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Reduction of post COVID-19 condition during the Omicron wave: results from the EuCARE POSTCOVID Study

Francesca Bai[1], Alessandro Cozzi-Lepri[2], Pontus Hedberg[3], Andrea Santoro[1*], Maria Francesca Greco[1], Matteo Sala[1], Julia Fonseca de Morais Caporali[4], Carolina Coimbra Marinho[4], Maria Mercedes Santoro[5], Francesca Ceccherini Silberstein[5], Dovile Juozapaite[6], Edita Strumiliene[7], André Almeida[8], Cristina Toscano[9], Jesus Arturo Ruiz Quinones[10], Chiara Mommo[11], Iuri Fanti[11], Francesca Incardona[11,12], Giulia Marchetti[1] **on behalf of the EuCARE Project**

Affiliations: 1 Clinic of Infectious Diseases, San Paolo Hospital, ASST Santi Paolo e Carlo, University of Milan, Italy; 2 Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, UCL, London, UK; 3 Division of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden; 4 Brazil School of Medicine, Federal University of Minas Gerais, Brazil; 5 Department of Experimental Medicine, University of Rome Tor Vergata, Roma, Lazio, Italy; 6 Vilnius Santaros Klinikos Biobank, Vilnius University Hospital Santaros Klinikos; 7 Clinic of Infectious Diseases and Dermatovenerology, Institute of Clinical Medicine, Medical Faculty, Vilnius University; 8 Centro Universitário de Lisboa Central, Centro Clínico Académico de Lisboa, Lisboa; 9 Centro Hospitalar de Lisboa Ocidental, Lisboa; 10 Hospital Juan Graham Casasus, Villahermosa, Tab, Mexico; 11 EuResist Network, Rome, Italy; 12 IPRO-InformaPRO S.R.L., Rome, Italy - *Presenting author

francesca.bai@asst-santipaolocarlo.it

Background **Post COVID-19 condition** (PCC) has been defined as ongoing symptoms at ≥4 weeks after acute COVID-19. **A reduction of cases is being observed following Omicron infection** compared to what was seen with previous variants. We investigated the risk of PCC and PCC clusters in a cohort of hospitalized patients according to viral variants.

Methods We included hospitalized patients in 6 centers (01/2020-06/2023); a subset of patients with ≥1 visit over the year after clinical recovery were analyzed. Viral variants were observed or estimated by mapping with GISAID data.

Because patients returning for a post-COVID-19 visit may have a higher risk of having PCC and variant could be associated with the probability of returning, we used **weighted logistic regressions** to control for collider bias; the weights were constructed as the inverse of the propensity score of returning using a logistic model, adjusting for confounders.

We estimated the proportion of the effect of wild-type (WT) virus *vs* Omicron on the PCC risk, which might be mediated by Intensive Care Unit (ICU) admission/Mechanical Ventilation (MV) by a counterfactual mediation analysis.

Results 1313/7248 (18.1%) hospitalized patients returned for a post-COVID visit at a median of 2.6 (IQR 1.84-3.97) months after clinical recovery.

Figure 1 Viral variants

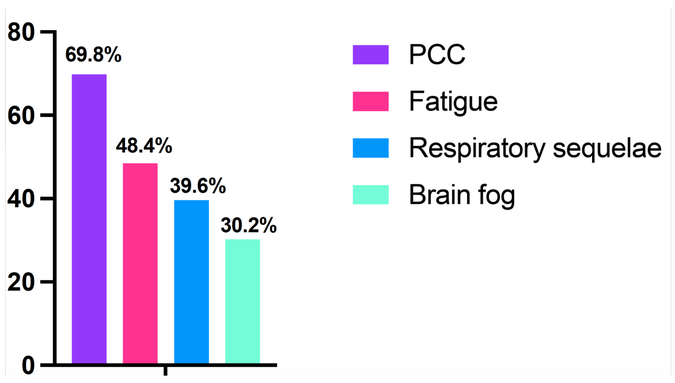

Figure 2 PCC and main clusters

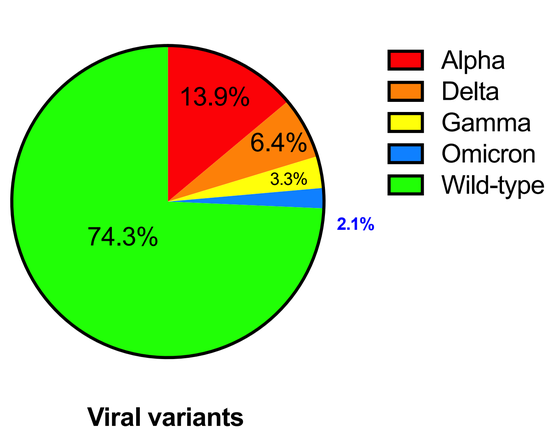

Table 1 Characteristics of the study population according to viral variants

VoC	WT virus N 975	Alpha N 183	Delta N 84	Gamma N 44	Omicron N 27	p values
Age, median (IQR)	59 (50, 68)	59 (51, 69)	58 (48, 73)	57(47, 65)	77 (69, 84)	<0.001
Female, n (%)	397 (40.7%)	74 (40.4%)	39 (46.4%)	28. (63.6%)	11 (40.7%)	0.041
Italian, n (%)	362 (37.1%)	122 (66.7%)	26 (31%)	0 (0%)	20 (74.1%)	<0.001
Comorbidities, n (%)	595 (61%)	96 (52.5%)	54 (64.3%)	34 (77.3%)	21 (77.8%)	0.007
Vaccination, 2+ doses,n (%)	0 (0%)	0 (0%)	27 (32.5%)	0 (0%)	5 (31.3%)	<0.001

LEGEND: Categorical variables are presented as absolute n, percentages, quantitative variables as median, interquartile range. Chi-square and Kruskal Wallis test for comparison.

Omicron variant *vs* WT was associated with a reduced risk of PCC; conversely, we observed a higher risk with Delta and Alpha variant vs WT (Table 2). Similar results were observed using PCC clusters as outcomes.

Table 2 Odds ratios of PCC by fitting logistic regression models

VoC	Unadjusted		Adjusted	
	OR (95% CI)	p	OR (95% CI)	p
	Unweighted analysis			
WT	1		1	
Alpha	1.18 (0.83-1.68)	0.352	1.23 (0.86-1.76)	0.258
Delta	1.42 (0.85-2.39)	0.184	1.35 (0.79-2.28)	0.270
Gamma	2.00 (0.92-4.35)	0.081	1.67 (0.76-3.69)	0.204
Omicron	0.22 (0.10-0.50)	<0.001	0.17 (0.07-0.40)	<0.001
	Analysis weighted for VoC and demographics			
WT	1		1	
Alpha	1.14 (0.98-1.31)	0.087	1.17 (1.01-1.35)	0.042
Delta	1.46 (1.22-1.75)	<0.001	1.39 (1.16-1.67)	<0.001
Gamma	1.94. (1.19-3.17)	0.008	1.65 (1.01-2.71)	0.047
Omicron	0.21 (0.17-0.25)	<0.001	0.17 (0.14-0.21)	<0.001
	Analysis weighted for VoC, demographics and CRP			
WT	1		1	
Alpha	1.32 (1.10-1.58)	0.002	1.33 (1.10-1.59)	0.003
Delta	1.44 (1.17-1.76)	<0.001	1.29 (1.05-1.60)	0.017
Gamma	1.90 (0.91-3.95)	0.085	1.68 (0.80-3.56)	0.172
Omicron	0.15 (0.13-0.18)	<0.001	0.10 (0.09-0.13)	<0.001

LEGEND: VoC, variant of concern; OR, odd ratio; CI, confidence interval. *Multivariable analysis is adjusted for age, gender, comorbidities. Unweighted analysis; model 1: weighted analysis for demographic characteristics, VoC; model 2: weighted analysis for demographic characteristics, VoC, C reactive protein (CRP).

The mediation analysis showed that **41.7%** (IC95% 14.0-69.5%) **of the total effect of WT virus *vs* Omicron variant on the PCC risk was mediated by ICU and MV** (*vs.* no oxygen therapy). However, almost zero proportion (0, 0-4.5%) of the effect of WT strain *vs.* Omicron variant on the PCC risk was explained by cPAP or NIV (*vs.* no oxygen). The same analysis was conducted using brain fog as the outcome and we found that only a small proportion of the effect of variant on PCC was caused by disease severity (Table 3).

Table 3 Odds ratios of PCC by fitting logistic regression models

	WT vs. Omicron four-way Decomposition-binary outcome PCC, admission in MV-ICU as the mediator		
Component	Excess RR (95% CI)	Proportion Attributable (95% CI)	p value
CDE[1]	3.41 (-1.53, 8.34)	74.8 (53.6, 95.9)	<0.001
INT-ref[2]	-0.75 (-2.18, 0.67)	-16.5 (-36.2, 3.2)	0.100
INT-med[3]	1.65 (-0.79, 4.10)	36.3 (15.0, 57.6)	<0.001
PIE[4]	0.25 (-0.05, 0.55)	5.4 (-3.4, 14.3)	0.228
TERR[5]	4.56 (-1.48, 10.60)	100.0	
ORTE[6]	5.56 (1.00, 11.60)		
Overall proportion due to Interaction		19.8 (5.1, 34.4)	
Overall proportion due to Mediation		**41.7 (14.0, 69.5)**	

LEGEND: 1. Controlled Direct Effect (neither mediation not interaction); 2. Reference Interaction (interaction but not mediation); 3. Mediated Interaction (both mediation and interaction); 4. Pure Indirect Effect (mediation but no interaction); 5. Total excess relative risk; 6. Odds ratio total effect. Model adjusted for age, sex and comorbidities.

Conclusions

Most common phenotypes of PCC are **fatigue**, **respiratory sequelae** and **brain fog**. **A reduced risk of PCC was observed following Omicron infection** compared to WT virus, suggesting a possible reduction of the burden of PCC over time. A large proportion of the effect of WT virus compared to Omicron variant on PCC risk appeared to be mediated by an **increased disease severity during the acute phase**.

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