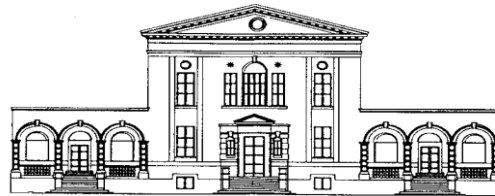


# La presa in carico ambulatoriale del paziente con COVID 19

Andrea Antinori

UOC Immunodeficienze Virali

INMI Lazzaro Spallanzani IRCCS, Roma

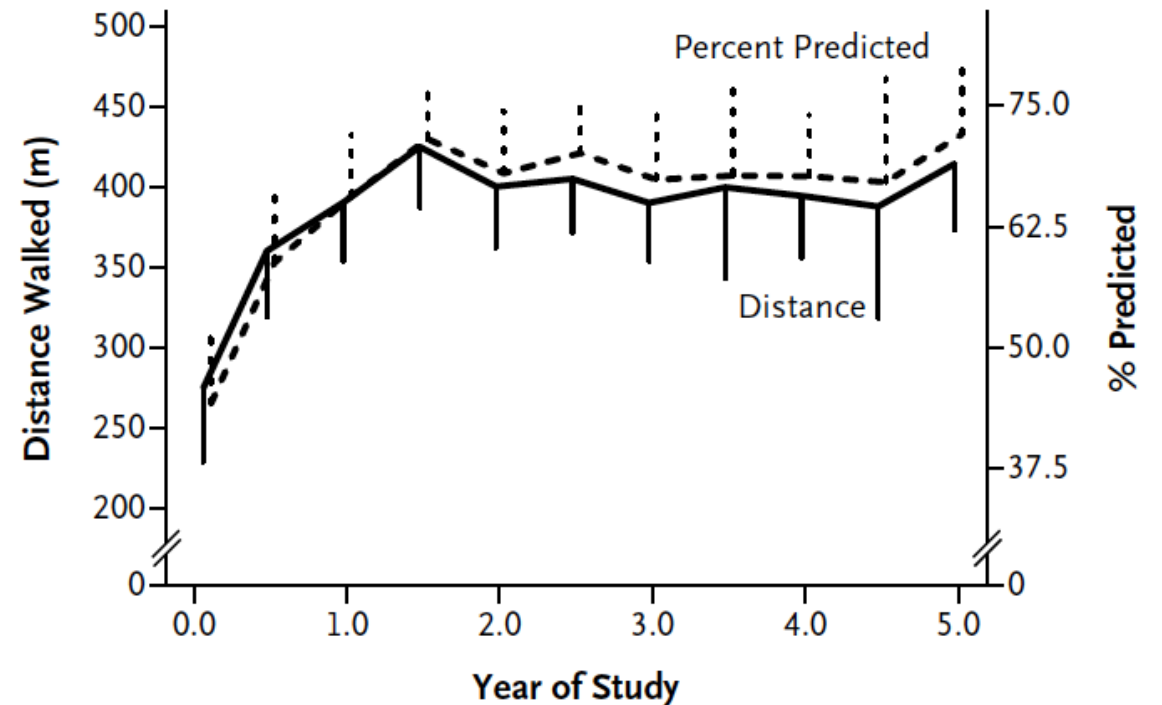


# Recovery of pulmonary function in patients with ARDS after 1 year and 5 years after discharge from ICU

**Table 2.** Recovery of Pulmonary Function among Patients with the Acute Respiratory Distress Syndrome during the First 12 Months after Discharge from the ICU.

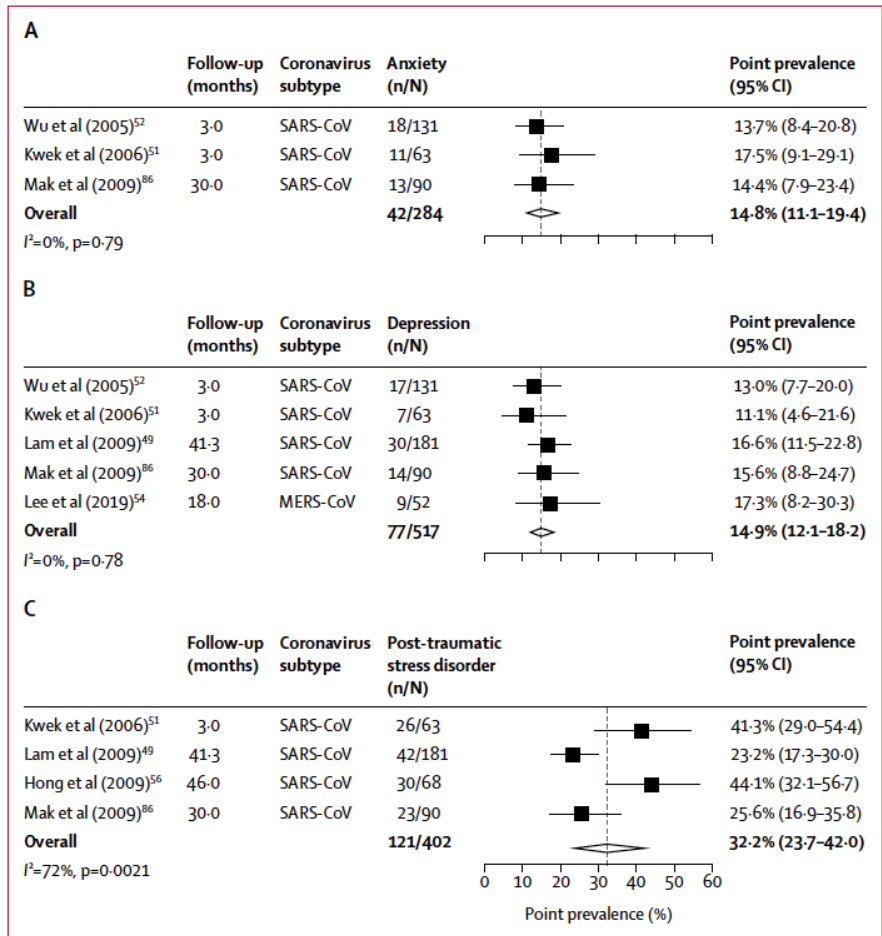
Variable	3 Mo (N=71)*	6 Mo (N=77)†	12 Mo (N=80)‡
	<i>median (interquartile range)</i>		
Forced vital capacity (% of predicted)	72 (57–86)	80 (68–94)	85 (71–98)
Forced expiratory volume in one second (% of predicted)	75 (58–92)	85 (69–98)	86 (74–100)
Total lung capacity (% of predicted)§	92 (77–97)	92 (83–101)	95 (81–103)
Residual volume (% of predicted)§	107 (87–121)	97 (82–117)	105 (90–116)
Carbon monoxide diffusion capacity (% of predicted)¶¶	63 (54–77)	70 (58–82)	72 (61–86)

Herridge MS, et al. N Engl J Med 2003;348:683-93.



Herridge MS, et al. N Engl J Med 2011;364:1293-304.

# Neuropsychiatric presentations and post-discharge outcomes associated with severe coronavirus infections



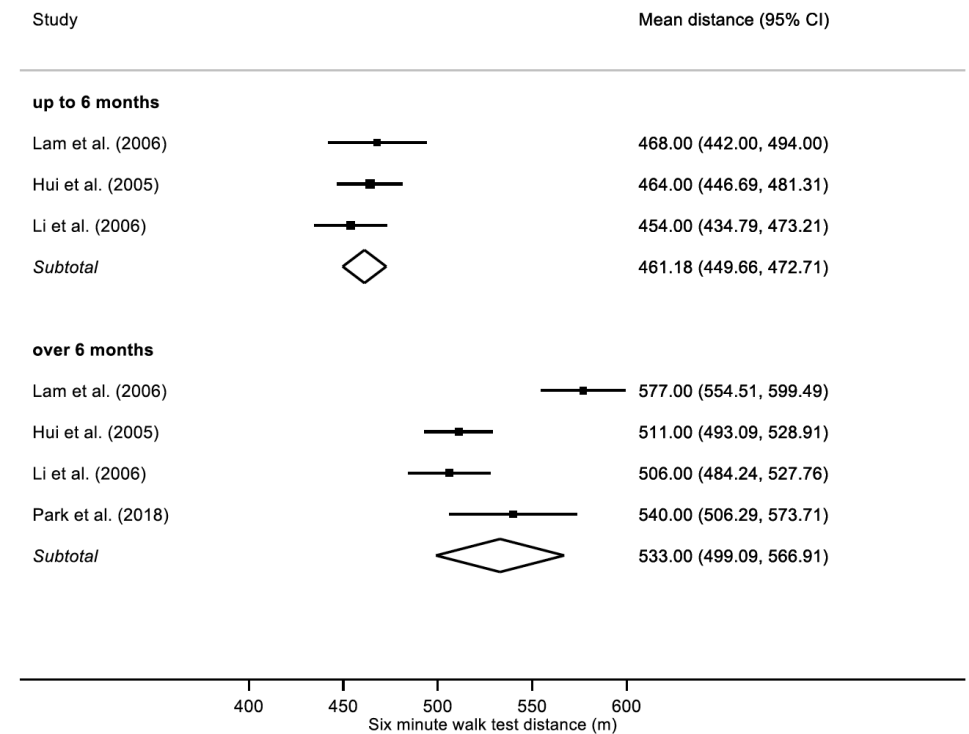
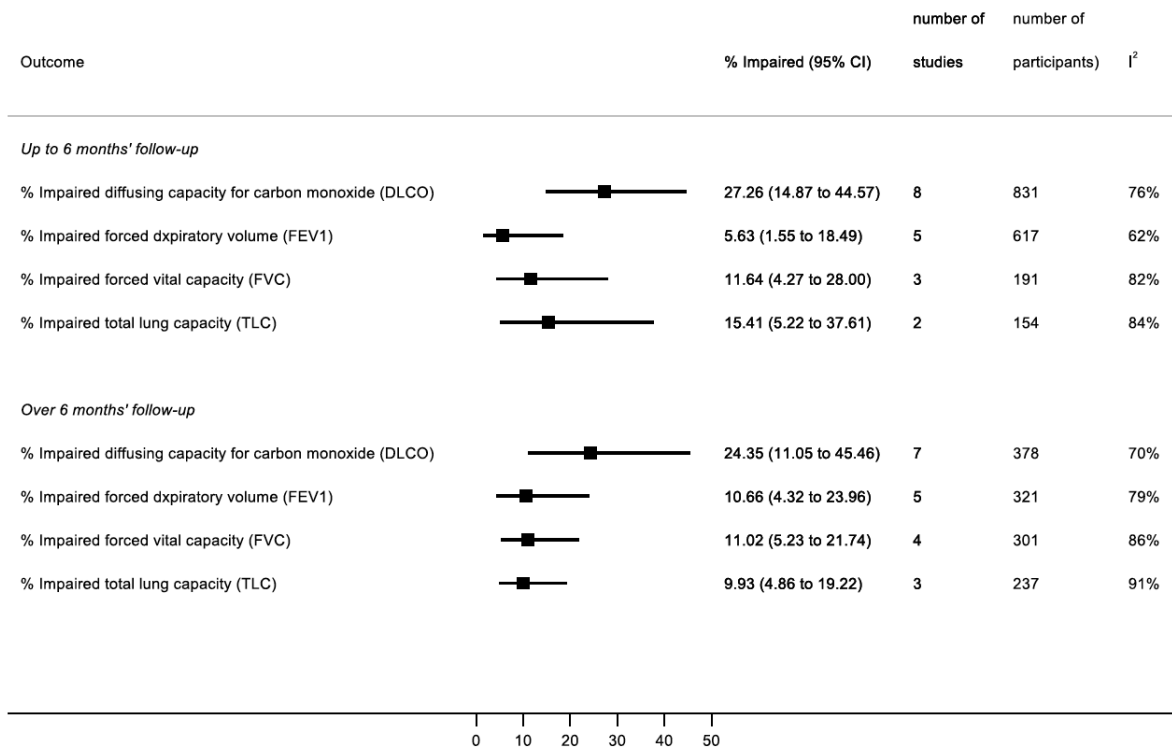
**Figure 2: Forest plots of pooled prevalence of anxiety (A), depression (B), and post-traumatic stress disorder (C) in individuals who recovered from coronavirus infection**  
MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus.

Study	Preprint	Setting	Virus subtype	Study design	Special population	Sample size	Mean (SD)* age, years	Male cases (%)	Females cases (%)	Outcomes
Moriguchi et al (2020) <sup>64</sup>	No	Japan	SARS-CoV-2	Case report	..	1 case	24 (NR)	1 (100%)	0	Symptom: impaired consciousness; diagnosis: meningitis-encephalitis
Helms et al (2020) <sup>65</sup>	No	France	SARS-CoV-2	Case series	ICU admissions	58 cases	NR	NR	NR	Symptoms: agitation, confusion, inattention, disorientation, and poorly organised movements in response to command; diagnoses: dysexecutive syndrome and encephalopathy; investigations: MRI brain, EEG, and CSF analysis
Chen et al (2020) <sup>63</sup>	No	Wuhan, China	SARS-CoV-2	Cohort	..	99 cases	55.5 (13.1)	67 (68%)	32 (32%)	Symptom: confusion
Chen et al (2020) <sup>62</sup>	No	Wuhan, China	SARS-CoV-2	Cohort	..	21 cases	Median 56.0 (IQR 50.0-65.0)	17 (81%)	4 (19%)	Symptom: coma; diagnosis: hypoxic encephalopathy
Zhang et al (2020) <sup>68</sup>	Yes	Wuhan, China	SARS-CoV-2	Cohort	Deaths	82 cases	Median 72.5 (IQR 65.0-80.0)	54 (66%)	28 (34%)	Symptom: consciousness problem
Qi et al (2020) <sup>60</sup>	Yes	Chongqing, China	SARS-CoV-2	Cohort	..	267 cases	Median 48.0 (IQR 35.0-65.0)	149 (56%)	118 (44%)	Symptom: confusion
Huang et al (2020) <sup>69</sup>	Yes	Wuhan, China	SARS-CoV-2	Cohort	Deaths	36 cases	69.2 (9.6)	25 (69%)	11 (31%)	Symptom: disturbance of consciousness
Mao et al (2020) <sup>73</sup>	No	Wuhan, China	SARS-CoV-2	Cohort	..	214 cases	52.7 (15.5)	87 (40%)	127 (60%)	Symptom: impaired consciousness
Leung et al (2020) <sup>61</sup>	Yes	Hong Kong	SARS-CoV-2	Cohort	..	50 cases	55.2 (19.5)	23 (46%)	27 (54%)	Symptom: confusion
Fu et al (2020) <sup>62</sup>	Yes	Wuhan, China	SARS-CoV-2	Cohort	..	50 cases	Median 64.0 (IQR 37.0-87.0)	27 (54%)	23 (46%)	Symptom: insomnia
Yang et al (2020) <sup>67</sup>	Yes	Zhejiang, China	SARS-CoV-2	Cohort	..	26 cases, 87 pneumonia controls, 30 healthy controls	Mean 56.0 (range 27.0-86.0)	9 (35%)	17 (65%)	Scales: HAMD and HAMA
Kong et al (2020) <sup>66</sup>	Yes	Wuhan, China	SARS-CoV-2	Cross-sectional	..	144 cases	50.0 (13.7)	70 (49%)	74 (51%)	Scales: HADS and PSSS

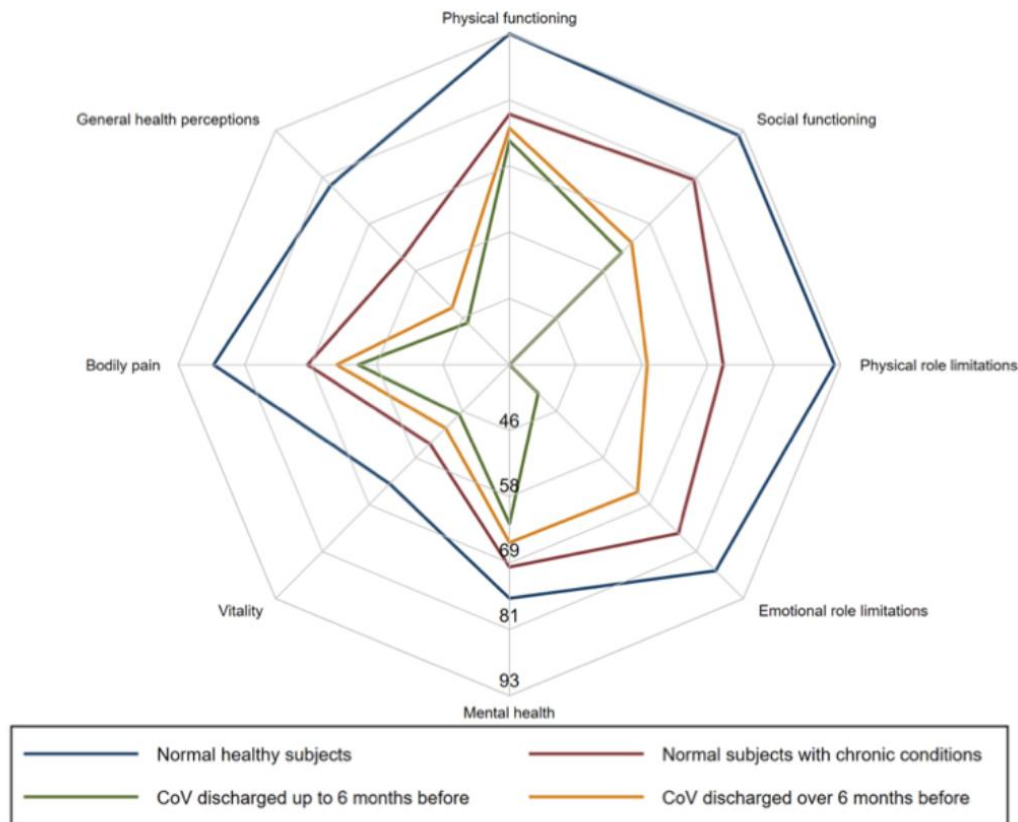
CSF=cerebrospinal fluid. EEG=electroencephalogram. HADS=Hospital Anxiety and Depression Scale. HAMA=Hamilton Anxiety Scale. HAMD=Hamilton Depression Scale. ICU=intensive care unit. NR=not reported. PSSS=Perceived Social Support Scale. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. \*Data are mean (SD) unless otherwise stated.

**Table 5: Studies reporting acute psychiatric and neuropsychiatric outcomes of SARS-CoV-2 infections**

# Pooled estimate of prevalence of different lung function abnormalities and of 6-minute walking distance in CoV survivors up to 6 months and over 6 months from discharge



# Pooled estimate of mean scores for different domains of SF-36 in CoV survivors up to 6 months and over 6 months from discharge



Study	Mean score (95% CI)
<b>up to 6 months</b>	
Hui et al., (2005)	59.00 (52.61, 65.39)
Lam et al. (2006)	64.70 (60.04, 69.36)
<i>Subtotal</i>	62.29 (56.77, 67.81)
<b>over 6 months</b>	
Hong et al. (2009)	70.00 (65.34, 74.66)
Hui et al., (2005)	60.60 (53.93, 67.27)
<i>Subtotal</i>	65.61 (56.42, 74.81)

0 20 40 60 80 100  
SF36 mental health score

Study	Mean score (95% CI)
<b>up to 6 months</b>	
Hui et al., (2005)	77.80 (71.55, 84.05)
Lam et al. (2006)	69.90 (64.83, 74.97)
<i>Subtotal</i>	73.63 (65.90, 81.36)
<b>over 6 months</b>	
Hong et al. (2009)	73.70 (66.97, 80.43)
Hui et al., (2005)	78.80 (70.92, 86.68)
<i>Subtotal</i>	75.85 (70.73, 80.97)

0 20 40 60 80 100  
SF36 physical functioning score

# INMI COVID-19 Dbase

## Hyperinflammation and laboratory profile at admission and discharge in 324 COVID-19 patients

Laboratory exams	At admission	At discharge	P
HB <12, g/dL	38/324 (11.7%)	47/318 (14.8%)	<0.001
PLT <100.000/mm <sup>3</sup>	12/323 (3.7%)	4/318 (1.3%)	0.695
Ferritin >500 ng/mL	119/324 (36.7%)	78/190 (41.1%)	0.106
PCR >3 mg/dL	159/319 (48.3%)	38/294 (12.9%)	<0.001
LDH >300 UI/L	90/314 (28.78%)	31/252 (12.3%)	<0.001
AST e/o ALT >UNL	260/321 (81.0%)	240/300 (80.0%)	0.816
D-dimer >1000 ng/mL	195/267 (73.0%)	163/232 (70.3%)	0.710
MDRD <60 ml/min	52/324 (16.1%)	8/190 (4.2%)	<0.001
Lymphocytes <1000/mm <sup>3</sup>	105/323 (32.5%)	47/318 (14.8%)	<0.001

**1° giorno**  
(mattina 7:30-10:30; 9:00-13:00)

**Apertura cartella**  
Presenza in carico infermieristica  
Visita Infettivologica apertura PAC  
Prelievo di sangue

**2° giorno e successivi**  
(mattina: 9:00-13:00  
pomeriggio: 14:00-18:00)

**Valutazioni specialistiche secondo Piano assistenziale**

TAC torace

ECG  
Ecocardiogramma

Ecografia vascolare (IMT)

PFR, DLCO, 6MWT

Endoscopia digestive

Ecografia addome  
Elastometria epatica

RMN morfologica e funzionale

PFR, DLCO, 6MWT

Pneumologo

Dermatologo

Cardiologo

Ematologo

Gastroenterologo

Oculista

Psicologo clinico  
Neuropsicologo

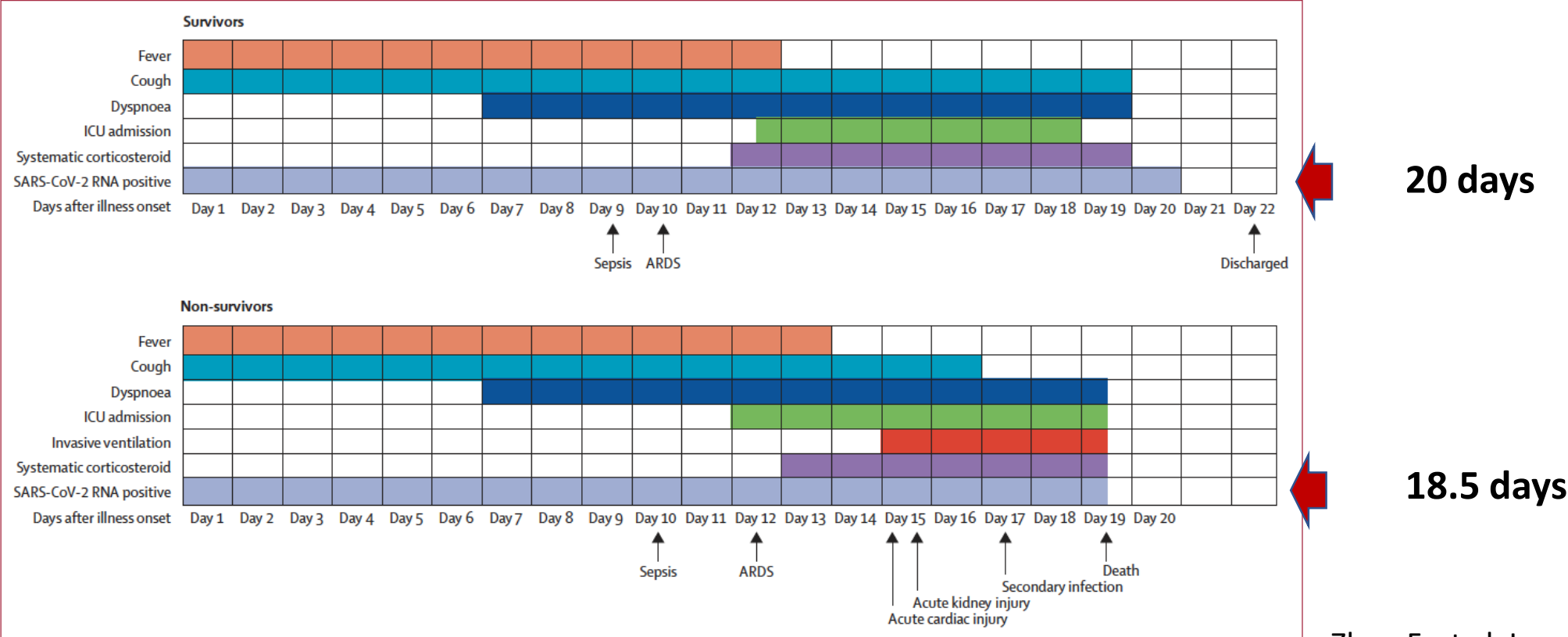
# Guidance on discharge and ending isolation in the context of widespread community transmission

COVID-19 case status	Description	Guidance
<b>Hospitalised suspected or confirmed COVID-19 cases</b>	<p>This category refers to:</p> <ul style="list-style-type: none"> <li>• Patients who are hospitalised with suspected or laboratory confirmed COVID-19 (mild, severe and critically ill) [27]</li> <li>• Confirmed COVID-19 patients discharged early, due to clinical improvement</li> </ul>	<p><b>If testing and hospitalisation capacity allows,</b></p> <ul style="list-style-type: none"> <li>• For a clinically recovered patient, two negative RT-PCR tests from respiratory specimens at 24 hours interval at least eight days after onset of symptoms [4]</li> </ul> <p><b>If limited/no testing capacity,</b></p> <ul style="list-style-type: none"> <li>• Patient can be discharged based on clinical criteria, per evaluation of the treating physician, AND</li> <li>• the discharged patient should self-isolate at home or in a safe place until resolution of fever for at least three days and clinical improvement of other symptoms AND</li> <li>• until eight days after the onset of symptoms for mild cases or for 14 days (severe cases) if these criteria have not been fulfilled in hospital.</li> <li>• Follow-up visits, or monitoring via phone or other electronic device can be considered.</li> <li>• These patients should be prioritised for testing.</li> </ul>
	<b>Discharged to closed population environment</b> (long-term care facility, prison, children with special needs etc.)	The patient should be placed in a single room until eight days after the onset of symptoms have passed AND resolution of fever for at least for three days AND clinical improvement of other symptoms.
	<b>Immunocompromised patients</b>	Self-isolation should last until all of the following criteria are fulfilled: at least 14 days after symptom onset AND resolution of fever for at least three days AND clinical improvement of symptoms other than fever.



# Clinical courses of major symptoms and duration of viral shedding from illness onset in patients hospitalised with COVID-19

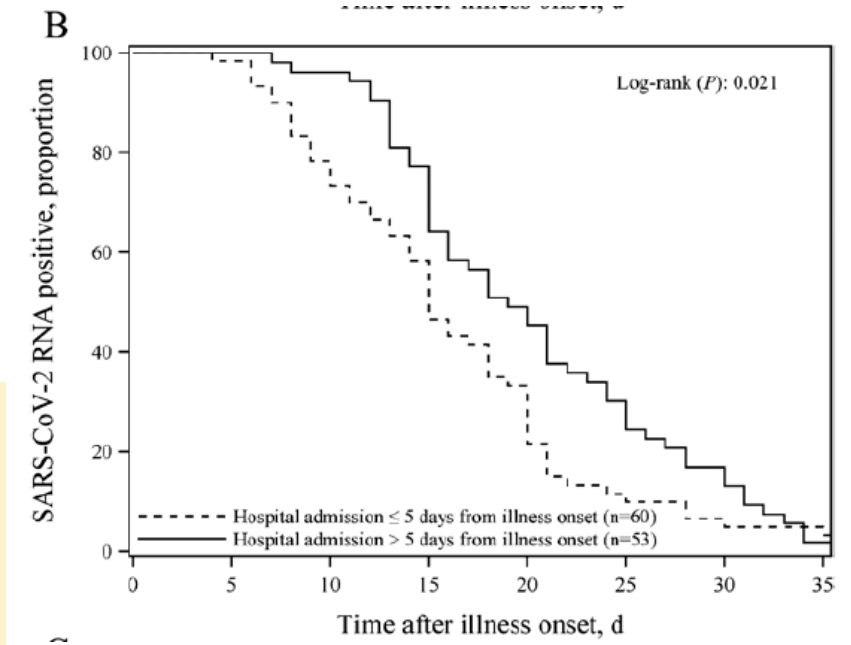
	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Duration of viral shedding after COVID-19 onset, days	20.0 (16.0–23.0)	18.5 (15.0–22.0)†	20.0 (17.0–24.0)	0.024



Zhou F, et al. Lancet 2020; 395: 1054–62

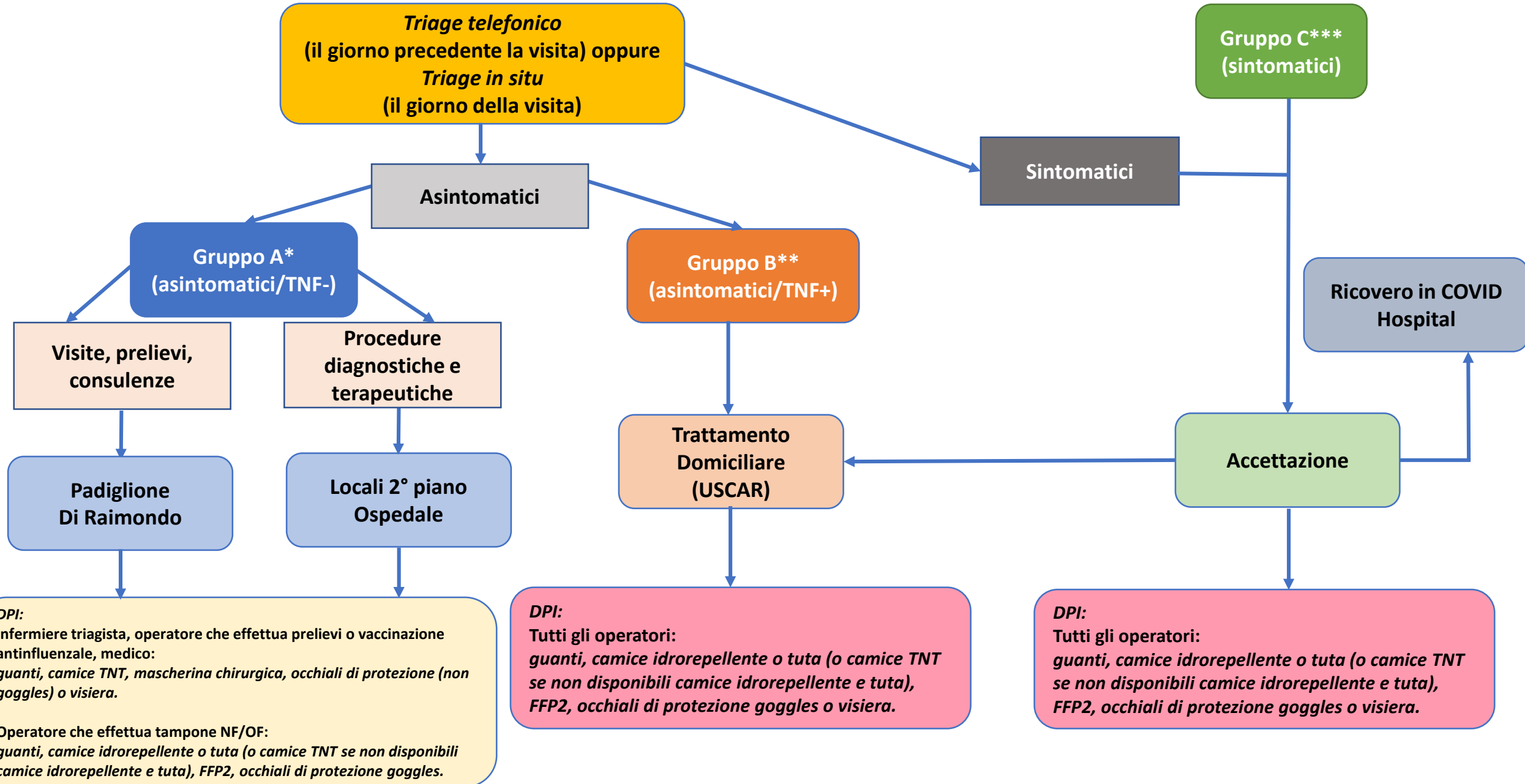
# Factors Associated With Prolonged Viral RNA Shedding in Patients with Coronavirus Disease 2019 (COVID-19)

Retrospective study on risk factors associated with severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) RNA shedding were evaluated in a cohort of **113 symptomatic patients** from 2 hospitals outside Wuhan. **The median duration of SARS-CoV-2 RNA detection was 17 (IQR 13–22) days** as measured from illness onset.



Variable	Multivariable Analysis			Stepwise Analysis		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Age	1.00	.96–1.03	.913	...	...	
Male sex	2.89	1.10–7.58	.031	3.24	1.31–8.02	.011
Hypertension	3.94	.86–18.15	.079	...	...	
Corticosteroid	1.38	.52–3.65	.519	...	...	
Time from illness onset to hospitalization, days	1.31	1.08–1.58	.005	1.30	1.10–1.54	.002
Patients with severe disease at admission	1.10	.32–3.81	.882	...	...	
Critical illness during hospitalization	.42	.03–5.22	.497	...	...	
Invasive mechanical ventilation	23.28	.72–750.09	.076	9.88	1.11–88.02	.04

Abbreviations: CI, confidence interval; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



\*Gruppo A=Pazienti asintomatici con pregressa diagnosi di COVID-19, con ultimo tampone NF/OF negativo per SARS-CoV-2

\*\*Gruppo B=Pazienti asintomatici con persistenza di positività alla RT-PCR per SARS-CoV-2 nel TNF/TOF già nota al momento della prenotazione della visita ambulatoriale o precedentemente negativizzati, con riscontro di nuova positività alla RT-PCR per SARS-CoV-2 nel TNF/TOF durante il tampone effettuato nel corso di un accesso ambulatoriale

\*\*\*Gruppo C=Pazienti sintomatici

# INMI COVID-19 Dbase

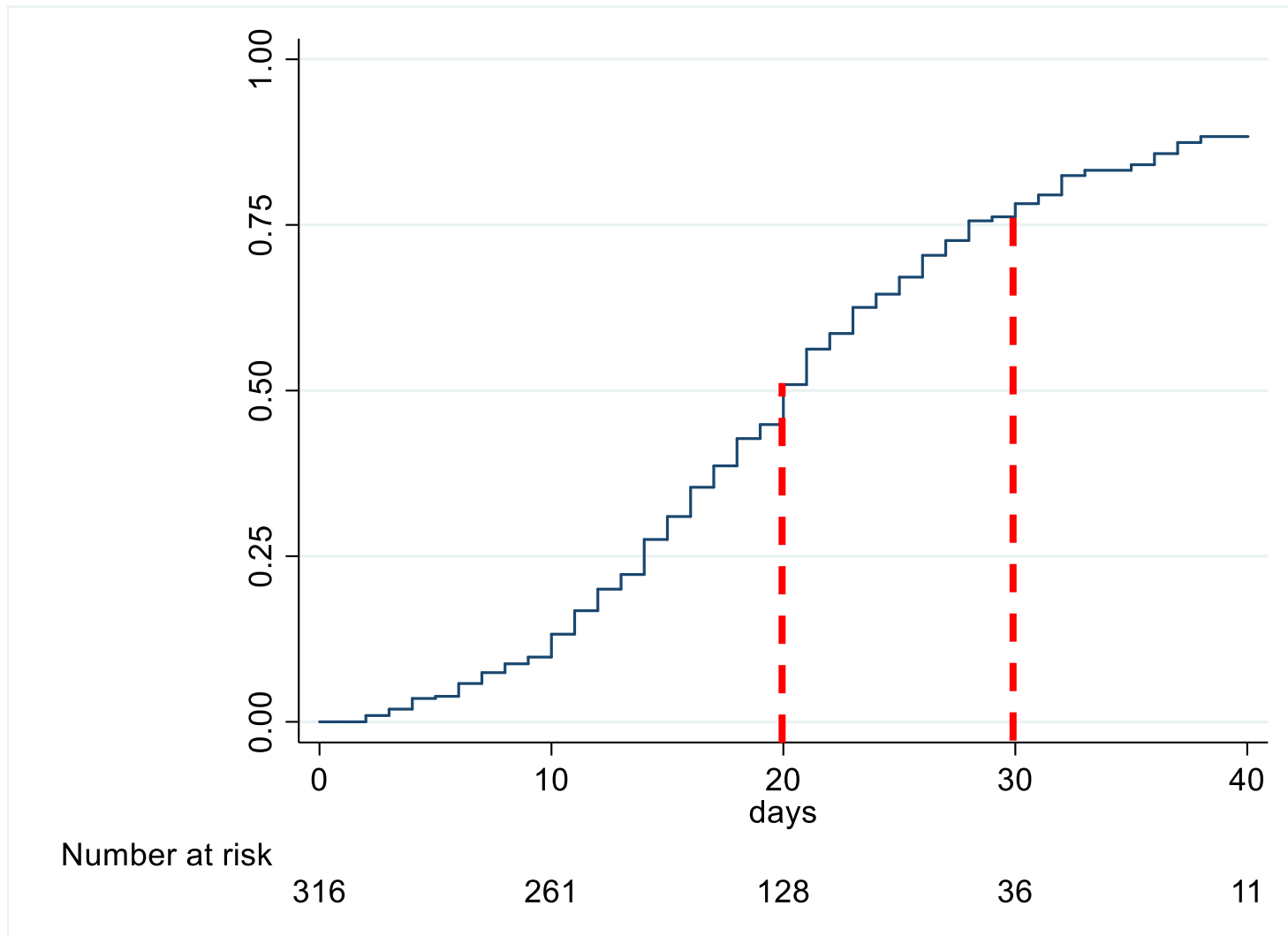
## Characteristics of COVID-19 patients discharged from the hospital (n=324)

<b>Characteristics</b>	
<b>Patients discharged from the hospital (n=324)</b>	
<b>Baseline characteristics (at admission)</b>	
Male gender	214 (66.1%)
Age, median years (IQR)	60 (49-71)
Comorbidities	221 (68.9%)
<b>Worst PaO<sub>2</sub>/FiO<sub>2</sub> during clinical course</b>	
<200 mmHg	100 (34.1%)
200-300 mmHg	74 (25.3%)
>300	119 (40.6%)
Starting NIV/CPAP/IOT	96 (29.6%)
Hyperinflammation during hospitalization	165 (50.9%)

<b>Time</b>	
Time from symptoms onset to admission, median (IQR)	8 (5-11)
Hospitalization length, median (IQR)	11 (7-17)
<b>Time from symptoms onset to starting therapy</b>	
<=12 gg	202 (80.5%)
>12 gg	49 (19.5%)
<b>Time from symptoms onset to negative NP swab</b>	
- median (IQR)	17 (12-23)
- range	2-61 days
<b>N. of patients discharged with positive NP swab</b>	77 (27.7%)

# INMI COVID-19 Dbase

## Probability of achieving SARS-CoV-2 clearance from NP swab



- 20 day-probability of viral clearance: 51% (95% CI 44.9-57.2)
- 30 day-probability of viral clearance: 78.2% (95% CI 72.2-83.7)

## Factors associated to more rapid viral clearance on NP swab (n=316)

	Multivariable Poisson regression					
	Total population (n=316)		Stratification according to illness severity			
			Non-severe illness PaO <sub>2</sub> /FiO <sub>2</sub> ≥300 (n=129)		Severe illness PaO <sub>2</sub> /FiO <sub>2</sub> <300 (n=187)	
	adjusted IRR (95% CI)	p-value	adjusted IRR (95% CI)	p-value	adjusted IRR (95% CI)	p-value
Female gender	1.10 (0.81-1.50)	0.548	1.33 (0.76-2.31)	0.317	0.93 (0.59-1.46)	0.749
Age for 10 years more	1.05 (0.95-1.17)	0.343	<b>1.24</b> <b>(0.01-1.51)</b>	<b>0.038</b>	0.85 (0.93-2.10)	0.511
Comorbidities for each more	<b>0.87</b> <b>(0.77-0.98)</b>	<b>0.027</b>	0.84 (0.64-1.11)	0.231	0.92 (0.79-1.06)	0.260
PaO <sub>2</sub> /FiO <sub>2</sub> (time dependent)						
>300 mmHg	1.00	-				
≤300 mmHg	<b>0.60</b> <b>(0.42-0.86)</b>	<b>0.005</b>				
Time from symptoms onset to admission						
for 1 day more	1.00 (0.98-1.02)	0.962				
>16 vs ≤16 days			<b>0.47</b> <b>(0.23-0.97)</b>	<b>0.042</b>	0.59 (0.27-1.26)	0.174
Antiviral therapy, yes vs no	0.73 (0.44-1.19)	0.207	0.59 (0.30-1.17)	0.132	0.83 (0.25-2.73)	0.765

# INMI COVID-19 Dbase

## Factors associated to prolonged (>21 days) viral shedding on NP swab (n=234)

	Multivariable logistic regression	
	Total population (n=234)	
	Adjusted OR (95% CI)	p-value
Female gender	1.27 (0.65-2.46)	0.484
Age for 10 years more	1.03 (0.81-1.30)	0.800
Comorbidities for each more	<b>1.25</b> <b>(0.97-1.61)</b>	<b>0.082</b>
PaO <sub>2</sub> /FiO <sub>2</sub> <200 mmHg	<b>1.0</b>	-
200-300	<b>0.30</b> <b>(0.14-0.67)</b>	<b>0.003</b>
>300	<b>0.51</b> <b>(0.24-1.07)</b>	<b>0.075</b>
Time from symptoms onset to admission for 1 day more	<b>1.13</b> <b>(1.08-1.20)</b>	<b>&lt;0.001</b>
Antiviral therapy, yes vs no	0.92 (0.30-2.79)	0.884

# SARS-CoV-2 detection by RT-PCR from clinical specimens

<b>Table 1: Transmission routes</b>			
<b>Source</b>	<b>Mode of transmission</b>	<b>RNA by PCR</b> (Days since onset of symptoms)	<b>Viable virus</b> (Days since onset of symptoms)
<b>Nasopharynx</b>	Droplet	Up to 37 days	Up to 7 days (in mild cases)
<b>Sputum</b>	Droplet / airborne during aerosolize-producing procedures	Up to 37 days	Up to 7 days (in mild cases)
<b>Stool</b>	No evidence of faecal-oral transmission	> 30 days	Only 1 report; uncertain
<b>Blood</b>	No viable virus to date	Up to 14 days	No
<b>Urine</b>	No viable virus to date	No	No
<b>Conjunctiva</b>	No viable virus to date Macaques with corneal inoculation develop infection	Yes	No
<b>Vertical</b>	No strong evidence of vertical transmission to date	No	N/A

1. Wolfel R, et al. Nature 2020; 2. OKBA NMA, et al. medRxiv 2020: 2020.03.18.20038059.3. Zhao J, et al. medRxiv 2020: 2020.03.02.20030189. 4. Amanat F, et al. medRxiv 2020: 2020.03.17.20037713. 5. Wu F, et al. medRxiv 2020: 2020.03.30.20047365. 6. Cai J, et al. Clinical Infectious Diseases 2020. 7. Young BE, et al. JAMA 2020. 8. To KK-W, et al. Clinical Infectious Diseases 2020. 9. Wang W, et al. JAMA 2020. 10. Peng L, et al. medRxiv 2020: 2020.02.21.20026179. 11. Zou L, et al. New England Journal of Medicine 2020; 382(12): 1177-9. 12. Liu Y, et al. The Lancet Infectious Diseases. 13. Xu Y, et al. Nature Medicine 2020.



# PCR Assays Turned Positive in 25 Discharged COVID-19 Patients

The study population included 172 discharged COVID-19 patients from Jan 23<sup>th</sup> 2020 to Feb 21<sup>th</sup> 2020.

These were **25 of discharged patients (total 14.5%)** sent to hospital again because of the **positive RT-PCR results on virus again.**

These 25 patients experienced **an average of 7.32±3.86 days** from their last negative RT-PCR result **to turning positive again.**

Characteristics	Mean days (SD)
Length of first hospital stay	15.36 (3.81)
Antiviral treatment duration	13.44 (4.08)
Time from negative PCR test to discharge	2.71 (1.88)
Time from last negative to positive again	7.32 (3.86)

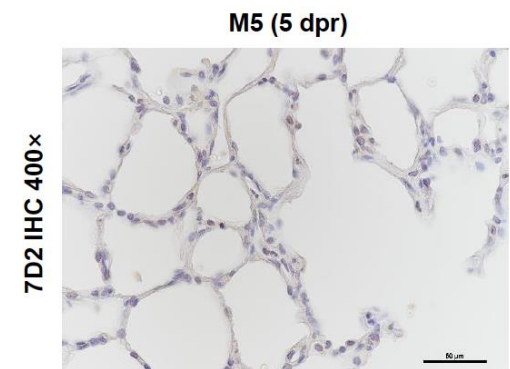
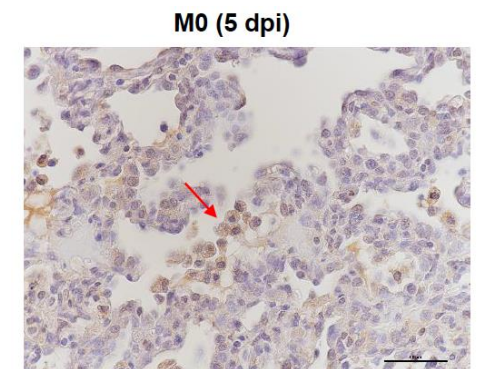
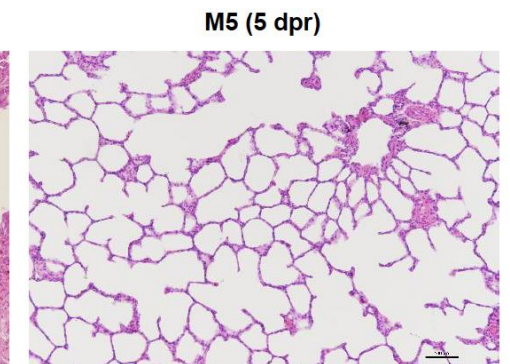
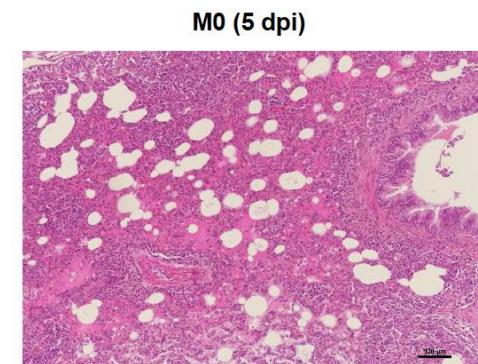
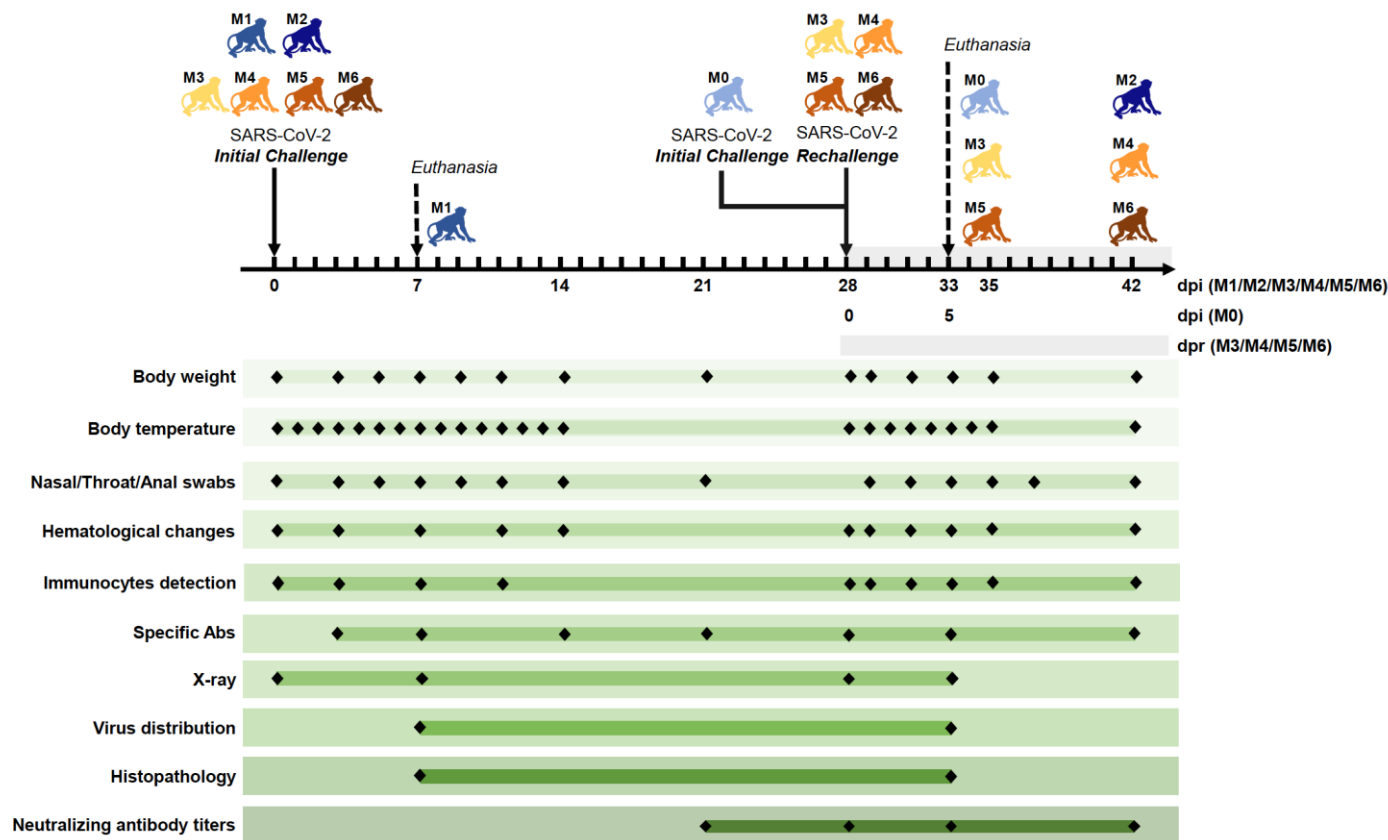
# False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence

Variables	All Patients (N=70)	Non-consecutive false-negative (n=55)	Consecutive false-negative (n=15)	p-value
Age, median (IQR), years	57 (44-65)	57 (43-65)	64 (51-73)	0.093
Gender, Male, n (%)	31 (44.3%)	22 (40.0%)	9 (60.0%)	0.172
Severity on admission				0.935
Moderate	66 (94.3%)	52 (94.5%)	14 (93.3%)	
Severe	4 (5.7%)	3 (5.5%)	1 (6.7%)	
Onset of symptom to nucleic acid conversion, median (IQR), d	22 (19-32)	21 (18-26)	36 (28-40)	<0.001

We found that 15/70 (21.4%) patients experienced a “turn positive” of nucleic acid detection by RT-PCR test for SARS-CoV-2 after two consecutive negative results, which may be related to the false negative of RT-PCR test and prolonged nucleic acid conversion.

# Lack of Reinfection in Rhesus Macaques Infected with SARS-CoV-2

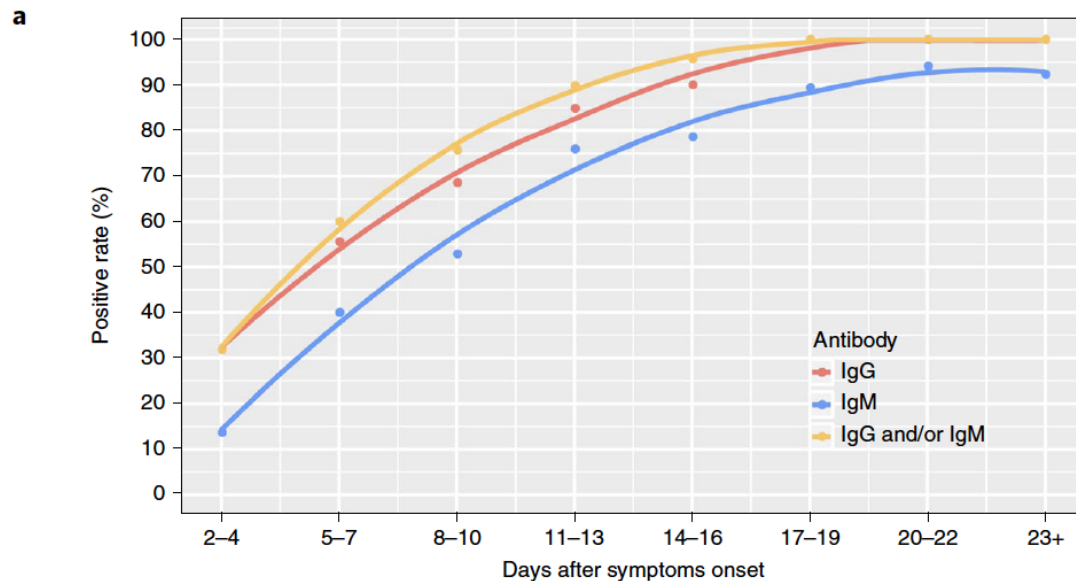
Rhesus macaques were rechallenged with SARS-CoV-2 during an early recovery phase from initial infection. The monkeys **rechallenged with the identical SARS-CoV-2 strain have failed to produce detectable viral dissemination**, clinical manifestations and histopathological changes. A notably **enhanced neutralizing antibody response** might contribute the protection of rhesus macaques from the reinfection by SARS-CoV-2. Our results indicated that **primary SARS-CoV-2 infection protects from subsequent reinfection**.



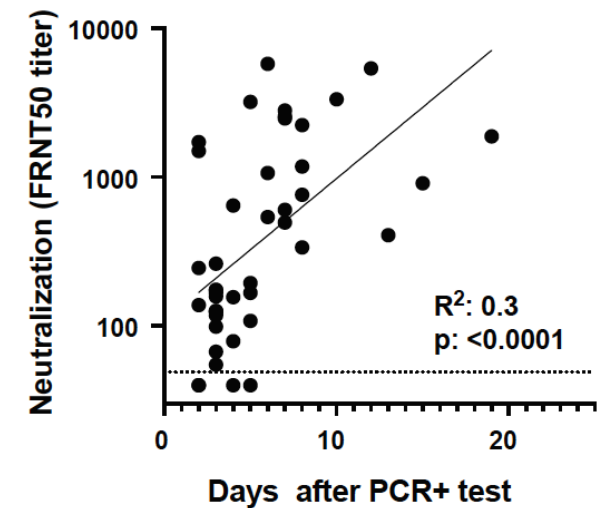
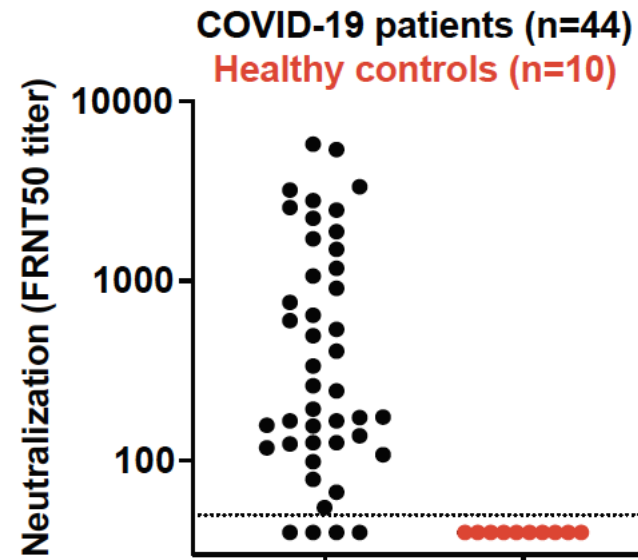
# Antibody response and neutralizing activity to SARS-CoV-2 in patients with COVID-19

Acute antibody responses to SARS-CoV-2 in 285 patients with COVID-19. Within 19 days after symptom onset, **100% of patients tested positive for antiviral immunoglobulin-G (IgG)**. Seroconversion for **IgG and IgM occurred simultaneously or sequentially**. Both IgG and IgM titers **plateaued within 6 days after seroconversion**.

**RBD-specific IgG responses were detectable in all patients 6 days after PCR confirmation**. Using a clinical isolate of SARS-CoV-2, **neutralizing antibody titers were also detectable in all patients 6 days after PCR confirmation**. The **magnitude of RBD-specific IgG binding titers correlated strongly with viral neutralization**.



Long QX, et al. Nat Med. 2020 Apr 29. doi: 10.1038/s41591-020-0897-1. [Epub ahead of print]



Suthar MS, et al. medRxiv preprint doi: <https://doi.org/10.1101/2020.05.03.20084442>.

**PAZIENTI CON COVID-19 CON  
GUARIGIONE CLINICA\* E VIROLOGICA\*\***

**RT-PCR da TNF/TOF  
per SARS-CoV-2  
positiva**

**Visita di  
arruolamento**

**Visite di  
follow-up  
(ogni 3 mesi)**

- raccolta delle caratteristiche demografiche e anamnesi (solo arruolamento)
- esame obiettivo e parametri vitali
- registrazione eventi clinici (polmonari, cardiaci, epatici, renali, trombotici, SNC)
- Esami strumentali (TC, ECG, ecocardiogramma, ecografia epatica, elastometria, IMT carotidea, neuroimaging)
- Spirometria, DLCO
- test neuro-cognitivi e ansia/depressione
- questionari PROs e QoL
- prelievo venoso per esami ematochimici: emocromo, creatinina, AST, ALT, glicemia, LDH, D-Dimero, Ferritina, PCR, Fibrinogeno
- test sierologici per SARS-COV-2 (IgM, IgA, IgG)
- test di siero-neutralizzazione di SARS-CoV-2
- test di risposta T-cellulare specifica per Ag di SARS-CoV-2 (nucleoproteina, proteina spike)
- dosaggio citochine plasmatiche (IL-6, IL-8, IL-1b, TNF-a)
- RT-PCR da TNF/TOF per SARS-CoV-2.

**A) Inquadramento clinico**

**B) Caratterizzazione virologica**

- RT-PCR per SARS-CoV-2 su sangue periferico
- Analisi della catena negativa
- Isolamento virale.

\*Guarigione clinica=almeno 2 settimane dalla remissione dei sintomi; stato clinico=asintomatici

\*\*Guarigione virologica=2 TNF/TOF a distanza di 24 ore negativi al test RT-PCR per SARS-CoV-2.

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