Impact of Variants of Concern and Vaccination on Long COVID phenotype

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Background

- A significant number of individuals experience prolonged recovery from COVID-19[1,2]
- The term long COVID has been coined by individuals experiencing this condition, but this is used to describe heterogeneous symptoms and clinical presentations
- Clinical definitions vary and diagnostic criteria are suboptimal, particularly in terms of selecting individuals for inclusion in therapeutic trials or translational studies that may only benefit certain phenotypes
- Both infecting VOC and vaccination have been reported to impact on long COVID symptoms[3], but the impact on long COVID phenotype has not been reported.

Methods

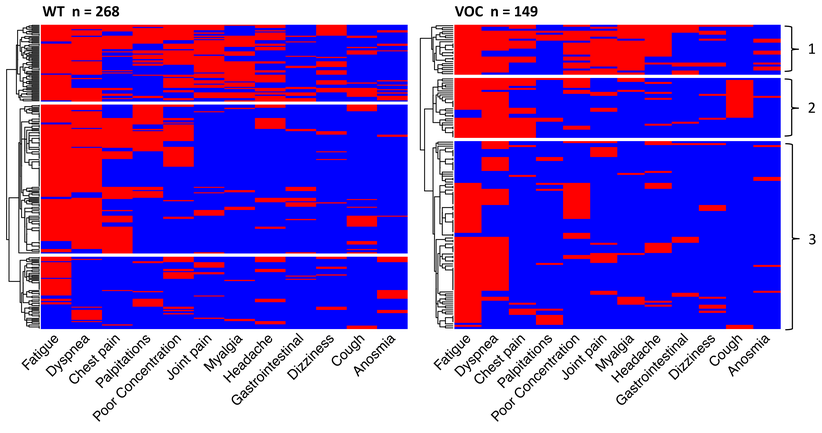
- **Design:** We selected participants for the All Ireland Infectious Diseases Cohort study, a prospective, multicentre cohort study that recruits individuals with infectious diseases related issues attending participating hospitals in Ireland.
- **Population:** Individuals with PCR confirmed COVID-19 still symptomatic >4 weeks post acute onset of symptoms
- **Variables:**
  - Demographics including age, sex, ethnicity and World Health Organisation acute disease severity
  - 12 symptoms – Fatigue, shortness of breath, chest pain, palpitations, poor concentration, joint pain, myalgia, GI symptoms, dizziness, cough and anosmia
  - Vaccination status – pre COVID or in the post acute period
  - Timing of acute SARS-CoV-2 which was mapped to one of two time periods:
    - WT – acute infection prior to 26th December 2020 – when the alpha variant became dominant in Ireland
    - VOC - acute infection after 26th December 2020 – the introduction of alpha and subsequent variants
- **Statistical analysis:**
- Data are presented as median (interquartile range) or number (%)
- We used multiple correspondence analysis (MCA) and unsupervised hierarchical clustering with k-means consolidation to derive symptom clusters in WT and VOC periods
- We compared quantitative and qualitative variables between groups using Kruskal Wallis and Chi square test
- We used univariable and multivariable logistic regression to explore the relationship between participant characteristics and the presence of individual symptoms

Results

- Between March 2020 & March 2022, we included 419 individuals for analysis
- MCA and cluster analysis demonstrated 3 distinct clusters which were similar across time periods. Demographics of the two time periods are shown in Table 1.

	WT (n = 268)	VOC (n = 149)	P value
Age	43 (36-54)	47 (34-57)	0.2
Female sex	196 (73)	109 (73)	0.9
Caucasian ethnicity	222 (84)	129 (87)	0.31
BMI	28 (24 – 32)	28 (24 – 33)	0.6
Healthcare worker	163 (61)	51 (35)	<0.001
Smoking	12 (4.5)	7 (4.7)	0.9
Alcohol	80 (30)	45 (30)	0.9
Comorbidity	152 (59)	89 (60)	0.9
Vaccination			
Pre COVID	0 (0)	15 (11)	<0.001
Post COVID pre review	60 (25)	97 (75)	<0.001
Time from symptom onset (weeks)	24 (16-38)	18 (10-31)	<0.001
Mild initial disease severity	217 (83)	112 (75)	0.07
Hospitalised during acute illness	75 (28)	54 (36)	0.11

➢ Heatmap demonstrating the differences in biomarkers between clusters



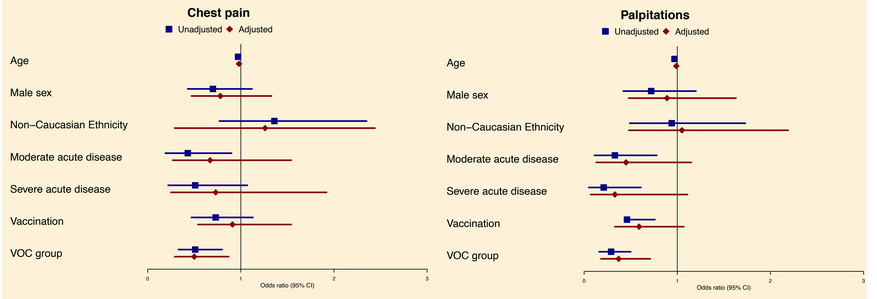
- **Cluster 1 – Musculoskeletal.** Characterised by joint pain and myalgia
- **Cluster 2 – Cardiorespiratory.** Characterised by shortness of breath, chest pain, cough or palpitations
- **Cluster 3 – Less symptomatic.** Fatigue and shortness of breath were the most common symptoms in this cluster but these were less prevalent than in the musculoskeletal or cardiorespiratory cluster

Results

- While similar symptom clusters were seen across periods, differences in characteristic symptoms were only seen in the cardiorespiratory cluster
- In the cardiorespiratory cluster, there was a decrease in the frequency of palpitations (10% vs 34% p = 0.008) and an increase in in the frequency of cough (63% vs 17% p<0.001) in the VOC compared to WT groups

➢ Change in symptoms across period of infection

- Given the change in characteristic symptoms in the cardiorespiratory cluster, we compared the frequency of all symptoms across the full cohort during WT and VOC periods to determine if an overall change in symptom frequency was mediating this difference.
- There were significant differences only in the frequency of palpitations (32% vs 12% in the WT vs VOC groups p < 0.0001) and chest pain (39% vs 25% p = 0.004) but not cough (16% vs 15% p= 0.9), or any other symptom.
- In univariate analysis, age, more severe acute disease and being in the VOC group were significantly associated with reduced odds of both palpitations or chest pain while being vaccinated was additionally associated with reduced odds of palpitations (OR (95% CI) 0.46 (0.28-0.76) p = 0.003).
- In adjusted analysis increasing age (0.98 (0.96-0.99) p = 0.02) and being in the VOC group (0.5 (0.29-0.87), p = 0.02) remained significantly associated with a lower odds of chest pain
- Only being in the VOC group (0.37 (0.18-0.71), p = 0.004) but not vaccination (0.59 (0.33-1.04) p = 0.08), was associated with less reported palpitations.



**Multivariate model adjusted for age, sex, ethnicity, BMI, hypertension, diabetes, immunosuppression, smoking and baseline anticoagulant use.*

Conclusions

- **This analysis demonstrates three clinical phenotypes of long COVID, observed across two distinct time periods**
- **Changes in long COVID phenotype in individuals infected later in the pandemic were observed, with less palpitations and chest pain reported**
- **Adjusted analyses suggest that these effects are mediated through introduction of variants rather than an effect from vaccination.**

References & Acknowledgments

[1]Menges D et al. PLoS One. 2021, [2]Logue J et al. JAMA Netw Open. 2021, [3]Canas et al. MedRxiv. 2022

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