ORIGINAL ARTICLE

Impaired Seroconversion After Severe Acute Respiratory Syndrome Coronavirus 2 mRNA Vaccine in Patients With Thymic Epithelial Tumors

Erica Pietroluongo, MD,[a] Pietro De Placido, MD,[a] Marianna Tortora, PhD,[b] Claudia Martinelli, MD,[a] Angela Viggiano, MD,[a] Maria Rosaria Saponaro, MD,[a] Aldo Caltavituro, MD,[a] Roberto Buonaiuto, MD,[a] Rocco Morra, MD,[a] Margaret Ottaviano, MD, PhD,[b,c] Vitantonio Del Deo, ScD,[b] Gustavo Cernera, PhD,[d,e] Monica Gelzo, PhD,[d,e] Anna Maria Malfitano, PhD,[f] Michele Francesco Di Tolla, PhD,[f] Carmine De Angelis, MD, PhD,[a] Grazia Arpino, MD, PhD,[a] Daniela Terracciano, PhD,[f] Roberto Bianco, MD, PhD,[a] Bianca Maria Veneziani, MD,[g] Pietro Formisano, MD, PhD,[f] Giuseppe Castaldo, MD, PhD,[d,e] Giovannella Palmieri, MD,[b,*] Sabino De Placido, MD,[a,b] Mario Giuliano, MD, PhD[a,b]

[a]*Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy*
[b]*Rare Tumors Coordinating Center of Campania Region (CRCTR), Naples, Italy*
[c]*Unit of Melanoma, Cancer Immunotherapy and Development Therapeutics, Italian National Cancer Institute— Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Pascale Foundation, Naples, Italy*
[d]*CEINGE, Biotecnologie Avanzate, Naples, Italy*
[e]*Department of Molecular Medicine and Medical Biotechnologies, University of Naples Federico II, Naples, Italy*
[f]*Department of Translational Medical Sciences, University "Federico II," Naples, Italy*
[g]*Department of Molecular Medicine and Medical Biotechnologies, University of Naples "Federico II," Naples, Italy*

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ABSTRACT

Introduction: Thymic epithelial tumors (TETs) are rare malignancies associated with dysregulation of the immune system and humoral- and cell-mediated immunity abnormalities. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine is effective in preventing coronavirus disease 2019 morbidity and mortality. The aim of this study was to evaluate the seroconversion in patients with TET after two doses of mRNA vaccine.

Methods: This is a prospective study in which consecutive patients with TET were enrolled before receiving the first dose of SARS-CoV-2 mRNA vaccine (BNT162b2 by Pfizer-BioNTech). SARS-CoV-2 spike-binding immunoglobulin (Ig) G antibody serologic levels were analyzed at different time points, including before first vaccine dose (T0), 1 month after the second dose (T2), and 3 months after the second dose (T3).

Results: Overall, 39 patients were included in the analysis. All patients had negative antibody titer results at T0. There were 19 patients (48.7%) in the follow-up with no residual tumor lesion/s (referred as no evidence of disease), and 20 (51.3%) had evidence of disease (ED) and were receiving systemic treatment. Dysregulations of the immune system were diagnosed in 29 patients (74.4%) with Good syndrome (GS) being the most frequent immune disorder (48.7%). At univariate analysis, lack of seroconversion at T2 was significantly associated with ED ($p < 0.001$) and with GS ($p = 0.043$). A significant association with impaired seroconversion was confirmed at multivariate analysis for ED ($p = 0.00101$) but not for GS ($p = 0.625$).

Conclusions: Our data revealed that patients with TET with ED had substantially higher probability of impaired

*Corresponding author.

Drs. Pietroluongo and P. De Placido contributed equally as co-first authors.

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Address for correspondence: Giovannella Palmieri, MD, Rare Tumors Coordinating Center of Campania Region (CRCTR), Naples, Italy. E-mail: palmierigiovannella2@gmail.com

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seroconversion after SARS-CoV-2 mRNA vaccine as compared with patients with no evidence of disease.

Keywords: Thymic epithelial tumors; Autoimmunity; Seroconversion; COVID-19; SARS-CoV-2; Vaccine

Introduction

Thymic epithelial tumors (TETs) are rare malignancies which originate from thymic epithelial cells and include thymomas, thymic carcinomas, and thymic neuroendocrine tumors.

The thymus is a central organ involved in the development of the immunologic repertoire of each individual. B and T lymphocytes originate in the bone marrow from a common precursor; B cells complete their development in the bone marrow and enter the circulation as mature lymphocytes, whereas the precursors of T cells migrate to the thymus, which represents the primary site of T lymphopoiesis. This may be the reason for which thymic malignancies are characterized by the coexistence of paraneoplastic syndromes, generally of an autoimmune nature.[1]

Good syndrome (GS) described for the first time in 1956 by Robert A. Good, who reported the first clinical case of hypogammaglobulinemia secondary to thymoma,[2] is diagnosed in approximately 0.2% to 6% of thymoma.[3] It is a rare adult immunodeficiency, most often associated with histotype A of thymoma. The pathophysiology underlying the immunodeficiency of patients with GS is still uncertain. The immunologic phenotyping of patients with GS reveals a deficiency of immunoglobulins (serum immunoglobulin G [IgG], immunoglobulin A (IgA), and immunoglobulin M [IgM]), low or absent B cells, inversion of CD4/CD8 lymphocyte ratio, and reduction of regulatory T-cell lymphocytes.[4] Immunodeficiency associated with GS seems to be severe; thus, the main cause of death in these patients are opportunistic infections.[5]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with TET needs to be managed with particular caution because it could be associated with particularly severe and complex clinical features.[6]

Currently, no data are available regarding the short- and long-term prognosis associated with SARS-CoV-2 infection in patients with TET, with or without paraneoplastic immune disorders. Moreover, there is no evidence regarding the development of immunization after the administration of the anti–SARS-CoV-2 vaccine in patients with TET, as these data are available only for healthy subjects[7] and for unselected patient populations with cancer.[8]

Here, we report the results of a prospective study carried out in patients with TETs to assess post-vaccine immunization and to evaluate whether it was affected by the presence of concomitant immune system dysfunctions, disease status, and antitumor treatments.

Materials and Methods

Study Design and Participants

This was a prospective study in which consecutive patients with thymic tumors, referred to the Regional Coordinating Center for Rare Tumors of Campania Region, at University Hospital Federico II (Naples, Italy), were enrolled from April 2021 to November 2021. All patients entered the study before receiving the first dose of SARS-CoV-2 mRNA vaccine (BNT162b2 by Pfizer-BioNTech), administered at the vaccination Center of University Hospital Federico II.

Inclusion criteria consisted of the following: age equal or older than 18 years, histologic diagnosis of thymoma or thymic carcinoma, known status (presence versus absence) of paraneoplastic autoimmune disorders, known disease status, defined as evidence of disease (ED) or no residual tumor lesion/s (no ED [NED]).

Patients with history of SARS-CoV-2 infection diagnosed before administration of first vaccine dose were excluded from the analysis (Fig. 1).

Immune-related disorders were diagnosed as per national guidelines,[9] using the following criteria:

1. Diagnosis of GS was defined by hypogammaglobulinemia, low or absent B cells, abnormal CD4/CD8 T-cell ratio, CD4 T-cell lymphopenia, and impaired T-cell mitogenic responses, associated with increased susceptibility to infections owing to encapsulated bacteria, fungi, or viruses.
2. Diagnosis of myasthenia gravis (MG) was defined by the presence of positive antibodies directed against postsynaptic antigens, muscle cholinergic receptor, muscle tyrosine kinase, or LRP4, accompanied or not by clinical signs of ptosis, diplopia, or muscle weakness.

In all the cases, the diagnosis of immune-related disorders was known before the study enrollment.

Clinical and anamnestic assessments were also performed every 4 weeks after vaccine administration for up to 12 months, to identify autoimmune disorder onset or worsening after vaccine.

Anti-SARS-CoV-2 Serologic Test

Anti–SARS-CoV-2 serologic test SARS-CoV-2 spike-binding IgG antibody serologic levels were centrally analyzed by chemiluminescent immunoassay at different time points: T0 (before the first vaccine dose), T1 (1 wk after the second dose), T2 (1 mo after the second dose),

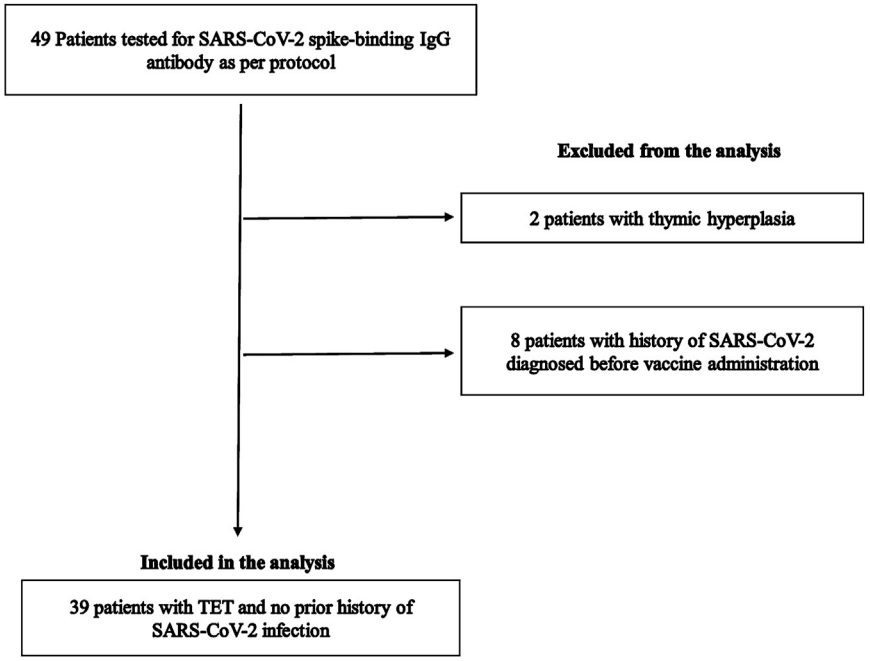

Figure 1. Study flowchart. IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TET, thymic epithelial tumor.

and late monitoring T3, T4, T5, and T6 (at 3, 6, 9, and 12 mo ± 2 wk after the second dose, respectively). Serum samples collected at the different time points were analyzed using Liaison SARS-CoV-2 TrimericS IgG chemiluminescent immunoassay kits provided by DiaSorin according to the manufacturer's protocol. Anti–SARS-CoV-2 IgG antibody levels were expressed in arbitrary binding units/mL of the WHO international standard (NIBSC code 20/268). Samples with values more than or equal to 33.8 arbitrary binding units/mL were considered positive.[10] White blood cell counts, absolute lymphocyte, neutrophil, monocyte, eosinophil, and basophil counts, including serum levels of immunoglobulins (IgA, IgG, IgM), were assessed at the same time points.

Ethical Aspects

The study was approved by the Ethical Committee of University of Naples Federico II protocol #201/20. All enrolled patients signed an informed consent at study entrance.

Statistical Analysis

Statistical analyses were performed using R Statistical Platform (https://www.R-project.org/) and the GraphPad Prism 8.2 software (GraphPad Software Inc., San Diego, CA), as previously described.[11] Briefly, to establish continuous variable distribution, the Shapiro-Wilk test was performed. According to the outcome, parametric distributions were reported as mean (range), whereas nonparametric distributions were reported as median (25th–75th percentile). Differences among parametric distributions were analyzed with a two-tailed Welch's t test for independent samples, whereas, for nonparametric distributions, a Mann-Whitney U test was used. Categorical distributions were reported as number of cases (relative percentage). Associations among categorical variables were analyzed with the Fisher's exact test. In case of statistical significance, the OR and its relative 95% confidence interval (CI) were reported. To further validate significant univariate associations between seroconversion levels at T2 with other parameters, and to investigate the potential effect of covariates, multivariable logistic regression models were built. OR and its relative 95% CI were reported. All p values lower than 0.05 were considered statistically significant.

Results

Patient Clinical Features

A total of 39 patients with TET with no prior history of SARS-CoV-2 infection were included in the analysis (Fig. 1). Patients and tumor characteristics are reported in Table 1. Overall, 29 patients had thymoma (74.4%) and 10 thymic carcinoma (25.6%). All patients had an Eastern Cooperative Oncology Group Performance Status (PS) less than or equal to 1. Autoimmune disorders were detected in 29 patients (74.4%), of whom 19 had GS (48.7%) and 13 MG (33.3%); of note, six of these

Table 1. Patient and Tumor Characteristics

Characteristics	Number of Patients (%)
Age, median (range)	58 (32-80)
Male	17 (43.6)
Female	22 (56.4)
ECOG PS	
0	33 (84.6)
1	6 (15.4)
Histologic type Thymoma	29 (74.4)
A	2 (5.1)
AB	8 (20.5)
B1	3 (7.7)
B2	9 (23.1)
B1-B2	1 (2.6)
B2-B3	2 (5.1)
B3	3 (7.7)
Not otherwise specified	1 (2.6)
Thymic carcinoma	10 (25.6)
Radiological stage of disease according to TNM	
I	7 (17.9)
II	4 (10.3)
III	2 (5.1)
IVA	15 (38.5)
IVB	11 (28.2)

ECOG PS, Eastern Cooperative Oncology Group performance status.

patients had both MG and GS and three patients (7.7%) had other autoimmune disorders (Table 2). At the time of study enrollment, 19 patients (48.7%) were in the follow-up with no residual tumor lesion/s and were referred as NED; the remaining 20 patients (51.3%) had evidence of the disease and were receiving systemic treatment (ED) (Table 3).

Seroconversion at T2

All the 39 patients included in the analysis had negative antibody titer results and no prior SARS-CoV-2 infection at T0. Overall, after 1 month since the second vaccine dose (T2), 17 of these 39 patients (43.6%) had positive SARS-CoV-2 spike-binding IgG antibody levels, whereas 19 patients (48.7%) did not achieve a seroconversion; for three patients (7.7%), antibody titer levels were not available at this time point. The rate of seroconversion was 11.8% among the patients with ED and 78.9% among the patients in the follow-up without evidence of tumor lesions. The negative association between seroconversion at T2 and ED was statistically significant ($p < 0.001$, OR = 0.036, 95% CI: 0.007–0.248) (Fig. 2*A*). This association retained its significance when adjusted for GS, histologic tumor type, and presence of any autoimmune disorders ($p = 0.00101$, OR = 0.039, 95% CI: 0.004–0.224) (Table 4). Moreover, the correlation between seroconversion at T2 and ED was statistically significant in patients with thymoma ($p = 0.0018$), but not in those with thymic carcinoma ($p = 0.143$), although in the latter case the lack of significance could be owing to the small sample size (Supplementary Fig. 1).

Table 2. Immune-Related Disorders

Immune-Related Disorder	Number of Patients (%)
Any immune-related disorder	29 (74.4)
GS	19 (48.7)
MG	13 (33.3)
Concomitant GS and MG	6 (15.4)
Other immune-related disorders	3 (7.7)

GS, Good syndrome; MG, myasthenia gravis.

The rate of seroconversion at T2 was 29.4% among the 17 patients with GS and 63.1% among those without GS. Lack of seroconversion at T2 was significantly associated with the presence of GS ($p = 0.043$, OR = 0.243, 95% CI: 0.056–0.988) (Fig. 2*B*), but not with MG ($p = 0.732$) or presence of any immune-related disorder ($p = 0.255$; Fig. 2*C*). Nevertheless, the association between seroconversion at T2 and GS was no longer significant when adjusted for ED, histologic tumor type, and presence of any autoimmune disorders ($p = 0.625$, OR = 0.585, 95% CI: 0.063–5.374) (Table 4).

Of note, six of the 17 patients with GS (35.3%) were in the follow-up with NED; thus, we assessed the association between disease status and seroconversion rate among the patients with GS. The rate of seroconversion in the patients with GS and ED was 9.09% as compared with 66.7% observed in the patients with GS and NED. This association was statistically significant ($p = 0.028$, OR = 0.050, 95% CI: 0.004–0.773) (Fig. 2*D*).

Conversely, seroconversion at T2 was not significantly associated with histologic type (thymoma versus thymic carcinoma, $p = 0.695$; Fig. 2*E*).

The systemic treatments administered in the patients with ED at the time of study entry, together with the corresponding seroconversion rates, are reported in Table 3. There were 11 patients (55.0%) receiving etoposide-based chemotherapy. Among the 15 patients with ED who did not achieve a seroconversion at T2, nine (60%) were receiving chemotherapy. In all nine cases, the administered treatment was oral low-dose etoposide. Importantly, lack of seroconversion at T2 was not significantly associated with either baseline serum IgA, IgM, and IgG levels or baseline white blood cell, lymphocytes, and neutrophil counts (Fig. 3A to F).

Seroconversion at T3

SARS-CoV-2 spike-binding IgG antibody levels evaluated 3 months after receiving the second vaccine dose (T3) were available in 38 of the 39 patients included in the analysis (97.4%). The rate of seroconversion at T3 remained substantially lower in the patients with ED

Table 3. Systemic Treatment Administered at Study Entry and Seroconversion in Patients With ED

Treatment	Total	Rate of Seroconversion at T2, %	Rate of Seroconversion at T3, %
Etoposide-based chemotherapy	11	0[a]	9.1
Octreotide-LAR plus dexamethasone	8	25.0	25.0
Immunoglobulins	1	N/A	0
Total	20	11.8	15.0

Note: Etoposide-based chemotherapy: seven single oral low-dose etoposide; two pembrolizumab + oral low-dose etoposide; one capecitabine + oral low-dose etoposide; one octreotide lar + oral low-dose etoposide.
[a]Data on seroconversion at T2 were not available for two patients in the treatment with etoposide-based chemotherapy.
ED, evidence of disease; LAR, long-acting release; N/A, not available.

(15.0%) as compared with those with NED (66.7%). This difference was statistically significant in the univariate analysis ($p = 0.002$, OR = 0.088, 95% CI: 0.023–0.435) and remained significant in the multivariate analysis after adjusting for GS, histologic tumor type, and presence of any autoimmune disease ($p = 0.00101$, OR = 0.041, 95% CI: 0.004–0.236). Of note, 10 of the 17 patients (58.8%) with ED who did not achieve seroconversion at T3 were receiving etoposide-based chemotherapy.

The rate of seroconversion at T3 in the patients with GS was not significantly different in comparison to those without GS (26.3% versus 52.6%, respectively, $p = 0.184$). None of the other variables, including histologic type, MG, and presence of any autoimmune disease, was significantly associated with seroconversion at T3.

None of the enrolled patients experienced serious adverse events related to vaccine administration, and no new immune-related disorder or flare occurred during the subsequent follow-up.

Discussion

Research Context and Rationale

The BNT162b2 vaccine was found to be safe and effective in preventing coronavirus disease 2019 (COVID-19) disease in the general population in pivotal vaccine trials.[12] There are several reports revealing the safety and efficacy of anti–SARS-CoV-2 vaccines, including the BNT162B2, in patients with cancer. Most studies revealed that seroconversion rates were lower in patients with cancer than in healthy controls.[8,13–15] Limited evidence exists on particularly frail patient subpopulations with cancer, such as those with tumor- or treatment-related disorders, including

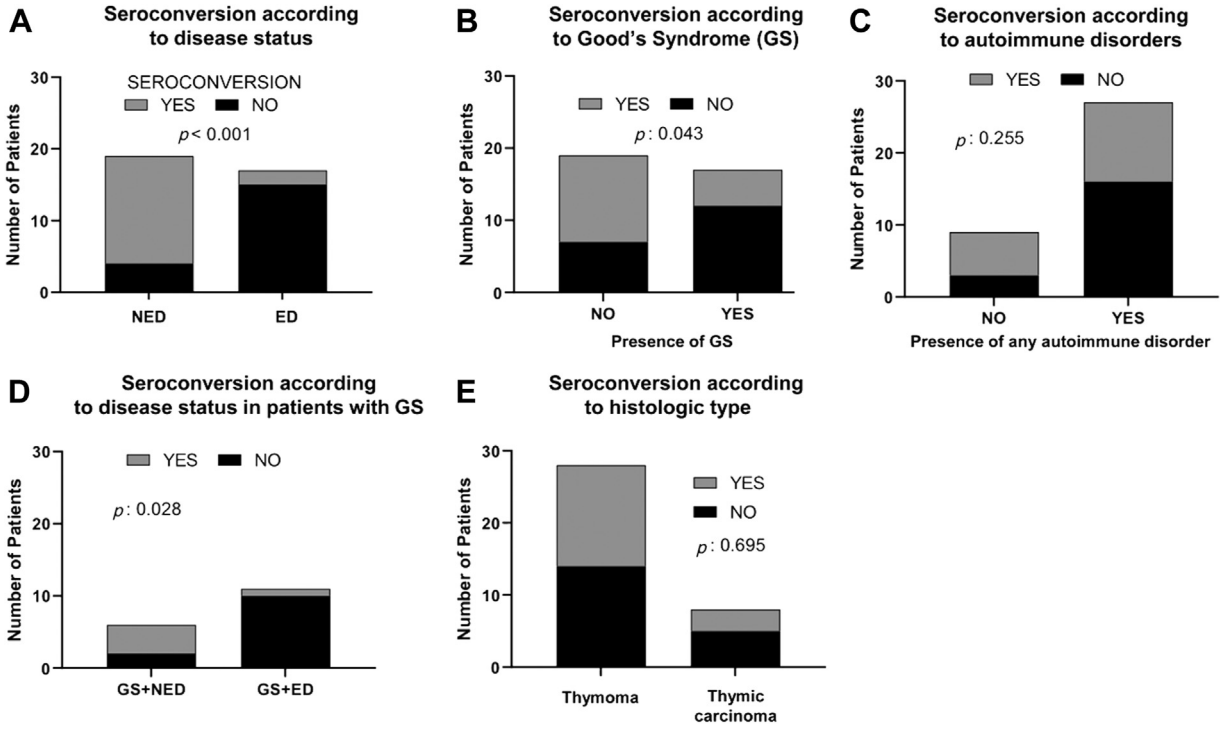

Figure 2. Association between seroconversion at (*A*) T2 and ED, (*B*) GS, (*C*) presence of any immune disorder, (*D*) ED in patients with GS, and (*E*) histologic type. ED, evidence of disease, GS, Good syndrome; NED, no evidence of disease.

Table 4. Univariate and Multivariate Logistic Regressions for Seroconversion at T2

	Univariate Model		Multivariate Model (S: ED + GS + HT + AD)	
Variable	Odds	*p* Value	Odds	*p* Value
ED	0.036 (0.004-0.188)	**0.000385*** **	0.039 (0.004-0.224)	**0.00101** **
GS	0.243 (0.056-0.943)	**0.0475***	0.585 (0.063-5.374)	0.625
HT	1.667 (0.341-9.423)	0.534	1.977 (0.233-18.82)	0.531
AD	0.344 (0.062-1.596)	0.186	0.501 (0.032-6.069)	0.592

Note. For each one of the reported variables, the univariate logistic regression odds and *p* value for the association with the predicted output of seroconversion at T2 are illustrated. In addition, the multivariable logistic regressions were built and reported. All odds are represented as estimate (95% confidence interval). All *p* values less than 0.05 are considered statistically significant. Emboldened p-values are less than 0.05 and therefore considered statistically significant (*p Value < 0.05; **p Value < 0.01; ***p Value < 0.001).
AD, presence of any autoimmune disorder; ED, evidence of disease; GS, Good syndrome; HT, histologic type.

immunodeficiency and autoimmune diseases. Despite this lack of evidence, several scientific societies had established recommendations for vaccination of all patients with cancer, regardless of the administration of systemic treatments and cancer histological features,[16,17] in the attempt to reduce COVID-19 morbidity and mortality and to avoid anticancer treatment interruptions and delay owing to the disease. In this complex scenario, we carried out a prospective study assessing antibody response to BNT162B2 mRNA vaccine in patients with TET with or without cancer-related immune system abnormalities.

Potential Reasons for Altered Response to Vaccine in Patients With TET

Disease-Related Features and Systemic Treatment. We found a statistically significant association between seroconversion rates and ED in the patients with TET. Despite the limited sample size, we believe that our findings are particularly relevant and have

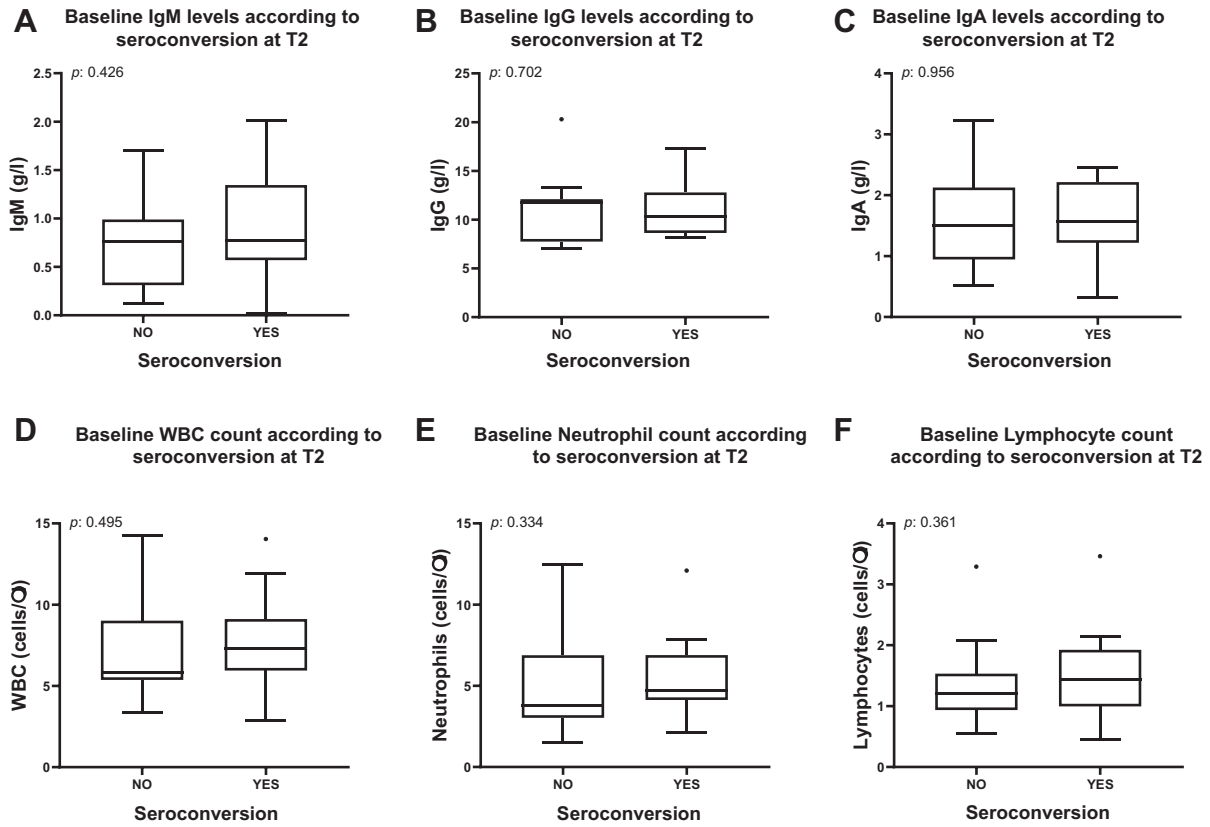

Figure 3. Comparison of baseline (*A*) IgM serum levels, (*B*) IgG serum levels, (*C*) IgA serum levels, (*D*) WBC count, (*E*) neutrophil count, and (*F*) lymphocyte count according to seroconversion at T2. IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; WBC, white blood cell.

potential clinical implications, considering that seroconversion at T2 was observed only in 11.8% of the patients with TET with ED. Moreover, the significant association between impaired seroconversion and ED was confirmed at multivariate analysis and consistently observed at a longer follow-up (i.e., at T3, 3 mo after the second vaccine). Therefore, it could be hypothesized that the lack of immunization in the patients with TET could be linked to immune dysregulation associated with active tumor disease affecting thymic gland.

Nevertheless, it might be argued that our findings are mostly related to the administration of immunosuppressive anticancer treatments, rather than to disease status, and that this would be independent from the cancer type and disease stage. Nevertheless, a relevant association between lack of seroconversion and anticancer treatments has been found mostly in patients with hematologic cancer treated with specific B-cell immunosuppressive therapy.[13–15,18–20] We recently completed a prospective observational study evaluating safety and immunogenicity of BNT162b2 in patients with breast and gynecologic cancers receiving antitumor treatments. Immune responses to the BNT162b2 vaccine were assessed in the same laboratory and using the same methods as those used in the present study. Overall, 86% of the patients with cancer achieved seroconversion after the second dose of the BNT162b2 vaccine. Importantly, there were no statistically significant differences in seroconversion rates between patients treated with chemotherapy and those receiving target therapy.[21] These results may suggest that the impaired seroconversion observed in the patients with TET may depend on disease-related mechanisms rather than concurrent administration of myelotoxic chemotherapy. As further support to this hypothesis, we observed that most patients with ED who did not achieve seroconversion were not receiving treatments to be considered particularly myelotoxic. Indeed, the most frequently administered treatment in these patients was metronomic etoposide, which is not reported to be particularly myelotoxic or to cause immunosuppression.[22] Moreover, lack of seroconversion at T2 was not associated with either total leucocyte, neutrophil, and lymphocyte counts or total IgG, IgM, and IgA levels.

Immune-Related Disorders. A recent study on immunization of patients affected by autoimmune diseases revealed that a fairly high percentage of patients (88.6%) achieved seroconversion.[23] Consistent results were also reported in a study including patients with inborn errors of immunity.[24] Nevertheless, it is still not clear whether the presence of cancer-related immune disorders could impair response to vaccination.

For this reason, our study cohort, which was particularly enriched of patients with GS and other TET-related immune disorders, may contribute to address this issue. Most patients with TET are referred to our Center from different regional and extraregional hospitals as they have particularly complex diseases and thus require high expertise and multidisciplinary management. These patients are extensively and systematically screened for autoimmune diseases and immunodeficiency.

We found no association between MG or other TET-related autoimmune disorders and impaired seroconversion. In contrary, we observed a statistically significant association between GS and impaired seroconversion at T2 in the univariate but not in the multivariate analysis.

Our findings may suggest that autoimmune disorders affecting patients with TET may not be a major cause of impaired seroconversion. GS, which depends on complex and largely unknown pathophysiological mechanisms including both autoimmunity and immunodeficiency,[25] may however affect vaccine-induced seroconversion in the patients with TET. Further studies are needed to fully understand the relationship between TET, GS, and response to vaccines, including the underlying mechanisms. We are currently collecting data on cell-mediated immunity in the patients with TET, which may better elucidate the molecular basis of the lack of seroconversion, particularly in the patients with GS.

Additional Factors. Poor PS represents another feature which may be related to altered response to vaccine in the patients with cancer because it identifies patients with worse clinical conditions and potential immune system dysregulations. A significant negative impact on seroconversion by the presence of an Eastern Cooperative Oncology Group PS more than 2 was found.[21] Nevertheless, in our cohort, all patients had PS 0 or 1.

An additional point of interest is that all the eight patients with TET who were excluded from the analysis owing to prior history of SARS-CoV-2 infection (Fig. 1) achieved seroconversion. Indeed, they all had positive anti-spike antibodies at T0, and all but one maintained positive antibody titers at both T2 and T3, regardless of disease status and presence of paraneoplastic immune disorders (data not found). This observation should be confirmed in larger studies which should also investigate the mechanism by which natural viral infections could trigger more effective immune response than that elicited by vaccines.

It could be also hypothesized that the patients with TET with ED may not respond to mRNA-based vaccines. Currently, there are no data supporting this theory; thus, further studies are needed to clarify this critical issue that may have important implications for the development of more effective vaccine strategies.

Conclusions and Clinical Implications

To the best of our knowledge, this is the first study evaluating the response to SARS-CoV-2 mRNA vaccine in a selected population of patients with TET. The major limitation of this study is the relatively limited sample size. Nevertheless, this should be put in the epidemiologic context depicting thymic tumors as extremely rare malignancies. Another limitation of our study is the lack of a T-cell response assessment, although it is hypothesized that humoral response could be considered a proper surrogate marker of protection against SARS-CoV-2 infection.[26]

Overall, our results suggest that patients with active TET should be carefully monitored for SARS-CoV-2 infection and considered for enhanced vaccine protocols or alternative strategies of immunization, such as monoclonal antibodies. Therefore, we have implemented in clinical practice a continued monitoring strategy for patients with TET to identify those not responding to vaccine booster and thus candidate to prophylactic therapy with monoclonal antibodies, such as tixagevimab and cilgavimab, as recommended by the European Medicines Agency.[27–30] Importantly, our results may have significant clinical implications for frail patients with cancer not only in the context of COVID-19 but also of other infectious diseases.

CRediT Authorship Contribution Statement

Erica Pietroluongo: Conceptualization, Data curation, Investigation, Formal analysis, Writing—original draft preparation, Validation, Visualization, Writing—review and editing.

Pietro De Placido: Conceptualization, Data curation, Investigation, Formal analysis, Writing—review and editing, Validation, Visualization.

Marianna Tortora: Data curation; Formal analysis, Methodology, Software, Validation, Visualization, Writing—review and editing.

Claudia Martinelli: Data curation, Writing—review and editing.

Angela Viggiano: Data curation, Writing—review and editing.

Maria Rosaria Saponaro: Data curation, Visualization, Writing—review and editing.

Aldo Caltavituro: Data curation, Writing—review and editing.

Roberto Buonaiuto: Data curation, Writing—review and editing.

Rocco Morra: Data curation, Writing—review and editing.

Vitantonio Del Deo: Data curation, Writing—review and editing.

Margaret Ottaviano: Conceptualization, Validation, Formal analysis, Visualization, Writing—review and editing.

Gustavo Cernera: Visualization, Writing—review and editing.

Monica Gelzo: Visualization, Writing—review and editing.

Anna Maria Malfitano: Validation; Visualization, Writing—review and editing.

Michele Francesco Di Tolla: Formal analysis, Software, Writing—review and editing.

Carmine De Angelis: Validation, Visualization, Writing—review and editing.

Grazia Arpino: Validation, Visualization, Writing—review and editing.

Daniela Terracciano: Methodology; Validation, Visualization, Writing—review and editing.

Roberto Bianco: Visualization, Writing—review and editing.

Bianca Maria Veneziani: Visualization, Writing—review and editing.

Pietro Formisano: Validation, Visualization, Writing—review and editing.

Giuseppe Castaldo: Validation, Visualization, Writing—review and editing.

Giovannella Palmieri: Conceptualization, Investigation, Validation, Visualization, Writing—review and editing.

Sabino De Placido: Project administration, Validation; Visualization, Writing—review and editing.

Mario Giuliano: Conceptualization, Methodology, Writing—review and editing, Supervision, Validation, Visualization.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.06.015.

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