba[a,*], Denise Battaglini[a,b], Lorenzo Ball[a,b], Nicolo' Patroniti[a,b], Maurizio Loconte[a], Iole Brunetti[a], Antonio Vena[c,d], Daniele Roberto Giacobbe[c,d], Matteo Bassetti[c,d], Patricia Rieken Macedo Rocco[e,1], Paolo Pelosi[a,b,1]





Respiratory Physiology & Neurobiology

Università
Dipartime
Genoa, It
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

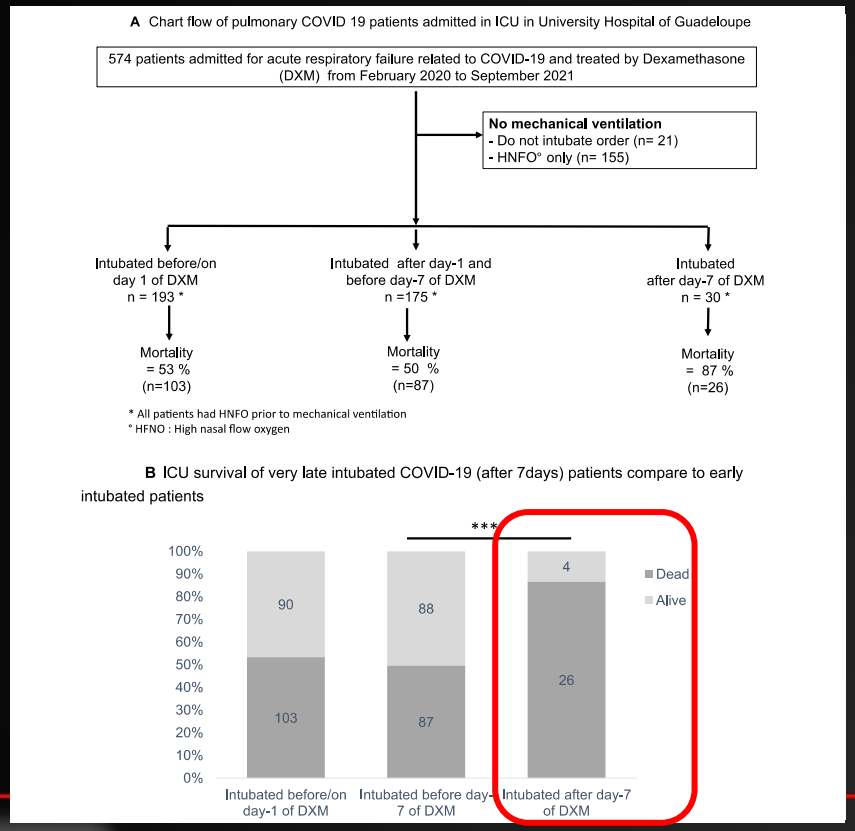
2020

Very late intubation in COVID-19 patients: a forgotten prognosis factor?

Camous L, et al Crit Care 2022

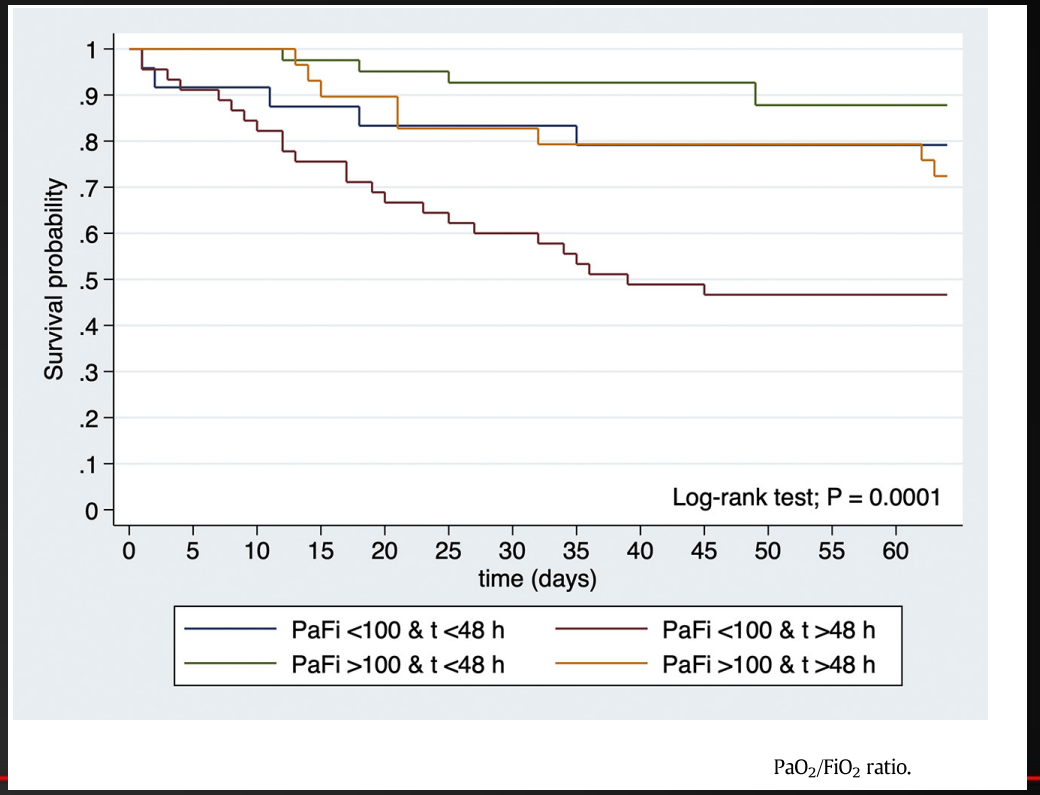
Vera M, et al. J Crit Care 2021

Studio retrospettivo monocentrico



In COVID-19 pts, late intubation after 7 gg DXM were associated with high ICU mortality (87%)

Studio prospettico osservazionale monocentrico



PaO_2/FiO_2 ratio.

In COVID-19 pts, late intubation, P/F < 100 > 48 h, older age were associated with increased ICU mortality

COVID-19: Sono già due anni. Come si cura oggi in Ospedale?

Arrivo ed utilizzo del Vaccino

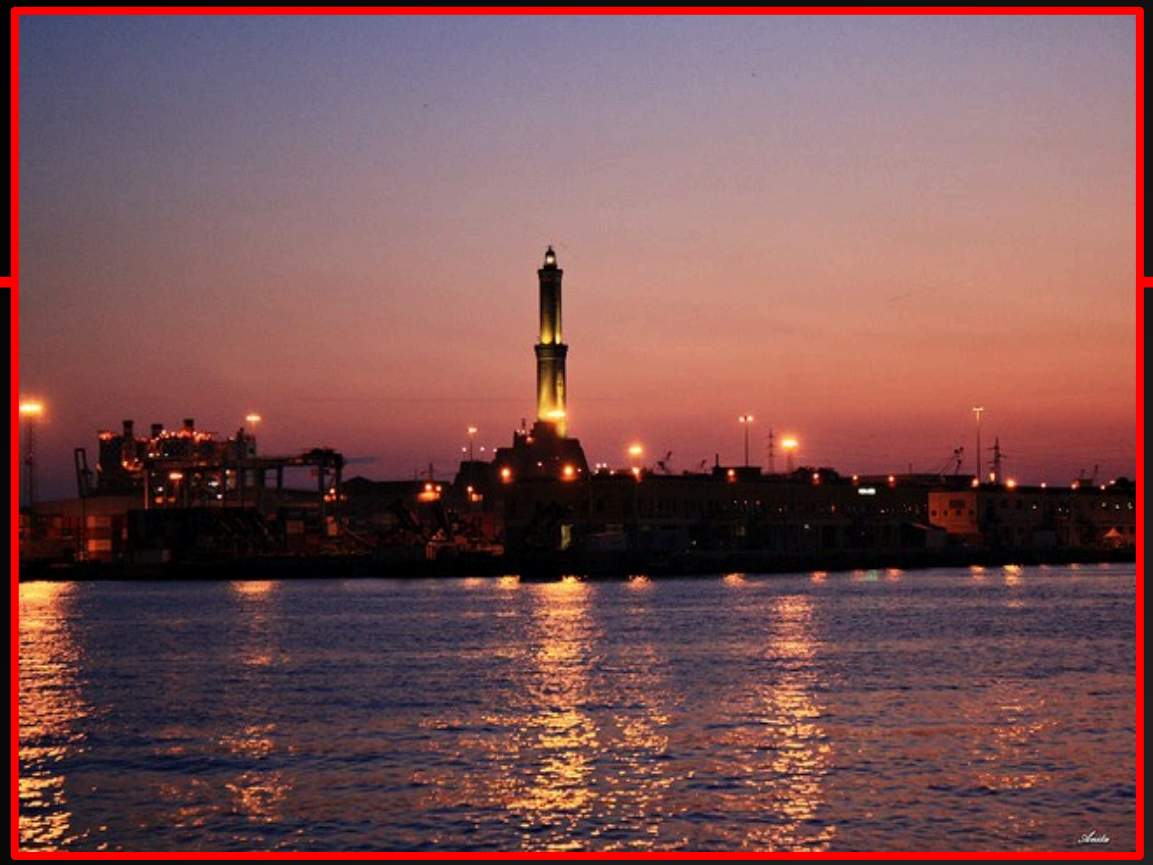
Terapia individualizzata su ospite

Ampia Conoscenza e Real life Experience

Work Together, Fast and Effective

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy



Grazie….

Università degli Studi di Genova
Dipartimento di Scienze della Salut
Genoa, Italy

Clinica Malattie Infettive
liclinico San Martino IRCCS
Genoa, Italy