IDENTIFICATION OF CLINICAL FEATURES ASSOCIATED WITH SARS-COV-2 REINFECTIONS

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BACKGROUND

Over 600 millions of COVID-19 cases have been reported. A remarkable fragment of these cases are reinfections, which are mostly explained by the genomic variability of the SARS-CoV-2 variants. However, little is known about other factors fostering these reinfections.

OBJECTIVE

To identify possible clinical and demographical features associated with SARS-CoV-2 reinfections and to investigate their potential implications for disease severity.

METHODS

- Clinical and demographic data from individuals (N = 3303, March 2020 – March 2022) with at least 2 PCR+ events separated by ≥90 were selected from the sample bank of the Microbiology Department (Germans Trias i Pujol Hospital, Badalona, Spain) (Table 1).
- Data collected included: age, sex, comorbidities, adjusted morbidity group, hospitalization, symptomatology, NAAT (PCR and TMA) tests, antigen tests, serology, and vaccination.
- Temporal data was encoded as shown in Table 2 and Fig. 1, and those codes were used to select confirmed reinfections (Fig. 2).
- Python and R programming were used to characterize confirmed reinfections.

Table 1. Study cohort - RECOVID

	All participants	Confirmed reinfections
N	3303	2344
Female, n (%)	2266 (68.6)	1692 (72.2)
Age, median [IQR]	43 [27-61]	45 [28-63]
Hospitalization, n (%)	188 (5.7)	121 (5.2)
N° comorbidities, median [IQR]	1 [0-2]	1 [0-2]
Advanced Chronic Disease, n (%)	73 (2.2)	61 (2.6)
Complex Chronic Patient, n (%)	367 (11.1)	291 (12.4)

Table 2. Codes for relevant events.

Event	Code
PCR/TMA+	A
PCR/TMA-	B
PCR sequenced	C
PCR potential sequencing	D
Antigen+	E
Antigen-	F
Serology+	G
Serology-	H
Pfizer vaccination	I
Moderna vaccination	J
AstraZeneca vaccination	K
Janssen vaccination	L
HIPRA vaccination	M
Hospital entry (probable COVID-19)	N
Hospital entry (possible COVID-19)	O
Hospital entry (ischemic embolic phenomena possibly derived from COVID-19)	P
Hospital discharge	Q
ICU/RICU entry	R
ICU/RICU discharge	S
Decease	T
Registered symptomatology	U

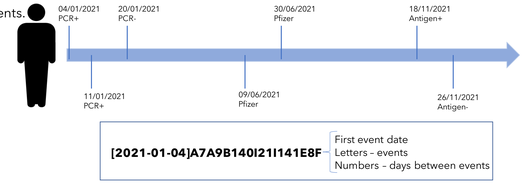


Figure 1. Example of clinical timeline codification of a participant.

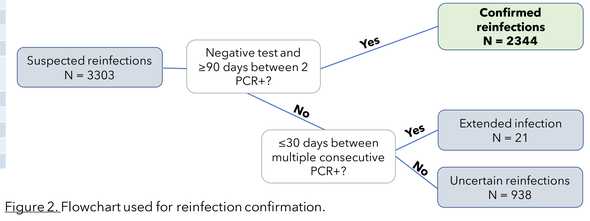


Figure 2. Flowchart used for reinfection confirmation.

✓ People with an undermined health status are more sensitive to SARS-CoV-2 reinfection, regardless of age.

✓ Both genetic variability of the variants and time between infections play a role in reinfection susceptibility.

RESULTS

DEMOGRAPHICAL CHARACTERIZATION

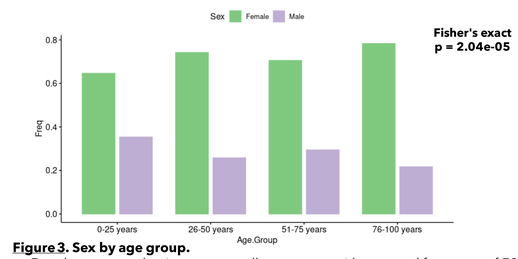


Figure 3. Sex by age group.
- Females were predominant among all age groups with a general frequency of 72.2%.
- Despite the longer lifespan and the higher presence of women in the healthcare system, the frequency of female reinfection is also increased in younger groups discarding a strong age-related bias.

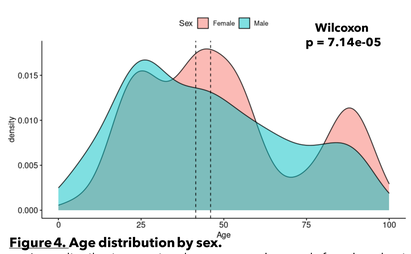


Figure 4. Age distribution by sex.
- Age distribution varies between males and females, having a median age of 41.5 and 46 years old, respectively.
- Both groups show three peaks at 24, 45, and 85 years, being clearer in females.

CLINICAL CHARACTERIZATION

Table 3. Comorbidities of participants compared with Catalonian population.

		Confirmed reinfections, %	Catalonia population, %
Adjusted morbidity group	**Healthy**	**4**	**17.8**
	Acute	7.2	8
	Pregnancy/Birth	2.5	1.3
	Chronic cond. 1 system	14	18.7
	Chronic cond. 2-3 systems	28	25.3
	Chronic cond. 4+ systems	**42.9**	**24.5**
	Active neoplasia	**1.6**	**4.4**
Comorbidity	Diabetes mellitus	11.2	8.2
	COPD	3.6	4.8
	Asthma	6.8	7
	Ischemic heart disease	3.8	2.9
	Stroke	3.5	3.4
	HBP	23.6	20.4
	CKD	**0.97**	**4.8**
	Cirrhosis	**1.1**	**0.35**
	HIV	0.24	0.42
	Malignant neoplasia	**2.9**	**7**
	Arthritis	**0.9**	**6.3**
	Organ transplantation	**0.4**	**0.01**

- Some comorbidities are overrepresented within participants, like chronic condition in ≥4 systems or organ transplantation.
- On the other hand, conditions such as malignant neoplasia, arthritis or kidney disease are less prevalent in our cohort.

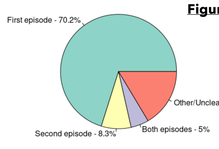


Figure 5. Episode of COVID-19 related hospitalization.
- 5.2% of participants were hospitalized during any of the COVID-19 episodes. 70.2% of them required hospitalization only during first infection, 8.3% during the second infection, and 5% in both.
- Half of the participants belonging to these two last groups were unvaccinated at the moment of hospitalization.

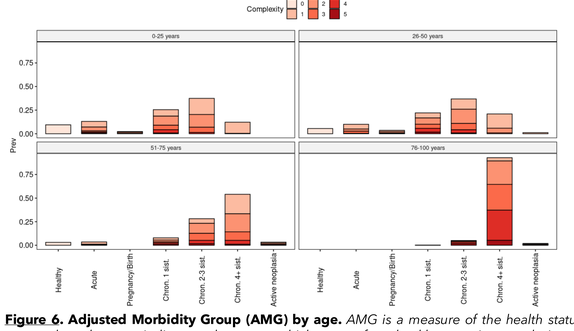


Figure 6. Adjusted Morbidity Group (AMG) by age. *AMG is a measure of the health status of a person, based on two indicators: the group, which ranges from healthy to active neoplasia, and the complexity, which rises with the healthcare needs of the individual.*
- 86.2% of all participants present at least one chronic condition, with 40.5% of having chronic conditions in ≥4 systems.
- 75.2% of participants <26 years old have at least one chronic condition.

TEMPORAL CHARACTERIZATION

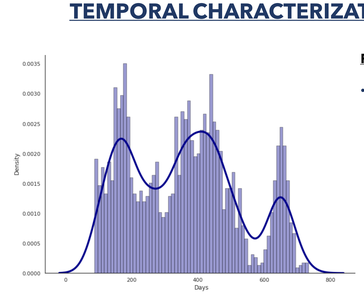


Figure 7. Time between episodes.
- Time between infections density analysis shows three peaks at ~200, ~400,and ~600 days, corresponding with time between waves.

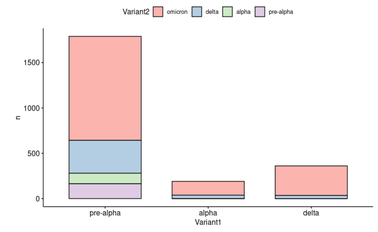


Figure 8. Estimated variant combinations within reinfections.
The first infection variant is indicated in the x-axis (bars) and the variant of the reinfection is color-coded. Variants were estimated using the date of infection according the circulating variant in Catalonia
- The most prevalent combinations are prealpha-omicron, prealpha-delta and delta-omicron.
- Both genetic variability of the variants and time between infections play a role in reinfection susceptibility.

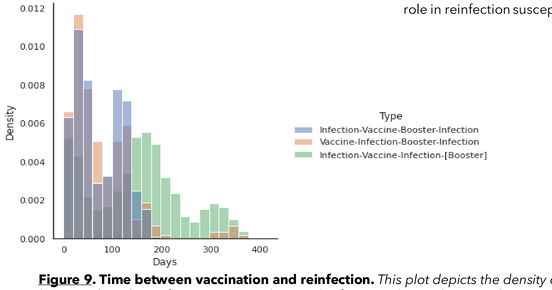


Figure 9. Time between vaccination and reinfection. *This plot depicts the density of time between last dose of vaccination and second infection. Blue and orange bars represents participants who had complete vaccination and booster before second infection, while green bars represents participants without booster.*
- A decrease of infections can be observed between 40 and 100 days after vaccination.

CONCLUSIONS

- COVID-19 reinfections are more prevalent in women in our RECOVID cohort.
- People with a fragile health status are more prone to be reinfected with SARS-CoV-2 in all age groups.
- In most cases no hospitalization is required in the second episode.
- The periods of higher reinfections match with the start of circulation of new evolved variants, suggesting that genetic variability rises the risk of reinfection, as well as time between infections.
- Vaccination seems to have a short protective effect on reinfection.

ACKNOWLEDGEMENTS

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