ANTI-S-RBD TITER AND RISK OF CLINICAL PROGRESSION IN PATIENTS WITH COVID19 PNEUMONIA

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BACKGROUND

- The presence of circulating antibodies against the spike protein receptor-binding-domain (anti-S-RBD) of SARS-CoV-2, elicited by either vaccination or natural infection, is deemed to be a correlate of protection against symptomatic COVID-19.
- However, there is currently no clear evidence that links the level of anti-S-RBD titer to protection from severe or critical forms of the disease nor a clearly established threshold at which such protection is exerted.
- In addition, it is unclear if levels of anti-S-RBD can predict the risk of progression to critical COVID-19 in those who develop pneumonia.
- Given this uncertainty, our study was designed to investigate whether there is an association between the level of anti-S-RBD titer and the clinical course and survival of patients hospitalized with COVID-19 pneumonia.

METHODS

Study design

- Observational retrospective cohort study on patients admitted for COVID-19 pneumonia between July 2021 and July 2022
- To be eligible, patients had to meet the following criteria:
  - Age of 18 years or older
  - Positive nasopharyngeal swab for SARS-CoV-2 RNA
  - Radiological or clinical evidence of COVID-19-related pneumonia, such as SpO_2 <94% on room air or need for oxygen therapy
  - Availability of anti-S-RBD titer determination within 72 hours of hospital admission.
- Patients who were admitted to the hospital for reasons other than COVID-19 and who tested positive for SARS-CoV-2 only incidentally, were excluded from the study.

Statystical analysis

- All analyses were conducted separately for vaccinated and unvaccinated individuals.
- Quantile regression was conducted to identify possible predictors of anti-S-RBD level.
- The following covariates were explored: age, gender, days since symptoms' onset, baseline clinical severity (based on oxygen requirement) and presence of immunosuppressive conditions (hematological malignancy, solid tumor, grade ≥4 chronic kidney disease or end-stage renal disease, diabetes, liver cirrhosis, HIV, organ transplant or use of immunosuppressive drug).
- The association between anti-S-RBD titer and the risk of 30-day death or need for mechanical ventilation was evaluated using logistic regression models, controlling for the same covariates.
- The impact of monoclonal antibody (mAb) infusions on the relationship between anti-S-RBD titer and the outcome of interest was also examined in a separate multivariable model.
- To determine the best-fitting model for anti-S-RBD titer, several models were explored (linear effect, cubic spline, linear effect on logarithm). The presented log_2 transformed model had the lowest prediction error, as measured by Brier score.

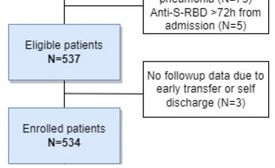
Low anti-S-RBD titer was associated with poor outcome among patients hospitalized for COVID19-related pneumonia, regardless of vaccination. In addition, older age and presence of immunosuppressive conditions remain important predictors of mortality.

RESULTS

Patients characteristics

- Five hundred thirty-four out of 1600 hospitalized patients were included in the analysis (Figure 1).
- Patients were predominantly male, with a mean age of 72 years; 61% had received at least 1 dose of COVID19 vaccine, 42% had ≥1 immunesuppressive condition.

Figure 1. Patient disposition (Consort diagram)



Vaccinated subjects were, on average, older and more likely to be immunocompromised than unvaccinated subjects.

These and other baseline characteristics, overall and stratified by vaccine status, are detailed in Table 1

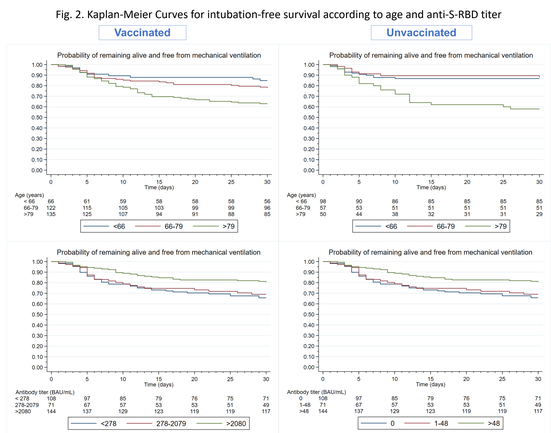
Table 1. Patients' charachteristics in the overall population and in the vaccinated and unvaccinated cohorts.

Patients' characteristics	Overall (N=534)	Vaccinated (N=328)	Unvaccinated (N=206)
Age, years (Mean [SD])	71.5 (14.4)	75 (12)	65 (15.8)
Male gender, N (%)	336 (62.9)	209 (63.7)	127 (61.6)
Vaccinated, N (%)	328 (61.4)	328 (100)	0 (0)
Days from symptoms onset, N (%)			
≤5 days	206 (38.6)	159 (48.4)	47 (22.8)
6-10 days	197 (38.9)	108 (32.9)	89 (43.2)
>10 days	131 (24.5)	61 (18.6)	70 (33.9)
Oxygen support on admission, N (%)			
No O2	26 (4.9)	16 (4.8)	10 (4.8)
Nasal prongs or facial mask with FiO2 <50%	225 (42.1)	145 (44.2)	80 (38.8)
Facial mask FiO2 >=50%	185 (34.6)	112 (34.1)	73 (35.4)
Non-invasive ventilation (CPAP helmet)	93 (17.4)	50 (15.2)	43 (20.8)
Mechanical ventilation	5 (0.9)	5 (1.5)	0 (0)
Antibody titer			
Anti-RBD-S titer, BAU/ml – Median (IQR)	216 (11-2080)	1370 (116-2080)	15.5 (0-107)
Not detectable (<5 BAU/ml)	104 (19.5)	31 (9.4)	73 (35.4)
Immunosuppressive conditions			
HIV +, N (%)	2 (0.4)	1 (0.3)	1 (0.4)
Diabetes, N (%)	110 (20.6)	78 (23.8)	32 (15.5)
Renal failure (stage IV CKD or ESRD), N (%)	26 (4.9)	3 (1.5)	23 (7.0)
Organ transplant recipients, N (%)	12 (2.2)	11 (3.3)	1 (0.4)
Haematological malignancies, N (%)	54 (10.1)	47 (14.3)	7 (3.4)
Solid malignancies, N (%)	40 (7.5)	30 (9.1)	10 (4.8)
Liver cirrhosis, N (%)	1 (0.2)	1 (0.3)	0 (0)
Immunosuppressive therapy, N (%)	62 (11.6)	53 (16.1)	9 (4.3)
At least 1 of the previoius conditions, N (%)	227 (42.5)	174 (53.0)	53 (25.7)
SARS-CoV-2 Variant, N (%)			
Omicron	95 (17.7)	72 (21.9)	23 (11.1)
Delta	176 (32.9)	85 (25.9)	91 (44.1)
Unknown	260 (48.6)	169 (51.5)	91 (44.1)
Other	3 (0.5)	2 (0.6)	1 (0.1)

Factors associated with Anti-S-RBD response

- Antibody titer was significantly higher among vaccinated than among unvaccinated patients (1166 vs 158 BAU/ml; p< 0.001). Among vaccinated, using multivariable analysis haematological malignancies (-985 BAU/ml; 95%CI -1601 to -368) and use of immunesuppressive drugs (-859; 95%CI -1446 to -272) were significantly associated with a lower median antibody titer. Conversely, longer durations of symptoms were associated with higher titers (*versus* ≤5 days, 6-10 days: +875, 95%CI 436-1314; >10 days: +875, 95%CI 341-1408). Age, gender and other immunesuppressive conditions were not associated with antibody titer to a significant extent.
- Among unvaccinated indivuduals, neither demographic characteristics nor presence of immunesuppressive conditions were associated with antibody titer. Using multivariable analysis, having symptoms for >10 days was associated with higher antibody titer (*versus* ≤5 days, 6-10 days: +2, 95%CI -31 to +35; >10 days: +55, 95%CI 22-89), independently of age, presence of severe renal impairment or use of immunesuppressive drugs.

Fig. 2. Kaplan-Meier Curves for intubation-free survival according to age and anti-S-RBD titer



Predictors of death or intubation (I)

- By day 30, 134 patients met the outcome of interest: 42 needed mechanical ventilation (of whom 13 died) and 92 died without access to mechanical ventilation
- As shown in Figure 2, older patients and those with lower anti-S-RBD had lower chances of 30-day survival.

Predictors of death or intubation (II)

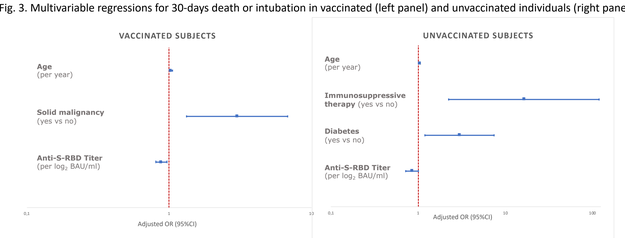
- Table 2 shows the results of the univariate logistic regression analysis exploring factors associated with 30-days death or intubation, among vaccinated and unvaccinated individuals.

Table 2. Univariate regression analysis assessing predictors of 30-days death or intubation in the vaccinated and unvaccinated cohorts.

Co-variate	Vaccinated (N=328)			Unvaccinated (N=206)		
	OR	95%CI	P	OR	95%CI	P
Anti-RBD-S titer (per log_2 BAU/ml increase)	0.90	0.84-0.97	0.009	0.89	0.78-1.03	0.129
Age (per 1 year increase)	1.03	1.01-1.05	0.004	1.05	1.02-1.07	<0.001
Male gender	1.34	0.80-2.23	0.264	0.62	0.31-1.22	0.168
Days of symptoms (*versus* ≤5 days)						
6-10 days	0.75	0.44-1.29	0.308	0.84	0.37-1.92	0.689
>10 days	0.45	0.22-0.94	0.034	0.49	0.19-1.24	0.131
Immunosuppressive conditions (yes *vs.* no)						
Diabetes	1.01	0.57-1.78	0.972	3.42	1.52-7.69	0.003
Renal failure (stage IV CKD or ESRD)	1.13	0.45-2.85	0.792	1.97	0.17-22.3	0.582
Haematological malignancy	1.56	0.81-2.98	0.183	5.65	1.21-26.3	0.027
Solid malignancy	2.47	1.15-5.29	0.020	0.42	0.05-3.41	0.417
Immunosuppressive therapy	1.13	0.59-2.15	0.705	16.2	3.2-81.3	<0.001
Transplant recipient	1.49	0.42-5.20	0.535	N.E.	-	-

- Using multivariable analysis, among vaccinated patients, anti-S-RBD titer (per log_2 BAU/ml, OR 0.88 [95%CI 0.81-0.97] p=0.009), age (per year, OR 1.03 [1.01-1.06] p=0.003) and solid malignancies (OR 3 [1.33-6.79] p=0.008) were associated with death or intubation, independently from haematological malignancies and days since symptoms' onset **(Fig. 3 left panel)**
- Among unvaccinated individuals, anti-S-RBD titer was marginally associated with the outcome (per log_2, OR 0.86 [95%CI 0.73-1.01] p=0.064), independently of age (OR 1.04 [1.01-1.07] p=0.004), immunosuppressive tx (OR 16.3 [2.2-119.5] p=0.006) and diabetes (OR 3 [1.24-7.48] p=0.015) **(Fig. 3 right panel)**

Fig. 3. Multivariable regressions for 30-days death or intubation in vaccinated (left panel) and unvaccinated individuals (right panel).



- Adjustment for mAb treatment, increased the strength of the association between the outcome and Anti-S-RBD titer (per log2, OR 0.81 [0.68-0.96] p=0.018), while acting as a protective factor itself (OR 0.31 [0.10-0.97] p=0.045).

CONCLUSIONS

Low anti-S-RBD titer is associated with poor outcome among patients hospitalized for COVID19-related pneumonia, regardless of vaccination status. In addition, older age and presence of immunosuppressive conditions remain important predictors of mortality.

Thus, anti-S-RBD titer represents a good correlate of protection against critical forms among those who develop COVID-19 pneumonia, despite previous vaccination.

Further studies could inform us on whether antibody dosing can guide the need for booster vaccination.