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Mortality predictors in hospitalised COVID-19 patients and the role of anti- SARS-CoV-2 IgG antibodies and remdesivir

Sergio Venturini[1], Daniele Orso[2], Francesco Cugini[3], Danilo Villalta[4], Maurizio Tonizzo[5], Alessandro Grembiale[5], Ada Zanier[5], Serena Cecco[5], Astrid Callegari[1], Silvia Duranti[1], Giovanni Del Fabro[1], Massimo Crapis[1]

[1]Department of Infectious Diseases, ASFO "Santa Maria degli Angeli" Hospital of Pordenone, Pordenone, Italy;
[2]Department of Anesthesia and Intensive Care, ASUFC "Santa Maria della Misericordia" University Hospital of Udine, Udine, Italy;
[3]Department of Emergency Medicine, ASUFC Hospital of San Daniele, Udine, Italy;
[4]Immunology and Allergy Unit, ASFO "Santa Maria degli Angeli" Hospital of Pordenone, Pordenone, Italy;
[5]Department of Medicine, ASFO "Santa Maria degli Angeli" Hospital of Pordenone, Pordenone, Italy

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SUMMARY

Background: In a pre-vaccination era serologic tests may be used to evaluate the seroprevalence and efficacy of containment strategies applied to the community. Subsequently, SARS-CoV-2 vaccination has successfully reduced hospitalization and admission to intensive care. The role of antiviral treatment for COVID-19 remains debated.
Objective: We investigated the effect of SARS-CoV-2 IgG Spike (S) antibody responses in hospitalized patients on 30-day mortality. Finally, we assessed whether other predictive factors affected mortality after 30 days.
Methods: Observational study on COVID-19 patients admitted from October 1, 2021, to January 30, 2022.
Results: 520 patients were studied; 108 died at the 30-day follow-up (21%). A borderline significance for mortality was observed in favour of the high antibody titer group (24% vs 17%, p=0.05). From the univariate Cox regression analysis, a high IgG-S titer was significantly correlated to lower 30-day mortality (p=0.04, HR: 0.7; 95%CI: 0.44-0.98). The administration of remdesivir (p=0.01) and the age <65 years (p=2.3e-05) were found to be protective for the considered outcome (respectively, HR: 0.5, 95%CI: 0.34-0.86, and HR: 0.1, 95%CI: 0.04-0.30).
Conclusions: S-antibodies and remdesivir could play a protecting role in increasing the survival of hospitalized COVID-19 patients who are not suffering from a critical disease. Advanced age is a risk factor for poor outcomes among infected people.

Keywords: SARS-CoV-2, antibody; remdesivir, vaccination.

INTRODUCTION

The ongoing COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a significant global public health issue. Symptoms of COVID-19 can be mild, such as flu-like symptoms, or severe, such as pneumonia and respiratory distress syndrome [1]. Vaccination is the most cost-effective medical response. It reduces the burden of infectious diseases and is an important tool to mitigate outbreaks caused by emerging pathogens. Vaccine-induced immunity is mediated by the complex interplay between innate, humoral and cellular immunity [2]. SARS-CoV-2 vaccines are highly effective in pro-

Corresponding author
Sergio Venturini
E-mail: sergio.venturini@asfo.sanita.fvg.it

tecting against COVID-19, although the determinants of vaccine efficacy have yet to be determined, especially in light of the emergence of new viral variants [3, 4]. SARS-CoV-2 vaccination and booster have limit hospitalisation and ICU admission. Indeed, immunity to natural infection might wane over time and reinfection cases occur and for this reason booster vaccine dose can continue to offer more protection [4]. Antibody responses to SARS-CoV-2 vaccines are influenced by several factors (age, gender, obesity, cancer). Serologic tests are used to evaluate the seroprevalence and effectiveness of community-based containment strategies.
This study examines the effect of IgG Spike (S) antibody responses of SARS-CoV-2 in inpatients on 30-day mortality. Lastly, we assessed whether other predictors have an impact on mortality after 30 days.

PATIENTS AND METHODS

Study protocol
We collected data from all patients admitted and recovered for SARS-CoV-2 in a medical ward at Pordenone "Santa Maria degli Angeli" Hospital, Italy, from October 1, 2021, to January 30, 2022. The patient's consent was obtained using the general consent system and the European General Data Protection Regulation 2016/679 was complied with.

Study population
The inclusion criteria were: patients >18 years of age admitted to the Pordenone hospital with a positive SARS-CoV-2 nasopharyngeal molecular and antigenic swab test and patients who performed SARS-CoV-2 serology within 48 hours of admitting medical ward.
The exclusion criteria were: pregnancy, paediatric patients, and refusal of consent.

Recorded data
Patient outcomes were recorded in terms of in-hospital mortality at 30-days follow-up. Clinical parameters such as age, gender and any co-morbidities resulting from medical history and clinical conditions of admission were recorded. A blood gas analysis was also recorded during the first assessment. The extent of pulmonary involvement by means of a chest CT scan was also recorded as "no" extension (normal CT results), less than 50% or more/equal to 50% of lung parenchyma. We also recorded the vaccination status of each patient (number of doses) and serologic status at admission.

Study aims
The main aim was to determine if two patients' sub-populations, identified by determination of different COVID-19 IgG spike antibodies titer (high vs low) could be different in 30-days survival. We then evaluated other possible prognostic factors in the whole patients' population.
The secondary objective was to determine whether other parameters were linked to survival after 30 days, by also identifying a multivariable predictive model.

Anti-SARS-CoV-2 antibody detection
Anti-SARS-CoV-2 antibodies were detected by a quantitative chemiluminescence immunoassay (CLIA), using the receptor binding domain of the Spike protein (S-RBD) as the capture antigen at the time of admission of the patients. All samples were processed according to the manufacturer's instructions using an automated CLIA platform (ADVIA Centaur XPT, Siemens Heathineers, Erlangen, Germany) with a cut-off level of 1.0/mL for a positive result (sensitivity 96.4%; CI95%: 92.7-98.5%; specificity 99.9%, CI95%: 99. 6-100%). Values ranging from 1.0 to 5.0 U/mL are considered to be weakly positive. Due to lack of evidence, according to other Italian experiences, we assumed low IgG titer to be five times lower than cut-off [5, 6]. The conversion factor in binding antibody units (BAU) following the WHO International Standard (NIBCS 20/136) is 21.8.

Statistical analysis
The distribution of continuous variables between the two groups was compared through a Mann-Whitney test (variables expressed as a median and interquartile range) after verifying the normality of the distribution employing the Shapiro-Wilk test. Fisher's exact (or Pearson) test was used for variables expressed as absolute frequency and relative percentage. A multiplicity correction using the Benjamini-Hochberg method has been implemented.
We also considered a propensity score matching method, by which we balanced all the variables between the two groups obtained by dividing the

global population on the basis of the antibody titer detected. The matching was optimal if the sum of the absolute distances between the two groups in each subclass was as small as possible. No replacement was considered, not determined cases were excluded.

We estimated the Kaplan-Meier curves and determined the hazard ratio for the variables of interest regarding survival by Cox regression. Finally, we determined a predictive model of survival through Cox multivariable regression. We also verified the correlation between the measured variables and

Table 1 - Demographic and clinical characteristics of the population studied. A propensity score matching method was performed, using mortality as a reference variable and balancing all factor variables.

		Population (n=520)	*Unadjusted*			*Adjusted*		
			Low-titer (n=297)	*High-titer (n=223)*	*p-value*	*Low-titer (n=50)*	*High- titer (n=50)*	*p-value*
Demographics								
Sex (males)		324 (62%)	183 (62%)	141 (63%)	0.776	27 (54%)	33 (66%)	0.307
Age (years)		76 (66-84)	76 (64-84)	77 (67-84)	0.286	76.0 (61-83)	73 (69-81)	0.885
BMI		27 (24-30)	26 (24-30)	27 (24-30)	0.638	27 (24-30)	27 (23-29)	0.331
Vaccination	No	226 (44%)	187 (63%)	39 (18%)	*<0.001*	30 (60%)	7 (14%)	*<0.001*
	Partial	205 (39%)	81 (27%)	124 (56%)		15 (30%)	35 (70%)	
	Complete	89 (17%)	29 (10%)	60 (27%)		5 (10%)	8 (16%)	
Serum antibody titer		2.30 (0.5-93.0)	0.50 (0.5-1.0)	100 (23.7-100)	*<0.001*	0.50 (0.50-0.86)	100 (20.8-100)	*<0.001*
History								
Hypertension		301 (58%)	161 (54%)	140 (63%)	*0.046*	27 (54%)	34 (68%)	0.219
CAD		71 (14%)	40 (14%)	31 (14%)	0.973	9 (18%)	6 (12%)	0.575
Diabetes Mellitus		120 (23%)	61 (21%)	59 (27%)	0.124	7 (14%)	14 (28%)	0.141
Obesity		108 (21%)	55 (19%)	53 (24%)	0.176	13 (26%)	12 (24%)	1.000
Atrial Fibrillation		105 (20%)	58 (20%)	47 (21%)	0.726	9 (18%)	9 (18%)	1.000
Neoplasm		75 (15%)	45 (15%)	30 (14%)	0.690	8 (16%)	7 (14%)	1.000
Rheumatological disease		48 (9%)	26 (9%)	22 (10%)	0.767	0	4 (8%)	0.117
Cognitive Impairment		48 (9%)	26 (9%)	22 (10%)	0.767	2 (4%)	2 (4%)	1.000
Respiratory disease		88 (17%)	54 (18%)	34 (15%)	0.458	14 (28%)	10 (20%)	0.482
Hematological disease		22 (4%)	13 (4%)	9 (4%)	1.000	0	0	/
Liver disease		47 (9%)	27 (9%)	20 (9%)	1.000	2 (4%)	4 (8%)	0.678
Smoking	Actual	31 (7%)	22 (9%)	9 (5%)	0.000	5 (10%)	3 (6%)	0.598
	Former	88 (21%)	48 (20%)	40 (23%)		16 (32%)	13 (26%)	
N° of comorbidities		3 (2-5)	3 (1-5)	3 (2-5)	0.051	3 (1-5)	3 (1-5)	0.422
Symptoms at onset								
Fever		324 (62%)	195 (66%)	129 (58%)	0.096	40 (80%)	38 (76%)	0.809
Cough		198 (38%)	126 (42%)	72 (32%)	0.026	26 (52%)	27 (54%)	1.000
Dyspnoea		235 (45%)	133 (45%)	102 (46%)	0.861	23 (46%)	25 (50%)	0.841
Asthenia/myalgia		90 (17%)	60 (20%)	30 (14%)	0.061	9 (18%)	9 (18%)	1.000
Diarrhoea		18 (3%)	13 (4%)	5 (2%)	0.286	0	0	/
Gastroenteritis		29 (6%)	15 (5%)	14 (6%)	0.672	4 (8%)	1 (2%)	0.362
Ageusia/anosmia		11 (2%)	6 (2%)	5 (2%)	1.000	2 (4%)	0	0.495

Abbreviations: CAD, coronary arteries disease.

the outcome by stepwise generalized linear regression analysis. A p-value ≤0.05 was considered statistically significant.
All the statistical analyses were performed using open-source software "R: A language and environment for statistical computing", implementing the "readODS", "compareGroups", "dplyr", "MatchIt", "survival", "ranger", "ggplot2", "ggfortify" packages.

RESULTS

During the period considered 520 patients were admitted with COVID-19. Of these, 108 died within the 30-day follow-up (21%). The characteristics of the study population are given in Table 1. The difference between the vital signs of the two groups is shown in Table 2.

Table 2 - Study population clinical and laboratory characteristics. WBC: white blood cell count; RBC: red blood cell count; CRP: C-reactive protein; AST: aspartate transaminase; ALT: alanine transaminase; gGT: gamma-glutamyl transpeptidase; LDH: lactate-dehydrogenase; PT: prothrombin time; aPTT: activated partial thromboplastin time.

	Population (n=520)	*Unadjusted*			*Adjusted*		
		Low- titer (n=297)	*High- titer (n=223)*	*p-value*	*Low- titer (n=50)*	*High- titer (n=50)*	*p-value*
Clinical Parameters							
Systolic Pressure (mmHg)	131 (116-148)	132 (117-147)	131 (115-150)	0.888	138 (122-147)	130 (119-153)	0.702
Diastolic Pressure (mmHg)	75 (67-83)	75 (66-84)	75 (70-93)	0.869	70 (66-86)	75 (70-85)	0.524
Heart Rate (bpm)	82 (74-95)	83 (74-96)	81 (74-93)	0.271	84 (71-95)	83 (76-90)	0.607
Temperature (°C)	37.0 (36.3-37.7)	37.1 (36.4-37.8)	36.7 (36.0-37.5)	0.012	37.2 (36.4-37.9)	37.3 (36.2-38.1)	0.817
pH	7.47 (7.44-7.50)	7.47 (7.44-7.50)	7.47 (7.44-7.50)	0.226	7.47 (7.43-7.50)	7.47 (7.45-7.49)	0.978
Labs							
WBC (x10^3/mm^3)	6.47 (4.55-9.16)	6.09 (4.18-8.46)	6.74 (4.99-9.70)	0.005	5.48 (3.73-7.18)	5.89 (4.59-8.03)	0.097
Neutrophils (x10^3/mm^3)	4.95 (3.27-7.32)	4.68 (3.01-6.81)	5.34 (3.40-8.19)	0.001	4.06 (2.77-6.14)	4.86 (3.33-7.00)	0.089
Lymphocytes (x10^3/mm^3)	0.81 (0.57-1.23)	0.79 (0.55-1.21)	0.83 (0.60-1.27)	0.169	0.74 (0.52-1.04)	0.76 (0.56-1.06)	0.617
RBC (x10^6/mm^3)	4.32 (3.82-4.70)	4.38 (3.91-4.81)	4.23 (3.72-4.64)	0.011	4.34 (4.04-4.62)	4.44 (4.07-4.69)	0.705
Hemoglobin (g/dL)	13.1 (11.6-14.2)	13.3 (11.7-14.4)	12.8 (11.5-13.9)	0.026	13.1 (12.3-14.2)	13.6 (12.4-14.3)	0.329
Ferritin (ng/mL)	506 (248-890)	482 (228-931)	516 (272-875)	0.642	532 (258-931)	717 (358-919)	0.260
CRP (mg/L)	7.00 (3.20-11.8)	6.70 (3.00-10.8)	7.60 (3.73-12.6)	0.042	5.25 (2.25-10.3)	8.90 (4.53-15.0)	0.018
Procalcitonin (ng/mL)	0.10 (0.04-0.24)	0.10 (0.04-0.24)	0.10 (0.04-0.24)	0.998	0.06 (0.01-0.26)	0.10 (0.03-0.22)	0.525
Creatinine (mg/dL)	0.92 (0.74-1.20)	0.89 (0.73-1.20)	0.94 (0.77-1.20)	0.548	0.79 (0.67-1.19)	0.87 (0.69-1.09)	0.510
AST (U/L)	33.0 (23.0-49.0)	34.0 (24.0-50.0)	30.0 (21.0-48.0)	0.051	33.0 (26.0-49.5)	32.0 (22.0-48.0)	0.915
ALT (U/L)	29.0 (20.0-45.0)	29.0 (20.0-46.0)	29.0 (20.0-45.0)	0.498	28.0 (21.0-40.8)	35.5 (24.0-52.8)	0.080
gGT (U/L)	46.0 (27.5-92.5)	46.0 (27.0-95.0)	46.0 (28.2-91.0)	0.928	43.5 (25.5-71.8)	45.0 (30.8-79.0)	0.562
Bilirubin (mg/dL)	0.50 (0.40-0.80)	0.50 (0.40-0.70)	0.60 (0.40-0.80)	0.045	0.50 (0.40-0.60)	0.70 (0.50-0.80)	0.006
LDH (mg/L)	278 (224-374)	296 (225-395)	263 (223-341)	0.042	268 (212-353)	257 (233-304)	0.839
Coagulation							
PT (sec)	12.7 (11.9-14.2)	12.5 (11.8-13.9)	12.9 (12.0-14.2)	0.032	12.3 (11.6-13.6)	12.8 (12.0-14.1)	0.161
aPTT (sec)	29.7 (27.5-32.5)	30.0 (27.7-32.5)	29.3 (27.1-32.5)	0.317	29.8 (26.6-32.2)	28.8 (27.2-31.8)	0.836
D-dimer (FEU/mL)	672 (455-1169)	631 (410-1092)	731 (501-1176)	0.139	534 (378-862)	693 (457-1084)	0.076
Anticoagulation tp.	109 (21%)	60 (20%)	49 (22%)	0.702	12 (24%)	12 (24%)	1.000

Comparing the two populations (223 vs 297 patients), a limit significance for mortality was observed in favour of the elevated antibody titer group (24% vs 17%, p=0.05). Patients with low IgG-S had a higher median temperature (37.1 C vs 36.7 C. p=0.01), and the PaO2/FiO2 ratio was lower (270 vs 280, p= 0.04) than patients with high IgG-S. Significantly, the C-reactive protein was lower in the low antibody titer group than in the high titer group (6.70 vs 7.60, p=0.04) (Table 2). In addition, the extent of lung involvement determined by chest CT scan was significantly greater in the low titer group (p=0.01), and patients needed more advanced oxygen delivery devices (NIV vs HFNC vs Venturi mask) in the low titer group compared to the high titer group (p=0.005) (Table 3).

Through a propensity score matching for mortality (see Supplemental Material), 100 patients were compared in a ratio of 1:1 (50 vs 50). The difference between the median values of C-reactive protein remains significantly lower in the group with low antibody titer (5.25 vs 8.90, p=0.02).

In addition, PaO2 (61 mmHg vs 67 mmHg, p=0.03) and SaO2 (93% vs 94%, p=0.02) were significantly lower in the low titer group (Table 4).

In both analyses (adjusted and non-adjusted), the percentage of patients with high titer who received at least one dose of vaccine was significantly higher

Table 3 - Therapeutic strategies used on the population studied.

		Population (n=520)	*Unadjusted*			*Adjusted*		
			Low- titer (n=297)	*High- titer (n=223)*	*p-value*	*Low- titer (n=50)*	*High- titer (n=50)*	*p-value*
Therapies								
Steroid		395 (76%)	238 (80%)	157 (70%)	0.014	46 (92%)	46 (92%)	1.000
Remdesivir		159 (31%)	99 (33%)	60 (27%)	0.139	22 (44%)	23 (46%)	1.000
Monoclonal Ab		76 (15%)	59 (20%)	17 (8%)	<0.001	12 (24%)	2 (4%)	0.009
O2-therapy	No	107 (21%)	53 (18%)	54 (24%)	*0.005*	8 (16%)	7 (14%)	0.217
	Venturi mask	249 (48%)	132 (44%)	117 (53%)		30 (60%)	37 (74%)	
	HFNC	81 (16%)	54 (18%)	27 (12%)		11 (22%)	4 (8%)	
	NIV	83 (16%)	58 (20%)	25 (11%)		1 (2%)	2 (4%)	

Abbreviations: HFNC: high-flow nasal cannulae; NIV: non-invasive ventilation.

Table 4 - Features of clinical severity of the population studied.

		Population (n=520)	*Unadjusted*			*Adjusted*		
			Low- titer (n=297)	*High- titer (n=223)*	*p-value*	*Low- titer (n=50)*	*High- titer (n=50)*	*p-value*
Severity Criteria								
PaO2 (mmHg)		64.0 (56.9-75.0)	63.9 (56.0-74.9)	64.2 (57.5-75.3)	0.389	61.1 (53.2-70.0)	67.0 (59.5-76.3)	0.026
PaO2/FiO2 (mmHg)		278 (219-317)	270 (202-314)	283 (227-321)	0.036	273 (233-316)	288 (265-326)	0.086
SaO2 (%)		93 (91-95)	93 (91-95)	94 (92-96)	0.315	93 (90-95)	94 (93-96)	0.020
CT scan extension	No/minimum finding	131 (25%)	60 (20%)	71 (32%)	0.008	6 (12%)	11 (22%)	0.443
	<50%	313 (60%)	188 (63%)	125 (56%)		39 (78%)	35 (70%)	
	≥50%	76 (15%)	49 (17%)	27 (12%)		5 (10%)	4 (8%)	
LOS (days)		9 (7-14)	10 (7-15)	9 (6-13)	0.332	9 (7-15)	8 (7-11)	0.259
Death (at 30-day follow up)		108 (21%)	71 (24%)	37 (17%)	0.054	6 (12%)	7 (14%)	1.000

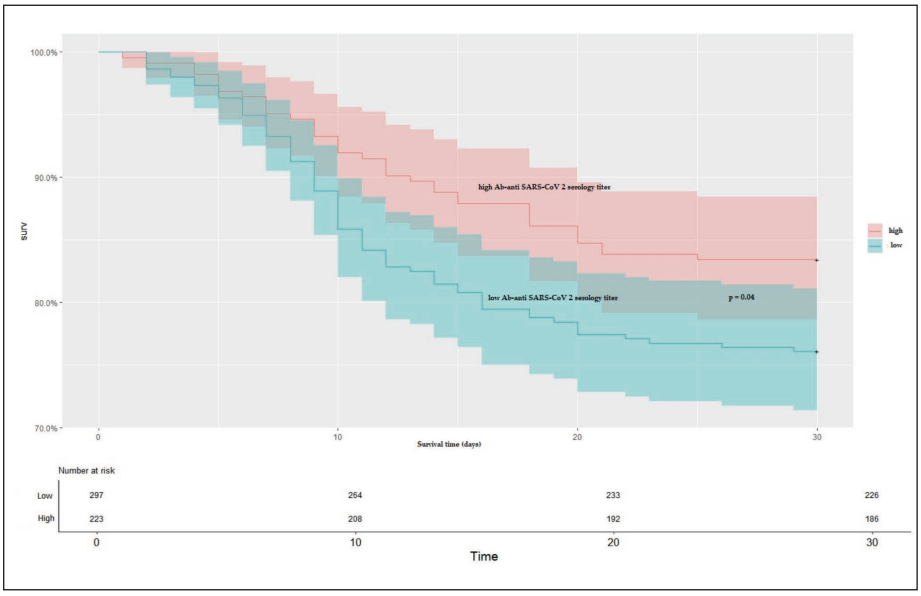

Figure 1 - Kaplan-Meier curve for population divided by igg-S antibody titer. By univariate Cox regression analysis, the antibody titer was significantly correlated to 30-day mortality (p=0.04).

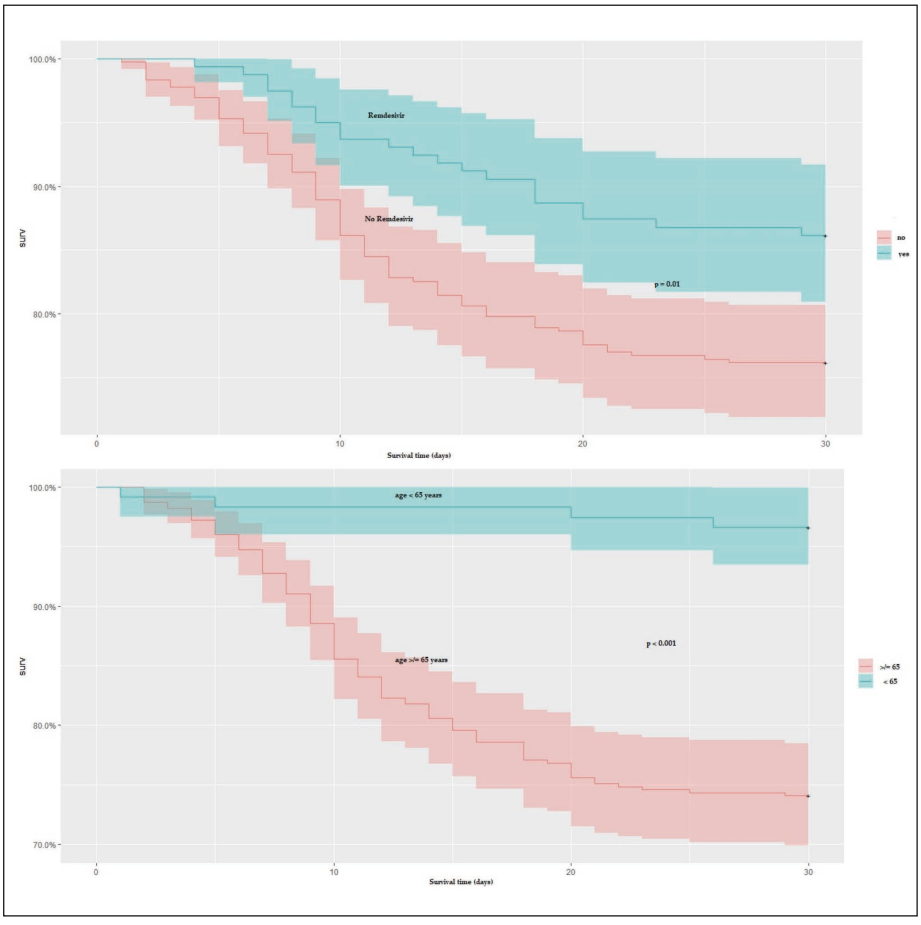

Figure 2 - Kaplan-Meier curves for remdesivir (top) and for age (bottom; greater or lesser than 65 years of age). The administration of remdesivir (p=0.01), and the age (less than 65 years; p=2.3e-05) were found to be protective with respect to the considered outcome (respectively, HR: 0.5, 95%CI: 0.34-0.86, and HR: 0.1, 95%CI: 0.04-0.30).

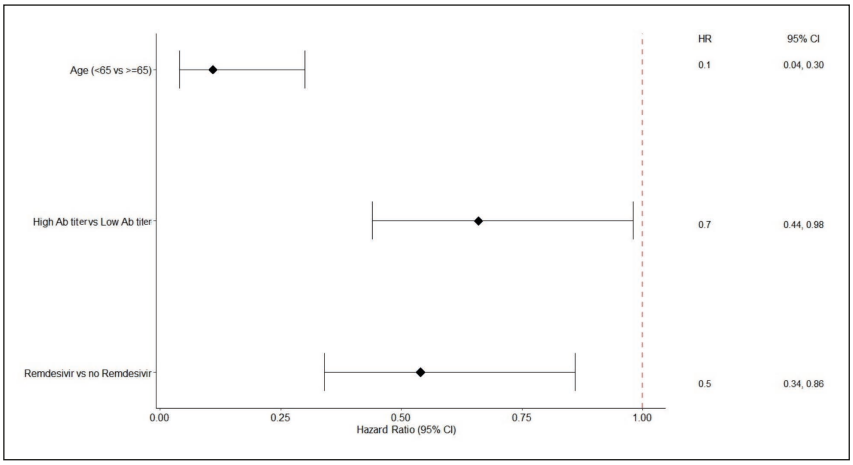

Figure 3 - By univariate Cox regression analysis, the antibody titer was significantly correlated to 30-day mortality (p=0.04; HR: 0.7; 95%CI: 0.44 - 0.98). The administration of remdesivir (p=0.01), and the age (less than 65 years; p=2.3e-05) were found to be protective with respect to the considered outcome (respectively, HR: 0.5, 95%CI: 0.34-0.86, and HR: 0.1, 95%CI: 0.04-0.30).

than the group of patients with low titer (83% vs 37%, in unadjusted analysis, and 76% vs 40% in adjusted analysis; p<0.001 for both analyses).

By univariate Cox regression analysis, the antibody titer was significantly correlated to 30-day mortality (p=0.04) (Figure 1). Patients with high titer present 0.7 times lower mortality risk than those with low antibody titer (95%CI: 0.44-0.98) (Figure 3).

Similarly, both the administration of remdesivir (p=0.01) and the age less than 65 years (p=2.3e-05) were found to be protective for the considered outcome (respectively, HR: 0.5, 95%CI: 0.34-0.86, and HR: 0.1, 95%CI: 0.04-0.30) (Figure 2). In multivariable analysis, only age was maintained as a predictive variable (HR: 0.06; 95%CI 0.03-0.09; p<0.00001).

DISCUSSION

The relationship between SARS-CoV2 antibody titer and mortality is poorly investigated. Our study showed that the IgG-S antibody titer against SARS-CoV-2 could be a predictor of 30-day in-hospital mortality. In addition to the important role of age in the adequate immune response to SARS-CoV-2 infection, patients with high antibody titers have a lower mortality rate of 30 days [7]. In a small inpatient population with COVID-19, Zhou et al. found similar results to our own [8]. Similarly, Sanghavi et al., in a population of 627 hospitalized vaccinated COVID-19 patients, found that the mortality of patients with low antibody titer was about three and a half times greater than those with a high antibody titer (21% vs 6%) [9]. De Vito et al., in a population of 99 COVID-19 patients, found that a high antibody titer against the viral nucleocapsid is a protective factor concerning in-hospital mortality [10].

The assessment of whether antibody titer is a direct protective factor or just an epiphenomenon of immune reactivity (or at least possible inflammatory dysregulation) is still unclear. In a plasma analysis of 58 patients hospitalized for COVID-19, Simons et al. identified 5 clusters linked to different sub-populations of distinct antibodies by the molecular target [11]. While the authors found direct linearity with the viral load, they found no correlation with clinical outcomes. Similar studies in small populations of COVID-19 patients have not found a correlation between mortality and antibody titer [12, 13]. However, it is noteworthy that the small populations studied in these studies make clinical correlations difficult.

Tretyn et al. have found that the serum antibody titer is often insufficient even in patients with previous SARS-CoV-2 infection, and only after the first (or, in some cases, after the second) vaccine dose reaches neutralizing antibody levels [14]. Petrone et al. reported a correlation between B and T lymphocyte responses to SARS-CoV-2 antigens [15]. This data could (in addition to being useful in terms of programming vaccination strategies and monitoring the antibody titer IgG-S) indicate the crucial role of immune activation in the early phase of COVID-19.

Levels of C-reactive proteins (7.6 vs 6.7 mg/dL) and neutrophils (5.34 x 10^3 vs 4.68 x 10^3/mm^3) are higher in the high antibody group. However, the

highest antibody subpopulation exhibits clinical signs of higher immune activation. Choteau et al. have argued that humoral immunity is not responsible for the clinical course of COVID-19 [16]. However, the authors also point out that the antibody titer remains elevated for at least three months after infection. The extent to which this is related to mortality and disease severity in reinfection is unknown. Ren et al. have extensively demonstrated that humoral immunity is activated within days immediately following infection [17]. However, the severity of the disease and the titer of newly acquired antibodies could be two events correlated by temporal simultaneity, but without affecting the clinical outcome. Dispinseri et al. have identified how neutralizing antibodies can limit virus spread and subsequent disease progression when they develop shortly after infection [18]. In 134 hospitalized patients, the antibody titer seen at the admission time to the hospital showed no impact on the duration of hospitalization but significantly correlated with the severity of COVID-19. The absence of antibody response soon after infection strongly predicted death when it was stratified over time by symptoms (RH 2.918, 95%CI 1.321-6.449; p=0.008).

Remdesivir is the first antiviral agent authorized to treat COVID-19. Although several studies do not demonstrate efficacy in terms of outcome, the National Institute of Allergy and Infectious Diseases Funded, in a large trial of 1,062 patients, that the mortality rate was lower in the remdesivir group (6.7% vs 11.9%) [19, 20]. Recent clinical data have also demonstrated the clinical activity of remdesivir in terms of faster time to recovery in patients with moderate COVID-19 [21].

We assume that our finding, showing a 30-day mortality reduction in the remdesivir group, is probably due to the time of administration.

In our study five-day course of intravenous remdesivir treatment (200 mg for the first day and then 100 mg for the next four days) has always been given within the first seven days of onset and early stages of pneumonia. Remdesivir is unlikely to reach an adequate concentration in the pulmonary tissue by intravenous infusion because of its low tissue distribution and low pulmonary penetration [22]. Based on recent literature, our study shows that remdesivir may be more effective when launched early in COVID-19 to prevent disease progression [23].

Although using steroids in ARDS by COVID-19 results in increased survival [24-27], Sahu et al., through a recent meta-analysis, showed that steroids in patients who do not require oxygen therapy could be detrimental [28]. The odds of progression to severe disease among non-oxygen-requiring COVID-19 patients receiving steroids was about 6, and the odds of death were 1.3 compared to the non-steroid arm. Similarly, Sarkar et al. found the same results in a heterogeneous population of almost 16,000 COVID-19 patients. The discordance results between critically ill and non-critically ill populations or, better to say, between high-demand oxygen patients and patients with mild COVID-19 is probably linked to immune dysregulation rather than a direct effect of SARS-CoV-2 [29].

With respect to the effect of sotrovimab, we did not find any significant difference in mortality over 30 days. Although Gupta et al. found that sotrovimab reduced disease progression, compared to our population, the Authors' patients had a prevalence of mild forms (non-hospitalized patients who did not require oxygen therapy) [30]. Mortality between the two populations differs: 0.2% for Gupta et al. vs 21% in our study. Despite the differences in study design (phase 3 trial vs observational study), the difference in efficacy is remarkable; therefore, sotrovimab is still to be tested on a COVID-19 hospitalized patient population before establishing its effectiveness.

In general, monoclonal antibody therapy remains not extensively clinically tested; however, the differences between antibody response developed following vaccination and administration of standard formulation are well evidenced by studies in the literature [31-33]. However, what monoclonal antibodies can be an additional or "tailor-made" therapy based on antibody titer (and therefore on certain subpopulations of patients) could be a fertile research strand yet to be explored. Further studies are needed to explore possible therapeutic interventions such as monoclonal antibodies or strategies to boost the COVID-19 vaccine to restore good functional humoral immunity in patients with inadequate antibody response during SARS-CoV-2 infection.

Limitations

Our study was an observational study conducted by a single centre, and therefore the findings may

not be very generalizable. In addition, our study did not include a comparison of patients in the intensive care unit.
In many cases, prior infection data are likely underestimated because of the low symptomatic nature of COVID-19.
Although understanding cell-mediated immunity may help to better understand the immune response to COVID-19, especially in individuals who do not produce a measurable antibody response or whose antibody responses have decreased over time, our study did not explore cell-mediated immunity.
Finally, although we have not achieved a full statistical significance regarding the difference in mortality between the two groups, we believe that this is due exclusively to the limited sample size that we have been able to collect. We believe that with an increase in the study population, it is likely that this will be achieved.
We must also note that the method of balancing the variables studied through propensity score, although it is methodologically the most appropriate solution to avoid imbalances linked to the observational nature of the study, does not guarantee an ideal balance. There may be imbalances linked to the recruitment method which may make the results of this study not fully reliable.

CONCLUSION

In conclusion, results from the present study suggest the role of the SARS-CoV-2 IgG Spike antibody as a protective factor in non-critically ill COVID-19 adult patients. Older age is a critical risk factor for poor outcomes in infected individuals. Remdesivir may play a key role in increasing the survival of COVID-19 patients hospitalized for non-critical conditions.

Conflict of interests
None to declare by any of the authors.

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