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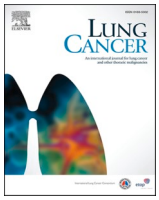

Immunogenicity of COVID-19 vaccines in lung cancer patients

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ABSTRACT

Objective: Patients with lung cancer are at increased risk of SARS-CoV-2 infection and severe complications from COVID-19, but information on the efficacy of anti-SARS-CoV-2 vaccine in these patients is scarce. We aimed at evaluating the safety and immunogenicity of COVID-19 vaccines in this population.
Patients and methods: The prospective, nationwide SOLID substudy, enrolled adults with lung cancer who were fully vaccinated against COVID-19. Serum anti-SARS-CoV-2 IgG antibody levels were quantitatively assessed two weeks and six months after receipt of the last dose using a chemiluminescent microparticle immunoassay. Multivariate odds ratios for the association between demographic and clinical factors and seronegativity after vaccination were estimated.

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Results: 1973 lung cancer patients were enrolled. Most patients had stage IV disease (66%) and were receiving active cancer treatment (82.7%). No significant differences were found in the probability of being seronegative for anti-SARS-CoV-2 IgG antibodies after full vaccination between patients who were receiving active cancer treatment and those who were not ($p = 0.396$). The administration of immunotherapy or oral targeted therapy and immunization with mRNA-1273 COVID-19 vaccine were factors independently associated with increased odds of being seropositive after vaccination. From all patients, 1405 received the second dose of vaccine and high levels of antibody titers were observed in 93.6% of patients two weeks after second dose. At six months, multivariate logistic regression analysis showed that performance status ≥ 2 was independently associated with a higher probability of being seronegative after full vaccination with an OR 4.15. On the other hand, received chemotherapy or oral target therapy and vaccination with mRNA-1273 were a factor independently associated with lower odds of being seronegative after full vaccination with an OR 0.52, 0.37 and 0.34, respectively.
Conclusions: Lung cancer patients can safely achieve a strong immune response against SARS-CoV-2 after full vaccination, regardless of the cancer treatment received.
Trial registration: NCT04407143.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected the global community with more than 240 million of confirmed cases and 5 million deaths from coronavirus disease (COVID)-19 [1–2]. Between 31 January 2020, when SARS-CoV-2 was first confirmed in Spain, and 17 November 2021, around 5 million cases were reported in our country, with more than 435,000 hospitalizations, over 40,000 admissions to intensive care unit (ICU), and almost 88,000 deaths, making it one of the countries hardest hit by the pandemic in Europe [3].

As many as 80% of SARS-CoV-2 infections are asymptomatic or mild, so seroprevalence surveys are essential to estimate the cumulative prevalence of infection in each population, and to guide health policy decisions [4–6]. A *meta*-analysis of 968 seroprevalence studies involving 9.3 million participants from 74 countries showed that, in general, estimates of population-wide seroprevalence during the first year of the COVID-19 pandemic were relatively low, with a median of 4.5% (2.4–8.4) [7]. In Spain, the prevalence of anti-SARS-CoV-2 IgG antibodies was estimated to be about 5% of the total population (3.7–6.2), with asymptomatic cases representing between 21.9% and 35.8% of all SARS-CoV-2 infections [8].

Although the COVID-19 pandemic has affected the entire population, patients with underlying comorbidities have been disproportionately affected [9]. The immunosuppressive effects of cancer treatment and supportive care, and the underlying malignancy itself, appear to place patients with cancer at increased risk of SARS-CoV-2 infection and severe clinical complications and mortality from COVID-19 [10–19]. Higher mortality has been reported in lung cancer patients, compared with other solid tumors [11,16,17,20–24], and in patients with progressive disease compared with those in remission, irrespective of cancer type [14].

To date, four COVID-19 vaccines have been licensed by the European Commission (EC) for use in the European Union following approval by the European Medicines Agency (EMA) [25]. However, because cancer patients have often been excluded from pivotal trials, information on the immunogenicity and durability of COVID-19 vaccination is limited [26]. Several recent reports have shown diminished immune responses to mRNA vaccines in cancer patients after the first dose, but most patients show increased antibody concentrations (not inferior to those of healthy individuals) after the second [27–29]. Íts important to know serum anti-SARS-CoV-2 IgG antibody levels six months after the first dose to plan vaccination strategies.

We report the final results of a substudy of SOLID trial [30] to evaluate the immunogenicity of the COVID-19 vaccine and the durability of the immune response in fully vaccinated participants, adjusting for vaccine type, presence or absence of prior SARS-CoV-2 infection, anticancer therapy, and demographic and clinical factors.

2. Methods

2.1. Study design

This was a substudy of the prospective, nationwide, longitudinal, multicenter SOLID study, to evaluate the immunogenicity of the COVID-19 vaccine and the durability of the immune response in fully vaccinated lung cancer patients. The study protocol was reviewed and approved by the Institutional Review Board of the Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain (No. PI 81/20) and the Spanish Agency for Medicines and Medical Devices (AEMPS). The study was conducted in accordance with all applicable laws and regulations, including the provisions of the Declaration of Helsinki.

This substudy was added as a protocol amendment to the SOLID study on 17 January 2021 to determine serum anti-SARS-CoV-2 IgG antibody levels in lung cancer patients fully vaccinated with any of the approved vaccines, two weeks and six months after the first dose, depending on the approved dose regimen (two-dose series: BNT162b2, mRNA-1273 and ChAdOx1 nCoV-19 vaccines; single-dose: Ad26.COV2.S vaccine).

2.2. Study participants

Eligible participants were adults aged 18 years or older, diagnosed with lung cancer at any stage of the disease, whether they had COVID-19 infection, and fully vaccinated against COVID-19. All participants signed written informed consent – approved by local Drug Research Ethics Committee (CEIm) – prior to enrolment.

2.3. Information retrieval

Data were collected from the patiénts medical records using an electronic data capture (EDC) system. Demographic and clinical data, including age, sex, performance status, smoking history, comorbidities, concomitant medications, cancer type, histology, disease stage, previous and current treatment for lung cancer, treatment-related adverse events, COVID-19 vaccine received, vaccine-related adverse events, and serum titers of anti-SARS-CoV-2 IgG antibodies, were collected from all patients at baseline.

2.4. Detection of SARS-CoV-2 antibodies

A chemiluminescent microparticle immunoassay was used for the quantitative determination of IgG antibodies against the receptor-binding domain of the spike protein (S-RBD) of SARS-CoV-2 in serum or plasma samples, using the fully-automated MAGLUMI analyzers (SARS-CoV-2 S-RBD IgG CLIA; Snibe diagnostic, China). According to the manufacturer's recommendations, the threshold value for positivity was established at 7.1 BAU/mL.

2.5. Statistical analysis

A descriptive analysis was performed by means of absolute and relative frequencies for categorical variables, and median (P25–P75) or mean (standard deviation, SD) for numerical variables. A univariate analysis was conducted using logistic regression models to examine the association of each demographic or clinical variable and outcomes. Significant variables were considered for inclusion in a multivariate regression model. For all regression analyses, the odds ratios (OR) of being seronegative, along with the 95% confidence intervals (95 %CI), were calculated. Internal validation of the model was carried out by bootstrap resampling techniques with 500 replications, including measures of global performance, calibration, and discrimination. Calibration was evaluated using a calibration plot and discrimination with the C-statistic and global performance was calculated using the Brier score. The significance level was established at a value of $\alpha = 0.05$. All statistical analyses were performed using the Stata/IC v.16 package (StataCorp. 2019. Stata Statistical Software: Release 16).

3. Results

A total of 1973 lung cancer patients were enrolled between 3 March 2021 and 30 September 2021, in 37 Spanish hospitals. The mean age was 66.8 (SD 9.37) years and 67.5% were male. Demographic characteristics of participants at baseline are shown in Table 1.

Regarding lung cancer characteristics, 90.1% of patients had a diagnosis of non-small cell lung cancer (NSCLC), being adenocarcinoma the most common histological type (71.3%). Sixty-six percent of patients had stage IV disease, and 82.7% were receiving active cancer treatment. Clinical characteristics of participants are shown in Table 2.

One hundred and fifty patients tested positive for anti-SARS-CoV-2 IgG antibodies prior to COVID-19 vaccination. We estimated an overall seroprevalence of 7.7% at baseline.

All patients were fully vaccinated against COVID-19: 39.8% received BNT162b2 (Pfizer-BioNTech), 53.7% mRNA-1273 (Moderna), 5.9% ChAdOx1 nCoV-19 (Oxford-AstraZeneca), 0.4% Ad26.COV2.S (Johnson & Johnson/Janssen), and 0.3% other vaccines. Adverse events following vaccination were reported in 371 patients (19%), 95.3% were grade 1 or 2. High anti-SARS-CoV-2 IgG antibody titers were observed in 95.3% of patients two weeks after first dose COVID-19 vaccination, with a geometric mean titer of 1274.7 BAU/mL. One hundred and seven patients (5.4%) became infected with SARS-CoV-2 within a median of 250.5 days after full vaccination.

The probability of being seronegative for anti-SARS-CoV-2 IgG antibodies after complete vaccination was significantly higher in males (OR 0.60, 95 %CI 0.35–0.96; $p = 0.034$); in patients older than 66.8 years (for each additional year of age, OR 1.05, 95 %CI 1.02–1.07; $p < 0.001$); with PS ≥ 2 (OR 6.40, 95 %CI 3.71–10.7); $p < 0.001$); with comorbidities (OR 2.82, 95 %CI 1.39–6.81; $p = 0.003$), including cardiovascular disease (OR 2.17; $p = 0.001$) and hypertension (OR 1.64; $p = 0.021$) and also in patients taking concomitant medication (OR 3.44, 95 %CI 1.69–8.30; $p < 0.001$) (Table 1).

The probability of seronegative IgG antibodies following vaccination did not differ significantly between patients receiving active cancer treatment or no treatment ($p = 0.396$). However, significant differences were observed according to the therapy received: patients treated with immunotherapy or oral targeted therapy were less likely to be seronegative than those treated with chemotherapy or radiotherapy (OR 0.56; $p = 0.014$ and OR 0.41; $p = 0.013$, respectively) (Table 2).

We found significant differences in the immune response induced by the different types of COVID-19 vaccines. Compared with patients vaccinated with BNT162b2, those vaccinated with Ad26.COV2.S were up to almost 40 times more likely to be seronegative after vaccination (OR 39.8, 95 %CI 8.60–306; $p < 0.001$), while patients vaccinated with mRNA-1273 were 2.6 times less likely to be seronegative (OR 0.38, 95 % CI 0.24–0.61; $p < 0.001$) (Table 3) (Table 4).

One thousand four hundred and five patients received the second dose of vaccine: 39.6% received the BNT162b2, 54.2% mRNA-1273, 6.1% ChAdOx1 nCoV-19 and 0.1% other vaccines. High levels of anti-SARS-CoV-2 IgG antibody titers were observed in 93.6% of patients after second dose, 6 months after the first dose, with a geometric mean titer of 488.9 BAU/mL.

Table 1
Population demographics and univariate analysis of its association with negative serologic response after vaccination.

Characteristic	Patients (*N*)	Patients (%)	OR	95% CI	*p*-value
Sex					
Male	1332	67.5	[Reference]		
Female	641	32.5	0.60	0.35–0.96	**0.034**
Age (years)	66.8	9.37	1.05	1.02–1.07	**<0.001**
Smoking history					
Never smoker	312	16.0	[Reference]		
Former smoker > 1 year	1059	54.2	1.36	0.74–2.70	0.338
Current smoker	583	29.8	1.07	0.53–2.25	0.859
Performance status					
0–1	1864	94.5	[Reference]		
≥ 2	109	5.5	6.40	3.71–10.7	**<0.001**
Comorbidities (Yes)	1609	81.6	2.82	1.39–6.81	**0.003**
Hypertension (Yes)	851	43.1	1.64	1.08–2.50	**0.021**
Cardiovascular disease (Yes)	414	21.0	2.17	1.38–3.35	**<0.001**
Diabetes mellitus (Yes)	374	19.0	1.19	0.70–1.94	0.515
COPD (Yes)	359	18.2	1.43	0.85–2.30	0.172
Renal insufficiency (Yes)	59	3.0	1.97	0.66–4.63	0.198
Renal disease (Yes)	43	2.2	2.19	0.63–5.63	0.190
Hepatitis (Yes)	53	2.7	1.74	0.51–4.40	0.339
Cerebrovascular disease (Yes)	43	2.2	2.1	0.73–5.99	0.167
Other chronic disease (Yes)	225	11.4	1.17	0.60–2.11	0.625
Active autoimmune disease (Yes)	41	2.1	0.57	0.02–2.64	0.551
Inactive autoimmune disease (Yes)	25	1.3	1.90	0.28–6.58	0.442
Immunocompromised condition (Yes)	5	0.2	NE		
Previous infections (Yes)	83	4.2	1.06	0.31–2.63	0.910
Other comorbidities (Yes)	974	49.4	1.20	0.79–1.83	0.388
Concomitant medication	1458	78.5	3.44	1.69–8.30	**<0.001**

CI, confidence interval; COPD, chronic obstructive pulmonary disease; NE, not estimable; OR, odds ratio.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 2
Clinical characteristics of participants and univariate analysis of its association with negative serologic response.

Characteristic	Patients (*N*)	Patients (%)	OR	95% CI	*p*-value
Cancer type					
NSCLC	1777	90.1	[Reference]		
SCLC	171	8.7	0.73	0.28–1.57	0.452
Other	25	1.3	0.93	0.04–4.46	0.946
Histology					
Adenocarcinoma	1267	71.3	[Reference]		
Adenosquamous carcinoma	14	0.8	3.75	0.53–14.4	0.157
Squamous carcinoma	396	22.3	1.37	0.83–2.22	0.215
NOS/Undifferentiated	61	3.4	NE		
Other	38	2.1	1.90	0.43–5.52	0.345
Disease stage					
IV	1291	66.0	[Reference]		
III	454	23.2	1.19	0.73–1.88	0.478
II	110	5.6	0.39	0.06–1.26	0.13
I	82	4.2	0.52	0.08–1.71	0.328
0	19	1.0	NE		
Receiving cancer treatment (Yes)	1632	82.7	1.29	0.73–2.46	0.396
Chemotherapy	902	55.7	2.80	1.67–4.92	**<0.001**
Immunotherapy	810	49.6	0.56	0.35–0.89	**0.014**
Radiotherapy	186	11.5	2.02	1.11–3.50	**0.024**
Oral targeted therapy	313	19.4	0.41	0.17–0.84	**0.013**
Any AEs cancer treatment	595	32.0	1.50	0.97–2.29	0.065
Immune-related toxicity	143	7.72	1.67	0.82–3.09	0.147
AE grade					
1-2	488	83.4	[Reference]		
3-4-5	99	16.9	1.36	0.56–2.94	0.474

AE, adverse event; CI, confidence interval; NE, not estimable; NOS, not otherwise specified; NSCLC, non-small-cell lung cancer; OR, odds ratio; SCLC, small-cell lung cancer.
Treatment-related AE between 1 month before vaccination and 3 months after vaccination.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 3
1st Dose COVID-19 vaccine types received and clinical outcomes.

Characteristic	Patients (*N*)	Patients (%)	IgG positive N (%)	IgG negative N (%)	OR	95% CI	*p*-value
Total	1973	100	1880	93			
Vaccine type							
BNT162b2 (Pfizer-BioNTech)	785	39.8	733 (39.0%)	52 (55.9%)	[Reference]	[Reference]	[Reference]
mRNA-1273 (Moderna)	1059	53.7	1031 (54.8%)	28 (30.1%)	0.38	0.24–0.61	**<0.001**
ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	116	5.9	109 (5.8%)	7 (7.5%)	0.92	0.37–1.96	0.845
Ad26.COV2.S (Johnson & Johnson/Janssen)	8	0.4	2 (0.1%)	6 (6.5%)	39.80	8.60–306	**<0.001**
Other	5	0.3	5 (0.3%)	0	NE		
Vaccine–related AE (Yes)	371	19.0	360 (19.4%)	11 (11.8%)	0.57	0.28–1.03	0.063
Maximum AE Grade							
1 + 2	342	95.3	335 (96.3%)	7 (63.6%)	[Reference]	[Reference]	[Reference]
3 + 4	17	4.7	13 (3.7%)	4 (36.4%)	14.6	3.33–56.5	**<0.001**
IgG result							
Positive (>7.1 BAU/mL)	1880	95.3					
Negative (≤7.1 BAU/mL)	93	4.7					
Infected before vaccine (Yes)	152	7.7	150 (8.0%)	2 (2.2%)	0.27	0.04–0.87	0.025
Infected after vaccine (Yes)	107	5.4	105 (5.6%)	2 (2.2%)	0.40	0.06–1.28	0.14
IgG results, BAU/mL (95% CI)	1274.7 (189.9–4310.9)						
Median time from vaccine to infection, days (P25-P75)	250.5 (122.0–279.2)						

AE, adverse event; BAU, binding antibody units; CI, confidence interval; NE, not estimable; OR, odds ratio.
Maximum AE (grade 3–4): myocardial infarction, fatigue, myalgia, febrile neutropenia, dyspnea, lymphadenopathy near the vaccine injection site, myasthenia gravis.
Bold values denote statistical significance at the $p < 0.05$ level.

Multivariate logistic regression analysis showed that PS ≥ 2 and chemotherapy were independently associated with a higher probability of being seronegative for anti-SARS-CoV-2 IgG antibodies after full vaccination with OR of 3.68 (95 %CI 1.86–6.97; $p < 0.001$) and 2.29 (95 %CI 1.12–4.85; $p = 0.026$), respectively. On the other hand, vaccination with mRNA-1273 was a factor independently associated with lower odds of being seronegative with OR of 0.52 (95 %CI 0.29–0.91; $p = 0.023$) (Table 5).

At six months, multivariate logistic regression analysis showed that PS ≥ 2, was independently associated with a higher probability of being seronegative after full vaccination with OR of 4.15 (95 %CI 1.73–9.42; $p < 0.001$). On the other hand, received chemotherapy or oral targeted therapy and vaccination with mRNA-1273 were factors independently associated with lower odds of being seronegative after complete vaccination with OR of 0.52 (95 %CI 0.27–0.96; $p = 0.041$), 0.37 (95 %CI 0.13–0.97; $p = 0.053$) and 0.34 (95 %CI 0.19–0.60; p greater than 0.001), respectively (Table 6).

Table 4
2nd Dose COVID-19 vaccine types received and clinical outcomes.

Characteristic	Patients (*N*)	Patients (%)	IgG positiveN (%)	IgG negativeN (%)	OR	95% CI	*p*-value
Total	1405	71.21	1315	90			
Vaccine type							
BNT162b2 (Pfizer-BioNTech)	557	39.6	497 (37.8%)	60 (66.7%)	[Reference]	[Reference]	[Reference]
mRNA-1273 (Moderna)	762	54.2	739 (56.2%)	23 (25.6%)	0.26	0.15–0.42	**<0.001**
ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	85	6.1	79 (6.0%)	6 (6.7%)	0.64	0.24–1.43	0.3
Ad26.COV2.S (Johnson & Johnson/Janssen)	0	0	0	0	NE	NE	
Other	1	0.1	0	1 (1.1%)	NE	NE	
Vaccine–related AE (Yes)	Not available						
Maximum AE Grade	Not available						
1 + 2							
3 + 4							
IgG result							
Positive (>7.1 BAU/mL)	1315	93.6					
Negative (≤7.1 BAU/mL)	90	6.4					
Infected before vaccine (Yes)	Not available						
Infected after vaccine (Yes)	Not available						
IgG results, BAU/mL (95% CI)	488.9 (66.0–3470.2)						
Median time from vaccine to infection, days (P25-P75)	Not available						

AE, adverse event; BAU, binding antibody units; CI, confidence interval; NE, not estimable; OR, odds ratio.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 5
Multivariate regression analysis of factors potentially associated with negative serologic response after full COVID-19 vaccination.

Characteristic	**OR**	**95% CI**	***p*-value**
Sex (female)	0.62	0.32–1.11	0.120
Age (years)	1.03	1.00–1.06	0.087
Performance Status ≥ 2	3.68	1.86–6.97	**<0.001**
Comorbidities (Yes)	1.94	0.82–5.73	0.171
Therapy type			
Chemotherapy	2.29	1.12–4.85	**0.026**
Immunotherapy	0.60	0.33–1.05	0.081
Oral target therapy	0.67	0.22–1.76	0.440
Radiotherapy	1.46	0.74–2.70	0.250
Vaccine type			
BNT162b2 (Pfizer-BioNTech)	[Reference]		
mRNA-1273 (Moderna)	0.52	0.29–0.91	**0.023**
ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	1.93	0.71–4.70	0.170
Ad26.COV2.S (Johnson & Johnson/ Janssen)	NE		
Other	NE		

AE, adverse event; CI, confidence interval; OR, odds ratio; NE, not estimable.
Bold values denote statistical significance at the $p < 0.05$ level.

Table 6
Multivariate regression analysis of factors potentially associated with negative serologic response six months after first dose vaccination against COVID–19.

Characteristic	OR	95% CI	*p*-value
Sex (female)	0.74	0.39–1.34	0.340
Age (years)	1.01	0.98–1.05	0.360
Performance Status ≥ 2	4.15	1.73–9.42	**<0.001**
Comorbidities (Yes)	1.55	0.72–3.89	0.302
Therapy type			
Chemotherapy	0.52	0.27–0.96	**0.041**
Immunotherapy	0.85	0.42–1.67	0.643
Oral target therapy	0.37	0.13–0.97	**0.053**
Radiotherapy	1.73	0.81–3.50	0.138
Vaccine type			
BNT162b2 (Pfizer-BioNTech)	[Reference]		
mRNA-1273 (Moderna)	0.34	0.19–0.60	**>0.001**
ChAdOx1 nCoV-19 (Oxford-AstraZeneca)	0.93	0.26–2.58	0.898
Ad26.COV2.S (Johnson & Johnson/ Janssen)	NE		
Other	NE		

AE, adverse event; CI, confidence interval; OR, odds ratio; NE, not estimable.
Bold values denote statistical significance at the $p < 0.05$ level.

4. Discussion

Previous evidence suggests that cancer patients have an increased risk of SARS-CoV-2 infection, serious complications and mortality with COVID-19 [10–17,24,31]. This is particularly true for advanced disease, hematologic malignancies, and lung cancer [11,16–17,21–24]. However, accurate information on the prevalence of SARS-CoV-2 IgG antibodies in unselected cancer patients is rare and usually limited to small patient series or single-center studies, resulting in considerable variability. In addition, little information is available on the immunogenicity of COVID-19 vaccines in this population, particularly in lung cancer patients. To our knowledge, the SOLID study, which enrolled 1973 lung cancer patients from all over Spain, is the world's largest study to evaluate the immunogenicity and durability of the immune response induced by COVID-19 vaccines in these patients. Overall prevalence of anti-SARS-CoV-2 IgG antibodies in our population was estimated at 8% at baseline. This percentage is significantly higher than that of the general population in Spain, estimated at around 5% [8], or that of the general population in other European countries and also worldwide, estimated between 3.4% and 5.5% [7,32–34]. The higher seroprevalence found in our population may reflect the higher risk of SARS-CoV-2 infection in lung cancer patients. It has also been reported that some patients with cancer, particularly those with hematologic malignancies, showed delayed or negligible seroconversion after SARS-CoV-2 infection compared to those without cancer. Other studies show that antibody responses are also significantly lower after the first dose of COVID-19 mRNA vaccine in cancer patients, but often improve after the second dose, even in those receiving active cancer therapy [27–29]. Delaying the second vaccination appears to have no clear benefit, highlighting the importance of early boosting in cancer patients [19]. Beyond the direct benefits to the patients, even limited vaccine-induced protection in cancer patients can have substantial indirect benefits to the general population. Therefore, cancer patients, especially those with lung cancer, should be given priority for COVID-19 vaccination. Cancer societies, including the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO), recommend vaccination of all cancer patients, including those receiving active cancer therapy [35].

Most of our patients (95.3%) were seropositive for SARS-CoV-2 two weeks after first dose vaccination and 93.6% were seropositive six

months after the first dose of vaccine. This demonstrates the high levels of antibody titers observed in lung cancer patients and suggests that lung cancer patients can safely achieve an immune response comparable to that of healthy patients after full-dose vaccination [36]. Some prospective studies evaluating the immunogenicity of COVID-19 mRNA vaccines in cancer patients have recently been published, showing results comparable to those found here. Addeo et al. [37] reported a seroconversion rate of 94% in 131 cancer patients (17% thoracic) who received full vaccination with BNT162b2 and mRNA-1273 vaccines. Consistent with previous evidence, seroconversion rates and antibody titers were significantly lower in patients with hematologic malignancy than in those with solid tumors. Another prospective cohort study of 102 cancer patients (25% lung cancer) receiving active treatment reported that after the second dose of BNT162b2 vaccine, 90% of patients were seropositive [38]. Similarly, in a single-center prospective study of 129 cancer patients (17% lung cancer), the seropositivity rate after the second dose of BNT162b2 vaccine was 84.1% [39]. An interim analysis of another prospective study of 151 cancer patients (95 solid cancers and 56 hematologic cancers) found that after the second dose of the BNT162b2 vaccine, 95% of patients with solid cancers and 60% of patients with hematologic cancers were seropositive [27]. All these studies, like ours, confirm the safety and efficacy of the COVID-19 vaccines in inducing strong immune responses in cancer patients following full-dose vaccination, particularly in patients with solid tumors, even those receiving active cancer treatment.

A direct association between antibody response to vaccination and effective protection against SARS-CoV-2 infection has not been well established in cancer patients. However, only 5.4% of our patients contracted SARS-CoV-2 after complete vaccination. Some recent reports point in this direction, seropositivity is associated with protection against SARS-CoV-2 infection and that infection could be used as a surrogate endpoint for vaccine efficacy [40–41]. Although vaccine-induced cellular immunity against COVID-19 has been observed in cancer patients at rates similar to those observed in healthy individuals, it is not expected to prevent SARS-CoV-2 infection to reduce the severity of the disease [42–44].

Most immunogenicity studies in cancer patients have evaluated the mRNA-based COVID-19 vaccines BNT162b2 and mRNA-1273. In our study, most patients (93.5%) also received these vaccines (39.8% and 53.7%, respectively), so our results are reasonably comparable to all previously published results. Multivariate logistic regression analysis showed that complete vaccination with mRNA-1273 vaccine was associated with a significantly higher probability of being seropositive than BNT162b2 vaccine, six months after the first and second doses (OR for seronegative 0.34; p greater than 0.001). Thakkar et al. [45] found similar seropositivity rates in cancer patients after full vaccination with BNT162b2 or mRNA-1273 vaccines (95% vs. 94%, respectively), but reported higher IgG titers with the mRNA-1273 than with BNT162b2 (median 11,963 AU/mL vs. 5,173 AU/mL, respectively). They also found a statistically significant positive association between the time of vaccination completion and IgG seropositivity ($p = 0.03$).

Baseline multivariate analysis in our cohort showed that PS $\geq$ 2 was also independently associated with a higher probability of being seronegative after full vaccination (OR 3.68, $p < 0.001$). Other studies have also found that coexisting comorbidities, such as hypertension or autoimmune disease, were significantly associated with decreased seropositivity (OR 0.22, $p < 0.012$) [39]. In general, comorbidities are associated with an impaired immune response and thus a higher risk of complications and mortality from COVID-19 [46].

Regarding cancer treatment, we found that patients receiving chemotherapy had lower probability of being seropositive for SARS-CoV-2 after full vaccination compared with other treatments. Some cancer patients, particularly those receiving chemotherapy, receive high doses of systemic steroids, which can attenuate cellular immune responses and antibody production, which may partially explain this observation [47]. On the other hand, although the specific susceptibility to viral infections in patients receiving immunotherapy has not been studied, it seems likely that immune checkpoint inhibitors may enhance the immune response to COVID 19 vaccines, as previously shown in the context of influenza infection [48–49]. Other studies have reported on the effect of cancer treatment on the immunogenicity and safety of COVID-19 vaccines [38,50–51]. Massarweh et al. [38] found that treatment with chemotherapy plus immunotherapy was significantly associated with lower antibody titers in cancer patients after complete vaccination. Similarly, Eliakim-Raz et al. found that treatment with chemotherapy plus immunotherapy or immunotherapy plus biological therapy was significantly associated with lower antibody titers in patients with solid tumors.

Our study has several strengths. The large sample size of unselected patients represents a true reflection of the lung cancer population from all over Spain. All serological analyses were performed centrally in a reference laboratory using a commercially available assay with very high clinical sensitivity and specificity. Moreover, many different clinical parameters were collected that will be potentially useful in determining the profiles of patients who respond or do not to the COVID-19 vaccine. The study also has limitations. In terms of determining immunogenicity, the main limitation is the lack of data on cellular immunity, which would probably have provided more complete information on the protective mechanisms of the vaccine. In addition, the percentage of patients who received non-mRNA COVID 19 vaccines, especially Ad26. COV2.S, was very low, making it difficult to draw robust conclusions in this group of patients. We did not have information on the Omicron variant at that time.

In conclusion, our study suggests that lung cancer patients can safely achieve a strong immune response against SARS-CoV-2 after full vaccination, regardless of whether they are receiving active cancer treatment or not. Specifically, patients receiving immunotherapy or oral targeted therapy are more likely to be seropositive, as are patients immunized with mRNA-1273 vaccine. In contrast, the probability of being seronegative after full vaccination was significantly higher in males, patients older than 66.8 years, with PS $\geq$ 2, comorbidities (cardiovascular disease and hypertension) and those taking concomitant medications.

Immunogenicity data for the COVID-19 vaccine six months after the first dose were analyzed and showed that PS $\geq$ 2 was independently associated with a higher probability of being seronegative. However, received chemotherapy or oral targeted therapy and vaccination with mRNA-1273 were independently associated with a lower likelihood of being seronegative. This is important because it provides information on the durability of the vaccine-induced immune response in lung cancer patients and emphasizes the importance of revaccination, for example, in patients with PS $\geq$ 2.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data sharing statement

The data analyzed and presented in this study are available from the corresponding author on reasonable request, providing the request meets local ethical and research governance criteria after publication. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. A research proposal should be included, which will be evaluated by the Spanish Lung Cancer Group and the Ethic Committee for clinical investigation.

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