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Respiratory Medicine

Supplementary appendix

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Supplement to: Gangneux J-P, Dannaoui E, Fekkar A, et al. Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study. *Lancet Respir Med* 2021; published online Nov 26. https://doi.org/10.1016/S2213-2600(21)00442-2.

Supplementary material

Table S1. Criteria used for the classification of patients according to the modified AspICU classification of Blot et al.[10] (2012) and the CAPA classification of Koehler et al.[8] (2020).

Criteria used for the classification of patients and the determination of the rates of invasive pulmonary aspergillosis Patients with COVID-19 needing intensive care and the temporal relationship

	Modified AspICU	CAPA proven/probable	CAPA possible
Clinical	Compatible signs and symptoms (one of the following) • Fever refractory to at least 3 d of appropriate antibiotic therapy • Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause • Pleuritic chest pain • Pleuritic rub • Dyspnea • Hemoptysis • Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support	At least one of the following: • Refractory fever • Pleural rub • Chest pain • Hemoptysis	At least one of the following: • Refractory fever • Pleural rub • Chest pain • Hemoptysis
Imaging	All ARDS patients had at least one chest CT as part of their routine follow up that showed pulmonary infiltrate, cavitating infiltrate, or other CT patterns that can be due to either the underlying COVID-19 condition or a secondary infection.		
Mycology	*Aspergillus*-positive lower respiratory tract specimen culture or PCR and at least one of the following: • Host factors*	At least one of the following: • Microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mold	At least one of the following: • Microscopic detection of fungal elements in non-bronchoscopic lavage indicating a mold • Positive non-bronchoscopic lavage culture;†

	• Semiquantitative *Aspergillus*-positive culture, galactomannan or PCR of BAL fluid, without bacterial growth • *Aspergillus*-positive galactomannan or PCR in blood	• Positive bronchoalveolar lavage culture† • Serum galactomannan index >0・5 or serum LFA index >0・5‡ • Bronchoalveolar lavage galactomannan index ≥1・0 or bronchoalveolar lavage LFA index ≥1・0‡ • Two or more positive *Aspergillus* PCR tests in plasma, serum, or whole blood† • A single positive *Aspergillus* PCR in bronchoalveolar lavage fluid (<36 cycles)† • A single positive *Aspergillus* PCR in plasma, serum, or whole blood, and a single positive in bronchoalveolar lavage fluid (any threshold cycle permitted)†	• Single non-bronchoscopic lavage galactomannan index >4・5 • Non-bronchoscopic lavage galactomannan index >1・2 twice or more • Non-bronchoscopic lavage galactomannan index >1・2 plus another positive non-bronchoscopic lavage mycology test (non-bronchoscopic lavage PCR or LFA)

* Host risk factors (one of the following conditions): neutropenia (absolute neutrophil count, 0.5 G/L) preceding or at the time of ICU admission, underlying hematological or oncological malignancy treated with cytotoxic agents, glucocorticoid treatment (prednisone equivalent, 20 mg/d), congenital or acquired immunodeficiency.

Table S2. Demographic and baseline characteristics, immunosuppressive and antimicrobial agents, and severity scores between CAPA and non-CAPA patients under mechanical ventilation.

	pr/pb/pos CAPA* (n=100)	Non-CAPA* (n=409)		
Onset factors of CAPA* (n, %)	n, %, or mean ± SD	n, %, or mean ± SD	Univariate OR [IC]	p
Sex at birth				
Female (109, 21%)	19, 19·0%	90, 22.0%	1·20 [0·69-2·09]	0·51
Male (400, 79%)	81, 81·0%	319, 78·0%		
Age, years	100	409	1·03 [1·01-1·05]	0·0009
Mean ± SD	63·1 ± 12·7	58·4 ± 12·3		
Weight, kg	96	395	0·99 [0·97-0·999]	0·048
Mean ± SD	83·7 ± 18·4	87·7 ± 17·4		
BMI, kg/m^2	95	392	0·96 [0·92-1·003]	0·07
Mean ± SD	28·3 ± 5·4	29·5±5·7		
Diabetes mellitus (167, 32·9%)	36, 36·0%	131, 32·1%	1·19 [0·75-1·88]	0·46
Hypertension (254, 50·1%)	50, 50·5%	204, 50·0%	1·02 [0·66-1·58]	0·93
COPD (34, 6·7%)	10, 10·0%	24, 5·9%	1·78 [0·82-3·86]	0·14
Asthma (14, 2·8%)	5, 5·0%	9, 2·2%	2·34 [0·77-7·14]	0·14
Solid organ transplantation (35, 6·9%)	9, 9·0%	26, 6·4%	1·46 [0·66-3·22]	0·35
Hematological malignancy (6, 1·2%)	0, 0·0%	6, 1·5%	0·00	0·98
All immunosuppression (55, 10·8%)	14, 14·0%	41, 10·0%	1·46 [0·76-2·8]	0·25
	Treatments received for COVID-19			
	n, %			
Lopinavir+Ritonavir (Kaletra) (111, 21·8%)	21, 21·0%	90, 22·0%	0·94 [0·55-1·61]	0·83
Remdisivir (20, 3·9%)	4, 4·0%	16, 3·9%	1·02 [0·33-3·13]	0·97
Oseltamivir (40, 7·9%)	10, 10·0%	30, 7·4%	1·40 [0·66-2·97]	0·38

Cefotaxime (25, 4·9%)	5, 5·0%	20, 4·9%	1·02 [0·37-2·80]	0·96
Rovamycin (15, 2·9%)	2, 2·0%	13, 3·2%	0·62 [0·14-2·80]	0·54
Azithromycin (10, 2·0%)	2, 2·0%	8, 2·0%	1·02 [0·21-4·89]	0·98
Hydroxychloroquine (167, 32·9%)	27, 27·0%	140, 34·3%	0·71 [0·44-1·15]	0·16
Dexamethasone + anti-IL6 (29, 5·7%)	12, 12·0%	17, 4·2%	3·14 [1·45-6·82]	0·0037
Dexamethasone (202, 40·1%)	46, 46·9%	156, 38·4%	1·42 [0·91-2·21]	0·12
Anti-IL6 (38, 7·5%)	12, 12·0%	26, 6·4%	1·99 [0·97-4·10]	0·006
Anti-IL1 (16, 3·1%)	3, 3·0%	13, 3·2%	0·94 [0·26-3·36]	0·92
Prone position (394, 77·6%)	81, 81·0%	313, 76·7%	1·29 [0·75-2·24]	0·36
		Clinical course data		
		n, mean ± SD		
Duration of mechanical ventilation (508)	100 30·9 ± 24·8	408 26·2 ± 18·2	1·01 [1·0007-1·02]	0·037
SAPS II – admission (485, 44·1 ± 16·2)	96 47·0 ± 17·1	389 43·3 ± 15·9	1·01 [1·0001-1·03]	0·049
SOFA – admission (398, 7·4 ± 3·9)	89 7·7 ± 3·7	309 7·3 ± 4·0	1·02 [0·96-1·08]	0·48
SOFA – day 7 (367, 8·7 ± 4·2)	82 9·4 ± 3·8	284 8·5 ± 4·3	1·05 [0·99-1·12]	0·07
SOFA – day 15 (261, 8·5 ± 4·6)	68 8·9 ± 4·32	193 8·3 ± 4·7	1·03 [0·97-1·09]	0·37
SOFA - discharge (285, 6·1 ± 6·0)	70 8·4 ± 6·2	215 5·4 ± 5·8	1·08 [1·04-1·13]	0·0004

*CAPA status according to Koehler et al·[8] with the exception of the category of possible CAPA that was here extended to patients with *Aspergillus* spp. positive non-bronchoalveolar lavage and/or bronchial or tracheal aspiration and with a compatible clinical context with aspergillosis, BMI: body-mass index, COPD: chronic obstructive pulmonary disease, SAPS II: Simplified Acute Physiology II, SOFA: Sequential Organ Failure Assessment.

Supplementary figure legends

Figure S1. Period of inclusion and number of patients included in each participating center.

Strasbourg : Strasbourg University hospital, Strasbourg, France
Tours : Tours University hospital, Tours, France
Brest : Brest University hospital, Brest, France
Paris APHP Necker : Necker University hospital, Paris, France
Paris APHP Avicenne : Bobigny University hospital, Bobigny, France
Poitiers : Poitiers University hospital, Poitiers, France
Lyon : Lyon University hospital, Lyon, France
Grenoble : Grenoble University hospital, Grenoble, France
Paris APHP HEGP : George Pompidou European University Hospital, Paris, France
Paris APHP Tenon : Tenon University hospital, Paris, France
Paris APHP Saint-Louis : Saint-Louis University hospital, Paris, France
Toulouse: Toulouse University hospital, Toulouse, France
Rennes : Rennes University hospital, Rennes, France
Paris APHP Henri Mondor : Henri Mondor University hospital, Créteil, France
Paris APHP La Pitié : La Pitié-Salpêtrière University hospital, Paris, France
Nantes : Nantes University hospital, Nantes, France
Paris APHP Bichat : Bichat University hospital, Paris, France
Lille : Lille University hospital, Lille, France

Figure S2. Study design.

Figure S3. Study flowchart.

Figure S4. Probability of survival according to proven/probable/possible CAPA status. The category of possible CAPA used here was adapted from Koehler et al.[8] extended to patients with *Aspergillus* spp. positive non-bronchoalveolar lavage and/or bronchial or tracheal aspiration and with a compatible clinical context with aspergillosis.

Figure S5. Probability of survival of proven/probable/possible CAPA patients receiving, or not, anti-*Aspergillus* treatment with voriconazole and/or isavuconazole. The category of possible CAPA used here was adapted from Koehler et al.[8] extended to patients with *Aspergillus* spp. positive non-bronchoalveolar lavage and/or bronchial or tracheal aspiration and with a compatible clinical context with aspergillosis.

Figure S1.

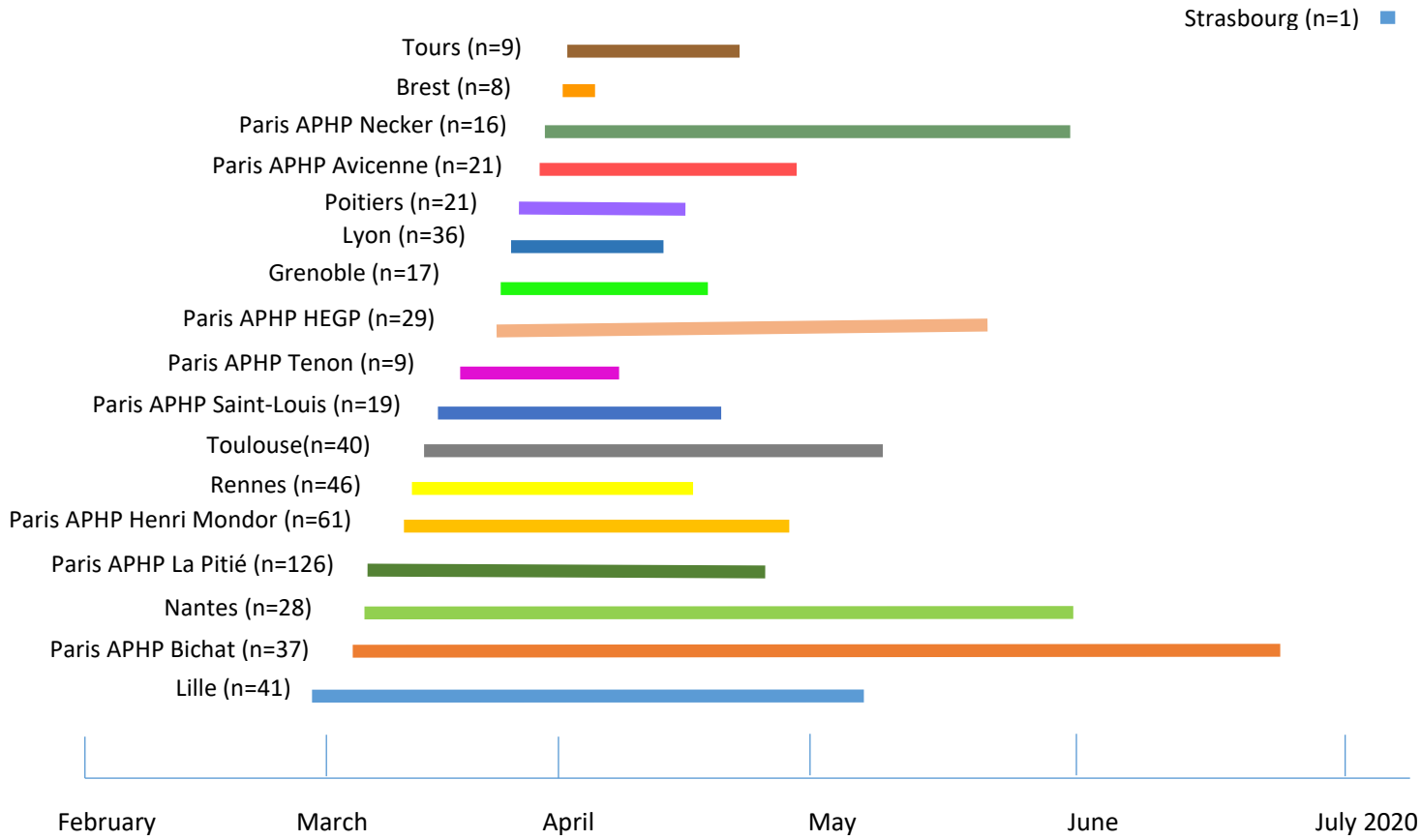

Strasbourg (n=1)
Tours (n=9)
Brest (n=8)
Paris APHP Necker (n=16)
Paris APHP Avicenne (n=21)
Poitiers (n=21)
Lyon (n=36)
Grenoble (n=17)
Paris APHP HEGP (n=29)
Paris APHP Tenon (n=9)
Paris APHP Saint-Louis (n=19)
Toulouse(n=40)
Rennes (n=46)
Paris APHP Henri Mondor (n=61)
Paris APHP La Pitié (n=126)
Nantes (n=28)
Paris APHP Bichat (n=37)
Lille (n=41)
February
March
April
May
June
July 2020

Figure S2.

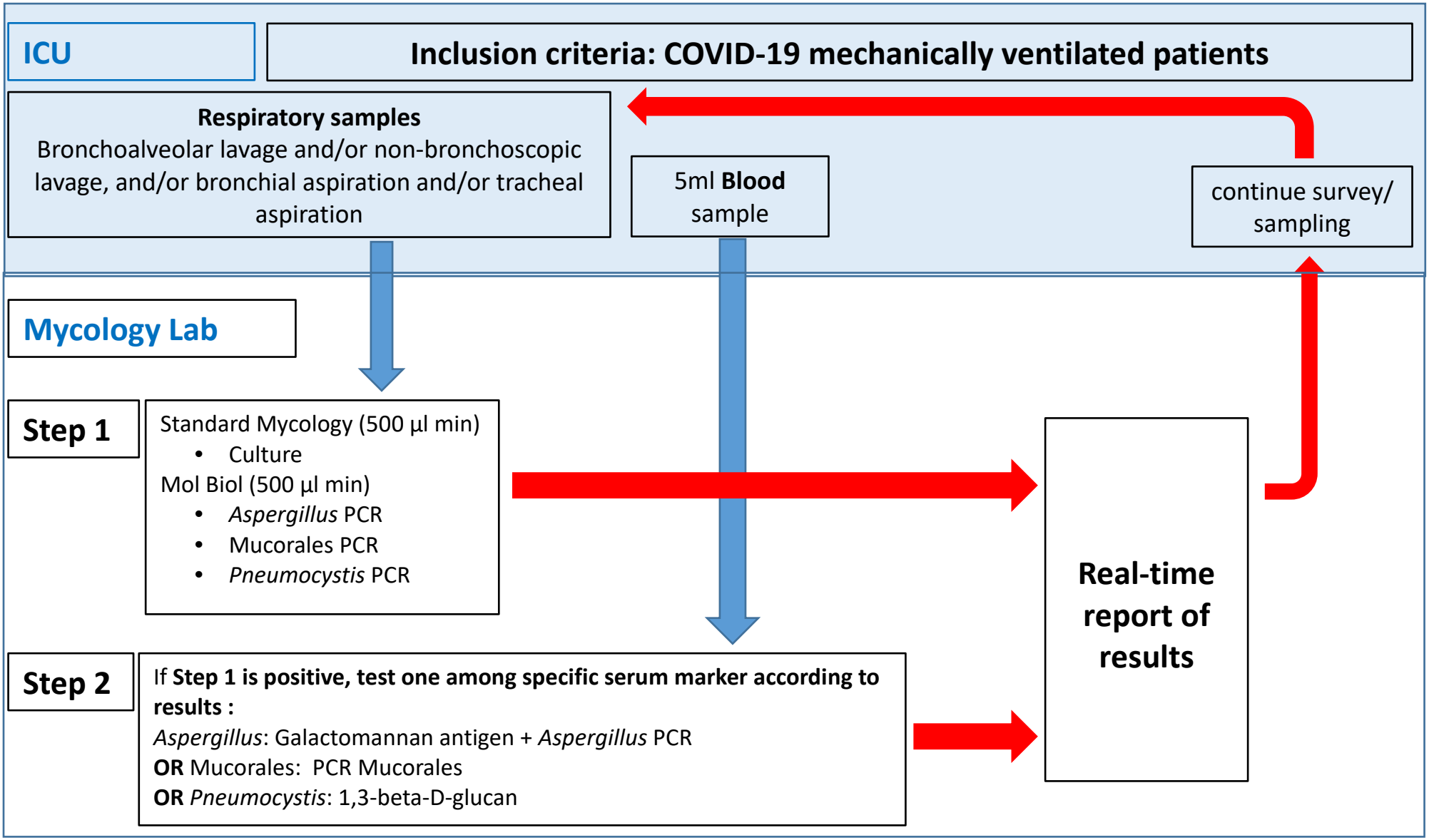

ICU
Inclusion criteria: COVID-19 mechanically ventilated patients
Respiratory samples
Bronchoalveolar lavage and/or non-bronchoscopic lavage, and/or bronchial aspiration and/or tracheal aspiration
5ml Blood sample
continue survey/ sampling
Mycology Lab
Step 1
Standard Mycology (500 µl min)
• Culture
Mol Biol (500 µl min)
• Aspergillus PCR
• Mucorales PCR
• Pneumocystis PCR
Step 2
If Step 1 is positive, test one among specific serum marker according to results :
Aspergillus: Galactomannan antigen + Aspergillus PCR
OR Mucorales: PCR Mucorales
OR Pneumocystis: 1,3-beta-D-glucan
Real-time report of results

Figure S3.

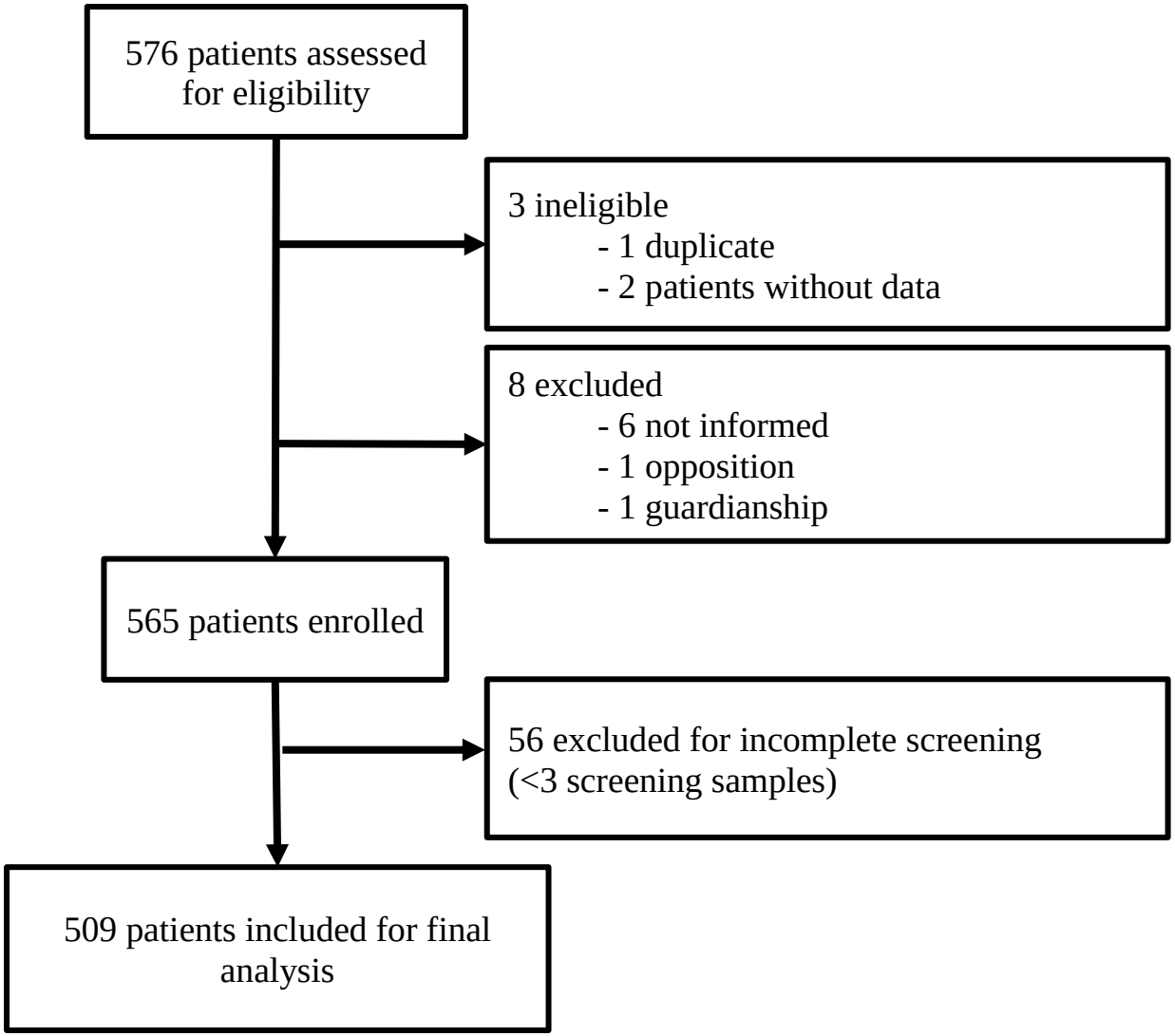

576 patients assessed for eligibility
3 ineligible
- 1 duplicate
- 2 patients without data
8 excluded
- 6 not informed
- 1 opposition
- 1 guardianship
565 patients enrolled
56 excluded for incomplete screening (<3 screening samples)
509 patients included for final analysis

Figure S4.

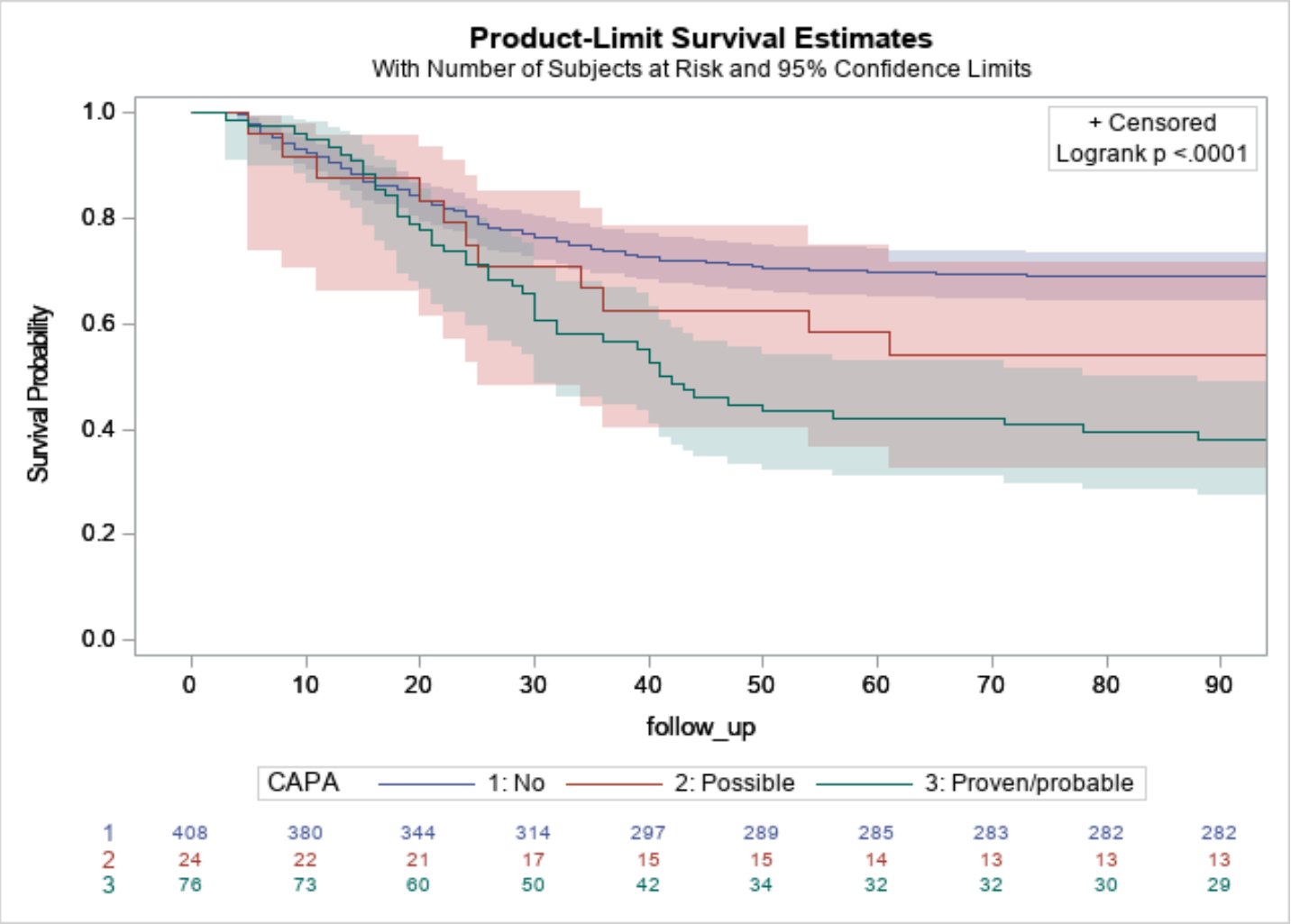
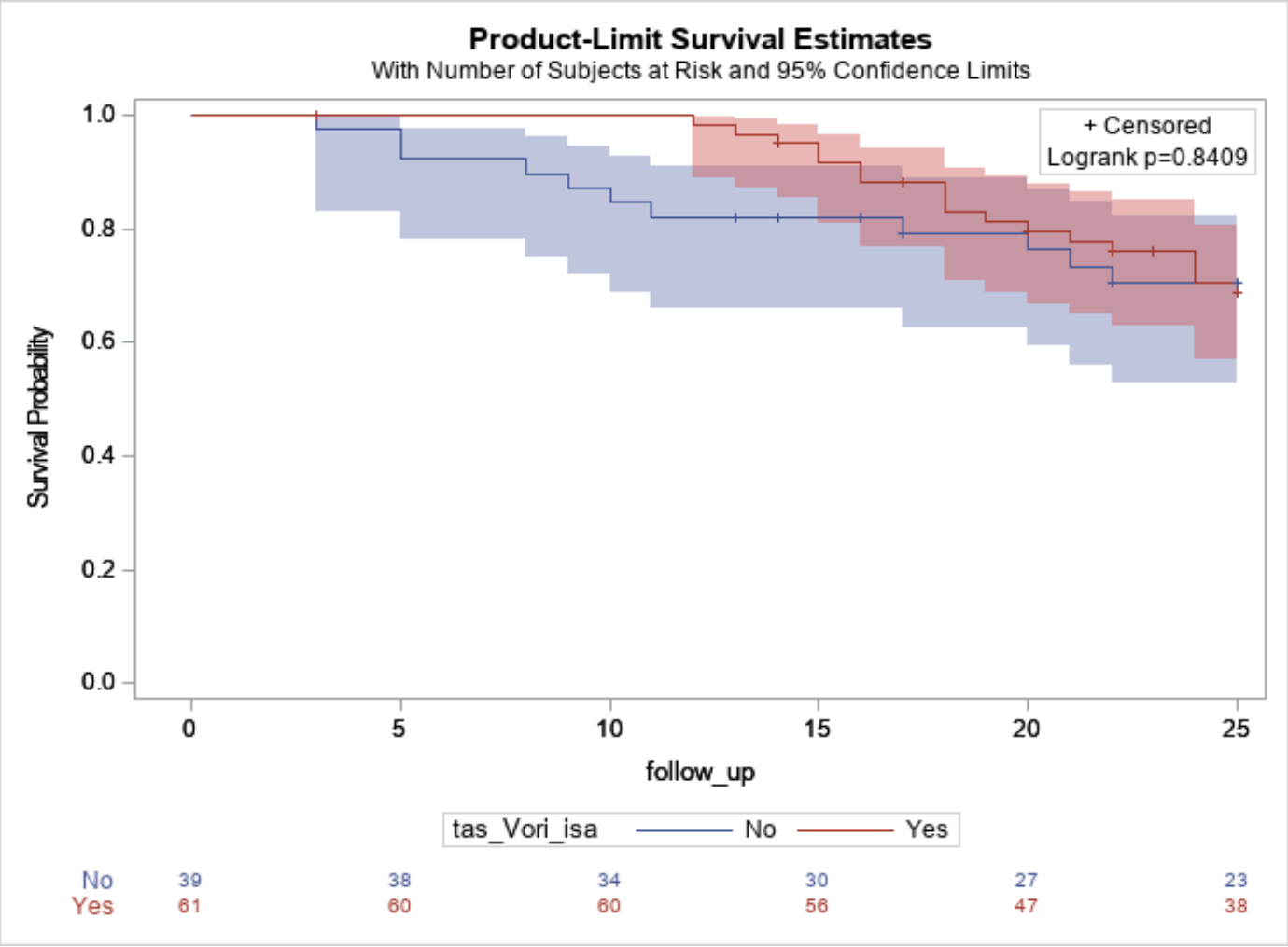

Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits
+ Censored
Logrank p <.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
70
80
90
follow_up
CAPA
1: No
2: Possible
3: Proven/probable
1 408 380 344 314 297 289 285 283 282 282
2 24 22 21 17 15 15 14 13 13 13
3 76 73 60 50 42 34 32 32 30 29

Figure S5.


Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits
+ Censored
Logrank p=0.8409
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
follow_up
tas_Vori_isa
No
Yes
No 39 38 34 30 27 23
Yes 61 60 60 56 47 38