



COVID-19 et soins critiques

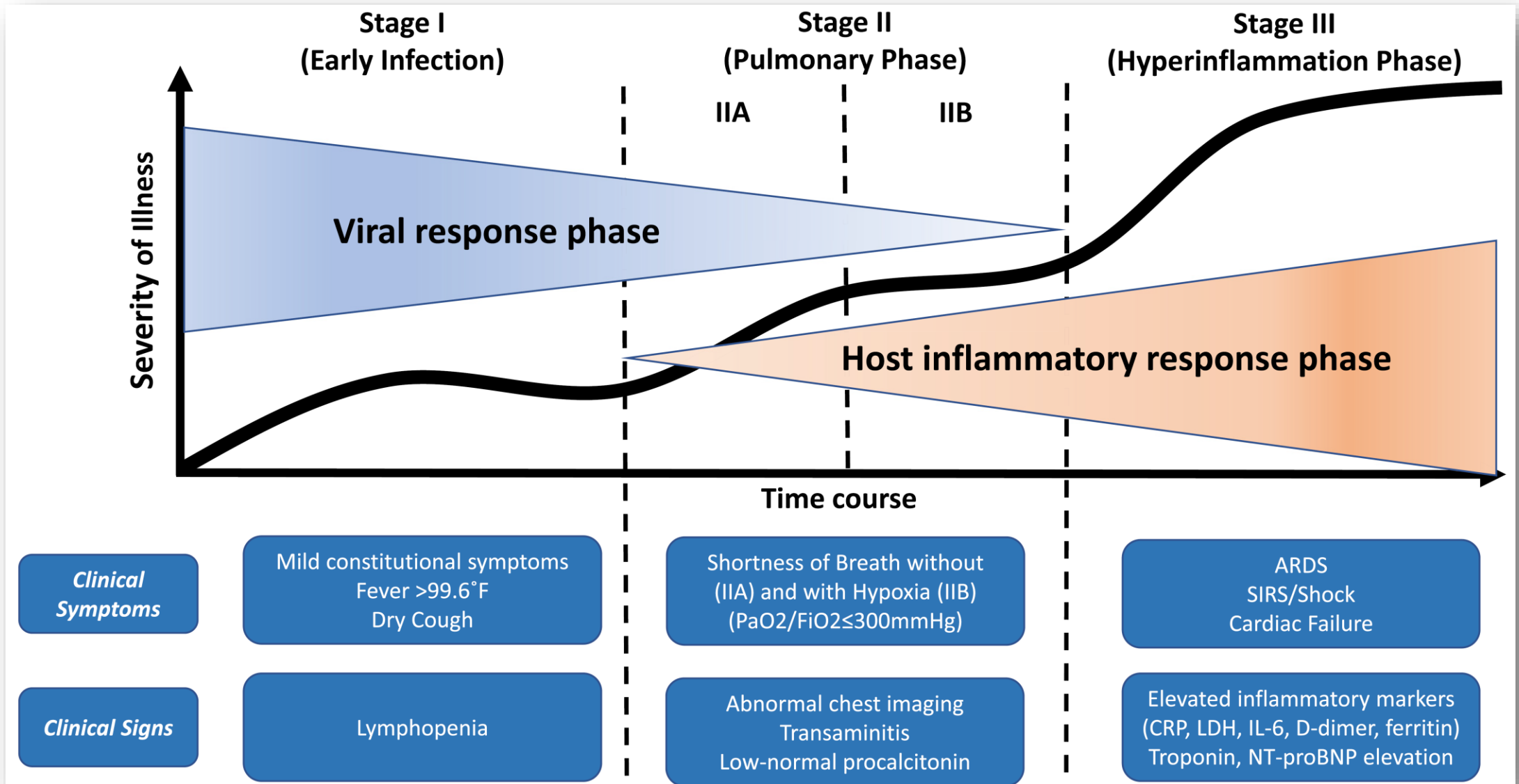
Pr J Poissy

Pôle de Médecine Intensive/Réanimation-CHU Lille

INSERM U1285-CNRS 8576-UGSF

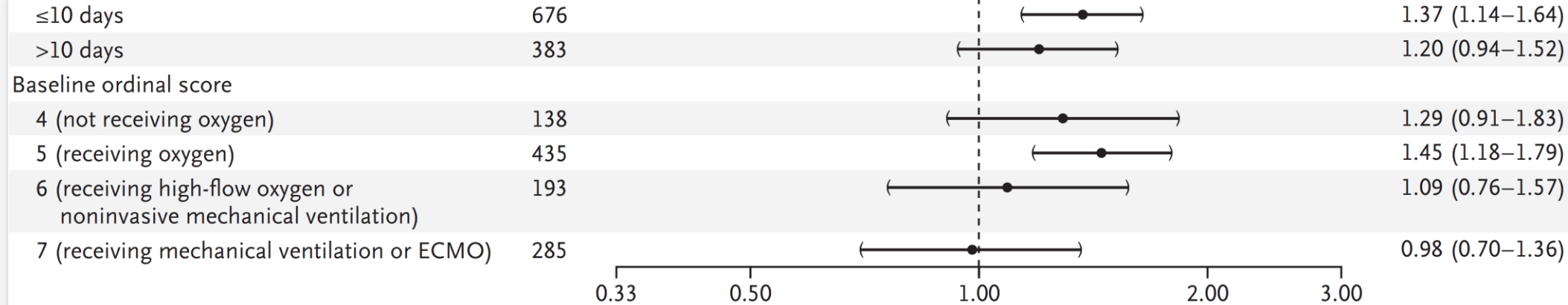


Fenêtre d'opportunité antivirale en réa ?



Remdesivir

Symptoms duration



ACCT 1 et time to recovery

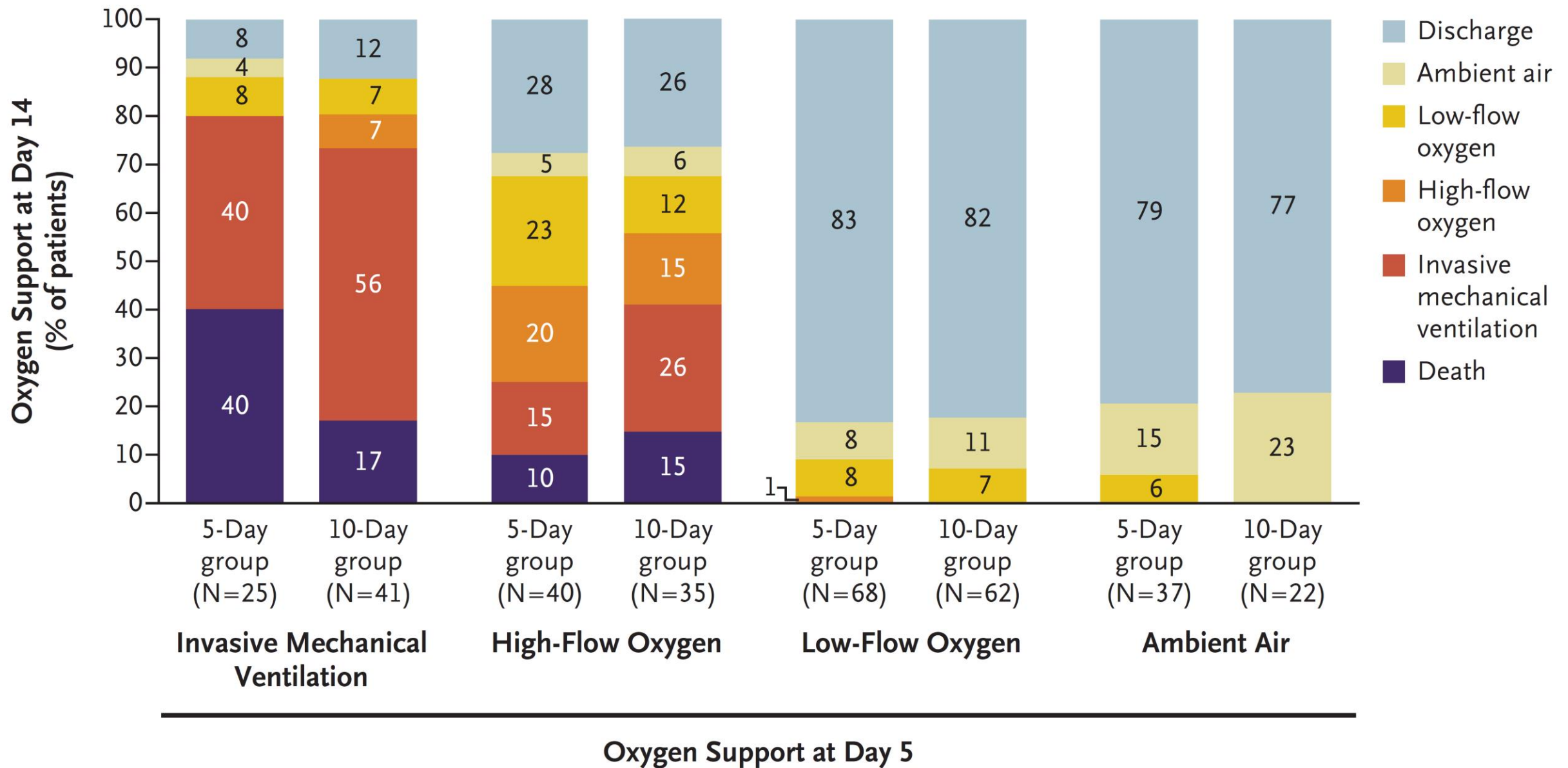
Beigel JH et al. NEJM. 2020

26% patients intubés ou ECMO

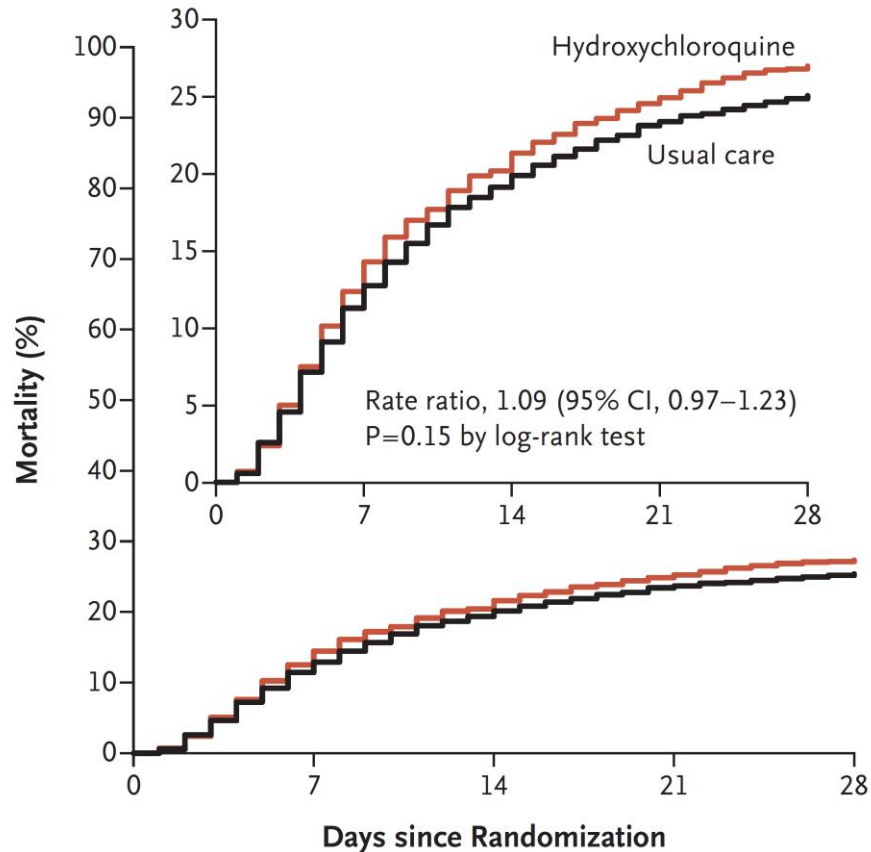
Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	65% amélioration 2 points Vs 54%
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7: Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)

Simple : 5 jours versus 10

Goldman JD et al. NEJM. 2020



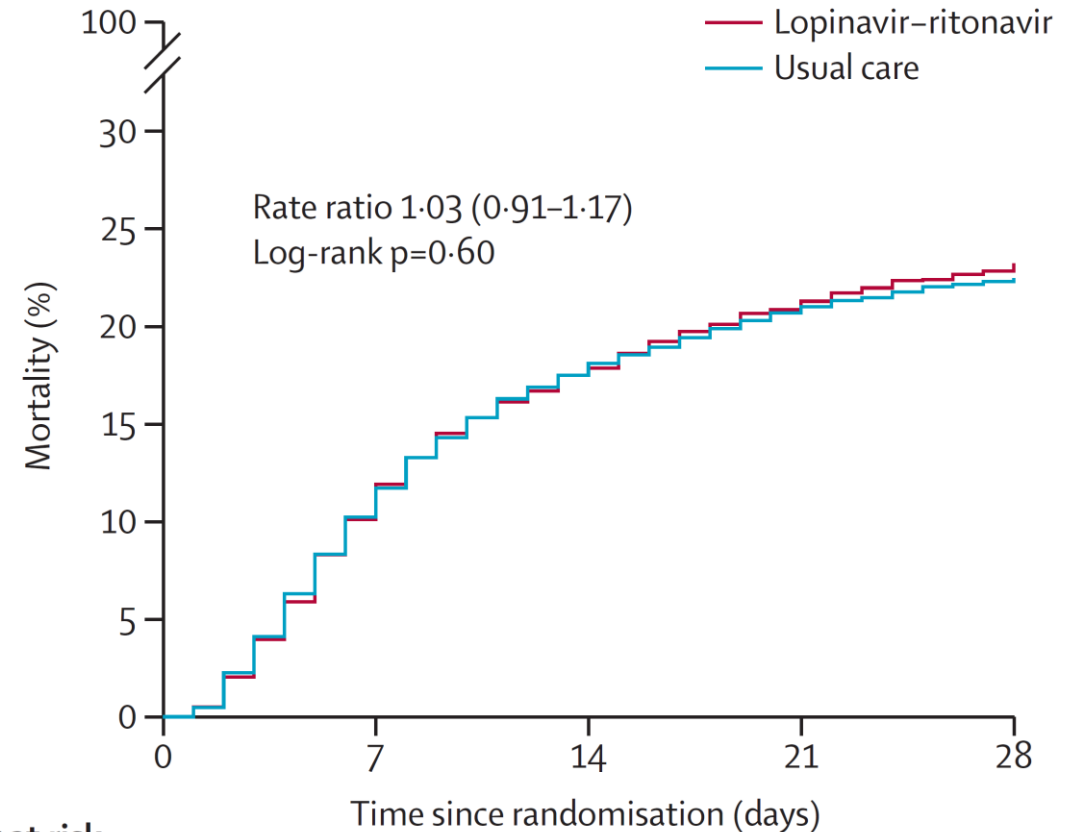
Recovery. Mortalité J28. OH-chloroquine et Lopi/r



No. at Risk					
Hydroxychloroquine	1561	1337	1227	1169	1137
Usual care	3155	2750	2525	2414	2360

Recovery collaborative group. NEJM. 2020

Pas d'o2 : 23%
O2 : 60%
Intubation : 16%



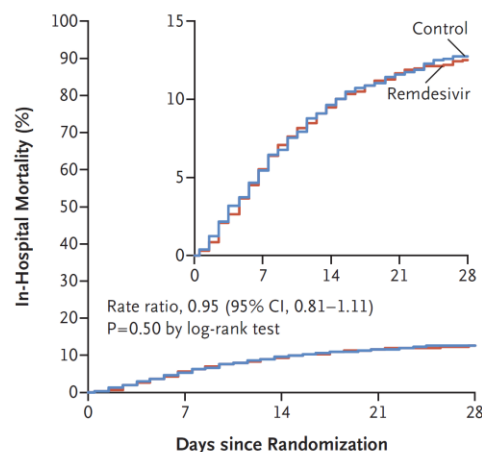
Number at risk					
Active	1616	1422	1325	1269	1238
Control	3424	3018	2799	2700	2650

Recovery collaborative group. Lancet. 2020

Pas d'o2 : 26%
O2 : 70%
Intubation : 4%

Remdesivir

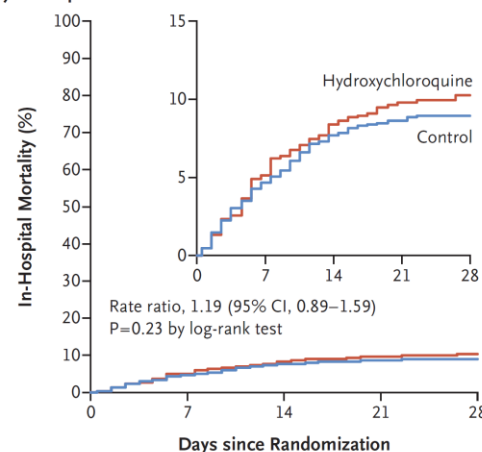
A Remdesivir vs. Its Control



Denominator	2743	2159	2029	1918	1838
Remdesivir					
Control	2708	2138	2004	1908	1833
No. Who Died					
Remdesivir	129	90	48	18	16
Control	126	93	43	27	14

OH-chloroquine

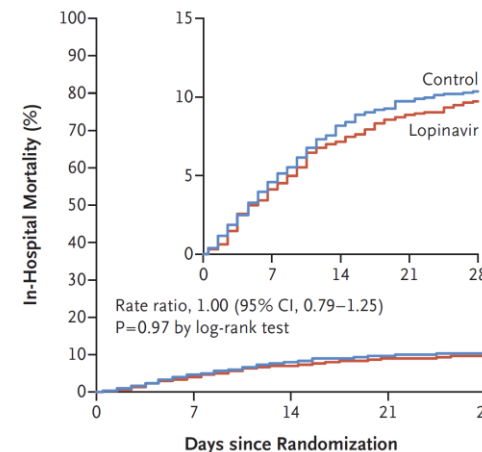
B Hydroxychloroquine vs. Its Control



Denominator	947	889	854	838	833
Hydroxychloroquine					
Control	906	853	823	814	809
No. Who Died					
Hydroxychloroquine	48	31	13	6	6
Control	42	27	8	4	3

Lopi/rito

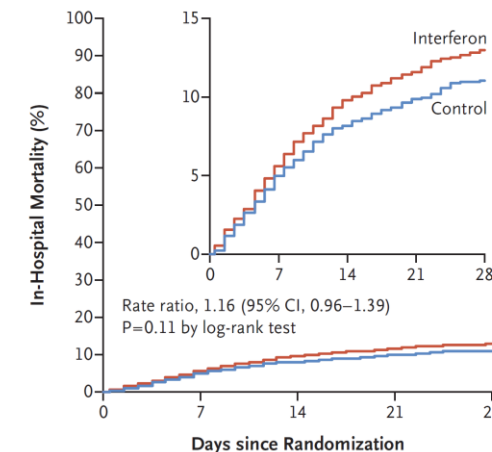
C Lopinavir vs. Its Control



Denominator	1399	1333	1282	1257	1243
Lopinavir					
Control	1372	1293	1239	1216	1203
No. Who Died					
Lopinavir	57	42	24	15	10
Control	62	48	21	10	5

Interféron

D Interferon vs. Its Control



Denominator	2050	1669	1554	1483	1410
Interferon					
Control	2050	1725	1636	1563	1498
No. Who Died					
Interferon	101	73	31	24	14
Control	91	58	31	21	15

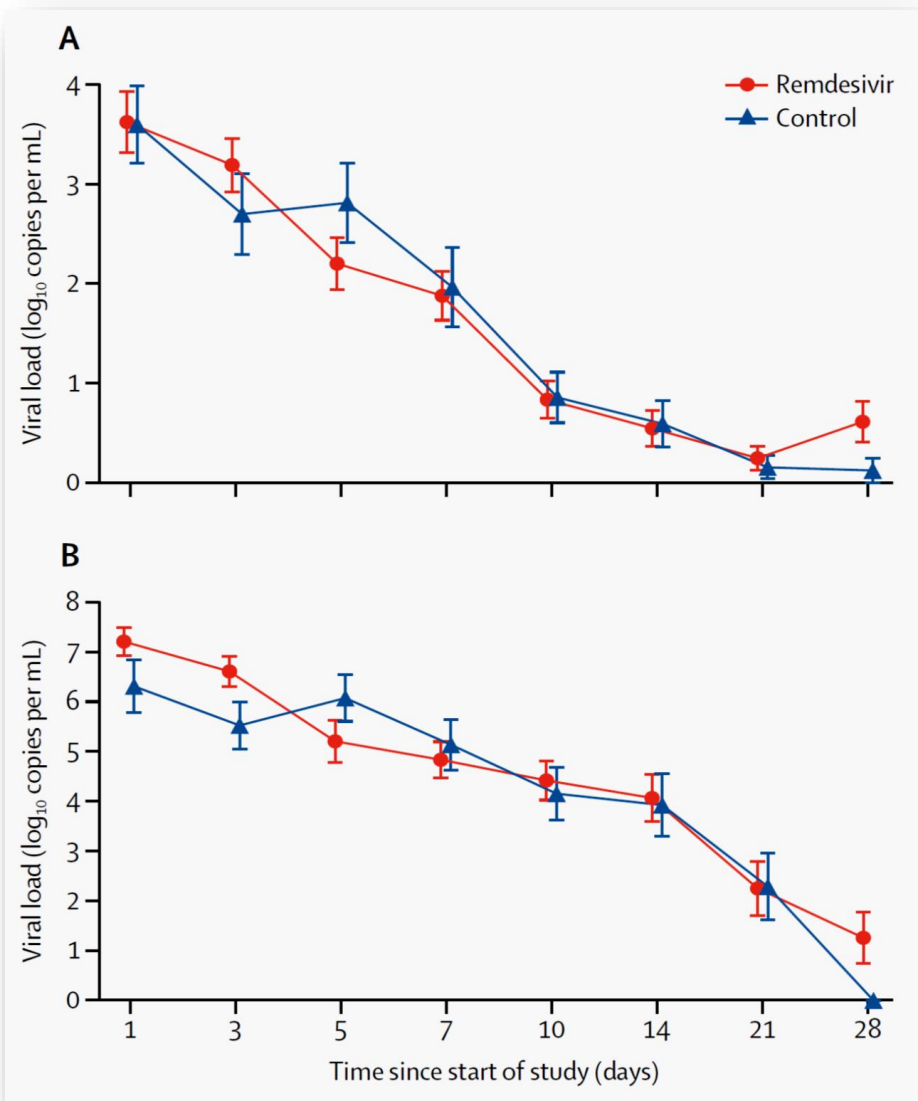
Pas d'O2 : 28%. O2 : 63%. Intubation : 8%

WHO Solidarity Trial Consortium. NEJM 2021

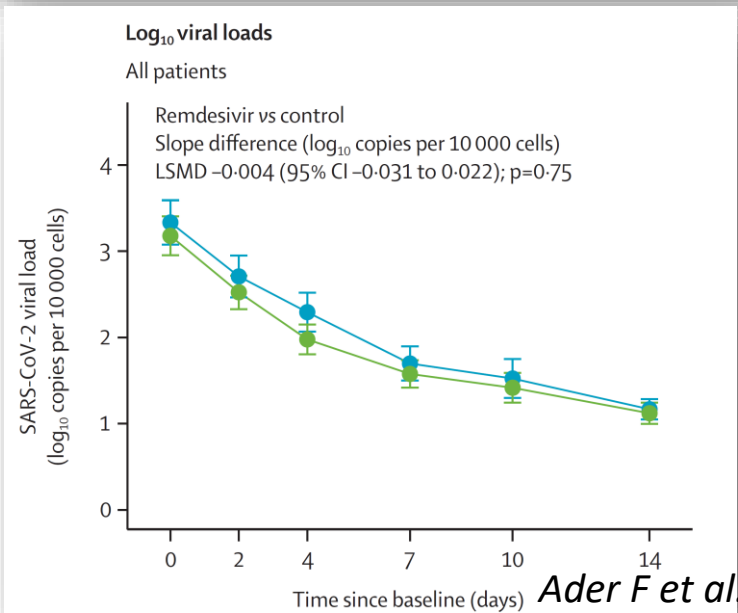
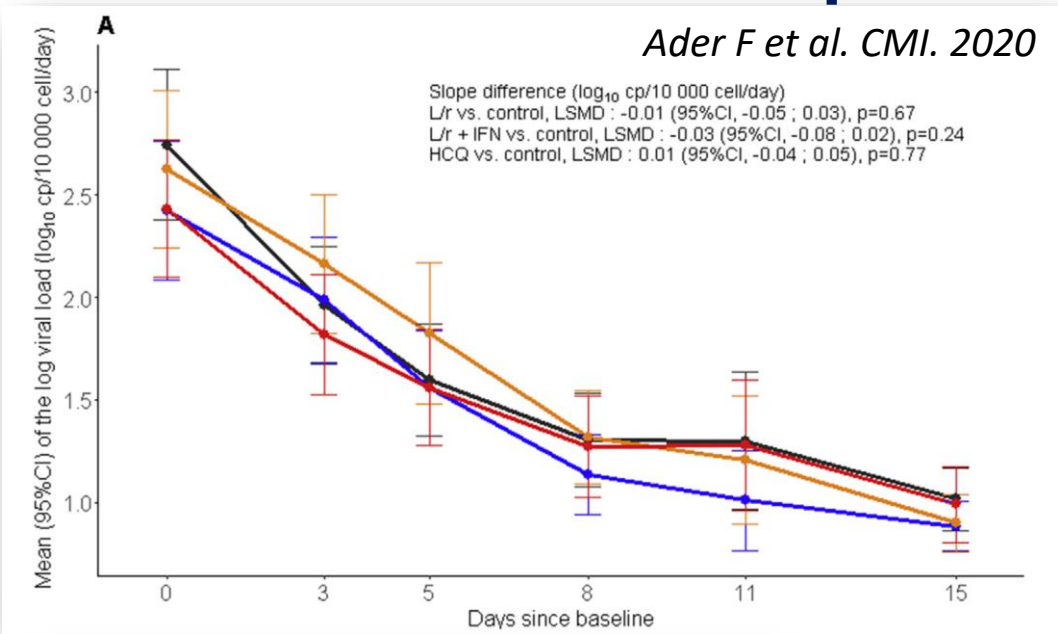
Outcome/analysis	Lopinavir-ritonavir (N= 255)	Hydroxychloroquine (N= 50)	Combination therapy (N= 27)	Control (N= 362)
Primary outcome, organ support-free days (OSFDs)				
Median (IQR)	4 (– 1, 15)	0 (– 1, 9)	– 1 (– 1, 7)	6 (– 1, 16)
Adjusted OR—median (95% CrI)	0.73 (0.55, 0.99)	0.57 (0.35, 0.83)	0.41 (0.24, 0.72)	1
Probability of futility, %	99.9	> 99.9	> 99.9	–
Probability of harm compared to control, %	98	99.9	> 99.9	–

Remap Cap (réa). Arabi YM et al. ICM 2021

Un manque d'efficacité intrinsèque ou une fenêtre antivirale dépassée ?

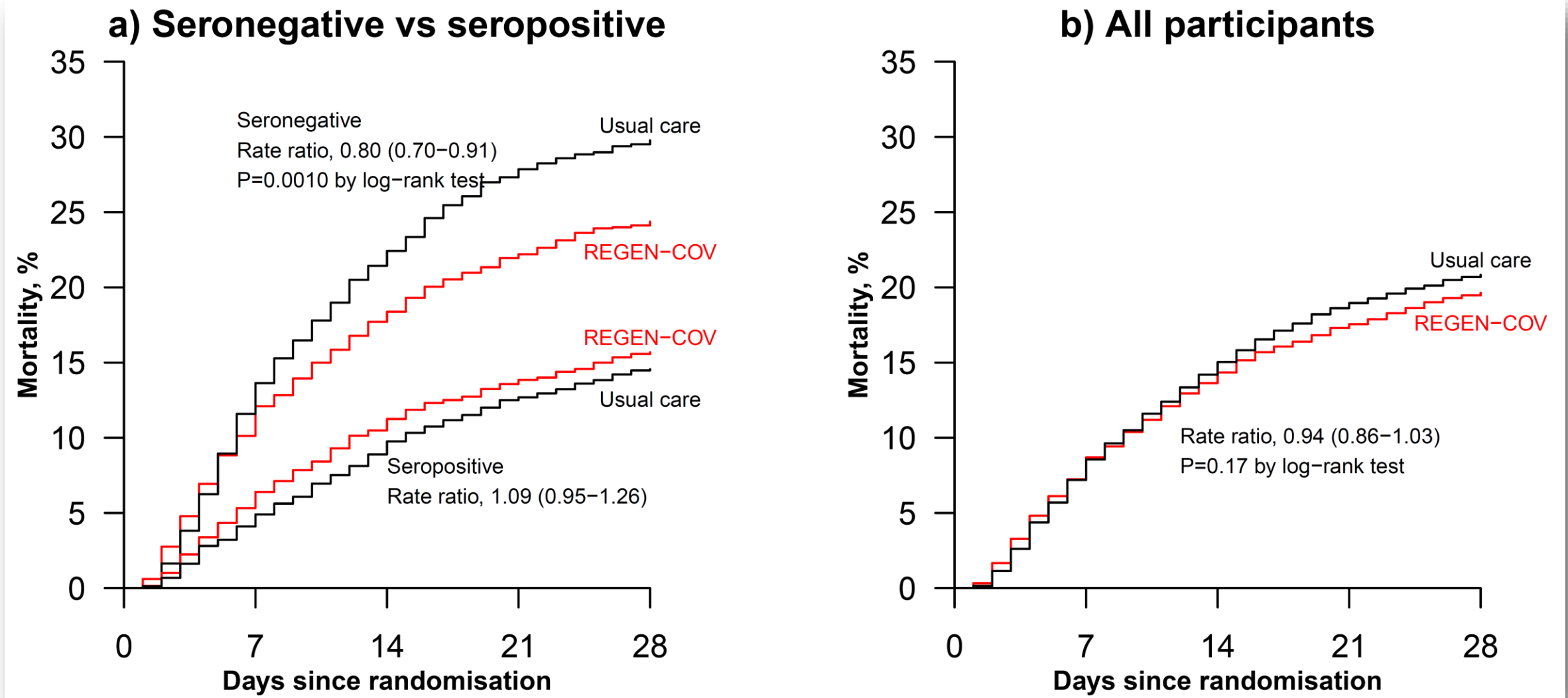


Wang Y et al. Lancet. 2020



Ader F et al. Lancet Inf Dis. 2021

REGEN-COV chez les malades hospitalisés : un intérêt chez les séronégatifs ?



2% de patients intubés ventilés. 60% d'O2

Recovery collaborative group. medRxiv. Non reviewed

COVID-19 grave : une maladie inflammatoire

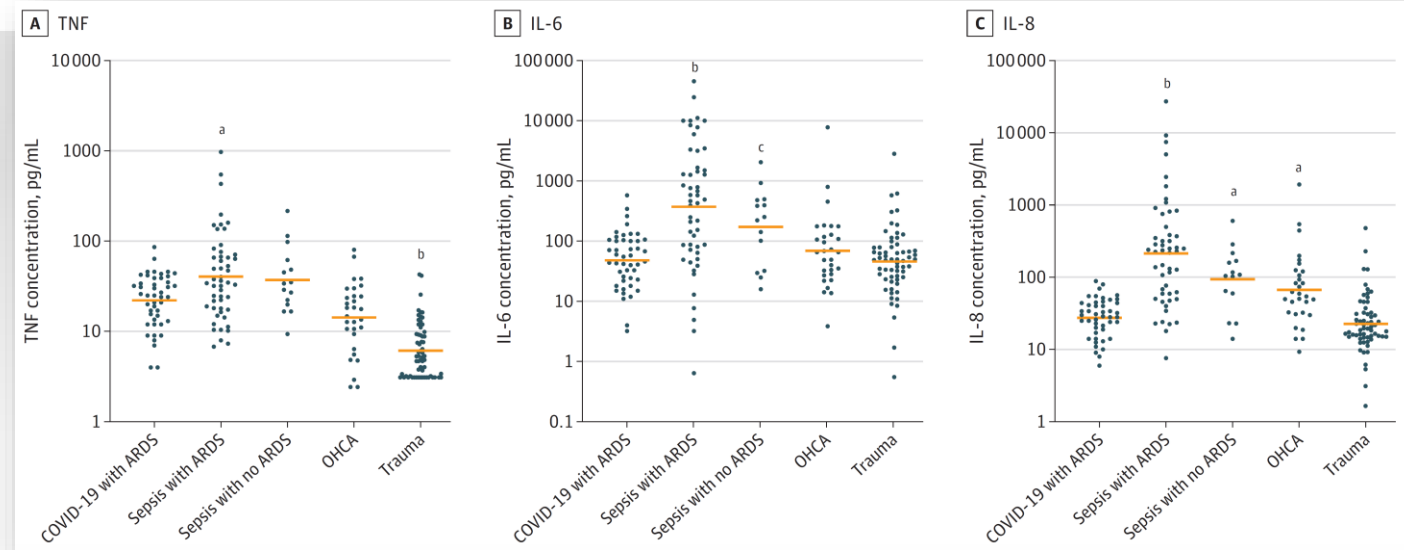
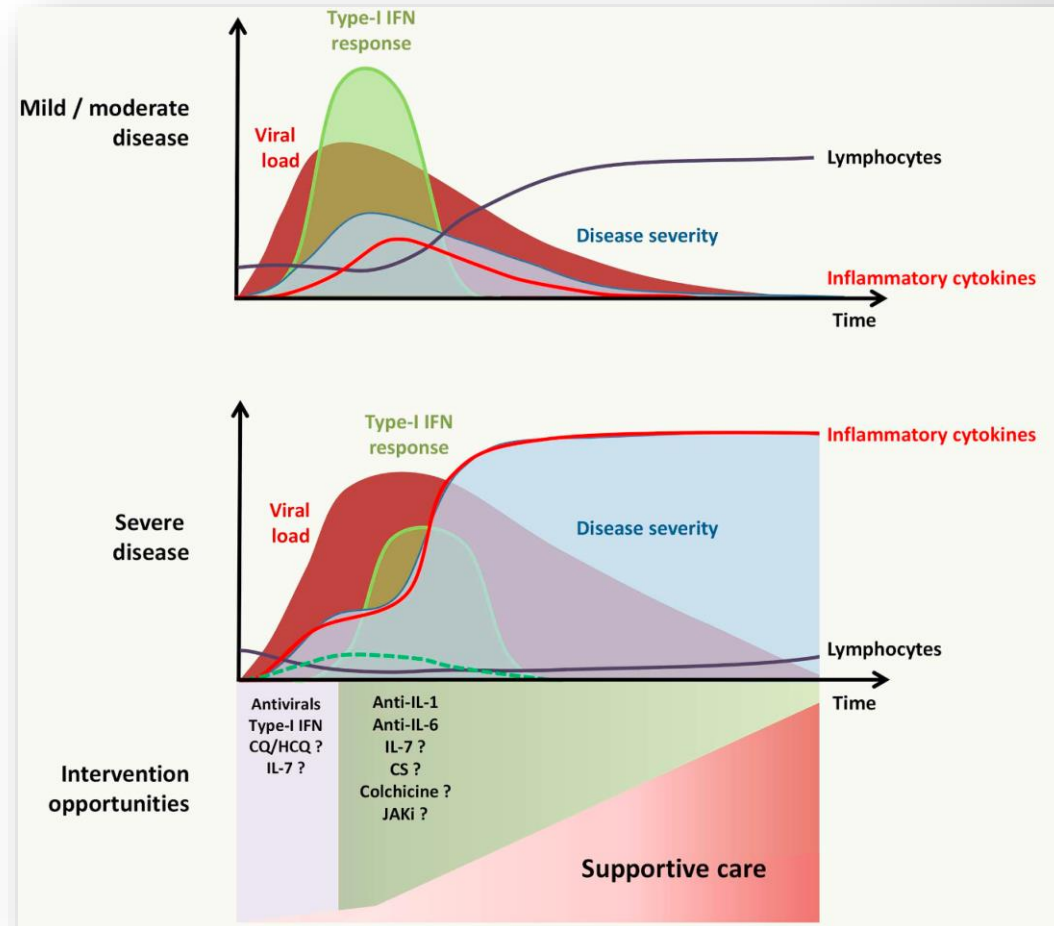


Table. Plasma Levels of Interleukin-6 Reported in COVID-19 Compared With Levels Previously Reported in ARDS^a

	Total population				Severe disease		Measurement platform
COVID-19	No.	IL-6 levels, pg/mL		No.	IL-6 levels, pg/mL		
Zhou et al ⁴	191	7 (5-11)		54 ^b	11 (8-14)		CL
Wu et al ¹	123	7 (6-9)		84 ^c	7 (6-11)		CL
Mo et al ⁵	155	45 (17-96)		85 ^d	64 (31-165)		CL
Qin et al ²	452	21 (6-47)		286 ^e	25 (10-55)		CL
Cummings et al ⁶	NR	NR		237 ^f	26 (11-69)		CL
	Total population		Hypoinflammatory		Hyperinflammatory		Measurement platform
ARDS	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	
ALVEOLI ⁷	521	238 (94-741) ^f	386	154 (67-344)	135	1525 (584-3802)	ELISA
FACTT ⁸	884	130 (46-411) ^f	638	86 (34-216)	246	578 (181-2621)	ELISA
SAILS ⁹	720	443 (173-1513) ^f	451	282 (115-600)	269	1618 (517-3205)	ELISA

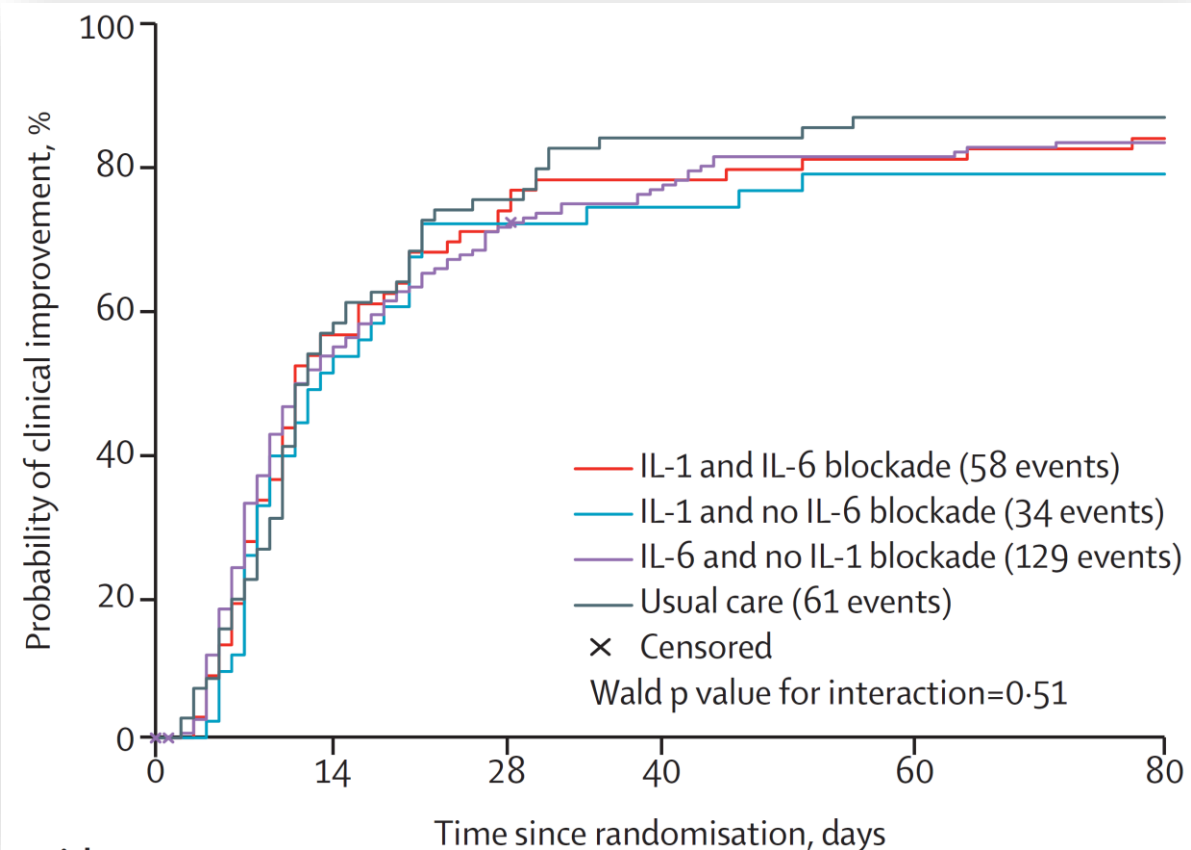
Jamillou Y et al. Autoimmunity Reviews. 2020

Sinha P et al. JAMA Internal Med. 2020

Pot pourri des RCT tocilizumab réa

Référence	Critères d'inclusion	Méthodo	Critères de jugement principal	Délai médian traitement	Résultats	Remarque
<i>Salvarani C et al. JAMA Int Med. 2020</i>	-200<P/F<300 mmHg -Optiflow et CPAP Venturi possible -fièvre + CRP -Exclusion réa	Randomisé Ouvert Pas de placebo	Aggravation clinique J14 : réa;DC;P/F<150 mmHg	8 j	NS	-cortico anecdotiques
<i>Gupta S et al. JAMA Int Med. 2020</i>	H48 réa	Essai émulé Rétrospectif	-Délai survenue DC -mortalité J28	48h réa	<u>Significatif</u>	-15% cortico <u>-bénéfice :les + sévères et <J3 des symptômes avant réa</u>
<i>Rosas IO et al. NEJM 2021 (COVACTA)</i>	-Hypoxie P/F<300 (37% de patients ventilés)	Randomisé Double aveugle placebo	Statut clinique échelle ordinaire à 7 points J28	10 j	-NS	-<50% de cortico -pas de différence de mortalité à J28 -bénéfice dans le sous-groupe de patients non ventilés ?
<i>REMAPCAP NEJM 2021</i>	-H24 réa -Support ventilatoire ou hémodynamique (30% ventilés, 30% O2 haut débit, 40% VNI)	-Randomisé Double aveugle Placebo -bras sari -méthode bayésienne	Nombre de jours sans support à J21	? (J hospit)	<u>Significatif</u>	-94% cortico -amélioration mortalité J90 (HR=1,61) -impact des autres traitements expérimentaux ???

Référence	Critères d'inclusion	Méthodo	Critères de jugement principal	Délai médian traitement	Résultats	Remarque
<i>Recovery</i> <i>NEJM 2021</i>	-hypoxie -CRP>75 (« VNI » 41%; VI : 13%)	Randomisé Double aveugle Placebo	Mortalité J28	9 j	Significatif Additif aux cortico	-90 % cortico -impact des autres traitements expérimentaux ??? -Flowchart ?? -Mortalité bras contrôle élevée



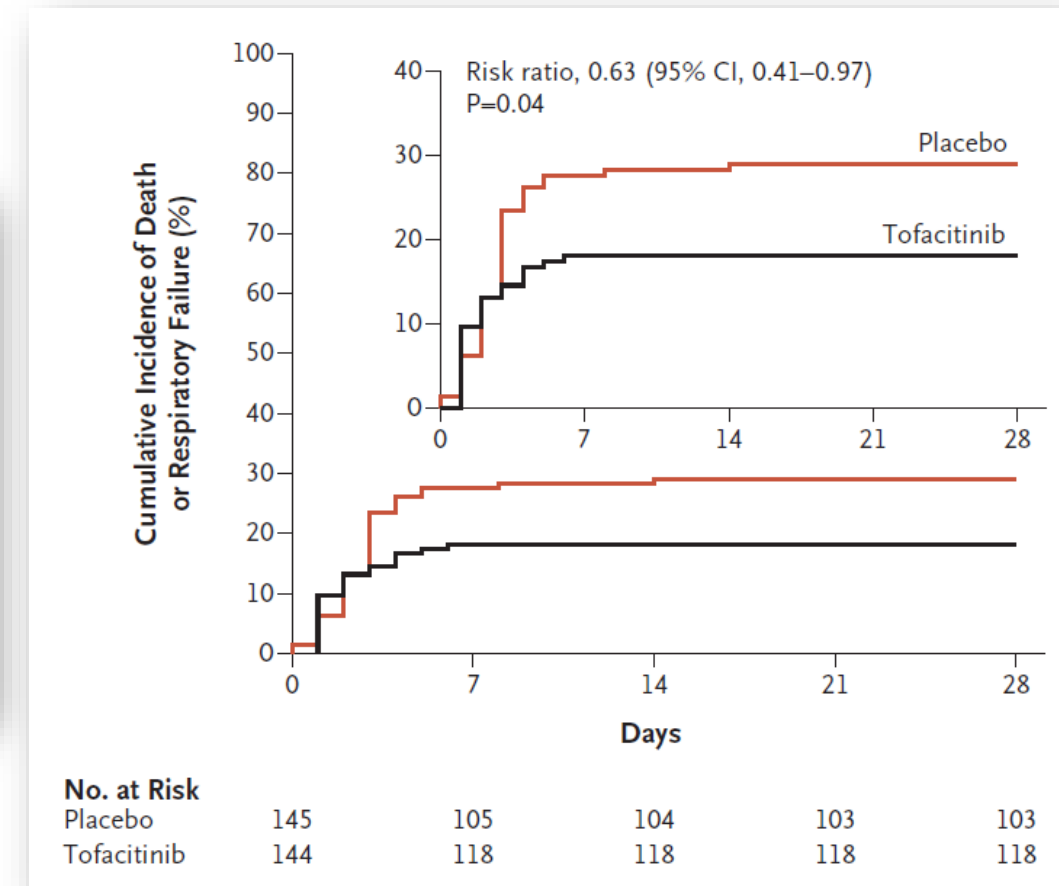
P/F<350 en air ambiant ou <280 sous O2
 +infiltrats pulmonaires bilatéraux
 +inflammation : ferritine, LDH, D-Dimères, CRP, lymphopénie
 -15% ventilation invasive
 -35% VNI/O2 haut débit
 -45% O2 standard

COV-AID. Declercq J et al. Lancet Respir Med. 2021

Anti-JAK ? Malades immunodéprimés et intubés exclus des études publiées

	Baricitinib group (n=764)	Placebo group (n=761)	Baricitinib vs placebo	
			Point estimate (95% CI)	p value*
Primary outcome				
Progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation (including ECMO), or death, by day 28†				
Population 1‡	27.8%	30.5%	OR 0.85 (0.67 to 1.08)	0.18
Population 2§	28.9%	27.1%	OR 1.12 (0.58 to 2.16)	0.73
Key secondary outcomes				
All-cause mortality	62/764 (8%)	100/761 (13%)	HR 0.57 (0.41 to 0.78)	0.0018

Essai COV BARRIER. Marconi VC et al. Lancet respir med. 2021



Guimaraes PO et al. NEJM. 2021

L'immunomodulation polyvalente tout terrain des formes graves : les corticoïdes

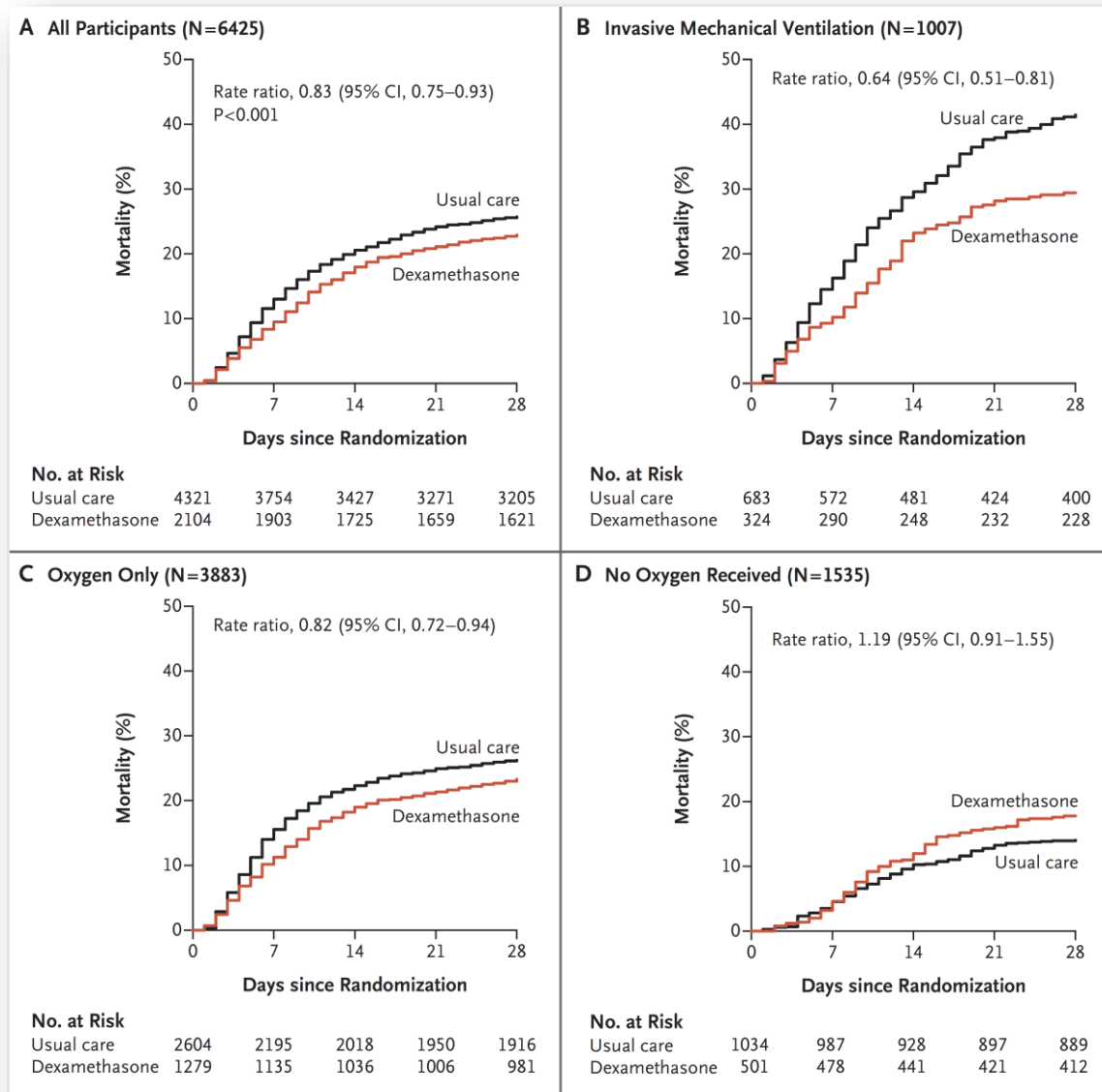


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

- Bénéfice en termes de mortalité à 28 jours
- Bénéfice en termes de recours à la ventilation mécanique
- Bénéfice chez les patients sous O2
- Rôle sur inflammation systémique et atteinte pulmonaire

Population

This recommendation applies only to people with these characteristics:



Interventions

	Disease severity		
	Non-severe	Severe	Critical
	Absence of signs of severe or critical disease	Oxygen saturation <90% on room air Signs of pneumonia Signs of severe respiratory distress	Requires life sustaining treatment Acute respiratory distress syndrome Sepsis Septic shock
Casirivimab and Imdevimab Neutralising monoclonal antibodies	Recommendation in favour (conditional) For those with highest risk of hospitalisation	Recommendation in favour (conditional) For those with seronegative status Assessed by accurate and rapid testing	
IL-6 receptor blockers Interleukin-6 receptor blockers		Recommendation in favour (strong)	
Ivermectin		Recommendation against (except in clinical trials)	
Hydroxychloroquine		Recommendation against (strong)	
Lopinavir-ritonavir		Recommendation against (strong)	
Remdesivir		Recommendation against (weak)	
Corticosteroids	Recommendation against (weak)	Recommendation in favour (strong)	

A mettre en perspective avec « l'ARDS » : quelle est la bonne dose chez les malades les plus sévères ?

Dexa 20mg 5 jours puis 10 mg 5 jours

	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12.3 (9.9)	7.5 (9.0)	4.8 (2.57 to 7.03)	<0.0001
All-cause mortality at day 60	29 (21%)	50 (36%)	-15.3% (-25.9 to -4.9)	0.0047
ICU mortality	26 (19%)	43 (31%)	-12.5% (-22.4 to -2.3)	0.0166
Hospital mortality	33 (24%)	50 (36%)	-12.5% (-22.9 to -1.7)	0.0235
Actual duration of mechanical ventilation in ICU survivors, days	14.2 (13.2)	19.5 (13.2)	-5.3 (-8.4 to -2.2)	0.0009
Actual duration of mechanical ventilation in survivors at day 60, days	14.3 (13.3)	20.2 (14.0)	-5.9 (-9.1 to -2.7)	0.0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5.2% (-5.2 to 15.6)	0.33
New infections in ICU	33 (24%)	35 (25%)	1.6% (-8.5 to 11.7)	0.75
Barotrauma	14 (10%)	10 (7%)	2.8% (-4.0 to 9.8)	0.41

Villar J et al. Lancet Respir Med. 2020

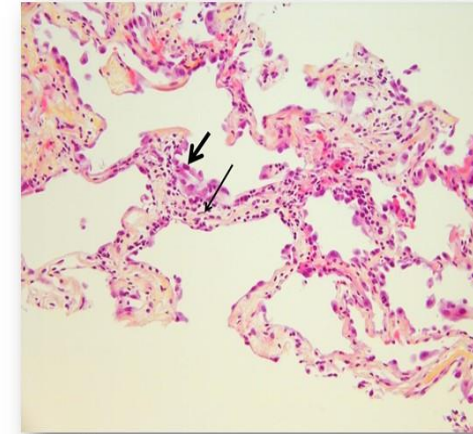


Fig.1A

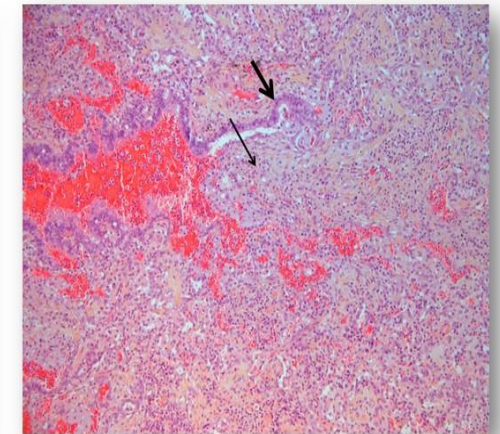


Fig.1B

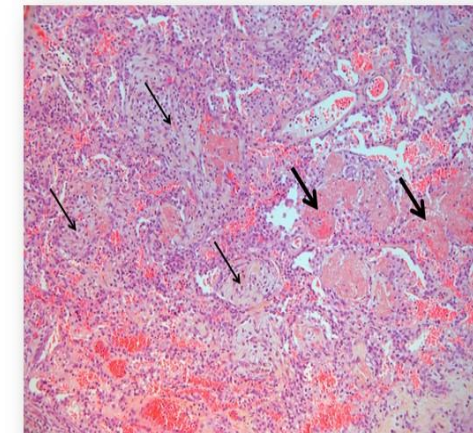


Fig.1C

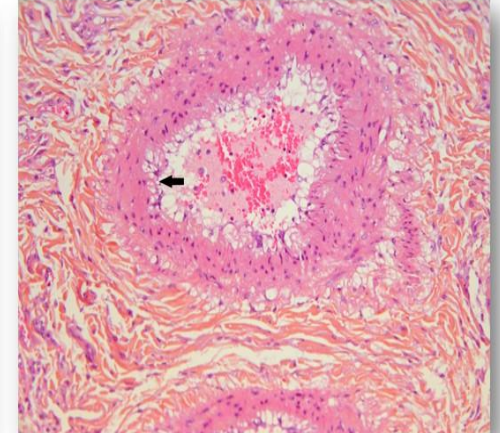
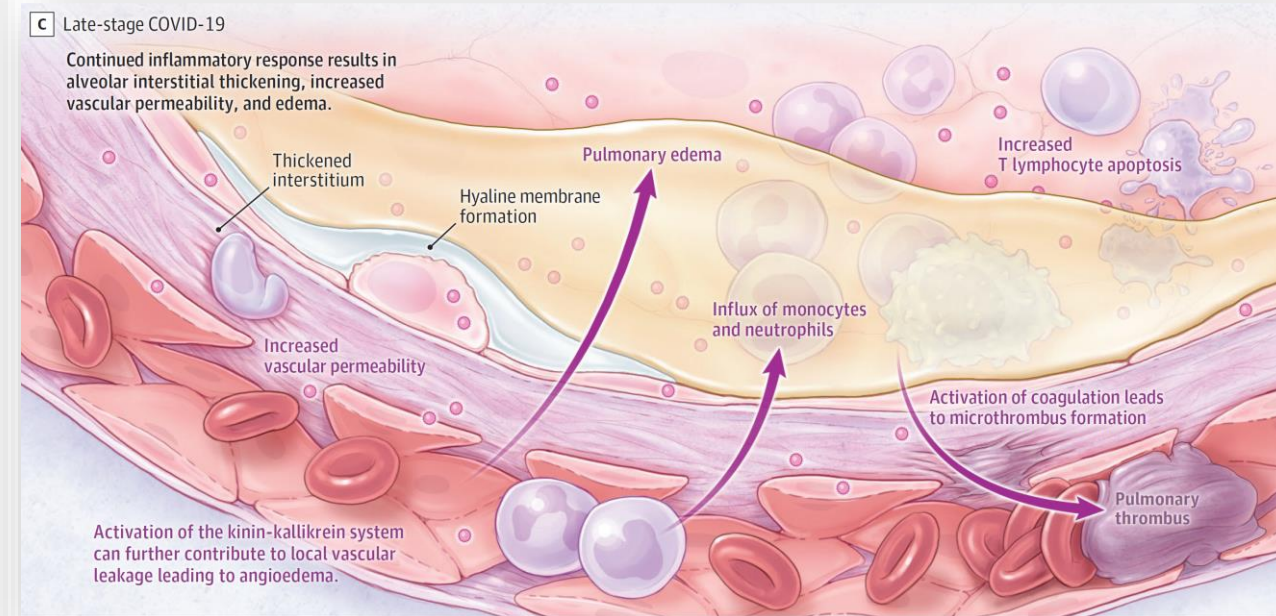
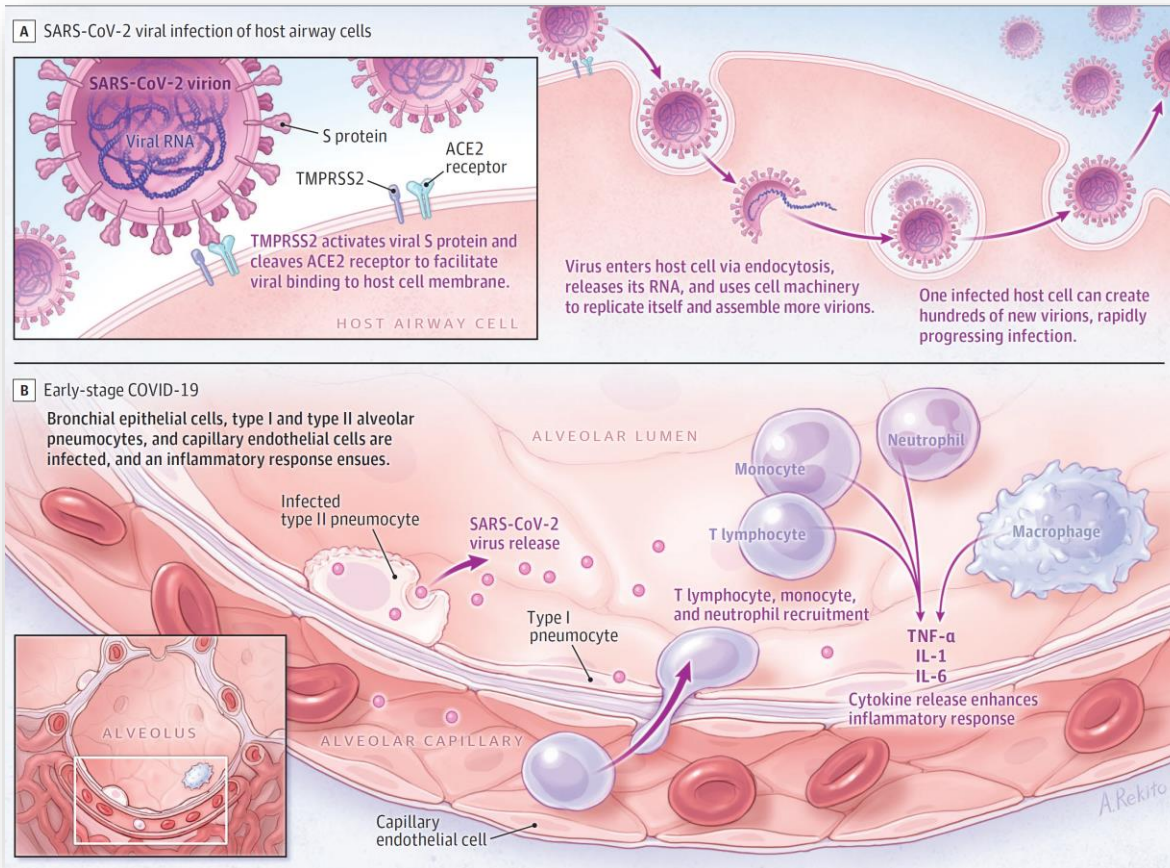
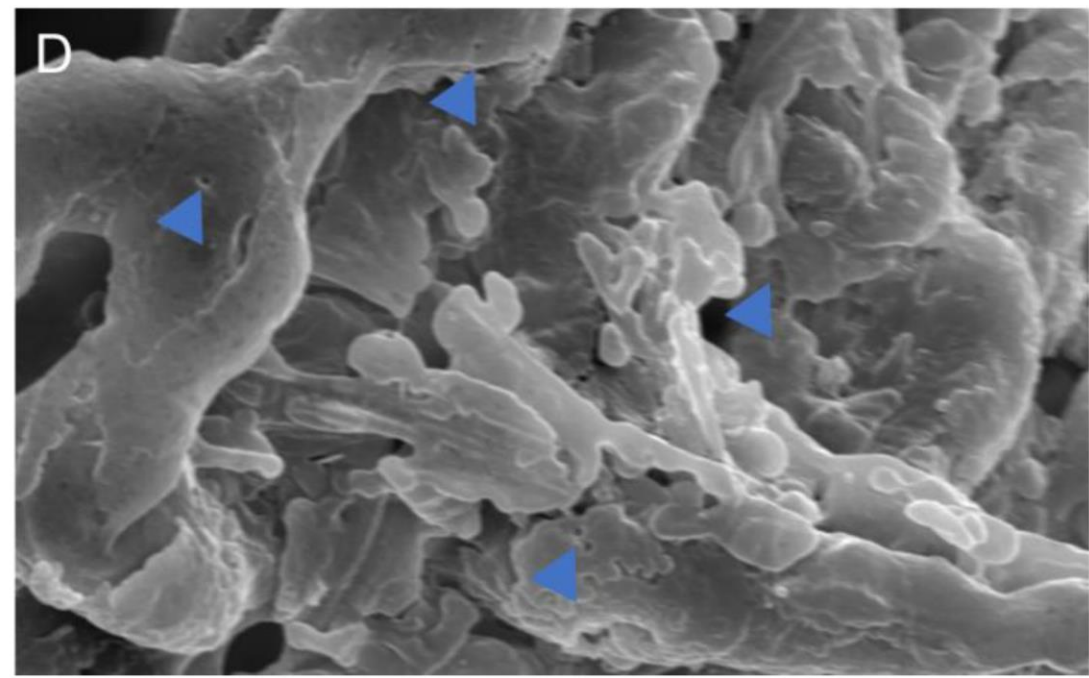
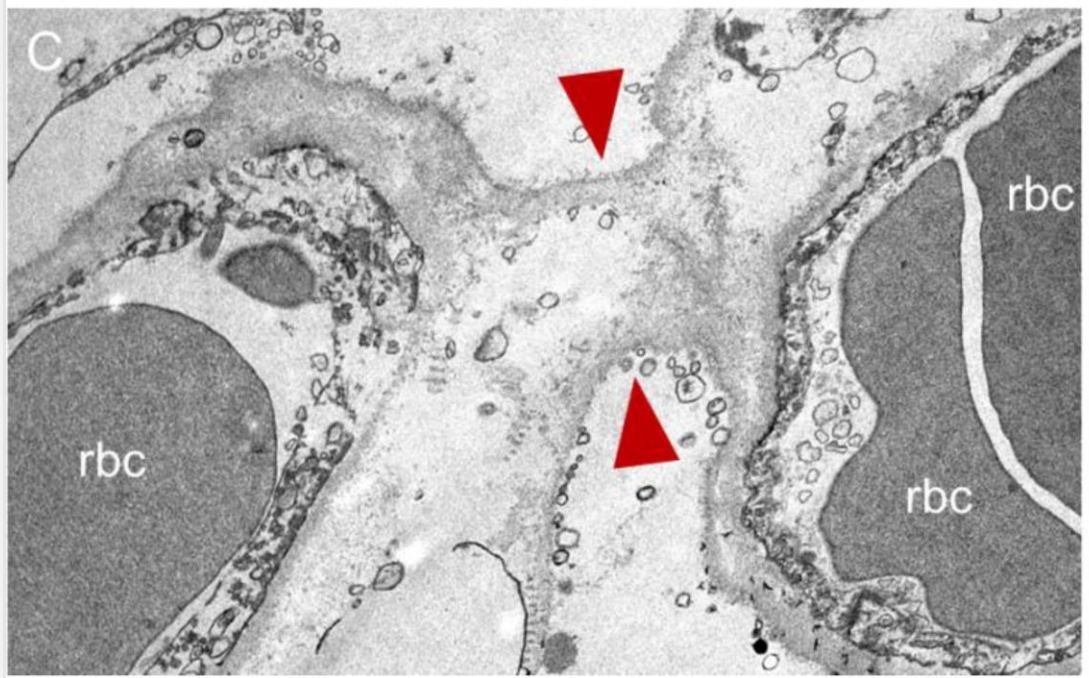
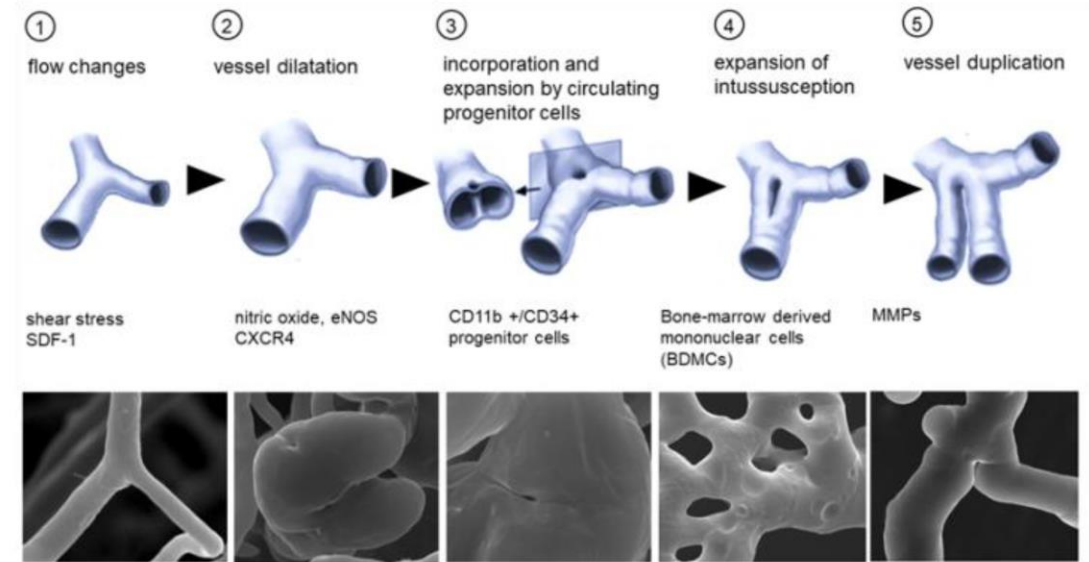
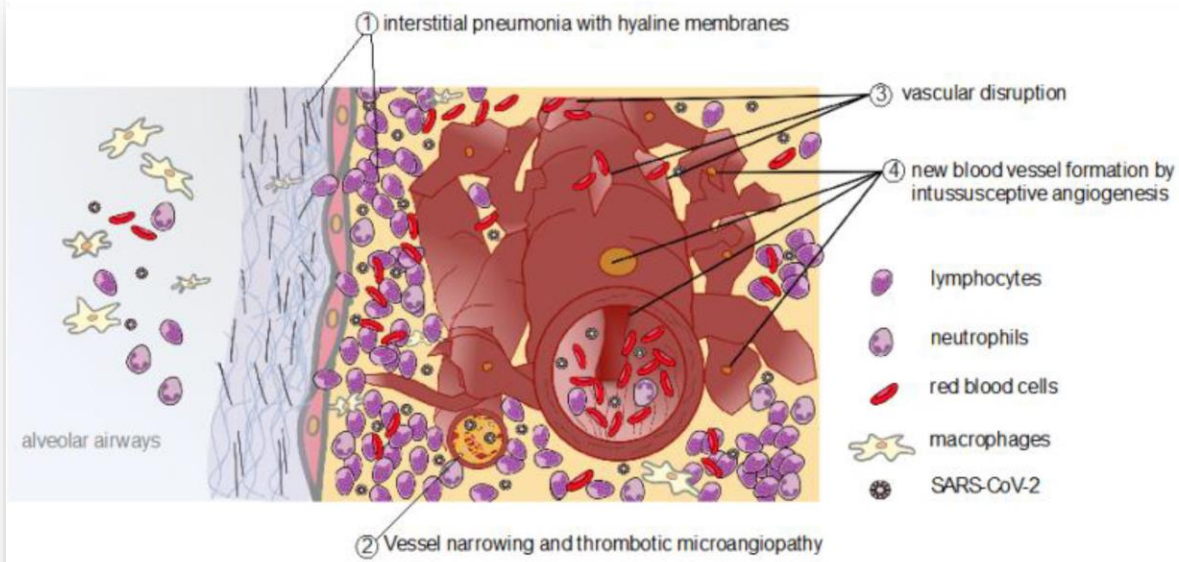


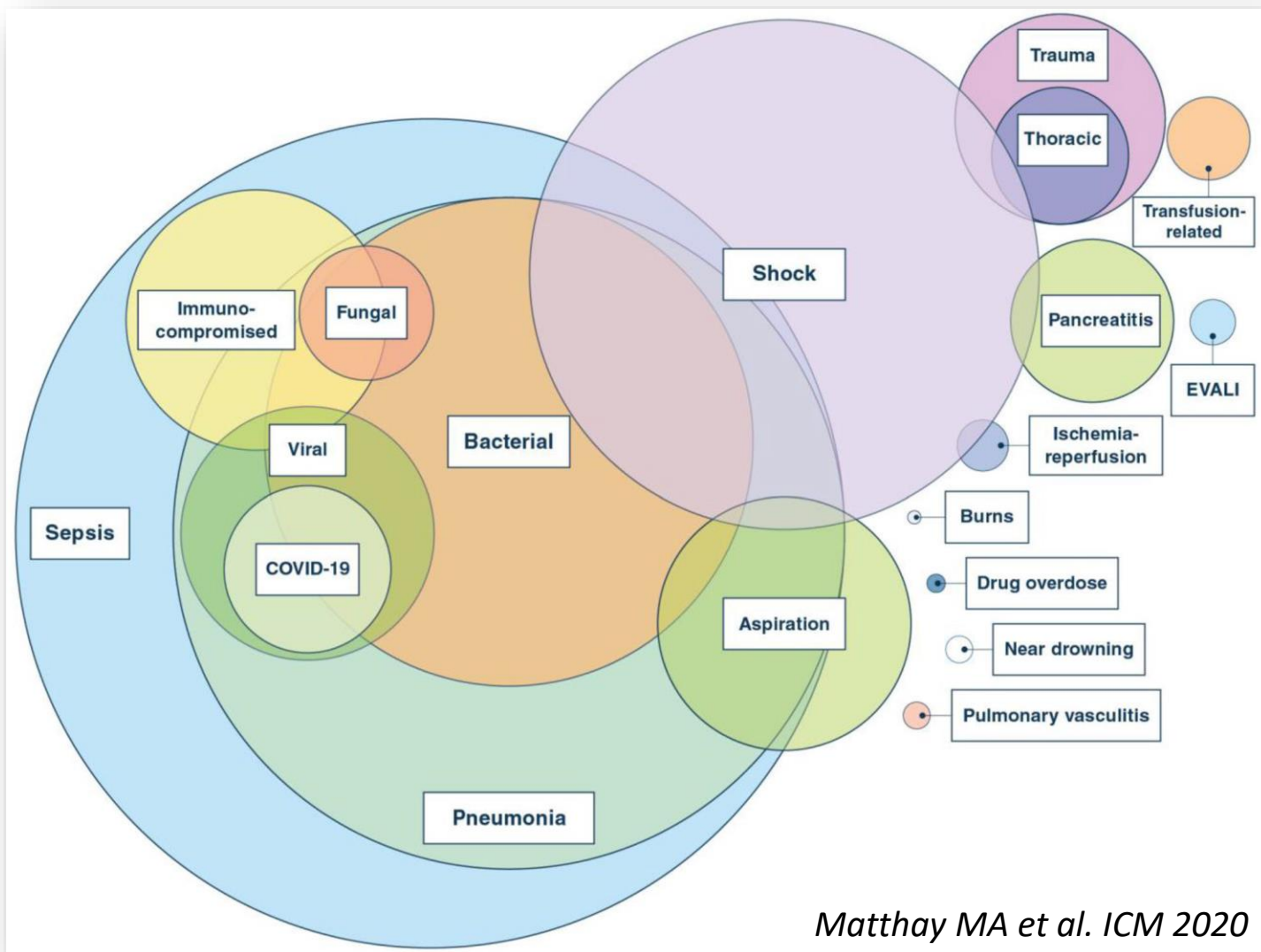
Fig.1D

Copin MC et al. ICM. 2020

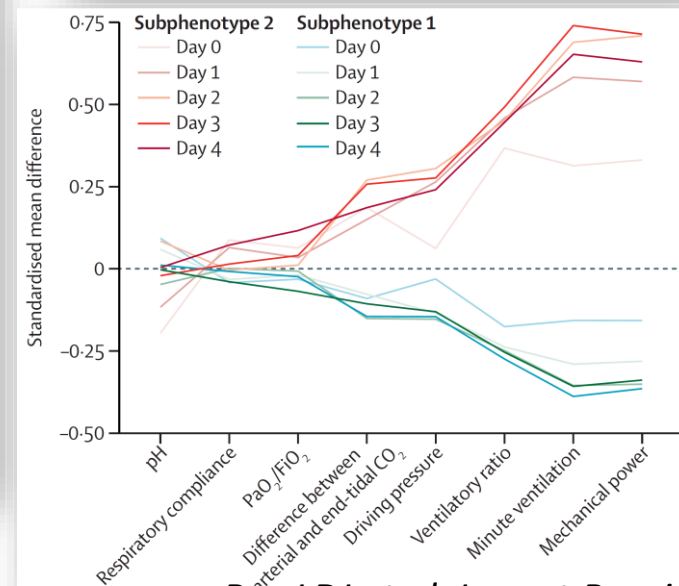
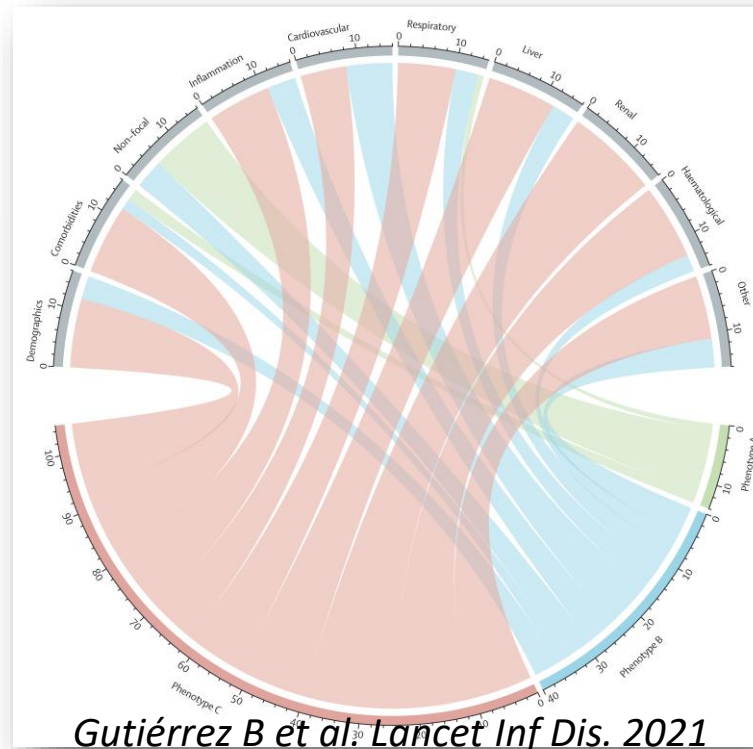
L'atteinte pulmonaire associe atteinte épithéliale (ARDS) et endothéliale. Inflammation « compartimentalisée »





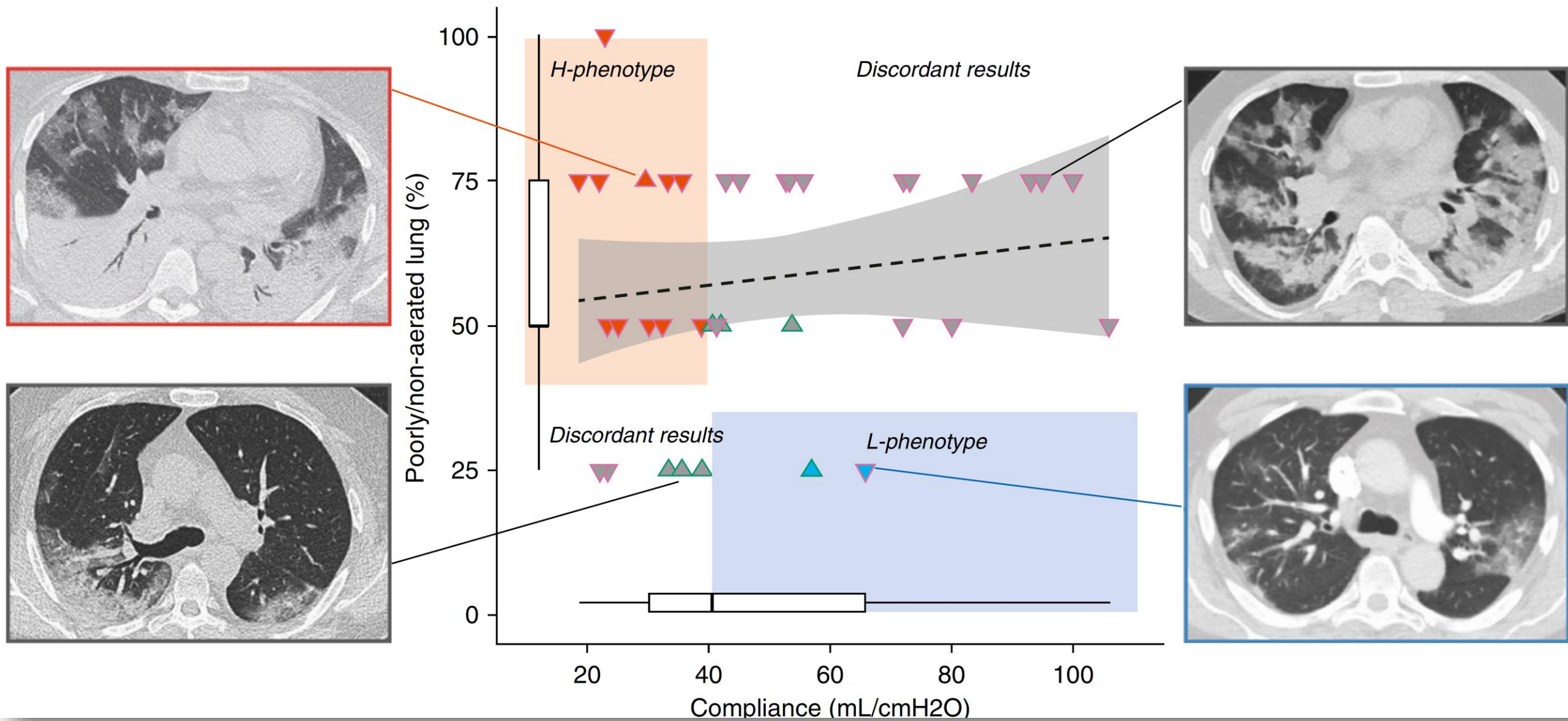


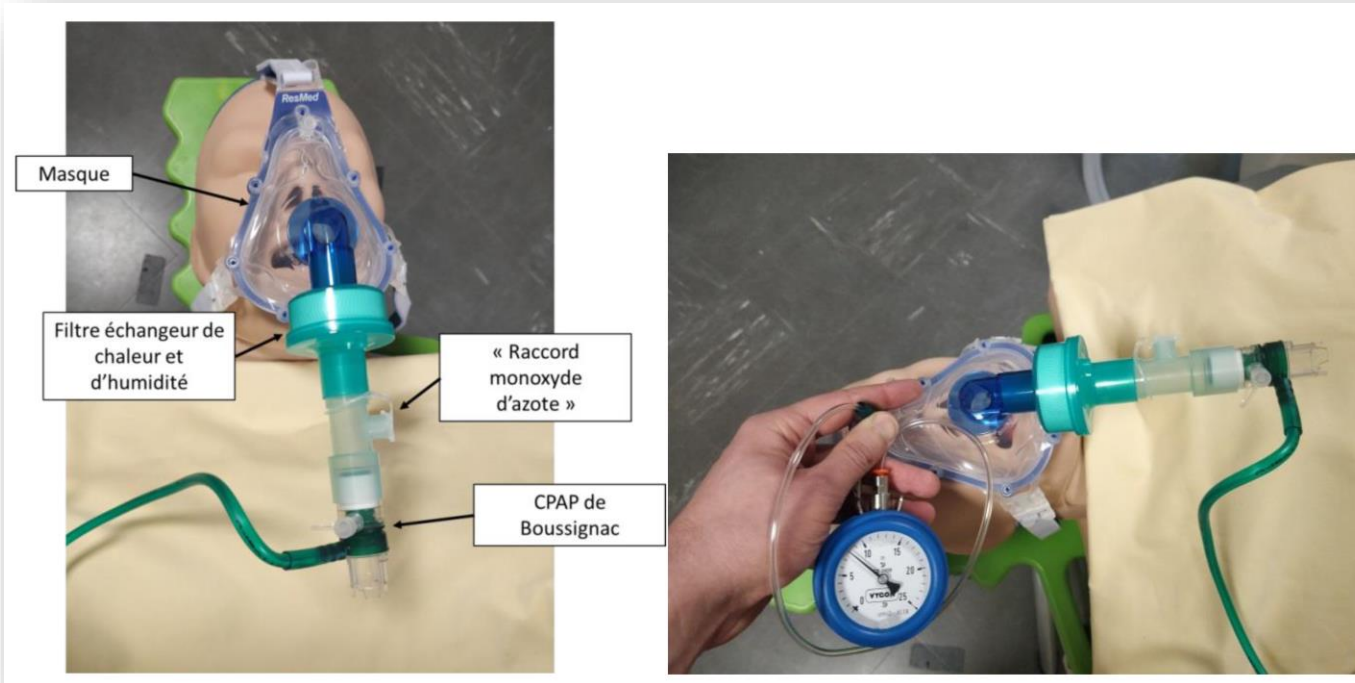
Matthay MA et al. ICM 2020



Bos LDJ et al. Lancet Respir Med. 2021

H- or L-phenotype COVID-19 related ARDS





Mekontso Dessap A, Carteaux G, Demoule A

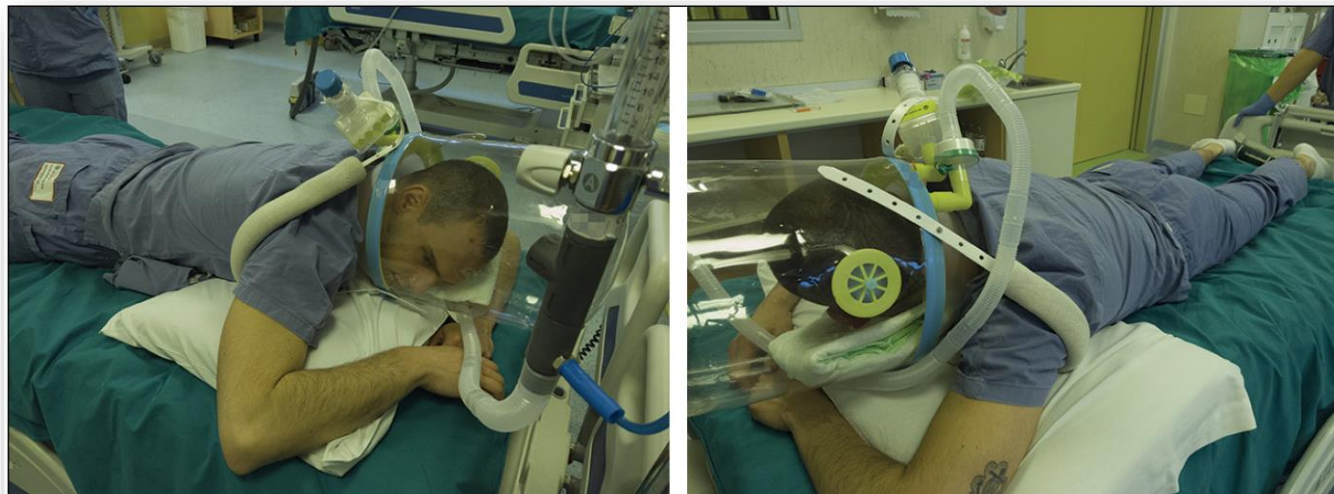
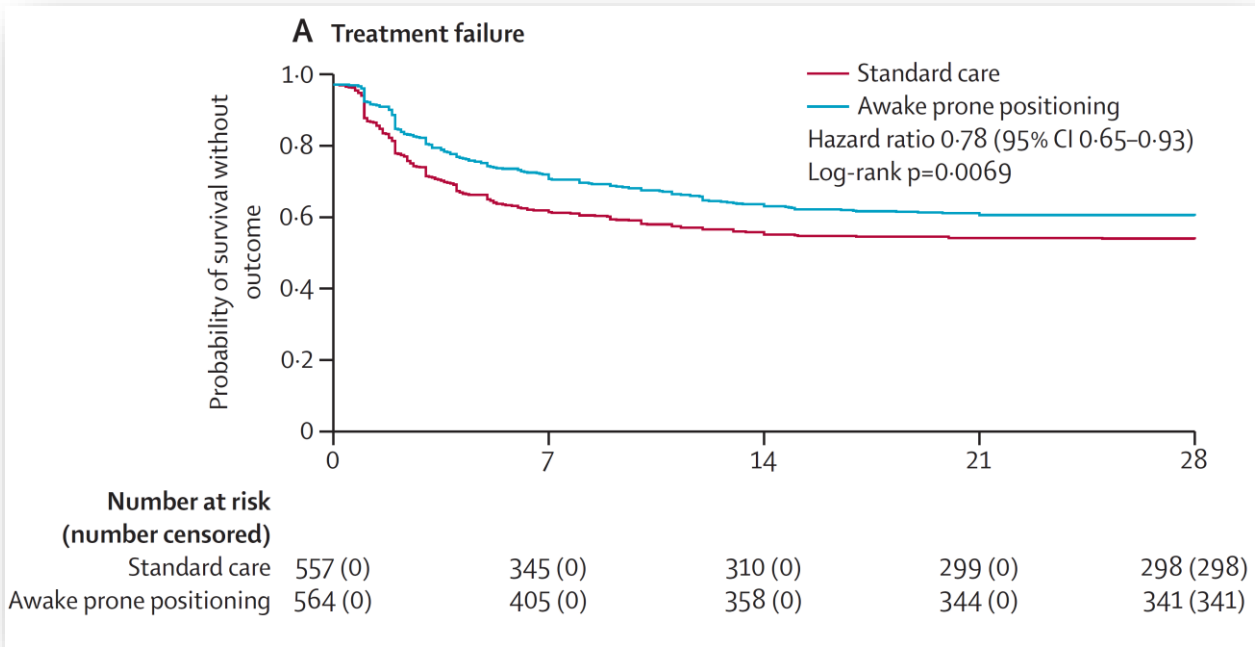


Figure 1: Prone positioning with a helmet interface to enable continuous positive airway pressure

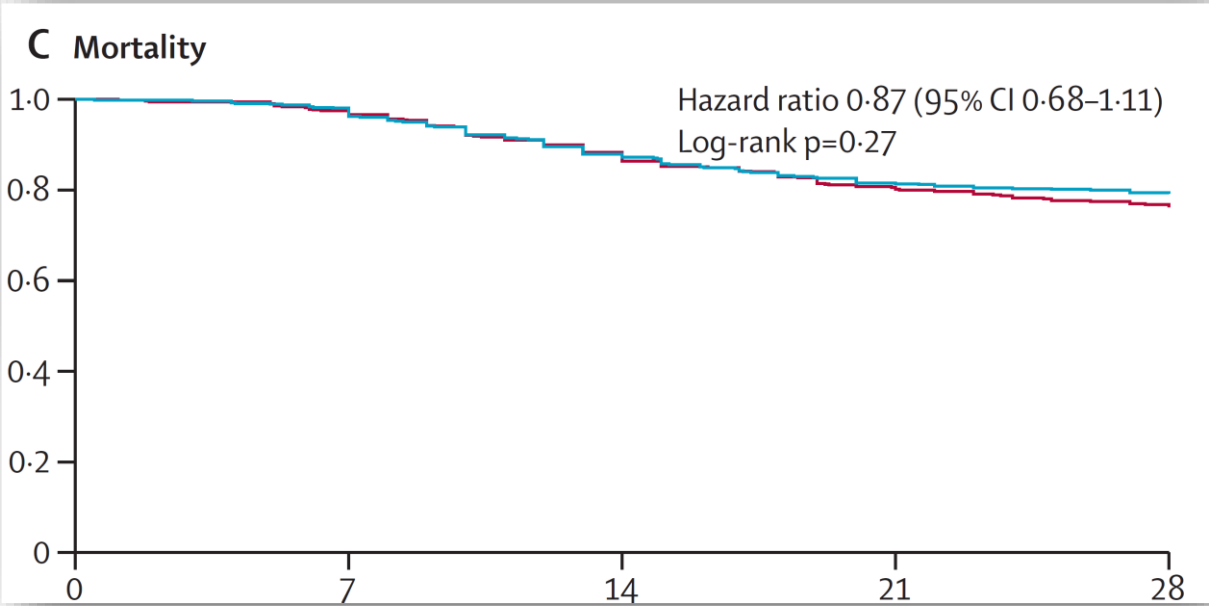
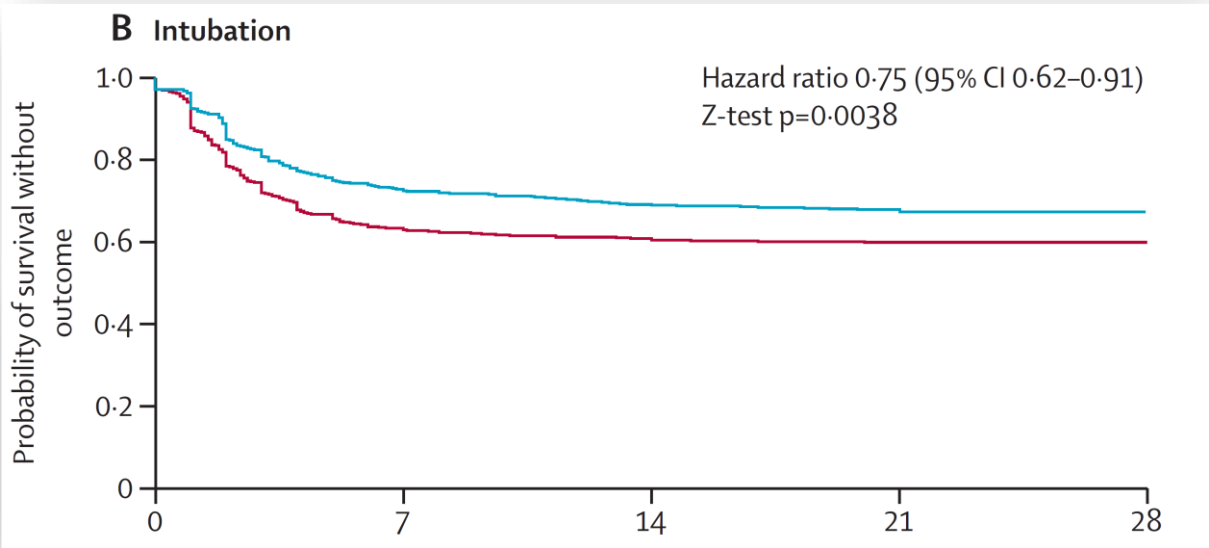
Example demonstrated by volunteer.

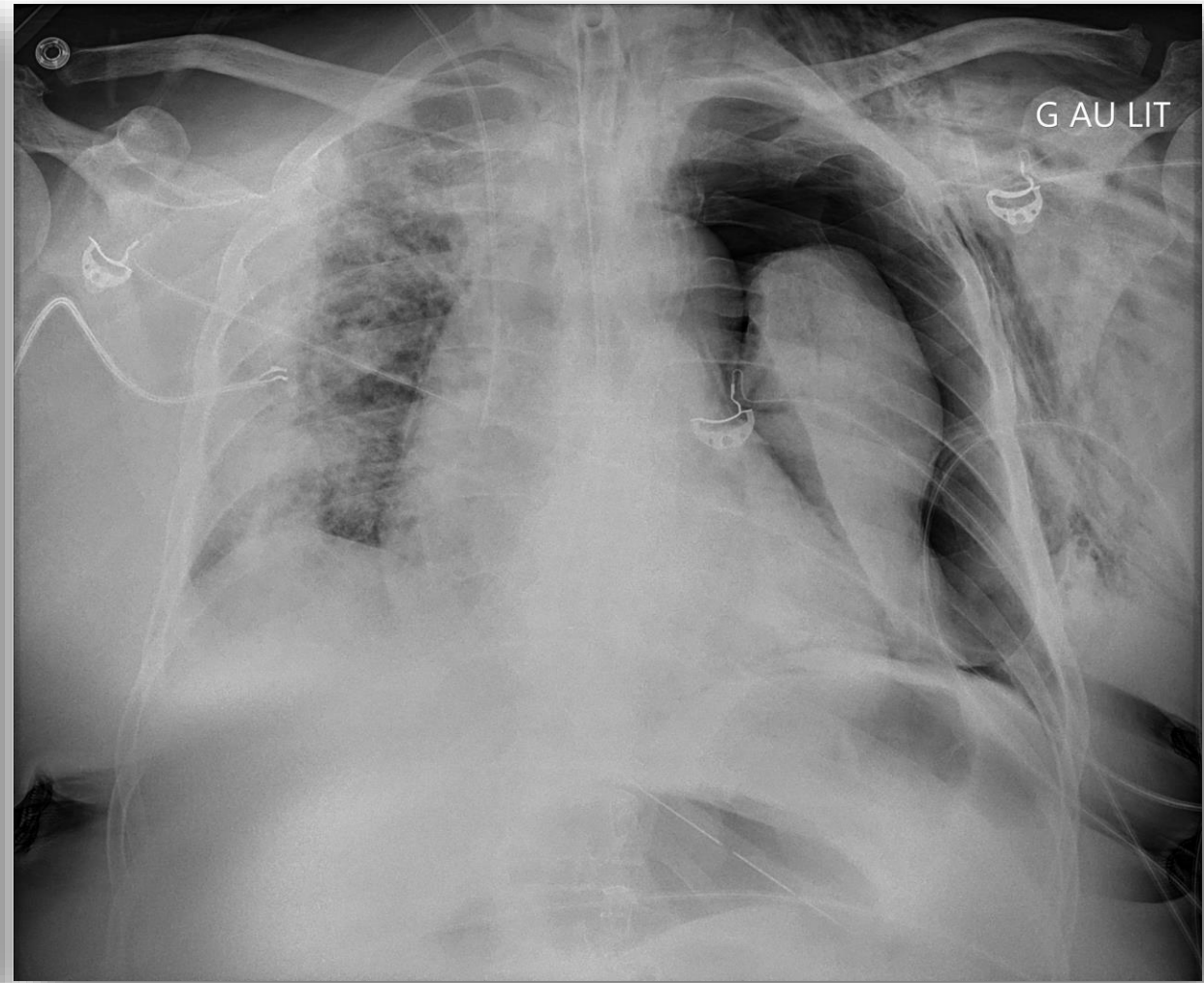
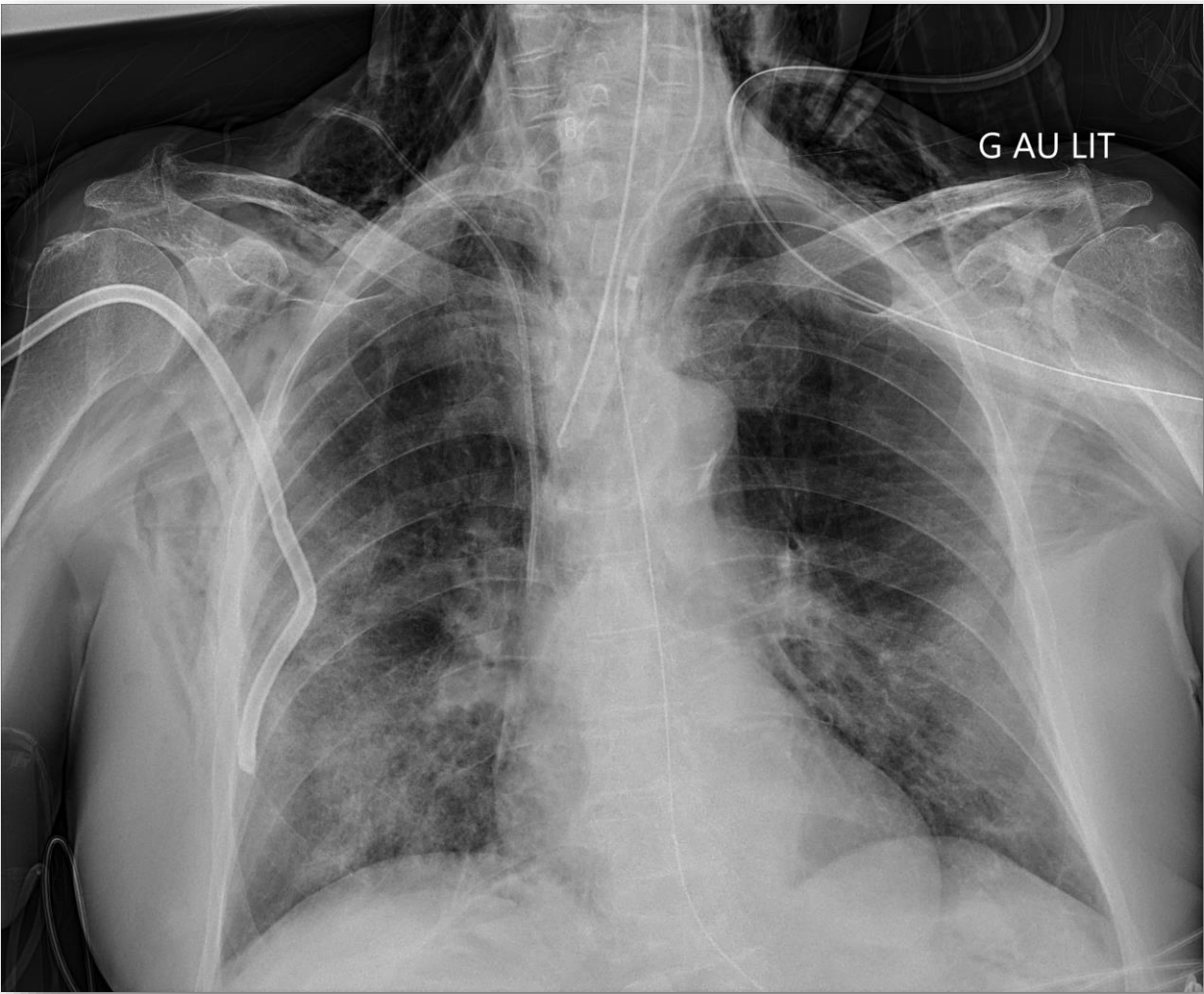
Coppo A et al. *Lancet Respir Med.* 2020

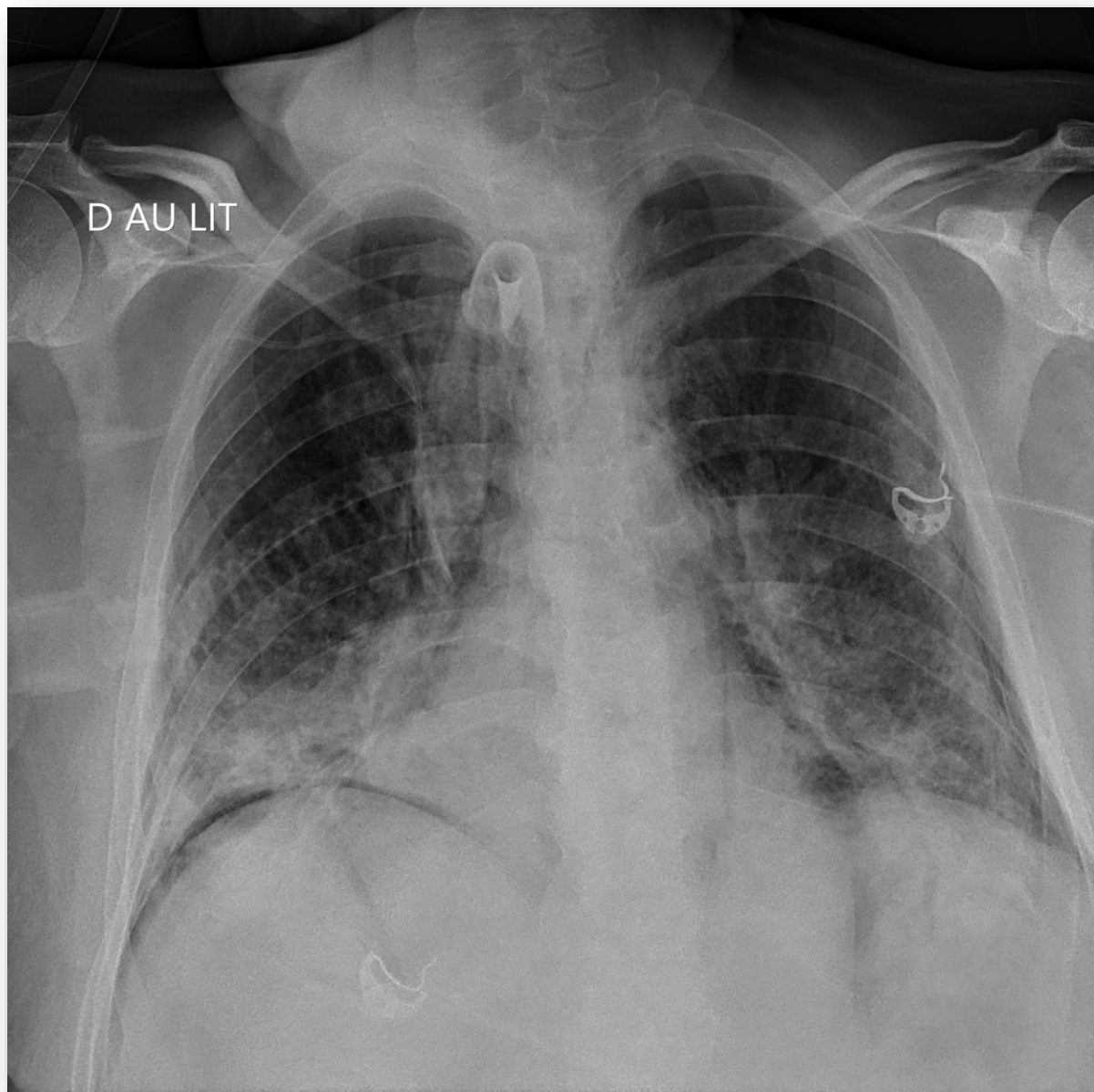
Décubitus ventral chez les patients conscients non intubés



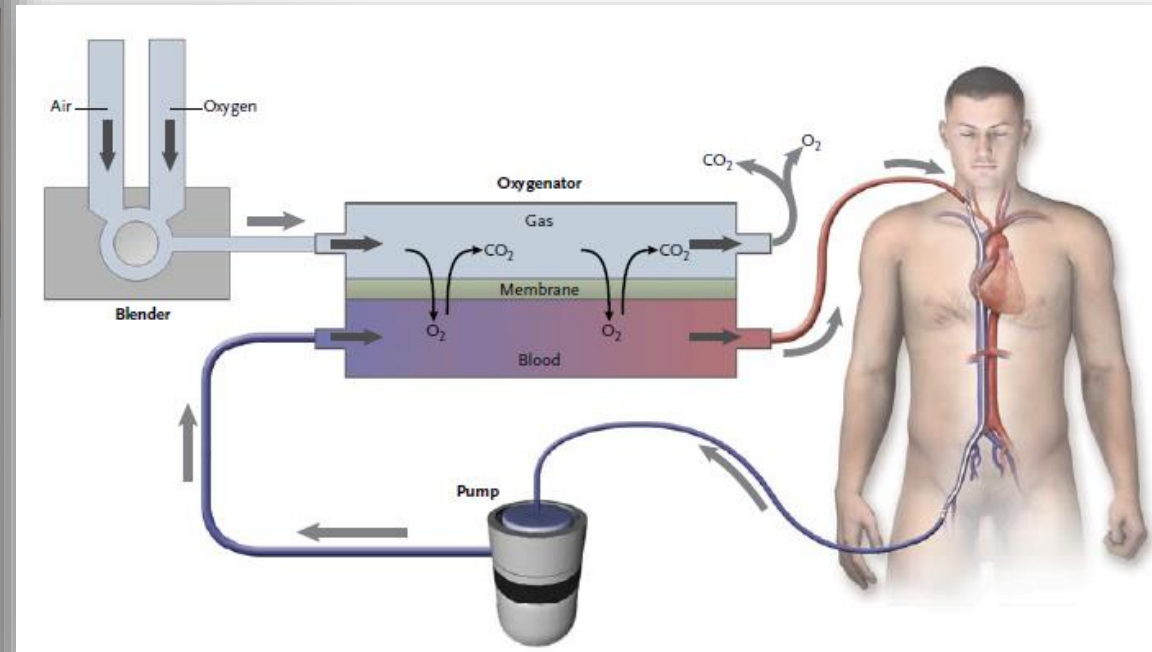
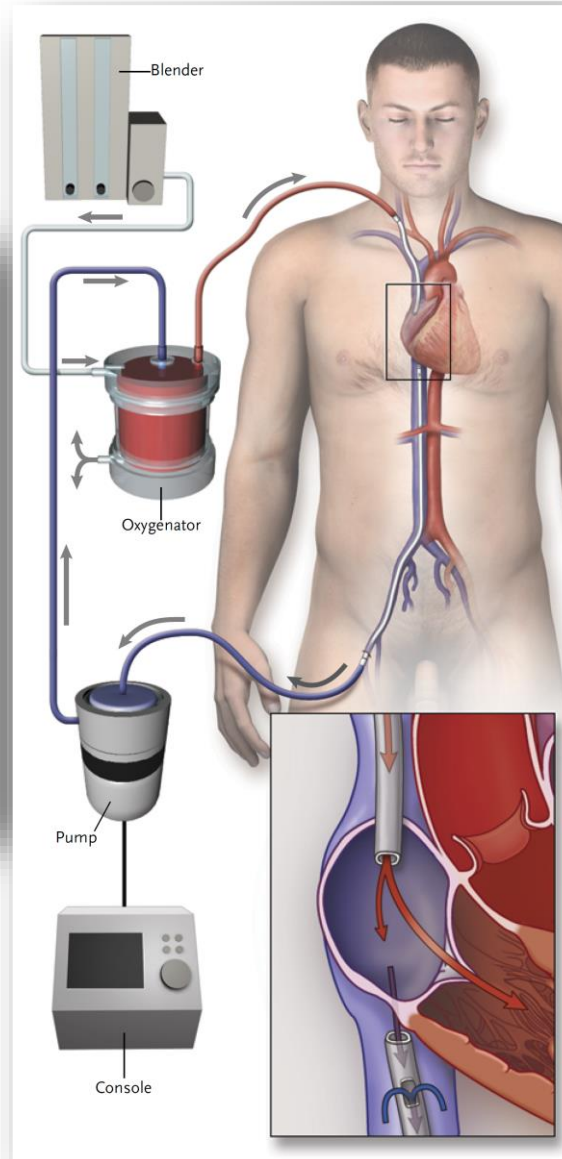
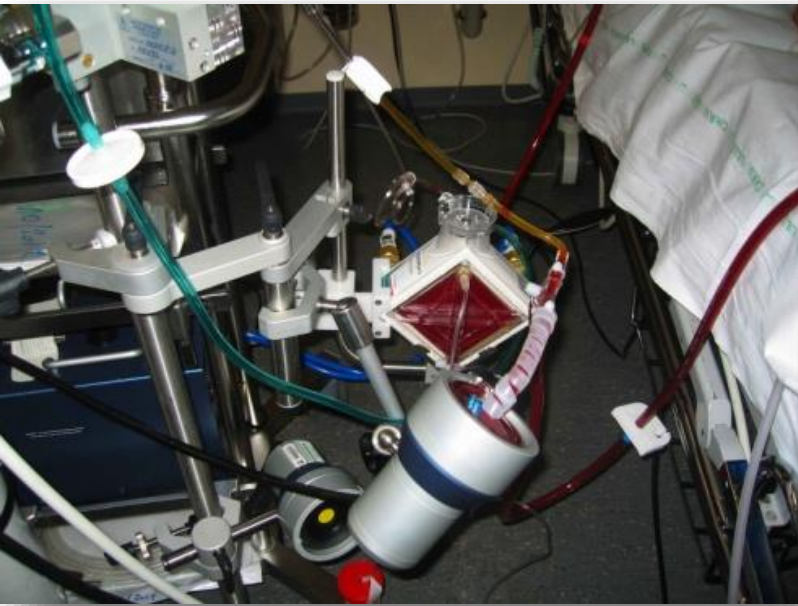
Ehrmann S et al. Lancet Respir Med. 2021







L'ECMO ou oxygénation extra-corporelle

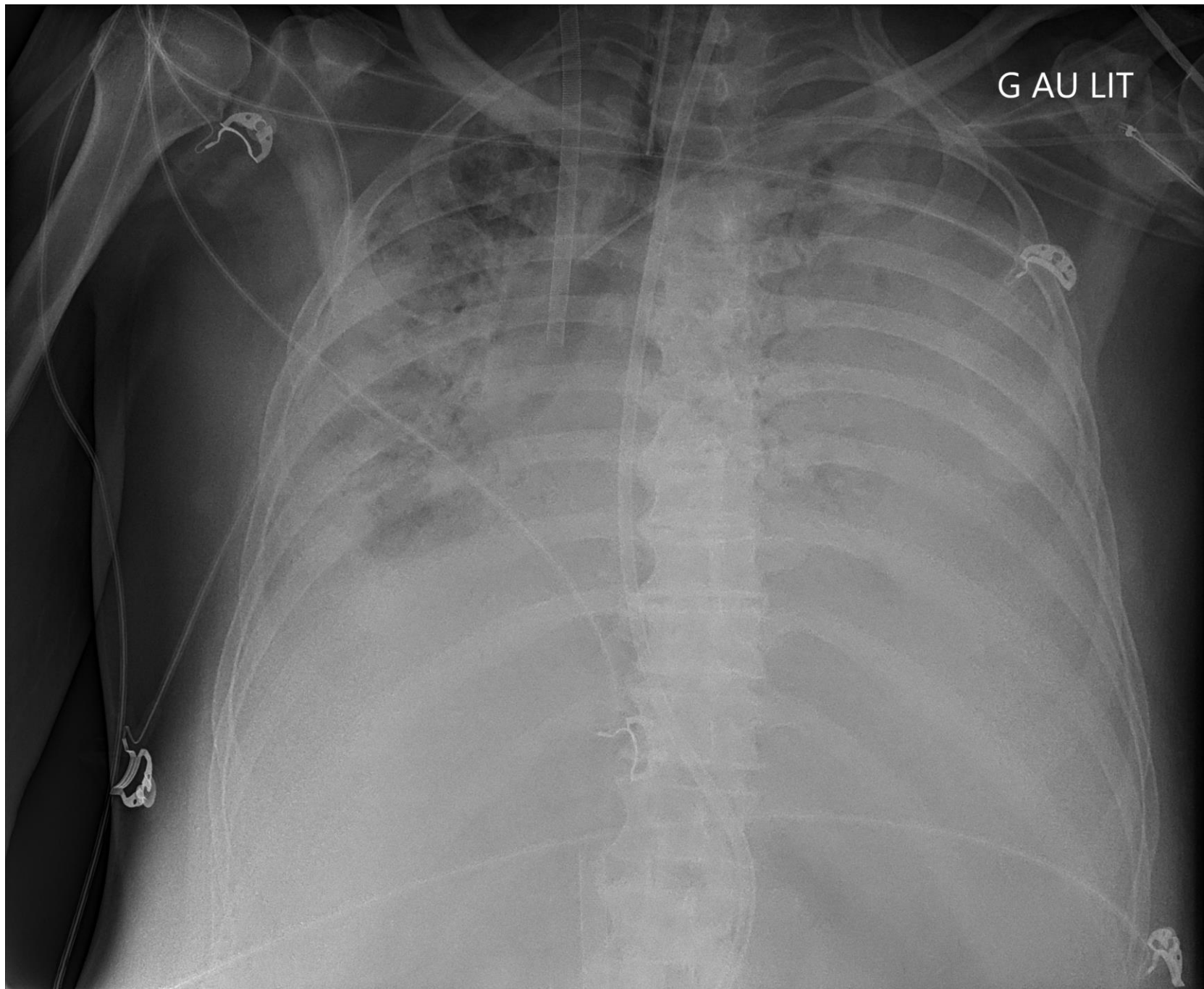


Brodie D. NEJM. 2011



Hill JD et al. NEJM. 1972





COVID-19 et soins intensifs

- Antiviraux :
 - Bof
 - Sauf Ac monoclonaux en association chez les immunodéprimés PCR+ séronégatifs
- Immunomodulation
 - Corticoïdes
 - Quid d'une intensification : anti IL1 ? Anti IL6 ? Anti JAK ? Personnalisation ?
- Ventilation
 - Stratégies non invasives possibles
 - Y compris « frugales » si ressources limitées
 - Mais ne pas rater le timing de l'intubation
 - Et la place de l'ECMO

Intensive Care Med (2021) 47:896–898

<https://doi.org/10.1007/s00134-021-06460-9>

EDITORIAL

Do not just sit there, do something ... but do no harm: the worrying aspects of COVID-19 experimental interventions

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