TUNISIE HAMMAMET du 19 nov. au 21 2021
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AFRAVIH
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VIH, Hépatites, Santé sexuelle
Infections émergentes

COVID-19: effets à long terme

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Liens d'interêt

Gilead
ViiV Healthcare
MSD
Janssen
AstraZeneca

Objectif principal

- Décrire les caractéristiques cliniques de la maladie

- **Critère d'inclusion**
  - Tout patient admis dans un établissement de santé, participant à la recherche, avec une infection confirmée par le SARS-CoV-2 (diagnostic confirmé virologiquement par PCR), enfants et femmes enceintes compris

Calendrier des visites de suivi

	Hospitalization				Convalescent phase				
	Initial phase	Resolutive phase[1]	DD (Day of Hospital Discharge)	DS +7/10 days [2]	DD + 4 Weeks (+10 days)	3 months (from D1)	6 months (from D1)	12 months (from D1)	18 months (from D1)
	D1-D3								
Informed consent	X								
Urine pregnancy test*	X								
Clinical assessment*	DAILY UNTIL DAY OF HOSPITAL DISCHARGE[3]			X	X[4]	X[4]	X	X	X
Urinary stick*	X					X	X	X	X
Self-administered questionnaire (7 symptoms)	TWICE DAILY UNTIL DAY OF HOSPITAL DISCHARGE			X	X	X	X	X	X
Self-administered questionnaires (HADS, MOS-SF-36)	X[5]		X[6]		X	X	X	X	X
Questionnaire IES-R							X	X	X
MRC, MoCA, RankinS								X	X
Chest radiography*	IF CLINICALLY INDICATED				IF CLINICALLY INDICATED AND ABNORMAL DURING HOSPITALIZATION				
Thoracic CT scan*	IF CLINICALLY INDICATED				IF CLINICALLY INDICATED	X	IF ABNORMAL OR MISSING AT M3	IF CLINICALLY INDICATED OR IF ABNORMAL AT LAST EVALUATION	IF CLINICALLY INDICATED OR IF ABNORMAL AT LAST EVALUATION
Six-minute walk test*						X	IF ABNORMAL OR MISSING AT M3	IF CLINICAL DYSPNEA	IF CLINICAL DYSPNEA
Pulmonary function tests (with DLCO)*						X	IF ABNORMAL OR MISSING AT M3	IF CLINICALLY INDICATED OR IF ABNORMAL AT LAST EVALUATION	IF CLINICALLY INDICATED OR IF ABNORMAL AT LAST EVALUATION
Arterial blood gas*	IF CLINICALLY INDICATED				IF CLINICALLY INDICATED AND ABNORMAL DURING HOSPITALIZATION			IF CLINICALLY INDICATED	IF CLINICALLY INDICATED
Cardiac echography followed by low intensity effort*								X[7]	
Cardiac MRI*								IF ABNORMAL CARDIAC ECHOGRAPHY	

* Done as part of care (CT scan, 6mwt, PFT at M3 following recommendations of SFP)

[1] Clinical improvement (no fever)

[2] **Clinical assessment or phone call at 7/10 days after the first symptoms ONLY IF THE PATIENT IS DISCHARGED BEFORE 7 DAYS AFTER THE FIRST SYMPTOMS**

[3] See the "Daily case record form" from CRF for details.

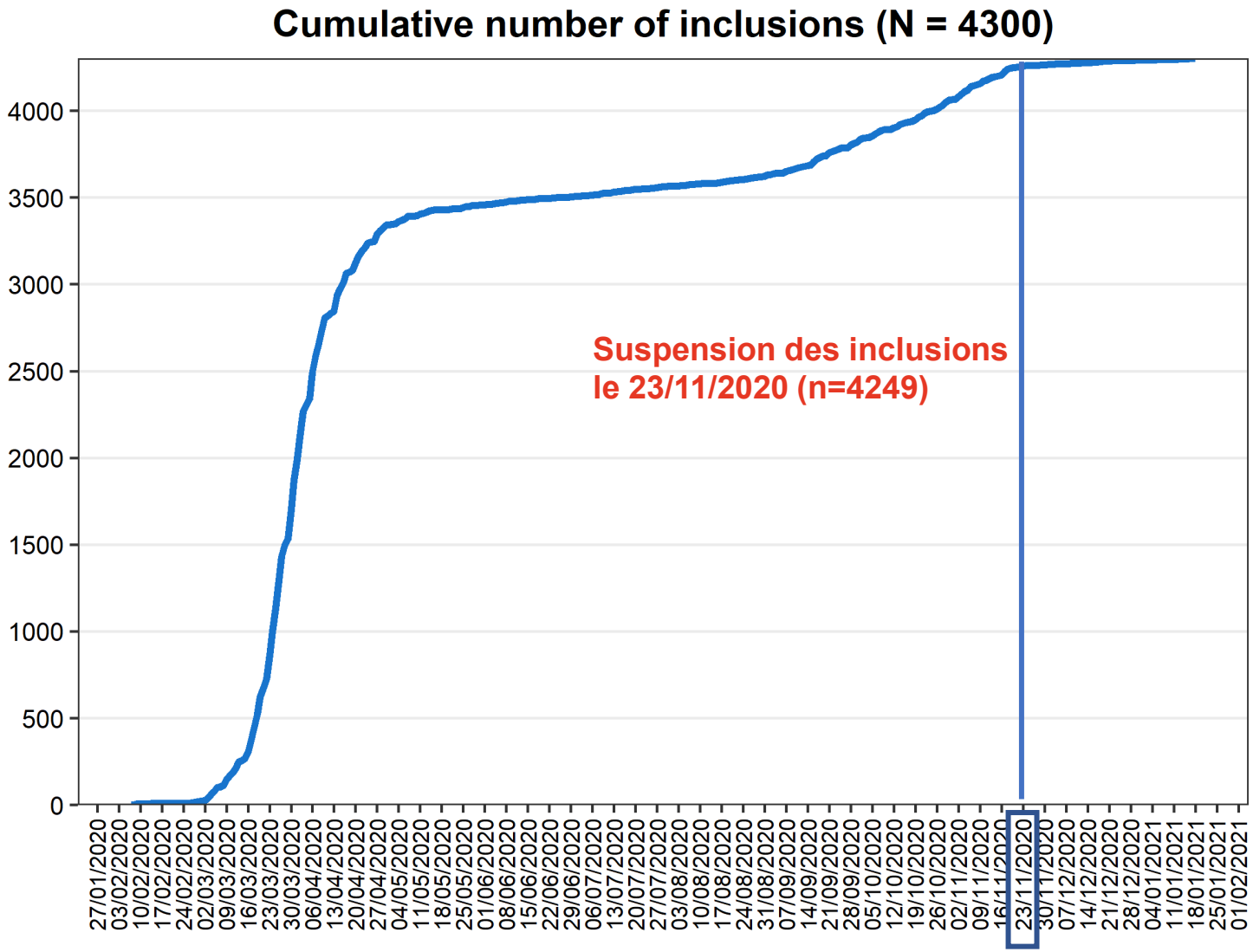
[4] See the clinical convalescent CRF

[5] As soon as possible after D1. **The self-questionnaire should be performed only if the baseline one has been done.**

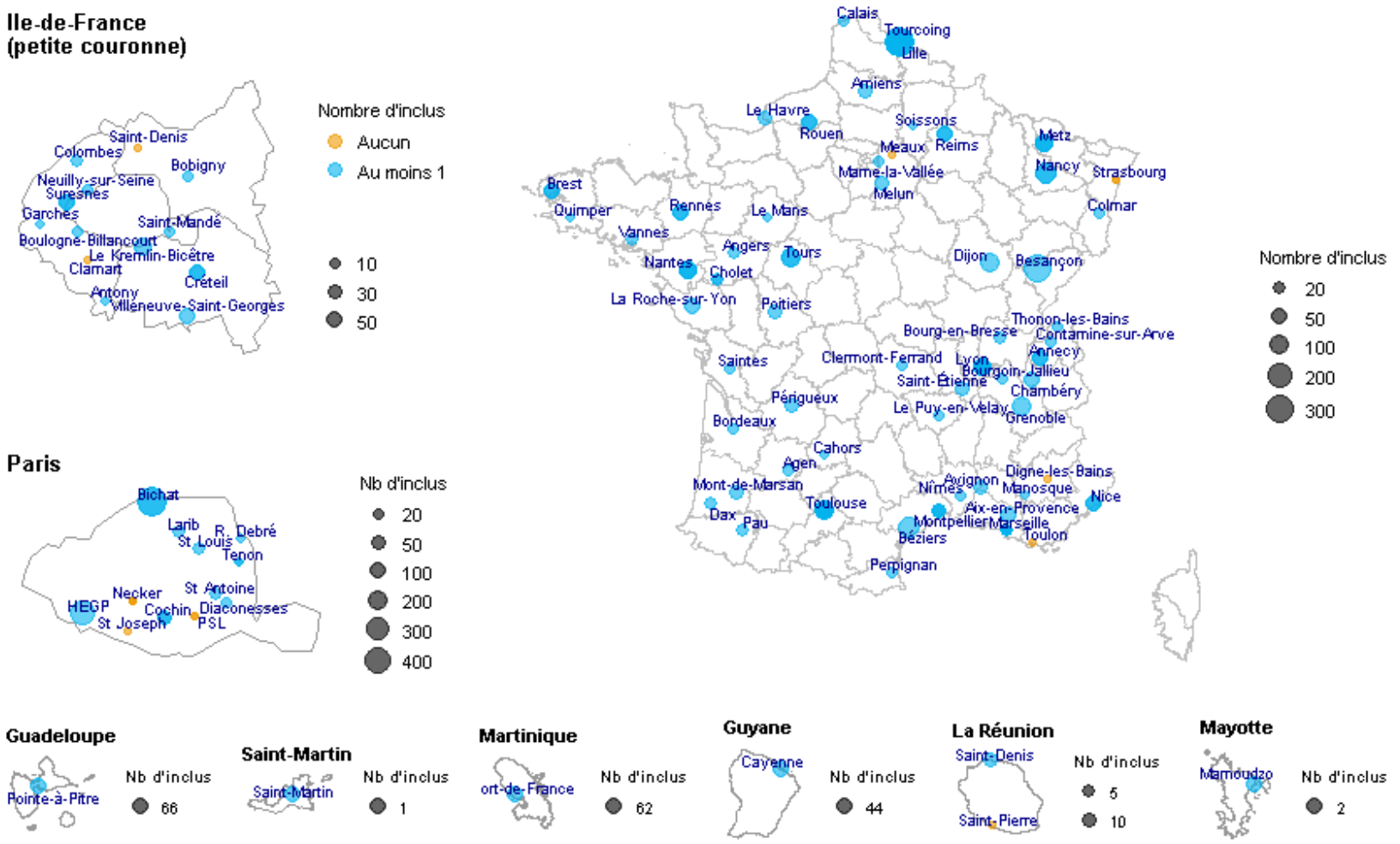
[6] If patient is hospitalized more than 7 days

[7] If troponin raised above 99th percentile at any time during hospitalization

Inclusions à ce jour



145 SERVICES (104 CENTRES)



- Au 09/12/20, visite M6 saisie pour **1137 participants** (63 services cliniques)

- Les 10 symptômes suivants étaient systematiquement recueillis:
  - fatigue
  - dyspnée
  - arthralgies
  - myalgies
  - céphalées
  - rhinorrhée
  - toux
  - mal à la gorge
  - anosmie
  - ageusie

Ghosn J et al, CMI 2021

Table 1: Characteristics at hospital admission and clinical symptoms at 6 months follow-up of 1137 patients enrolled in the French COVID cohort

Characteristics	Value	Missing
At hospital admission		
Age - Median [IQR] - yr	61 [51 ; 71]	7
Female sex - no/total no (%)	424/1136 (37)	1
Ethnic group - no/total no (%)		286
Arab - no/total no (%)	72/851 (8)	
Black - no/total no (%)	82/851 (10)	
Asian - no/total no (%)	12/851 (1)	
Latin American - no/total no (%)	8/851 (1)	
White - no/total no (%)	641/851 (75)	
Other - no/total no (%)	36/851 (4)	
Smoking history - no/total no (%)		176
Never smoked	625/961 (65)	
Former smoker	280/961 (29)	
Current smoker	56/961 (6)	
Days since symptom onset - Median [IQR]	194 [188 ; 205]	93

Ghosn J et al, CMI 2021

Comorbidities - no/total no (%)	
Chronic cardiac disease (not hypertension)	195/1060 (18)
Hypertension	405/1058 (38)
Chronic kidney disease	72/1062 (7)
Malignant neoplasm	77/1059 (7)
Moderate or severe liver disease	10/1062 (1)
Obesity (clinician definition)	230/1049 (22)
Chronic pulmonary disease (not asthma)	101/1062 (10)
Diabetes (type 1 and 2)	206/1062 (19)
No of comorbidities - no/total no (%) *	
0	309/1065 (29)
1	314/1065 (29)
>=2	442/1065 (42)
Symptoms - no/total no (%) **	
None	56/1045 (5)
1-2	337/1045 (32)
>=3	652/1045 (62)

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Follow-up during hospitalisation

Intensive care unit during acute phase	288/999 (29)
Oxygen therapy - no/total no (%)	728/1011 (72)
Non-invasive ventilation (e.g. BIPAP, CPAP) - no/total no (%)	153/996 (15)
Pharmacological treatment during acute COVID-19	
Antiviral agent - no/total no (%)	219/1005 (22)
Hydroxychloroquine - no/total no (%)	161/977 (16)
Antibiotic - no/total no (%)	645/1010 (64)
Immunomodulator (for example anti-IL6) - no/total no (%)	24/965 (2)
Corticosteroid – no/total no (%)	179/999 (18)
Length of hospital stay - Median [IQR] - days	9 [5 ; 15]

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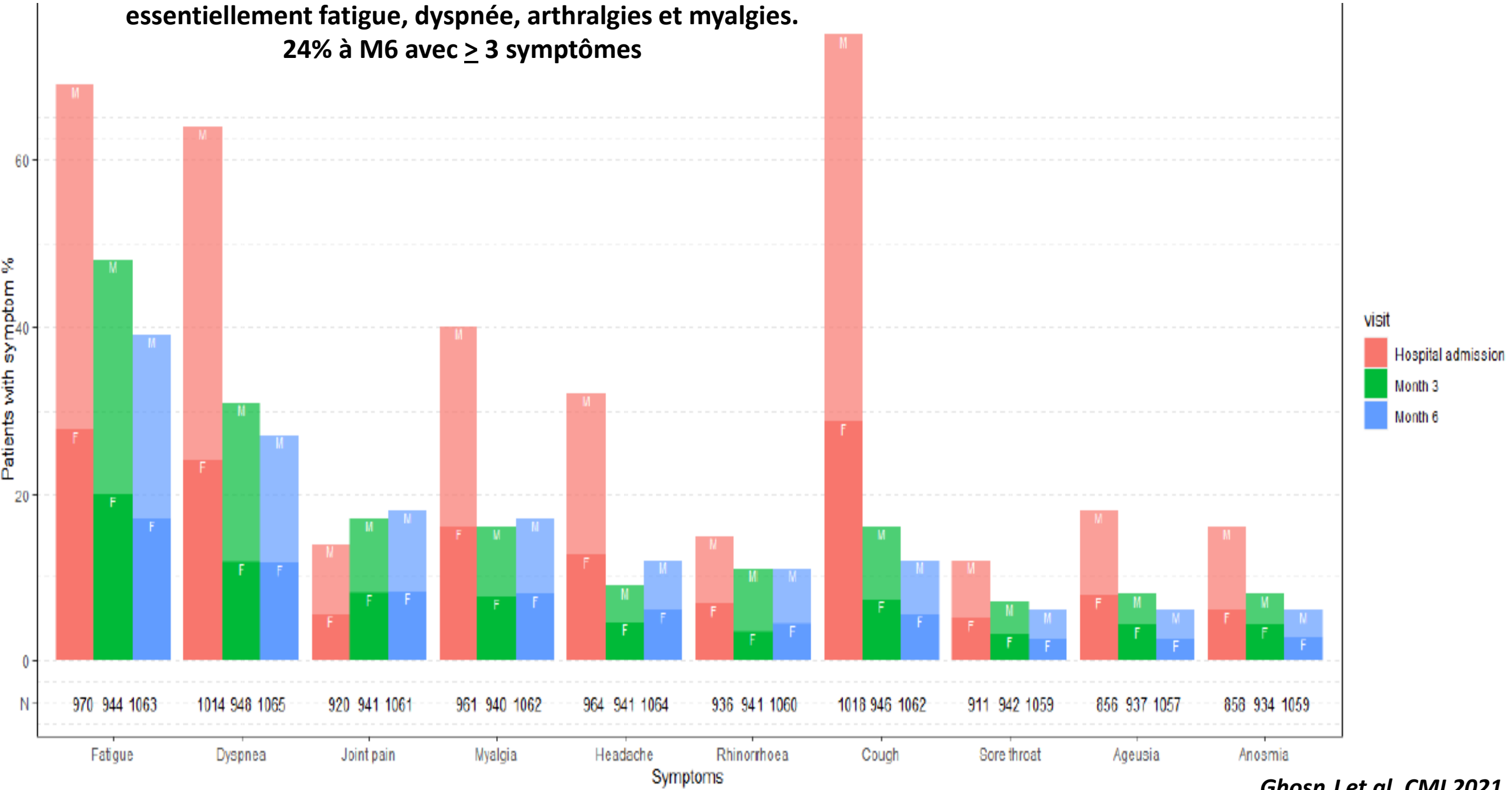
Follow-up after discharge

Days since symptom onset - Median [IQR]	194 [188 ; 205]
Days since hospital discharge - Median [IQR]	177 [168 ; 186]
Persistent symptoms 3 months after hospital admission - no/total no (%) **	
None	302/957 (32)
1-2	398/957 (42)
>=3	257/957 (27)
Persistent symptoms 6 months after hospital admission - no/total no (%) **	
None	429/1068 (40)
1-2	384/1068 (36)
>=3	255/1068 (24)
If applicable, back to work- no/total no (%)	304/429 (71)

Ghosn J et al, CMI 2021

68% et 60% des participants avec ≥ 1 symptôme à M3 et à M6, essentiellement fatigue, dyspnée, arthralgies et myalgies.
24% à M6 avec ≥ 3 symptômes



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Association entre persistance de symptômes et caractéristiques à l'inclusion

(analyse uni et multivariée, regression logistique)

		<3 symptoms at M6	≥3 symptoms at M6	Bivariate analysis		Multivariate analysis	
	Missing	(N=813)	(N=255)	OR [95% CI]	p-value	aOR [95% CI][a]	p-value
Age >= 65 years	7	361 (44.7%)	96 (37.9%)	0.76 [0.57; 1.01]	0.059		
Female gender	1	271 (33.4%)	128 (50.2%)	2.01 [1.51; 2.68]	<0.001	2.40 [1.75; 3.30]	<0.001
>= 3 symptoms at admission	91	440 (59.1%)	173 (74.2%)	1.99 [1.44; 2.78]	<0.001	2.04 [1.45; 2.89]	<0.001
Intensive care unit during acute phase	135	194 (27.4%)	71 (31.7%)	1.23 [0.89; 1.70]	0.210	1.55 [1.09; 2.18]	0.013
>= 2 comorbidities	71	308 (40.5%)	111 (46.8%)	1.29 [0.96; 1.73]	0.086		

- La présence d'au moins 3 symptômes à M6 était significativement associée
  - *Au sexe féminin*
  - *Avoir rapporté ≥ 3 symptômes à l'admission*
  - *Avec un séjour en Réanimation (admission directe ou transfert)*

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Conclusions

- 60% des personnes hospitalisées pour COVID-19 se plaignent toujours d'**au moins un symptôme** à M6 *(cohorte Chine: 68% avec ≥ 1 symptôme à M6)*
- 24% des personnes hospitalisées pour COVID-19 se plaignent toujours d'**au moins trois symptômes** à M6

- Persistance de ≥ 3 symptômes à M6 associée
  - au sexe féminin
  - à la sévérité initiale de la maladie (nbre de symptômes à J0 et séjour en Réanimation)

- Symptômes invalidants : 30% de ceux qui avaient une activité professionnelle avant la maladie n'ont pas repris le travail à M6

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En Juillet 2021, 599 participants inclus entre Janvier et Mai 2020 avaient effectué une visite M12

Characteristics	Value	Missing
At hospital admission		
Age - Median (IQR) - yr	61 [52 ; 71]	1
Female sex - no/total no (%)	200/597 (34)	2
No of comorbidities - no/total no (%) [a]		28
0	156/571 (27)	
1	170/571 (30)	
≥2	245/571 (43)	
Symptoms - no/total no (%) [b]		51
None	30/548 (5)	
1-2	218/548 (40)	
≥3	300/548 (55)	
Management during hospitalisation		
Intensive care unit during acute phase	202/534 (38)	65

Chine n= 1276

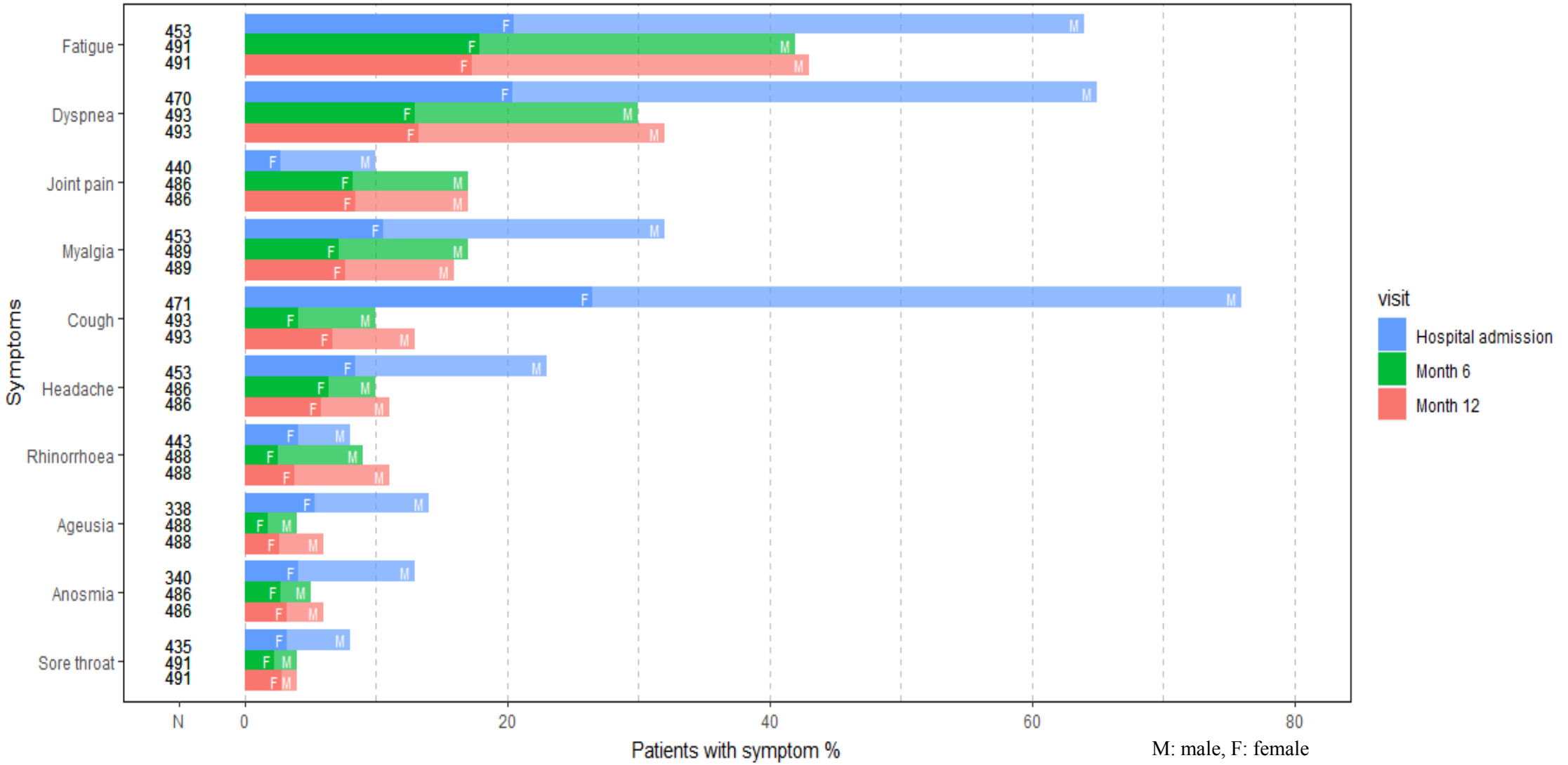
59 ans

47%

Symptômes liés au COVID-19 chez 530 patients ayant fait les visites M6 et M12

66% ont encore ≥ 1 symptôme à M12

26% ont encore ≥ 3 symptomes à M12



M: male, F: female

Characteristics	Value	Missing
Follow-up after discharge		
Days from symptom onset to M12 visit - Median (IQR) - d	388 [373 ; 411.8]	29
Days from discharge to M12 visit - Median (IQR) - d	367 [351 ; 392]	32
CRP - Median (IQR) – mg/L	3 [1 ; 4]	249
Six-minute walk test (6MWT) done	223/444 (50)	155
Distance walked in %	88 [74 ; 100]	376
Medical research council scale (force musculaire)	60 [60 ; 60]	182
Simplified Modified Rankin Scale (score de dépendance)		196
0	197/403 (49)	
1	117/403 (29)	
2	66/403 (16)	
3	20/403 (5)	
4	2/403 (0)	
5	1/403 (0)	
Presence of symptoms 12 months after hospital admission - no/total no (%) [b]		15
None	196/584 (34)	
1-2	239/584 (41)	
≥3	149/584 (26)	

The scale runs from 0-6, running from perfect health without symptoms to death.
0 - No symptoms.
1 - No significant disability.
2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3 - Moderate disability. Requires some help, but able to walk unassisted.
4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6 - Dead.

Association entre ≥ 3 symptômes à M12 et caractéristiques à l'inclusion

	<3 symptoms at M12	≥3 symptoms at M12	Bivariate analysis			Multivariate analysis	
	(N=435)	(N=149)	OR [95% CI]		p	OR [95% CI]	p
Age, median [IQR]	61 [52 ;70]	60 [52 ;69]	1.00	0.98, 1.01	0.53		
Female gender, n (%)	122 (28.2%)	75 (50.3%)	**2.58**	**1.76, 3.80**	**<0.001**	**2.58 [1.76, 3.80]**	**<0.001**
≥3 symptoms at admission, n (%)	204 (52.2%)	88 (62.0%)	**1.49**	**1.01, 2.22**	**0.045**		
ICU during acute phase, n (%)	147 (38.2%)	49 (36.6%)	0.93	0.62, 1.40	0.74		
≥2 comorbidities, n (%)	170 (41.3%)	67 (46.5%)	1.24	0.84, 1.81	0.27		
Oxygen therapy, n (%)	286 (77.7%)	106 (76.3%)	0.92	0.58, 1.47	0.73		
Non-invasive ventilation (e.g. BIPAP, CPAP), n (%)	57 (15.8%)	22 (15.9%)	1.01	0.58, 1.70	0.98		
Antiviral agent, n (%)	92 (25.3%)	39 (28.1%)	1.15	0.74, 1.78	0.53		
Corticosteroids, n (%)	68 (18.3%)	33 (23.6%)	1.38	0.85, 2.19	0.18		

Conclusions

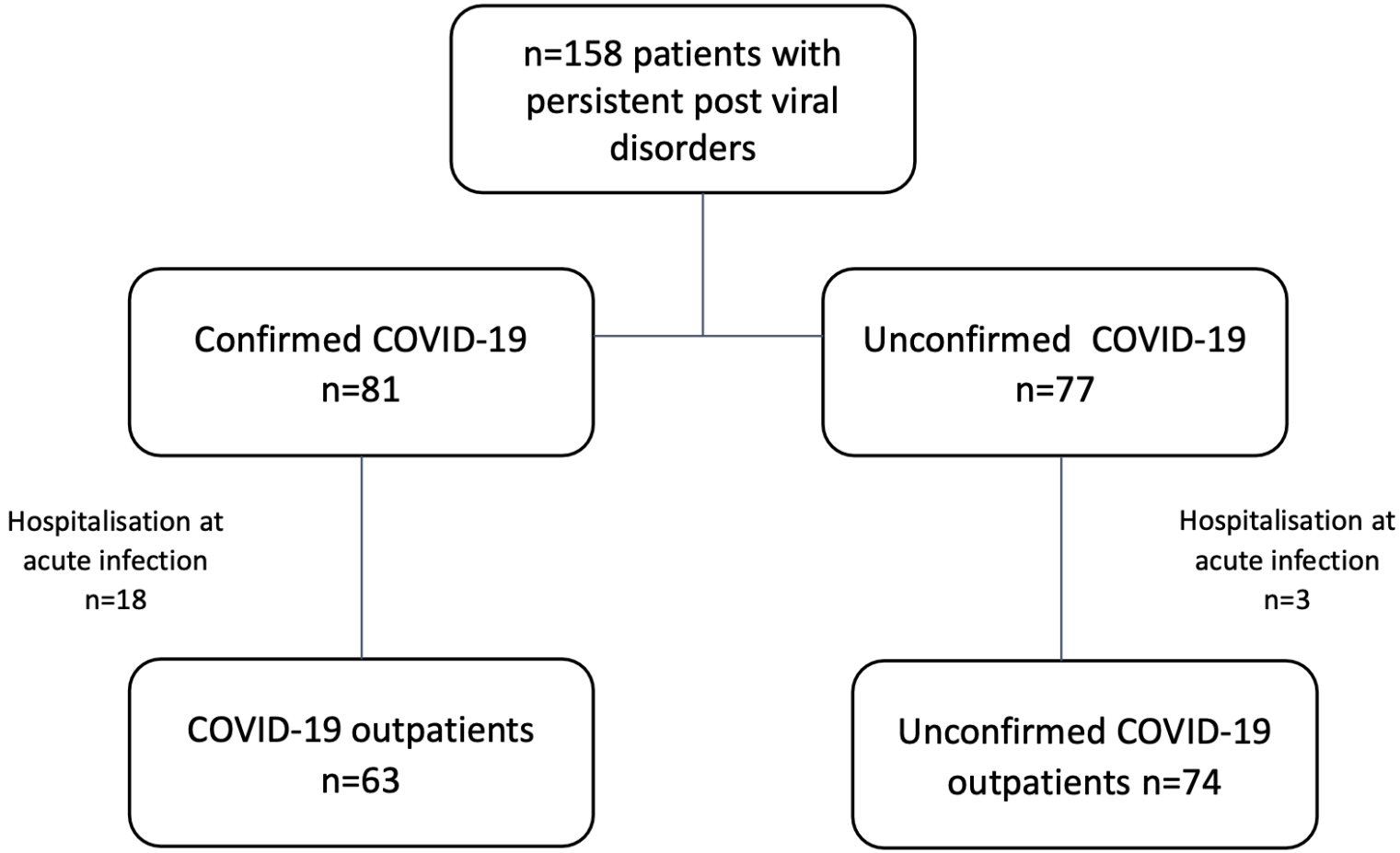
- 66% des personnes hospitalisées pour COVID-19 se plaignent encore **d'au moins un symptôme à M12 (49% cohorte Chine)**

- 26% des personnes hospitalisées pour COVID-19 se plaignent encore **d'au moins trois symptômes à M12**

- La persistance de ≥ 3 symptômes à M12 était associée au sexe féminin

- Symptômes invalidants: 25% de ceux qui avaient une activité professionnelle avant la maladie n'ont pas repris le travail à M12 (12% cohorte Chine)

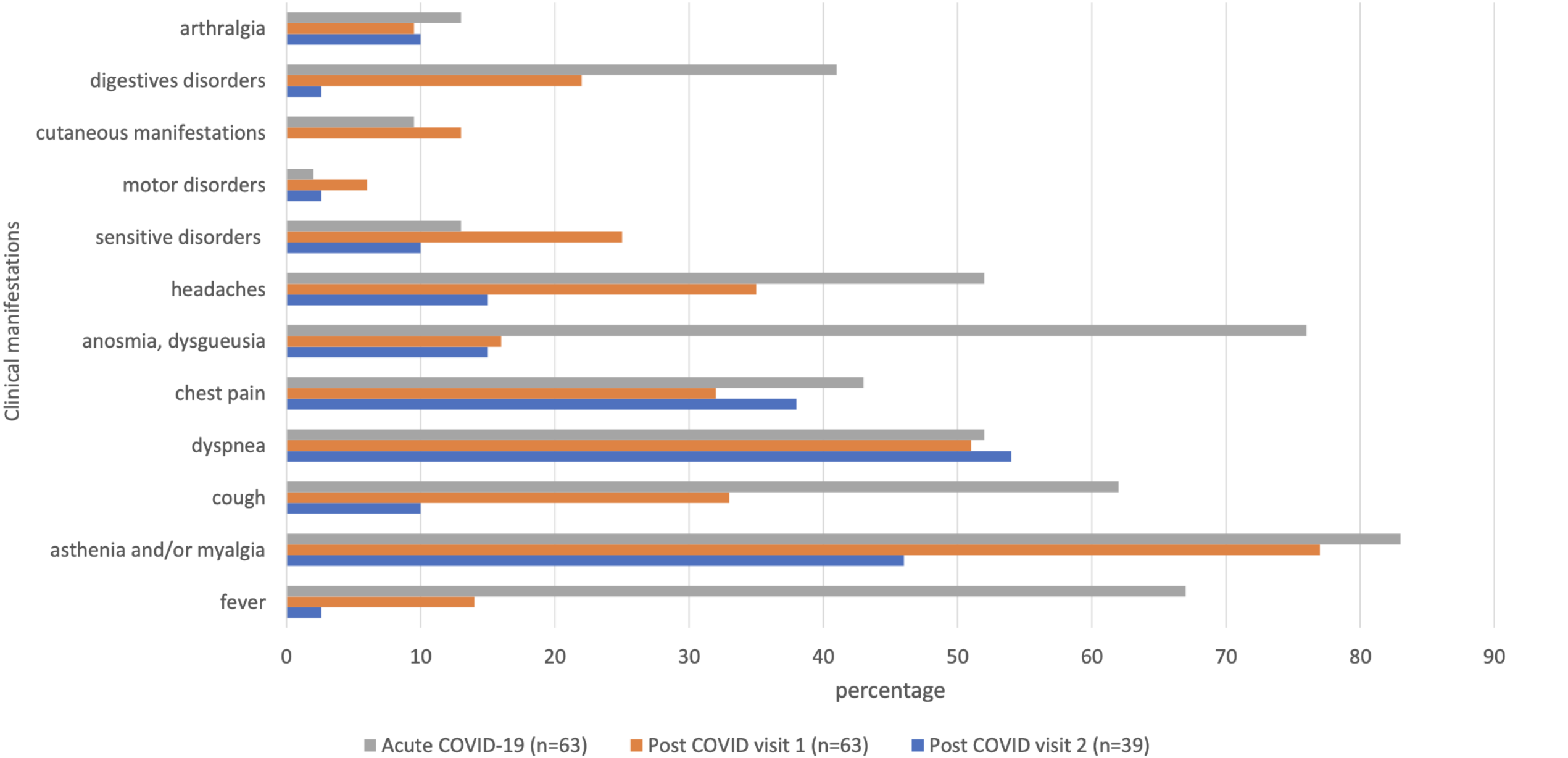
Formes ambulatoires: symptômes à M6



Seang S et al, Inf Dis Now 2021

À M6, 27% des participants ont ≥ 2 symptômes (essentiellement dyspnée et asthénie/myalgie)

Fluctuations des symptômes au cours du temps



Seang S et al, Inf Dis Now 2021

Cohorte SAPRIS - SERO

- Cohorte CONSTANCES en population générale (n = 35 852)
- 26 823 (74%) ont participé à cette sous-étude
  - Test sérologique sur papier buvard envoyé à domicile entre Mai et Nov 2020
  - Auto-questionnaire sur la croyance d'avoir été infecté par le SARS-CoV-2 et sur la présence de 18 symptômes liés à l'infection (envoyés entre 12/20 et 01/21)
    - présents dans les 4 dernières semaines (au moment du remplissage du questionnaire)
    - et ayant persisté plus de 8 sem
  - Âge médian : 49 ans
  - Femmes : 51,2%
  - Bac et plus : 86,5%

Matta J et al, JAMA Intern Med 2021

Cohorte SAPRIS - SERO

- 914/26 823 croyaient avoir été infecté par le SARS-CoV-2
  - dont 453 (49,6%) avaient une sérologie POS

- 1 091/26 823 avaient une sérologie POS
  - dont 453/1 091 (41,5%) avaient rapporté des symptômes avant le résultat de la sérologie

Matta J et al, JAMA Intern Med 2021

Table 3. Associations Between Persistent Symptoms, Belief, and Serology Test Results

Symptom	No.	Odds ratio (95% CI)[a]			
				Model 3	
		Model 1 Belief 15/18	Model 2 Serology 10/18	Belief 16/18	Serology 01/18
Sleep problems	2729	1.09 (0.88-1.36)	0.96 (0.77-1.19)	1.14 (0.89-1.46)	0.91 (0.71-1.15)
Joint pain	1894	1.32 (1.01-1.71)	1.03 (0.79-1.35)	1.39 (1.03-1.86)	0.89 (0.65-1.21)
Back pain	1630	1.41 (1.10-1.80)	1.16 (0.91-1.49)	1.40 (1.05-1.85)	1.01 (0.76-1.33)
Digestive tract problems[b]	909	1.92 (1.43-2.57)	1.06 (0.73-1.50)	2.19 (1.57-3.06)	0.73 (0.49-1.08)
Muscular pain, sore muscles	867	1.79 (1.29-2.48)	1.33 (0.94-1.87)	1.78 (1.22-2.59)	1.01 (0.68-1.50)
Fatigue	766	5.20 (4.20-6.43)	2.59 (2.03-3.30)	4.90 (3.79-6.33)	1.13 (0.84-1.52)
Poor attention or concentration	644	3.63 (2.79-4.71)	2.10 (1.57-2.82)	3.42 (2.50-4.67)	1.13 (0.79-1.61)
Skin problems	632	1.36 (0.92-2.00)	0.65 (0.39-1.06)	1.79 (1.17-2.73)	0.49 (0.29-0.85)
Other symptoms[c]	514	3.07 (2.22-4.25)	1.91 (1.32-2.75)	2.93 (1.99-4.31)	1.10 (0.71-1.70)
Sensory symptoms	492	1.60 (1.02-2.51)	0.77 (0.43-1.38)	2.06 (1.25-3.40)	0.54 (0.28-1.03)
Hearing impairment	479	1.47 (0.90-2.41)	1.22 (0.73-2.03)	1.45 (0.82-2.55)	1.03 (0.57-1.84)
Headache	360	2.52 (1.71-3.73)	1.69 (1.10-2.59)	2.40 (1.52-3.80)	1.10 (0.67-1.82)
Breathing difficulties	256	8.16 (5.95-11.19)	3.60 (2.48-5.24)	7.75 (5.25-11.43)	1.11 (0.70-1.76)
Palpitations	213	5.27 (3.55-7.82)	2.61 (1.62-4.19)	5.14 (3.18-8.29)	1.05 (0.59-1.87)
Dizziness	178	3.23 (1.88-5.56)	2.37 (1.33-4.24)	2.71 (1.40-5.24)	1.42 (0.70-2.88)
Chest pain	174	7.34 (4.95-10.88)	3.70 (2.33-5.87)	6.58 (4.02-10.75)	1.25 (0.70-2.22)
Cough	167	4.67 (3.00-7.25)	2.22 (1.25-3.97)	4.85 (2.75-8.56)	0.91 (0.45-1.83)
Anosmia	146	28.66 (20.16-40.74)	15.69 (10.85-22.70)	16.37 (10.21-26.24)	2.72 (1.66-4.46)

Matta J et al, JAMA Intern Med 2021

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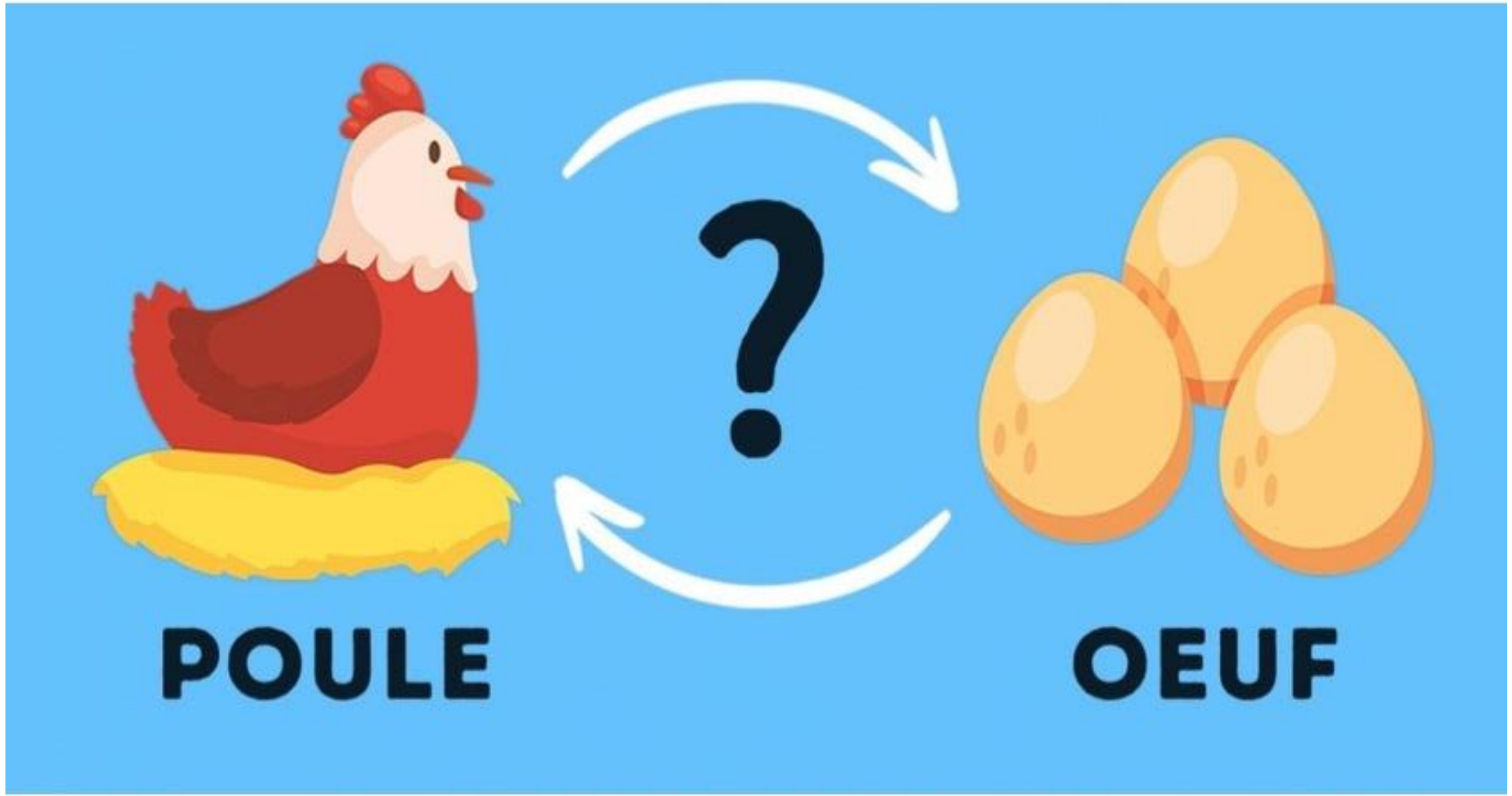
TABLE 2 | Variables associated with cognitive complaints at 1-month follow-up in logistic regression models.

	Univariable analyses		**Multivariable analysis (*n* = 96)**	
	Crude OR (CI 95%)	***p***	**Adjusted OR (CI 95%)**	***p***
HADS	**1.94 (1.15–3.27)**	**0.014**	**1.96 (1.08–3.57)**	**0.028**
Age	**1.04 (1.01–1.08)**	**0.015**	**1.05 (1.01–1.09)**	**0.026**
Female sex	1.80 (0.72–4.52)	0.211	0.99 (0.33–3.05)	0.99
ICU admission	**0.18 (0.05-0.64)**	**0.008**	**0.22 (0.05-0.90)**	**0.035**
SVFT	0.95 (0.88–1.02)	0.176	0.93 (0.84–1.03)	0.152
DSST	0.98 (0.96–1.01)	0.163	1.01 (0.97–1.05)	0.611

Gouraud C et al, Frontiers in Psychiatry 2021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- We compared the baseline characteristics (age, gender, symptoms at admission, intensive care unit during acute phase) between patients who attended the M6 visit to the eligible patients who did not (excluding deceased patients) using a chi-squared test. We computed the observed proportion of three or more persistent symptoms at M6 and its 95% CI according to each combination of the risk factors found in the multivariate model to impute patients without M6 visit. Therefore, as a sensitivity analysis, we obtained three estimations of the proportion of patients with three or more persistent symptoms on the overall population of eligible patients for the M6 visit using three imputations: the mean proportion and the proportions from the lower bound and the upper bound of the 95% CI.

- In the sensitivity analysis, we obtained three estimations of the proportion of three or more persistent symptoms at M6 among all eligible patients for the M6 visit: the mean proportion was 24% (95% CI 22 - 26), the proportion from the lower bound of the 95% CI was 20%, and the imputed proportion from the upper bound of the 95% CI was 29%.
- Comparing the 1137 patients who attended the M6 visit to the 1587 eligible patients who did not, no statistically significant difference were found except for reporting three or more symptoms at admission. Less patients who did not attend the M6 visit had three or more symptoms at admission (56% versus 62%, $p < 0.001$)