The Daily COVID-19 Literature Surveillance Summary

September 25, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

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

Management

- A 31-year-old female kidney transplant recipient on immunosuppressants tested negative twice 18 days after initial positive test for SARS-CoV-2, yet tested positive again for SARS-CoV-2 via RT-PCR on day 20 with recurrence of symptoms. Despite treatment with lopinavir-ritonavir and resolution of symptoms 6 days after treatment, the patient continued to test positive by rectal swab for an additional 21 days and was monitored by serial cycle threshold of viral RNA.

R&D: Diagnosis & Treatments

- An observational study of 242 patients with severe COVID-19 pneumonia and corresponding elevated inflammatory markers (including 61 patients receiving methylprednisolone in week 2 of infection) found 22 patients (9%) died and 31 (12.8%) suffered death or intubation. Hazard ratios for death and death or intubation for the week-2 MP group had lower adjusted risk for both outcomes compared to out-of-week-2 MP (administered Week 1 or Week 3), non-pulse glucocorticoids (<100mg/day), or no glucocorticoids, but these values were only significant in patients with low SpO2/FiO2 (<353).

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PEDIATRICS

GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 DETECTION AND CORONAVIRUS DISEASE 2019 IN A CHILD

Khalifa M, Zakaria F, Ragab Y, Saad A, Bamaga A, Emad Y, Rasker JJ.. J Pediatric Infect Dis Soc. 2020 Sep 17;9(4):510-513. doi: 10.1093/jpids/piaa086.
Level of Evidence: Other - Case Report

BLUF

This report details one of the first reported pediatric cases of Guillain-Barré Syndrome (GBS) following a SARS-CoV-2 infection. An 11-year-old male from Saudi Arabia was admitted to the hospital on April 10, 2020 for neurological symptoms, with subsequent confirmation of GBS followed by positive SARS-CoV-2 test (see summary). Authors emphasize the importance of prompt recognition and treatment of neuromuscular presentations in pediatric COVID-19 cases.

SUMMARY

An 11-year-old boy presented to Bagedo General Hospital in Jeddah, Saudi Arabia on April 10, 2020 with acute onset unsteady gait, inability to walk, and tingling sensation in bilateral lower extremities. There was no known contact with anyone positive for COVID-19, however he did have a mild upper respiratory tract infection on March 20, 2020 for which he received antibiotics. Physical exam revealed lower extremity muscle weakness and decreased reflexes, with subsequent nerve conduction studies confirming the diagnosis of GBS, and spinal imaging further supporting the diagnosis (Figures 1A, 1B). Additional imaging revealed abnormalities in the patient's lungs with basal veiling opacities (Figures 1C, 1D) and subsegmental faint opacity with atelectasis (Figures 1E, 1F). SARS-CoV-2 was suspected, and confirmed via RT-PCR on April 15, 2020. The patient was started on acetaminophen as needed, hydroxychloroquine twice daily, and thromboprophylaxis with heparin. Respiratory symptoms were mild throughout the course, and neurological symptoms slowly improved, though the patient also developed dermatological manifestation with a nonpruritic morbilliform skin rash on bilateral palms (Figure 1G). The patient's symptoms fully resolved and he was discharged home on April 25, 2020.

ABSTRACT

Coronavirus disease (COVID-19) is caused by SARS-CoV-2. Physicians in China reported what is believed to be the first adult case of a SARS-CoV-2 infection associated with acute Guillain-Barre syndrome (GBS), followed by five adult Italian patients and another case in the United States of America. In the current report we present one of the first descriptions of an association of GBS and SARS-CoV-2 infection within a child. In our facility, and eleven year old boy presented with typical features of GBS and after five days a morbilliform skin rash over the palms of both hands. Three weeks before the start of the neurological symptoms, the boy had experienced an episode of mild febrile illness with mild respiratory manifestations and a persisting cough. The diagnosis of the SARS-CoV-2 infection was confirmed by oropharyngeal swab on reverse transcription polymerase chain reaction assay. The disease course of our patient strongly suggests a possible relationship between the development of GBS and SARS-CoV-2 infection. The case is discussed in view of the previous case reports with the association of GBS and Covid-19.

FIGURES

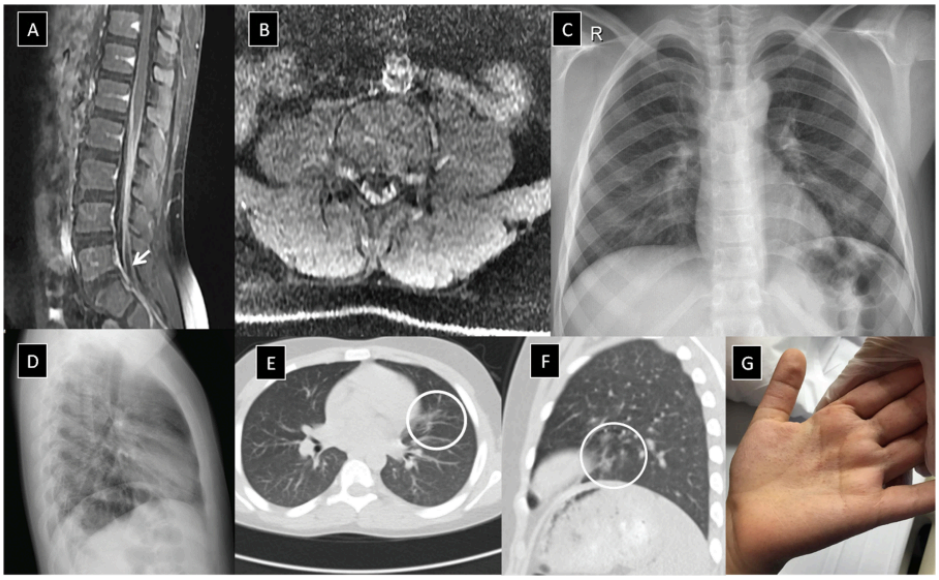

Figure 1. A and B, Sagittal and axial T1 fat saturation postcontrast magnetic resonance imaging showing cauda equina nerve root enhancement (white arrow) indicative of Guillain-Barré syndrome. C and D, Chest radiograph postanterior and left lateral views showing bilateral paracardiac and basal veiling. E and F, Computed tomography of the chest showing small patchy subsegmental faint opacity with atelectasis band in the lingula on the week after admission (white circles). G, Morbilliform skin rash over the palmar aspect of the left hand.

UNDERSTANDING THE PATHOLOGY

IN VITRO

SARS-COV-2 INFECTS AND INDUCES CYTOTOXIC EFFECTS IN HUMAN CARDIOMYOCYTES

Bojkova D, Wagner JUG, Shumliakivska M, Aslan GS, Saleem U, Hansen A, Luxán G, Günther S, Pham MD, Krishnan J, Harter PN, Ermel UH, Frangakis AS, Milting H, Zeiher AM, Klingel K, Cinatl J, Dendorfer A, Eschenhagen T, Tschöpe C, Ciesek S, Dimmeler S.. Cardiovasc Res. 2020 Sep 23:cvaa267. doi: 10.1093/cvr/cvaa267. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

An in vitro study conducted by cardiac researchers in Germany found that SARS-CoV-2 can infect stem cell-derived cardiomyocytes and cardiospheres, as well as infect living human cardiac tissue slices obtained from explanted hearts (Figure 6). In an endomyocardial biopsy of a patient with COVID-19, remdesivir (in addition to recombinant ACE2 and neutralizing antibodies) successfully inhibited viral spike protein expression in the human cardiac tissue. The authors concluded that SARS-CoV-2 infects cardiomyocytes in vitro in an ACE2 and cathepsin dependent manner which can be inhibited by remdesivir (Figure 5), suggesting the need for more research to understand if COVID-19 related heart injury is caused directly through viral infection or via secondary causes.

FIGURES

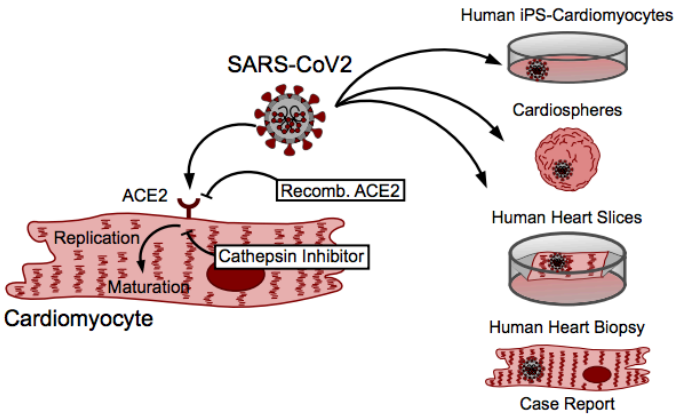

Figure 6. Graphic depicting SARS-CoV-2 infection of cardiac tissue. (caption by COVID-19 LST)

Figure 5

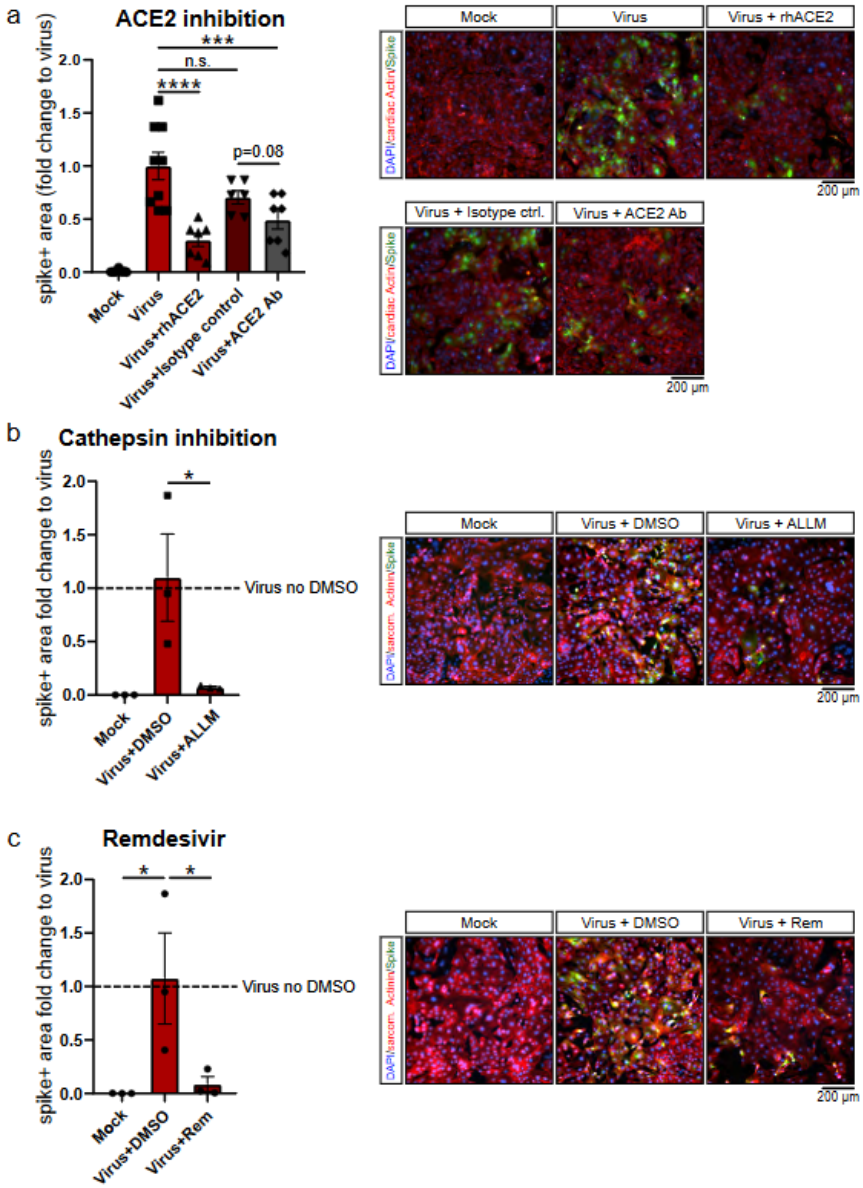

Figure 5: Cardiomyocyte infection is inhibited by ACE2, cathepsin and RNA polymerase inhibition. a, Effect of recombinant ACE2 (5 µg/ml) or neutralizing antibodies (80 µg/ml) on SARS-CoV-2 infection. Spike protein was quantified after 48 h of infection (MOI=1). n=9 (virus), n=7 (virus+rhACE2), n=6 (Isotope control) und n=7 (virus + ACE2 AB), all biological replicates. b, Effect of the protease inhibitor N-Acetyl-L-leucyl-L-leucyl-L-methional(ALLM; 1 µM; added during and post infection) on spike protein expression after infection with SARS-CoV-2 (MOI=1) at 48h.n=3 biological replicates.c, Effect of remdesivir (1 µM, added post-infection). Since ALLMand remdesivir were solved in DMSO, virus infected cells were also treated with DMSO in panels b and c. n=3 biological replicates.Data were statistically assessed using one-way ANOVA with post hoc Dunnett's (a, b) or post hoc Holm-Sidak's test (c). n.s. = not significant, *p<0.05, ***p<0.001, ****p<0.0001.

TRANSPLANT SURGERY

A CASE OF "RELAPSING" COVID-19 IN A KIDNEY TRANSPLANT RECIPIENT

Mingyao MB, Ngai HIF, Wang CGC, Raymond TA, Kay CSS, Kwan WBC, Kenichiro F, Takanori O, Yung YK, Mao CT..
Nephrology (Carlton). 2020 Sep 20. doi: 10.1111/nep.13786. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

Investigators affiliated with The University of Hong Kong present a 31-year-old female, kidney transplant recipient on immunosuppressants who re-tested positive for SARS-CoV-2 following consecutive negative results. Specifically, the patient tested negative twice 18 days after initial positive test for SARS-CoV-2, yet tested positive again for SARS-CoV-2 via RT-PCR on day 20 with reoccurrence of symptoms. Despite treatment with lopinavir-ritonavir and resolution of symptoms 6 days after treatment, the patient continued to test positive by rectal swab for an additional 21 days and was monitored by serial cycle threshold (Ct) of viral RNA (Table 2; Figure 1). In reviewing this case, the authors highlight:
-the challenge in managing transplant recipients with COVID-19
-the potential for "relapse" of COVID-19 infection or ongoing viral shedding in an immunosuppressed patient
-the crucial role that viral load monitoring may play in managing these patients
-the difficulty in balancing transplant rejection risk and the potential interactions between immunosuppressant drugs and antiviral agents.

ABSTRACT

Clinical outcomes of COVID-19 vary considerably between patients. Little was known about the clinical course and optimal management of immunosuppressed patients infected with SARS-CoV-2. We report a kidney transplant recipient with COVID-19 who presented with pneumonitis and acute kidney injury (AKI). She improved after reduction of immunosuppressive treatment and had two consecutive negative reverse transcription polymerase chain reaction (RT-PCR) tests. Her respiratory tract samples turned positive again afterwards, and she was treated with lopinavir-ritonavir. She had satisfactory virological and clinical response after a prolonged disease course. This case illustrates the risk of relapse or persisting shedding of SARS-CoV-2 in immunosuppressed patients, the important role of viral load monitoring in management, the challenges in balancing the risks of COVID-19 progression and transplant rejection, and the pharmacokinetic interaction between immunosuppressive and antiviral medications.

FIGURES

Table 2. Serial RT-PCR cycle threshold values in a kidney transplant recipient with COVID-19

	Day[†]22	Day24	Day26	Day28	Day30	Day32	Day34	Day36	Day38
Ct value	33.4	33.9	31.8	36.9	37.1	36.3	undetermined[‡]	38.9	undetermined

Abbreviations: Ct, RT-PCR cycle threshold value
[†]Day, the number of days since the first diagnosis of COVID-19
[‡]Undetermined, the quantity of viral RNA does not exceed a detection threshold (i.e. Ct value >40 cycles)

Table 2: Serial RT-PCR cycle threshold values in a kidney transplant recipient with COVID-19

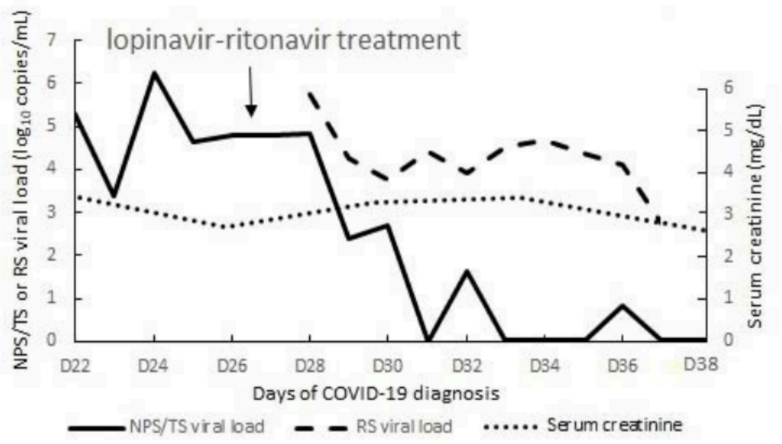

Figure 1. Serial profile of SARS-CoV-2 viral load in nasopharyngeal swab/throat swab and rectal swab specimens, and of serum creatinine level, in a kidney transplant recipient

ADJUSTING PRACTICE DURING COVID-19

SURGERY AND COVID-19

Kibbe MR.. JAMA. 2020 Sep 22;324(12):1151-1152. doi: 10.1001/jama.2020.15191.
Level of Evidence: Other - Expert Opinion

BLUF

A commentary piece by a surgeon and JAMA editor from UNC Chapel Hill discusses the various challenges the surgical field has faced due to the COVID-19 pandemic (described in summary below). The author draws attention to the lasting effects the pandemic poses on the specialty for patients, medical students, and the healthcare workforce. The author stresses the need for awareness of such changes, asking readers for acceptance of adaptive change.

SUMMARY

The author discusses the following effects of the pandemic on the surgical specialty and the responses needed:

- There is a need for adequate appropriate personal protective equipment (PPE) for surgical personnel.
- Use of smoke evacuators in operating rooms is imperative in protecting healthcare personnel from aerosolized tissues.
- A study has shown increased odds of 30-day mortality risk, perioperative pulmonary complications, and thrombotic complications in postoperative individuals (Doglietto et al, Italy).
- There has been a significant decrease in non-urgent procedures, which will need to be addressed when the pandemic ends.
- The pandemic has restricted medical students from fully experiencing the surgical specialty, likely negatively impacting the amount of students applying to the specialty in the future.
- The surgical workforce, especially those in private practice, has been affected by pay cuts and lay offs due to drastic reductions in surgical services.

OTOLARYNGOLOGY

OTOLARYNGOLOGY-HEAD AND NECK SURGERY AND COVID-19

Piccirillo JF.. JAMA. 2020 Sep 22;324(12):1145-1146. doi: 10.1001/jama.2020.15779.
Level of Evidence: Other - Expert Opinion

BLUF

An otolaryngologist from the Washington University School of Medicine in Missouri discusses that due to tight association with the upper airway, COVID-19 has caused major practice changes in the field of otolaryngology–head and neck surgery (most effected being rhinology and head and neck cancer). These limitations include reducing certain invasive procedures to high acuity cases only and transitioning to using medical or conservative management whenever possible (e.g. watchful waiting for indolent neoplastic disease). The author concludes by stating he believes some of these changes will likely become permanent in the otolaryngology field long after COVID-19 ends.

SECOND WEEK METHYL-PREDNISOLONE PULSES IMPROVE PROGNOSIS IN PATIENTS WITH SEVERE CORONAVIRUS DISEASE 2019 PNEUMONIA: AN OBSERVATIONAL COMPARATIVE STUDY USING ROUTINE CARE DATA

Ruiz-Irastorza G, Pijoan JI, Bereciartua E, Dunder S, Dominguez J, Garcia-Escudero P, Rodrigo A, Gomez-Carballo C, Varona J, Guio L, Ibarrola M, Ugarte A, Martinez-Berriotxoa A; Cruces COVID Study Group.. PLoS One. 2020 Sep 22;15(9):e0239401. doi: 10.1371/journal.pone.0239401. eCollection 2020.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

An observational comparative study at Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain between March 1 - April 30, 2020 involving 242 patients with severe COVID-19 pneumonia with corresponding elevated inflammatory markers, including 61 patients receiving methylprednisolone (MP) in week 2 of infection, found 22 patients (9%) died and 31 (12.8%) suffered death or intubation. Hazard ratios for death and death or intubation for the week-2 MP group had lower adjusted risk for both outcomes compared to out-of-week-2 MP (administered Week 1 or Week 3), non-pulse glucocorticoids (<100mg/day), or no glucocorticoids (Table 2 & Figure 2), but these values were only significant in patients with low SpO2/FiO2 (<353). These findings suggest the potential benefit of early MP use in the second week of infection to improve prognosis of patients with inflammatory activity and respiratory deterioration secondary to COVID-19 pneumonia.

ABSTRACT

OBJECTIVE: To analyze the effects of a short course of methyl-prednisolone pulses (MP) during the second week of disease (week-2) in patients with severe coronavirus disease 2019 (COVID-19) pneumonia. METHODS: Comparative observational study using data collected from routine care at Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain in patients with COVID-19 pneumonia. We compared patients who received week-2-MP (125-250 mg/d x3) with those who did not, with the end-points time to death and time to death or endotracheal intubation. RESULTS: We included 242 patients with COVID-19 pneumonia and elevated inflammatory markers at admission. Sixty-one patients (25%) received week-2-MP. Twenty-two patients (9%) died and 31 (12.8%) suffered death or intubation. The adjusted HRs for death and death or intubation for patients in the week-2-MP group were 0.35 (95%CI 0.11 to 1.06, p = 0.064) and 0.33 (95%CI 0.13 to 0.84, p = 0.020), respectively. These differences were specifically seen in the subcohort of patients with a SpO2/FiO2 at day 7 lower than 353 (adjusted HR 0.31, 95% CI 0.08 to 1.12, p = 0.073 and HR 0.34, 95%CI 0.12 to 0.94, p = 0.038, respectively) but not in patients with higher SpO2/FiO2. Patients receiving out-of-week-2-MP, non-pulse glucocorticoids or no glucocorticoids had an increased adjusted risk for both outcomes compared with week-2-MP group: HR 5.04 (95% CI 0.91-27.86), HR 10.09 (95% CI 2.14-47.50), HR 4.14 (95% CI 0.81-21.23), respectively, for death; HR 7.38 (95% CI 1.86-29.29), HR 13.71 (95% CI 3.76-50.07), HR 3.58 (95% CI 0.89-14.32), respectively, for death or intubation. These differences were significant only in the subgroup with low SpO2/FiO2. CONCLUSIONS: Week-2-MP are effective in improving the prognosis of patients with COVID-19 pneumonia with features of inflammatory activity and respiratory deterioration entering the second week of disease. The recognition of this high-risk population should prompt early use of MP at this point.

Table 2. Predictors of death: Final models.

Variable	HR (95%CI)	p
WHOLE COHORT (n = 242)		
Week-2-MP	0.35 (0.11–1.06)	0.064
Non-pulse glucocorticoids	3.01 (1.28–7.14)	0.012
Hypertension	2.89 (0.91–9.17)	0.072
SpO2/FiO2	0.94 (0.91–0.98)	0.001
CURB65		
Low risk	Reference	
Intermediate risk	1.64 (0.55–4.88)	0.371
High risk	7.72 (2.56–23.26)	<0.001
PATIENTS WITH SpO2/FiO2 ≤353 (n = 122)		
Week-2-MP	0.31 (0.08–1.12)	0.073
Non-pulse glucocorticoids	2.98 (1.09–8.17)	0.034
Hypertension	3.14 (0.84–11.75)	0.089
SpO2/FiO2	0.92 (0.87-0-97)	0.002
CURB65		
Low risk	Reference	
Intermediate risk	1.48 (0.41–5.34)	0.546
High risk	10.29 (2.72–38.94)	0.001

Week-2-MP: methyl-prednisolone pulses in week 2. HR: hazard ratio; CI: confidence interval.
*HR for SpO2/FiO2 is change in hazard for each increase of 10 units in its value.

https://doi.org/10.1371/journal.pone.0239401.t002

Table 2: Predictors of death: Final models.

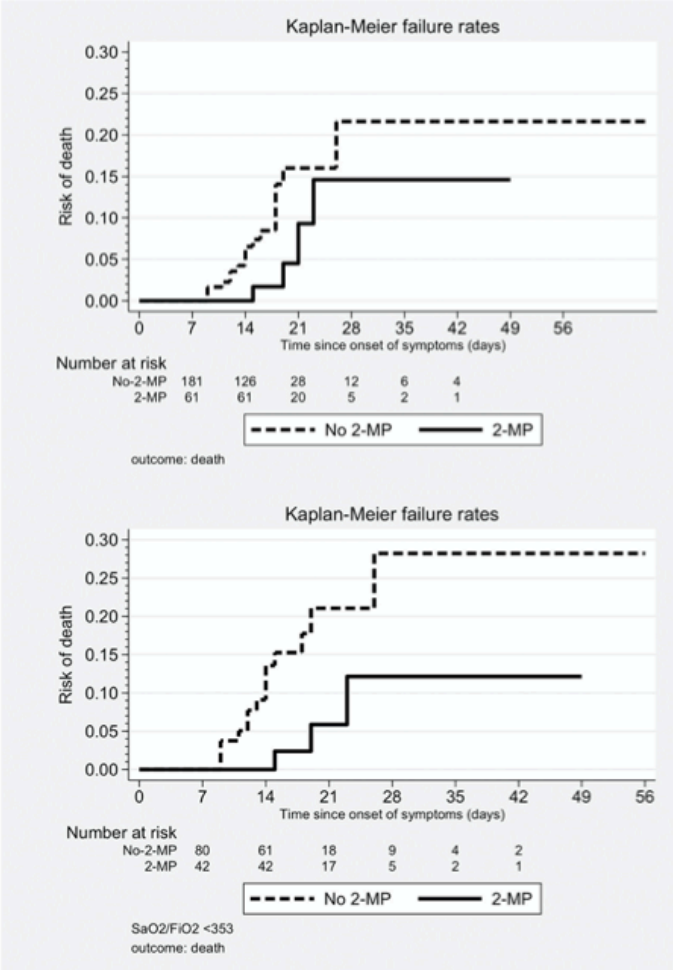

Fig 1. Kaplan-Meier failure curves, second week methyl-prednisolone pulses (2-MP) vs. no 2-MP. Outcome: death. (a) Whole cohort (n = 242). Log-rank test, p = 0.102. (b) Patients with low SpO2/FiO2 (n = 122). Log-rank test, p = 0.041.

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