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Clinical Research Article

Increased Risk of Thyroid Eye Disease Following Covid-19 Vaccination

Ilaria Muller,[1,2] Dario Consonni,[3] Erica Crivicich,[1] Francesco Di Marco,[1] Nicola Currò,[2,4] and Mario Salvi[2]

[1]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy
[2]Graves' Orbitopathy Center, Endocrinology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy
[3]Epidemiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy
[4]Ophthalmology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy

Correspondence: Ilaria Muller, MD, PhD, Department of Clinical Sciences and Community Health, University of Milan, Endocrinology Unit—Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milan, Italy. Email: ilaria.muller@unimi.it, ilaria.muller@policlinico.mi.it.

Abstract

Context: SARS-CoV-2 infection and Covid-19 vaccines have been associated with thyroid disorders.

Objective: We analyzed the risk of thyroid eye disease (TED) following Covid-19 vaccination. This was a self-controlled case series study at a tertiary referral center for TED. A total of 98 consecutive patients with newly developed (n = 92) or reactivated (n = 6) TED occurring between January 1, 2021, and August 31, 2022, were included. TED was assessed in patients undergoing Covid-19 vaccination. Person-days were defined as exposed if TED occurred 1 to 28 days after vaccination, and unexposed if occurring outside this time window. Conditional Poisson regression models were fitted to calculate incidence rate ratio (IRR) and 95% CI of exposed vs unexposed. Sensitivity analyses were conducted considering different exposed periods, and effect modification by potential TED risk factors.

Results: Covid-19 vaccines were administered in 81 people, 25 (31%) of whom developed TED in exposed and 56 (69%) in unexposed periods. The IRR for TED was 3.24 (95% CI 2.01-5.20) and 4.70 (95% CI 2.39-9.23) in patients below 50 years of age. Sex, smoking, and radioiodine treatment did not modify the association between TED and vaccination. TED risk was unrelated to the number of vaccine doses, and progressively decreased over time following vaccination (P trend = .03).

Conclusion: The risk of TED was significantly increased after Covid-19 vaccination, especially in people below 50 years of age. Possible mechanisms include spike protein interaction with the angiotensin-converting enzyme II receptor, cross-reactivity with thyroid self-proteins, and immune reactions induced by adjuvants. We suggest monitoring of individuals undergoing Covid-19 vaccination, especially if young and at risk for autoimmunity.

Key Words: thyroid eye disease, Graves orbitopathy, Covid-19 vaccines, SARS-CoV-2

Abbreviations: ACE-II, angiotensin-converting enzyme II; Ad26.COV2.S, Janssen, Johnson & Johnson Covid-19 vaccine; AZD1222, Vaxzevria, Astrazeneca Covid-19 vaccine; BNT162b2, Comirnaty, Pfizer–BioNTech Covid-19 vaccine; Covid-19, Coronavirus disease 2019; EUGOGO, EUropean Group on Graves' Orbitopathy; GD, Graves disease; IRR, incidence rate ratio; mRNA-1273, SpikeVax Moderna Covid-19 vaccine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCCS, self-controlled case series; TED, thyroid eye disease.

The Coronavirus disease 2019 (Covid-19) pandemic was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA virus that emerged in China in late 2019 and quickly spread worldwide (1). The Covid-19 pandemic represented an unprecedented global health emergency, and a major health measure adopted to control it has been the implementation of the greatest and fastest mass vaccination in human history (2, 3). In Italy, where our institution is based, Covid-19 vaccination began in late December 2020 with 4 types of gene-based Covid-19 vaccines, all encoding for the whole SARS-CoV-2 spike protein: 2 mRNA lipid nanoparticle vaccines (BNT162b2 Comirnaty, Pfizer–BioNTech; and mRNA-1273 SpikeVax, Moderna), and 2 DNA adenoviral vector vaccines (AZD1222 Vaxzevria, Astrazeneca; and Ad26.COV2.S, Janssen, Johnson & Johnson) (2).

Several viruses are associated with the onset of thyroid disorders, especially subacute thyroiditis and thyroid autoimmune diseases (4). For instance, some vaccines against common influenza and influenza A virus subtype H1N1 are associated with subacute thyroiditis (5-7). Similarly, cases of subacute or atypical thyroiditis are associated both with SARS-CoV-2 infection (8-10) and Covid-19 vaccination (11, 12).

Newly occurring Graves' disease (GD) has also been reported after SARS-CoV-2 infection (13, 14). GD, also known as autoimmune hyperthyroidism, is caused by autoantibodies stimulating the thyrotropin receptor that determine an excessive production of thyroid hormones (15). About 30% to 50% of patients with GD, and more rarely patients with other autoimmune thyroid diseases, may develop Graves' orbitopathy or thyroid eye disease (TED), characterized by

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inflammatory and congestive orbital tissue changes, leading to face disfiguration, psychological distress, and visual disturbances with risk of sight loss (16, 17). Several reports have described a temporal relation between Covid-19 vaccination and the occurrence of thyroid autoimmunity, including GD and TED (18-26), but until now no clinical studies have assessed the risk of developing TED after Covid-19 vaccination.

In this study, we analyzed the risk of de novo development or reactivation of TED following Covid-19 vaccination in patients attending our TED center, a member of the European Group on Graves' Orbitopathy (EUGOGO) association (27). We have used the self-controlled case series (SCCS) model, a study design specifically for assessing the risks of vaccination, which is well validated in the scientific literature (28, 29). This study type has also been previously used to assess other risks of Covid-19 vaccination, such as thromboembolic and thrombocytopenic events (30), myocarditis (31), and thyroid dysfunction, also including GD (32).

Materials and Methods

Study Population

The study included 98 consecutive patients with newly occurring, or relapsing, TED that occurred between January 1, 2021, and August 31, 2022, who attended our tertiary referral center for TED in the Endocrinology Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. Our TED center represents a valid setting for this study, since it has been operating for 2 decades, and has gained national and international standing for the management of hundreds of patients with TED. The diagnosis of TED was made in a combined endocrine/ophthalmological clinic according to the EUGOGO Guidelines (16) and the Consensus Statement by the American Thyroid Association and the European Thyroid Association (17). Active TED was defined as the presence of a clinical activity score above 3 points out of 7 at the first examination, or 4 points out of 10 at the following examinations. TED severity was classified as mild, moderate to severe, or sight threatening, according to the EUGOGO consensus document (16, 17). We determined the date of TED de novo onset or reactivation based on ocular signs or symptoms reported by patients and objective assessment, as defined in EUGOGO established practice (33). Patients were diagnosed as having de novo occurring TED if they had no previous history of TED, or as having reactivating TED if they had a previous history of TED that suddenly became active or more severe.

The diagnosis of GD was based on the presence of hyperthyroidism with positive autoantibodies to the thyrotropin receptor, or diffusely increased thyroid uptake at scintigraphy. Hashimoto thyroiditis was diagnosed according to the presence of hypothyroidism and positive thyroid peroxidase autoantibodies or thyroglobulin autoantibodies. Patients were also diagnosed with euthyroid TED if they had normal thyroid function, with or without circulating thyroid autoantibodies.

The clinical history of patients was collected, including Covid-19 vaccination or natural infection with SARS-CoV-2, smoking habits, radioiodine treatment, and family history of thyroid and autoimmune disorders. The effective vaccination dates, and information on the vaccine types, were also retrieved from the regional Covid-19 vaccination registry for all residents in the region of Lombardy (n = 67), where our TED center is based.

The study was approved by the ethics committee of Milano Area 2 (document 1036-2022 of 24/11/2022).

Statistical Analysis

We used an SCCS study, following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. The SCCS design is a case-only analysis, in which the relative incidence of clinical events occurring in defined time intervals after vaccination is compared with that of a control period, using only data on cases (28). It is akin to a cohort study, and has been frequently used in pharmacoepidemiology to evaluate adverse events after vaccination (29). The advantage of this model is that comparisons are self-matched, thus automatically adjusting for confounders that do not vary over time, such as sex, ethnicity, genetics, associated diseases, and socioeconomic factors (28, 29).

Since the vaccination campaign in Italy started at the end of December 2020, we elected the period from January 1, 2021, to August 31, 2022, for analysis. For each vaccinated case, we calculated person-days in various time windows after each vaccination dose. Each subject contributed person-time for the entire period. We defined "exposed" (ie, at risk) as 1 to 28 days after each vaccination dose, and "unexposed" as the person-days outside this time window (ie, before Covid-19 vaccination, or 29 days after vaccination and onward) (Fig. 1). Then we fitted conditional (fixed effect) Poisson regression models to calculate the incidence rate ratio (IRR) and the 95% CI of exposed vs unexposed periods.

We performed 3 analyses (29): in analysis 1 we created 4 separated variables of exposure for each of the 4 Covid-19 vaccine doses (not mutually exclusive), and each variable was adjusted for the others; in analysis 2 we created a single variable of exposure with 4 mutually exclusive levels for each vaccine dose, in which we assigned cases and person-days to the most recent dose in overlapping exposed periods; in analysis 3 we created a single 28-day exposure risk period after Covid-19 vaccination, irrespective of the dose number (overall analysis).

We performed 2 sensitivity analyses, 1 restricted to residents in Lombardy (because we had access to the Covid-19 vaccination registry only for residents in this region), and the second restricted to patients with de novo TED. In addition, we analyzed different exposure time windows of 1 to 28, 29 to 56, and 57 to 84 days post-Covid-19 vaccine, and also in 2 more restricted risk periods of 1 to 14 and 15 to 28 days. We studied effect modification by sex, age (<50, 50+ years), cigarette smoking, radioiodine treatment, and Covid-19 vaccine type (mRNA only, DNA only, mixed). Statistical analyses were performed with Stata 17 (StataCorp. 2021), using the commands stset, stsplit, and xtpoisson.

Results

General Characteristics of the Study Population

At the time of analysis, 98 consecutive patients seen in our center, 71 females and 27 males (mean ± SD age 50.8 ± 15.6 years), presented with de novo onset or reactivation of TED in the period from January 1, 2021, to August 31, 2022. Of them, 81 (83%) received at least 1 dose of Covid-19 vaccine, and were considered to be "exposed" if their TED onset/reactivation occurred within 28 days from Covid-19 vaccine

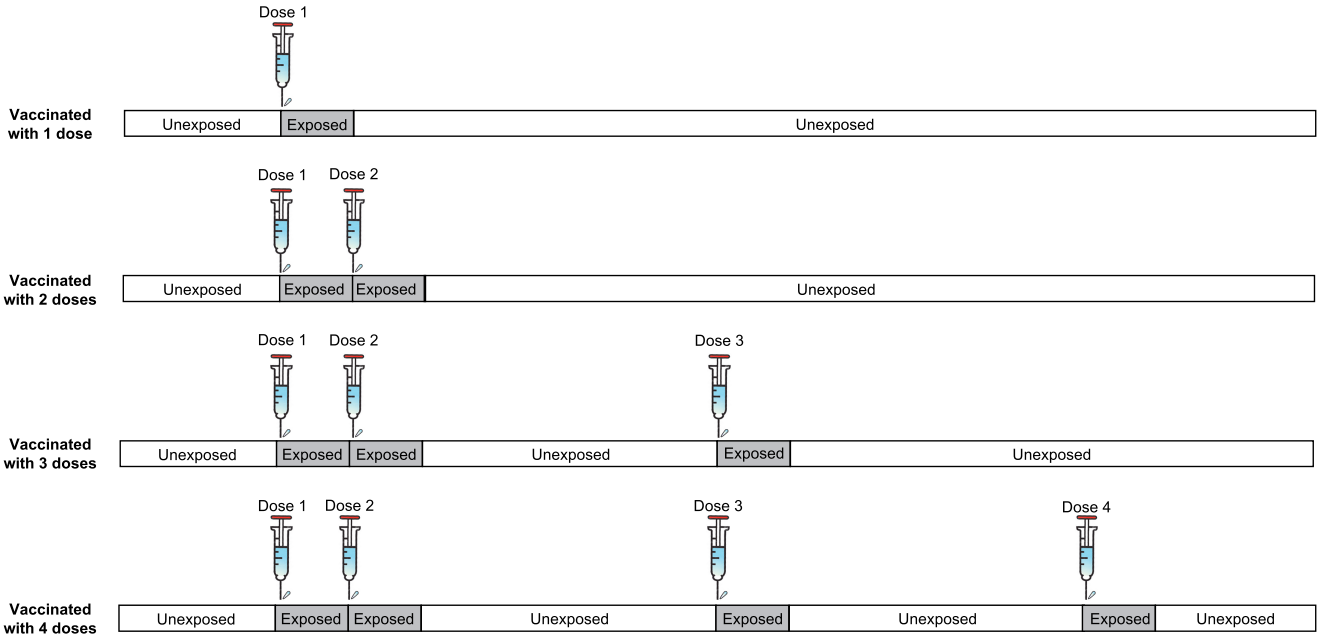

Figure 1 Visual representation of exposed and unexposed periods in relation to Covid-19 vaccine doses administered. Shaded boxes indicate the 1- to 28-day exposed periods following Covid-19 vaccine doses. White boxes indicate the unexposed periods of 29 days or more after Covid-19 vaccination, or before its administration.

administration (any dose), or "unexposed" if TED occurred before or after that period (Table 1 and Fig. 1). Of the remaining 17/98 (17%) patients, 13 never received the Covid-19 vaccine, and 4 had unknown vaccination status. After dose 1, subsequent Covid-19 vaccine doses were administered after a median (interquartile range) of 34 (21-77) days for dose 2, 223 (202-249) days for dose 3 (or booster), and 460 (447-470) days for dose 4 (or second booster) (Fig. 2). Among the 81 vaccinated patients, 65% received 3 doses during the study period, for a total of 220 doses of Covid-19 vaccine administered: 142 (65%) BNT162b2, 48 (22%) mRNA-1273, 27 (12%) AZD1222, and 3 (1%) Ad26.COV2.S.

SARS-CoV-2 infections affected 6/98 (6%) and 23/98 (23%) patients before and during the study period (from January 1, 2021, to August 31, 2022), respectively. In 2 patients the date of infection was unknown (Table 1). Of the 23 patients who contracted SARS-CoV-2 infection during the study period, 14 (61%) developed TED before the infection, 5 (22%) more than 28 days after infection, and only 4 (17%) in the 1- to 28-day window after infection.

Thyroid and TED Characteristics in the Whole Study Population

Table 1 shows the clinical characteristics of patients in relation to their vaccination status. De novo onset TED was diagnosed in 92/98 (94%) patients, and 91/98 patients (93%) had associated GD. The thyroid disease preceded the development of TED in 69/98 (70%) of the patients, while in 29/98 (30%) patients thyroid dysfunction was detected at the same time as TED, or developed later, or had not yet developed by the end of the observation period. The majority of patients were not current smokers (75%) and had no other associated autoimmune diseases (95%). Nine patients (9%) were treated with radioiodine ablation treatment, due to uncontrolled hyperthyroidism, administered 18.7 ± 12.4 months (mean ± SD; range 2.3-36.1 months) before TED onset or reactivation. Fifty-five percent of patients with TED had a positive family history of thyroid or autoimmune disorders. Thyroid function status, at the time of first referral to our TED center, did not show differences among groups.

Table 2 summarizes the clinical characteristics of TED in the entire study population, as presented at the time of the first clinical evaluation at the TED center. There were no differences in the clinical presentation of TED in terms of disease duration, activity, severity, and administered therapy in relation to Covid-19 vaccination status.

Analysis of TED Risk Among Vaccinated Patients

All 81 patients who had received at least 1 dose of Covid-19 vaccine were included in the SCCS analysis, by comparing "exposed" and "unexposed" cases and person-days. Table 3 reports the IRR and 95% CI resulting from the 3 main analyses: (1) nonmutually exclusive Covid-19 vaccine doses; (2) mutually exclusive Covid-19 vaccine doses; (3) overall analysis irrespective of Covid-19 vaccine dose numbers. In only 3 exposed patients, the interval between the first 2 doses of Covid-19 vaccine was less than 28 days, thus both doses were administered in the same 28-day risk period. Therefore analyses 1 (not mutually exclusive) and 2 (mutually exclusive) yielded similar results. Analysis 1 included 22 patients receiving 1 dose, and 3 patients receiving 2 doses (total doses 28), while analysis 2 was conducted based on the last received dose of vaccine only (total doses 25). Since in either analysis 1 and 2 the TED risk did not depend on the number of administered doses (95% CIs were overlapping), analysis 3 was performed based on the most recent dose of vaccine received before TED onset.

Figure 2 summarizes the occurrence of TED in relation to Covid-19 vaccine doses. After restricting the overall analysis

Table 1. Clinical characteristics of patients with TED attending the TED center in Milan, Italy, from January 1, 2021 to August 31, 2022

Variable	TED onset in unexposed periods[a]		TED onset in exposed periods[a]		Vaccination No/Unknown[b]	
	n	%	n	%	n	%
Total	56	100	25	100	17	100
Sex						
Female	38	67.9	18	72.0	15	88.2
Male	18	32.1	7	28.0	2	11.8
Age (years)						
<50	22	39.3	14	56.0	10	58.8
50+	34	60.7	11	44.0	7	41.2
Cigarette smoking						
Never	26	46.4	13	52.0	6	35.3
Former	14	25.0	6	24.0	4	23.5
Current	13	23.2	6	24.0	5	29.4
Missing	3	5.4	0	0.0	2	11.8
TED event						
De novo onset	51	91.1	25	100	16	94.1
Reactivation	5	8.9	0	0.0	1	5.9
Associated thyroid disorder						
Graves' disease	51	91.1	23	92.0	17	100
Hashimoto's thyroiditis	1	1.8	1	4.0	0	0.0
Euthyroid TED	4	7.1	1	4.0	0	0.0
TED onset in relation to the associated thyroid disorder[c]						
Before	6	10.7	3	12.0	1	5.9
After	38	68.0	17	68.0	12	70.6
Concomitant	8	14.3	4	16.0	4	23.5
Thyroid status at first visit						
Hyperthyroid on ATD	7	12.5	0	0.0	4	23.5
Euthyroid on ATD	29	51.8	18	72.0	8	47.1
Euthyroid on LT4	16	28.6	5	20.0	4	23.5
Euthyroid no treatment	4	7.1	2	8.0	1	5.9
Radioiodine treatment for hyperthyroidism						
No	50	89.3	22	88.0	17	100.0
Yes	6	10.7	3	12.0	0	0.0
Other autoimmune disorders						
No	52	92.9	24	96.0	17	100
Yes	4	7.1	1	4.0	0	0.0
Family history of thyroid or autoimmune disorders						
No	20	35.7	14	56.0	8	47.1
Yes	35	62.5	11	44.0	8	47.1
Unknown	1	1.8	0	0.0	1	5.9
SARS-CoV-2 infection						
No	37	66.1	18	72.0	12	70.6
<1 Jan 2021	3	5.4	2	8.0	1	5.9
1 Jan 2021-31 Aug 2022	15	26.8	4	16.0	4	23.5
Yes, date unknown	1	1.8	1	4.0	0	0.0
COVID-19 vaccine						
1 dose	1	1.8	1	4.0		
2 doses	16	28.6	6	24.0		
3 doses	35	62.5	18	72.0		
4 doses	4	7.1	0	0.0		

(*continued*)

Table 1. Continued

Variable	TED onset in unexposed periods[a]		TED onset in exposed periods[a]		Vaccination No/Unknown[b]	
	n	%	n	%	n	%
Vaccine type						
mRNA only	41	73.2	20	80.0		
DNA only	2	3.6	1	4.0		
Mixed	13	23.2	4	16.0		

Abbreviations: ATD, antithyroid drugs; LT4, levothyroxine; TED, thyroid eye disease.
[a]Exposed periods: TED new onset or reactivation in the 1- to 28-day risk period following any Covid-19 vaccination dose. Unexposed periods: TED new onset or reactivation before or after the risk period.
[b]Unvaccinated: n = 13; unknown: n = 4.
[c]Patients with euthyroid TED were excluded, since not presenting thyroid dysfunction.

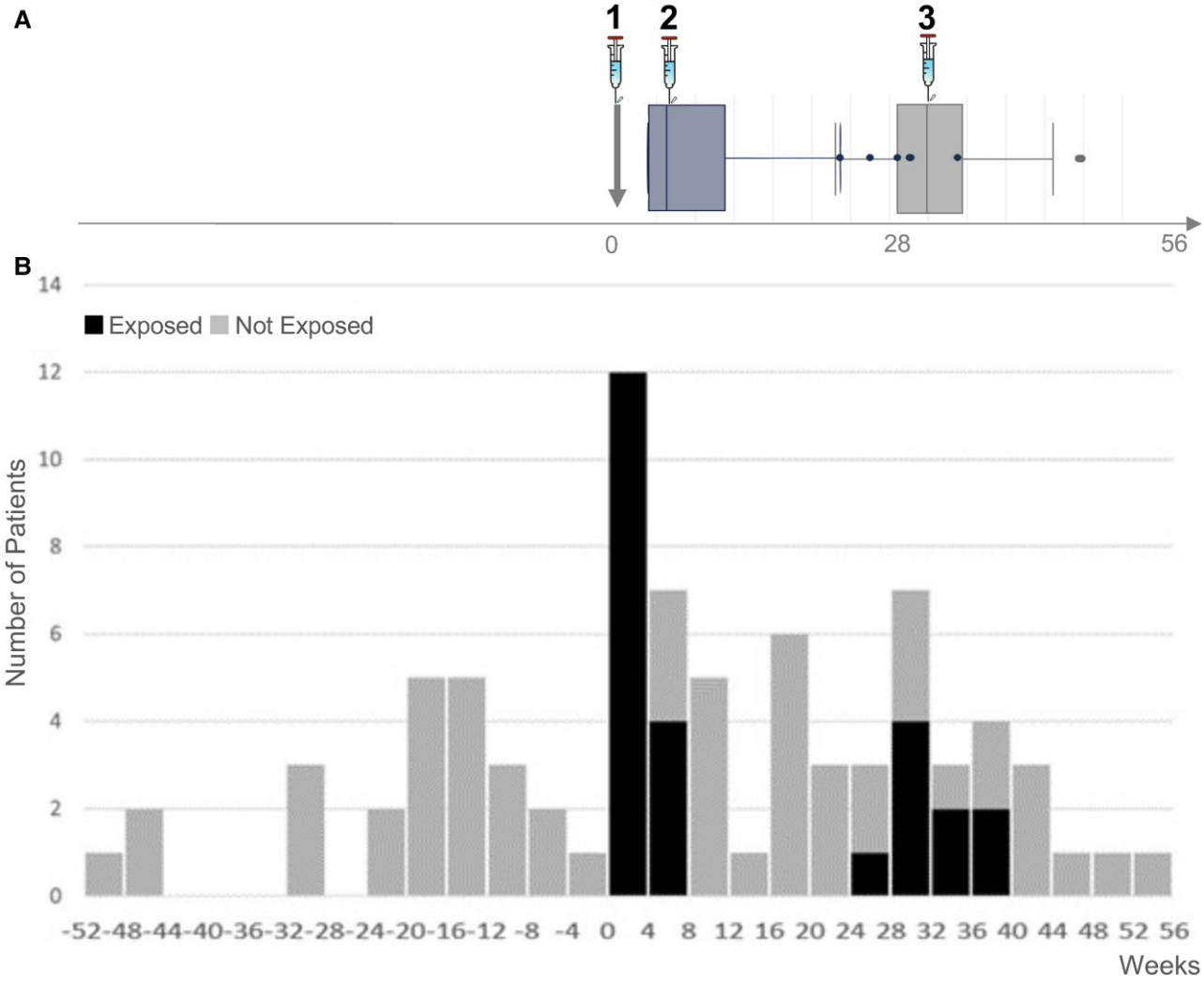

Figure 2 . Covid-19 vaccination and thyroid eye disease (TED) de novo onset or reactivation. (A) Box plots of Covid-19 vaccine doses 2 and 3 (or booster dose) administered following dose 1 (time 0). Dose 4 (or second booster dose) is not represented since it was administered in only 4 patients, all of whom had already developed TED. (B) Histogram of TED de novo onset or reactivation cases observed during the study period in relation to the first dose of Covid-19 vaccine (time 0). Dark and light columns indicate the TED cases that occurred within or outside the 1-to 28-day (4 weeks) risk period after Covid-19 vaccination, respectively.

Table 2. Characteristics of TED presented by patients followed at the TED center in Milan, Italy, from January 1, 2021 to August 31, 2022

TED variable	TED onset in unexposed periods[a]	TED onset in exposed periods[a]	Vaccination No/Unknown	*P*
	n = 56	n = 25	n = 17	
Disease duration weeks (mean ± SD)				
From clinical onset to first visit	27.0 (18.2)	25.3 (16.0)	29.1 (16.5)	.80
Activity n (%)				
Active	16 (28.6)	4 (16.0)	4 (23.5)	.48
Inactive	40 (71.4)	21 (84.0)	13 (76.5)	
Severity n (%)				
Mild	11 (19.6)	4 (16.0)	6 (35.3)	.23
Moderate to severe	36 (64.3)	19 (76.0)	11 (64.7)	
Sight threatening (DON)	9 (16.1)	2 (8.0)	0 (0.0)	
Therapy n (%)[b]				
None	40 (71.4)	20 (80.0)	12 (70.6)	.80
Immunosuppression	13 (23.2)	5 (20.0)	4 (23.5)	
Surgery	3 (5.4)	0 (0.0)	1 (5.9)	

Abbreviations: DON, dysthyroid optic neuropathy; TED, thyroid eye disease.
[a]Exposed periods: TED de novo onset or reactivation in the 1- to 28-day risk period following any Covid-19 vaccination dose. Unexposed periods: TED de novo onset or reactivation before or after the risk period.
[b]TED therapy refers to the treatments administered during the study period; immunosuppression includes any immunosuppressive drugs (ie, steroids) or orbital radiotherapy. Surgery includes orbital decompression both preceded (n = 3) or not (n = 1) by immunosuppression.

Table 3. Analyses of IRRs of TED de novo onset or reactivation in the exposed vs unexposed periods in the self-controlled case series study of adverse effects after COVID-19 vaccination conducted at the TED center in Milan, Italy, from January 1, 2021 to August 31, 2022

Variable	TED onset in unexposed periods[a]		TED onset in exposed periods[a]		IRR	95% CI
	Cases	Person-days	Cases	Person-days		
Analysis 1[b]						
Dose 1	69	46 899	12	2268	3.83	2.06-7.12
Dose 2	73	46 955	8	2212	2.04	0.93-4.48
Dose 3	73	47 571	8	1596	4.04	1.89-8.62
Dose 4	81	49 055	0	112	NC	
Analysis 2[b]						
Unexposed	56	43 146			1.00	Reference
Dose 1			10	2101	3.67	1.87-7.20
Dose 2			7	2212	2.45	1.11-5.38
Dose 3			8	1596	4.00	1.87-8.53
Dose 4			0	112	NC	
Analysis 3[b]	56	43 146	25	6021	3.24	2.01-5.20

Abbreviations: IRR, incidence rate ratio, from conditional Poisson regression models; NC, not calculated; TED, thyroid eye disease.
[a]Exposed periods: TED new onset or reactivation in the 1- to 28-day risk period following any Covid-19 vaccination dose. Unexposed periods: TED new onset or reactivation before or after the risk period.
[b]Analysis 1 refers to single Covid-19 vaccine doses administered before TED new onset or reactivation (not mutually exclusive). Analysis 2 refers to single Covid-19 vaccine doses administered before TED new onset or reactivation (5 mutually exclusive levels), 3 patients developing TED 1 to 28 days from both first and second Covid-19 vaccine doses (overlapping exposed risk periods) were considered within the exposed risk period of the second dose only (most recent). Analysis 3 is irrespective of Covid-19 vaccine dose numbers administered before TED new onset or reactivation (overall analysis).

only to Lombardy residents, the IRR was 3.27 (95% CI 1.94-5.49; 21 cases exposed, 46 unexposed). When we analyzed only patients with de novo onset TED, the IRR was 3.55 (95% CI 2.19-5.74; 25 cases exposed, 51 unexposed).

As shown in Table 4, the risk after Covid-19 vaccination changed over time, being maximum (IRR = 3.80) within the first 28-day time window, and progressively declining during the following 2 28-day time windows (*P* trend = .03). Indeed, the majority of TED cases (n = 15) occurred in the first 1- to 14-day risk period after vaccination (IRR = 4.44), compared with the subsequent 15- to 28-day risk period (n = 10, IRR = 3.13).

Table 4. Risk of TED de novo onset or reactivation in different time windows of exposed vs unexposed periods in the self-controlled case series study of adverse effects after COVID-19 vaccination conducted at the TED center in Milan, Italy, from January 1, 2021 to August 31, 2022

Variable	TED onset in unexposed periods		TED onset in exposed periods		IRR	95% CI
	Cases	Person-days	Cases	Person-days		
Unexposed	38	33 977			1.00	Reference
1-28 days			25	6021	3.80	2.28-6.33
1-14 days			*15*	*3094*	*4.44*	*2.43-8.10*
15-28 days			*10*	*2927*	*3.13*	*1.55-6.31*
29-56 days			9	4747	1.74	0.84-3.62
57-84 days			9	4422	1.87	0.90-3.88

Abbreviations: IRR, incidence rate ratio, from conditional Poisson regression models; TED, thyroid eye disease.
P trend = .03.

Table 5. Effect modification analysis of incidence rate ratios of TED de novo onset or reactivation in the exposed vs unexposed periods in the self-controlled case series study of adverse effects after COVID-19 vaccination conducted at the TED center in Milan, Italy, from January 1, 2021 to August 31, 2022

Variable	TED onset in unexposed periods[a]		TED onset in exposed periods[a]		IRR	95% CI
	Cases	Person-days	Cases	Person-days		
Sex						
Females	38	29 840	18	4152	3.45	1.96-6.06
Males	18	13 306	7	1869	2.80	1.16-6.74
Age						
<50 years	22	19 213	14	2639	4.70	2.39-9.23
50+ years	34	23 933	11	3.382	2.31	1.16-4.58
Cigarette smoking						
Never	26	20 749	13	2924	3.59	1.83-7.03
Former	14	10 685	6	1455	3.20	1.22-8.39
Current	13	10 108	6	1425	3.31	1.25-8.75
Vaccine type						
mRNA only	41	32 518	20	4509	3.57	2.08-6.11
DNA only	2	1653	1	168	4.92	0.45-54.3
Mixed	13	8975	4	1344	2.06	0.67-6.36
Radioiodine treatment						
No	50	38 339	22	5365	3.18	1,92-5.27
Yes	6	4807	3	656	3.70	0.92-14.9

The *P* values associated with interaction (product) terms between the risk period and each variable in conditional Poisson regression models were .70 for sex, .15 for age, .98 for cigarette smoking, .65 for vaccine type, and .84 for radioiodine treatment.
Abbreviations: IRR, incidence rate ratio, from conditional Poisson regression models; TED, thyroid eye disease.
[a]Exposed periods: TED de novo onset or reactivation in the 1- to 28-day risk period following any Covid-19 vaccination dose. Unexposed periods: TED de novo onset or reactivation before or after the risk period.

We found no evidence of effect modification by sex (*P* interaction = .70), cigarette smoking (*P* interaction = .65), radioiodine treatment (*P* interaction = .84), and vaccine type (*P* interaction = .65) (Table 5). The IRR was found to be markedly higher (4.70) in patients less than 50 years of age compared with older patients (IRR 2.31, *P* interaction = .15).

Discussion

This study shows an increased risk of developing TED shortly after Covid-19 vaccination, with the majority of patients presenting with *newly* occurring TED. The administration of at least 1 dose of Covid-19 vaccine was associated with a greater than 3-fold increased risk of TED in the first 4 weeks following vaccination. The effect was not influenced by sex, but the risk was double in patients younger than 50 years. The risk of TED did not depend on the number of vaccine doses administered, and was shown to progressively decrease over time, being maximum in the first 2 weeks from Covid-19 vaccine administration. Definitive conclusions about the risk of TED according to different Covid-19 vaccine types cannot be drawn, considering the disproportional distribution in

favor of mRNA-only formulations, with only 3 patients receiving DNA-only vaccines. A history of SARS-CoV-2 natural infection did not seem to influence the occurrence of TED, although this study was not designed to address this outcome. Patient characteristics and clinical presentation of TED did not differ according to vaccination status. The reported treatments for TED only include those administered during the limited observation period of this study, thus need to be fully addressed in dedicated longitudinal analyses. In our study, the risk of TED after vaccination was not modified by 2 known major risk factors consistently reported in the literature: cigarette smoking (OR 7.7, 95% CI 4.3-13.7) (34) and radioiodine treatment (OR 4.05, 95% CI 1.95-8.43) (35). In particular, the IRR was not higher in smokers; this may be consistent with the reduced immune response triggered by Covid-19 vaccines in people who are active smokers compared with people who are nonsmokers (36).

The SCCS model is well validated to test vaccine safety, and has been previously used for the study of several vaccines (28, 29), including those for Covid-19 (30-32). Using the SCCS model, Wong and colleagues did not find an increased risk of thyroid dysfunction or autoimmunity following Covid-19 vaccination (32). In their work, patients were studied at the time of first thyroid biochemical assessment or when commencing antithyroid therapy, which may greatly vary depending on the patients' report of symptoms or their referral to specialist care. We elected not to study the relationship between Covid-19 vaccination and the onset of GD or hyperthyroidism, due to the difficulty in reliably assessing their actual onset.

There are several potential biological mechanisms that may explain the association between Covid-19 vaccines and TED (37), as well as other adverse events related to Covid-19 vaccines, mainly immune driven, that are increasingly being reported (38-40). Firstly, a direct effect of the SARS-CoV-2 spike protein may be hypothesized, due to its intrinsic toxic activity, both direct and immune mediated (39, 41). Indeed, it has been observed that the spike protein may persist in blood and lymph nodes from days to months after the injection, both as mRNA or as protein (41-45). The vaccine spike protein may travel to target organs, including the thyroid gland and the orbital tissues, where it may bind to several molecules, including the cluster of differentiation 147, toll-like receptors, and the angiotensin-converting enzyme II (39, 41). Angiotensin-converting enzyme II, which is the main receptor of the spike protein, has been found to be widely expressed in multiple organs and systems and especially in the thyroid gland. Thus, direct action of the spike protein at a tissue level in thyroid diseases may be involved (46). Indeed, the expression of vaccine-induced spike protein associated with inflammatory cardiomyopathy has been found in the cardiac tissue of patients with Covid-19 vaccine–induced myocarditis/pericarditis and no previous exposure to SARS-CoV-2 infection (47). Secondly, the spike protein seems to have significant sequence homology with several self-proteins, including thyroid peroxidase, one of the main thyroid autoantigens. This would support the possibility that vaccine-induced antispike antibodies, or other immune cells or components, may injure the thyroid gland, thereby triggering cross-reactive immunity (48, 49). Indeed, the local inflammatory reaction to sublethal injury breaks immune tolerance, and may trigger epitope spreading in thyroid autoimmunity to other autoantigens, such as the thyrotropin receptor (bystander activation) (50). We have recently identified intrathyroidal tissue–resident memory T cells in patients with thyroid disorders induced by both Covid-19 disease or vaccination, some of which were specific for SARS-CoV-2 (51). Thirdly, the gut microbiota seems to play a key role in thyroid autoimmunity, including TED (52, 53), and microbiome alterations have been described following Covid-19 vaccination (54). Fourthly, autoimmunity may also be triggered via nonantigen-dependent mechanisms by adjuvants of Covid-19 vaccines, used to polyclonally boost the immune response, as previously described in the autoimmune/inflammatory syndrome induced by adjuvants syndrome (55). In the case of mRNA vaccines, their lipid nanoparticle platform itself has a plausible proinflammatory action (39), and has also been shown to induce long-term immunological changes that are inherited by offspring in murine models (56). Adverse events, usually observed with all types of Covid-19 vaccines, are more likely to be due to direct involvement of the spike protein, or its triggered immune response, rather than to other components of Covid-19 vaccines, which may differ between the available vaccine products.

In this study, the risk of Covid-19 vaccine–induced TED was higher in younger patients (IRR 4.70 vs 2.31 in those below 50 years of age), similarly to what has been observed with other side effects, including myocarditis and pericarditis (31, 57-60). These observations suggest that the more active immune system in young people (61) may play a key role in Covid-19 vaccine–induced adverse events. Elderly people show a lower systemic inflammatory response following vaccination compared with young individuals (62), but they also have a senescent dysfunctional immune system that makes them more prone to autoimmunity (63). This mechanism might explain the contrasting finding of a higher incidence of Covid-19 vaccine–induced GD in elderly men compared with younger people (18). Further studies are needed to explore mechanisms behind Covid-19 vaccine–induced side effects and their relationship with age.

In TED, the hypothesized immune disruption following Covid-19 vaccination may be compared with that induced by radioiodine treatment, which triggers an immunological activation due to massive thyroid antigen release, with consequent increase in serum thyroid autoantibodies titers (64). Indeed, an increase in thyroglobulin autoantibodies, thyroid peroxidase autoantibodies, and autoantibodies stimulating the thyrotropin receptor has also been reported following Covid-19 vaccination (65, 66), as well as changes in serum thyrotropin concentrations (67). As observed with the radioiodine-induced form, TED triggered by Covid-19 vaccination is not transient, has the same clinical characteristics as the spontaneous form, can present with all grades of severity, and has been approached with conventional treatments. The randomized trial of Träisk and colleagues showed that in patients with GD, radioiodine treatment increased 4 times the odds of TED in a 4-year observation period, especially new-onset cases (64). This is consistent with the data of the present study, in which 70% of vaccinated patients had pre-existing GD or other autoimmune thyroid diseases, and TED developed de novo in 94% of cases.

To determine the precise magnitude of TED risk following Covid-19 vaccination, cohort or case–control studies would be the most appropriate instrument. However, the currently existing longitudinal trials for Covid-19 vaccines have important limitations, since people with immune disorders were

excluded, and nonrandom differences between vaccinated and unvaccinated participants were introduced after the placebo group had been offered the Covid-19 vaccination (41, 68). As a consequence, to date the safety profile of Covid-19 vaccines, especially in patients with pre-existing autoimmunity, has been mainly assessed by passive surveillance, which may imply significant underreporting of potential side-effects (41, 69). Based on the results of this study, we encourage the development of an efficient program of prospective active surveillance and longitudinal studies during future vaccination campaigns to assess the incidence of TED, thyroid dysfunction, or autoimmunity.

A severe course of Covid-19 disease is strongly related to male sex, older age, and comorbidities (70), thus a balanced and personalized harm–benefit analysis of Covid-19 vaccination should also be encouraged (68), especially for young people and those already affected with thyroid autoimmunity. This should also apply to individuals at risk of autoimmune diseases, especially females (50), as in this study 30% of patients developing TED within 28 days from Covid-19 vaccination had no previous history of thyroid dysfunction, consistent with what was previously reported in the literature (71, 72).

Strengths of the present study are the standardized and validated clinical assessment of TED performed in a EUGOGO specialized center, and the availability of precise dates of Covid-19 vaccinations, granted by the access to the regional registry. In addition, we underscore the adequacy of the number of studied patients: in fact, the SCCS approach model has been successfully applied in the analysis of adverse event numbers comparable with those reported in the present study, or even smaller. Intrinsic limitations of the SCCS epidemiological design include the lack of follow-up data, and the impossibility to compare clinical and biochemical parameters, including thyroid function, before and after vaccination. Furthermore, too few patients received DNA-based Covid-19 vaccines only, thus no conclusions can be drawn about Covid-19 vaccine type and TED risk.

In conclusion, the risk of TED was increased after Covid-19 vaccination, independently of the number of administered doses, and other known risk factors for TED. This risk was maximum in the first 14 days following vaccination, and progressively decreased with time. Young people had a suggestively higher risk of TED than elderly people. Other studies are needed to verify this association, and to assess whether the TED risk may change in relation to different Covid-19 vaccine types, and to elucidate the plausible underlying pathogenic mechanisms.

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Author Contributions

I.M. and M.S. contributed to study conception and design, literature search, and interpretation. D.C. performed statistical analyses. I.M., M.S., D.C., E.C., F.D.M., and N.C. contributed to data collection and figures. I.M. wrote the first draft of the manuscript and M.S., D.C., N.C., E.C., and F.D.M. revised and approved the last version of the manuscript.

Disclosures

The authors have no conflicts of interest to declare.

Data Availability

Restrictions apply to the availability of some data analyzed during this study to preserve patient confidentiality. The corresponding author will detail the restrictions and any conditions under which access to some data may be provided upon reasonable request.

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