



Long COVID in età pediatrica

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Long COVID in età pediatrica

1. Long COVID in età pediatrica:
cosa ci dice la letteratura scientifica



2. La nostra esperienza su circa
600 bambini con pregressa infezione da
SARS-CoV-2



Long Covid: definizione

- Sintomi persistenti che si protraggono al di fuori dell'infezione acuta



A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021
(WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1)

Post COVID-19 condition occurs in individuals with a history of probable or confirmed **SARS-CoV-2** infection. usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.

Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others* and generally have an **impact on everyday functioning**. Symptoms may be **new onset** following initial recovery from an acute COVID-19 episode or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time.

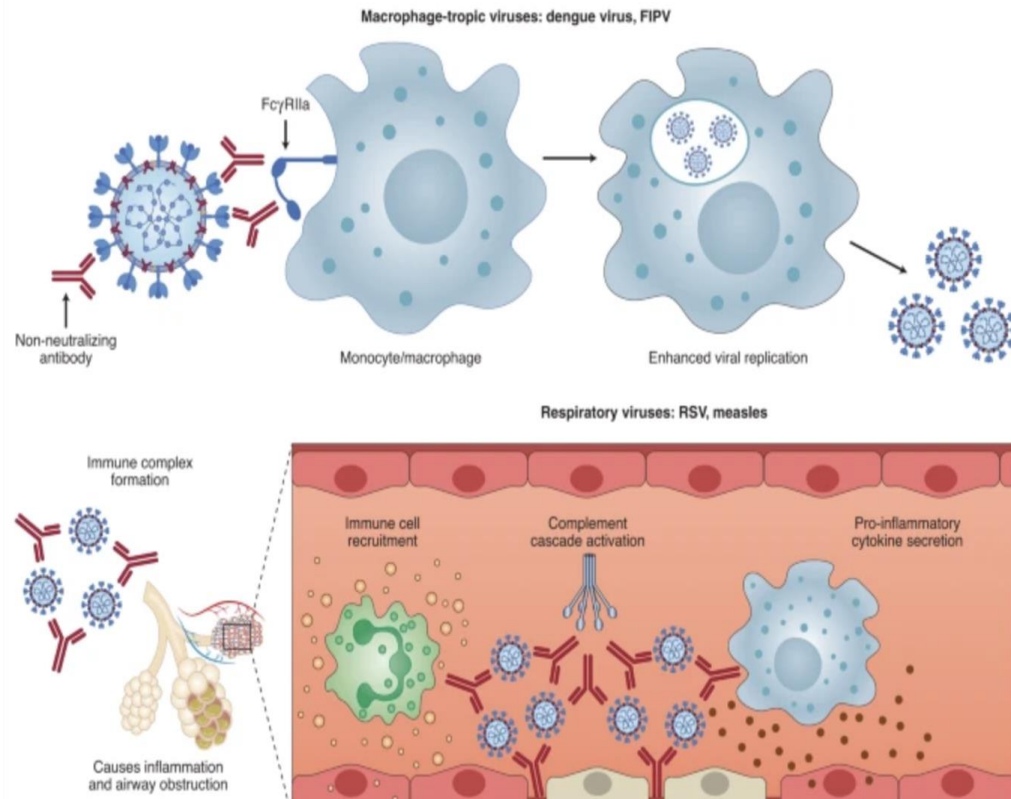


Long COVID: patogenesi

Gli anticorpi anti-SARS-CoV-2 possono esacerbare i sintomi del COVID-19 attraverso il **meccanismo dell' ADE** (antibody-dependent enhancement)



anticorpi non neutralizzanti si legano al virus senza riuscire a distruggerlo → **immunocomplessi** → **infiammazione** (richiamo di **citochine** proinfiammatorie e attivazione della **cascata del complemento**)



Long Covid

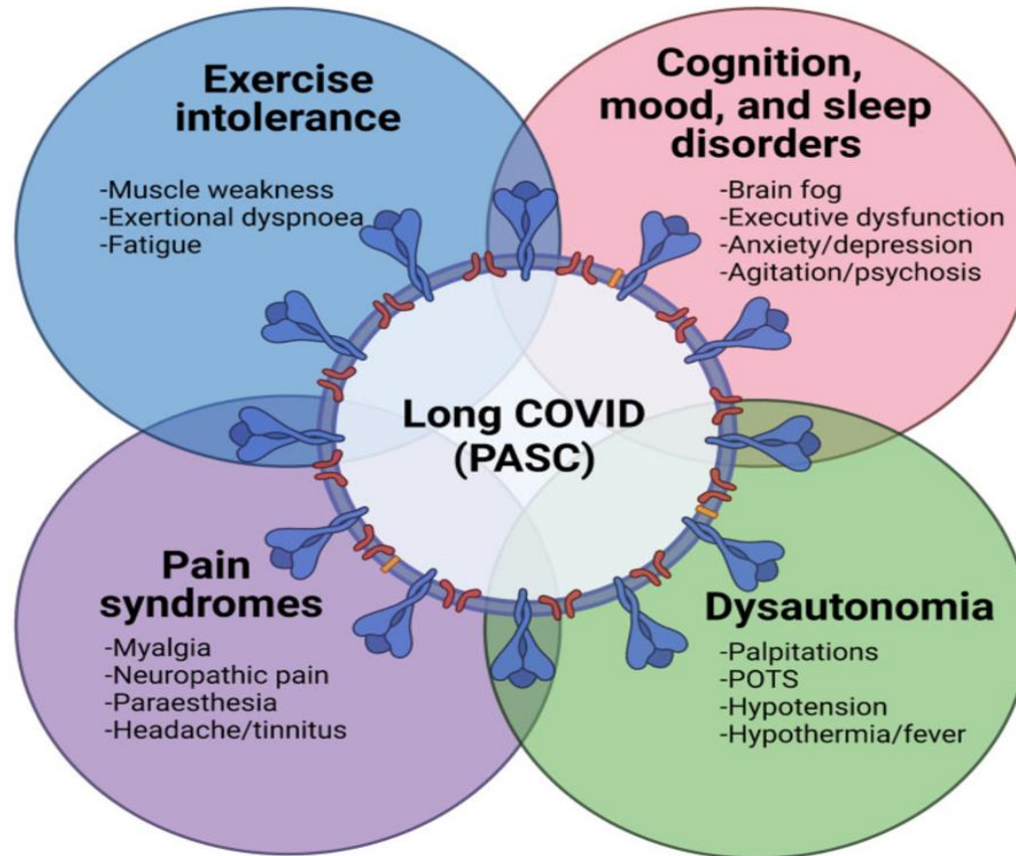


Figure 3 Chronic neurological sequelae of COVID-19. Several long-term neurological syndromes result from SARS-CoV-2 among hospital- and community-treated patients, termed long COVID or post-acute sequelae of COVID-19 (PASC). These syndromes include neurocognitive, mood and sleep disorders, dysautonomia, diverse pain syndromes, as well as marked exercise intolerance and fatigue. These protracted syndromes remain to be fully defined in longitudinal cohort studies.

Balcom et al, Brain 2021



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Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2



Erika Molteni*, Carole H Sudre*, Liane S Canas, Sunil S Bhopal, Robert C Hughes, Michela Antonelli, Benjamin Murray, Kerstin Kläser, Eric Kerfoot, Liyuan Chen, Jie Deng, Christina Hu, Somesh Selvachandran, Kenneth Read, Joan Capdevila Pujol, Alexander Hammers, Tim D Spector, Sebastien Ourselin, Claire J Steves, Marc Modat, Michael Absoud, Emma L Duncan

- ❖ Although COVID-19 in children is usually of **short duration with low symptom burden**, some children with COVID-19 experience prolonged illness duration.
- ❖ Symptom burden in these children did not increase with time, and **most recovered by day 56**.
- ❖ A **holistic approach** for all children with persistent illness during the pandemic inappropriate.

Lancet Child Adolesc Health 2021; 5: 708–18. Published Online August 3, 2021. [https://doi.org/10.1016/S2352-4642\(21\)00198-X](https://doi.org/10.1016/S2352-4642(21)00198-X)



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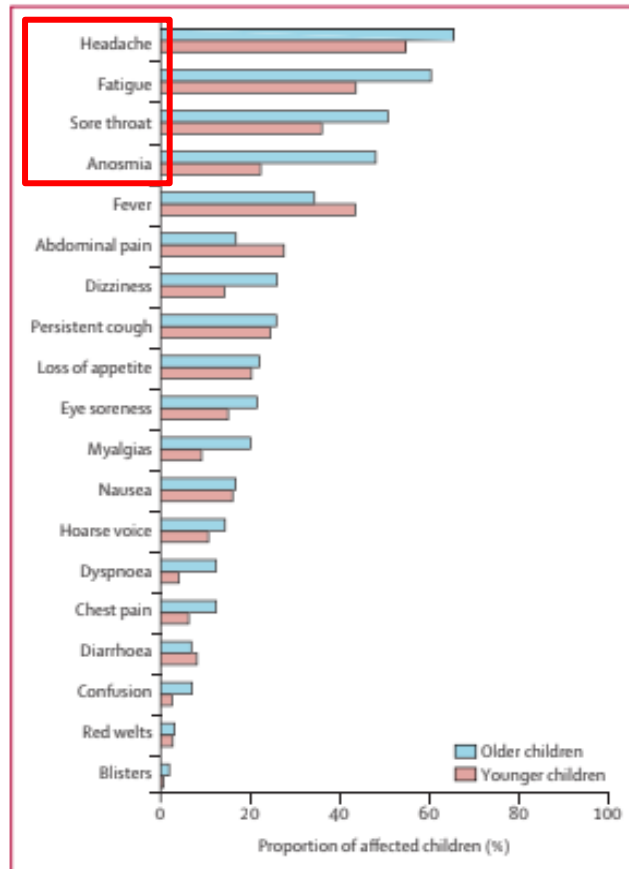


Figure 2: Prevalence of symptoms reported over the course of illness in younger (age 5-11 years, n=588) and older (age 12-17 years, n=1146) children testing positive for SARS-CoV-2

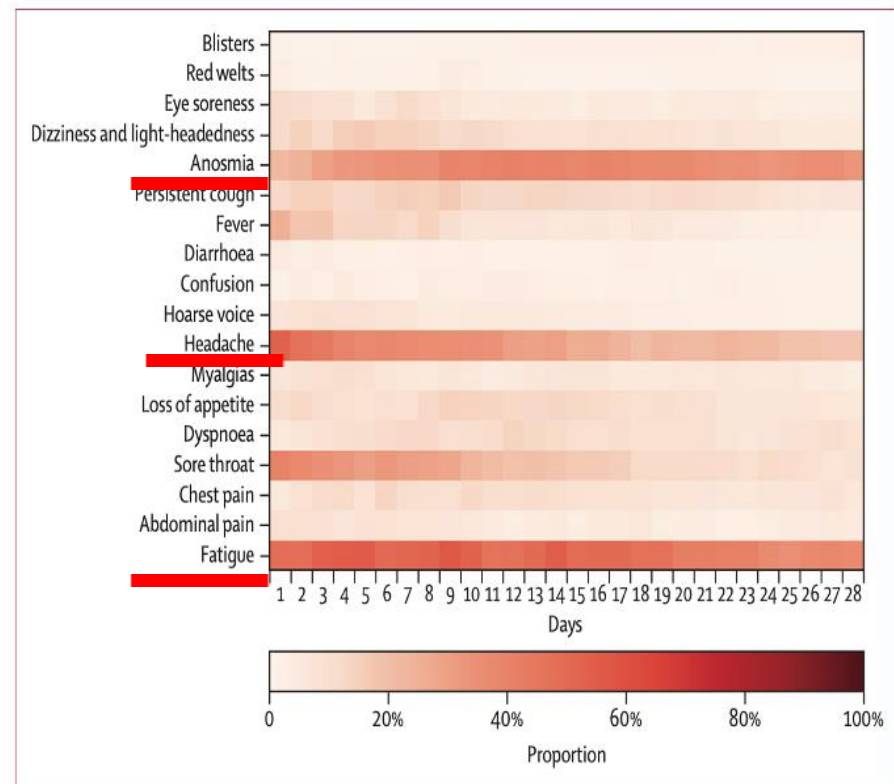


Figure 4: Heat maps showing symptom duration in school-aged children (age 5-17 years) testing positive for SARS-CoV-2 in whom at least one symptom persisted for at least 28 days (n=77). Colour bar provides a percentage comparison. Data refers to children with symptom onset between Sept 1, 2020, and Jan 24, 2021.

Epatite acuta grave e COVID-19



- ❖ 650 probable cases of **acute hepatitis of unknown aetiology in children** from 33 countries between 5 April and 26 May 2022.
- ❖ While **adenovirus** is a plausible hypothesis, further investigations are ongoing for the causative agent; adenovirus infection **does not fully explain the more severe clinical picture** observed
- ❖ **Increased susceptibility** amongst young children following a lower level of circulation of adenovirus during the COVID-19 pandemic, the potential emergence of **a novel adenovirus, SARS-CoV-2 co-infection** or a **complication of previous SARS-CoV-2 infection** proposed a causal mechanism of multisystem inflammatory syndrome in children need to be further investigated
- ❖ Hypotheses related to side effects from **COVID-19 vaccines** are currently not supported as most of the affected children did not receive these vaccines



e dal punto di vista pneumologico?

Long COVID in Children

Observations From a Designated Pediatric Clinic

Ashkenazi-Hoffnung, Liat MD^{*,†}; Shmueli, Einat MD^{*,†}; Ehrlich, Shay MD^{*,†}; Ziv, Adi MD^{*,†}; Bar-On, Ophir MD^{*,†}; Birk, Einat MD^{*,†}; Lowenthal, Alexander MD^{*,†}; Prais, Dario MD^{*,†}

Author Information ☺

The Pediatric Infectious Disease Journal: December 2021 - Volume 40 - Issue 12 - p e509-e511
doi: 10.1097/INF.00000000000003285



Pulmonary evaluation

Chest radiograph changes	12 (133) ^{††}
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Pulmonary function tests

Abnormal spirometry, FEV1 < 80% or FEV1/FVC < 0.8, n = 60	5 (8.3)
Abnormal exercise challenge test, ^{‡‡} ΔFEV1 ≥ 12%, n = 51	3 (5.9)
Positive bronchodilator response, ΔFEV1 ≥ 12%, n = 29	15 (51.7)
Air trapping by plethysmography, RV/TLC > 125%, n = 55	15 (27.3)
Diffusion capacity < 70%, n = 50	1 (2.0) ^{§§}





I nostri dati

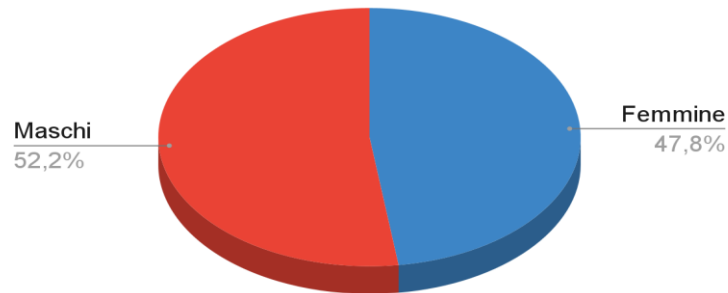


- ❖ **589 bambini** tra **gli 0 e i 18 anni** con **pregressa infezione da SARS-CoV-2**
- ❖ Hanno effettuato:
 - **visita pneumologica**
 - **prove di funzionalità respiratoria**
 - **ecografia polmonare**
 - **valutazione neuropsicologica**
- ❖ Sono state **raccolte informazioni demografiche e dati anamnestici** riguardo all'**infezione da SARS-CoV-2**

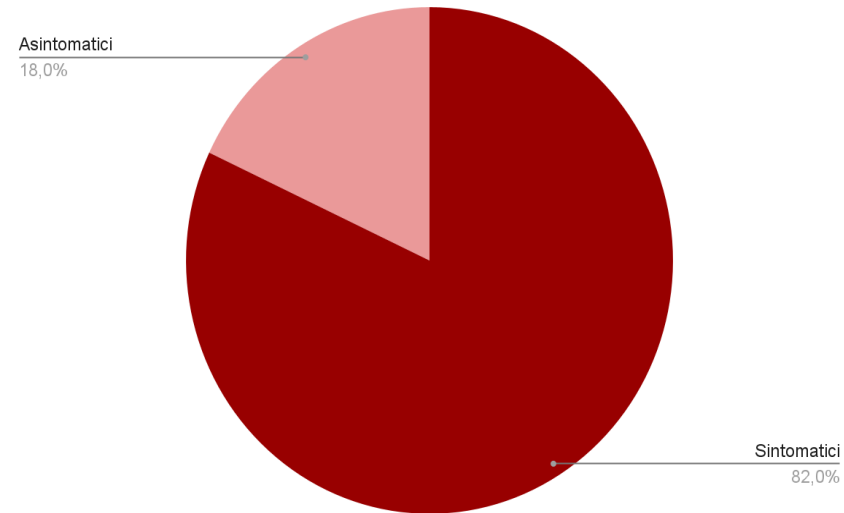
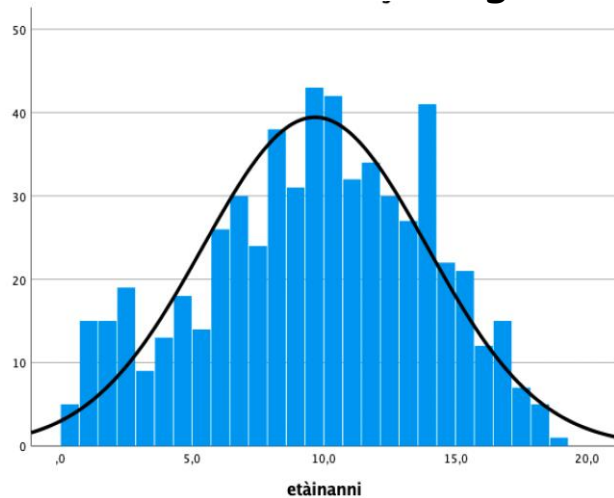


589 bambini con pregressa infezione da SARS-CoV-2

Sesso



Età in anni (mediana, range) 9,8 (0,1-18,6)

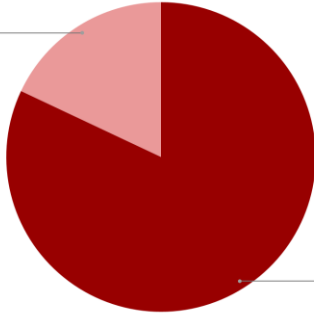


Caratteristiche cliniche in fase acuta

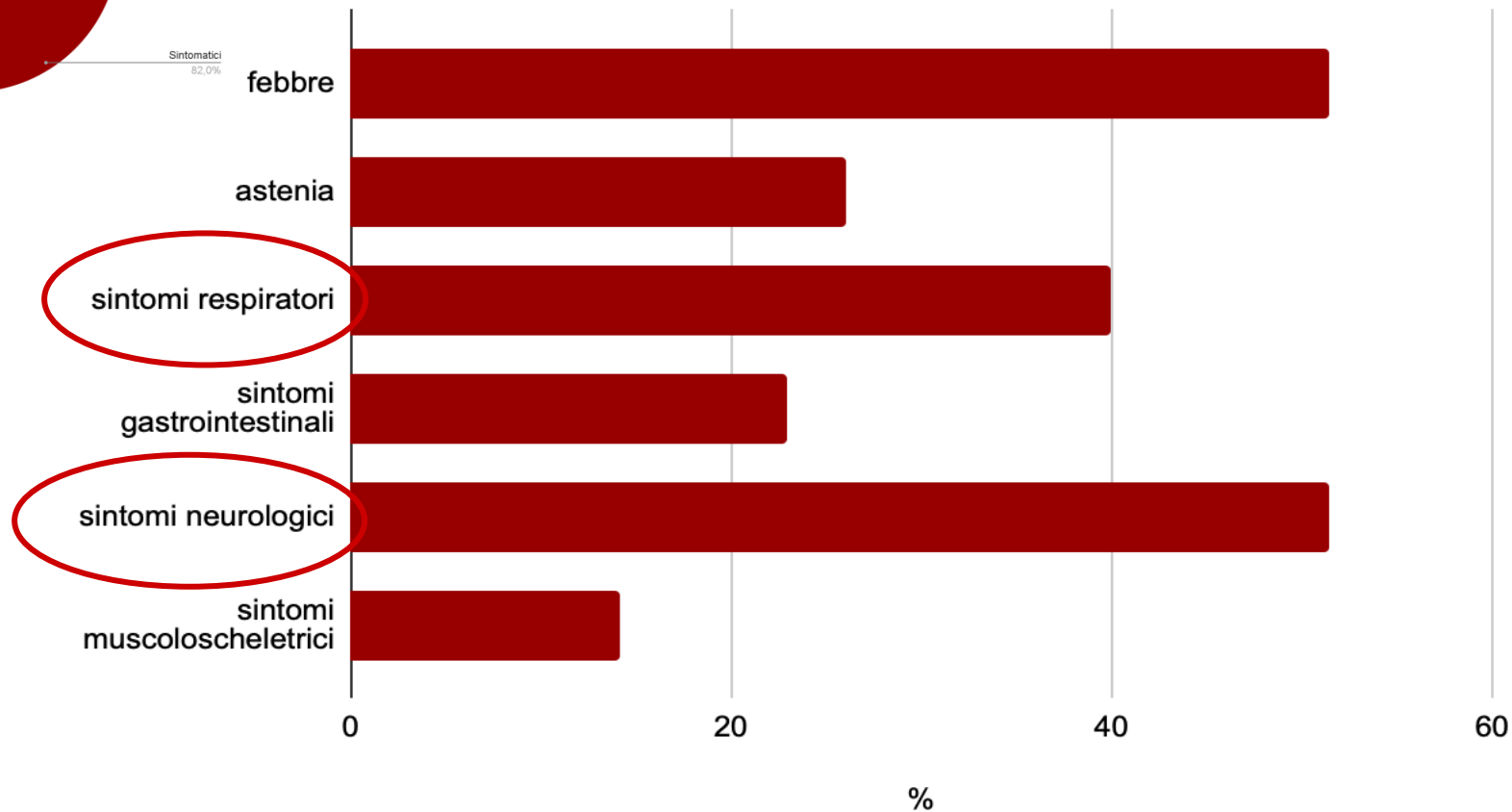


Caratteristiche cliniche nella fase acuta di infezione da SARS-CoV-2

Asintomatici
18,0%



Sintomatici
82,0%



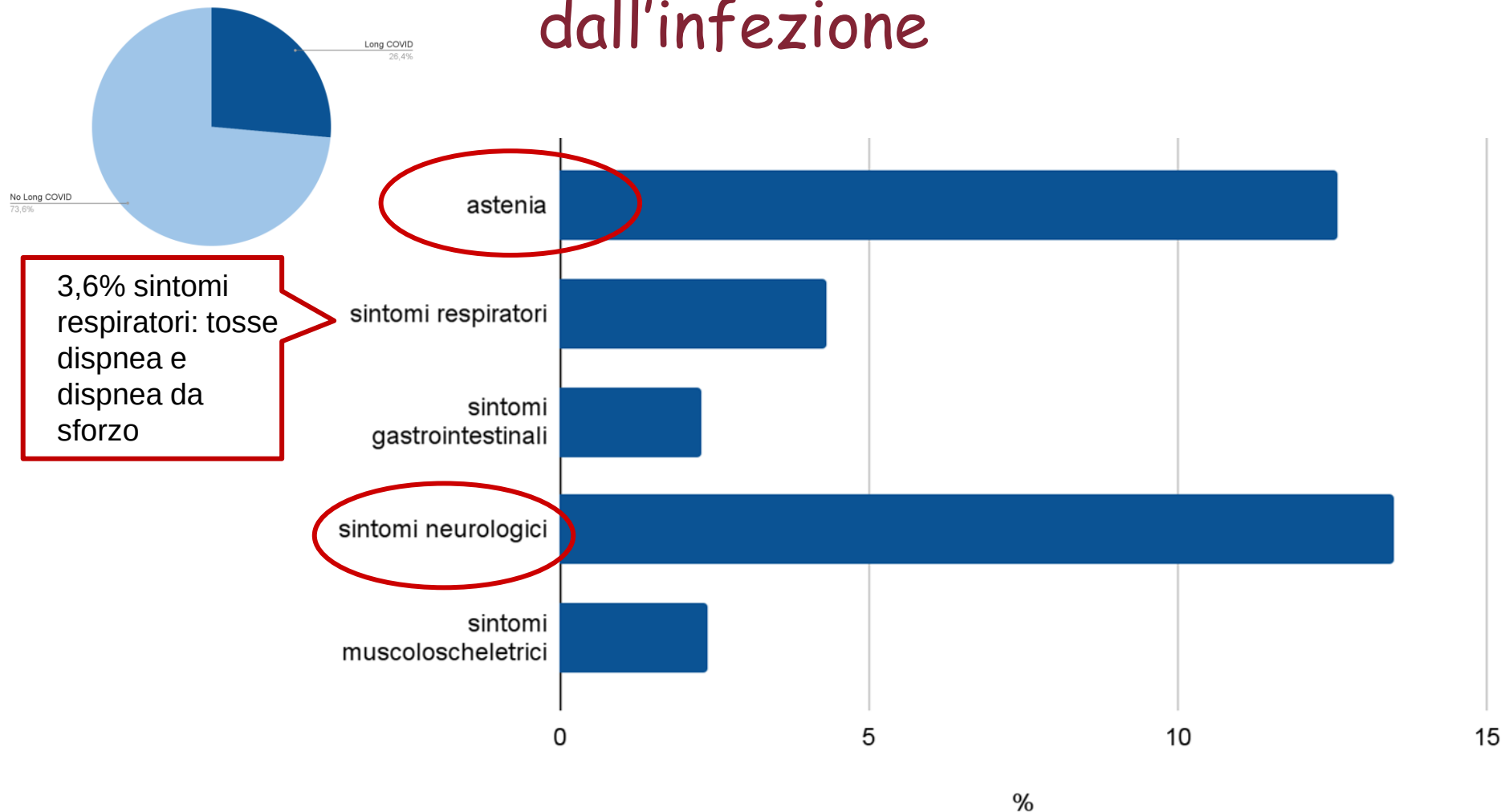
Quanti bambini hanno sintomi persistenti?



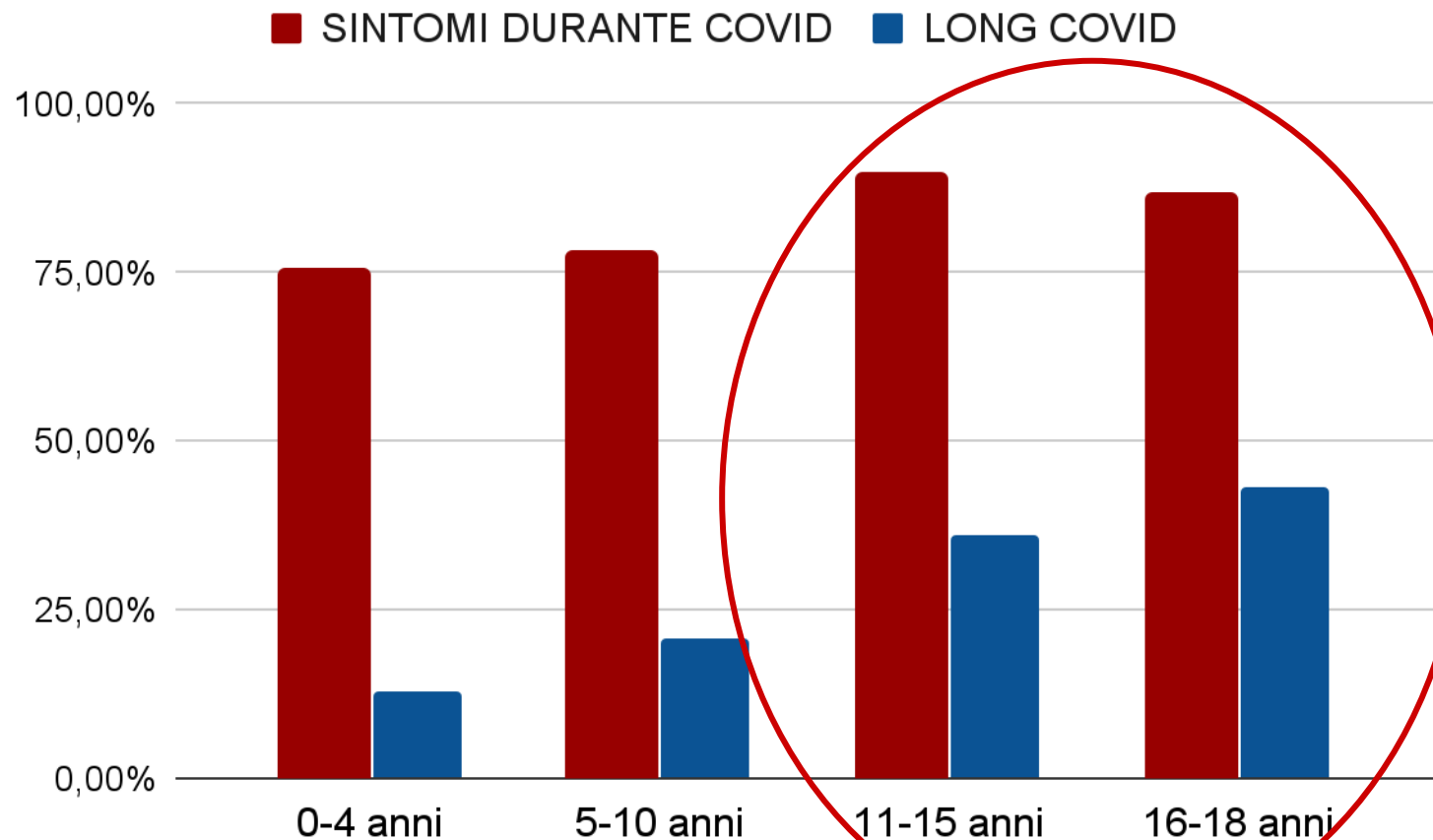
Nessuna differenza significativa tra maschi e femmine



Caratteristiche cliniche dei bambini con sintomi dopo 30 giorni dall'infezione



Sintomi in fase acuta e del Long Covid nella popolazione divisa per fasce d'età



Associazione tra sintomi in fase acuta e a distanza di 30 giorni

	Pazienti con sintomi dopo 30 giorni N= 154	Pazienti senza sintomi dopo 30 giorni N= 435	<i>p-Value</i>
Sintomi (%)	92,7	78,0	<i><0,001</i>
Più di 5 sintomi (%)	39,6	12,6	<i><0,001</i>
Dispnea (%)	18,8	3,0	<i><0,001</i>
Sintomi neurologici (%)	72,7	43,9	<i><0,001</i>
Astenia (%)	40,9	20,9	<i><0,001</i>



Valutazione pneumologica: dati preliminari su 589 bambini

- Spirometrie valutabili: 433/589 (73,5%)

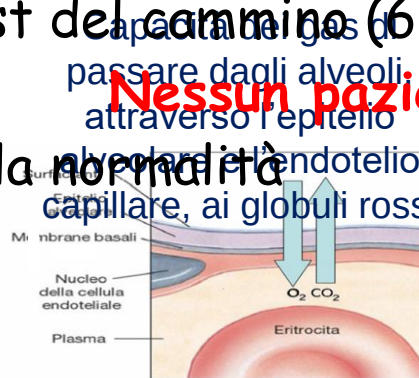
Pazienti con PRE FEV1 $\leq$ 80%: 14 su 433 (3,2%)

- DLCO valutabili: 78/589 (13,2%)

Pazienti con DLCO/VA $\leq$ 80%: 12 su 78 (15,4%)

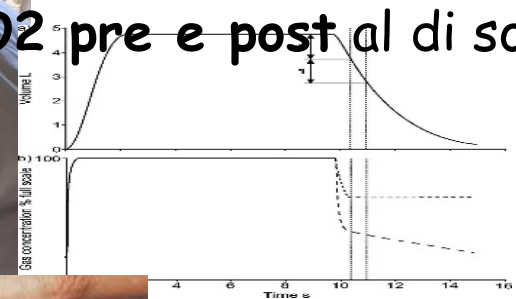
- Test del cammino (6MWT): 376 su 589 bambini (63,8%)

Nessun paziente con valori di SpO₂ pre e post al di sotto della normalità



Strutture comprese nella membrana alveolo-capillare.

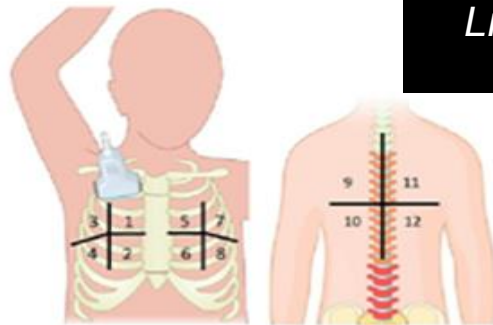
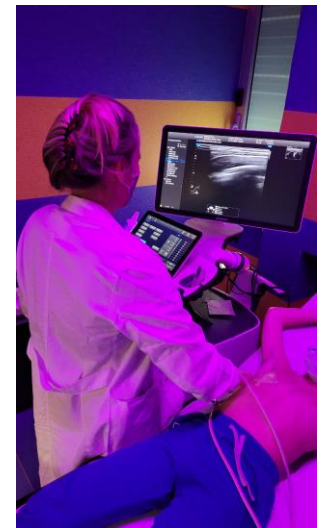
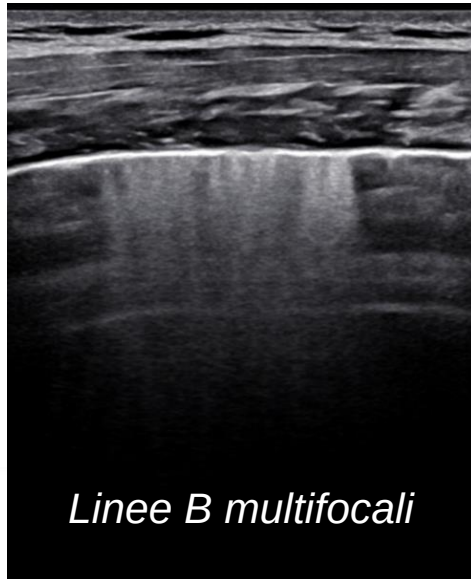
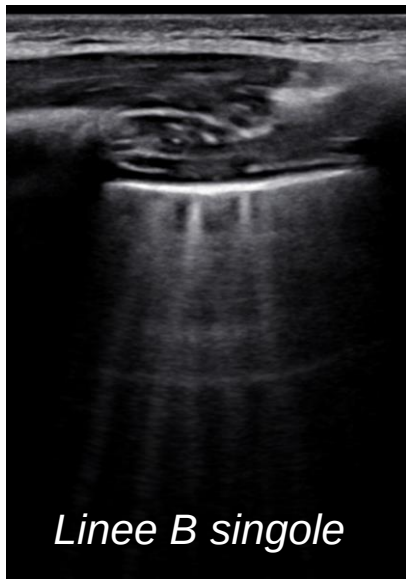
Pifferi M. et al. La diffusione alveolo-capillare in età pediatrica. *Pneumologia Pediatrica*. Volume 16, numero 62, giugno 2016 www.simri.it



Standardisation of the single-breath determination of gas uptake in the lung. *Eur Respir J*. 2005



Ecografia Polmonare: 532 bambini



Ecografia Polmonare

Pattern ecografici per ogni quadrante

A1

Linea pleurica regolare senza segni di interruzione. A livello subpleurico presenza di linee A o massimo 2 Linee B “isolate” e non confluenti.

A2

Linea pleurica irregolare (granulare, ondulata, ispessita). A livello subpleurico presenza di linee A o massimo 2 Linee B “isolate” e non confluenti.

B1

Presenza di **linee B multiple** (>2 per quadrante) non confluenti (multifocali) e/o addensamenti subpleurici **< 0.5 cm**

B2

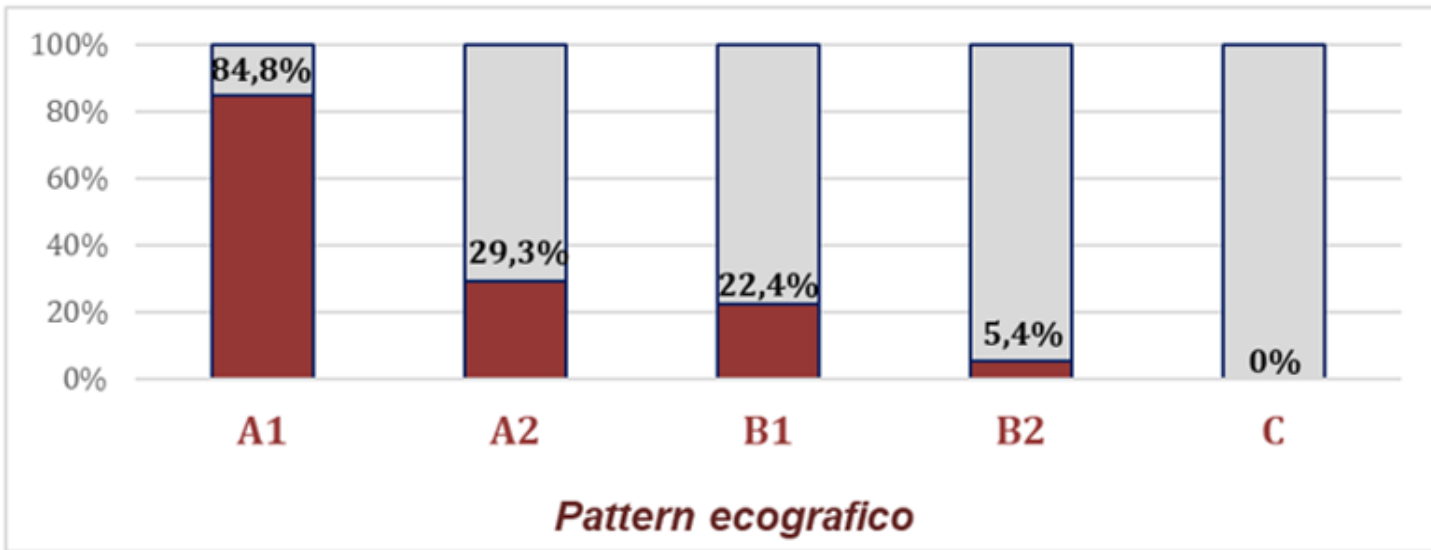
Presenza di **linee B multiple addensate/confluenti** o white lung e/o addensamenti subpleurici **0.5-1cm**

C

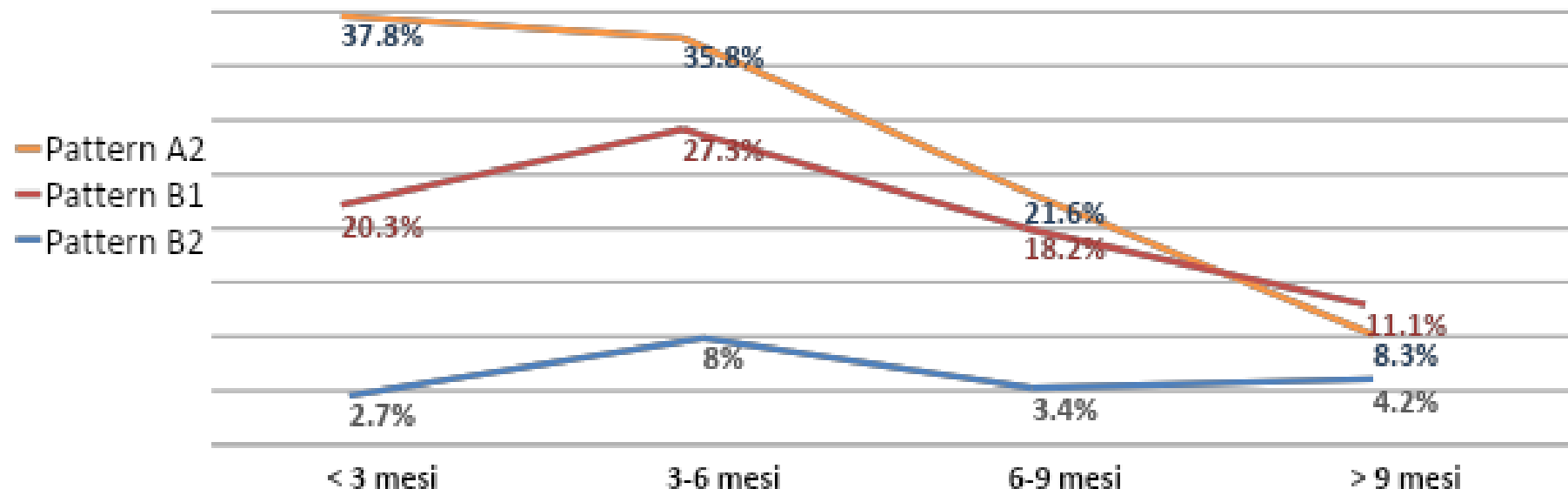
Presenza di consolidamenti subpleurici **>1cm**



Ecografia Polmonare



Ecografia Polmonare



Distribuzione dei pattern ecografici in relazione al tempo tra infezione da SARS-CoV-2 e visita.

N=532

		Pattern A2	Pattern B1	Pattern B2
Intervallo di tempo tra infezione e visita	< 3 mesi (N=74)	27 (37,8%)	15 (20,3%)	2 (2,7%)
	3-6 mesi (N=238)	86 (35,8%)	65 (27,3%)	19 (8,0%)
	6-9 mesi (N=148)	32 (21,6%)	27 (18,2%)	5 (3,4%)
	>9 mesi (N=72)	6 (8,3%)	8 (11,1%)	3 (4,2%)
P-Value		< 0,001	0,012	0,145



Associazione tra Long COVID e risposta immunitaria innata

Dati preliminari su una coorte di 10 pazienti con pregresso COVID-19 e con sintomi di **Long COVID** e di 10 pazienti con pregresso COVID-19 ma **senza sintomi di Long COVID**

- ❖ I Long COVID avevano una significativa **down regolazione degli Interferoni di tipo I** rispetto ai non Long COVID.
- ❖ I Long COVID e i pazienti con pregresso COVID-19 ma senza sintomi di Long COVID avevano una **maggiore espressione dei miR-141** rispetto ai controlli negativi.

Lo stato infiammatorio prolungato, legato ad una disregolazione della risposta dell'interferone e dei microRNA coinvolti nell'infiammazione, potrebbe essere responsabile dei sintomi di Long COVID



Case Report

Serum NGF and BDNF in Long-COVID-19 Adolescents: A Pilot Study

Carla Petrella ^{1,†}, Raffaella Nenna ^{2,†}, Laura Petrarca ², Francesca Tarani ², Roberto Paparella ²,
Enrica Mancino ², Greta Di Mattia ², Maria Giulia Conti ², Luigi Matera ², Enea Bonci ³, Flavio Maria Ceci ³,
Giampiero Ferraguti ³, Francesca Gabanella ¹, Christian Barbato ¹, Maria Grazia Di Certo ¹, Luca Cavalcanti ⁴,
Antonio Minni ⁴, Fabio Midulla ², Luigi Tarani ^{2,†} and Marco Fiore ^{1,*}

- ❖ NGF serum content was lower in post-infected-COVID-19 individuals when compared to healthy controls.
- ❖ BDNF levels were found to be higher compared to healthy individuals only in post-infected-COVID-19 symptomatic and future long-COVID-19 girls, leaving the BDNF levels unchanged in asymptomatic individuals if compared to controls.
- ❖ We predicted that NGF and/or BDNF could be used as early biomarkers of COVID-19 morbidity in adolescents.

In conclusione, in base alla nostra esperienza....

- ❖ Nonostante l' infezione da SARS-CoV-2 in età pediatrica decorra in maniera **asintomatica o paucisintomatica** nella maggior parte dei casi, circa un **quarto dei bambini** con infezione da SARS-CoV-2 presenta **sintomi persistenti**.
- ❖ I **sintomi di Long COVID** sono prevalentemente **neurologici e comportamentali**; solo il 3,6% presenta sintomi respiratori
- ❖ I **sintomi di Long COVID** non peggiorano nel tempo, tendono anzi a **diminuire** e la maggior parte **scompare** entro 90 giorni
- ❖ **Lo stato infiammatorio prolungato** potrebbe essere responsabile dei sintomi di Long COVID.





Grazie per l'attenzione



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