

Long-Term effects of COVID-19

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Disclosures

Cristina Mussini has served as a paid consultant to Gilead Sciences, Angelini, Abbvie, Janssen, MSD, ViiV Healthcare and received research fundings from Gilead Sciences, Janssen, MSD and ViiV Healthcare.

SARS-CoV-2 Can Affect Organs Other than Respiratory Tract

JAMA Neurology | Original Investigation

Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China

Ling Mao, Huijuan Jin, Mengdie Wang, Yi He, Shengzhi Chen, Qianwei He, Jang Chang, Congdong Hong, Yilan Zhou, David Wang, Xiaoping Miao, Yanan Li, MD, PhD, Bo Hu, MD, PhD

Acute cerebrovascular disease, impaired consciousness, skeletal muscle injury

Chen L, et al. *Br J Ophthalmol* 2020;0:1-4. doi:10.1136/bjophthalmol-2020-316304



Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease

Lu Chen, Meizhou Liu, Zheng Zhang, Kun Qiao, Ting Huang, Miaohong Chen, Na Xin, Zuliang Huang, Lei Liu, Guoming Zhang, Jiantao Wang

Systemic Disorders

Fever, Cough, Fatigue, Sputum Production, Headache

Respiratory Disorders

Rhinorrhoea, Sneezing, Sore Throat

Conjunctivitis

Smell, taste

Pneumonia

Haemoptysis,

Acute Cardiac Injury

Ground-glass Opacities

Hypoxemia

RNAemia, Acute Respiratory Distress Syndrome

Dyspnoea, Lymphopenia

Diarrhoea

Kidney

JAMA Cardiology | Original Investigation

Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China

Shaobo Shi, MD, Mu Qin, MD, Bo Shen, MD, Yuli Cai, MD, Tao Liu, MD, Fan Yang, MD, Wei Gong, MMSc, Xu Liu, MD, PhD, Jinyun Liang, MD, Qiyun Zhao, MD, PhD, He Huang, MD, PhD, Do Yang, MD, PhD, Congchun Huang, MD, PhD



Two Cases of COVID-19 Related Cardiomyopathy in Pregnancy.

Alexander Juusela, MD, MPH, Munir Nazir, MD, Martin Gimovsky, MD.

JAMA Otolaryngology-Head & Neck Surgery | Published online April 8, 2020

OBSERVATION

Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19

European Archives of Otorhinolaryngology
https://doi.org/10.1007/s00405-020-05965-1

RHINOLOGY

Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study

Jerome R. Lechien^{1,2,3,4}, Carlos M. Chiesa-Estomba^{1,5}, Daniele R. De Sio^{1,6}, Mihaela Horac⁴, Serge D. Le Bon⁴, Alexandra Rodriguez⁴, Didier Duquanter⁴, Serge Bleic⁴, Fahd El Afia^{1,3}, Lea Distinguin^{1,3}, Younes Chekkouy-Idrissi^{1,6}, Stephane Hans¹, Irene Lopez Delgado^{1,6}, Christian Calvo-Henriquez^{1,6}, Philippe Lavigne^{1,6}, Chiara Falanga^{1,11}, Maria Rosaria Barberi^{1,11}, Giovanni Cammarota^{1,11}, Mohamed Khalife^{1,11}, Pierre Leclerc^{1,11}, Christel Souchay^{1,11}, Camilla Rossi^{1,11}, Fabrice Joume^{1,11}, Julien Hsieh^{1,11}, Mylène Edjbal^{1,11}, Robert Carlier^{1,11}, Laurence Ris^{1,11}, Andrea Lovato^{1,11}, Cosimo De Filippi^{1,11}, Frederique Coppez^{1,11}, Nicolas Fakhry^{1,11}, Tarek Ayad^{1,11}, Sven Saussez^{1,11,12}

Lin L, et al. *Gut* 2020;0:1-5. doi:10.1136/gutjnl-2020-321013

Gut immunity

ORIGINAL RESEARCH

Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection

Lu Lin, Xiayang Jiang, Zhenling Zhang, Shwen Huang, Zhenyi Zhang, Zhaoxiong Fang, Zhiqiang Gu, Liangqing Gao, Honggang Shi, Lei Ma, Yuan Liu, Xiangqi Lin, Renxu Lai, Zhixiang Yan, Xiaofeng Li, Hong Shan

Perotti et al. *Crit Care* 2020;24:139
https://doi.org/10.1186/s13054-020-2872-2

Critical Care

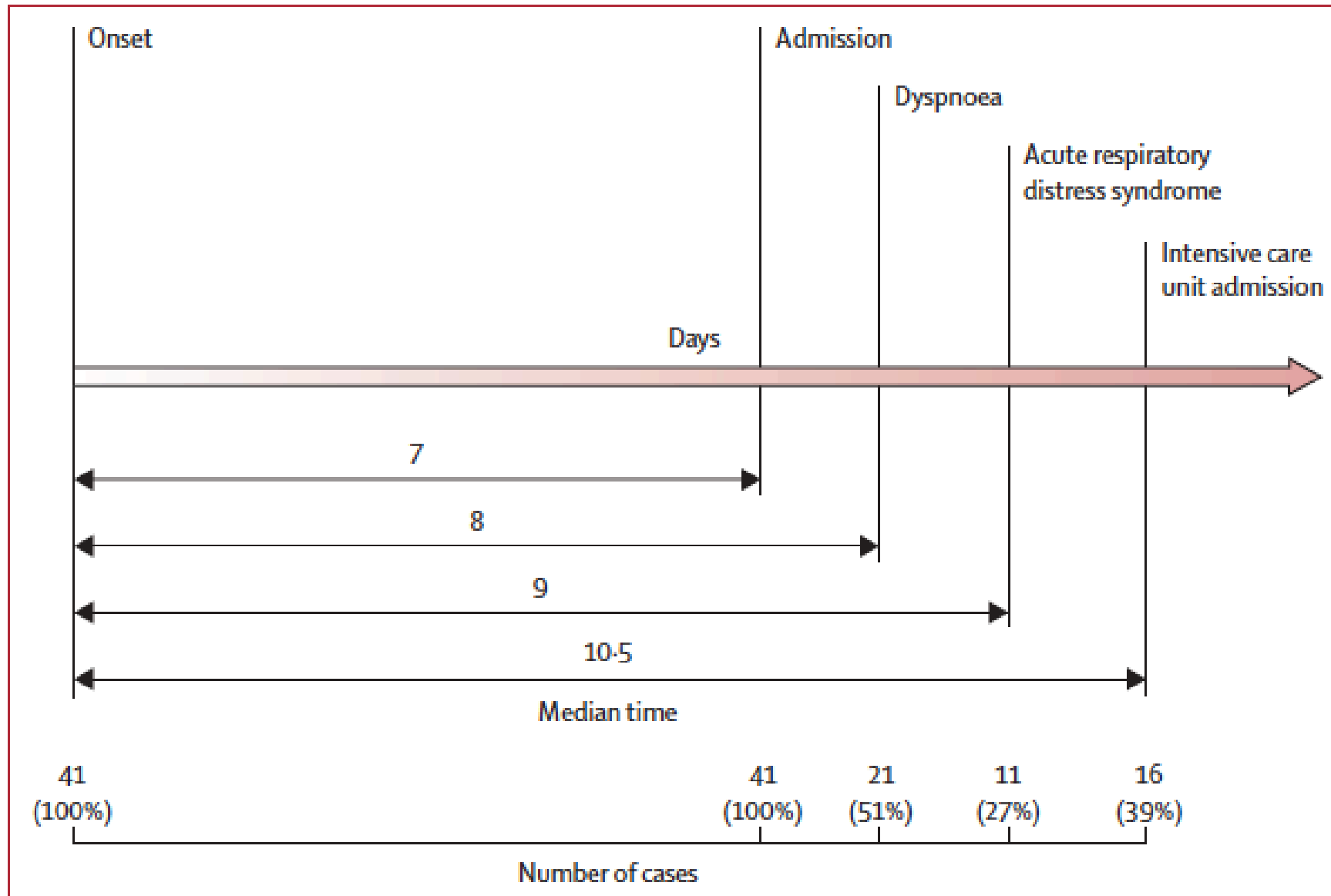
COMMENTARY

Open Access

Acute kidney injury in SARS-CoV-2 infected patients

Yao Fanelli, Marco Fioresi, Vincenzo Catalappo, Loreo Gesualdo, Giovanni Stallone, Claudio Ronco, and Giuseppe Carraro

Timeline of COVID






Characteristics and prognosis

Characteristics	Recruiting center			P-value*	Total
	Modena	Bologna	Reggio Emilia		
	N= 354	N= 80	N= 110		N= 544
Age, years				0.653	
Median (IQR)	66 (55, 76)	68 (56, 78)	68 (59, 77)		67 (56, 77)
Gender, n(%)				<.001	
Female	109 (30.8%)	44 (55.0%)	32 (29.1%)		185 (34.0%)
Baseline PaO₂/FiO₂				0.006	
Median (IQR)	227 (126, 289)	255 (213, 310)	255 (155, 340)		239 (139, 306)
SOFA Score				<.001	
Median (IQR)	2 (0, 3)	2 (2, 3)	3 (2, 4)		2 (1, 4)
Follow-up, days				0.039	
Median (IQR)	9 (4, 15)	12 (6, 18)	8 (4, 14)		9 (4, 15)
Intervention, n(%)				<.001	
Tocilizumab subcutaneous	84 (23.7%)	4 (5.0%)	3 (2.7%)		91 (16.7%)
Tocilizumab intravenous	48 (13.6%)	24 (30.0%)	16 (14.5%)		88 (16.2%)
SoC	222 (62.7%)	52 (65.0%)	91 (82.7%)		365 (67.1%)
Events, n(%)					
Mechanical ventilation	54 (15.3%)	9 (11.3%)	27 (24.5%)	0.028	90 (16.5%)
Death	52 (14.7%)	16 (20.0%)	18 (16.4%)	0.494	86 (15.8%)

*Chi-square or Kruskal-Wallis test as appropriate

RESEARCH ARTICLE

Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation

Stephen J. Halpin^{1,2,3}  | Claire McIvor⁴ | Gemma Whyatt² | Anastasia Adams² | Olivia Harvey² | Lyndsay McLean⁵ | Christopher Walshaw⁵ | Steven Kemp⁶ | Joanna Corrado² | Rajinder Singh² | Tamsin Collins³ | Rory J. O'Connor^{1,2}  | Manoj Sivan^{1,2,3} 

Median 48 days after discharge

TABLE 3 Prevalence of reported problems after COVID-19 in patients discharged from hospital

Domain	Ward patients (68)		ICU patients (32)	
	Number	%	Number	%
Fatigue				
Any new fatigue	41	60.3	23	72.0
Mild (0-3)	17	25.0	6	18.8
Moderate (4-6)	14	20.6	13	40.6
Severe (7-10)	10	14.7	4	12.5
Breathlessness				
Any new or worsened breathlessness ^a	29	42.6	21	65.6
Mild (increased by 1-3/10)	14	20.6	10	31.3
Moderate (increased by 4-6/10)	10	14.7	7	21.9
Severe (increased by 7-10/10)	5	7.4	4	12.5
Increased at rest	13	19.1	9	28.1
Increased on dressing	18 (i/66) ^b	27.3	10	31.3
Increased on stairs	24 (i/57) ^b	42.1	21	65.6
Neuropsychological				
Any PTSD symptoms related to illness	16	23.5	15	46.9
Mild symptoms	12	17.6	9	28.1
Moderate symptoms	4	5.9	4	12.5
Severe symptoms	0	0.0	2	6.3
Thoughts of self-harm	1	1.5	1	3.1
New or worsened concentration problem	11	16.2	11	34.4
New or worsened short-term memory problem	12	17.6	6	18.8
Speech and swallow				
Swallow problem	4	5.9	4	12.5
Laryngeal sensitivity	9	11.8	8	25.0
Voice change	12	17.6	8	25.0
Communication difficulty	4	5.9	2	6.3
SLT referral criteria met (impact rating of 1 or more in any SLT domain)	14	20.6	9	28.1
Nutrition				
Concern about weight/nutrition	10	14.7	2	6.3
Appetite problem severity 2 or more	6	8.8	2	6.3
Dietetics referral criteria met (either of the above criteria)	12	17.6	4	12.5
Continence				
New bowel control problem	2	2.9	1	3.1
New bladder control problem	6	8.8	4	12.5
EQ-5D-5L				
Mean EQ-5D-5L index value on day of screen	0.724		0.693	
Mean change	-0.061		-0.155	
Decreased by at least 0.05 (MCID ^c)	31	45.6	22	68.8
Worsened mobility	21	30.9	16	50
Worsened self-care	12	17.6	4	12.5
Worsened usual activities	25	36.8	19	29.4
Worsened pain/discomfort	10	14.7	9	28.1
Worsened anxiety/depression	11	16.2	12	37.5

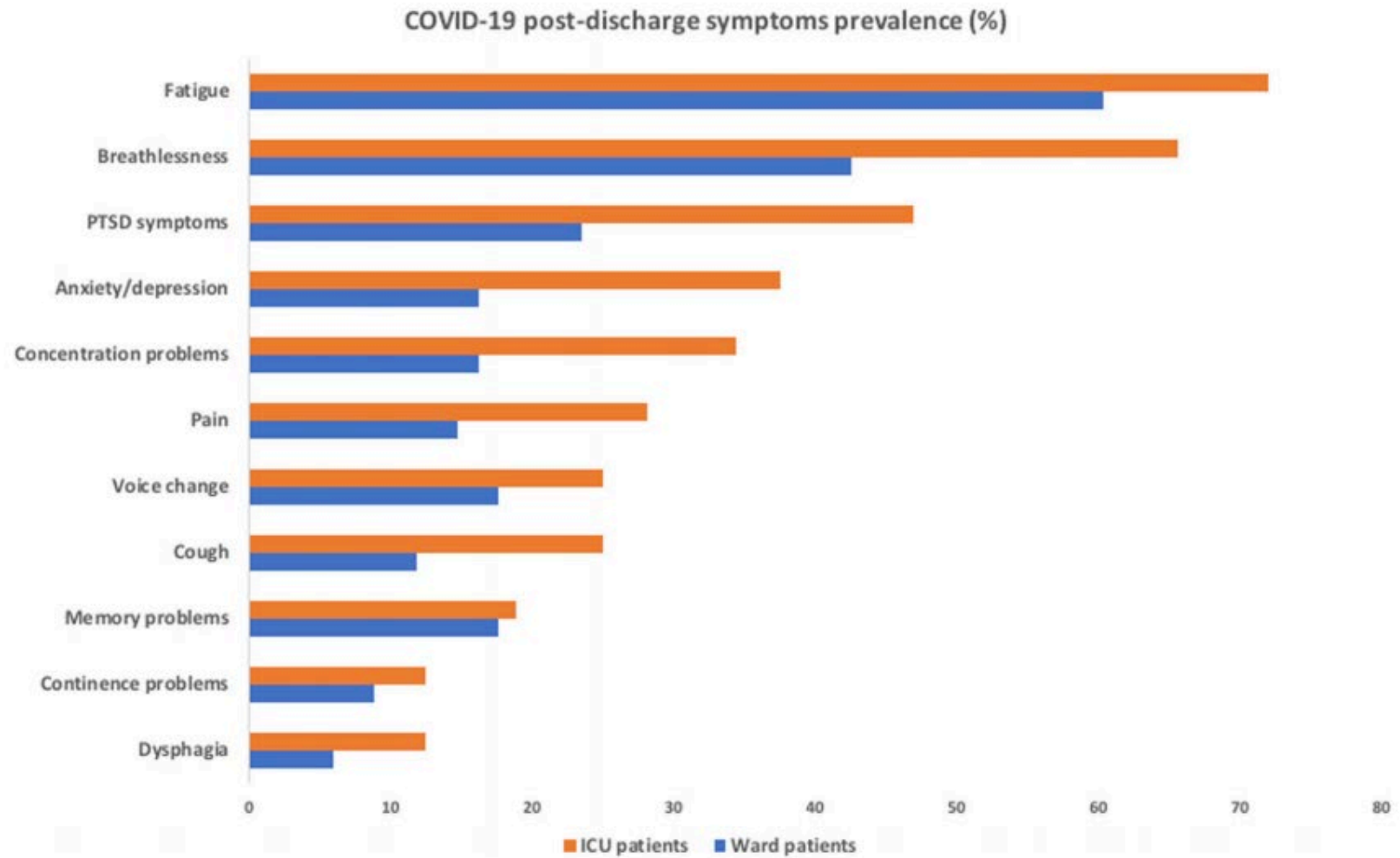


FIGURE 1 Prevalence of persistent symptoms in the intensive care unit and ward groups

Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19

Eve Garrigues,^a Paul Janvier,^b Yousra Kherabi,^a Audrey Le Bot,^a Antoine Hamon,^a H el ene Gouze,^a Lucile Doucet,^a Sabryne Berkani,^a Emma Oliosi,^a Elise Mallart,^a F elix Corre,^a Virginie Zarrouk,^a Jean-Denis Moyer,^c Adrien Galy,^a Vasco Honsel,^a Bruno Fantin,^a and Yann Nguyen^{a,d,*}

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Table 1

Post-discharge persistent symptoms and health-related quality of life of 120 patients after a mean of 110.9 days after their admission for COVID-19.

	Overall	Ward patients	ICU patients	P value
	<i>N</i> = 120	<i>N</i> = 96	<i>N</i> = 24	
Age, years	63.2 (15.7)	64.1 (16.1)	59.6 (13.7)	0.208
Sex, male	75 (62.5)	56 (58.3)	19 (79.2)	0.099
Comorbidities				
Diabetes	26 (21.7)	22 (22.9)	4 (16.7)	0.698
Hypertension	56 (46.7)	45 (46.9)	11 (45.8)	1.000
Body mass index (kg/m ²)				<0.001
<25, n (%)	35 (29.2)	32 (33.3)	3 (12.5)	
≥25, n (%)	57 (47.5)	37 (38.5)	20 (83.3)	
Missing, n (%)	28 (23.3)	27 (28.1)	1 (4.2)	
Clinical features at admission				
Confusion	7 (5.8)	6 (6.2)	1 (4.2)	1.000
Cough	87 (72.5)	69 (71.9)	18 (75.0)	0.959
Dyspnoea	88 (73.3)	68 (70.8)	20 (83.3)	0.327
Myalgia	19 (15.8)	16 (16.7)	3 (12.5)	0.851
Diarrhoea	29 (24.2)	25 (26.0)	4 (16.7)	0.488
Admission data				
Length of stay in hospital, days	11.2 (13.4)	7.4 (5.4)	26.5 (22.3)	<0.001
Length of stay in ICU, days	–	–	17.1 (15.7)	–

HOW TO INVESTIGATE THESE SYMPTOMS?

The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19

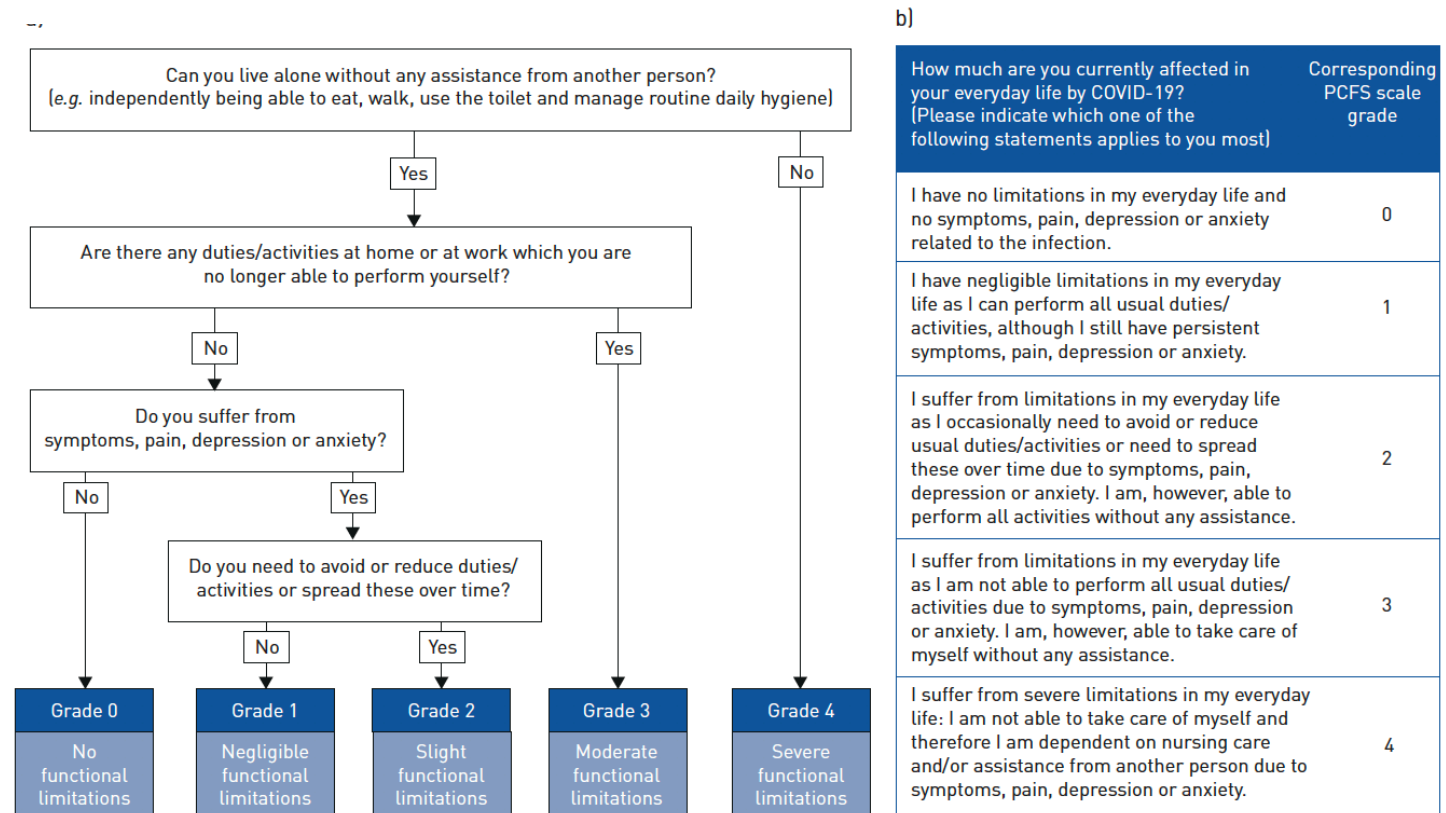


FIGURE 1 Patient self-report methods for the Post-COVID-19 Functional Status (PCFS) scale. a) Flowchart. b) Patient questionnaire. Instructions for use: 1) to assess recovery after the SARS-CoV-2 infection, this PCFS scale covers the entire range of functional limitations, including changes in lifestyle, sports and social activities; 2) assignment of a PCFS scale grade concerns the average situation of the past week (exception: when assessed at discharge, it concerns the situation of the day of discharge); 3) symptoms include (but are not limited to) dyspnoea, pain, fatigue, muscle weakness, memory loss, depression and anxiety; 4) in case two grades seem to be appropriate, always choose the highest grade with the most limitations; 5) measuring functional status before the infection is optional; 6) alternatively to this flowchart and patient questionnaire, an extensive structured interview is available. The full manual for patients and physicians or study personnel is available from <https://osf.io/qgpdv/> (free of charge).



Early View

Research letter

Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived the hospitalisation

Figure. Proportion of patients with abnormal physical functioning and/or abnormal performance of activities of daily living

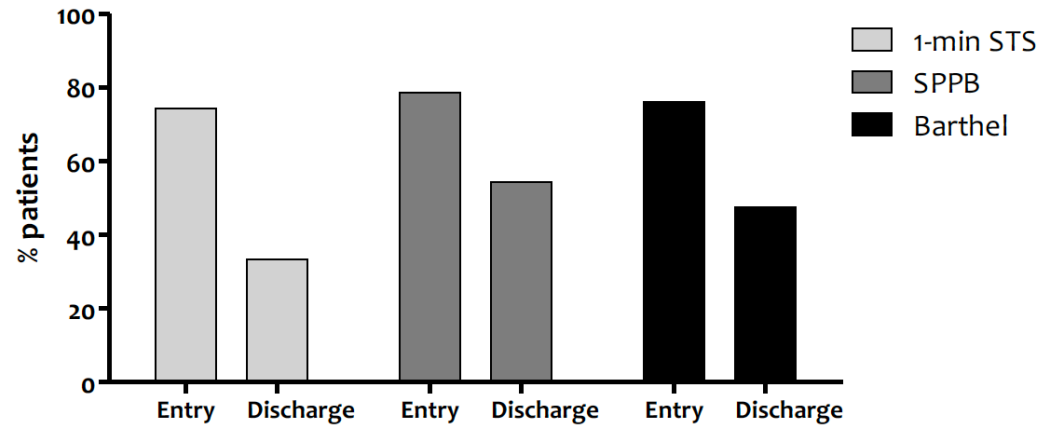


Figure legend: The proportion of patients (at entry in Veruno and at discharge home) with an abnormal low number of 1-minute chair stands (below percentile 2.5 of the reference values ^[8]); with a summary score on the Short Physical Performance Battery (SPPB) of 0-6 points (=low performance); or with a poor score (≤ 60 points) on the Barthel index. 1-min-STS: one minute sit-to-stand test, SPPB: Short Physical performance Battery.

WHICH COULD BE THE PATHOGENESIS?

Post–COVID-19 chronic symptoms: a postinfectious entity?

Benjamin Davido^{1,*}, Sophie Seang², Roland Tubiana², Pierre de Truchis¹¹) *Maladies Infectieuses, Hôpital Universitaire Raymond-Poincaré, APHP, Garches, France*²) *Maladies Infectieuses, Hôpital Universitaire Pitié Salpêtrière, APHP, Paris, France*

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As clinicians working for the Assistance Publique–Hôpitaux de Paris (39 hospitals, 20 000 beds), we admitted numerous patients for a severe coronavirus disease 2019 (COVID-19) during the first wave of the epidemic. On 18 May 2020, Santé Publique France confirmed 142 903 cases of COVID-19, including 61 728 patients who had returned home since 1 March 2020 [1]. In the Paris–Île-de-France area, more than 50 000 outpatients were monitored during 30 days using the Covidom telemedicine platform [2]. During the lockdown from 16 March 2020 until 11 May 2020, numerous symptomatic outpatients could not be tested by PCR and stayed home in compliance with the laws in force.

Surprisingly, today, while we are fearing a second wave, we find ourselves receiving more and more of those outpatients who experienced mild symptoms attributable to COVID-19 such as anosmia and ageusia [3], followed by a short period of convalescence (on the order of few days). Subsequently they complained of a relapse with persistent symptoms, especially myalgia, intense fatigue, sensation of fever, shortness of breath, chest tightness, tachycardia, headaches and anxiety.

Since mid-May (right after the lockdown ended), we now evaluate an average of 30 individuals per week for whom symptoms have not completely subsided, essentially young women (sex ratio 4:1) around 40 years old with no relevant medical history.

Interestingly, few of them present biological abnormalities (especially no lymphocytopenia or increased C-reactive protein) and in rare case traces of infection on chest computed tomographic scan. While nasopharyngeal PCR can be still positive even after 30 days of onset symptoms [4], we found no argument for a reinfection when repeating PCR testing. It is more likely a postviral syndrome that requires no specific treatment, as described in Epstein-Barr virus infection [5]. Up to today, and based on preliminary data, only a small proportion of patients who sought care (up to 30%) had a proven history of COVID-19 by PCR amplifying the betacoronavirus E gene and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *RdRp* gene on nasopharyngeal swab. By repeating in-hospital serology using the Abbott Architect platform (Abbott Diagnostics, Chicago, IL, USA), the rate can reach up to 50%. Indeed, it has been recently established that serodiagnosis of SARS-CoV-2 using IgG enzyme-linked immunosorbent assay antibodies on the Abbott Architect like the one performed in our centres had a sensitivity of 84.5% (95% confidence interval, 66.5–94.1) 21 days after the onset of symptoms [6], making large-scale screening of patients feasible.

This post–COVID-19 entity is worth addressing because we are facing an unprecedented pandemic, which explains why suddenly patients are all at the same time seeking care for what might otherwise be a banal chronic fatigue syndrome. Although there are discrepancies between the results of the clinical examination and the patients' complaints, the symptoms are compatible with dysautonomia, as previously described in the ALBACOV registry (2.5%) [7], and should be considered as such. Such a neurologic disorder might be related to microangiopathy and endothelial injury, as already reported in brain biopsy samples of severe COVID-19 [8], and look like a recent late Kawasaki syndrome described after COVID-19 in children [9].

Close to this so-called post–COVID-19 syndrome, a post-chikungunya syndrome was described after the Reunion Island outbreak in 2006, possibly related to an inadequate inflammatory disorder, sometimes with no seroconversion [10]. SARS-CoV-2 could probably play the same role of an immune trigger, as already known in Guillain-Barré syndrome and other autoimmune diseases. Therefore, patients should be tested for antinuclear antibodies and the tests repeated over time after 6 weeks, especially if

reassurance. In case of persistent symptoms beyond 3 months, it could be relevant to investigate deeply the possible relationship between those chronic inflammatory symptoms and COVID-19, and to work hand in hand with other specialists, including a psychologist, a pneumologist, a neurologist and a specialist in physical medicine and rehabilitation. Thereafter, a better understanding of this entity might help the medical community propose an adequate treatment that depends on the acknowledged physiopathology.

Re: 'Post-COVID-19 chronic symptoms' by Davido et al.

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²⁾ Department of Neurology, Mayo Clinic, Scottsdale, AZ, USA

³⁾ Department of Neurology, Eastern Virginia Medical School, USA

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Davido et al. [1] describe a subset of coronavirus disease 2019 (COVID-19) patients in the Paris-Ile-de-France area with persistent symptoms of at least 2 months' duration after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection characterized by fatigue, myalgias, subjective fevers, headaches and symptoms of autonomic impairment. The authors hypothesize that these symptoms represent a postviral syndrome that requires no specific treatment, possibly related to microangiopathy and endothelial injury in susceptible patients.

We too have observed that a subset of individuals with COVID-19 may develop a chronic condition that persists well after initial presentation, with prominent fatigue, cognitive slowing and symptoms of autonomic impairment such as orthostatic intolerance, exaggerated postural tachycardia and episodic hyperadrenergic surges; however, we disagree that these sequelae require no specific treatment. On the contrary, there are several treatment paradigms to consider for such patients with precedent in the autonomic literature, including fluid and salt loading [2], graduated exercise therapy starting in a reclined position [2] and targeted pharmacologic treatment [3] for symptomatic improvement, depending on the symptom complex. In addition, postviral autonomic impairment may have an autoimmune basis and in some cases is amenable to immunotherapy [4,5].

Nonpharmacologic and symptomatic pharmacologic treatments are commonly used to treat postural orthostatic tachycardia

syndrome (POTS) and orthostatic intolerance (OI), common autonomic disorders that are frequently reported after viral infection [6,7]. While we have observed many phenotypic similarities between POTS, OI and the postviral syndrome that appear in some COVID-19 patients, presenting, as we observe, in women aged 40 and younger, there may be significant clinical variation in such patients, and further research is necessary to confirm and further characterize these initial reports. While at the moment there is no universal treatment protocol, it should be emphasized that treatment does exist for postviral autonomic impairment and has the potential to reduce symptom burden and improve quality of life in affected patients. However, it should be noted that while these treatment recommendations are based on evidence supported by studies on patients with POTS, there are no such studies in patients with autonomic impairment resulting from COVID-19. Thus, prospective longitudinal studies are needed to quantify the symptom burden in those with persistent symptoms—and, more importantly, evaluate the response to these and other potential therapies.

Transparency Declaration

All authors report no conflicts of interest relevant to this letter.

References

- [1] Davido B, Seang S, Tubiana R, de Truchis P. Post-COVID-19 chronic symptoms: a postinfectious entity? *Clin Microbiol Infect* 2020.
- [2] Fu Q, Levine BD. Exercise and nonpharmacological treatment of POTS. *Auton Neurosci Basic Clin* 2018;215:20–7.
- [3] Miller AJ, Raj SR. Pharmacotherapy for postural tachycardia syndrome. *Auton Neurosci Basic Clin* 2018;215:28–36.
- [4] Vernino S, Stiles LE. Autoimmunity in postural orthostatic tachycardia syndrome: current understanding. *Auton Neurosci* 2018;215:78–82.
- [5] Vernino S, Sandroni P, Singer W, Low PA. Autonomic ganglia: target and novel therapeutic tool. *Neurology* 2008;70:1926–32.
- [6] Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S, et al. Postural orthostatic tachycardia syndrome: the Mayo Clinic experience.

Case Report

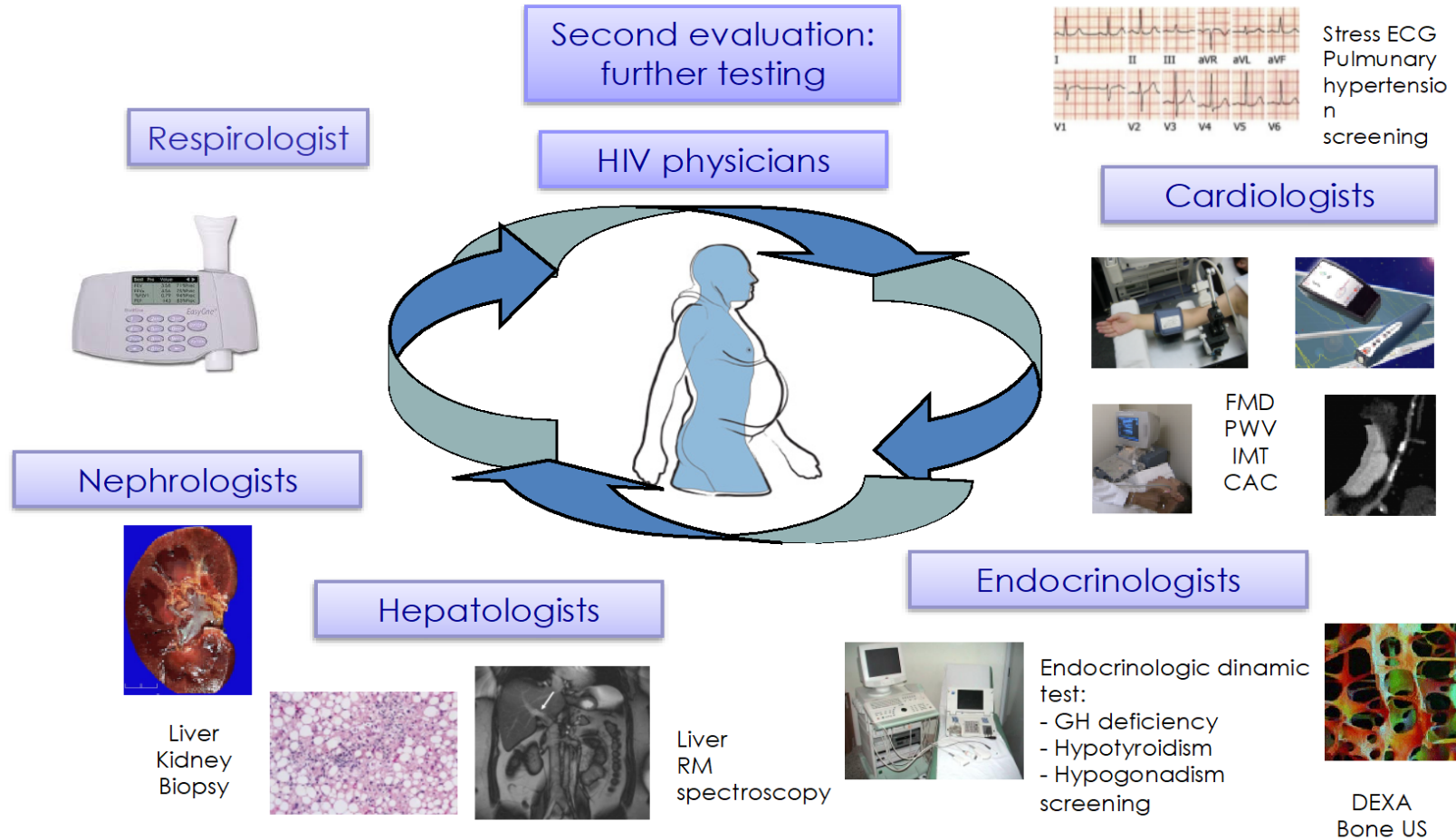
Oral Corticosteroid Relieves Post-COVID-19 Anosmia in a 35-Year-Old Patient

INTRODUCTION.

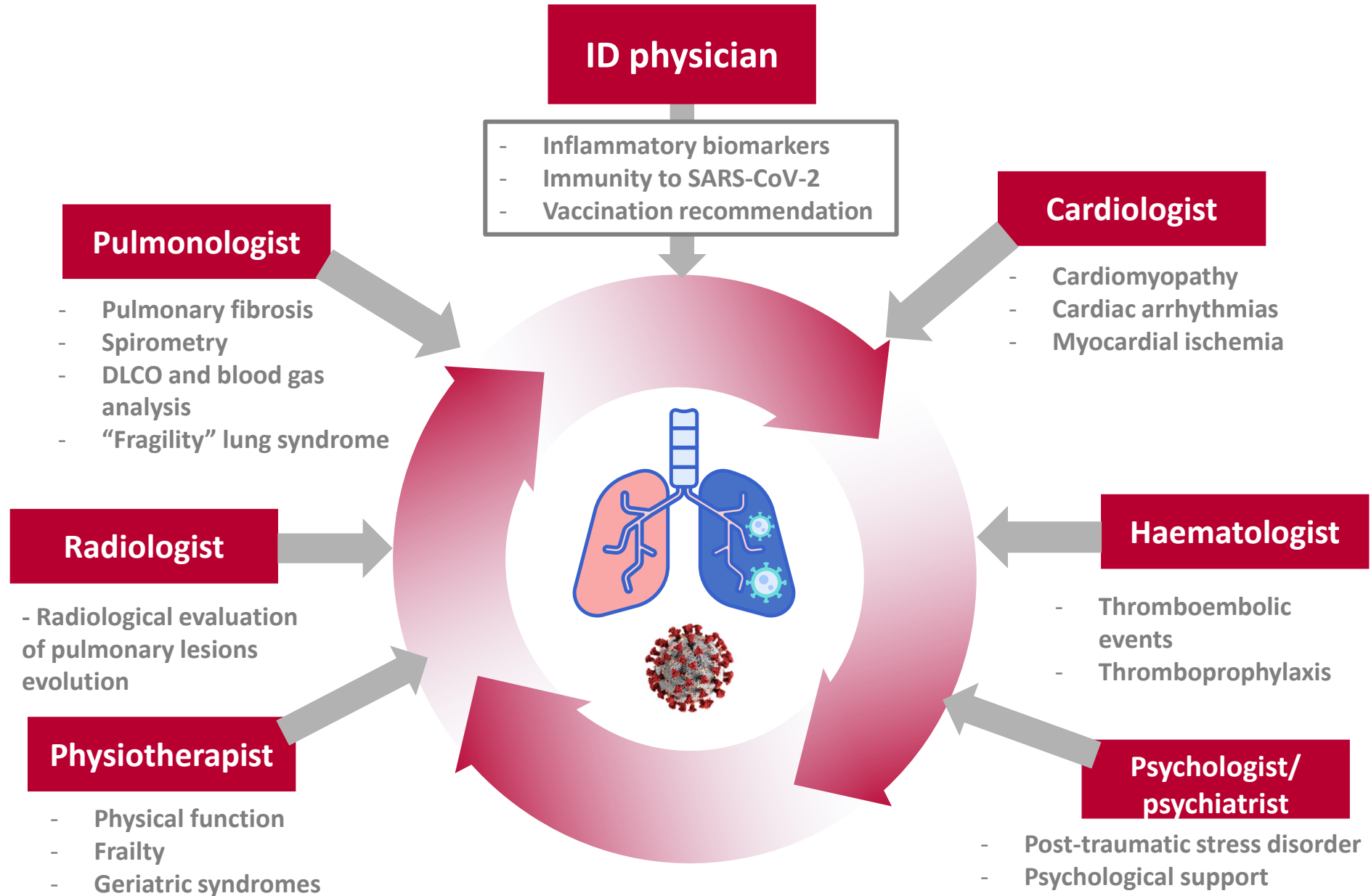
She was referred to an otolaryngologist for her anosmia. A complete head and neck examination was performed. The nasal cavity, oral cavity, and cranial nerve functions (II–V, VII–IX, and XII) were normal. The patient was diagnosed with postviral olfactory dysfunction. Rhinocort spray, one puff BID for 10 days, was prescribed for her. However, no improvement was observed. A throat swab sample was taken, and reverse real-time PCR was performed again. The second PCR result was negative. Oral prednisolone was prescribed. After 6 days of consuming prednisolone, her anosmia reversed.

The Modena experience

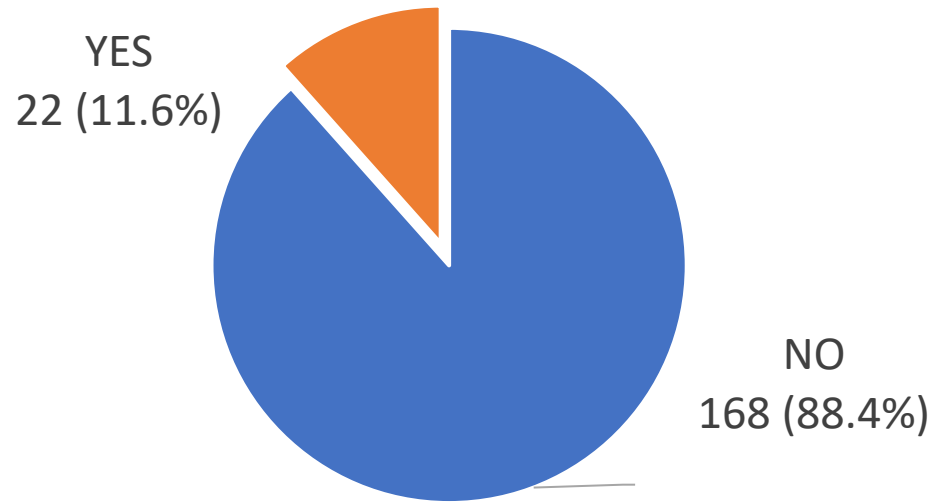
Modena HIV Metabolic clinic: an integrated multidisciplinary approach



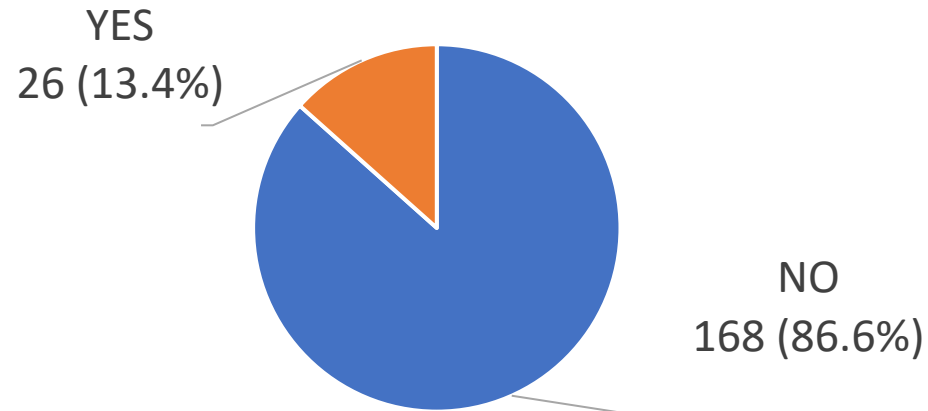
From a **single** organ disease to **multisystemic** disease and **multidisciplinary** assessment



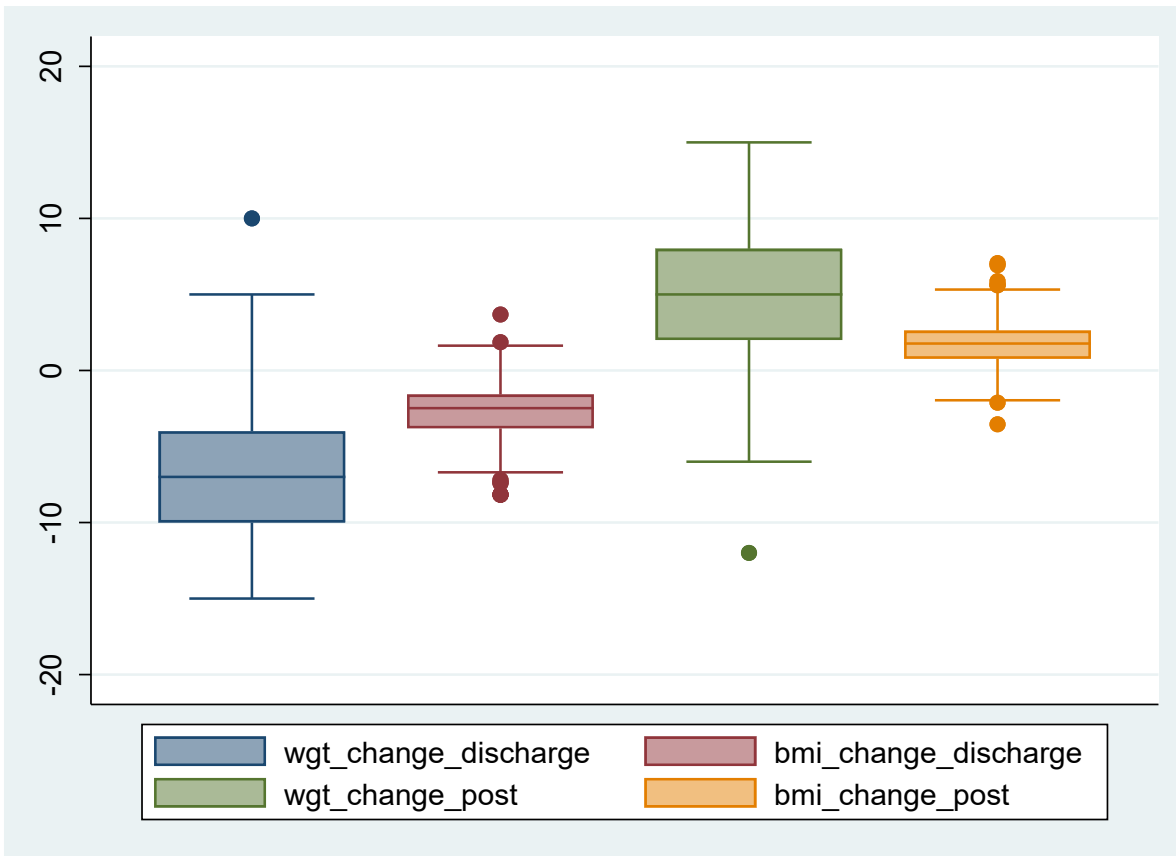
SKIN DRYNESS



COUGH

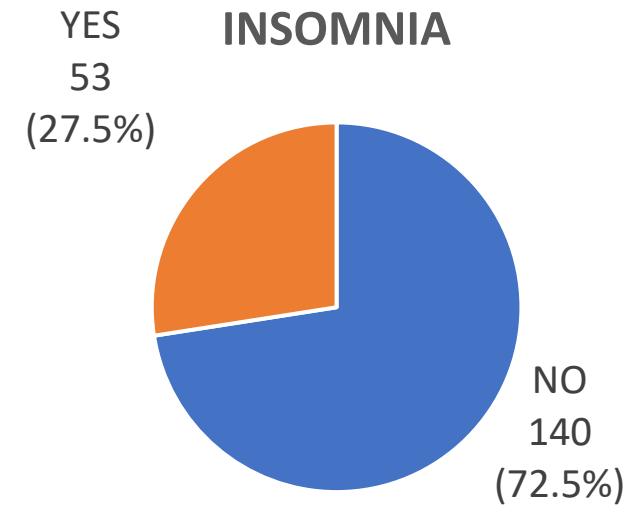


BREATH ALTERATION	Freq(%) o Median(IQR)
BORG score (Borg Scale of Perceived Exertion)	
0 – No	112 (65.9)
0.5 – Very Very Mild	18 (10.6)
1 – Very Mild	12 (7.0)
2 – Mild	19 (11.2)
3 – Moderate	8 (4.7)
4 – Quite intense	1 (0.6)
6' Walking Test positive	18 (11)
SpO2 in ambient air <=94	
>94	7 (5)
	146 (95)
EGA in ambient air SO2	
pO2	96.8 (96.1-97.3)
	86.7 (80-93.6)

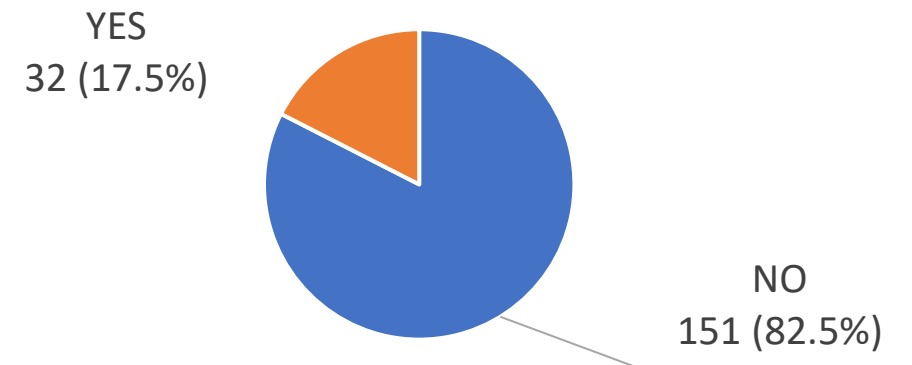


Weight Med(IQR): 85 (78-95) 78 (70-87) 84 (75-91)

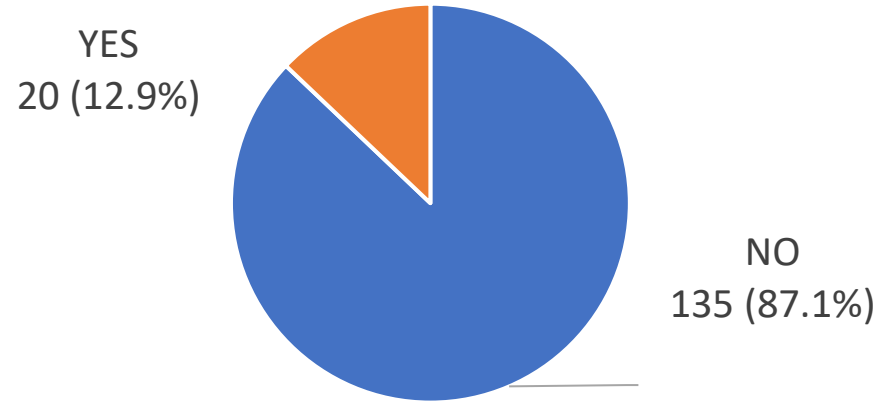
183 patients



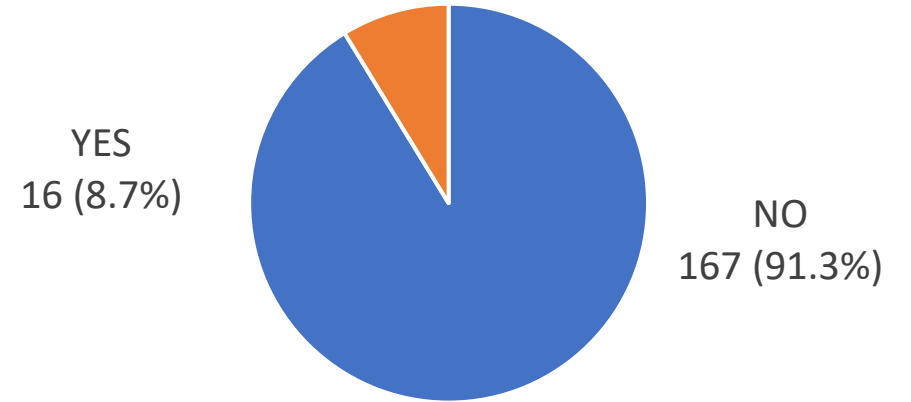
COGNITIVE/PSYCHOLOGICAL ALTERATION



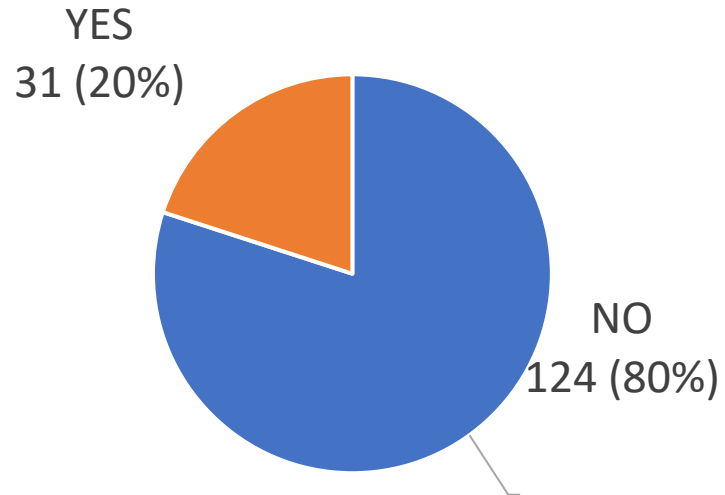
HEARING LOSS



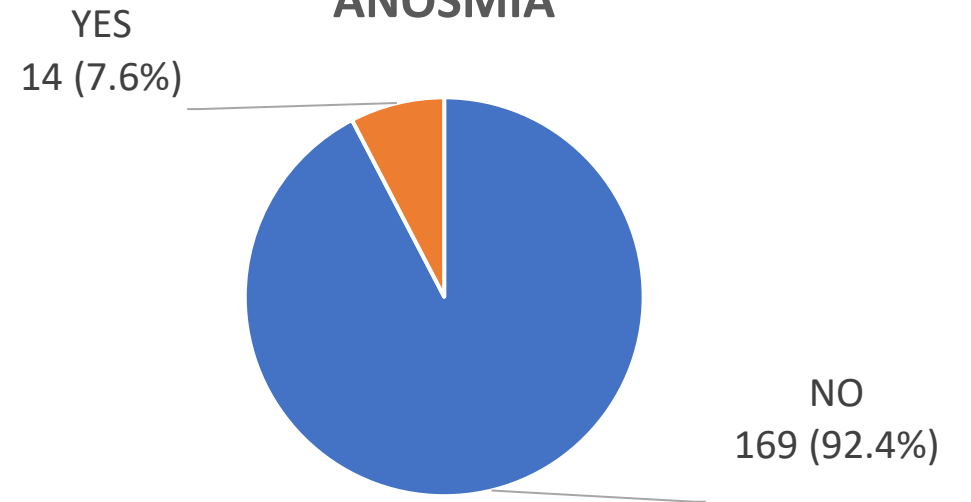
AGEUSIA



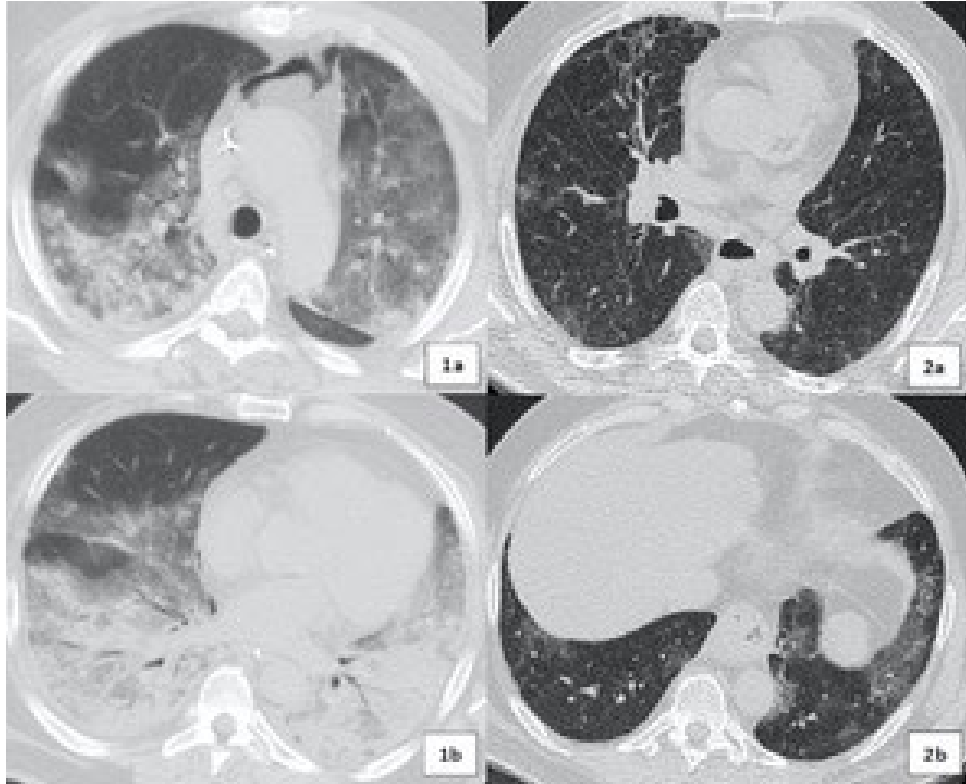
LOSS OF VISION



ANOSMIA



What happens to the lung?



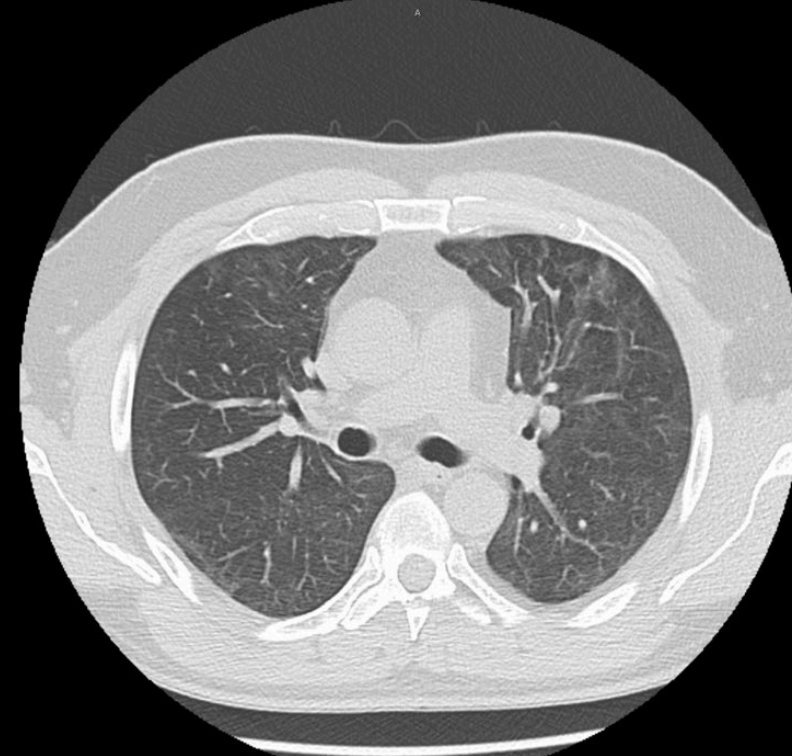
Chest CT scans of H1N1 induced ARDS (frames 1 a-b) and COVID-19 induced ARDS (frames 2 a-b).

We describe the clinical presentation and management of a patient who survived H1N1 induced ARDS complicated with onset of lung fibrosis and who developed COVID19 severe pneumonia.

Taking this case as a paradigm we introduce the concept of “**lung fragility**” and discuss potential implication for further follow-up of patients who survive SARS-CoV-2 induced ARDS.

We suggest a multidimensional approach focused on:

- ✓ Evolution of lung fibrosis
- ✓ Proactive vaccination treatment
- ✓ Preservation of functional capacity and QoL
- ✓ Prevention of Frailty



Not always so lucky



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Even worse

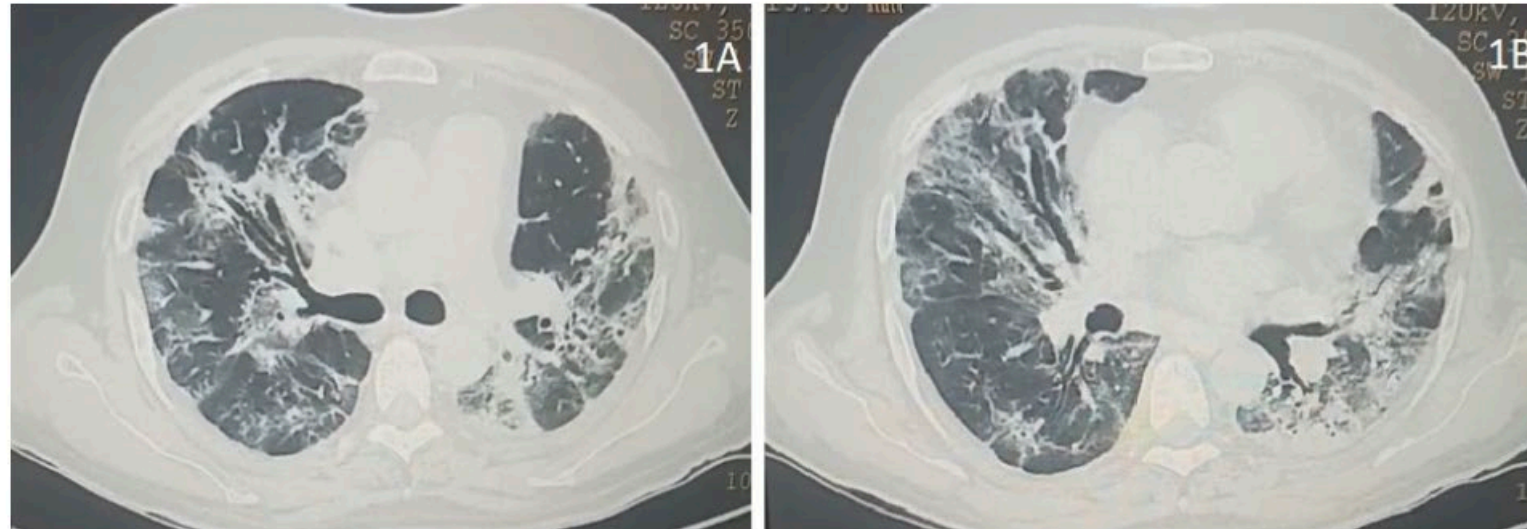
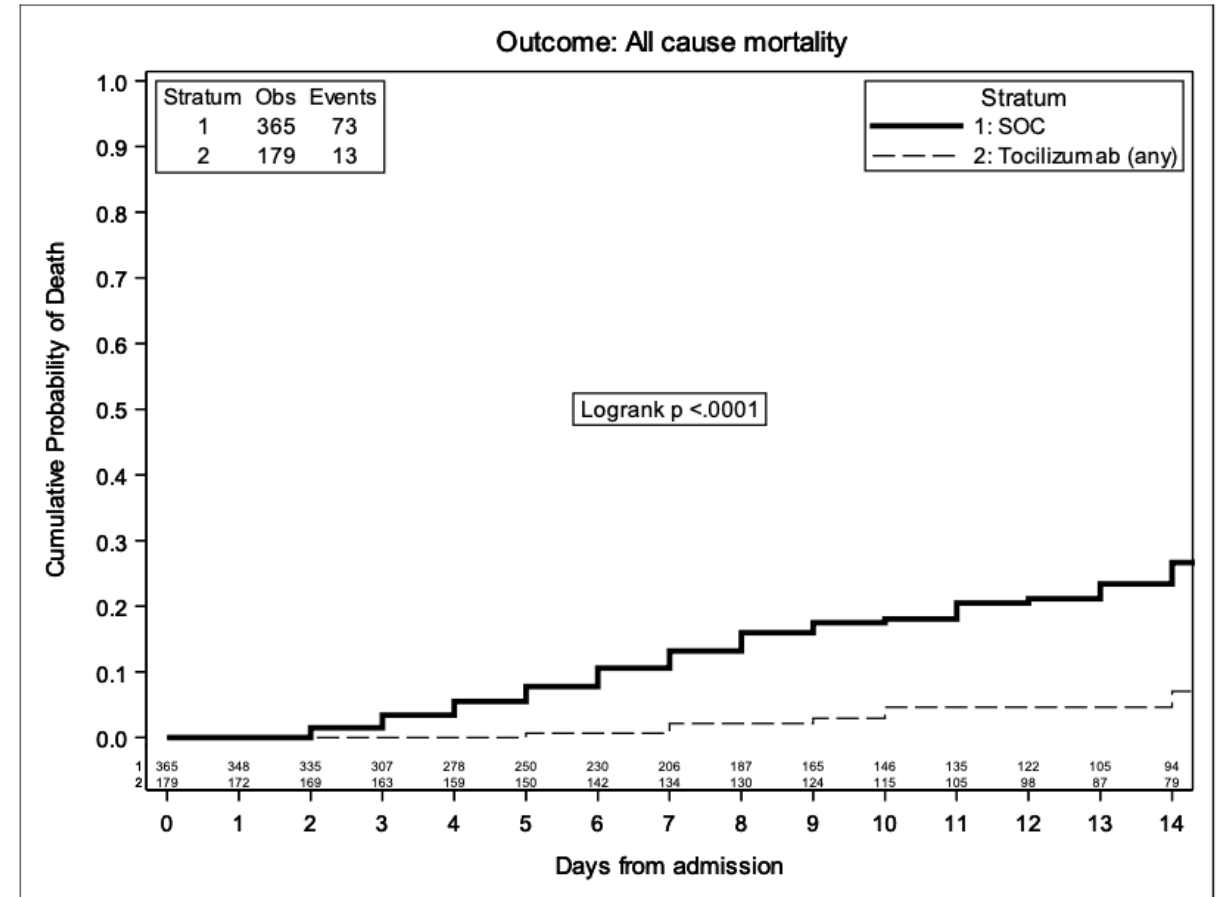
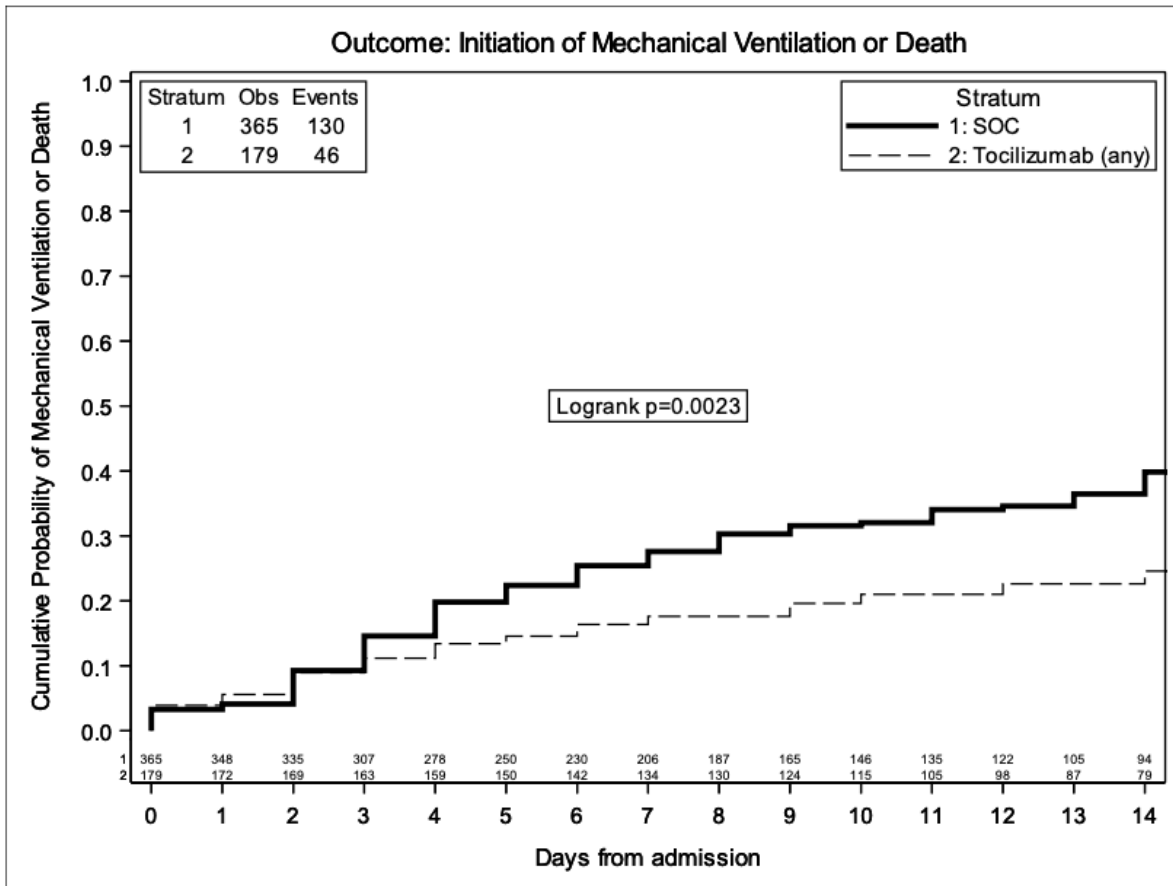


Figure 1A and 1B: showing traction bronchiectasis, architectural distortion and interlobar septal thickening suggestive of pulmonary fibrosis.

78x27mm (300 x 300 DPI)

Is there any role of treatments?



- 48% reduction in risk of invasive mechanical ventilation/death was observed versus controls.
- The all-cause mortality was reduced by 75%.

Conclusions

- COVID 19 is a new disease and it will take time to understand the variety of post-discharge symptoms, their pathogenesis and duration.
- Fortunately respiratory consequences seem to be rare, but many patients are far from complete recovery even after several months

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