

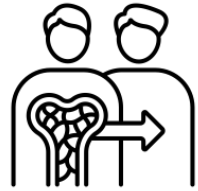
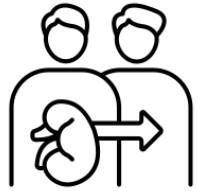
Détection de virus respiratoire par PCR multiplexe nasopharyngée dans l'insuffisance respiratoire aiguë des patients immunodéprimés

Alexis Maillard, Jérôme Le Goff, Mariame Barry, Virginie Lemiale, Séverine Mercier-Delarue, Alexandre Demoule, Linda Feghoul, Samir Jaber, Kada Klouche, Achille Kouatchet, Laurent Argaud, Francois Barbier, Naïke Bigé, Anne-Sophie Moreau, Emmanuel Canet, Frédéric Pène, Maud Salmona, Djamel Mokart, Elie Azoulay

Déclaration des liens d'intérêt – Alexis Maillard

Aucun lien d'intérêt

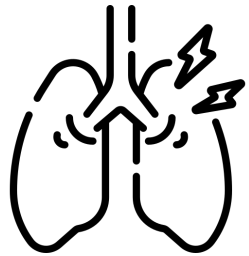
Déficit immunitaire = fréquent en soins intensifs



Wallace et al. 2021
Azoulay et al. 2017



Détresse respiratoire aigue = 1^{ère} cause d'admission en réanimation



- ✓ > 50% de VM invasive
- ✓ Importante mortalité

Azoulay et al. 2017,2019

Jusqu'à 30% de cause indéterminée



- ✓ ↑ risque de VMI
- ✓ ↑ mortalité

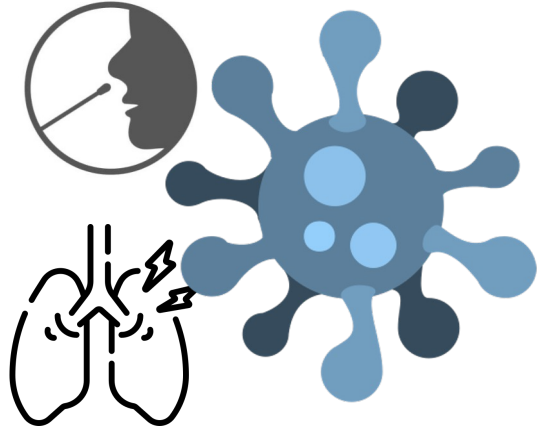
Contejean et al. 2016

PCR respiratoire multiplexe nasopharyngée



- ✓ Facile, non invasifs
- ✓ Résultats rapides
- ✓ Panel de pathogènes

Détection d'un virus respiratoire sur écouvillon nasopharyngée



Infection respiratoire basse = cause de la DRA

Facilitateur d'une autre infection (bactérie, champignon)

Portage asymptomatique

Infection respiratoire haute bénigne

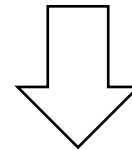


Self et al. 2016

Liu et al. 2021

Das et al. 2015

Gangneux et al. 2022



Quelle est la signification clinique des virus respiratoires détectés dans le nasopharynx des patients immunodéprimés atteints d'IRA ?

1. Cause de la détresse respiratoire

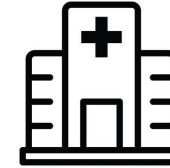
2. Pronostic de la détresse respiratoire

Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure
The HIGH Randomized Clinical Trial

Analyse *post hoc* planifiée de l'essai HIGH



776 adultes immunodéprimés avec une insuffisance respiratoire aigue hypoxémique (besoin d'oxygène ≥ 6 L/min)



32 réanimations en France, 2016-2017

Pré-COVID-19

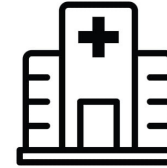
		Décès à J28		IOT à J28	
Oxygénation nasale haut-débit	n=388	35.6%	NS	38.7%	NS
Oxygénation standard	n=388	36.1%		43.8%	

Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure
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32 réanimations en France, 2016-2017



Écouvillons nasopharyngés à l'inclusion : analysés après la fin de l'essai



QIAstat-Dx Respiratory SARS-CoV-2 Panel (2022) sur un QIAstat-Dx Rise Instrument

Détection de 23 pathogènes respiratoires (avec Ct)

Virus grippe-like

Influenza virus A, A-H1, H1N1, A-H3
RSV A and B
PIV 1, 2, 3 and 4
hMPV A and B
(SARS-CoV-2)

Autres virus respiratoires

Rhinovirus and/or enterovirus
Coronavirus 229E, HKU1, NL63,
OC43
Adenovirus
Bocavirus

Bactéries

Bordetella pertussis
Chlamydomphila pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae



776 patients inclus



510 patients échantillonnés

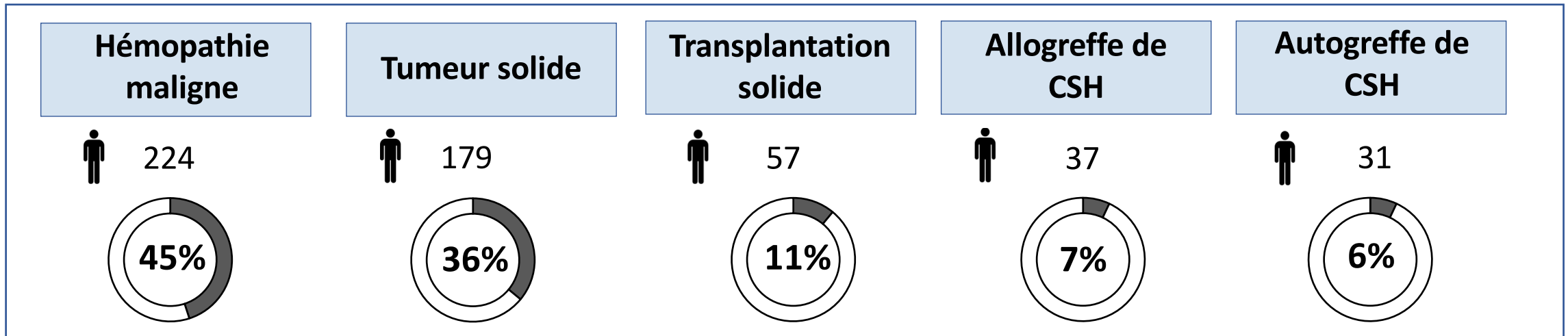


Age médian = 64 ans (IQR 57-71)
Homme 77.3%
SOFA score médian = 4 (IQR 1-6)



Oxygène : 10 L/min (IQR 6-15)
PaO₂/FiO₂ 118 (IQR 84-167)
FR = 32/min (IQR 28-38)

Causes d'immunodépression





776 patients inclus

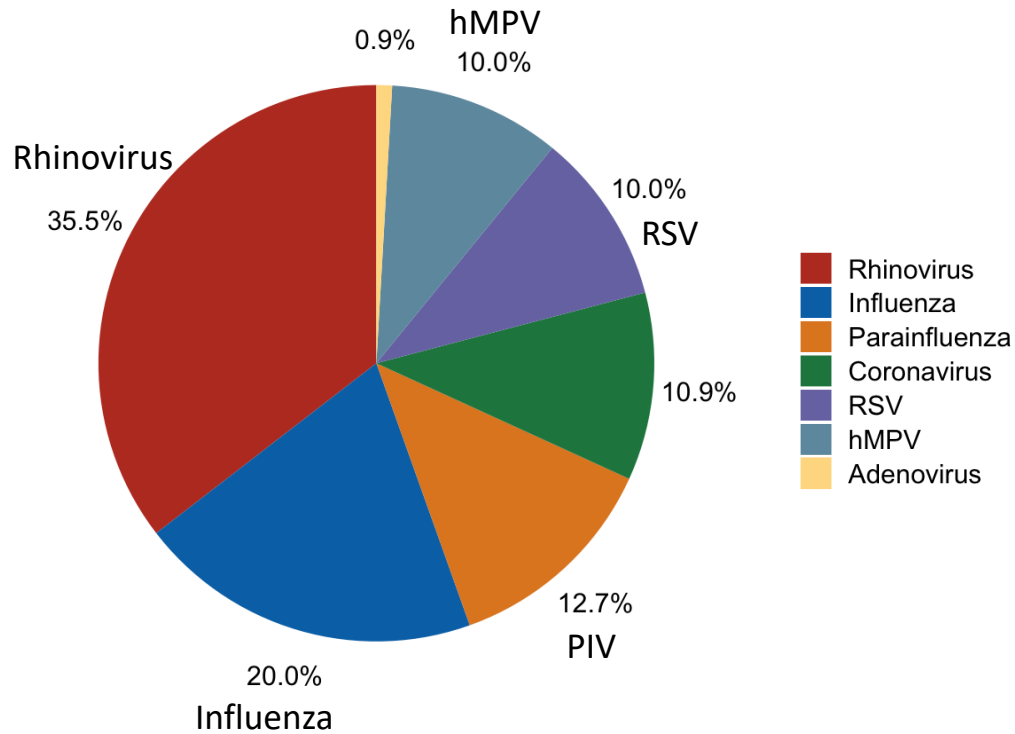


510 patients échantillonnés

103 positives (20%)
Virus respiratoire pour 102



407 négatives (80%)



Influenza : 22 (20%)

PIV : 14 (13%)

RSV : 11 (10%)

hMPV : 11 (10%)

Virus grippe-like

Rhino/entérovirus : 39 (36%)

Coronavirus : 12 (11%)

Adenovirus : 1 (0.9%)

Autres virus



776 patients inclus

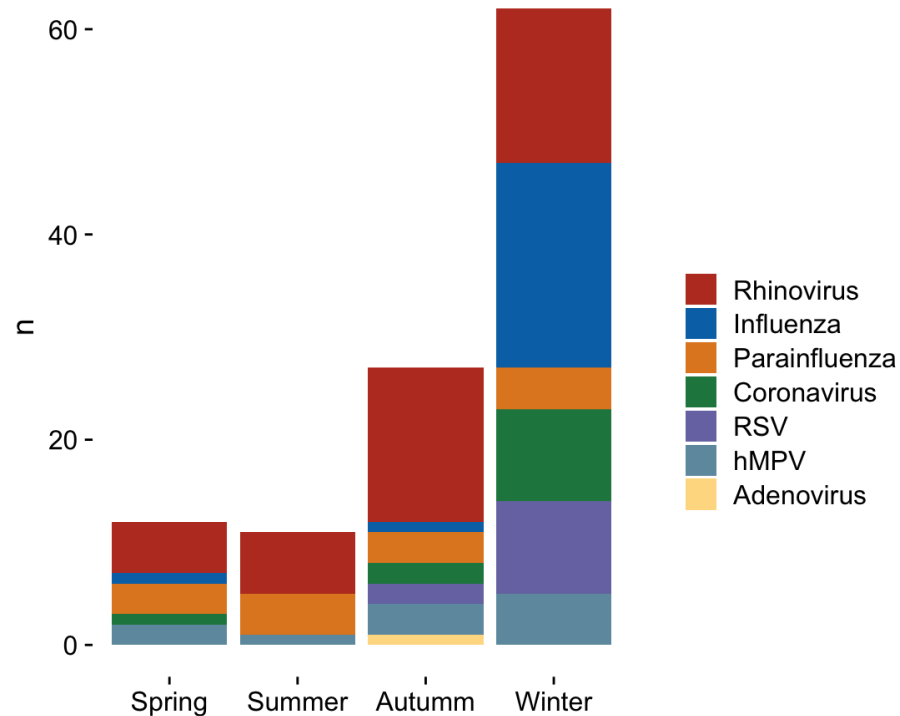


510 patients échantillonnés

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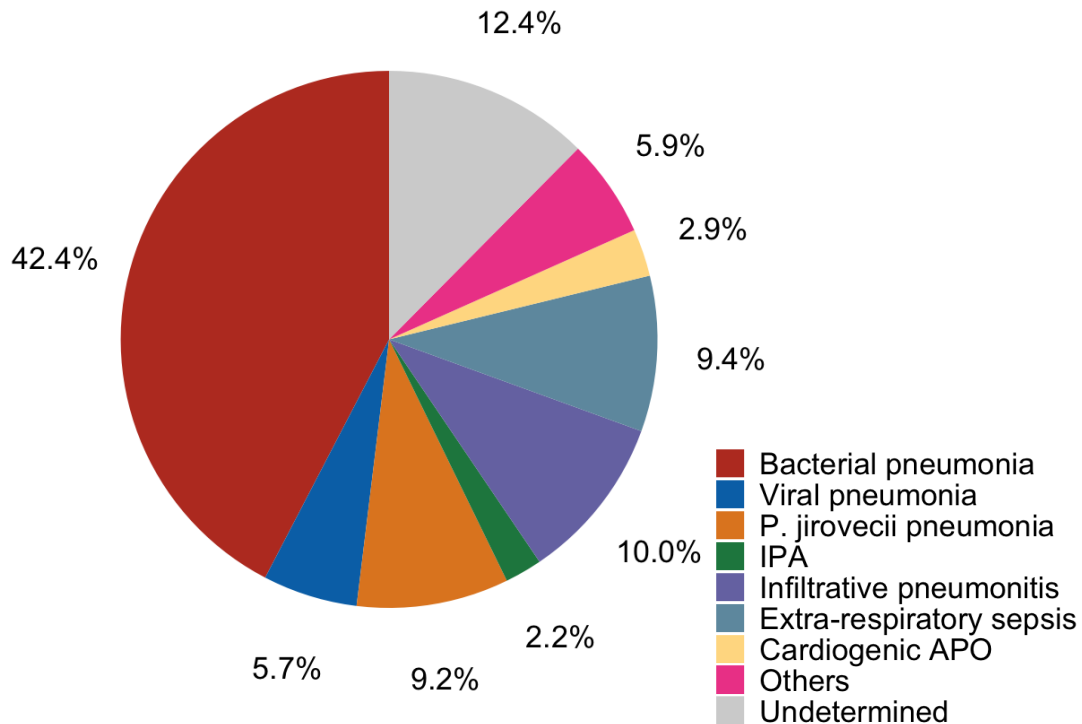
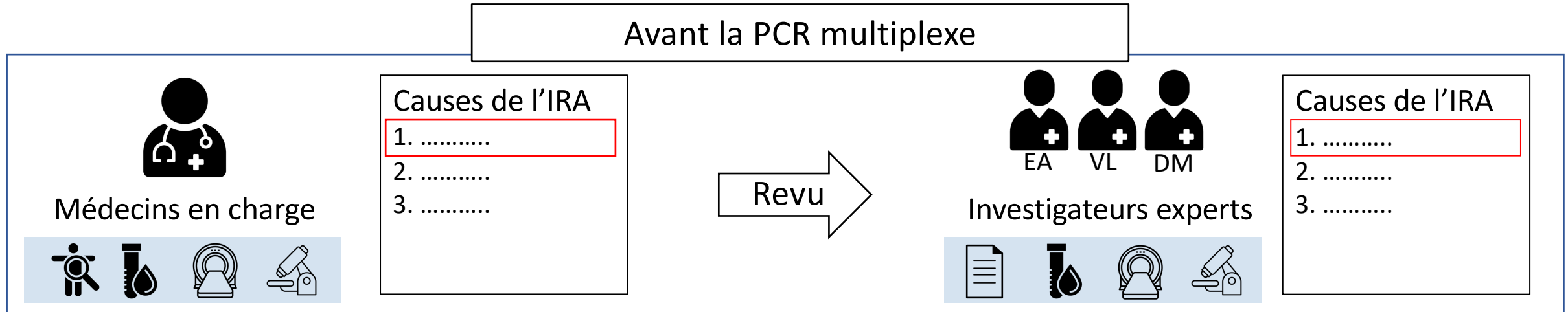
La moitié des virus étaient détectés en hiver

Saisonnalité significative

- ✓ Influenza
- ✓ Coronavirus
- ✓ VRS

Hiver : 40% des PCR nasopharyngée positive
Eté : 9% des PCR nasopharyngée positive

La détection du virus fournit-elle des informations sur l'étiologie de l'IRA ?



Pneumonie bactérienne 42%

Pneumopathie infiltrative spécifique 10%

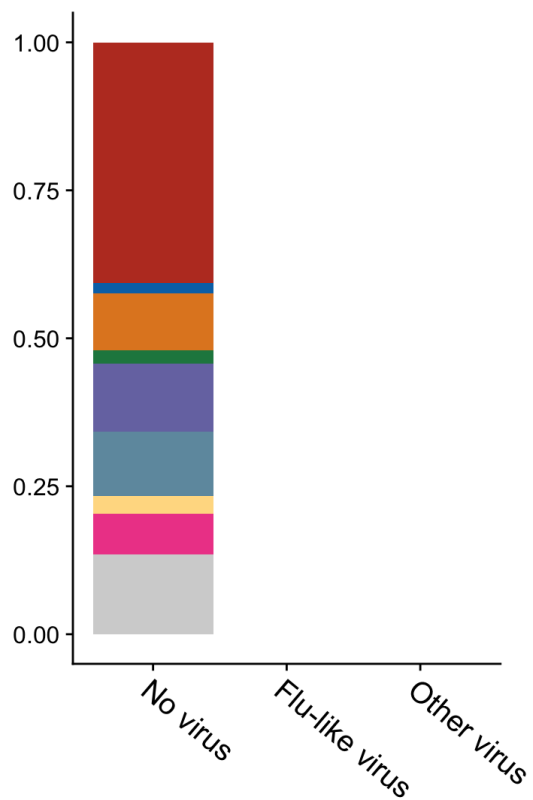
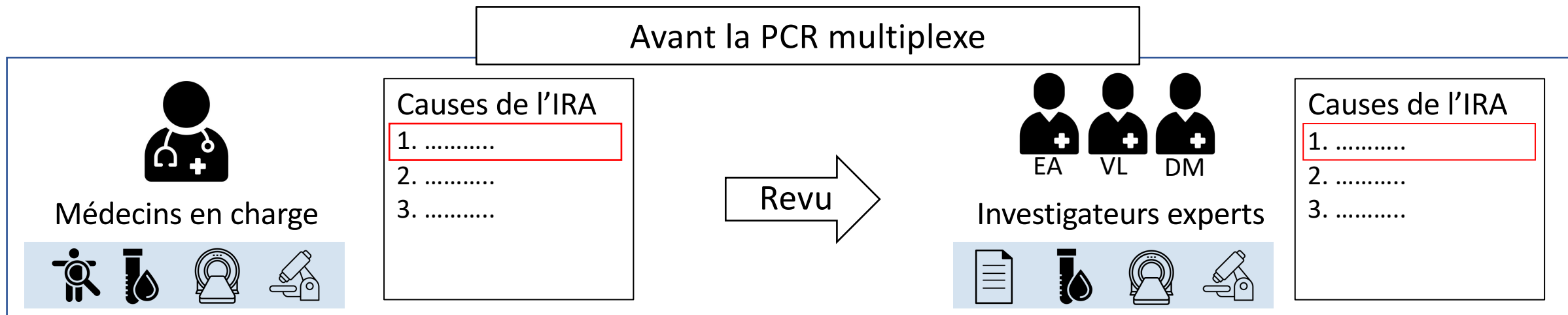
Pneumonie virale 6%

Pneumocystose 8%

OAP cardiogénique 4%

Non déterminé 12%

La détection du virus fournit-elle des informations sur l'étiologie de l'IRA ?



PCR multiplexe

Aucun virus

- ✓ Pneumonie bactérienne 41%
- ✓ Pneumonie virale 2%

Virus grippe-like

Influenza, RSV, hMPV, PIV

- ✓ Pneumonie bactérienne 39%
- ✓ Pneumonie virale 33%

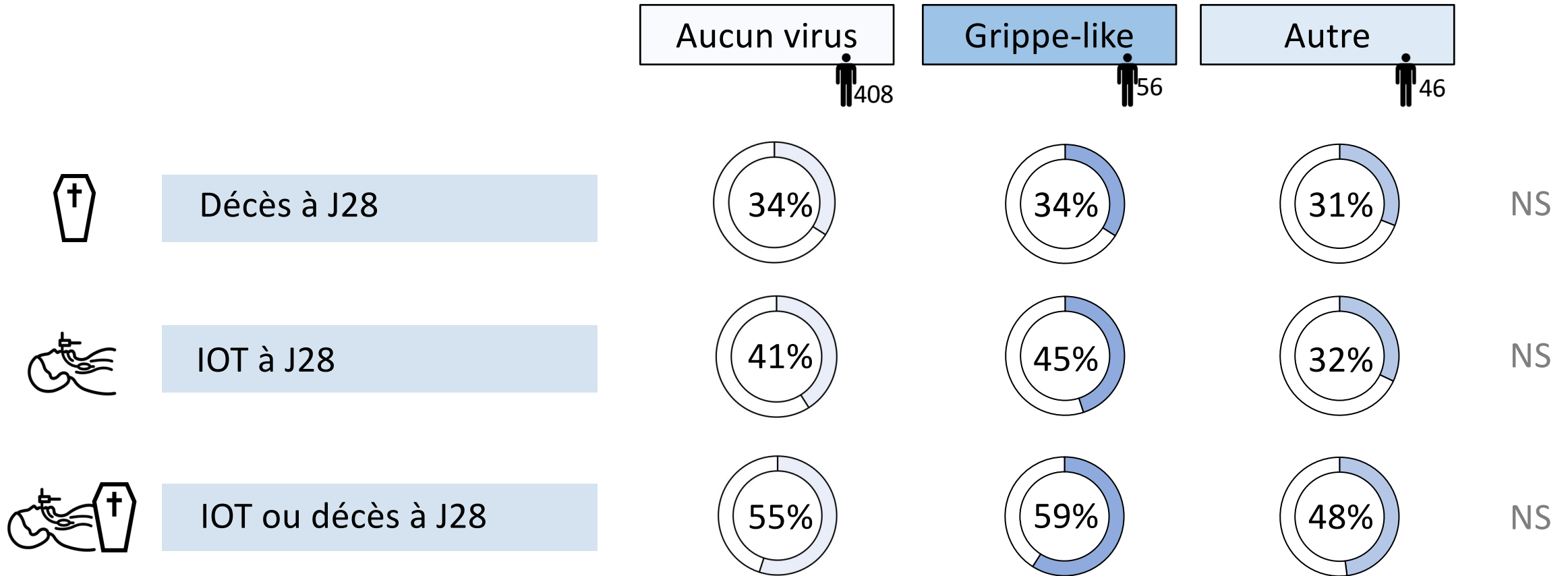
Autres virus

Rhinovirus, Coronavirus, ADV

- ✓ Pneumonie bactérienne 64%
- ✓ Pneumonie virale 7%

- Bacterial pneumonia
- Viral pneumonia
- P. jirovecii pneumonia
- IPA
- Infiltrative pneumonitis
- Extra-respiratory sepsis
- Cardiogenic APO
- Others
- Undetermined

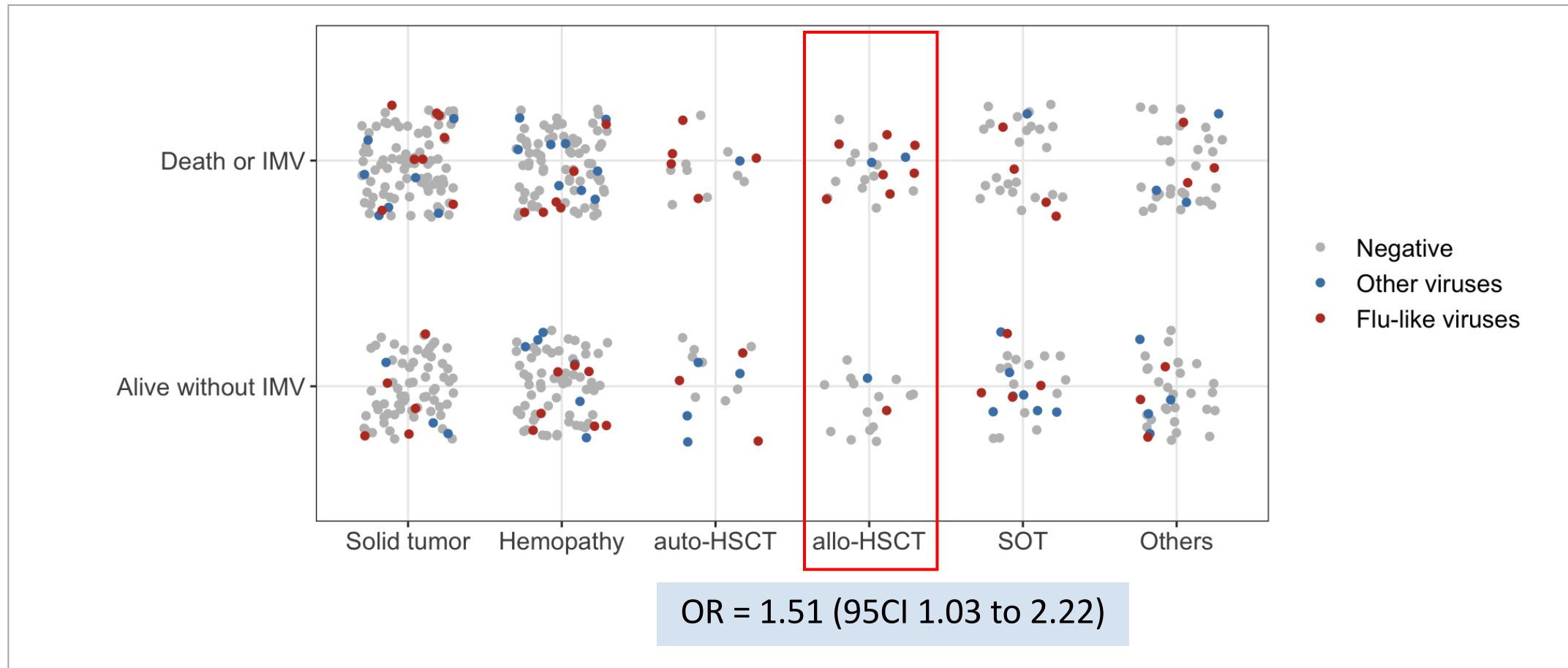
La détection du virus fournit-elle des informations sur le pronostic de l'IRA ?



Pas de différence de pronostic selon la détection de virus respiratoires

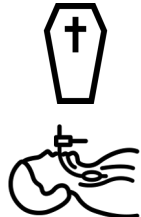
Analyse en sous-groupe planifiée selon le type d'immunodépression

Décès ou IOT à J28

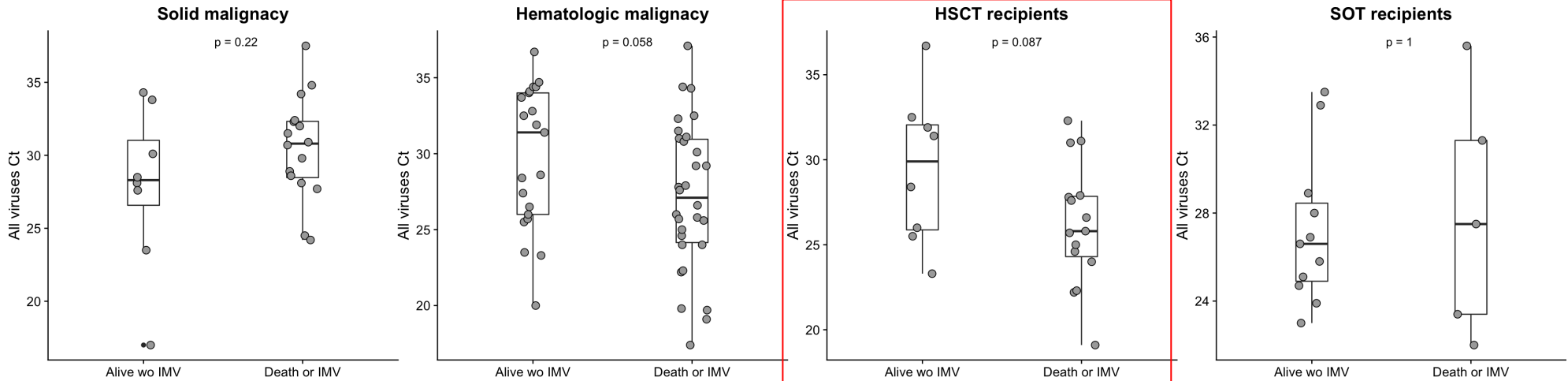


Association entre Ct et pronostic ?

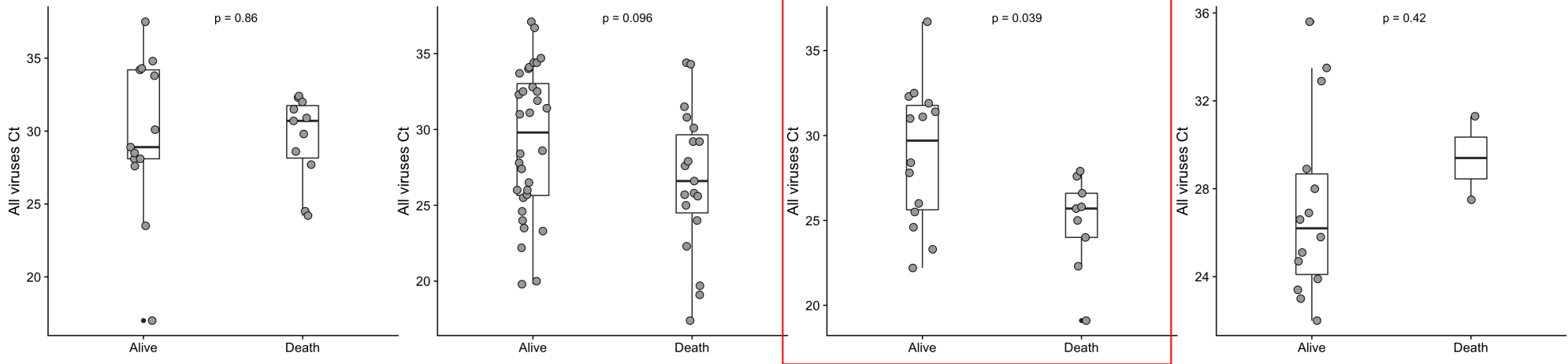
Pas de différence de pronostic en fonction des valeurs de Ct des virus respiratoires détectés



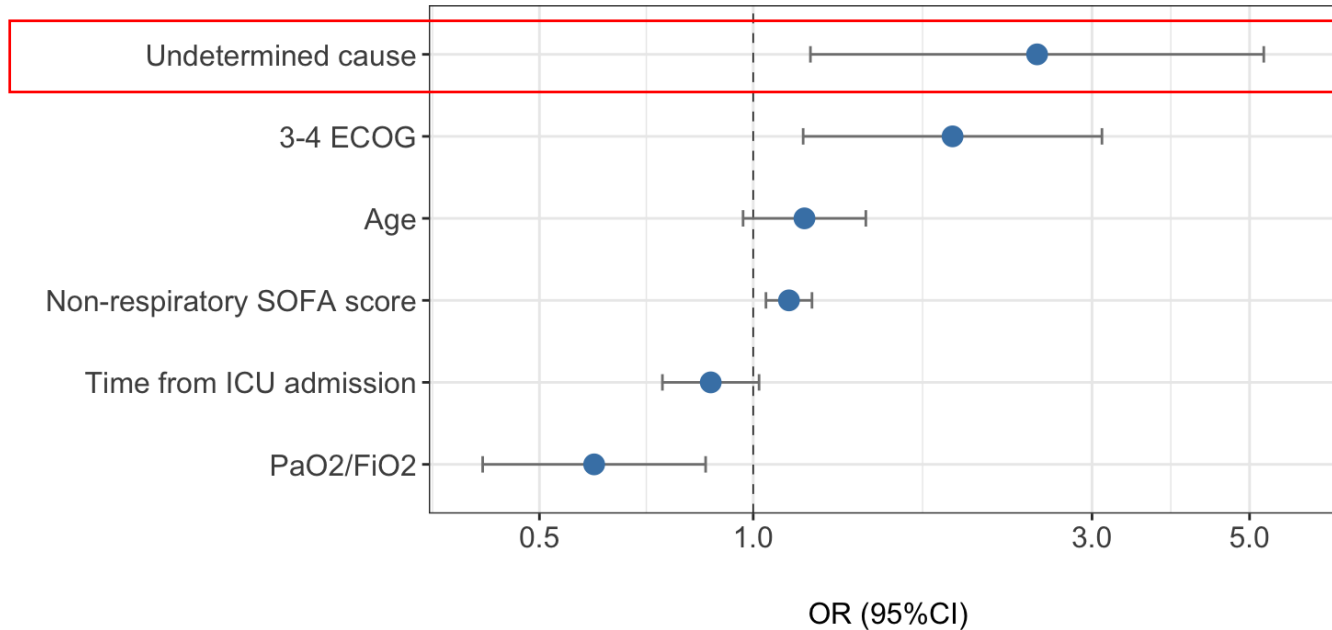
Décès ou IOT à J28



Décès à J28



Décès à J28



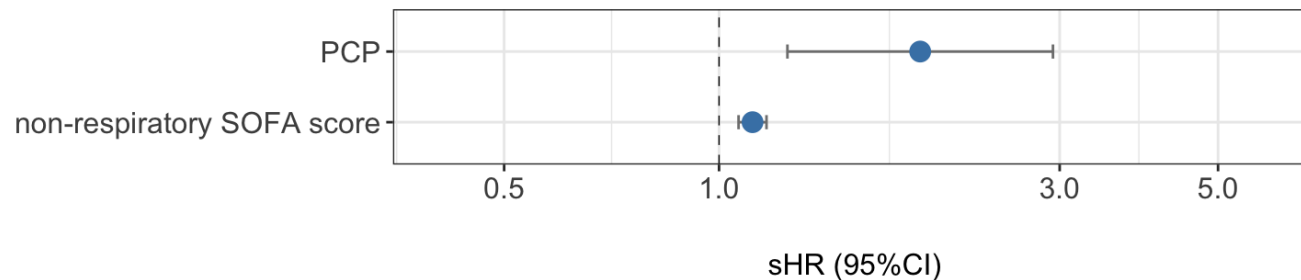
Cause indéterminée OR 2.5 (1.2 to 5.2)

PaO₂/FiO₂ (per 100) OR 0.7 (0.6 to 0.9)

SOFA-score OR 1.1 (1.0 to 1.2)

PS ≥ 3 OR 1.9 (1.2 to 3.1)

Ventilation mécanique invasive à J28



PCP sHR 1.9 (1.3 to 2.9)

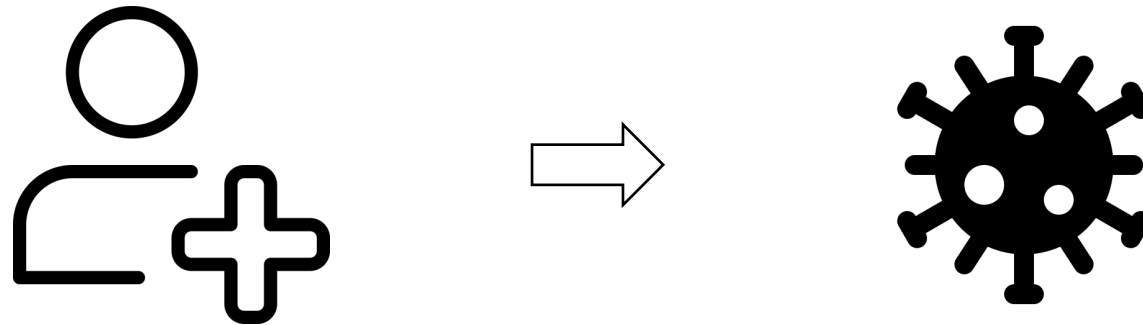
SOFA-score sHR 1.1 (1.1 to 1.17)

Take home messages

- ✓ Détection de virus respiratoire chez 1/5ème des IRA de l'immunodéprimé
- ✓ Pas d'association avec outcomes cliniques
- ✓ Association avec les causes d'insuffisance respiratoire
- ✓ Une cause indéterminée reste un facteur de risqué de mortalité

Pour mieux déterminer la signification des virus détectés : analyse de la réponse de l'hôte ?

Langelier PNAS 2018



Merci pour votre attention !

Nous remercions QIAGEN pour le don des cartouches QIAstat-Dx Respiratory SARS-CoV-2 Panel and le prêt d'un appareil QIAstat-Dx Rise instrument

Hôpital Saint-Louis, APHP, Paris

Réanimation: **Virginie Lemiale, Elie Azoulay**

Virologie: Mariame Barry, Séverine Mercier-Delarue,
Linda Feghoul, Maud Salmona, **Jérôme Le Goff**



**MINISTÈRE
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Réanimation : Anne-Sophie Moreau

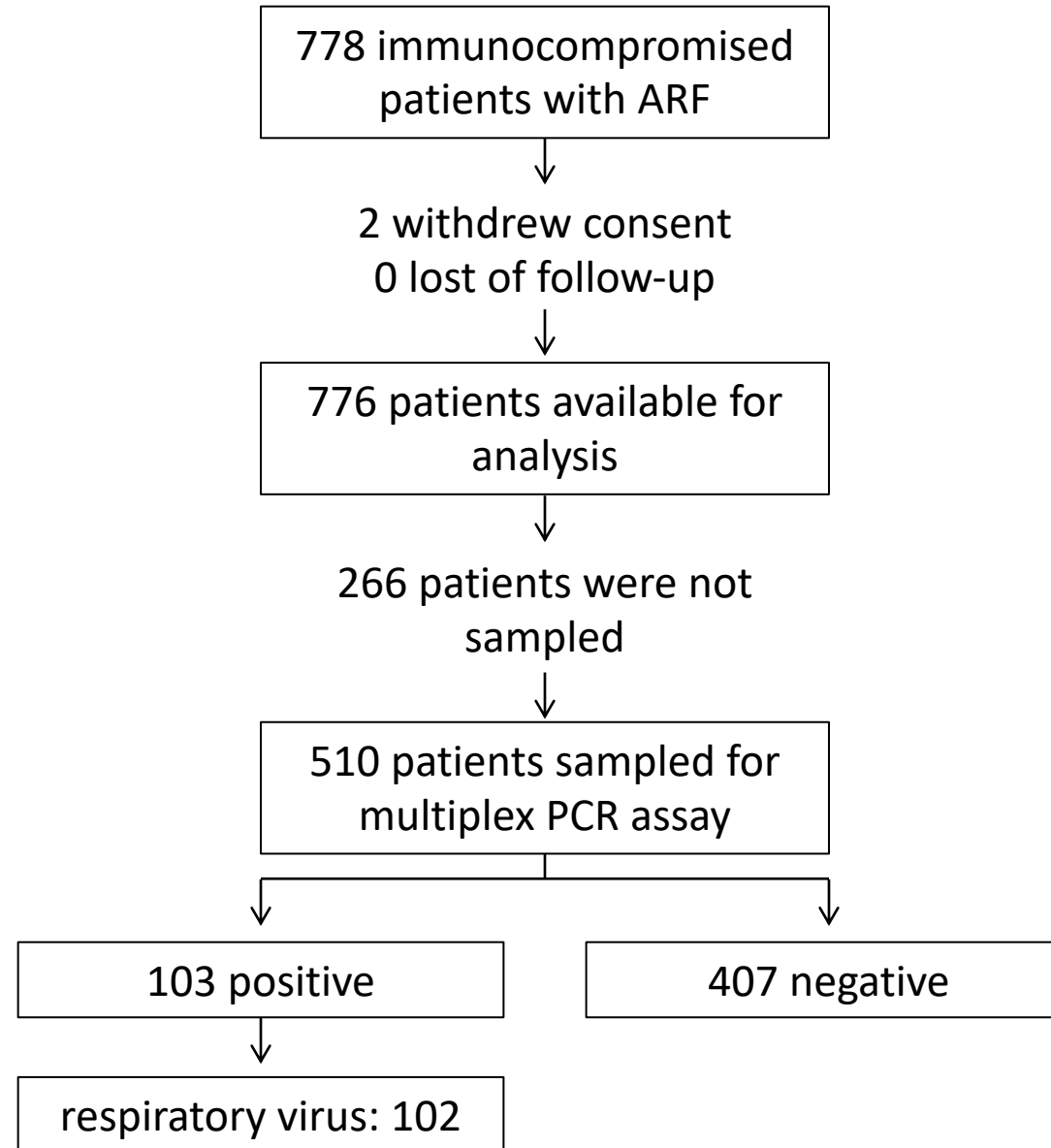
Hôtel-Dieu, Nantes

Réanimation : Emmanuel Canet

Hôpital Cochin, Paris

Réanimation : Frédéric Pène

Flow-chart





776 patients enrolled

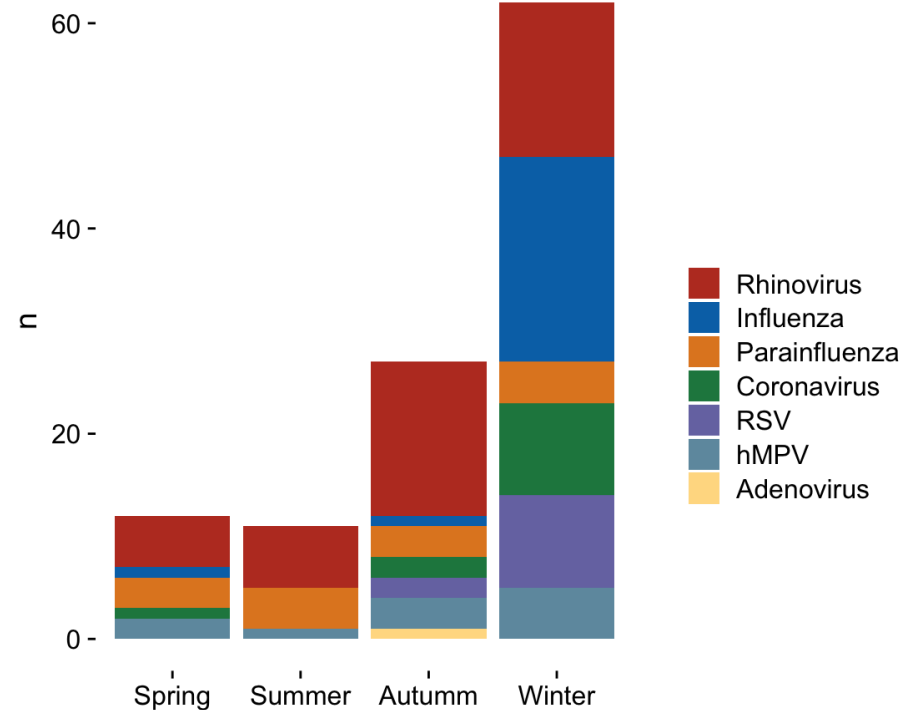


510 sampled patients

Positive in 103 (20%)
Respiratory virus in 102



Negative in 407 (80%)



Half viruses were detected in winter

Significant seasonal variation

- ✓ Influenza
- ✓ Coronavirus
- ✓ RSV

No significant seasonal variation for other viruses



776 patients enrolled

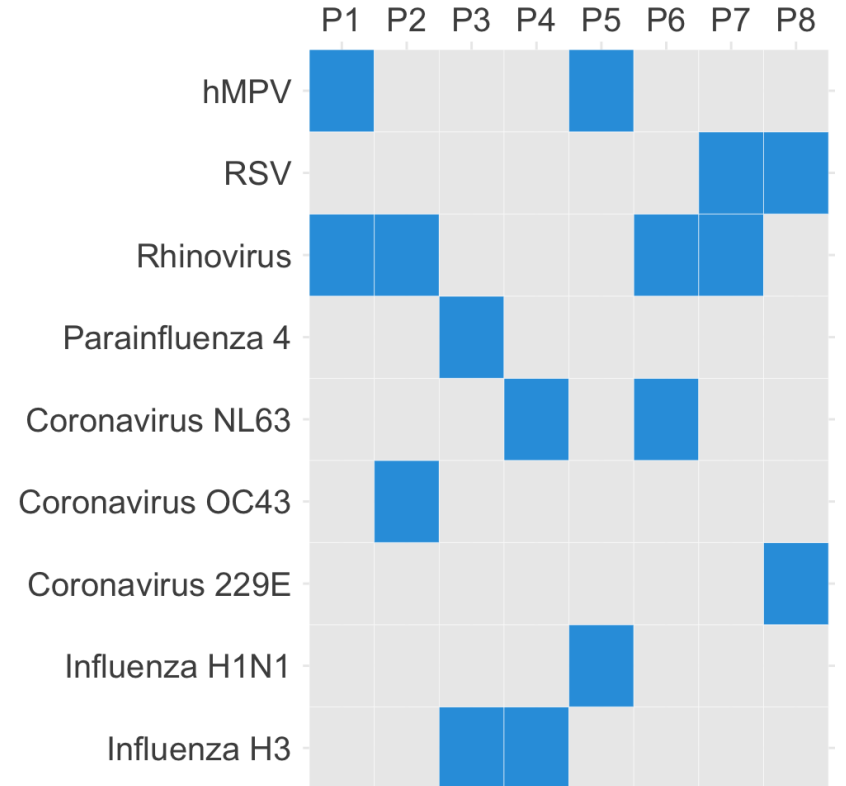
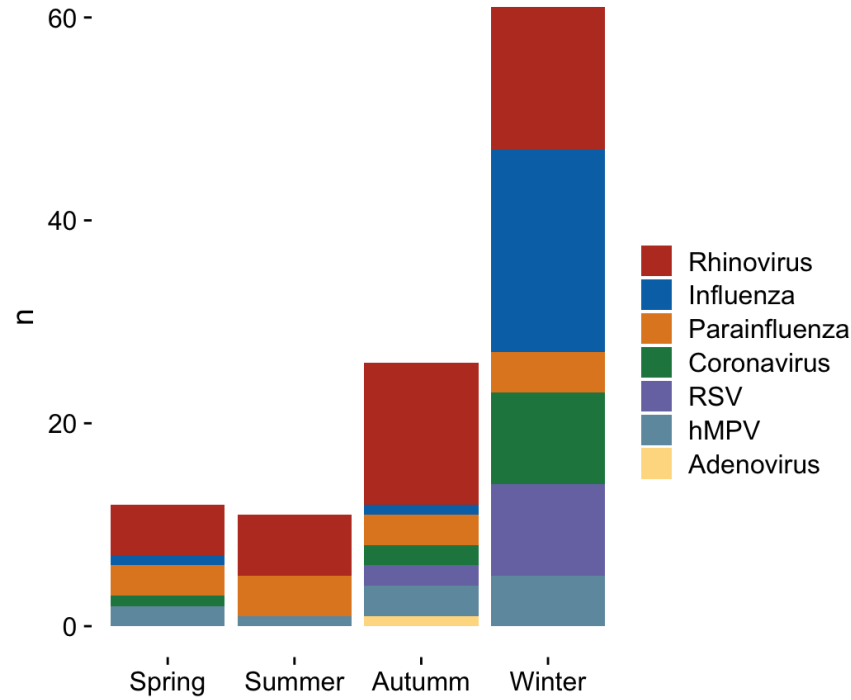
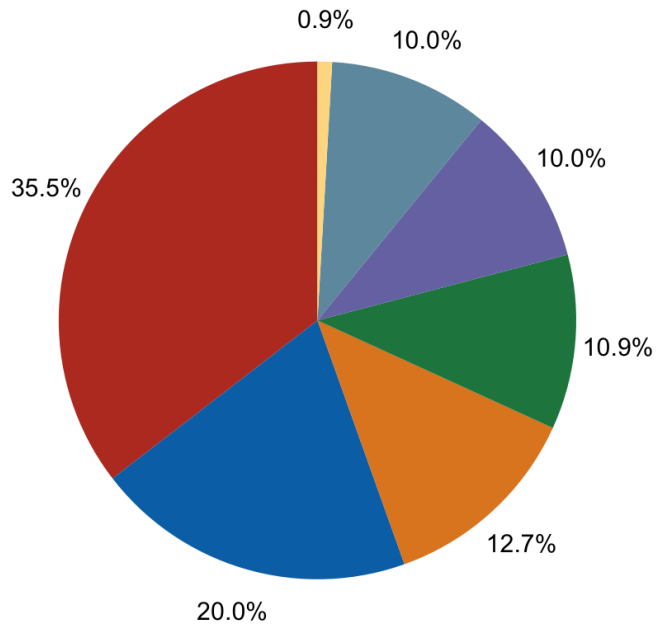


510 sampled patients

Positive in 103 (20%)
Respiratory virus in 102



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776 patients enrolled



510 sampled patients

Positive in 103 (20%)
Respiratory virus in 102



Negative in 407 (80%)

Age (year)	64 (54-74)	64 (57-71)	NS
Sex (female)	42%	31%	p < 0.05
Poor PS (3 or 4)	31%	45%	p < 0.05
Hematologic malignancy	52%	43%	NS
Solid tumor	24%	39%	p < 0.05
Solid organ transplant	16%	10%	NS
HSCT	36%	18%	p < 0.05



776 patients enrolled



510 sampled patients

Positive in 103 (20%)
Respiratory virus in 102



Negative in 407 (80%)

SOFA score	4 (1-6)	4 (1-6)	NS
Vasopressors	4%	12%	p < 0.05
Respiratory rates (/min)	33 (28-38)	32 (27-38)	NS
Oxygen flow (L/min)	10 (6-15)	10 (6-15)	NS
PaO ₂ /FiO ₂ ratio	125 (92-176)	117 (82-166)	NS

Clinical presentation

	No virus detected	Flu-like viruses	Other viruses	p-value
n	408	56	46	
Temperature	38.0 [37.0 - 39.0]	38.2 [37.4 - 38.8]	37.7 [37.0 - 38.2]	NS
Cough				NS
Dry	23%	29%	18%	
Productive	20%	34%	27%	
Purulent sputum	13%	18%	20%	NS
Rhinorrhea	1%	5%	0%	p < 0.05
Myalgia	2%	4%	4%	NS
Abdominal pain	10%	13%	2%	NS
Diarrhea	9%	13%	9%	NS
Time from the onset of respiratory symptoms (days)	1 [0-3]	1 [0-4]	1 [0-4]	NS

Detection of respiratory viruses hardly correlates with clinical presentation

CT scans



n=341 (67%)

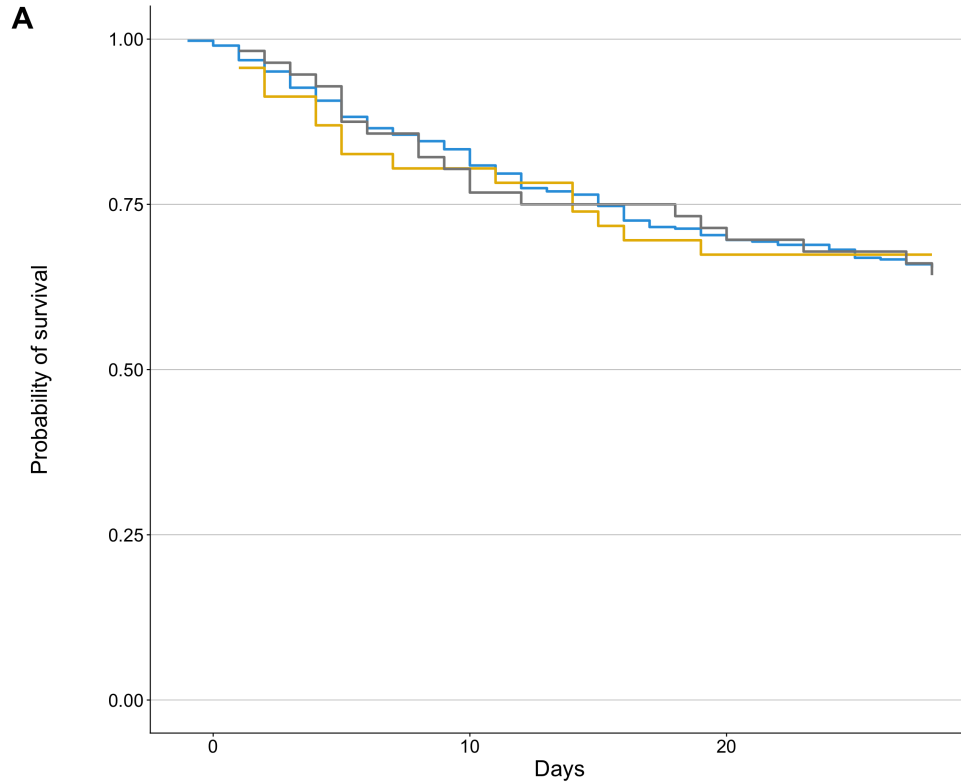
	No virus detected	Flu-like viruses	Other viruses	p-value
n	271	36	34	
Normal	12 (4.4)	2 (5.6)	2 (5.9)	NS
Ground-glass opacities				
Localized	53 (19.6)	8 (22.2)	9 (26.5)	NS
Diffuse	76 (28.0)	8 (22.2)	2 (5.9)	p < 0.05
Nodular opacities				
Centrilobular	18 (6.6)	5 (13.9)	2 (5.9)	NS
Peri-bronchovascular	11 (4.1)	2 (5.6)	2 (5.9)	NS
Subpleural	16 (5.9)	1 (2.8)	1 (2.9)	NS
Alveolar condensations				
Localized	79 (29.2)	14 (38.9)	12 (35.3)	NS
Diffuse	38 (14.0)	5 (13.9)	6 (17.6)	NS
Interlobular septal thickening	46 (17.0)	5 (13.9)	8 (23.5)	NS
Pleural effusion	124 (45.8)	11 (30.6)	16 (47.1)	NS
Bronchia wall thickening	32 (11.8)	4 (11.1)	5 (14.7)	NS

Detection of respiratory viruses hardly correlates with radiological presentation

Association between detected respiratory virus and outcomes



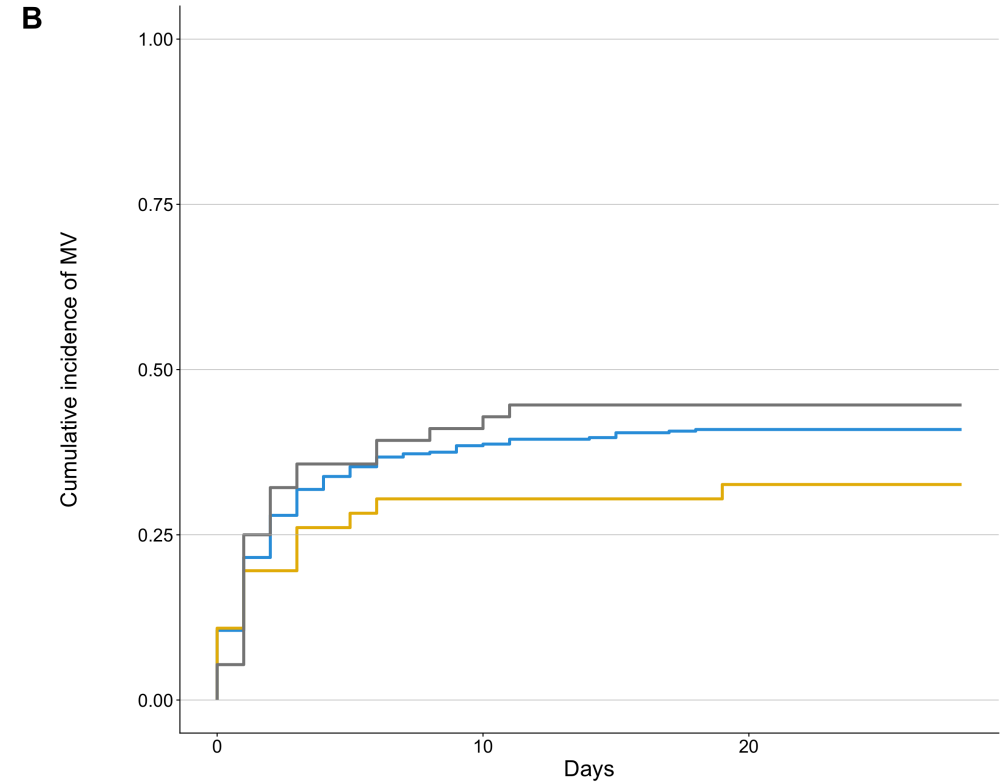
Death on Day 28



	Number at risk			
	0	7	14	21
Negative Qiastat	407	340	287	0
Other viruses	46	37	31	0
Flu-like viruses	56	45	40	0



IMV on Day 28



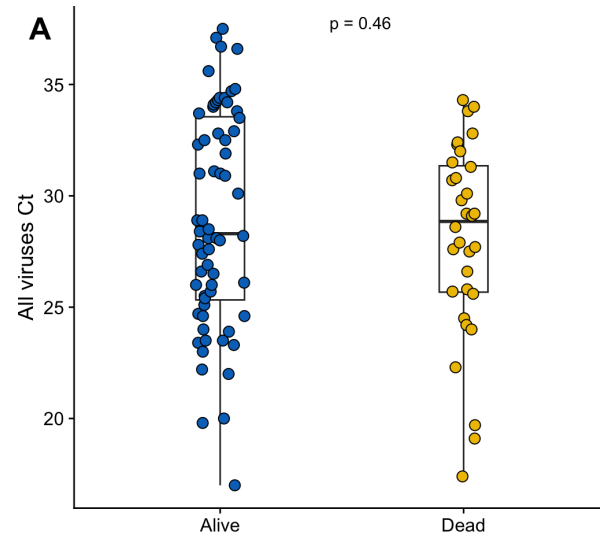
	Number at risk			
	0	7	14	21
Negative Qiastat	407	218	195	0
Other viruses	46	28	23	0
Flu-like viruses	56	29	24	0

Association between Ct values and outcomes

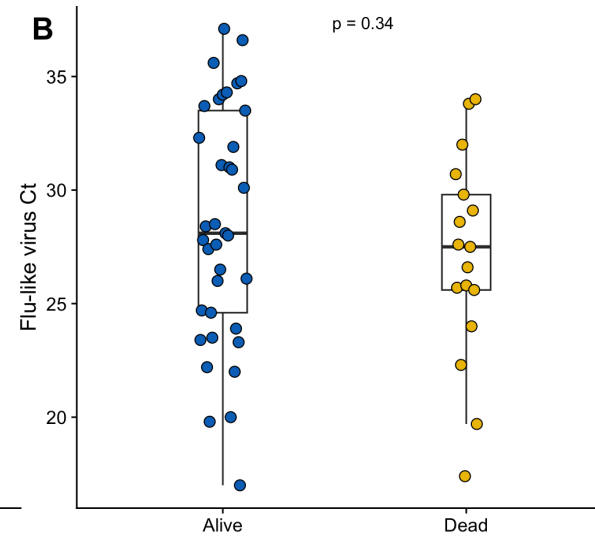


Death on Day 28

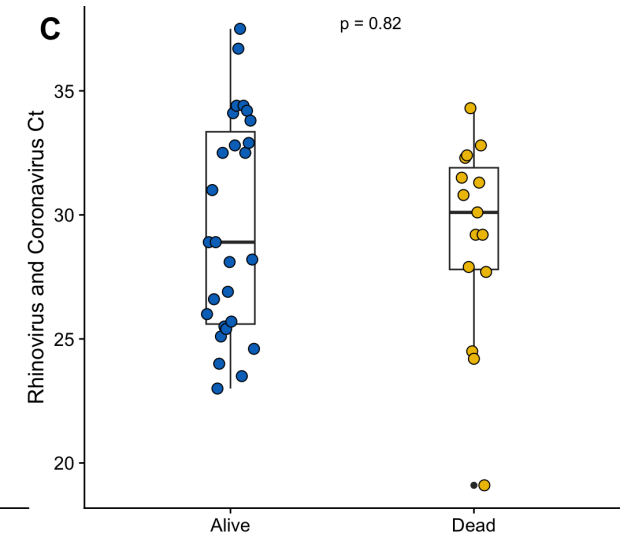
All viruses



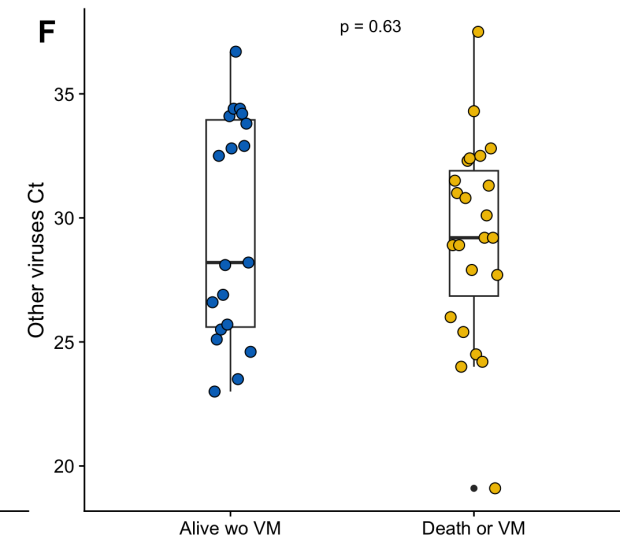
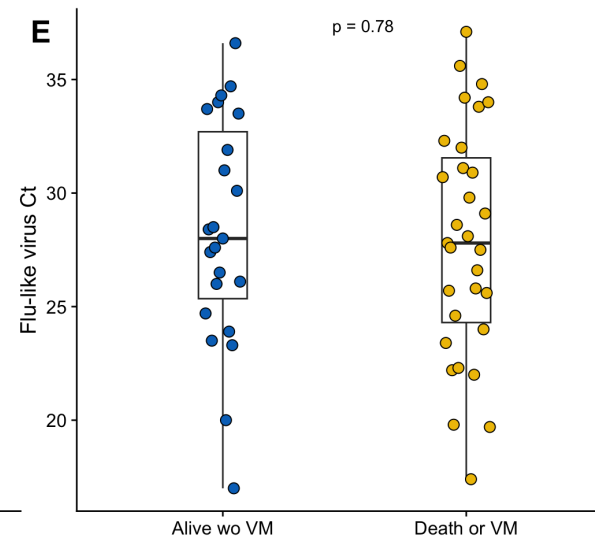
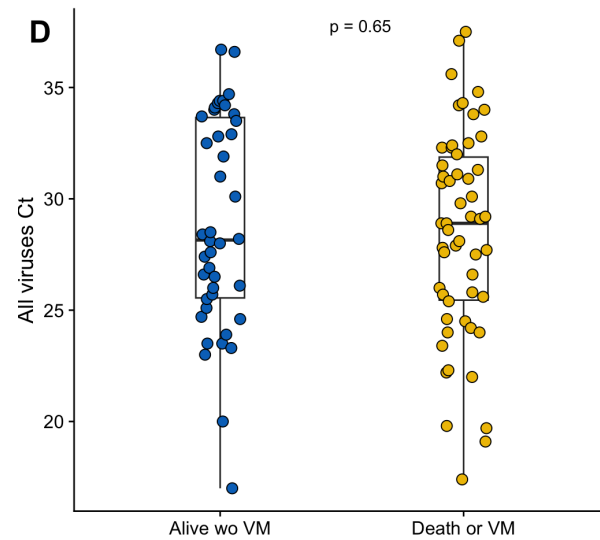
Flu-like viruses



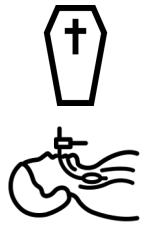
Other viruses



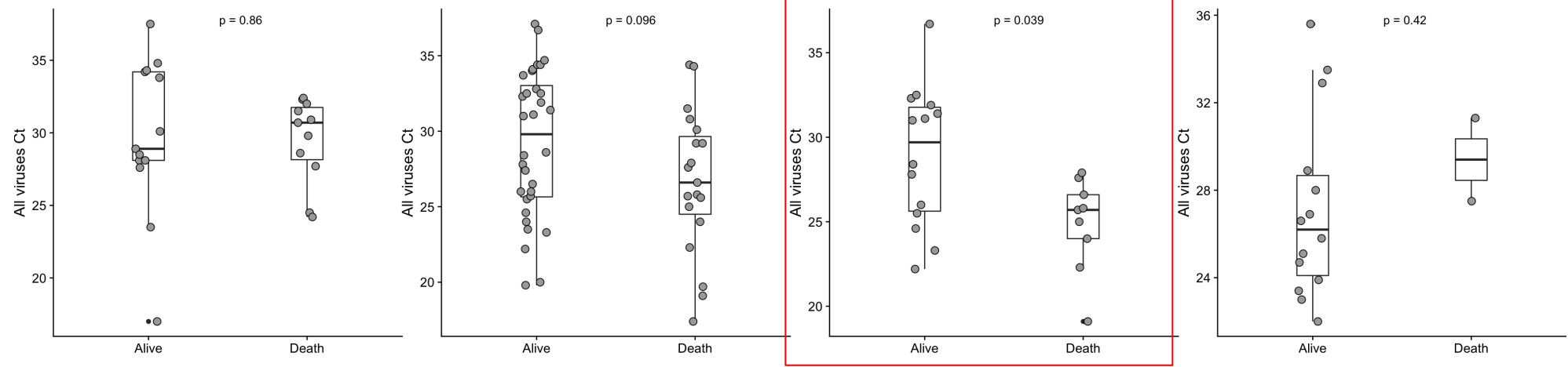
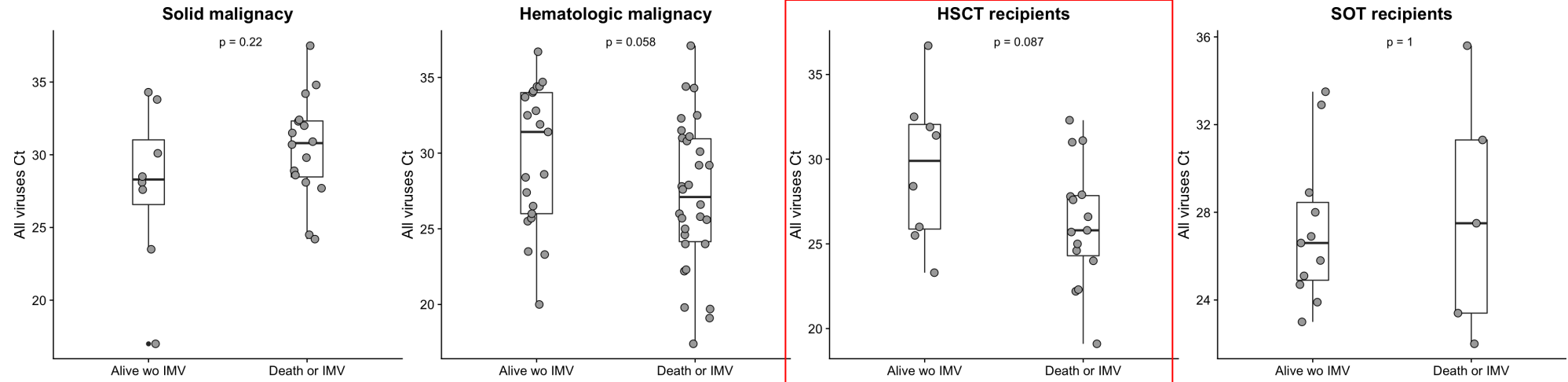
IMV on Day 28



Association between Ct values and outcomes



IMV or
death on
Day 28



Death on
Day 28

	Overall	No virus detected	Flu-like viruses	Other viruses	p-value
n	510	408	56	46	
Infectious					
Bacterial pneumonia					
Microbiologically documented	149 (30.3)	118 (29.9)	14 (25.9)	17 (39.5)	0.325
Clinically documented	82 (16.7)	60 (15.2)	11 (20.4)	11 (25.6)	0.167
Viral pneumonia	48 (9.8)	14 (3.6)	27 (50.0)	7 (16.3)	<0.001
Opportunistic infections					
Pneumocystis jirovecii pneumonia	45 (9.2)	38 (9.6)	3 (5.6)	4 (9.3)	0.620
Invasive aspergillosis	20 (4.1)	16 (4.1)	4 (7.4)	0 (0.0)	0.186
Other opportunistic infection	5 (1.0)	4 (1.0)	0 (0.0)	1 (2.6)	0.537
Noninfectious lung involvement					
Specific infiltrative pneumonitis	59 (12.0)	55 (14.0)	0 (0.0)	4 (9.3)	0.011
Drug related pneumonitis	9 (1.8)	9 (2.3)	0 (0.0)	0 (0.0)	0.324
Cardiogenic pulmonary edema	22 (4.5)	18 (4.6)	3 (5.6)	1 (2.3)	0.734
Pulmonary embolism	12 (2.4)	12 (3.0)	0 (0.0)	0 (0.0)	0.220
Other causes	10 (2.0)	9 (2.3)	1 (1.9)	0 (0.0)	0.599
Extra-respiratory sepsis	47 (9.6)	43 (10.9)	4 (7.4)	0 (0.0)	0.059
Undetermined	61 (12.4)	53 (13.5)	5 (9.3)	3 (7.0)	0.358
More than one cause	73 (14.9)	51 (12.9)	17 (31.5)	5 (11.6)	0.001

	Overall	No virus detected	Flu-like viruses	Other viruses	p-value
n	510	408	56	46	
Interventions (until day 28)					
Chemotherapy	75 (14.7)	65 (15.9)	2 (3.6)	8 (17.4)	0.043
Anti-infectious therapies					
Antibacterial therapy	462 (94.9)	368 (94.8)	51 (92.7)	43 (97.7)	0.533
Antiviral therapy	152 (29.8)	104 (25.5)	31 (55.4)	17 (37.0)	<0.001
Antifungal therapy	169 (33.1)	140 (34.3)	18 (32.1)	11 (23.9)	0.359
Other therapies					
Corticosteroid boluses	161 (33.0)	132 (33.8)	16 (29.6)	13 (30.2)	0.768
Diuretics	225 (44.1)	172 (42.2)	31 (55.4)	22 (47.8)	0.152
Vasoactive drugs	239 (48.9)	193 (49.6)	27 (49.1)	19 (42.2)	0.643
Life-supporting interventions (until day 28)					
Invasive mechanical ventilation	207 (40.7)	167 (41.1)	25 (44.6)	15 (32.6)	0.441
Renal-replacement therapy	82 (16.9)	69 (17.9)	8 (14.5)	5 (11.1)	0.460
Prone positioning	43 (8.8)	31 (7.9)	8 (14.8)	4 (8.9)	0.245
Outcomes					
Death at day 28	174 (34.3)	140 (34.5)	19 (33.9)	15 (32.6)	0.967
Death or mechanical ventilation at day 28	279 (54.7)	223 (54.7)	33 (58.9)	23 (50.0)	0.665
ICU mortality	149 (29.2)	123 (30.1)	14 (25.0)	12 (26.1)	0.647
Hospital mortality	200 (39.4)	161 (39.6)	20 (35.7)	19 (42.2)	0.789

Limitations

- ✓ 266 patients out of 776 (34%) were not sampled
- ✓ Diagnostic and therapeutic strategies were not standardized
 - ⇒ Etiological diagnoses were reviewed by 3 expert investigators
- ✓ Before COVID-19 pandemic
- ✓ Observational design

Take home

- ✓ Respiratory virus detected in 1/5 immunocompromised patients ARF
- ✓ No association with clinical outcome
- ✓ Association with ARF aetiologies
- ✓ Undetermined aetiologies remained associated with increased mortality

Better understand the significance of viral detection: host transcriptional response?