The Daily COVID-19 Literature Surveillance Summary

January 15, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Climate

- A cross-sectional study conducted by researchers at multiple US medical centers investigated patients from 52 clinical sites from the Type 1 diabetes (T1D) Exchange clinical network from April to August 2020. They found that among 180 patients with lab-confirmed COVID-19 and T1D, 79 (44%) were non-Hispanic (NH) whites, 55 (31%) were NH Black, and 46 (26%) Hispanic. NH Black and Hispanic patients had higher median HbA1C values, were less likely to be using an insulin pump or continuous glucose monitoring, more likely to be hospitalized for COVID-19, and had increased prevalence of DKA compared to NH white patients. Age-adjusted COVID-19 mortality was found to be higher in Hispanic and NH Black groups compared to NH White patients highlighting current racial inequities in COVID-19 patients with T1D.

Understanding the Pathology

- Researchers from the Department of Radiology and Cardiology at multiple Chinese hospitals and the Perelmen School of Medicine at University of Pennsylvania in Philadelphia conducted a single-center, prospective observational study at No. 2 People's Hospital in Anhui, China from May to September 2020 involving 40 patients who recovered from COVID-19 with moderate or severe pneumonia without either symptoms or past medical history of cardiac conditions. Cardiac MRI revealed increased extracellular volume fraction (ECV) > 29% in 24/40 patients, as well as subclinical changes in myocardial function leading to reduction in left ventricular 2D-global longitudinal strain in 28/40 patients after recovering from moderate or severe COVID-19 compared to healthy controls. These findings suggest that cardiac MRI could prove to be a sensitive tool in identifying cardiac involvement of SARS-CoV-2 infection, however further investigation is needed to fully understand the prevalence of subclinical myocardial findings in association with COVID-19 infection.

Management

- Pulmonologists and a radiologist from the United Kingdom conducted a single-center prospective observational study of 837 adult COVID-19 patients four weeks after hospital discharge. They found evidence of post-COVID interstitial lung disease (ILD) in 35 patients (4.8%), and that early treatment with corticosteroids resulted in significant radiologic and symptomatic improvement. Authors suggest that early treatment of post-COVID ILD may prevent further functional impairment and recommend further studies on its natural history and management.

TABLE OF CONTENTS

COVID-19: RETHINKING THE NATURE OF VIRUSES

de Chadarevian S, Raffaetà R.. Hist Philos Life Sci. 2021 Jan 7;43(1):2. doi: 10.1007/s40656-020-00361-8.
Level of Evidence: 5 - Opinion

BLUF

These scientists contend the current means by which viruses are viewed throughout our society. They argue that viruses are considered to be microscopic, villainous entities that instill a war-like response by us humans, the sufferers. However, we neglect to view viruses for all they are worth, and this has limited our capacity to fully understand how viruses have shaped human evolution as well as effected our society today. The COVID-19 pandemic has exemplified this notion in its unique way of impacting not only the medical landscape, but society as a whole.

ABSTRACT

In this brief essay, we combine biological, historical, philosophical and anthropological perspectives to ask anew the question about the nature of the virus. How should we understand Sars-CoV-2 and why does it matter? The argument we present is that the virus undermines any neat distinction between the natural and the human-made, the biological and the social. Rather, to understand the virus and the pandemic we need to understand both as intimately connected to our own social and historical condition. What started as a reflection on the nature of the virus thus turns into a reflection on the human condition as refracted in this pandemic or an anthropology of the virus.

FULL INEQUITIES IN DIABETIC KETOACIDOSIS AMONG PATIENTS WITH TYPE 1 DIABETES AND COVID-19: DATA FROM 52 US CLINICAL CENTERS

Ebekozien O, Agarwal S, Noor N, Neil AAO, Wong JC, Seeherunvong T, Sanchez J, DeSalvo D, Lyons SK, Majidi S, Wood JR, Acharya R, Aleppo G, Sumpter KM, Cymbaluk A, Shah NA, Van Name M, Cruz-Aviles L, Alonso GT, Gallagher MP, Sanda S, Feuer AJ, Cossen K, Rioles N, Jones NY, Kamboj MK, Hirsch IB.. J Clin Endocrinol Metab. 2021 Jan 7:dgaa920. doi: 10.1210/clinem/dgaa920. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross-sectional study conducted by researchers at multiple US medical centers investigated patients from 52 clinical sites from the Type 1 diabetes (T1D) Exchange clinical network from April to August 2020. They found that among 180 patients with lab-confirmed COVID-19 and T1D, 79 (44%) were non-Hispanic (NH) whites, 55 (31%) were NH Black, and 46 (26%) Hispanic. NH Black and Hispanic patients had higher median HbA1C values, were less likely to be using an insulin pump or continuous glucose monitoring, more likely to be hospitalized for COVID-19, and had increased prevalence of DKA compared to NH white patients (See Table 3). Age-adjusted COVID-19 mortality was found to be higher in Hispanic and NH Black groups compared to NH White patients highlighting current racial inequities in COVID-19 patients with T1D.

ABSTRACT

OBJECTIVE: We examined whether diabetic ketoacidosis (DKA), a serious complication of type 1 diabetes (T1D) was more prevalent among Non-Hispanic (NH) Black and Hispanic patients with T1D and laboratory-confirmed COVID-19 compared to NH Whites. METHOD: This is a cross-sectional study of patients with T1D and laboratory-confirmed COVID-19 from 52 clinical sites in the US, data was collected April - August 2020. We examined the distribution of patient factors and DKA events across NH White, NH Black, and Hispanic race/ethnicity groups. Multivariable logistic regression analysis was performed to examine the odds of DKA among NH Black and Hispanic patients with T1D as compared to NH White patients, adjusting for potential confounders, such as age, sex, insurance, and last HbA1c. RESULTS: We included 180 patients with T1D and laboratory-confirmed COVID-19 in the analysis. Forty-four percent (n=79) were NH White, 31% (n=55) NH Black, 26% (n=46) Hispanic. NH Blacks and Hispanics had higher median HbA1c than Whites ((%-points) [IQR]:11.7[4.7], p<0.001, and 9.7[3.1] vs. 8.3[2.4], p=0.01). We found that more NH Black and Hispanic presented with DKA compared to Whites (55% and 33% vs. 13%, p<0.001 and p=0.008, respectively). After adjusting for potential confounders, NH Black patients continued to have greater odds of presenting with DKA compared with NH Whites (OR [95%CI]: 3.7 [1.4,10.6]). CONCLUSION: We found that among T1D patients with COVID-19 infection, NH Blacks were more likely to present in DKA compared with NH White patients. Our findings demonstrate additional risk among NH Blacks with T1D and COVID-19.

Table 3: Odds Ratios for DKA Comparing Racial-ethnic Minority with NH White Patients with type 1 Diabetes and COVID-19 (N=163; DKA=55, No adverse events=108)

	Unadjusted OR (95% CI)	Adjusted Model [a] OR (95% CI)	Adjusted Model [b] OR (95% CI)
Race			
Hispanic vs NH White	3.7 (1.4-9.6)**	1.9 (0.7-5.7)	1.6 (0.5-4.9)
NH Black vs NH White	8.8 (3.8-22.0)**	3.7 (1.4-10.6)**	3.3 (1.2-9.6)
Age (yrs)	-	1.0 (0.9-1.0)	1.0 (0.9-1.0)
Sex (M vs F)	-	0.8 (0.3-1.7)	0.8 (0.4-2.0)
A1c (%)	-	1.3 (1.1-1.5)**	1.2 (1.1-1.5)**
Insurance	-		
Public vs. Private		2.7 (1.1-6.7)*	2.7 (1.1-7.0)*
Newly diagnosed (Yes vs. No)		-	5.9 (1.5-30.1)*

*<0.05,**<0.001

[a] Adjusted for Age, HbA1c (as continuous variables), Sex, Insurance

[b] Adjusted for Age, HbA1c (as continuous variables), Sex, Insurance and Newly diagnosed T1D status

Table 3: Odds Ratios for DKA Comparing Racial-ethnic Minority with NH White Patients with type 1 Diabetes and COVID-19 (N=163; DKA=55, No adverse events=108)

ADVANCED AGE

CONFIRMED REINFECTION WITH SARS-COV-2 VARIANT VOC-202012/01

Harrington D, Kele B, Pereira S, Couto-Parada X, Riddell A, Forbes S, Dobbie H, Cutino-Moguel T.. Clin Infect Dis. 2021 Jan 9:ciab014. doi: 10.1093/cid/ciab014. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Physicians from Barts Health NHS Trust in London present the case of a 78-year-old man with SARS-CoV-2 reinfection with the novel variant (VOC-202012/01). Although the initial infection was mild, reinfection with the variant strain caused critical illness and the authors propose that the increased severity upon reinfection could be due to waning immunity as a result of the initial infection in the setting of multiple cardiac, pulmonary and renal comorbidities (see summary). Authors also point out that severe reinfection illness has been reported with strains other than VOC-202012/01, which they believe suggests that the variant strain does not entirely explain the critical outcome.

SUMMARY

Patient Background:
-78-year-old male
- History of Type II Diabetes with diabetic nephropathy, chronic obstructive pulmonary disease, sleep apnea, ischemic heart disease
- SARS-CoV-2 infection was confirmed through a combined nose and throat swab (NTS) test
- The reinfection caused severe COVID-19 pneumonia with myocardial infarction, tri-fascicular block, AV dissociation, and pulmonary edema
- Whole Genome Sequencing was used to confirm reinfection with the new variant VOC-202012/01

UNDERSTANDING THE PATHOLOGY

ELEVATED EXTRACELLULAR VOLUME FRACTION AND REDUCED GLOBAL LONGITUDINAL STRAINS IN PATIENTS RECOVERED FROM COVID-19 WITHOUT CLINICAL CARDIAC FINDINGS

Li X, Wang H, Zhao R, Wang T, Zhu Y, Qian Y, Liu B, Yu Y, Han Y.. Radiology. 2021 Jan 12:203998. doi: 10.1148/radiol.2021203998. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from the Department of Radiology and Cardiology at multiple Chinese hospitals and the Perelmen School of Medicine at University of Pennsylvania in Philadelphia conducted a single-center, prospective observational study at No. 2 People's Hospital in Anhui, China from May to September 2020 involving 40 patients who recovered from COVID-19 with moderate or severe pneumonia without either symptoms or past medical history of cardiac conditions (See Figure 1). Cardiac MRI revealed increased extracellular volume fraction (ECV) > 29% in 24/40 patients (See Table 3), as well as subclinical changes in myocardial function leading to reduction in left ventricular 2D-global longitudinal strain in 28/40 patients after recovering from moderate or severe COVID-19 compared to healthy controls (See Figure 5). These findings suggest that cardiac MRI could prove to be a sensitive tool in identifying cardiac involvement of SARS-CoV-2 infection, however further investigation is needed to fully understand the prevalence of subclinical myocardial findings in association with COVID-19 infection.

ABSTRACT

Background It is unknown if there are cardiac abnormalities in participants recovered from COVID-19 without cardiac symptoms and those who have normal biomarkers and normal ECGs. Purpose To evaluate cardiac involvement in participants recovered from COVID-19 without clinical evidence of cardiac involvement using cardiac MRI Materials and methods In this prospective observational cohort study, 40 participants recovered from COVID-19 with moderate(n=24) or severe(n=16) pneumonia and no cardiovascular medical history, without cardiac symptoms, with normal ECG, normal serological cardiac enzyme levels, and discharged > 90 days between May and September 2020. Demographic characteristics, serum cardiac enzymes, and cardiac MRI were obtained. Cardiac function, native T1, ECV and Two-dimensional (2D) strain were quantitatively evaluated and compared with controls (n = 25).The Comparison among the 3 groups were performed using one-way analysis of variance (ANOVA) with Bonferroni corrected post-hoc comparisons(for normal distribution) or Kruskal-Wallis tests with post-hoc pairwise comparisons(for non-normal distribution). Results Forty participants (54+-12 years; 24 men) enrolled with a mean time between admission and CMR of 158 +-18 days and discharge and CMR examination of 124 +-17 days. There was no LV and RV size or functional differences among participants recovered from COVID-19 and healthy controls. Only one (3%) participants had positive LGE located at the mid inferior wall. Global ECV values were elevated in both participants recovered from COVID-19 with moderate or severe pneumonia, compared to the healthy controls [median ECV (IQR)], [29.7% (28.0%-32.9%), versus 31.4% (29.3%-34.0%), versus 25.0% (23.7%-26.0%); both p<.001]. The 2D-global LV longitudinal stains (GLS) were reduced in both groups of participants [COVID-19 moderate group,-12.5%(-10.7%--15.5%), COVID-19 severe group, -12.5%(-8.7%--15.4%) compared to healthy control group -15.4%(-14.6%-17.6%), p=.002 and p=.001, respectively]. Conclusion CMR myocardial tissue and strain imaging parameters suggest that a proportion of participants recovered from COVID-19 had subclinical myocardial abnormalities detectable months after recovery.

FIGURES

Cardiac MRI Findings	Healthy Controls (n=25)	COVID-19 Moderate (n=24)	COVID-19 Severe (n=16)	P value[a]	P value[b]	P value[c]
Global ECV (%)	25.0(23.7-26.0)	29.7(28.0-32.9)	31.4(29.3-34.0)	<.001	<.001	0.33
2D-GLS (%)	-15.4(-14.6--17.6)	-12.5(-10.7--15.5)	-12.5(-8.7--15.4)	0.002	0.001	>.99

Data are medians, with interquartile range (IQR) in parentheses for continuous variables

Abbreviations:
ECV = extracellular volume fraction; GLS =global longitudinal strain

[a] Statistical difference between participants with moderate COVID-19 and healthy Controls
[b] Statistical difference between participants with severe COVID-19 and healthy Controls
[c] Statistical difference between participants with moderate COVID-19 and participants with severe COVID-19.

P<.002 (0.05/27) is considered to indicate statistical significance

Figure 1: Flowchart of participant enrollment. COVID-19 = coronavirus disease 2019

Cardiac MRI Findings	Healthy Controls (n=25)	COVID-19 Moderate (n=24)	COVID-19 Severe (n=16)	P value[a]	P value[b]	P value[c]
Global ECV (%)	25.0(23.7-26.0)	29.7(28.0-32.9)	31.4(29.3-34.0)	<.001	<.001	0.33
2D-GLS (%)	-15.4(-14.6--17.6)	-12.5(-10.7--15.5)	-12.5(-8.7--15.4)	0.002	0.001	>.99

Table 3: Subgroups Comparisons with Cardiac MRI Parameters of Participants Recovered from COVID-19 Compared with Controls

Data are medians, with interquartile range (IQR) in parentheses for continuous variables

Abbreviations:

ECV = extracellular volume fraction; GLS =global longitudinal strain

a Statistical difference between participants with moderate COVID-19 and healthy Controls

b Statistical difference between participants with severe COVID-19 and healthy Controls

c Statistical difference between participants with moderate COVID-19 and participants with severe COVID-19.

P<.002 (0.05/27) is considered to indicate statistical significance

TRANSMISSION & PREVENTION

HERD IMMUNITY TO COVID-19

Kadkhoda K.. Am J Clin Pathol. 2021 Jan 5:aqaa272. doi: 10.1093/ajcp/aqaa272. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

An immunologist from the Cleveland Clinic calculates that 63% to 76% of the population need to be immunized to achieve herd immunity (Reproductive value <1) with a vaccine efficacy of 95%. The author also points out that with unknowns such as variable antibody titers and possible seasonal recurrence, we still have much to learn regarding long term efficacy of the currently available vaccines, and suggests that transmission mitigation measures such as mask wearing and social distancing should still be practiced after receiving the vaccination.

MANAGEMENT

PERSISTENT POST-COVID-19 INFLAMMATORY INTERSTITIAL LUNG DISEASE: AN OBSERVATIONAL STUDY OF CORTICOSTEROID TREATMENT

Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, Preston R, Thillai M, Dewar A, Molyneaux PL, West AG.. Ann Am Thorac Soc. 2021 Jan 12. doi: 10.1513/AnnalsATS.202008-1002OC. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

Pulmonologists and a radiologist from the United Kingdom conducted a single-center prospective observational study of 837 adult COVID-19 patients four weeks after hospital discharge (Figure 1). They found evidence of post-COVID interstitial lung disease (ILD) in 35 patients (4.8%)(Table 5), and that early treatment with corticosteroids resulted in significant radiologic and symptomatic improvement (Figure 3). Authors suggest that early treatment of post-COVID ILD may prevent further functional impairment and recommend further studies on its natural history and management.

ABSTRACT

RATIONALE: The natural history of recovery from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) remains unknown. Since fibrosis with persistent physiological deficit is a previously-described feature of patients recovering from similar coronaviruses, treatment represents an early opportunity to modify the disease course, potentially preventing irreversible impairment. OBJECTIVES: Determine the incidence of and describe the progression of persistent inflammatory interstitial lung disease (ILD) following SARS-CoV2 when treated with prednisolone. METHODS: A structured assessment protocol screened for sequelae of SARS-CoV2 pneumonitis. 837 patients were assessed by telephone four weeks after discharge. Those with ongoing symptoms had outpatient assessment at six weeks. Thirty patients diagnosed with persistent interstitial lung changes at multi-disciplinary team meeting were reviewed in the interstitial lung disease service and offered treatment. These patients had persistent, non-improving symptoms. RESULTS: At four weeks post-discharge, 39% of patients reported ongoing symptoms (325/837), and were assessed. Interstitial lung disease, predominantly organising pneumonia, with significant functional deficit was observed in 35/837 survivors (4.8%). Thirty of these patients received steroid treatment, resulting in a mean relative increase in transfer factor following treatment of 31.6% (standard deviation +- 27.64, p <0.001), and FVC of 9.6% (standard deviation +- 13.01, p = 0.014), with significant symptomatic and radiological improvement. CONCLUSION: Following SARS-CoV-2 pneumonitis, a cohort of patients are left with both radiological inflammatory lung disease and persistent physiological and functional deficit. Early treatment with corticosteroids was well tolerated and associated with rapid and significant improvement. This preliminary data should inform further study into the natural history and potential treatment for patients with persistent inflammatory ILD following SARS-CoV2 infection.

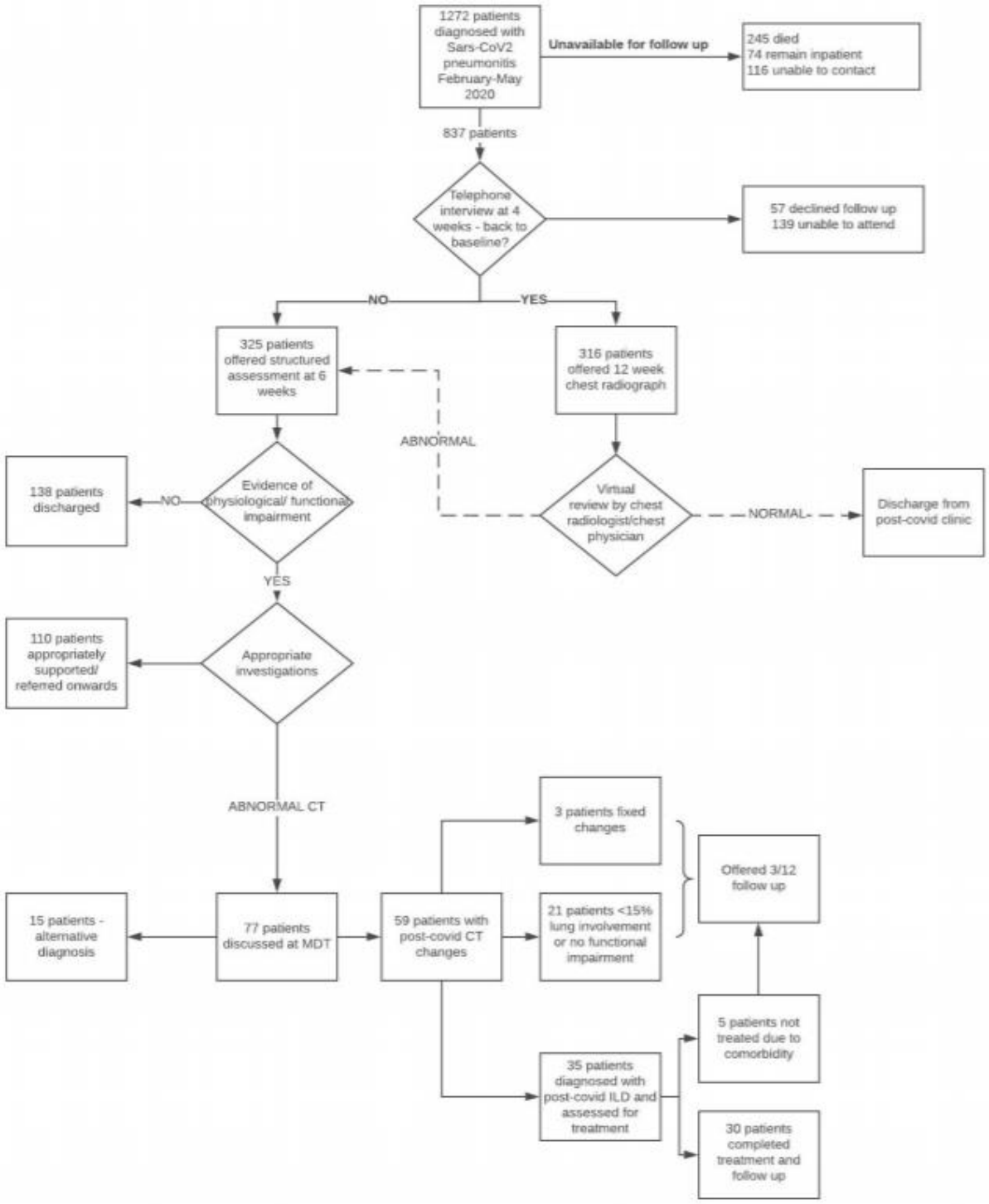

Figure 1: Flowchart of the study population recruited between February and May 2020.

Table 1: Baseline characteristics of patients with interstitial lung disease following infection with SARS-CoV-2. Data are presented as percentage value or mean ± standard deviation (SD) as appropriate. CKD: Chronic Kidney Disease; HIV: Human Immunodeficiency Virus; COPD: Chronic Obstructive Pulmonary Disease.

n=35		
Age		60.5 ± 10.7
Sex	**Male**	25 (71.4%)
	Female	10 (28.6%)
BMI		28.3 ± 4.0
Smoking history	**Ever smoker**	21 (34.2%)
	Never smoker	14 (65.7%)
Comorbidities	**Obesity**	9 (25.7%)
	Hypertension	11 (31.4%)
	Diabetes	8 (22.9%)
	CKD	2 (5.8%)
	HIV	1 (2.9%)
	Sickle cell	1 (2.9%)
	Asthma	8 (22.9%)
	COPD	2 (5.8%)
	Pre-existing ILD	0

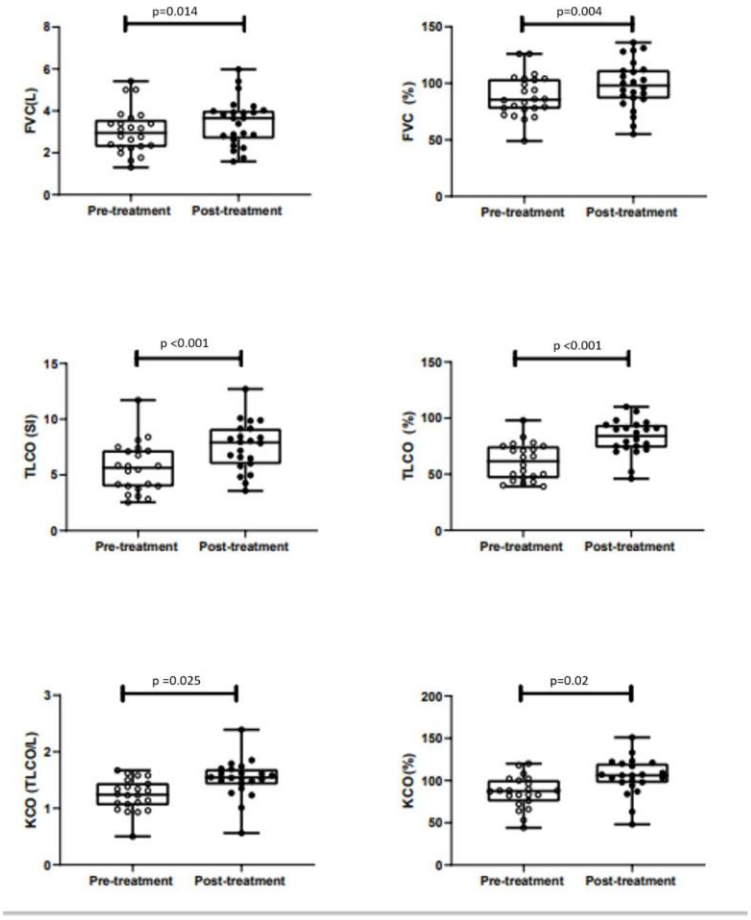

Figure 3: Change in lung function following treatment with oral prednisolone in patients with interstitial lung disease following infection with SARS-CoV-2

NEUROLOGY

SARS-COV-2 ENCEPHALITIS IS A CYTOKINE RELEASE SYNDROME: EVIDENCES FROM CEREBROSPINAL FLUID ANALYSES

Pilotto A, Masciocchi S, Volonghi I, De Giuli V, Caprioli F, Mariotto S, Ferrari S, Bozzetti S, Imarisio A, Risi B, Premi E, Benussi A, Focà E, Castelli F, Zanusso G, Monaco S, Stefanelli P, Gasparotti R, Zekeridou A, McKeon A, Ashton NJ, Blennov K, Zetterberg H, Padovani A.. Clin Infect Dis. 2021 Jan 4:ciaa1933. doi: 10.1093/cid/ciaa1933. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A study conducted by multiple medical institutions in Italy, the United States, Sweden, and England between February 20 and June 30, 2020 analyzed laboratory markers in 13 patients admitted with SARS-CoV-2-related encephalitis, 18 neurologically healthy controls, and 21 patients with non-SARS-CoV-2-related encephalitis. Results showed elevated neuroinflammatory markers including GFAP, TREM2, YKL-40 as well as increased cytokines (IL-6, IL-8, beta-2 microglobulin, and TNF-alpha) in the cerebrospinal fluid (CSF) analysis of the SARS-CoV-2 patients (See Table 2), which were found to be similar to non-SARS-CoV-2-related encephalitis patients who additionally had elevated CXCL13 (See Figure 1). Authors suggest these systemic inflammatory mediators present in cytokine release syndrome act directly across the blood-brain barrier to induce astrocyte activation and neuroinflammation within glial cells. They believe this evidence supports potential for immunomodulatory treatment targeting specific cytokines as well as management of SARS-CoV-2-encephalitis with high-dose corticosteroids after excluding other bacterial/viral co-infections.

ABSTRACT

BACKGROUND: Recent findings indicated that SARS-CoV-2 related neurological manifestations involve cytokine release syndrome along with endothelial activation, blood brain barrier dysfunction, and immune-mediated mechanisms. Very few studies have fully investigated the CSF correlates of SARS-CoV-2 encephalitis. METHODS: Patients with PCR-confirmed SARS-CoV-2 infection and encephalitis (COV-Enc), encephalitis without SARS-CoV-2 infection (ENC) and healthy controls (HC) underwent an extended panel of CSF neuronal (NfL, T-tau), glial (GFAP, TREM2, YKL-40) and inflammatory biomarkers (IL-1beta, IL-6, Il-8, TNF- alpha, CXCL-13 and beta2-microglobulin). RESULTS: Thirteen COV-Enc, 21 ENC and 18 HC entered the study. In COV-Enc cases, CSF was negative for SARS-CoV-2 real-time PCR but exhibited increased IL-8 levels independently from presence of pleocytosis/hyperproteinorracchia. COV-Enc patients showed increased IL-6, TNF- alpha, and beta2-microglobulin and glial markers (GFAP, sTREM-2, YKL-40) levels similar to ENC but normal CXCL13 levels. Neuronal markers NfL and T-Tau were abnormal only in severe cases. CONCLUSIONS: SARS-CoV-2-related encephalitis were associated with prominent glial activation and neuroinflammatory markers, whereas neuronal markers were increased in severe cases only. The pattern of CSF alterations suggested a cytokine-release syndrome as the main inflammatory mechanism of SARS-CoV-2 related encephalitis.

ID	Age, sex	CSF								ICANS grade	Final mRS
		cells*	Prot#	TAU	NfL	GFAP	sTREM-2	IL-6	IL-8	β-2-Mg¶		
#1	70 F	5	34.2	189	707	300	2875	3.5	51	0.9	2	2
#2	60 M	19	69.6	231	789	244	4609	2.3	1106	3.1	3	0
#3	65 F	5	68.7	256	368	197	2499	1.5	57	1.3	3	0
#4	77 M	1	49.5	322	837	253	917	0.6	74	1.8	3	0
#5	60 F	9	46.7	344	150	184	469	1.7	72	0.8	2	0
#6	78 F	1	36.2	344	1353	151	469	1.8	88	1.4	2	0
#7	70 F	1	19.7	456	1394	492	1460	0.9	188	1.9	4	6
#8	52 M	19	80.5	258	1825	607	4166	1.7	57	1.9	4	0
#9	51 M	5	125.2	1044	3004	456	8955	2.1	92	5.9	4	0
#10	50 M	10	77.0	1047	8382	280	4100	290	1106	1.3	3	2
#11	60 M	26	74.0	1272	13801	744	4867	531	1106	2.7	4	6
#12	75 M	0	40.0	1245	19082	789	2531	2.1	259	2.8	3	6
#13	74 F	16	23.3	1741	19126	358	1839	2.1	252	2.2	4	6

Table 2. Clinical features, imaging and CSF biochemical analyses of COV-Enc cases. Values are expressed in and cytokine levels if no otherwise indicated. Abbreviations: F, female; GFAP, Glial fibrillary acidic protein; ICANS, Immune effector cell-associated neurotoxicity syndrome; IL-8, interleukin 8; M, male; mRS, modified Ranking score; NfL, neurofilament light chain; prot, protein in the CSF; sTREM-2, triggering receptor expressed on myeloid cells 2, β-2-Mg, beta-2 microglobulin (levels in mg/dL) ⍰ cell count per uL # protein levels in mg/dL ¶ levels in mg/L

Figure 1

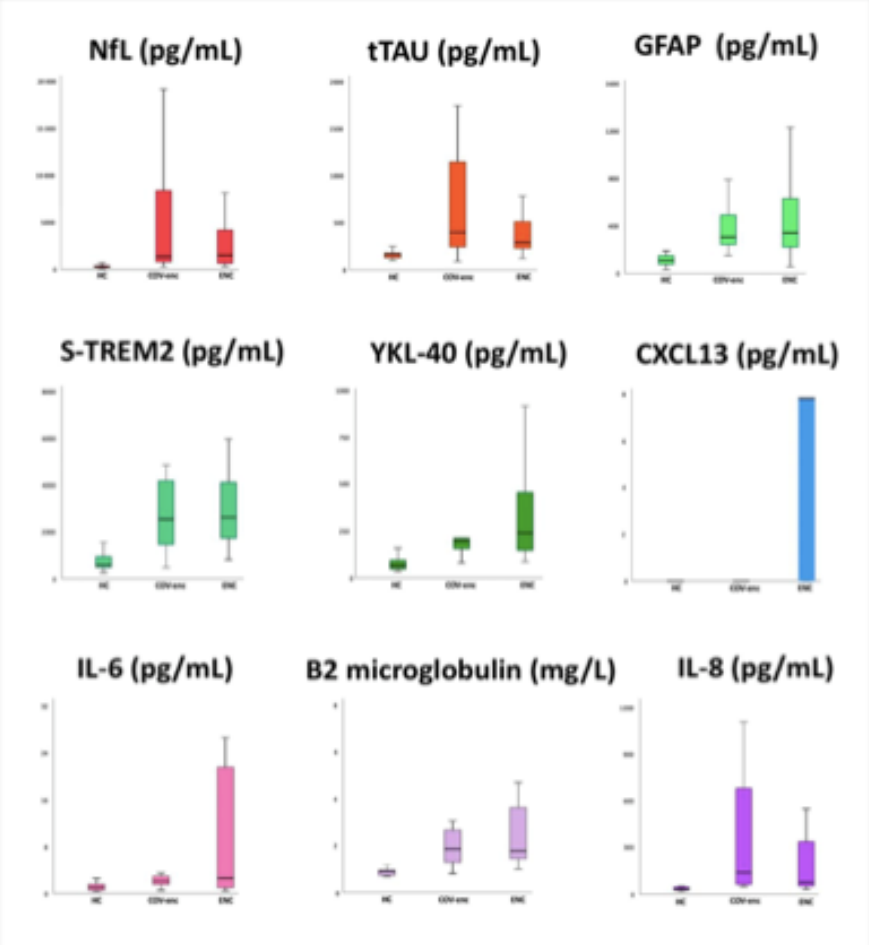

Figure 1. Differences in neuronal, glial and inflammatory markers according to the clinical diagnosis. Boxplot indicate median and interquartile ranges-

Abbreviations: COV-ENC, encephalitis cases concomitant COVID-19 disease; CXCL13, chemokine (C-X-C motif) ligand 13; ENC, encephalitis without concomitant COVID-19; GFAP, Glial fibrillary acidic protein; HC, control group; IL-6, interleukin 6; IL-8, interleukin 8; NfL, neurofilament light chain; sTREM-2, triggering receptor expressed on myeloid cells 2; YKL-40, Chitinase-3-like protein 1; post-hoc comparison post-hoc comparison.

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