Organizing pneumonia in patients who develop late onset symptoms of COVID-19 or are in post COVID state

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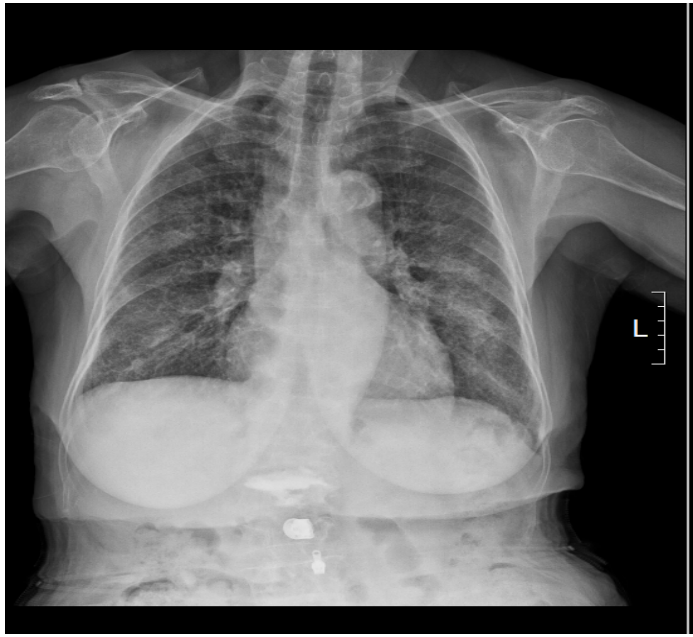
Case : 82/F

C/C) dyspnea (onset : 5 days ago ,2022.04.03.)

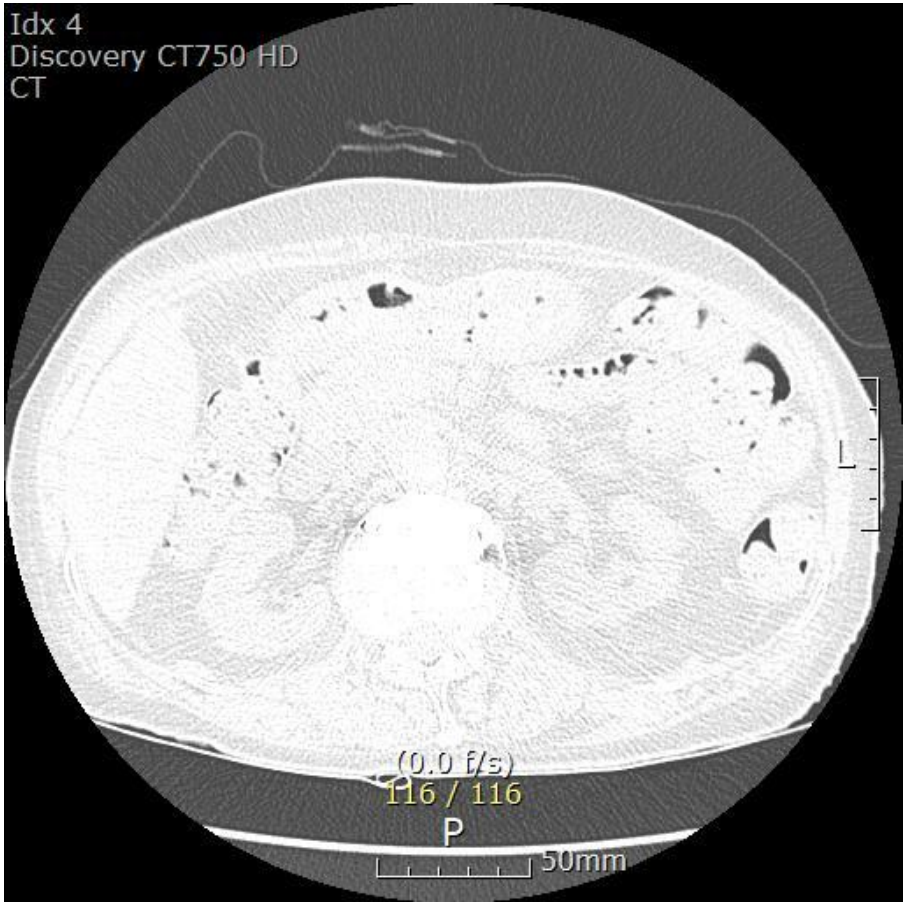
P/H)
COVID_19 : Rapid antigen test (+, 2022.03.18)
isolation 2022.03.18 ~ 2022.3.24
CHB
CKD
depression

2022.04.03



2022.04.08

Pip/taz + levofloxacin 2022.04.03 ~



- **P/E & ROS**

C/S +/- ,fever –
Dyspnea :Mmrc Gr 4 , O2 3L
Crackles on both lung field

- **Lab**

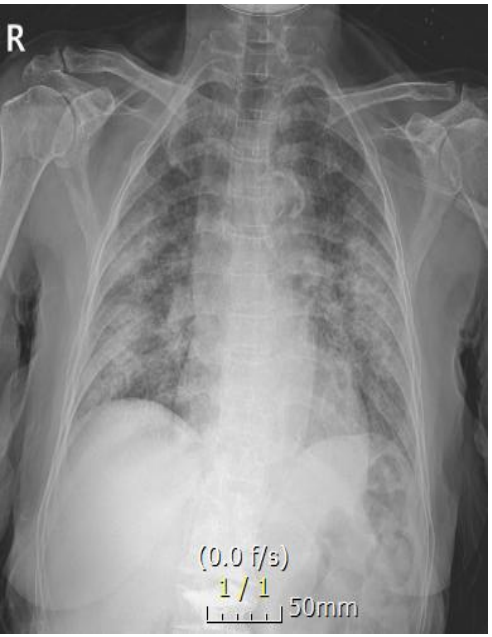
WBC count	9.6
CRP (Quantitation)	5.82
Procalcitonin	0.088

- **Pneumonia w/u**

Gram stain & culture : No growth
Pneumoccocal urine Ag : Negative
Pneumobacter PCR : negative
Respiratory viral PCR : negative

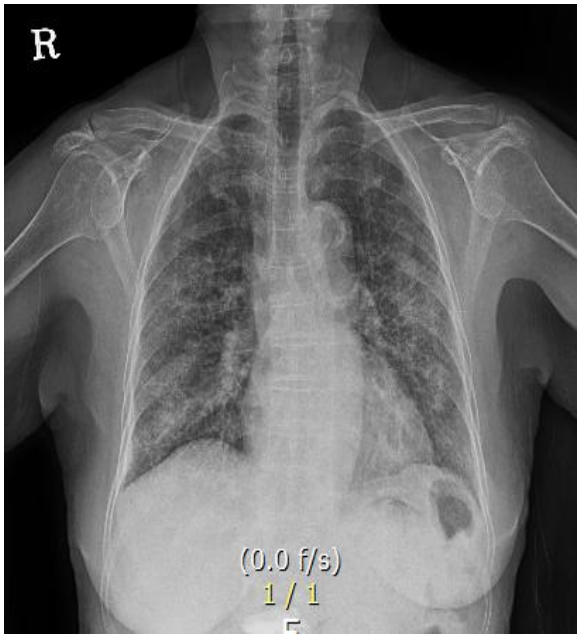
2019-nCoV PCR (Upper respiratory tract)	Negative

Hospital course



HD 1

HD 4

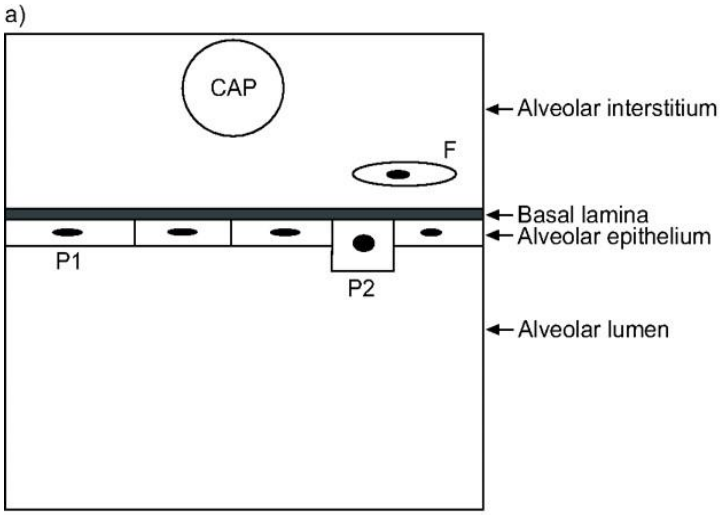


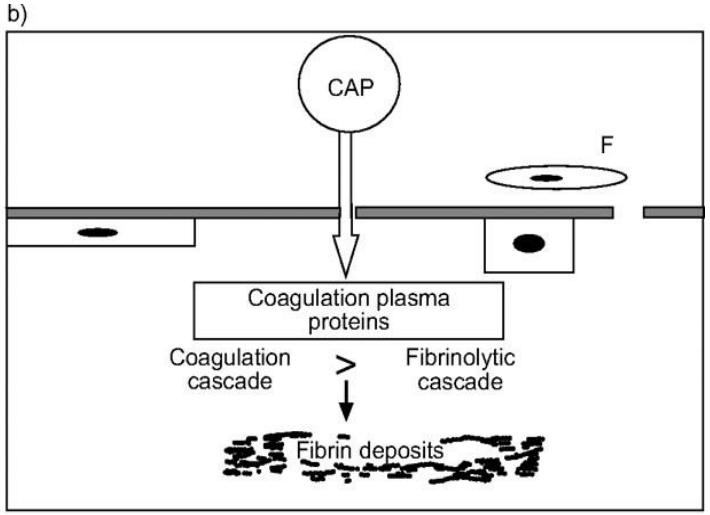
HD8

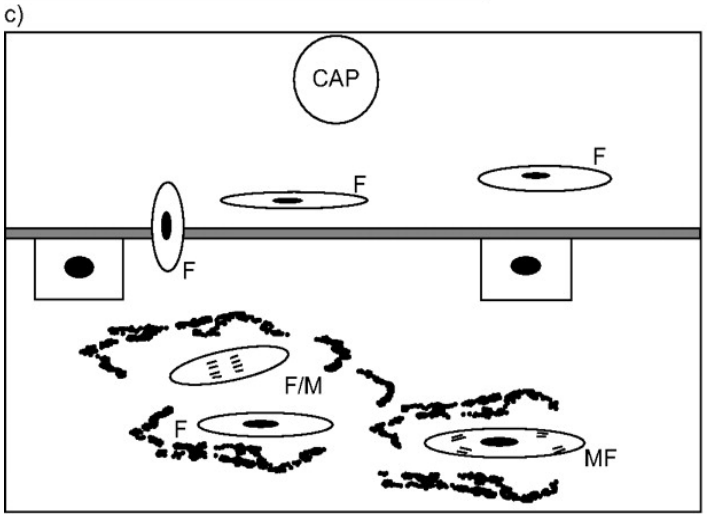
HD 13

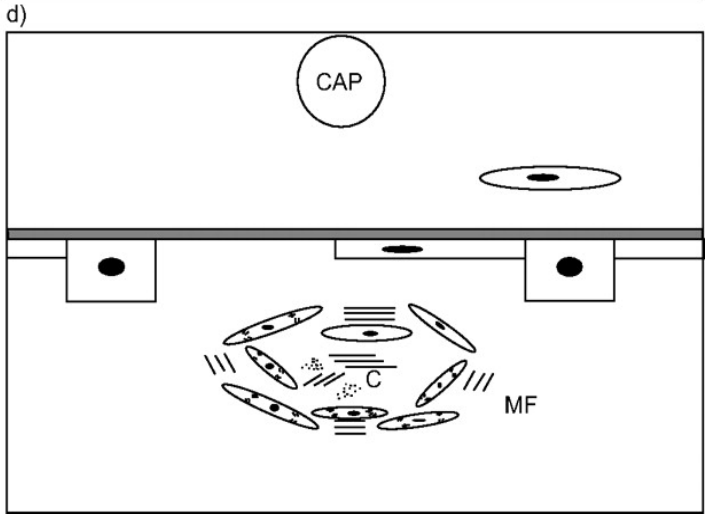
mPRD 62.5mg Qd for 4 days | mPRD 40mg qD for 2days | PRD 20mg qD ~

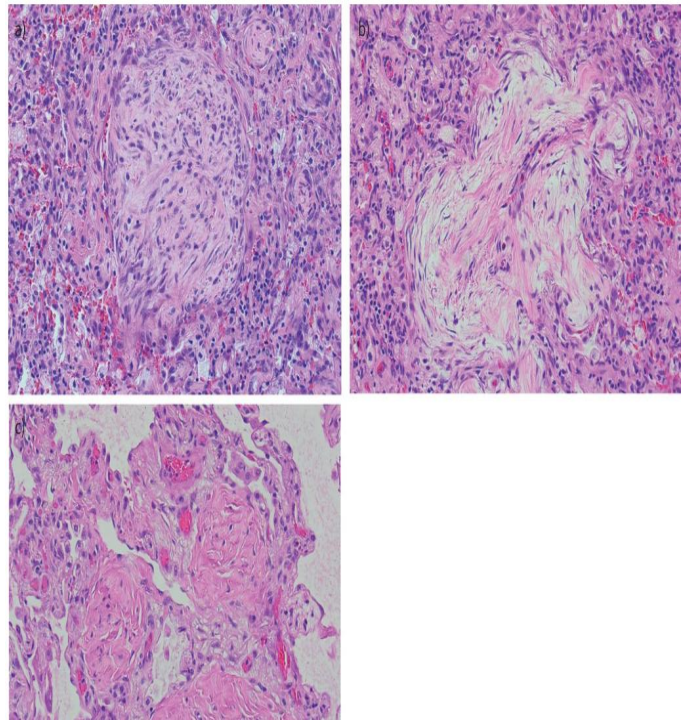
Organizing pneumonia - pathophysiology











European Respiratory Journal 2006 28: 422-446

Organizing pneumonia

TABLE 1

Conditions associated with organising pneumonia (OP)[#]

Connective tissue disorders
Hypersensitivity pneumonitis (acute)
Adverse drug reactions
Bone marrow, stem cell or solid organ transplantation
Infection
Airway diseases complicated by infection
Airway obstruction (distal changes)
Inhalation injury
Aspiration syndromes
Chronic eosinophilic pneumonia
Radiation pneumonitis
Inflammatory bowel disease
Neoplasms and myeloproliferative disorders
Organising diffuse alveolar damage
Coexistent with pathologic changes of IIP (*e.g.* UIP or NSIP)
Acute exacerbation of IPF (OP lesions superimposed on chronic UIP pattern)
Proximal bronchial obstruction (OP found distal to focus of obstruction)
Miscellaneous
Immunodeficiency syndromes
Cryoglobulinemia
Granulomatosis with polyangiitis
Other vasculitis

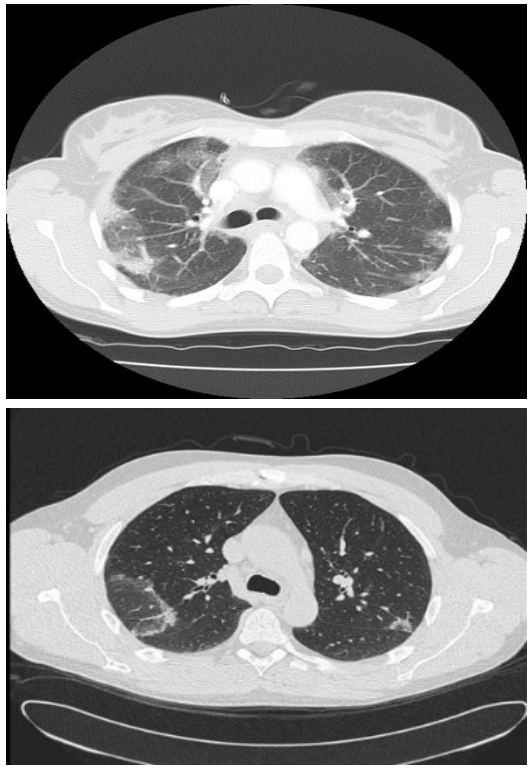
IIP: idiopathic interstitial pneumonia; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; IPF: idiopathic pulmonary fibrosis. [#]: conditions other than cryptogenic organising pneumonia (idiopathic OP) that have been associated with histopathologic findings of OP in lung tissue specimens.

European Respiratory Review 2021 30: 210094

TABLE 2

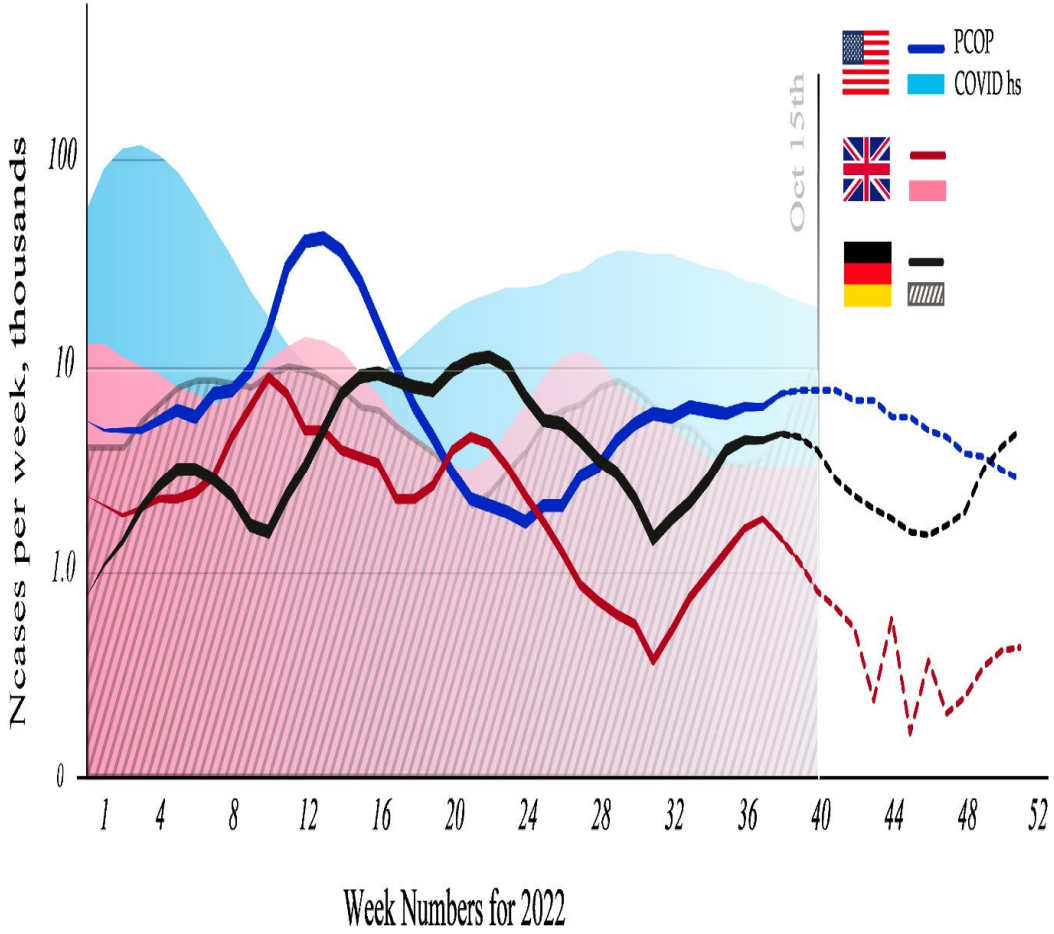
Radiographic imaging patterns of organising pneumonia

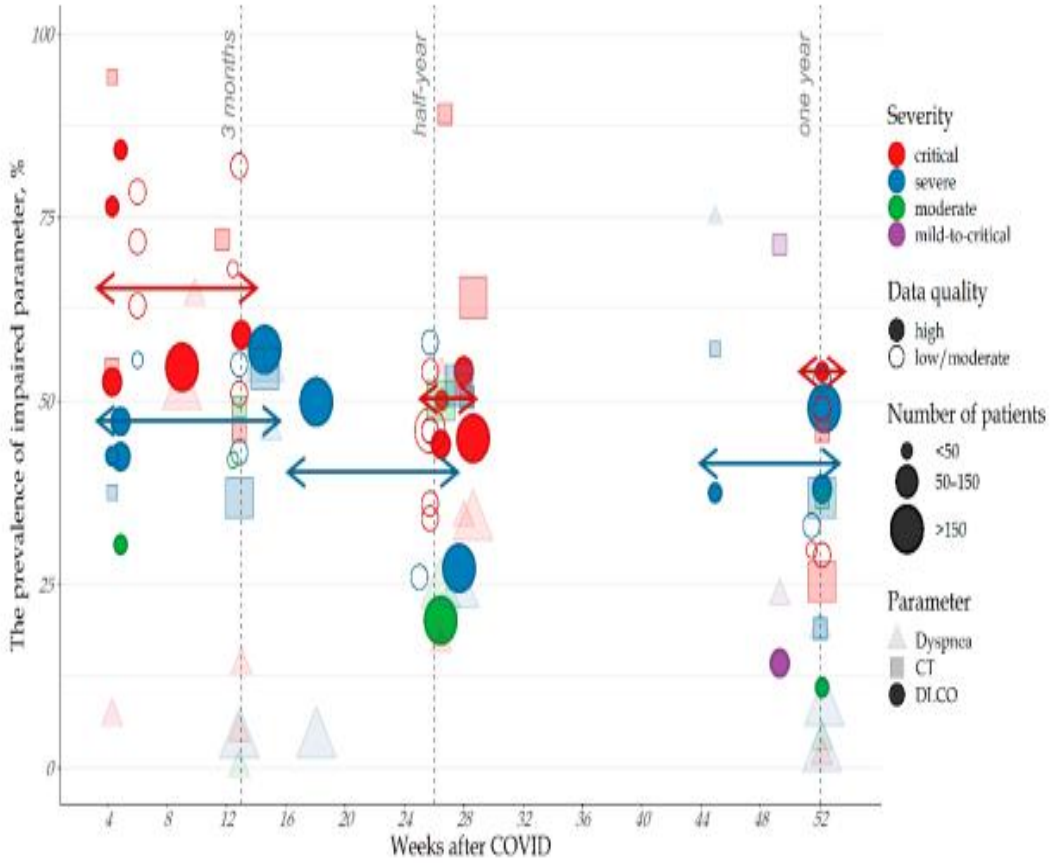
Consolidation
Subpleural and/or peribronchial
Mid to lower lung zone predominance
Can be perilobular
Opacities may migrate, wax, wane or disappear
Spontaneous regression of consolidated areas may occur
Combination of bilateral subpleural consolidation and mid to lower zone predominance observed in majority of patients
Other patterns
Focal with single nodule or mass
Nodular (variable size, can be solitary or multiple)
Reversed halo sign (ground-glass opacity, surrounded by a crescent or ring of consolidated parenchyma)
Ground-glass opacities (usually bilateral, patchy, seen in up to 90% of patients with cryptic organising pneumonia)
Parenchymal bands (often associated with multifocal consolidations)
Perilobular (arcade-like or polygonal opacities that are poorly defined and border secondary pulmonary lobules)
Fibrotic
Reticular opacities with basilar predominance, architectural distortion and superimposed alveolar opacities
Honeycomb change, traction bronchiectasis
Rare changes
Diffuse micronodules (centrilobular or peribronchial)
Mediastinal lymph node enlargement
Pleural effusion



European Respiratory Review 2021 30: 210094

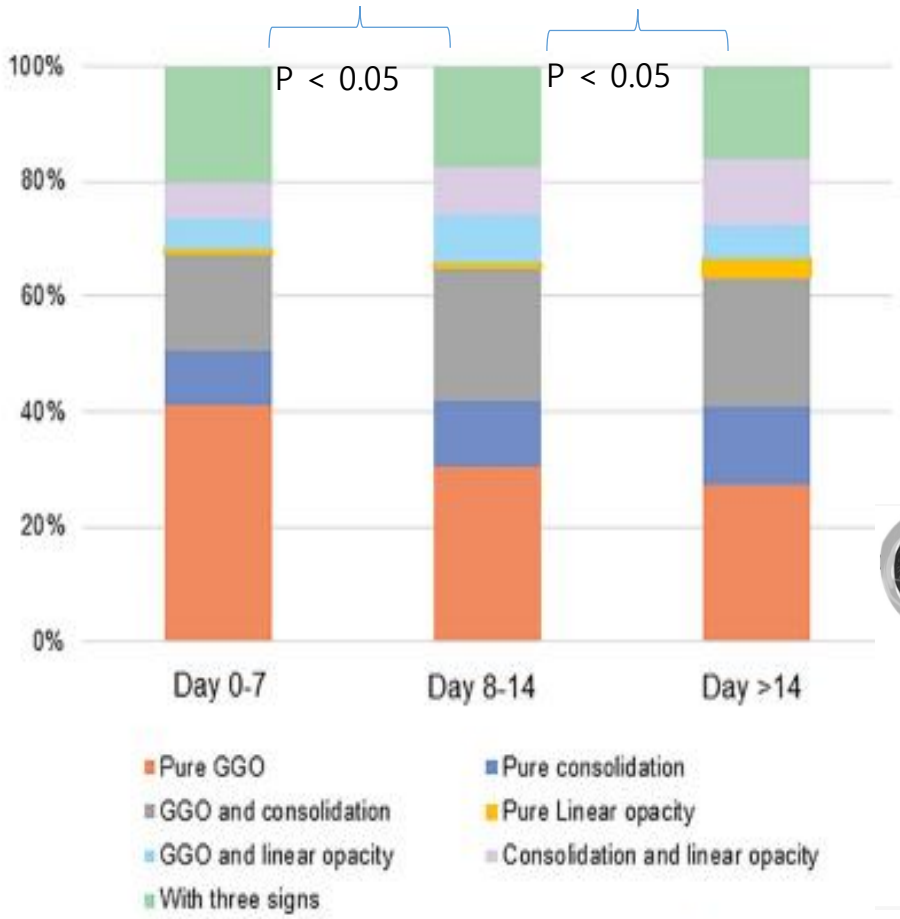
Post COVID organizing pneumonia

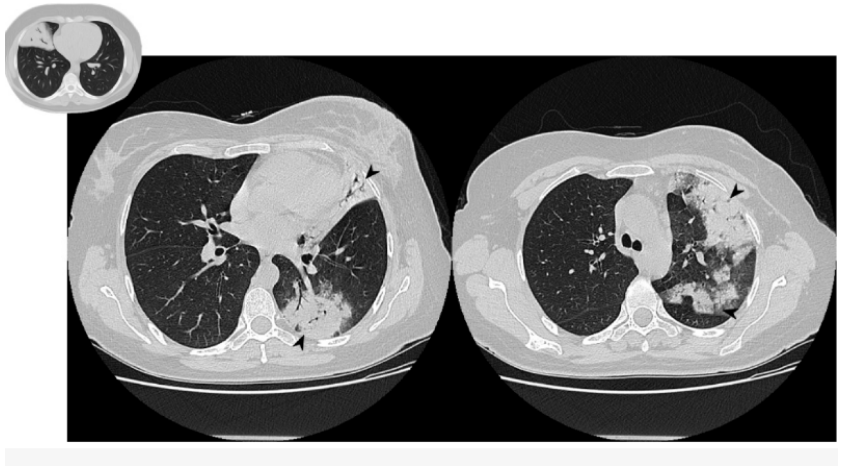


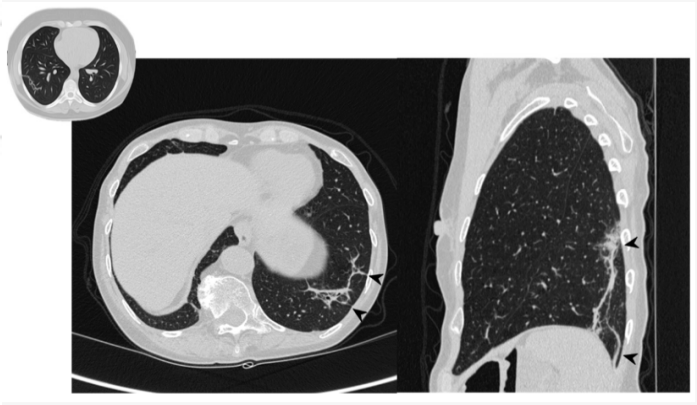


The Hidden Pandemic of COVID-19-Induced Organizing Pneumonia *Pharmaceuticals* **2022**, *15*(12), 1574

Post COVID Organizing pneumonia - radiology







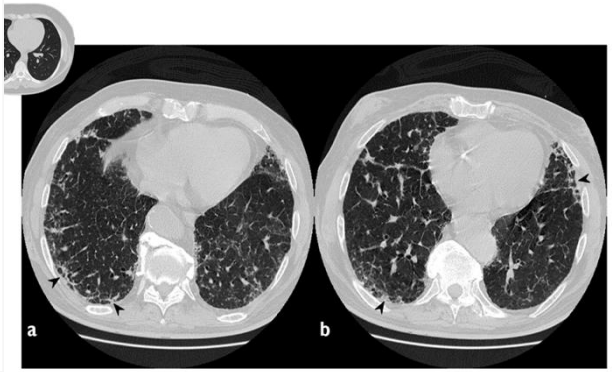


Fig 2. The evolution of CT findings across the three time groups (day 0–7, day 8–14, day >14) in COVID-19 patients with organizing pneumonia pattern. GGO = ground glass opacity; with three signs = GGO, consolidation and linear opacity.

Organizing pneumonia of COVID-19: Time-dependent evolution and outcome in CT findings. PLoS ONE 15(11): e0240347.

Post COVID Organizing pneumonia -pathology

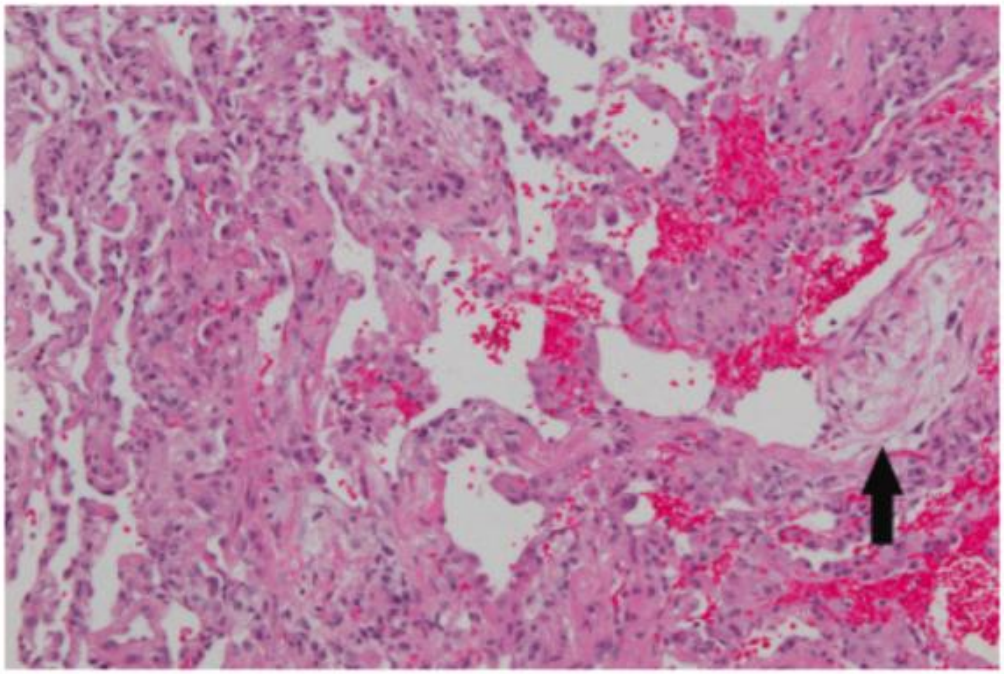


Fig. 2. Histopathological findings of TBLB in case 1 (hematoxylin and eosin stain; ×10). Arrow indicates an intra-alveolar granulation. There were interstitial lymphocyte infiltrations and fibroblastic tissue proliferation in the interstitium.

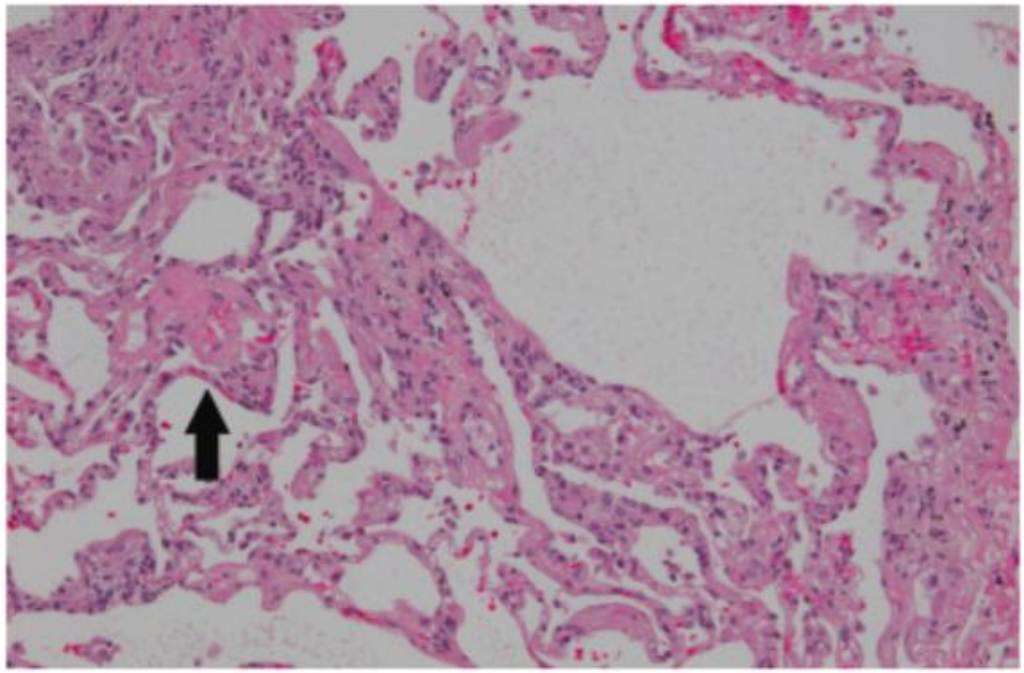
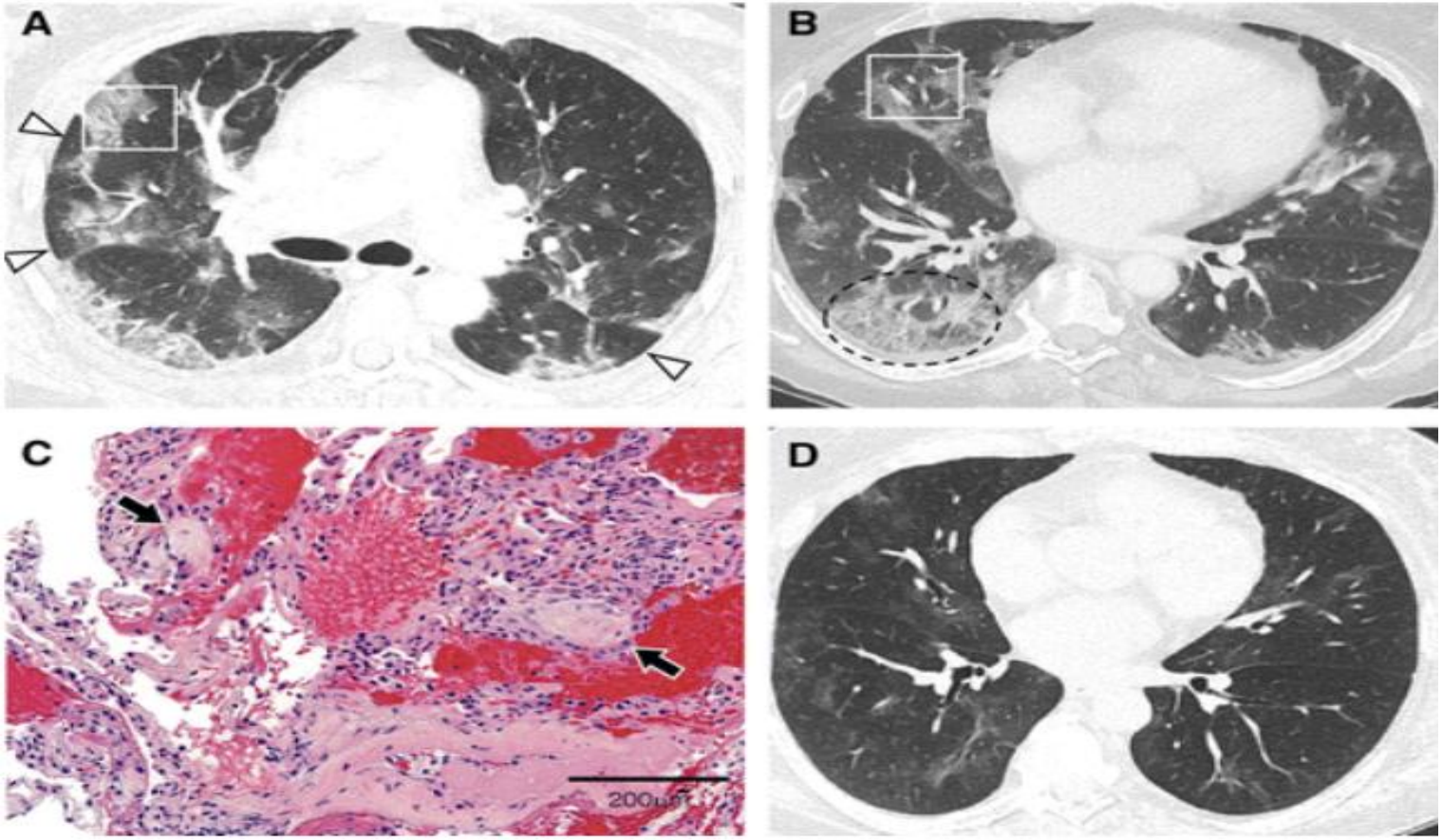


Fig. 4. Histopathological findings of TBLB in case 2 (hematoxylin and eosin stain; ×10). Arrow indicates interstitial and intra-alveolar infiltrations of lymphocytes and macrophages. There were fibroblastic connective tissue proliferations in the interstitium.

Respir Med Case Rep 2021; 32:

Post COVID Organizing pneumonia -pathology



American Journal of Respiratory and Critical Care Medicine Volume 202 Number 4|August 15 2020

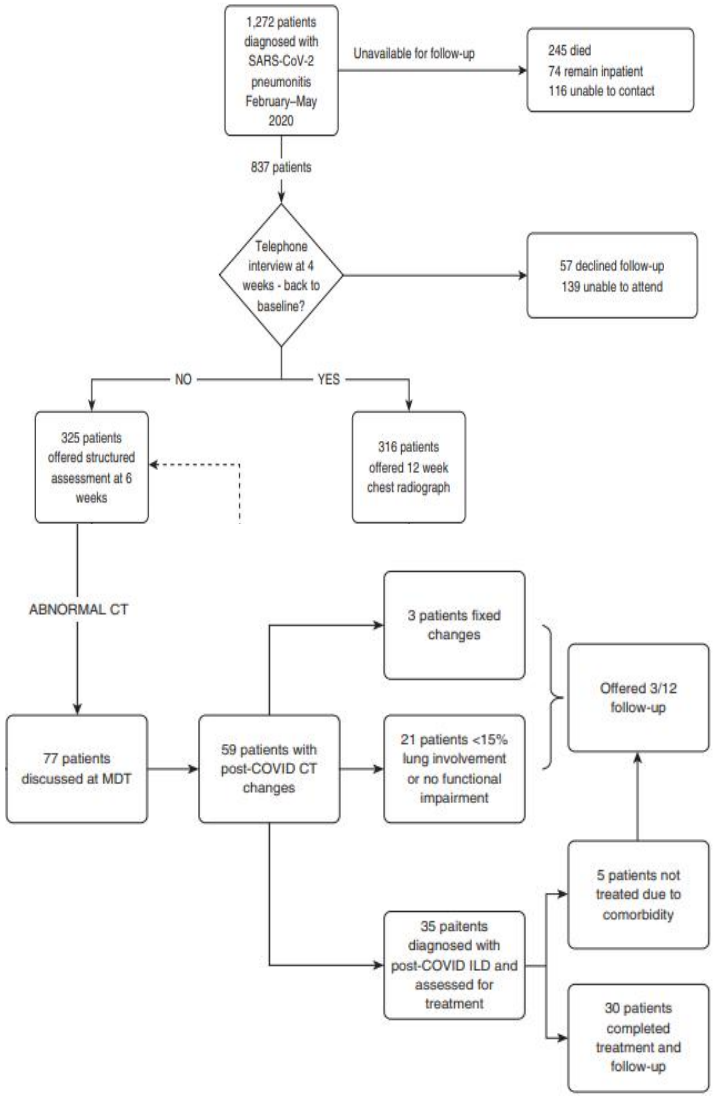
Cases of COVID-19-associated organizing pneumonia identified in the literature.

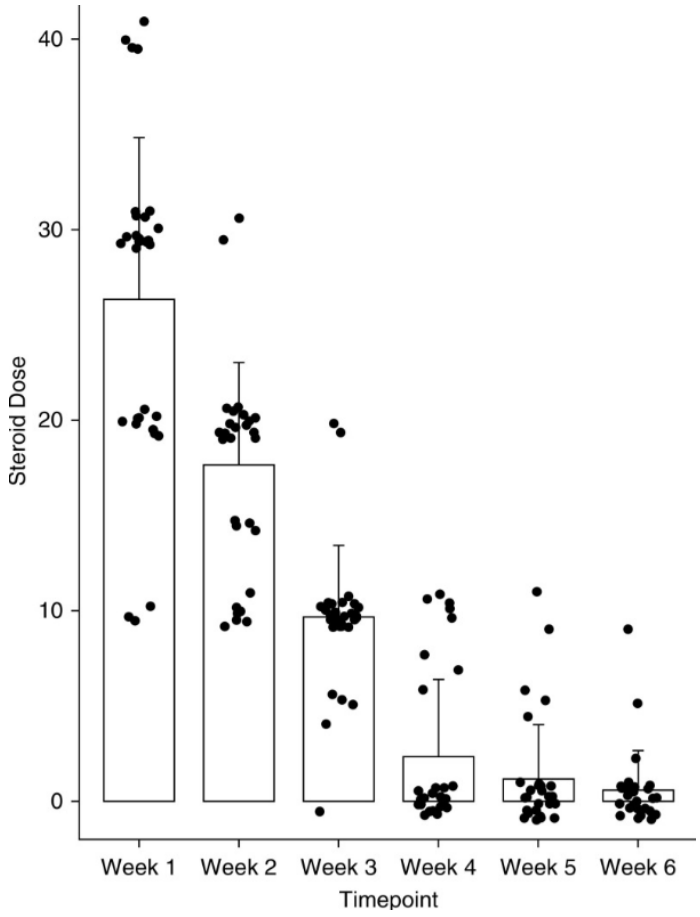
[i] F, female; M, male; TBLB, transbronchial lung biopsy.

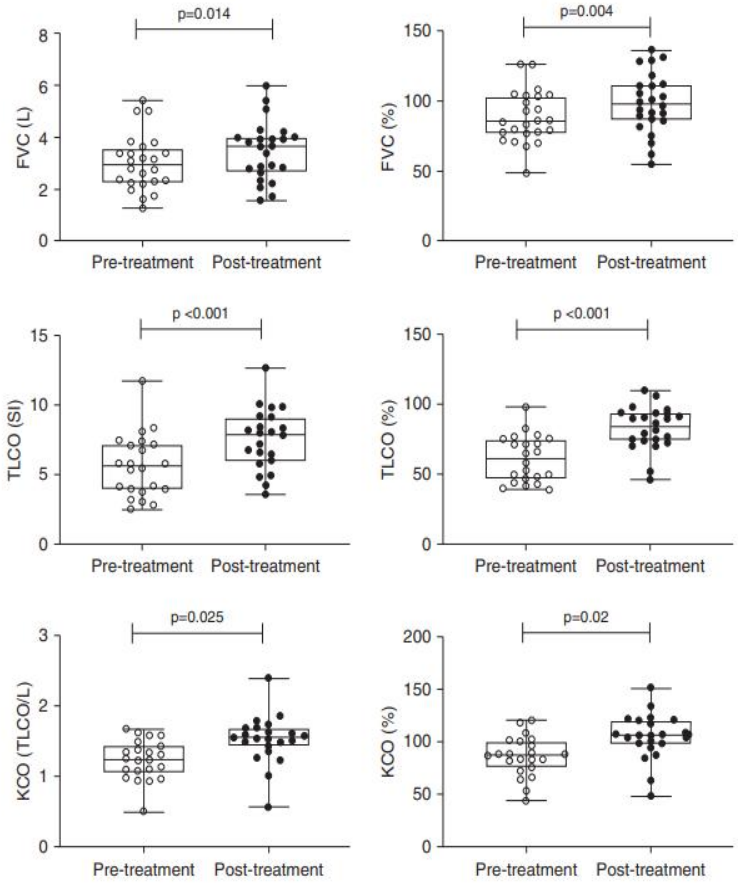
Table I - Cases of COVID-19-associated organizing pneumonia identified in the literature.

Case no.	Author/(Refs.)	Diagnosis	Management	Outcome
1	Alsulami *et al* (13)	Radiological	Corticosteroids	Recovery
2	Alsulami *et al* (13)	Radiological	Corticosteroids	Recovery
3	Alsulami *et al* (13)	Radiological	Corticosteroids	Recovery
4	Alsulami *et al* (13)	Radiological	Corticosteroids	Recovery
5	Alsulami *et al* (13)	Radiological	Corticosteroids	Recovery
6	Alsulami *et al* (13)	Radiological	Corticosteroids	Recovery
7	Ng *et al* (14)	Radiological	Corticosteroids	Recovery
8	de Oliveira Filho *et al* (15)	Radiological	Corticosteroids	Recovery
9	de Oliveira Filho *et al* (15)	Radiological	Corticosteroids	Recovery
10	de Oliveira Filho *et al* (15)	Radiological	Corticosteroids	Recovery
11	Horii *et al* (16)	Radiological	Corticosteroids	Recovery
12	Okamori *et al* (17)	Radiological	Corticosteroids	Recovery
13	Okamori *et al* (17)	Radiological	Corticosteroids	Recovery
14	Kim *et al* (18)	Radiological	Corticosteroids	Recovery
15	Simões *et al* (19)	Radiological	Corticosteroids	Recovery
16	Simões *et al* (19)	Radiological	Corticosteroids	Recovery
17	Ng *et al* (14)	TBLB, histopathological examination	Corticosteroids	Recovery
18	Seo *et al* (20)	TBLB, histopathological examination	Spontaneous remission	Recovery
19	Funk *et al* (21)	TBLB, histopathological examination	Spontaneous remission	Recovery
20	Golbets *et al* (22)	TBLB, histopathological examination	Corticosteroids	Recovery
21	Kanaoka *et al* (23)	TBLB, histopathological examination	Corticosteroids	Recovery
22	Kanaoka *et al* (23)	TBLB, histopathological examination	Corticosteroids	Recovery
23	Cortés Colorado *et al* (24)	TBLB, histopathological examination	Corticosteroids	Recovery
24	Vadász *et al* (25)	TBLB.histopathological examination	Corticosteroids	Recovery
25	Vadász *et al* (25)	TBLB,histopathological examination	Corticosteroids	Recovery
26	Vadász *et al* (25)	TBLB, histopathological examination	Corticosteroids	Recovery

Post COVID organizing pneumonia







AnnalsATS Volume 18 Number 5| May 2021

Table 2. Clinical trials for the treatment of OP-like PCPS.

	Treatment or Intervention	Study Design (Status)	Enrollment and Key Inclusion Criteria (DLCO Impairment|CT Abnormalities|Inflammation|Respiratory Symptoms|Time since COVID-19)	Objectives
Anti-inflammatory therapy	Methylprednisolone PO 0.5 mg/kg QD/1 mth (NCT04988282) [132]	MC, RCT, Ph 4 (RECRUITING)	642 patients in 2 groups (+ | + | − | + | ≥30 d)	**Primary:** % of pts with mMRC = 0, FVC and CT imprv **Secondary:** % CT improvement, DLCO, FVC, SaO2, 6MWD
	Prednisone PO 20 mg QD/14 d (NCT04551781) [133]	SC, SBRCT (COMPLETED)	450 patients in 2 groups (− | + | − | −)	**Primary:** improved resolution of CT infiltrates, <5%, 5–25%, and >25% infiltrates
	Prednisone PO QD/6 wk [1], PO 10 mg QD/6 wk (NCT04657484) [134]	SC, RCT (COMPLETED)	130 patients in 2 groups (+ | + | − | + | 3–8 wk)	**Primary:** % of pts with ≥90% CT improvement **Secondary:** CT improvement (>50%, but <90%), FVC, SpO2, dyspnea score (mMRC), 1 m STS, 6MWD, KBILD, SF-36
	Prednisone PO QD/24 wk [2], PO QD/12 wk [3], (NCT04534478) [135]	SC, RCT, Ph 4 (NOT YET RECRUITING)	120 pts in 2 groups (ratio 1:1) (+ | + | − | +)	**Primary:** change in DLCO **Secondary:** % of pts with DLCO <80%, 6MWD, CT, complications, mortality
	Montelukast PO 10 mg QD/1 mth (NCT04695704) [136]	MC, DBRCT, Ph 3 (RECRUITING)	284 pts in 2 groups (− | − | CRP | mMRC | 1–12 mth)	**Primary:** COPD Assessment Test Scale **Secondary:** 1 min sit-to-stand test; O2 desaturation; VAS; mortality; etc.
	Treamid PO 50 mg QD/1 mth (NCT04527354) [137]	MC, DBRCT, Ph 2 (COMPLETED)	60 pts in 2 groups (ratio 1:1) (DLCO < 80% | + | − | mMRC | 2–8 wk)	**Primary:** % pts with FVC and/or DLCO improvement **Secondary:** change in 6MWD, mBDS, mMRC, FEV1, FVC, FEV1/FVC, DLCO, TLC, FRC, KBILD, rate of reduction in the lung damage (CT)
	Treamid PO 50 mg QD/1 mth (NCT05516550) [138]	DBRCT, Ph 2/3 (NOT YET RECRUITING)	412 pts in 4 groups (ratio 1:1:1:1) (DLCO < 80% | >10% | − | mMRC | 1–3 mth)	**Primary:** % of pts with CT and 6MWT improvement **Secondary:** frequency of clinically significant change in DLCO, rate of clinically significant recovery of exercise tolerance (Borg, BDI/TDI, MFIS scores)
	Colchicine PO 0.5 mg BID/3 wk (NCT04818489) [139]	SC, SBRCT, Ph 4 (COMPLETED)	260 pts in 2 groups (− | + | − | − | −)	**Primary:** % of participants with fibrosis **Secondary:** FVC and FEV1, C-reactive protein, ferritin, erythrocyte sedimentation rate, LDH
	BIO 300 (genistein) PO 1500 mg QD/3 mth (NCT04482595) [140]	MC, DBRCT, Ph 2 (RECRUITING)	66 pts in 2 groups (ratio 1:1) (− | + | + | + | <12)	**Primary:** RAND 36 score **Secondary:** change in RHI, 6MWD, 30/60 sec chair stand
Antifibrotic therapy	Nintedanib PO 150 mg BID/12 mth (NCT04541680) [141]	SC, DBRCT, Ph 3 (RECRUITING)	250 pts in 2 groups (DLCO < 70% | ≥10% | − | − | −)	**Primary:** change in FVC **Secondary:** DLCO, HRCT, Dyspnea, Biomarker assay (KL-6, NT-proBNP, CRP, D-dimers), etc.
	Nintedanib PO 150 mg BID/6 mth (NCT04619680) [142]	MC, DBRCT, Ph 4 (RECRUITING)	170 pts in 2 groups (ratio 1:1) (DLCO < 80% | + | − | − |1 mth)	**Primary:** change in FVC **Secondary:** HRCT, SGRQ, KBILD, LCQ, etc.
	Nintedanib PO 150 mg BID/2 mth (NCT04338802) [143]	RCT, Ph 2 (UNKNOWN STATUS)	96 pts in 2 groups (− | + | − | − | −)	**Primary:** change in FVC **Secondary:** DLCO, CT, 6MWT
	Nintedanib PO 150 mg BID/6 mth (NCT04856111) [144]	SC, SBRCT, Ph 4 (ACTIVE, NOT RECRUITING)	48 pts in 2 groups (− | ≥10% | − | − | ≤4 mth)	**Primary:** change in FVC **Secondary:** % of pts with composite response (mMRC score < 2, FVC ↑, improvement in SaO2 >92%); mMRC score, 6MWD, SaO2, HRCT scores, SF-36 score, KBILD score; FACIT-Dyspnea-10 scale; etc.
	Pirfenidone 2400 mg QD/6 mth (NCT04856111) [144]			
	LYT-100 PO BID/3 mth (NCT04652518) [145]	MC, DBRCT, Ph 2 (COMPLETED)	185 pts in 2 groups (− | + | − | mMRC | −)	**Primary:** change in 6MWD **Secondary:** change in Dyspnoea-12, SGRQ-I and mBDS scores, SF-36 score assessment
	Fuzheng Huayu PO 1600 mg TID/3 mth (NCT04279197) [146]	SC, DBRCT, Ph 2 (COMPLETED)	142 pts in 2 groups (− | + | + | − | ≥1 wk)	**Primary:** % of pulmonary fibrosis and FVC impairment **Secondary:** 6MWD, % of pulmonary inflammation, clinical symptoms, QOL-BREF, PHQ-9, and GAD-7

Annex 1. Repository of published/available definitions of post COVID-19 condition

Source	Text
Wellcome	Symptoms persisting beyond 4 weeks after symptom onset suggestive of COVID-19 *(33)*.
Lancet	Multiorgan symptoms after COVID-19 are being reported by increasing numbers of patients. They range from cough and shortness of breath, to fatigue, headache, palpitations, chest pain, joint pain, physical limitations, depression, and insomnia, and affect people of varying ages. At the Lancet–Chinese Academy of Medical Sciences conference on 23 November 2020, Bin Cao presented data (in press at the Lancet) on the long-term consequences of COVID-19 for patients in Wuhan, and warned that dysfunctions and complications could persist in some discharged patients for at least 6 months. So-called long COVID is a burgeoning health concern and action is needed now to address it *(34)*.
NICE	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis *(35)*.
Scientific American	Individuals whose symptoms persist or develop outside the initial viral infection, but the duration and pathogenesis are unknown *(36)*.
Royal Society	The onset of persistent or recurrent episodes of one or more of the following symptoms, within x* weeks of infection with SARS-CoV-2 and continuing for y* weeks or more: severe fatigue, reduced exercise capacity, chest pain or heaviness, fever, palpitations, cogintive impairment, anosomia or ageusia, vertigo and tinnitus, headache, peripheral neuropathy, metallic or bitter taste, skin rash joint pain or swelling *(3)*. * Maximum period between acquisition of the infection (if known) and the onset of symptoms, and the minimum duration of symptoms, should be specified in the definition.
Haute Autorité de santé, France	Three criteria: Having presented with a symptomatic form of COVID-19; presenting with one or more initial symptoms 4 weeks after the start of the disease; and none of these symptoms can be explained by another diagnosis *(37)*.
CDC	Long COVID: While most persons with COVID-19 recover and return to normal health, some patients can have symptoms that can last for weeks or even months after recovery from acute illness. Even people who are not hospitalized and who have mild illness can experience persistent or late symptoms *(38)*.
Wikipedia	Condition characterized by long-term sequelae – persisting after the typical convalescence period – of coronavirus disease 2019 (COVID-19) *(39)*.
Nature	Post-acute COVID-19 as persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms *(40)*.

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.

A separate definition may be applicable for children.

A clinical case definition of post COVID-19 condition by a Delphi consensus 6 October 2021

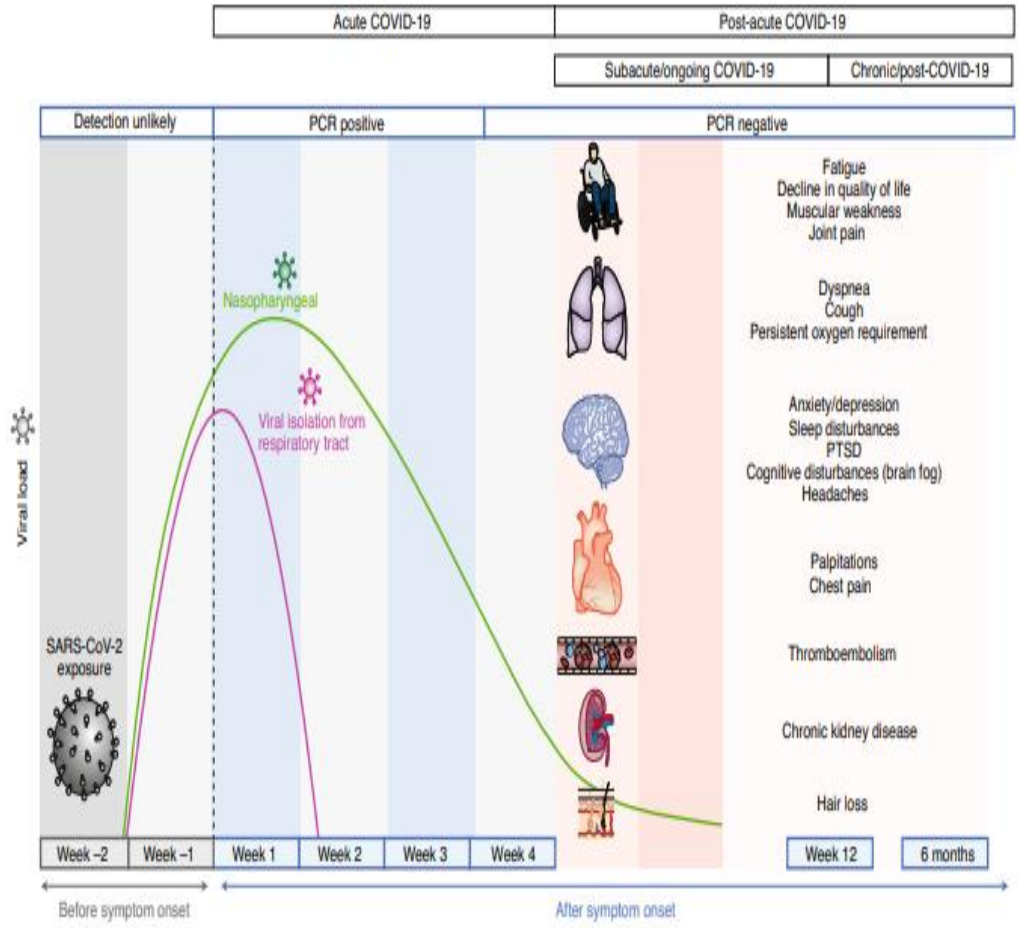
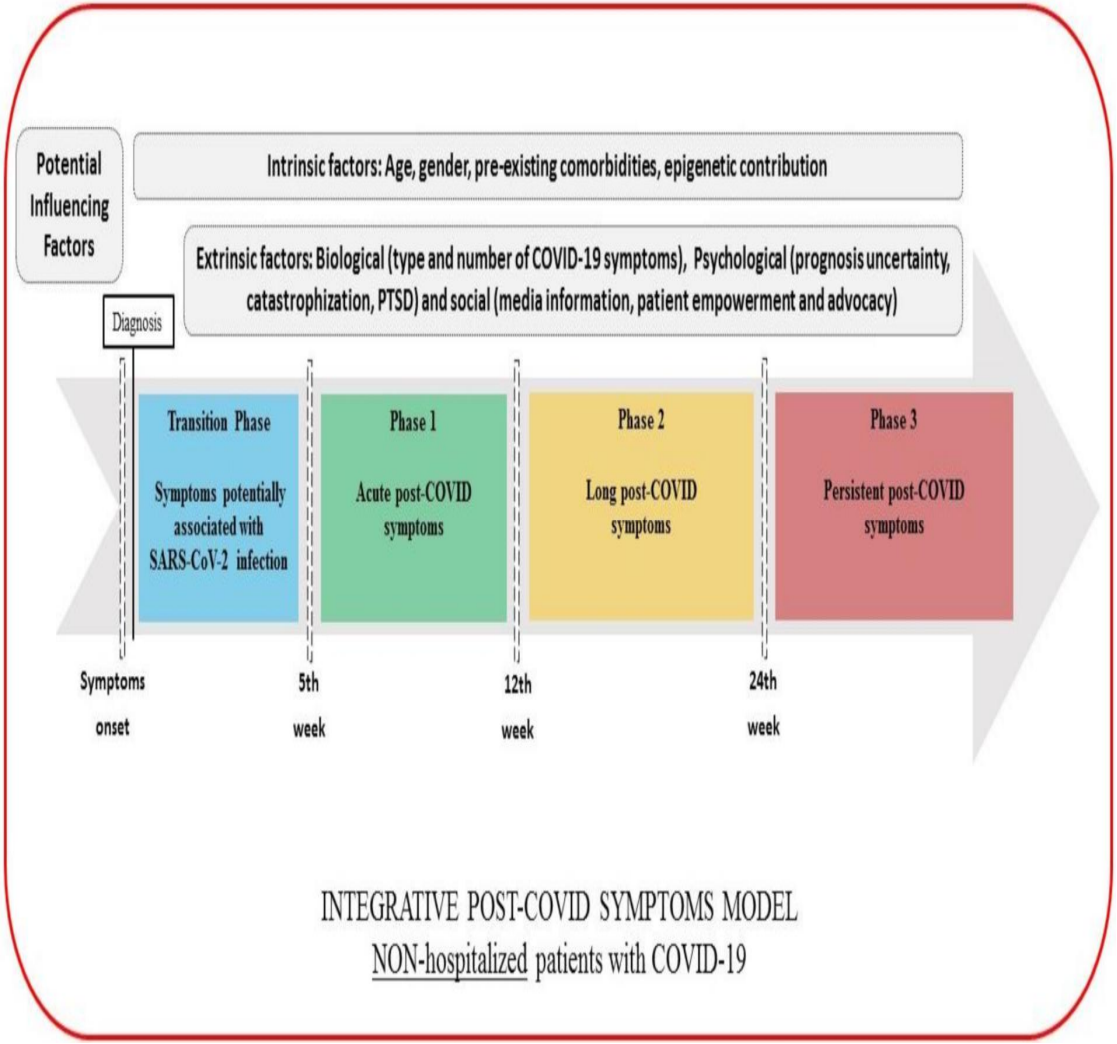


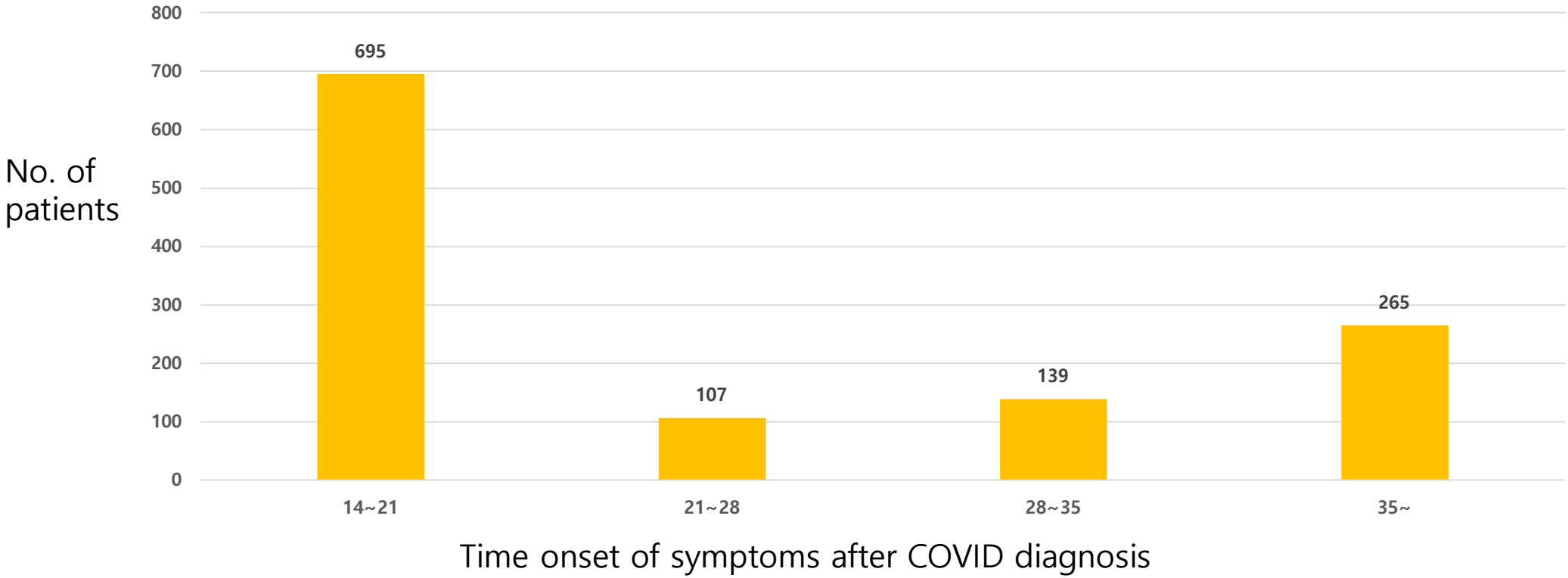
Fig. 1 | Timeline of post-acute COVID-19. Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated. Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. The common symptoms observed in post-acute COVID-19 are summarized.

Nature Medicine volume 27, pages601–615 (2021)

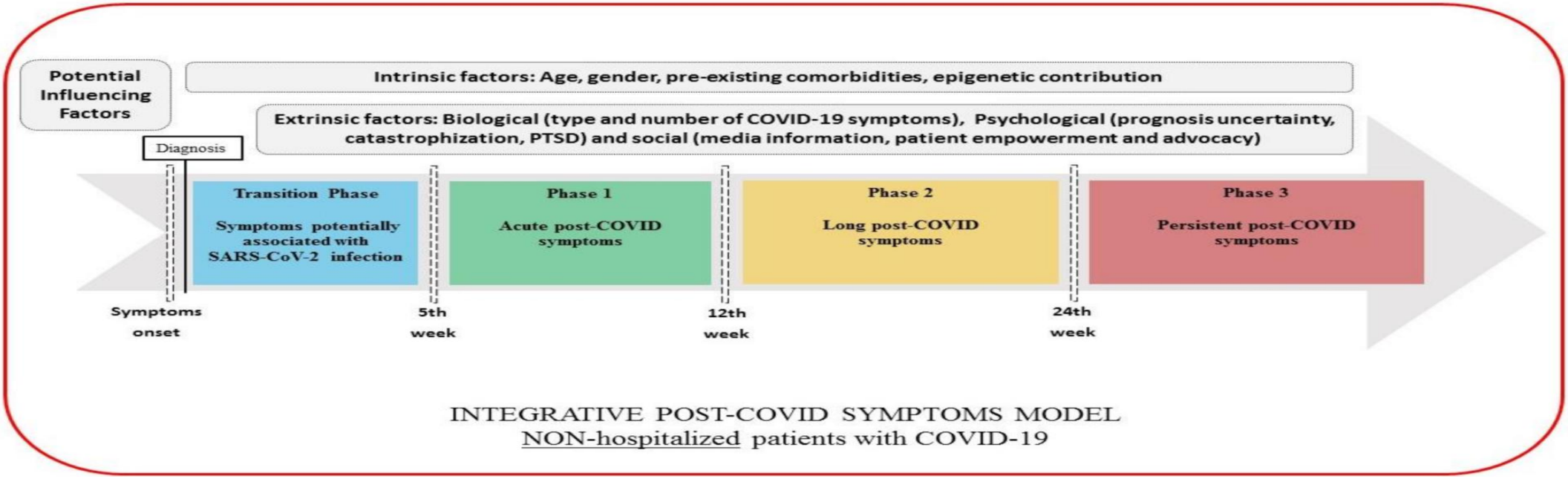


Int. J. Environ. Res. Public Health 2021, 18, 2621

No. of patients of post COVID state (2022.01 ~ 2022.12)



Concepts



INTEGRATIVE POST-COVID SYMPTOMS MODEL
NON-hospitalized patients with COVID-19

Post COVID*
(late onset)

Post COVID

Int. J. Environ. Res. Public Health ***2021***, *18(5), 2621;*

Hypothesis

1. Early application of corticosteroid for late symptoms onset patients of post COVID organizing pneumonia (onset after 2weeks)

2. Early application of corticosteroid for patients who remained respiratory symptoms after 2 weeks after treatment of COVID -19 management

1. decreased steroid requirement & duration
2. favorable outcome

Population

- Retrospective study ,single center (CNUH)
- October 2020 to December 2022

1. Inclusion

- >18 yrs
- Visited ED or OPD due to respiratory symptoms (esp. dyspnea) after more than 2 weeks diagnosis of COVID-19 (RAT or PCR) requiring hosipitalization
- Or remained respiratory symptoms after 2 weeks after treatment of COVID -19 management (hospitalized or home isolation) requiring hosipitalization
- CT finding : Organizing pneumonia pattern at visit
- Repeated COVID PCR : negative

2. Exclusion

1) Evidence of pulmonary bacterial or viral infection
   - Symptoms : fever, purulent sputum
   - procalcitonin > 0.5
   - positive result of pneumonia work up : pneumococcal urine Ag, gram stain & culture of sputum, respiratory viral PCR, pneumobacter PCR
   - definitive findings of bacterial pneumonia : consolidation of dependent portion, unilateral consolidation…
2) Evidence of pulmonary edema in radiological findings
3) Combined with

-other acute medical condition : MACEs (major acute cardiovascular events), acute liver disease, acute severe metabolic disease, acute kidney injury, other infection focus, Connective tissue disease

- acute Cerebrovascular accident
- trauma
- etc.

4) Repeated COVID PCR at visit : positive

Outcome

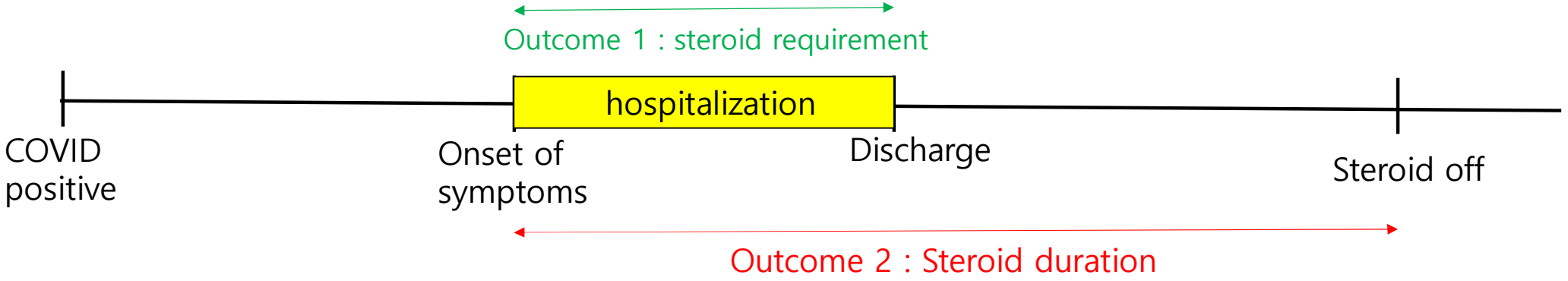
1. **Steroid requirement during hospitalization**

   = total steroid dose/hospitalized days/body weight (mg/kg/days)

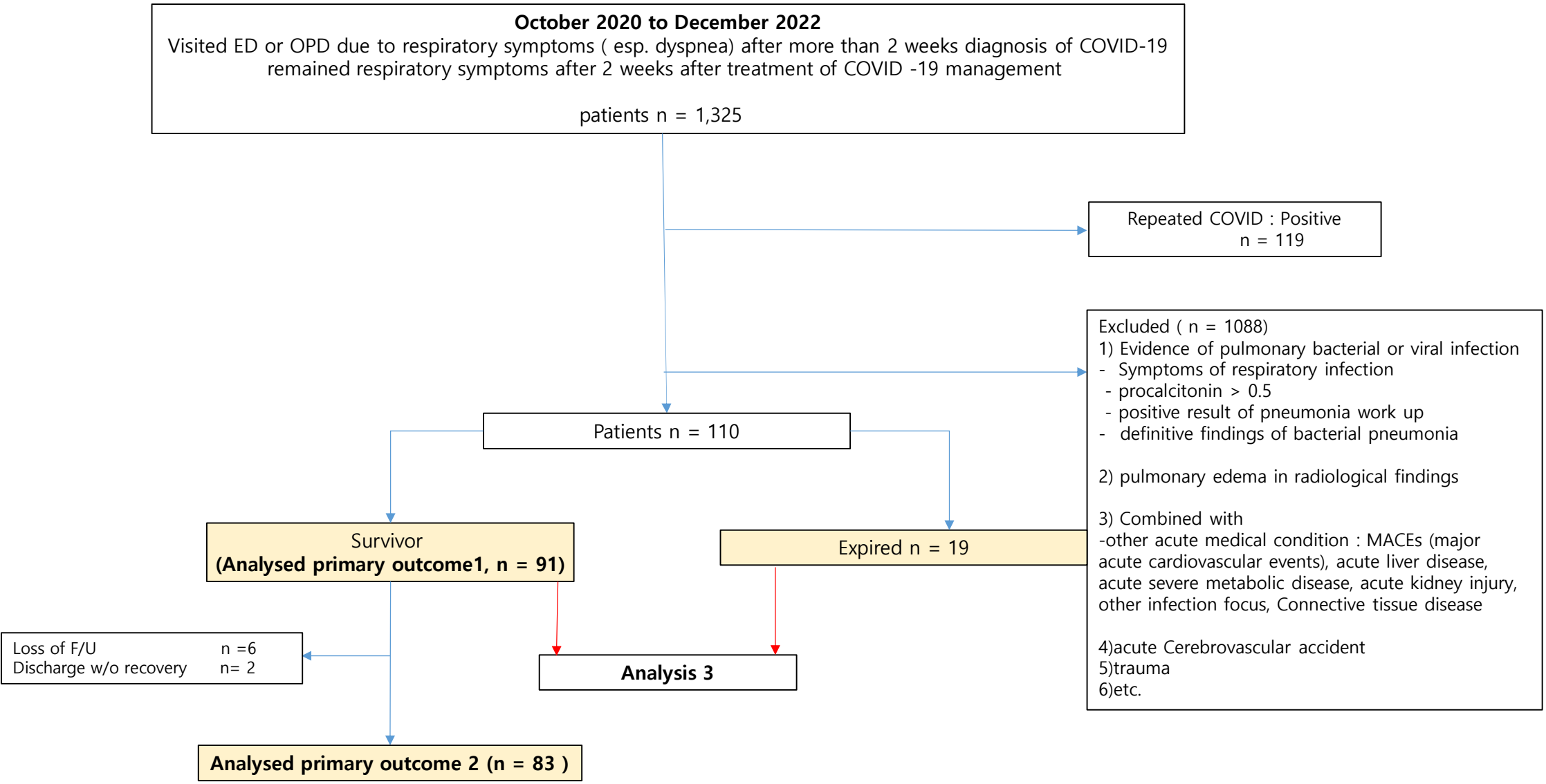
   (adjusted dose for methylprednisolone equivalent)

2. **Steroid duration from admission to taper off** (or physiologic dose) (days)

3. **Comparison between survivor and death of Post COVID organizing pneumonia**



Result


October 2020 to December 2022
Visited ED or OPD due to respiratory symptoms (esp. dyspnea) after more than 2 weeks diagnosis of COVID-19
remained respiratory symptoms after 2 weeks after treatment of COVID -19 management
patients n = 1,325
Repeated COVID : Positive
n = 119
Excluded (n = 1088)
1) Evidence of pulmonary bacterial or viral infection
- Symptoms of respiratory infection
- procalcitonin > 0.5
- positive result of pneumonia work up
- definitive findings of bacterial pneumonia
2) pulmonary edema in radiological findings
3) Combined with
-other acute medical condition : MACEs (major acute cardiovascular events), acute liver disease, acute severe metabolic disease, acute kidney injury, other infection focus, Connective tissue disease
4)acute Cerebrovascular accident
5)trauma
6)etc.
Patients n = 110
Survivor
(Analysed primary outcome1, n = 91)
Expired n = 19
Loss of F/U n =6
Discharge w/o recovery n= 2
Analysis 3
Analysed primary outcome 2 (n = 83)

Result - baseline characteristic

Variables	Total (n=110)	survivor (n =91)	Death (n =19)	P
Median age, year (range)	69.9 (56.6 -83.2)	69.5(55.8 – 83.2)	72(60.1 – 83.4)	0.85
≥ 65 years, n (%)	75 (70.4)	56(60.1)	14(73.6)	
Gender, n (%)				0.775
Male	70 (63.6)	59(64.8)	11 (57.9)	
Female	40 (36.4)	32(35.2)	8 (42.1)	
Cormobidity , n (%)				
HTN	45 (40.9)	32(35.2)	13 (68.4)	0.007*
DM	28 (25.5)	20(22.0)	8(42.1)	0.067
DL	11(10.0)	8(8.8)	3(15.8)	0.355
Chronic kidney disease	10 (9.1)	10(11.0)	3(15.8)	0.555
liver disease	28(25.5)	8(8.8)	2(10.5)	0.811
pulmonary disease	16(15.5)	18(19.8)	10(52.6)	0.003*
COPD	12(10.9)	10(11.0)	6(31.6)	0.021*
ILD	2(1.8)	5(5.5)	7(36.8)	<0.001*
asthma	4(3.6)	2(2.2)	0(0.00)	0.514
pulmonary infection	3(5.4)	4(4.4)	0(0.00)	0.352
etc.	4(3.6)	2(2.2)	2(10.5)	0.911
recent infection	6(5.5)	4(4.4)	2(10.5)	0.284
cardiovascular	22(10.0)	15(16.5)	7(36.8)	0.044*
cerebrovascular	15(13.6)	9(9.9)	6(31.6)	0.012*
neuroendocrine	6(5.5)	6(6.6)	0(0.00)	0.250
malignancy	22(20.8)	12(13.0)	10(52.6)	0.038*
immunosuppressant	20(18.1)	10(10.1)	10(52.6)	0.018*

Abbreviations: HTN, hypertension; DM, diabetes mellitus; DL, dyslipidemia; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; FiO2, fraction of inspired oxygen; WBC, white blood cells; CRP, C- reactive protein; KI-6, Krebs von den Lungen-6; GGO, ground glass opacity

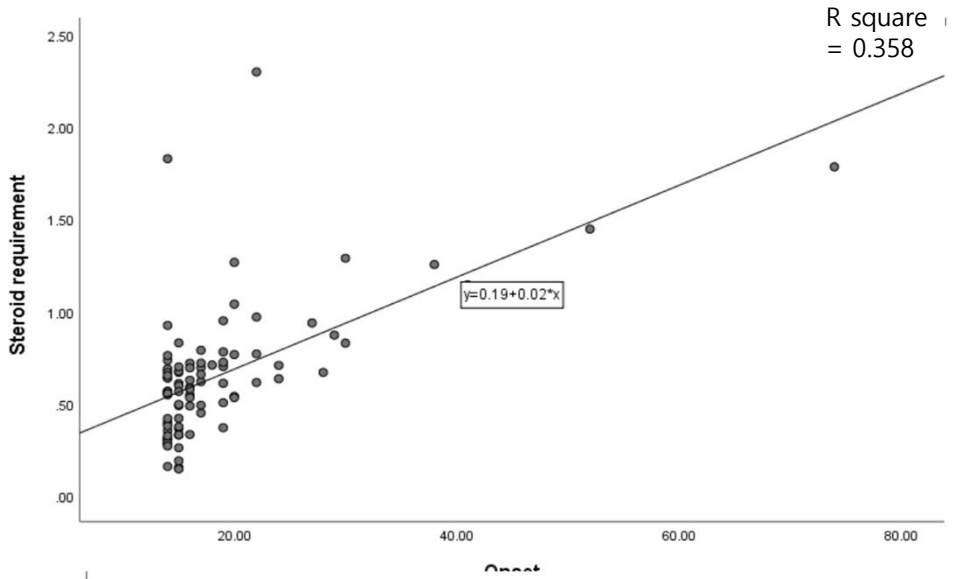
Variables	Total (n=110)	Survirvivor (n= 91)	Death (n = 19)	p
CT finding				0.438
pure GGO	35(31.8)	31(34.1)	4(21.2)	
GGO and consolidation	2(1.8)	2(2.2)	0(0.00)	
pure consolidation	1(0.9)	1(1.1)	0(0.00)	
pure linear opacity	5(4.5)	5(5.5)	0(0.00)	
GGO and linear opacity	10(9.1)	9(9.9)	1(5.3)	
consolidation and linear opacity	2(1.8)	2(2.2)	0(0.00)	
with three sign	55(50.0)	41(45.1)	14(73.7)	
involvement of lung lobes				0.092
N <3	21(19.1)	20(22.0)	1(5.3)	
N>3	89(80.9)	71(78.0)	18(94.7)	
COVID-19 management, n (%)				0.129
Isolation	42 (38.2)	38(41.8)	4(21.1)	
Remdesivir	52 (47.3)	42(46.2)	10(52.6)	
Remdesivir + dexamethasone	16 (14.5)	11(12.1)	5(26.3)	
Onset after covid diagnosis, (days)	18.7 ±8.65	18.4±8.58	20.31±9.06	0.064
14 – 21, n (%)	88 (80.0)	76(83.5)	12(63.2)	
22 - 28, n (%)	12(10.9)	8(8.8)	4(21.1)	
29 - 35 , n (%)	5(4.5)	3(3.3)	2(10.5)	
36 - , n (%)	5(4.5)	4(4.4)	1(5.3)	
FiO2	0.51±0.26	0.39±0.23	0.66±0.26	0.003
WBC [WBCs/µl] , n(%)	11133.9 ±7310.9	9359±6680	13515.8±8827	0.108
CRP [mg/dL], n (%)	11.60±8.65	8.63±7.85	14.1±9.46	0.564
KI – 6 [U/mL], n (%)	834.21±881.30	725.3±510.3	1509.6±933.2	0.001

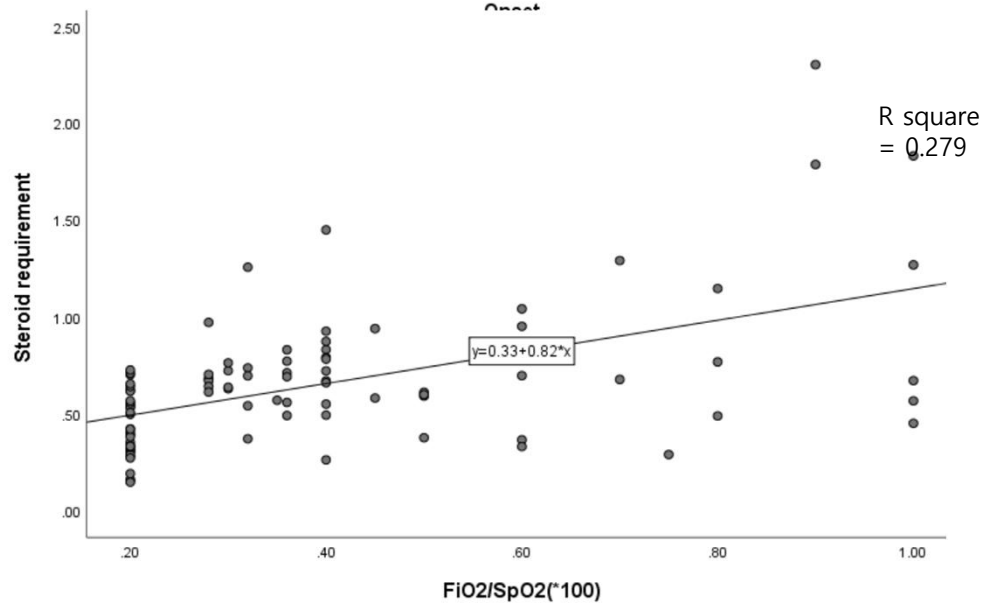
Abbreviations: HTN, hypertension; DM, diabetes mellitus; DL, dyslipidemia; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; FiO2, fraction of inspired oxygen; WBC, white blood cells; CRP, C- reactive protein; KI-6, Krebs von den Lungen-6; GGO, ground glass opacity

Result – outcome

Variables	Total (n=110)	Survirvivor (n= 91)	Death (n = 19)	p
Hospital day (=days)	13.12 ± 9.47	13.0±8.38	13.8±13.7	0.032
Steroid requirement (steroid/BW/days) (= mg/kg/days)	0.86±1.07	0.65±0.36	1.85±2.24	<0.001
Steroid duration (= days)	NA	50.68±21.32	NA	

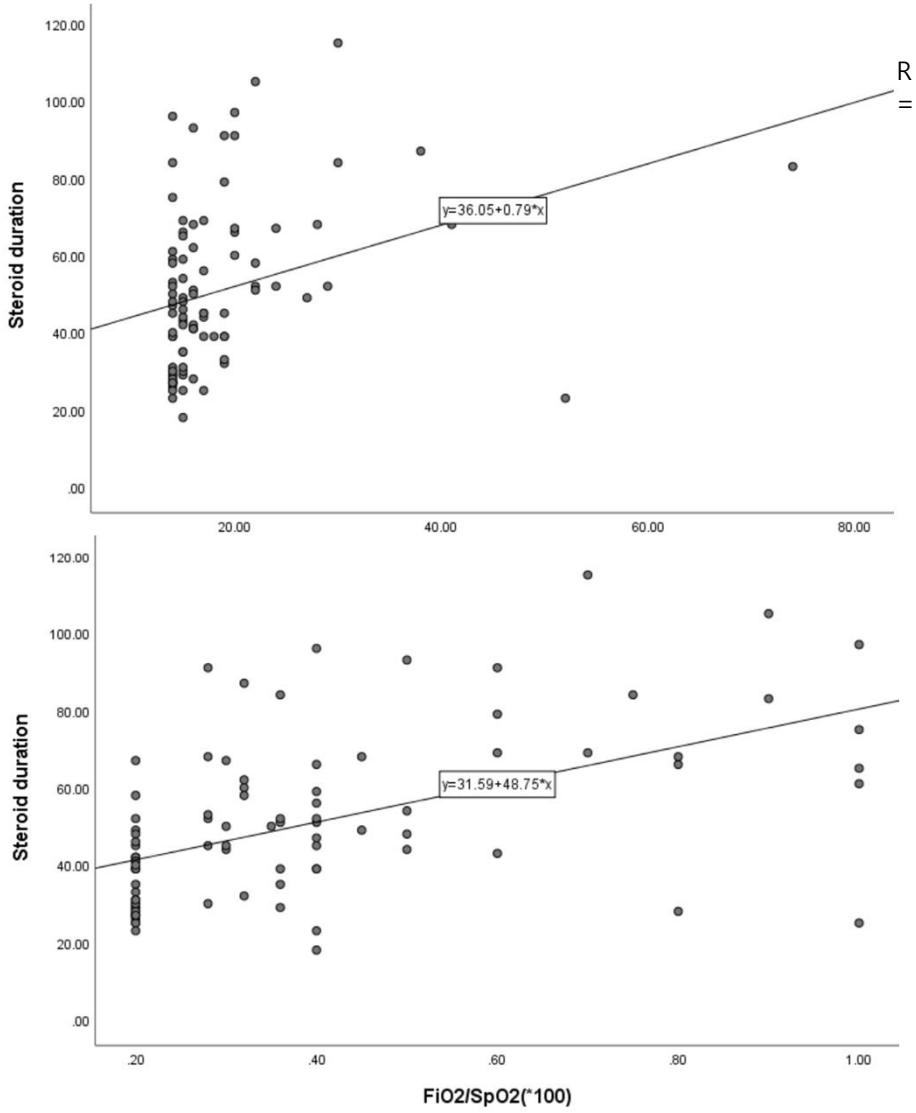
parameter	univariate analysis		*multivariate analysis*	
	β	*p-value*	*β*	*p-value*
Age	0.01	0.215	-0.002	0.354
Sex	0.056	0.835	-0.002	0.148
HTN	0.509	0.052	0.151	0.123
DM	-0.264	0.362	-0.040	0.547
DL	-0.084	0.836	-0.475	0.637
CKD	0.841	0.028*	-0.599	0.551
Liver disease	-0.127	0.776	0.082	0.420
Pulmonary disease	0.686	0.015*	0.055	0.957
COPD	0.027	0.939	0.55	0.616
ILD	1.262	<0.001*	2.029	0.047**
Asthma	-0.243	0.841	-0.781	0.438
Pulmonary infection	-0.163	0.817	-1.374	0.175
Recent infection	0.286	0.665	-0.055	0.956
Cardiovascular	-0.047	0.880	1.481	0.144
Cerebrovascular	0.148	0.674	2.242	0.129
Neuroendocrine	-0.128	0.818	-0.118	0.907
Malignancy	0.104	0.705	1.024	0.310
Immunocompromised	0.033	0.903	1.225	0.225
COVID treatment				
Antiviral agent	-0.144	0.057	0.011	0.991
dexamethasone	-0.012	0.914	-0.065	0.494
CT finding				
GGO & consolidation	0.019	0.939	-1.636	0.107
Pure consolidation	-0.336	0.323	0.064	0.950
Pure linear opacity	-0.043	0.788	-0.578	0.565
GGO & linear opacity	0.227	0.075	2.091	0.441
Consolidation & linear opacity	0.216	0.377	-0.730	0.468
With three sign	0.305	< 0.001*	0.321	0.749
No. of infiltrated lobes				
N <3				
N > 3	0.424	0.240	0.829	0.234
Onset	0.025	<0.001*	6.130	<0.001**
FiO2	0.815	<0.001*	2.172	0.034**
CRP	0.002	0.632	0.224	0.824
WBC	4.133E-6	0.466	0.703	0.485
KL-6	0.000	0.242	0.000	0.367





Result -outcome 1

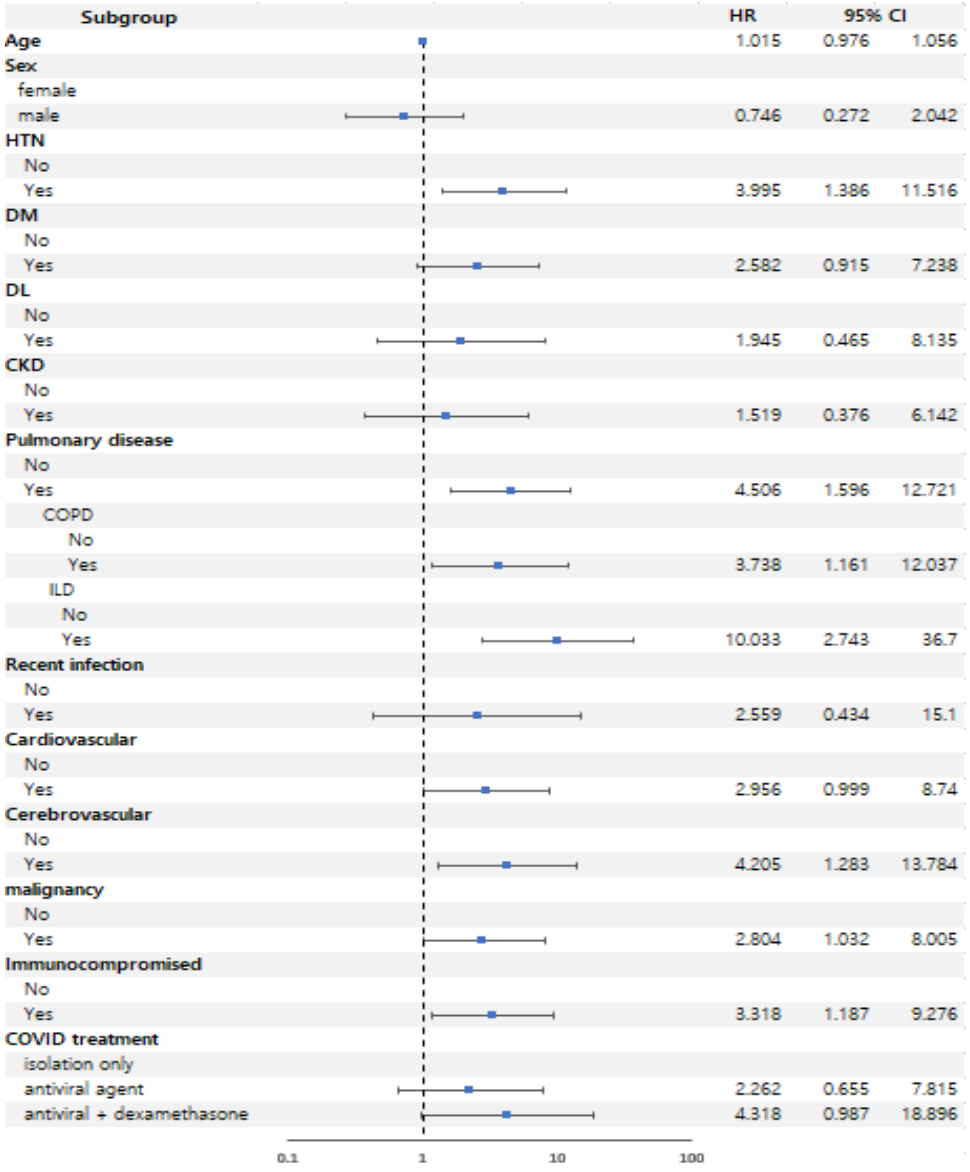
parameter	univariate analysis		*multivariate analysis*	
	β	*p-value*	*β*	*p-value*
Age	-0.027	0.871	--0.010	0.926
Sex	-2.034	0.666	--0.109	0.233
HTN	1.745	0.712	-0.137	0.204
DM	0.921	0.866	--0.068	0.587
DL	0.349	0.965	-0.045	0.694
CKD	-4.585	0.524	--0.081	0.457
Liver disease	--7.325	0.356	-0.117	0.309
Pulmonary disease	6.699	0.234	0.055	0.957
COPD	-4.136	0.566	-1.316	0.193
ILD	20.865	0.033*	0.609	0.545
Asthma	3.904	0.799	-0.263	0.794
Pulmonary infection	1.379	0.900	--0.174	0.099
Recent infection	-13.787	0.208	-1.586	0.118
Cardiovascular	8.204	0.175	1.568	0.122
Cerebrovascular	9.972	0.184	0.757	0.452
Neuroendocrine	20.147	0.024*	-0.173	0.108
Malignancy	-15.691	<0.001*	-0.137	0.335
Immunocompromised	-5.583	0.238	-0.004	0.973
COVID treatment				
Antiviral agent	-18.350	<0.001*	-0.584	0.561
dexamethasone	-9.565	0.164	--0.201	0.059
CT finding				
GGO & consolidation	-7.343	0.633	-0.024	0.792
Pure consolidation	--8.778	0.685	-0.002	0.984
Pure linear opacity	-7.070	0.474	-0.056	0.584
GGO & linear opacity	-10.251	0.172	0.002	0.984
Consolidation & linear opacity	-10.921	0.477	-0.048	0.667
With three sign	20.822	< 0.001*	0.350	0.023*
No. of infiltrated lobes				
N <3				
N > 3	20.355	<0.001*	0.117	0.271
Onset	0.795	0.002*	0.267	0.011*
FiO2	48.750	<0.001*	0.362	0.001*
CRP	0.390	0.172	0.039	0.718
WBC	0.000	0.710	-0.801	0.426
KL-6	0.018	0.014*	0.000	0.063



Result -outcome 2 (Steroid duration)

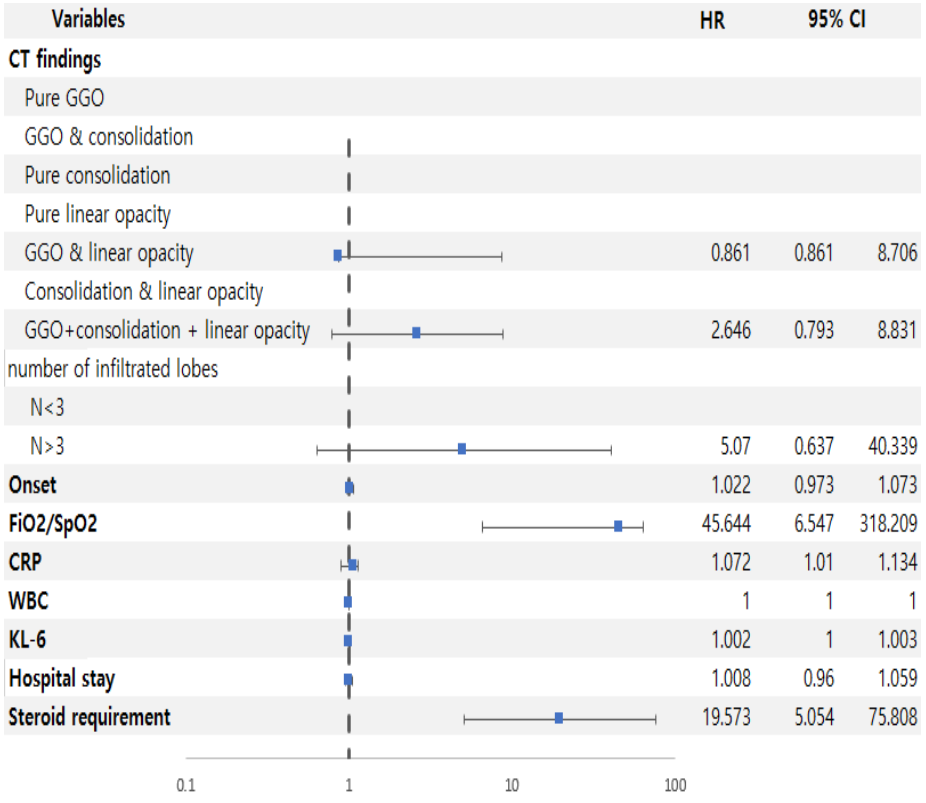
Univariable analysis- Outcome 3

Variables		B	SE	Wald	*P*	OR	95% CI	
							LLCI	ULCI
Age		0.015	0.020	0.542	0.462	1.015	0.976	1.056
Sex	Female							
	male	-2.275	0.514	0.326	0.568	0.746	0.272	2.042
HTN	No							
	Yes	1.385	0.540	6.574	0.01*	3.995	1.386	11.516
DM	No							
	Yes	0.948	0.529	3.213	0.073	2.582	0.915	7.238
DL	NO							
	Yes	0.665	0.730	0.831	0.362	1.945	0.465	8.135
CKD	No							
	Yes	0.418	0.713	0.344	0.558	1.519	0.376	6.142
Pulmonary disease	No							
	Yes	1.505	0.529	8.084	0.004*	4.506	1.596	12.721
COPD	No							
	Yes	1.319	0.597	4.885	0.027*	3.738	1.161	12.037
ILD	No							
	Yes	2.306	0.662	12.145	<0.001*	10.033	2.743	36.70
Recent infection	No							
	Yes	0.940	1.076	1.076	0.3	2.559	0.434	15.1
Cardiovascular	No							
	Yes	1.084	0.553	3.838	0.05	2.956	0.999	8.740
Cerebrovascular	No							
	Yes	1.436	0.606	5.623	0.018*	4.205	1.283	13.784
Malignancy	No							
	Yes	1.056	0.523	4.080	0.043*	2.874	1.032	8.005
Immunocompromised	No							
	Yes	1.199	0.525	5.229	0.022*	3.318	1.187	9.276
COVID treatment	Isoliation							
	Anitival	0.816	0.633	1.665	0.197	2.262	0.655	7.815
	AV + Dexa	1.463	0.753	3.773	0.052	4.318	0.987	18.896



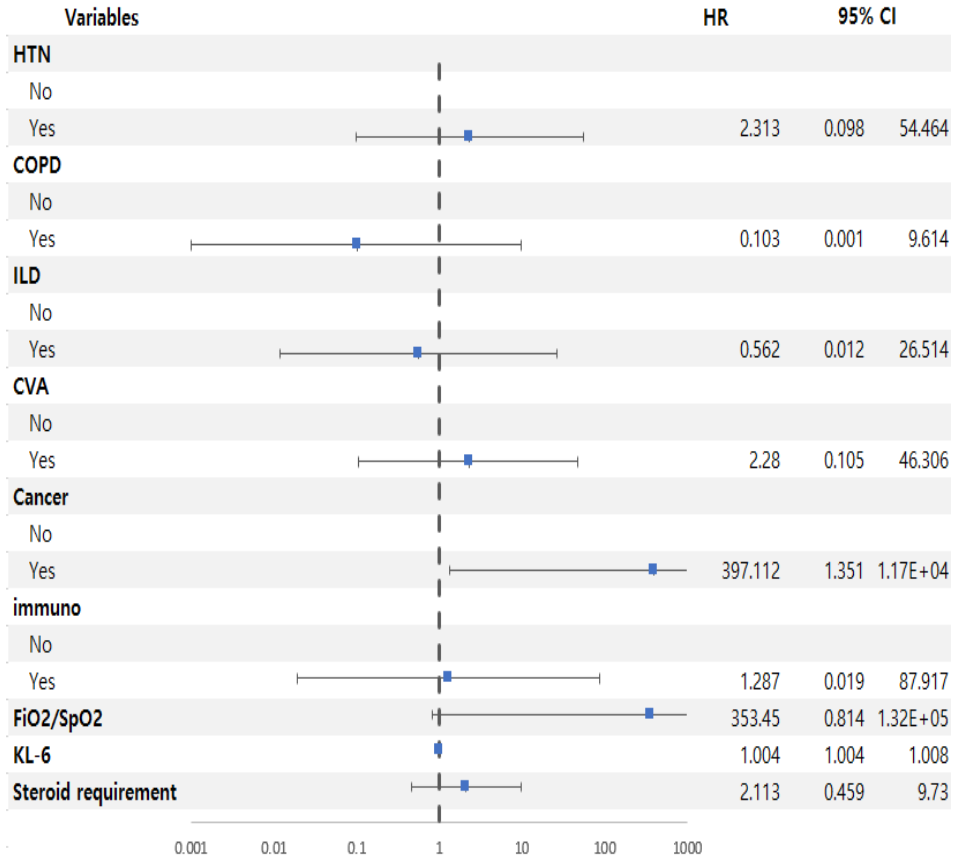
Univariable analysis- Outcome 3

Variables		B	SE	Wald	*P*	OR	95% CI	
							LLCI	ULCI
CT	Pure GGO							
	GGO & consolidation	-19.155	28420	0.00	0.999	0.00	0.00	
	Pure consolidation	-19.155	40192	0.00	1.0	0.00	0.00	
	Pure linear opacity	-19.155	17974	0.00	0.999	0.00	0.00	8.706
	GGO & linear opacity	-0.15	1.18	0.16	0.899	0.861	0.861	
	consolidation&linear opacity	-19.155	28420	0.00	0.999	0.00	0.00	
	three sign	0.973	0.615	2.505	0.113	2.646	0.793	8.831
	N < 3 N > 3	1.623	1.058	2.354	0.125	5.070	0.637	40.339
Onset		.021	0.025	0.733	0.392	1.022	0.973	1.073
FiO2/SpO2		3.821	0.991	14.873	<0.001*	45.644	6.547	318.209
CRP		0.07	0.028	6.032	0.114	1.072	1.014	1.134
WBC		0.00	0.00	4.643	0.31	1.00	1.00	1.00
KL-6		0.002	0.001	6.843	0.009*	1.002	1.000	1.003
Hospital day		0.008	0.025	0.113	0.737	1.008	0.96	1.059
Steroid requirement		2.974	0.691	18.534	<0.001*	19.573	5.054	75.808

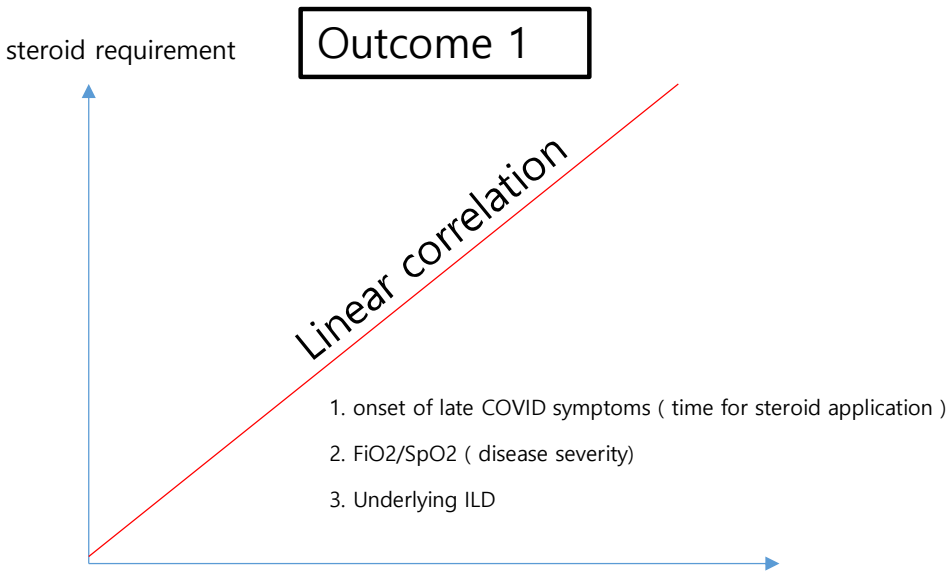


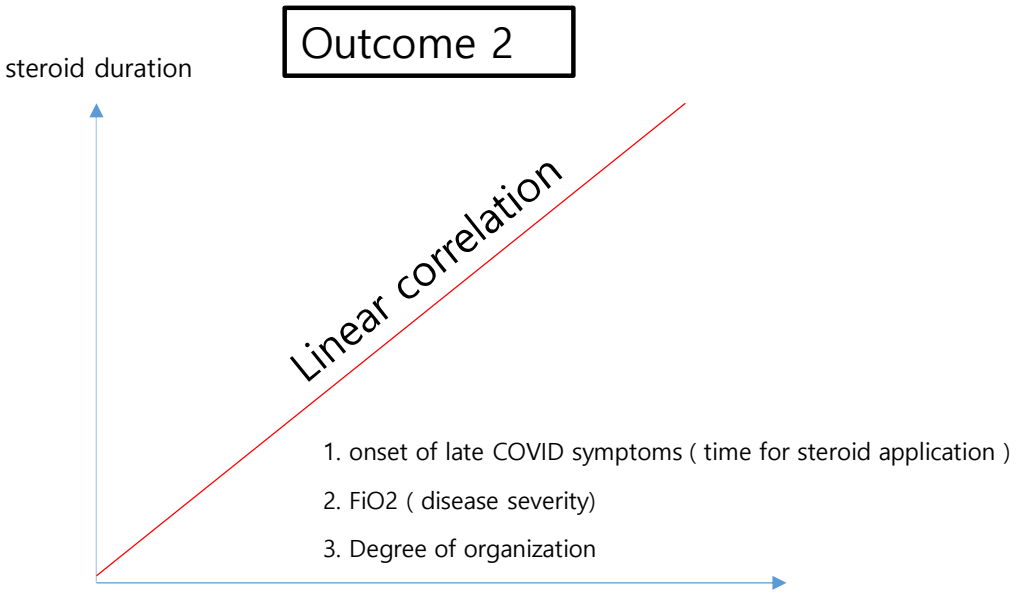
Multivariable analysis - Outcome 3

Variables		B	SE	Wald	*p*	OR	95% CI	
							LLCI	ULCI
HTN	No							
	Yes	0.839	1.614	0.27	0.603	2.313	0.098	54.464
Pulmonary disease								
COPD	No							
	Yes	-2.275	2.316	0.966	0.326	0.103	0.001	9.614
ILD	No							
	Yes	-0.576	1.966	0.086	0.769	0.562	0.012	26.514
CVA	No							
	Yes	0.792	1.553	0.26	0.61	2.28	0.105	46.306
Cancer	No							
	Yes	5.984	2.9	4.259	0.039*	397.112	1.351	1.17E4
Immunocompromised	No							
	Yes	0.252	2.155	0.014	0.907	1.287	0.019	87.917
FiO2		9.245	4.822	3.676	0.055	353.45	0.814	1.32E5
KL-6		0.004	0.002	6.146	0.013*	1.004	1.001	1.008
Steroid requirement		0.748	0.779	0.921	0.337	2.113	0.459	9.730



Result



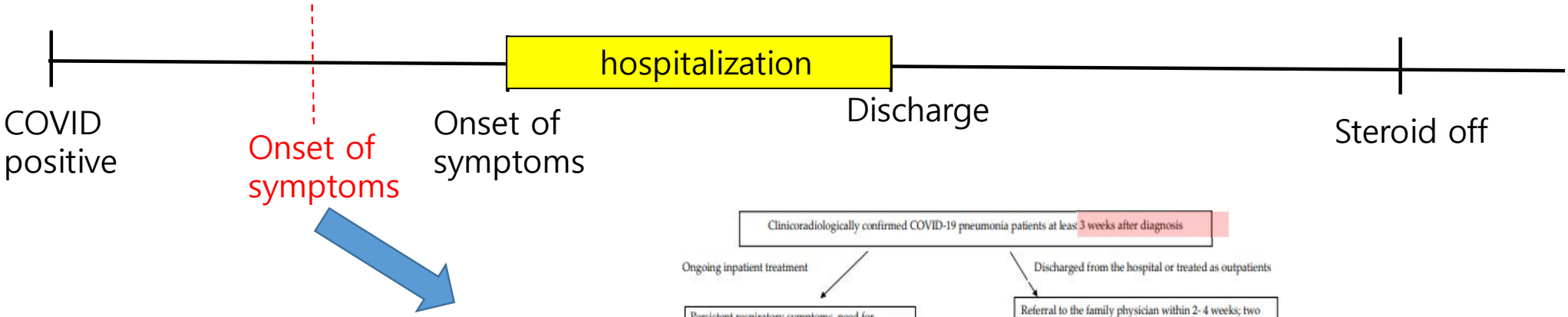


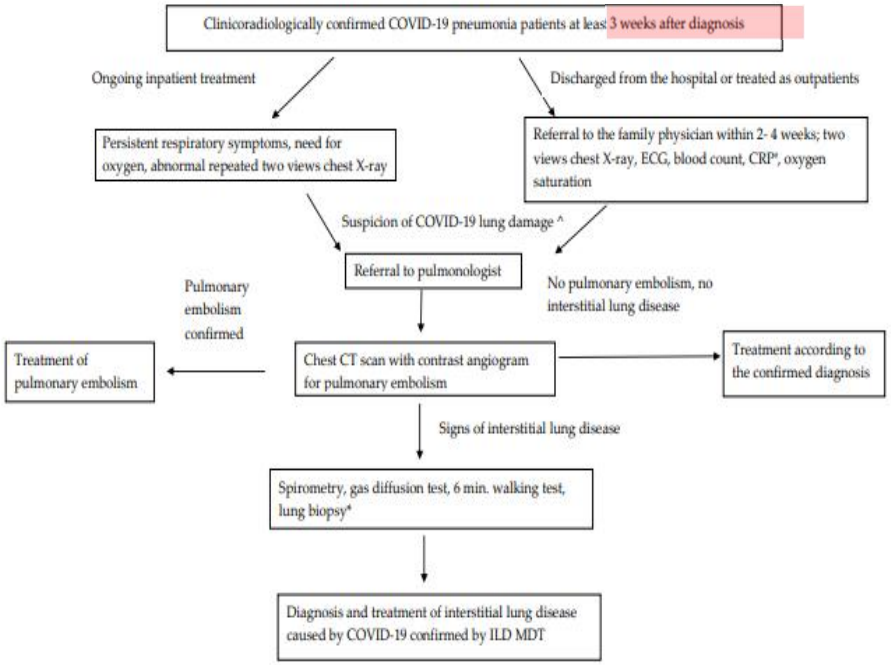
Outcome 3

KL-6
malignancy

mortality

Disccusion-Outcome 1

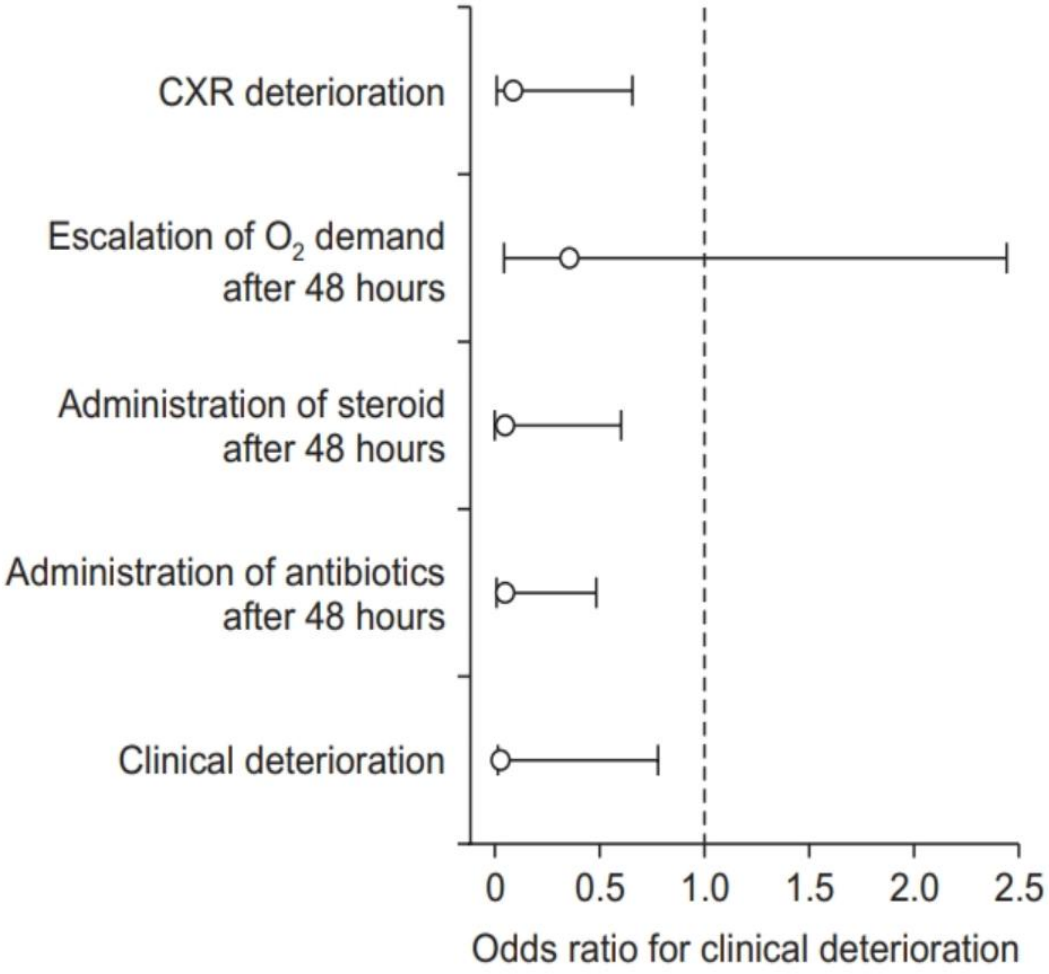




ECG –electrocardiogram; *C reactive protein; ^ persistent respiratory symptoms, supplementary oxygen need, abnormal two view chest X-ray repeatedly; *according clinical situation; ILD- interstitial lung disease; MDT – multidisciplinary team;

Medicina 2021, 57, 283

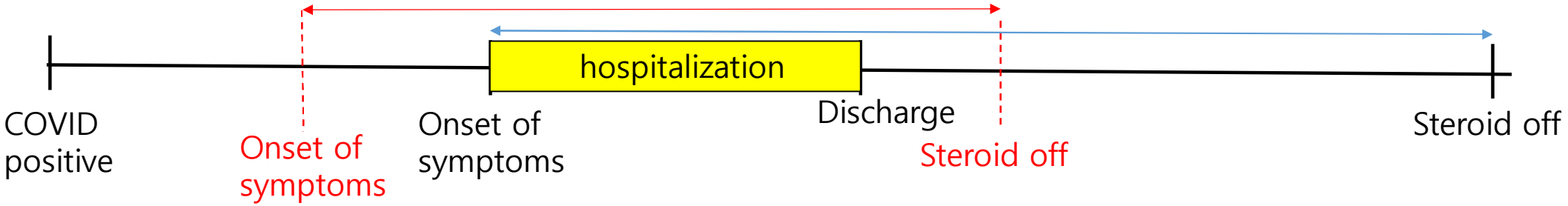
Disccusion- Outcome 1



- Multicenter, retrospective study, 8 centers in South Korea from July 2021 to April 2022.
- at least one week after the acute phase of COVID-19 pneumonia, according to physicians' diagnosis.

Tuberculosis and Respiratory Diseases 2022;85(4):358-360.

Disccusion- Outcome 2



Cryptogenic organising pneumonia (COP)

- COP usually responds to corticosteroid therapy but the optimum dose and length of treatment is not known. Initial doses of 0.75–1 mg/kg, weaning over 6–12 months, are reasonable. [C]
- Relapses of COP are common but are only rarely associated with poor outcome. The risk versus benefit of prolonged corticosteroid therapy should be carefully considered in patients with relapsing COP. [D]

Thorax 2009;64(Suppl III):iii1–iii55. doi:10.1136/thx.2009.121434

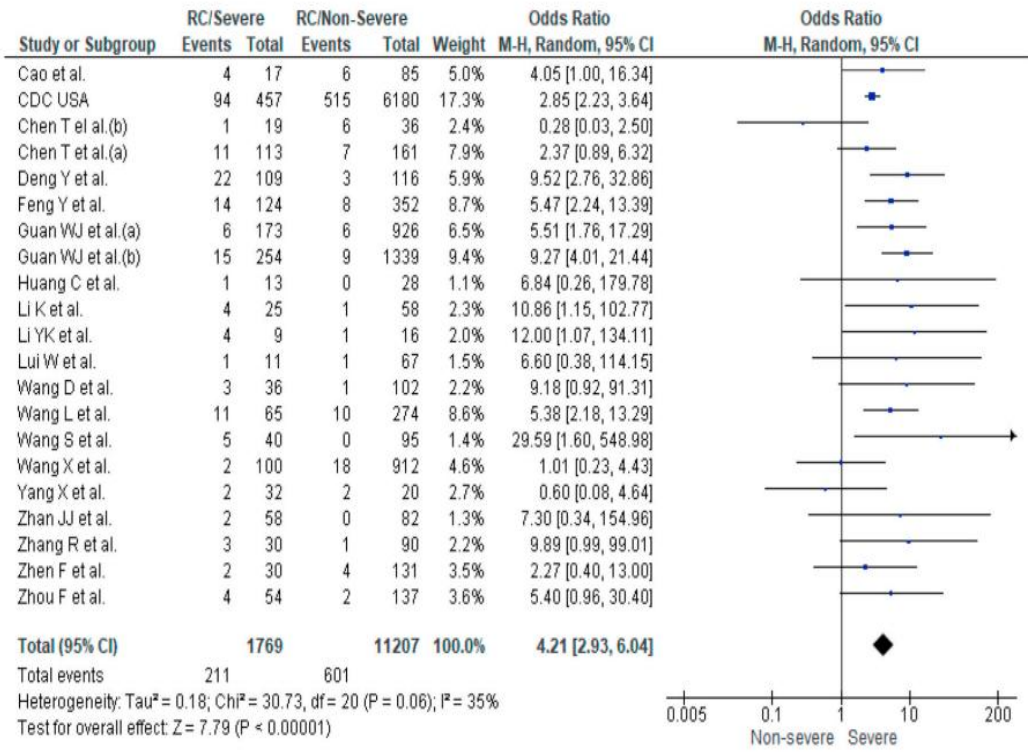
권고사항

- 특발성기질화폐렴(COP) 치료는 스테로이드를 권장한다(근거수준: 전문가 의견, 권고수준: 강함).
- 특발성기질화폐렴(COP) 환자에서 스테로이드 단독 치료가 효과가 없는 경우 azathioprine이나 cyclophosphamide, 그리고 cyclosporin과 같은 면역억제제와 병합치료를 하지 않을 것을 고려한다(근거수준: 전문가 의견, 권고수준: 약함).

2018 간질성폐질환 (ILD) 임상진료지침

Variables	Total (n=110)	Survirvivor (n= 91)	Death (n = 19)
Steroid duration (= days)	NA	50.68±21.32	NA

Discussion- outcome 3



Study or Subgroup	RC/Severe Events	RC/Severe Total	RC/Non-Severe Events	RC/Non-Severe Total	Weight	Odds Ratio M-H, Random, 95% CI
Cao et al.	4	17	6	85	5.0%	4.05 [1.00, 16.34]
CDC USA	94	457	515	6180	17.3%	2.85 [2.23, 3.64]
Chen T el al.(b)	1	19	6	36	2.4%	0.28 [0.03, 2.50]
Chen T et al.(a)	11	113	7	161	7.9%	2.37 [0.89, 6.32]
Deng Y et al.	22	109	3	116	5.9%	9.52 [2.76, 32.86]
Feng Y et al.	14	124	8	352	8.7%	5.47 [2.24, 13.39]
Guan WJ et al.(a)	6	173	6	926	6.5%	5.51 [1.76, 17.29]
Guan WJ et al.(b)	15	254	9	1339	9.4%	9.27 [4.01, 21.44]
Huang C et al.	1	13	0	28	1.1%	6.84 [0.26, 179.78]
Li K et al.	4	25	1	58	2.3%	10.86 [1.15, 102.77]
Li YK et al.	4	9	1	16	2.0%	12.00 [1.07, 134.11]
Lui W et al.	1	11	1	67	1.5%	6.60 [0.38, 114.15]
Wang D et al.	3	36	1	102	2.2%	9.18 [0.92, 91.31]
Wang L et al.	11	65	10	274	8.6%	5.38 [2.18, 13.29]
Wang S et al.	5	40	0	95	1.4%	29.59 [1.60, 548.98]
Wang X et al.	2	100	18	912	4.6%	1.01 [0.23, 4.43]
Yang X et al.	2	32	2	20	2.7%	0.60 [0.08, 4.64]
Zhan JJ et al.	2	58	0	82	1.3%	7.30 [0.34, 154.96]
Zhang R et al.	3	30	1	90	2.2%	9.89 [0.99, 99.01]
Zhen F et al.	2	30	4	131	3.5%	2.27 [0.40, 13.00]
Zhou F et al.	4	54	2	137	3.6%	5.40 [0.96, 30.40]
Total (95% CI)		**1769**		**11207**	**100.0%**	**4.21 [2.93, 6.04]**
Total events	211		601			

Heterogeneity: Tau² = 0.18; Chi² = 30.73, df = 20 (P = 0.06); I² = 35%
Test for overall effect: Z = 7.79 (P < 0.00001)

Fig. 2. Prevalence of underlying respiratory conditions (RC) in severe patients compared to non-severe patients with COVID-19.

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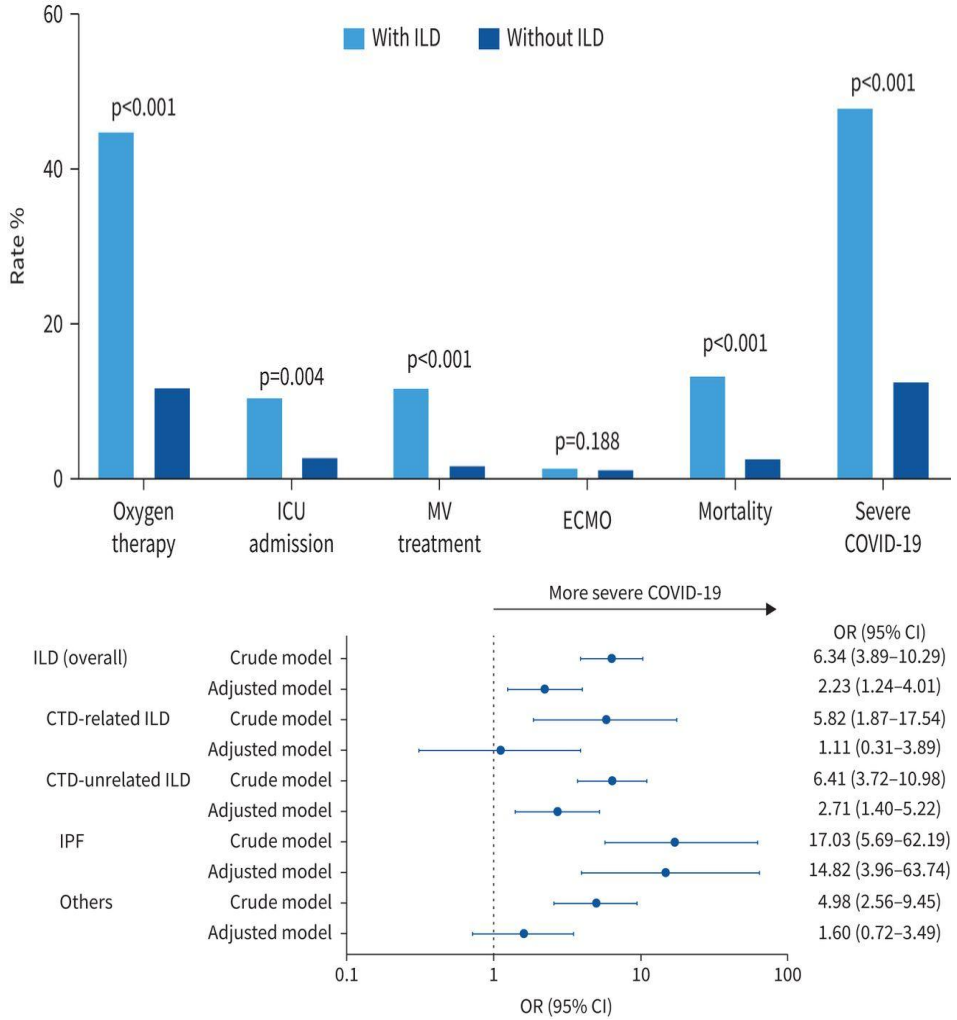

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Limitation

1. Small size of sample

2. Retrospective study

- Heterogenicity : ex) Heterogenicity of cause of death…
- Mismatch Time between :

  Steroid application(symptom onset) and objective organization

3. No evaluation for recurrence for Post COVID organizing pneumonia

4. No record of Vaccination