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Risk of immune thrombocytopenia following COVID-19 vaccination and SARS-CoV-2 infection

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Data sharing statement: According to French law, we cannot share data from the French National Health Insurance Database. However, any individual or organization can access the data to conduct studies of public interest, upon authorization from the French Data Protection Authority (CNIL) and the French ethical and scientific committee (CESRESS).

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Authors contributions

M.L., M.L-M, A.S, and G.M., designed the study and interpreted the results; M.L. conducted the data management and the statistical analyses; A.R., J.Z., and Y.Z. contributed to the data management, statistical analyses and interpretation of the results. M.L., and G.M. wrote the manuscript; and all other authors critically reviewed the manuscript and gave final approval for publication.

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AI use declaration

During the preparation of the manuscript, the authors used ChatGPT (OpenAI) to improve the clarity and language of the text. All AI-assisted edits were reviewed and revised by the authors,

who take full responsibility for the final content of the manuscript. The tool was not used to generate or analyse data and interpret results.

Dear Editor,

Cases of immune thrombocytopenia (ITP) occurring after SARS-CoV-2 infection and COVID-19 vaccination have been reported.^{1,2} The question of a clear increased risk at the population level is of importance, in the context of massive worldwide exposure. Previous observational studies failed to definitely address this question for various reasons, notably the low number of ITP cases selected.^{4,5} Given the considerable vaccine hesitancy, particularly regarding innovative platforms, this issue had public health implications for future mass vaccination campaigns.³

We aimed to investigate the risk of ITP following COVID-19 vaccination and SARS-CoV-2 infection at the population scale in France.

We conducted the present study using the FAITH cohort built within the French Health Insurance Database (SNDS).^{6,7} All adult patients with a new diagnosis of primary ITP between January 1st, 2021 (start of the vaccination campaign in France) and December 31st, 2023 were included.

We used two self-controlled designs: a self-controlled case series (SCCS) and a case-crossover (CCO) designs (Figure 1).^{8,9} We also conducted a case-control design with 5 controls from the general population matched on year of birth, sex, insurance scheme and department of residency. We defined the risk period for ITP occurrence as the 42-days following each vaccination, and as the period from 7 days before ITP (to account for time from infection onset to testing) to 42 days after ITP for the SARS-COV-2 infection (measured as a positive antigenic test or RT-PCR). Sensitivity analyses with risk periods of 28 and 56 days were conducted.

For SCCS analyses, incidence rate ratios (IRR) were estimated using Poisson regression models adjusted for seasonality and age. Supplementary analyses were conducted to investigate the potential impact of the healthy vaccinee effect and event-dependent exposure on risk estimates.^{10,11} For CCO and case-control analyses, conditional logistic regression models were used to calculate odds ratios (OR). Subgroups' analyses were performed by sex, age (< or ≥60 years), and ITP duration (< or ≥3 months).

In case of significant association, we estimated the number of attributable ITP cases per 100,000 individuals who were infected/vaccinated (as $[(IRR-1)/IRR] \times n_{event}/n_{exposed} \times 100,000$ with n_{event} =number of ITP cases during the risk period and $n_{exposed}$ =number of individuals who were infected/vaccinated at least once in the general population during the study period).

All analyses were performed using SAS 9.4TM (SAS Institute, Cary, North Carolina, USA).

The study was authorized by the Toulouse University Hospital ethics committee (January 2024) and use the permanent access to the French Health Insurance Database (SNDS; decree No.2016-1871, law articles R.1461-13/14). The FAITH cohort is registered no.4574 in the ENCePP registry, and NCT03429660 in ClinicalTrials.gov. Informed consent was not required.

During the study period, approximately 162 million COVID-19 vaccine doses were administered in France, 123 million doses of COMIRNATY[®] (Pfizer-BNT) and 12.9 million of SPIKEVAX[®] (Moderna), the two mRNA-based vaccines. Mostly in 2021, 7.8 million doses of VAXZEVRIA[®] (AstraZeneca) and 1 million of JCOVDEN[®] (Janssen), the two adenovirus-bases vaccines, were administered. Two protein subunit vaccines (NUVAXOVID[®] and VIDPREVTYN[®]) were scarcely used. A total of 4,609 patients aged ≥18 years with a new

diagnosis of primary ITP were selected. Patients' characteristics are described in Supplementary Table 1. Among them, 53.0% were female, the median age was 62 years and 63.0% had an ITP duration ≥ 3 months. In this cohort, 87.4% of patients received at least one dose of a COVID-19 vaccine, with COMIRNATY® accounting for 80.0% of all administered doses. Moreover, 77.0% of patients had been vaccinated before ITP onset, including 9.3% within the 42 days preceding diagnosis, while 37.2% received at least one vaccine dose after ITP onset. Regarding SARS-CoV-2 infection, 62.2% of ITP patients had at least one documented infection during the study period, including 28.8% before ITP diagnosis and 7.4% during the risk period.

Associations between COVID-19 vaccination or SARS-CoV-2 infection and ITP occurrence are presented in Figures 2 and 3, Supplementary Table S2 and Figure S1. All three designs and sensitivity analyses yielded consistent results. No increased occurrence of ITP was observed after COVID-19 vaccination overall, nor after mRNA vaccines (overall: aIRR: 1.00, 95%CI: 0.90-1.10; for COMIRNATY® aIRR: 1.03, 95%CI: 0.92-1.14 and for SPIKEVAX® aIRR: 0.71, 95%CI: 0.53-0.96). Results were consistent across doses, except for Booster 3. An association between VAXZEVRIA® and ITP occurrence was observed (aIRR: 2.72, 95%CI: 1.84-4.02). This association was persistent for both doses, ITP duration, age and sex groups. The number of attributable ITP cases was 0.78 (95%CI: 0.56-0.92) per 100,000 individuals who received at least one VAXZEVRIA® dose (0.52 [95%CI: 0.35–0.63] and 0.34 [95%CI: 0.20–0.41] cases per 100,000 for the first and the second dose, respectively). Comparative analyses could not be performed for JCOVDEN® and for protein subunit vaccines due to the very small number of ITP exposed patients (n=83 and 14, respectively). An association was also found for SARS-CoV-2 infection (aIRR: 2.50, 95%CI: 2.22-2.82; attributable cases per 100,000 individuals infected at least once: 0.69, 95%CI: 0.63 to 0.75), particularly for patients with ITP during <3 months (aIRR: 4.23; 95%CI: 3.57-5.03).

In this nationwide study, we provide robust real-world evidence on the risk of ITP following COVID-19 vaccination and SARS-CoV-2 infection in adults. While our findings are reassuring regarding mRNA-based vaccines, VAXZEVRIA®, an adenovirus-based vaccine, was associated with an increased incidence of ITP with an estimated number of attributable cases comparable to that associated with SARS-CoV-2 infection.

Regarding mRNA vaccines, our findings do not confirm the increased incidence of ITP reported following the first dose (only in the 0-7 day risk interval) with COMIRNATY® found in the Welsh study using a SCCS design.¹² Of note, we used a longer and unique risk period of 42 days, based on ITP cases reported to pharmacovigilance systems.² The increased incidence observed in the present study following the third booster dose of COMIRNATY® should be interpreted with caution, as the limited post-dose follow-up may have reduced the likelihood of capturing ITP events during the post-vaccination non-exposed period. The decreased risk with SPIKEVAX® was unexpected and needs to be confirmed. However, our results confirm the post-hoc SCCS analyses of the nationwide study conducted in Scotland, which reported an increase incidence of ITP following the first dose of VAXZEVRIA® (aIRR: 1.98, 95%CI: 1.29-3.02).¹³ Compared to mRNA vaccines, we may hypothesize that adenovirus-based vaccines exhibit surface glycoproteins that could cross-react with platelet antigens. We could estimate in the same population that the number of attributable ITP cases to VAXZEVRIA® were of similar magnitude to those attributable to the SARS-CoV-2 infection itself (0.8 versus 0.7 per 100,000 individuals). Regarding the protein subunit vaccines, no case report has been published in the literature, possibly due to a substantially lower exposure rate. As expected, we also demonstrate an increased incidence of ITP following SARS-CoV-2 infection with similar estimation than in the study conducted in Wales (IRR: 2.46, 95%CI: 1.14-5.33).¹² The risk was the highest for ITP with a duration <3

months, i.e. for ITP that do not progress to a persistent or chronic disease, like with other viral triggers.¹⁴

The strengths of the present study include the nationwide assessment in France, where more than 80% of the population was vaccinated, providing sufficient statistical power to detect even weak associations. Although built in a medico-administrative database, the reliability of the FAITH cohort is well established, with patient characteristics similar to clinical cohorts.^{6,15} The algorithm used to identify patients with a new diagnosis of ITP has been validated using clinical data.⁷ Importantly, all COVID-19 vaccination and SARS-CoV-2 tests were prospectively and exhaustively recorded in the database. Secondly, two self-controlled designs, recommended for vaccine safety studies due to their implicit adjustment for time-independent measured and unmeasured confounding factors, were conducted and complemented by a matched case-control design.^{8,9} The consistency of the results across all the analyses substantially reinforces the robustness of our conclusions.

This study has also some limitations. As it was conducted in a medico-administrative database, some misclassification cannot be totally excluded, particularly concerning ITP and VITT. However, among the 58 patients with ITP diagnosed during the 42 days after adenovirus-based vaccination, only one had a concomitant thrombotic event, resulting in unlikely misclassification overall. We cannot exclude that the global increased awareness concerning VITT could have led to a surveillance bias detecting thrombocytopenia eventually diagnosed as ITP. SARS-CoV-2 infections could have been underestimated due to home-testing without confirmation or undiagnosed cases. Recurrence and aggravation of previous ITP were out of the scope of the present study. Self-controlled designs require accurate dates of both events and exposures. As the initial symptoms cannot be identified in the database, we cannot rule out some inaccuracy in the estimate. However, sensitivity analyses using different

risk periods yielded similar results, and the ITP algorithm used accurately estimated symptom onset.⁷

This nationwide study provides reassuring results for mRNA-based vaccines (COMIRNATY[®] Pfizer-BNT and SPIKEVAX[®] Moderna) mainly used during the pandemic and which remain the cornerstone of COVID-19 vaccination, due to their highly favorable benefit-risk ratios. In contrast, we demonstrate an increased incidence of ITP following the adenovirus-based vaccine VAXZEVRIA[®] AstraZeneca, no longer marketed worldwide, leading to a similar number of attributable cases than following SARS-CoV-2 infection (approximately 0.8 per 100,000 individuals).

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Figure legends

Figure 1. Study designs. Panel A: The self-controlled case series design. Panel B: the case-crossover design.

Abbreviation: ITP: immune thrombocytopenia.

*The healthy vaccinee effect refers to the bias whereby individuals are more likely to receive vaccination when they are in relatively good health, leading to an artificially lower incidence of adverse events in the period immediately preceding vaccination. In the principal analyses, we did not account for this effect, because excluding the 2 weeks before vaccination would have substantially shortened the post-first-dose risk period, given the 3-4-week interval initially recommended between the first two COVID-19 vaccine doses. This could have led to an overestimation of the risk associated with the first dose. Sensitivity analyses with the exclusion of the two weeks preceding each dose to assess the potential impact of this bias were performed.

**As sensitivity analyses, we also applied the event-dependent exposure extension of the SCCS method, since the occurrence of ITP could have influenced the likelihood of subsequent vaccination due to patient and/or physician vaccine refusal.

Figure 2. Associations between COVID-19 vaccination (overall, by vaccine platforms and by vaccines) and immune thrombocytopenia; and association between SARS-CoV-2 infection with immune thrombocytopenia. Principal analyses with 42-day risk periods.

Abbreviations: CI: confidence interval; COVID-19: Coronavirus disease 2019; IRR: incident rate ratio; ITP: immune thrombocytopenia; OR: odds ratio. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

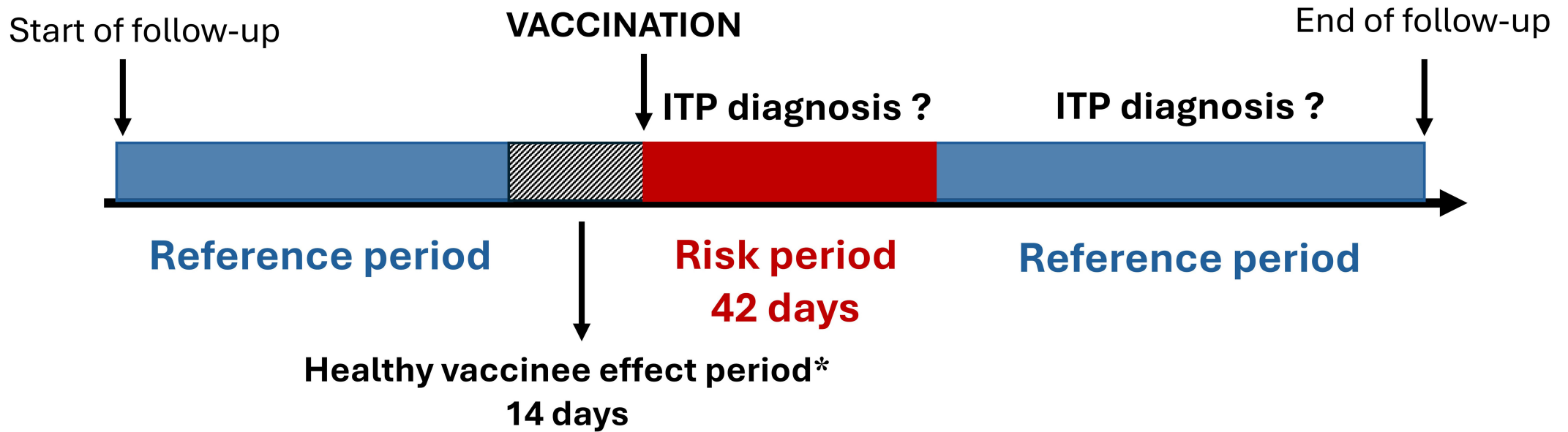
In the self-controlled case series analysis for the SARS-CoV-2 infection, risk period was extended from 7 days before ITP (to account for time from infection onset to testing) to 42 days after ITP.

All self-controlled cases series analyses were adjusted for seasonality (cut-off points: 31st March, 30th June, 30th September and 31st December) and age (by periods of 20 years).

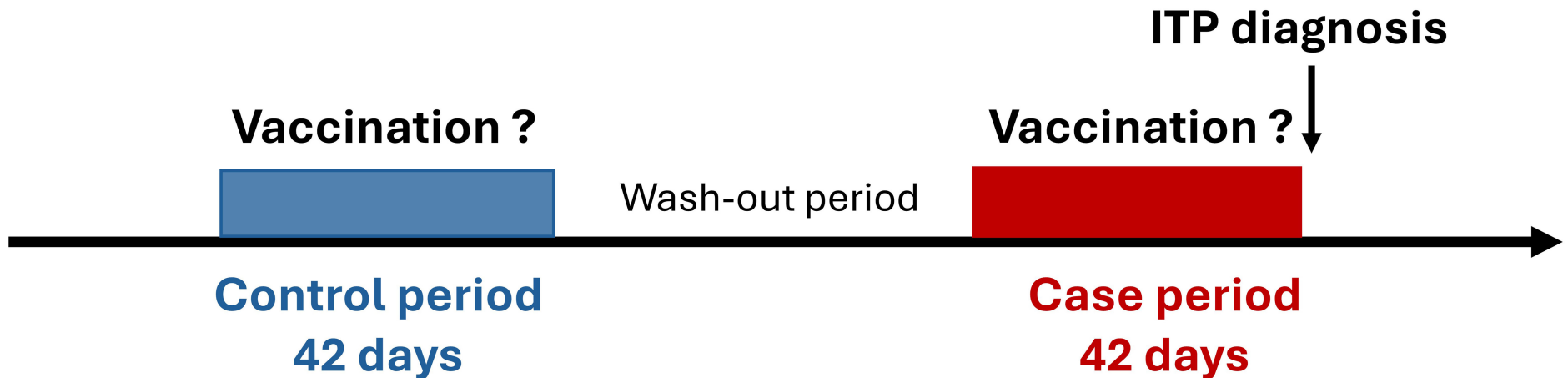
Figure 3. Associations between each dose of COVID-19 vaccine and immune thrombocytopenia. Self-controlled case series design. Principal analyses with 42-day interest periods.

Abbreviation: aIRR: adjusted incident rate ratio; COVID-19: Coronavirus disease 2019.

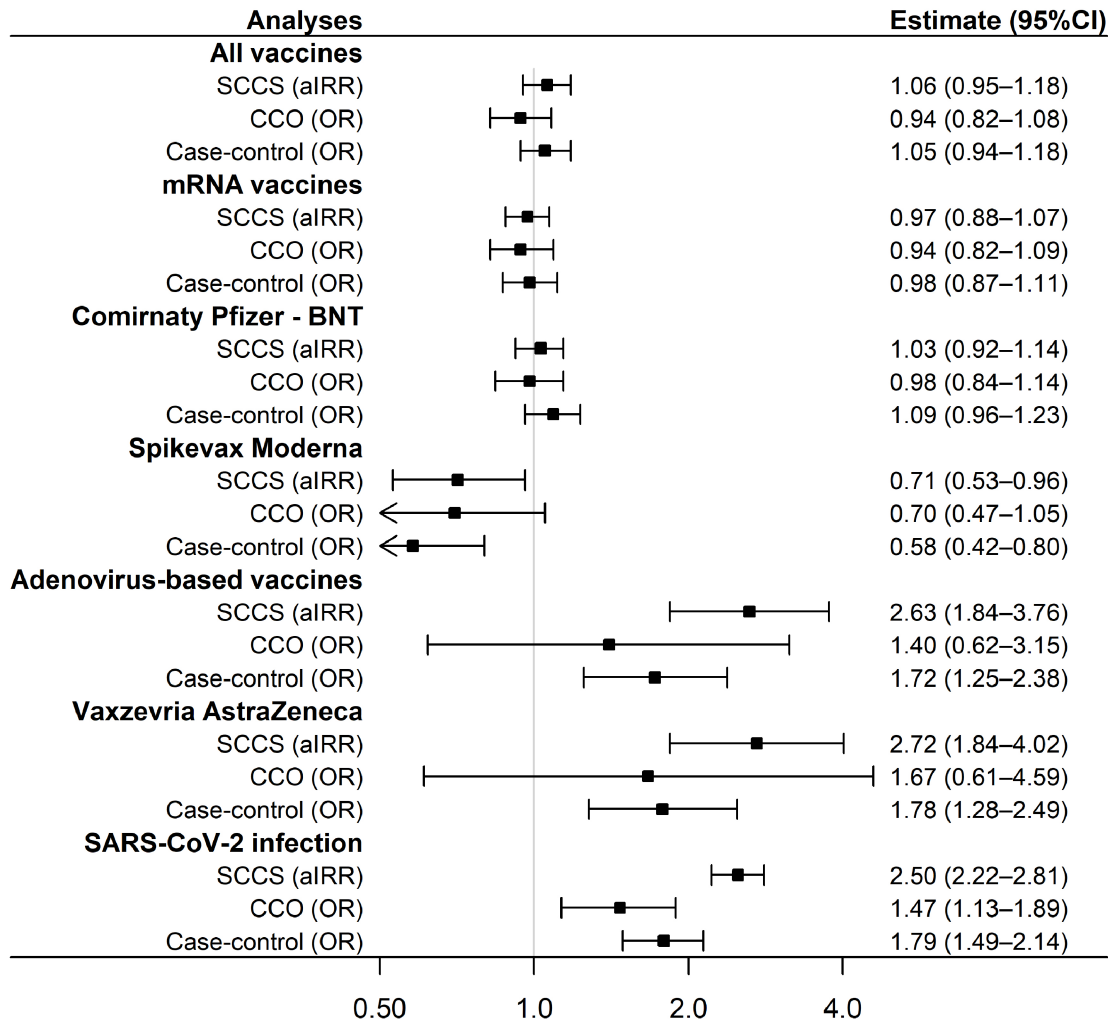
All analyses were adjusted for seasonality (cut-off points: 31st March, 30th June, 30th September and 31st December) and age (by periods of 20 years).

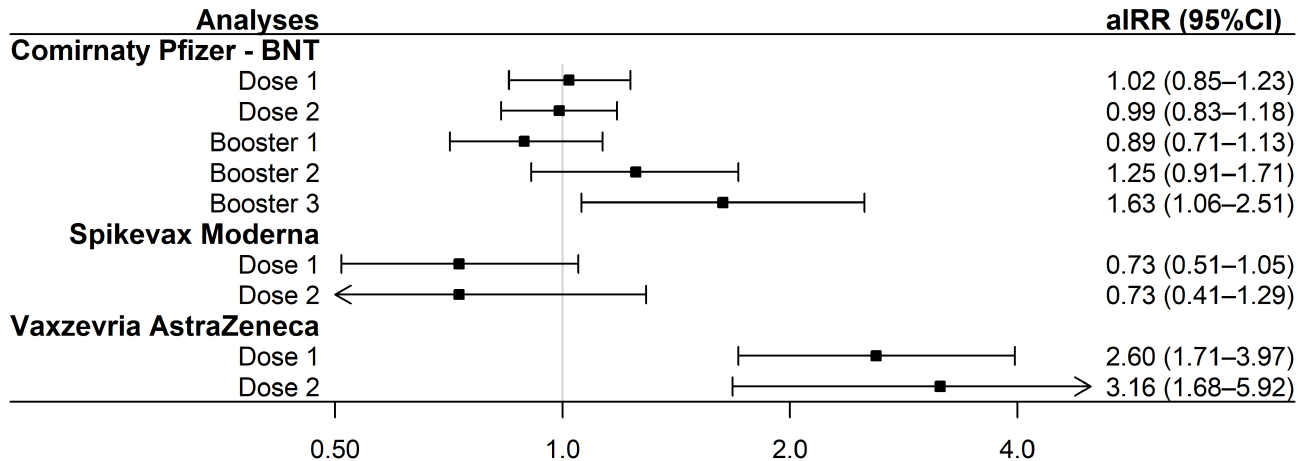


Panel A. Self-controlled case series design**



Panel B. Case-crossover design





Supplementary Data

Risk of immune thrombocytopenia following COVID-19 vaccination and SARS-CoV-2 infection

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Supplementary Table S1. Characteristics of the patients with a new diagnosis of primary immune thrombocytopenia, overall, within the risk period after COVID-19 vaccine (42 days) and SARS-CoV-2 infection (-7 to 42 days around a positive test), between January 2021 and December 2023.

Supplementary Table S2. Associations between COVID-19 vaccination (overall, by vaccine platforms and by vaccines) and immune thrombocytopenia; and association between SARS-CoV-2 infection and immune thrombocytopenia. Principal and sensitivity analyses.

Supplementary Figure S1. Associations between COVID-19 vaccination (overall, by vaccine platforms and by vaccines) and immune thrombocytopenia; and association between SARS-CoV-2 infection and immune thrombocytopenia. Panel A. Subgroup analyses by age at diagnosis. Panel B. Subgroup analyses by sex. Panel C. Subgroup analyses by disease duration.

Supplementary Tables

Table S1: Characteristics of the patients with a new diagnosis of primary immune thrombocytopenia, overall, within the risk period after COVID-19 vaccine (42 days) and SARS-CoV-2 infection (-7 to 42 days around a positive test), between January 2021 and December 2023.

Characteristics	Overall N=4,609	Within the 42 days after COVID-19 vaccine N=497	Within the - 7 to 42 days period around a SARS- CoV-2 positive test* N=342
Female, n (%)	2,443 (53.0)	256 (51.5)	167 (48.8)
Median age (Q1-Q3), years	63 (41 – 76)	67 (50 – 79)	60 (45 – 75)
Charlson Comorbidity Index			
0, n (%)	3 376 (73.3)	344 (69.2)	215 (62.9)
1 – 2, n (%)	814 (17.7)	102 (20.5)	78 (22.8)
≥3, n (%)	419 (9.1)	51 (10.3)	49 (14.3)
Severe bleeding at diagnosis, n (%)	283 (3.9)	12 (2.4)	10 (2.9)
ITP duration ≥3 months, n (%)	2,903 (63.0)	308 (62.0)	163 (47.7)
Death at 1 year,† n (%)	284 (7.1)	40 (8.5)	22 (6.2)
COVID-19 vaccines, n (%)			
Before ITP diagnosis, n (%)	3,553 (77.0)	497 (100)	231 (67.5)
After ITP diagnosis, n (%)	1,715 (37.2)	247 (49.7)	138 (40.4)

Abbreviations: COVID-19: Coronavirus disease 2019; ITP: immune thrombocytopenia; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

*The SARS-CoV-2 testing database was available until the 30 June 2023 due to its nationwide discontinuation.

† Death at 1 year was estimated using the Kaplan-Meier method.

Table S2. Associations between COVID-19 vaccination (overall, by vaccine platforms and by vaccines) and immune thrombocytopenia; and association between SARS-CoV-2 infection and immune thrombocytopenia. Principal and sensitivity analyses.

Analyses	Self-controlled case series design						Case-crossover design			Case-control design		
	Number of patients			aIRR ^a (95% CI)	Sensitivity analyses		Number of patients		OR (95% CI)	Number of patients		OR (95% CI)
	Included in the analysis	Exposed	ITP during risk periods		Considering the impact of HVE aIRR ^a (95% CI)	Event-dependent exposure model aIRR ^a (95% CI)	Exposed in case period and unexposed in control period	Unexposed in case period and exposed in control period		Exposed cases (%)	Exposed controls (%)	
<u>Principal (42 days)</u>												
COVID-19 vaccines												
All vaccines	4,609	4,025	497	1.03 (0.93-1.13)	1.06 (0.96-1.17)	1.00 (0.91-1.09)	381	407	0.94 (0.82-1.08)	494 (11.1)	2,376 (10.7)	1.05 (0.94-1.18)
mRNA-based	4,609	3,990	438	0.97 (0.88-1.07)	1.00 (0.90-1.10)	0.94 (0.86-1.04)	367	390	0.94 (0.82-1.09)	435 (9.8)	2,193 (9.9)	0.98 (0.87-1.11)
COMIRNATY®	4,609	3,721	393	1.03 (0.92-1.14)	1.00 (0.91-1.11)	1.00 (0.90-1.10)	327	334	0.98 (0.84-1.14)	390 (8.8)	1,828 (8.3)	1.09 (0.96-1.23)
SPIKEVAX®	3,685	909	45	0.71 (0.53-0.96)	0.68 (0.49-0.93)	0.70 (0.52-0.95)	41	58	0.70 (0.40-1.05)	45 (1.3)	369 (2.1)	0.58 (0.42-0.80)
Adenovirus-based	956	128	58	2.63 (1.84-3.76)	2.49 (1.57-3.94)	1.70 (1.22-2.37)	14	10	1.40 (0.62-3.15)	58 (6.4)	182 (4.0)	1.72 (1.25-2.38)
VAXZEVRIA®	857	107	54	2.72 (1.84-4.02)	2.74 (1.86-4.03)	1.64 (1.14-2.31)	10	6	1.67 (0.61-4.59)	54 (6.7)	164 (4.1)	1.78 (1.28-2.49)
JCOVDEN®	740	12	<5	-	-	-	<5	<5	-	<5 (<0.5)	16 (0.4)	-
SARS-CoV-2 infection	3,811	2,039	342	2.50 (2.22-0.81)*	-	-	145	99	1.47 (1.13-1.89)	174 (4.8)	512 (2.8)	1.79 (1.49-2.14)
<u>Sensitivity (28 days)</u>												
COVID-19 vaccines												
All vaccines	4,609	4,025	360	1.06 (0.95-1.18)	-	-	289	292	0.99 (0.84-1.17)	360 (8.0)	1,705 (7.6)	1.07 (0.94-1.21)
mRNA-based	4,609	3,990	311	0.97 (0.87-1.09)	-	-	269	283	0.95 (0.80-1.12)	311 (6.9)	1,585 (7.1)	0.97 (0.85-1.12)
COMIRNATY®	4,609	3,721	281	1.03 (0.91-1.17)	-	-	242	246	0.98 (0.82-1.18)	281 (6.3)	1,312 (5.9)	1.08 (0.94-1.25)
SPIKEVAX®	3,685	909	30	0.69 (0.48-0.99)	-	-	27	37	0.73 (0.44-1.20)	30 (0.8)	247 (1.5)	0.52 (0.35-0.77)
Adenovirus-based	956	129	48	3.15 (2.19-4.54)	-	-	20	6	3.33 (1.34-8.30)	48 (5.0)	119 (2.5)	2.20 (1.53-3.15)
VAXZEVRIA®	857	107	44	3.14 (2.12-4.67)	-	-	16	<5	-		44 (5.1)	110 (2.6)
JCOVDEN®	740	12	<5	-	-	-	<5	0	-		<5 (0.5)	9 (0.2)
SARS-CoV-2 infection	3,811	2,039	304	3.02 (2.67-3.42)*	-	-	111	71	1.56 (1.16-2.11)	135 (3.7)	352 (1.9)	2.00 (1.62-2.46)
<u>Sensitivity (56 days)</u>												
COVID-19 vaccines												
All vaccines	4,609	4,025	622	1.01 (0.93-1.10)	-	-	459	517	0.89 (0.78-1.01)	615 (14.0)	3,022 (13.8)	1.02 (0.91-1.14)
mRNA-based	4,609	3,990	548	0.96 (0.87-1.05)	-	-	445	497	0.90 (0.79-1.02)	542 (12.3)	2,780 (12.7)	0.96 (0.86-1.07)

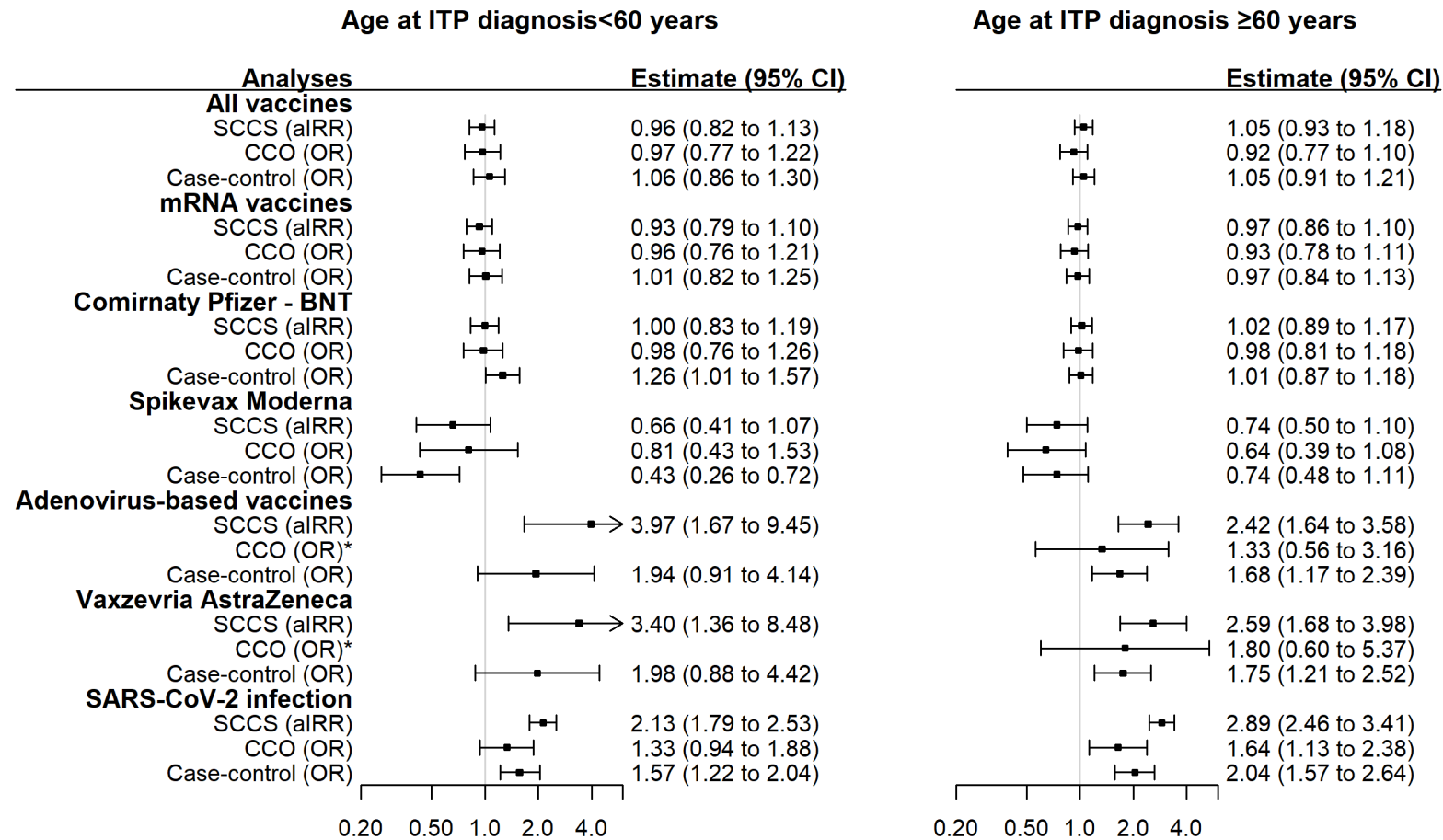
COMIRNATY®	4,609	3,721	495	1.02 (0.93-1.13)	-	-	400	429	0.93 (0.80-1.07)	489 (11.1)	2,309 (10.5)	1.08 (0.96-1.21)
SPIKEVAX®	3,685	909	54	0.66 (0.50-0.87)	-	-	47	71	0.66 (0.46-0.96)	54 (1.5)	473 (2.7)	0.53 (0.40-0.72)
Adenovirus-based	956	129	73	2.87 (2.01-4.12)	-	-	14	10	1.40 (0.62-3.15)	72 (8.3)	242 (5.6)	1.61 (1.20-2.16)
VAXZEVRIA®	857	107	66	2.87 (1.92-4.31)	-	-	8	7	1.14 (0.41-3.15)	65 (8.4)	217 (5.6)	1.62 (1.19-2.21)
JCOVDEN®	740	12	6	3.02 (0.91-10.01)	-	-	6	<5	-	6 (0.8)	19 (0.5)	1.61 (0.63-4.11)
SARS-CoV-2 infection	3,811	2,039	447	2.10 (1.87-2.36)*	-	-	170	137	1.24 (0.99-1.55)	202 (5.6)	647 (3.6)	1.64 (1.39-1.94)

Abbreviations: CI: confidence interval; COVID-19: coronavirus disease 2019; HVE: healthy vaccinee effect IRR: incident rate ratio; ITP: immune thrombocytopenia; OR: odds ratio. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

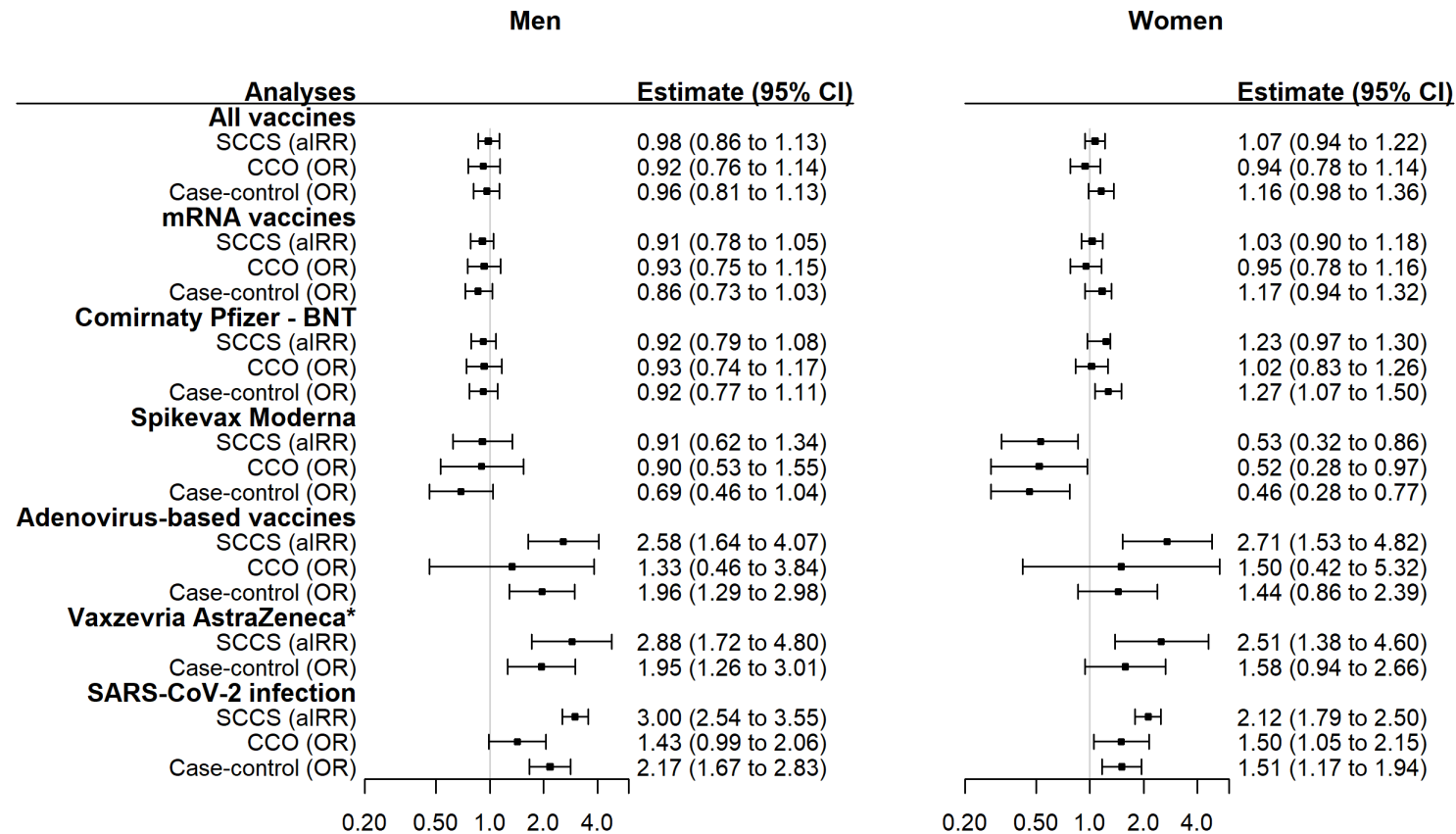
^aAdjusted for seasonality (cut-off points: 31st March, 30th June, 30th September and 31st December) and age (by periods of 20 years).

* In the self-controlled case series analyses assessing the incidence of ITP after SARS-CoV-2 infection, the risk period was extended from 7 days before the positive test (i.e. symptoms onset) up to 42 days after for principal analysis and up to 28 and 56 days in sensitivity analyses.

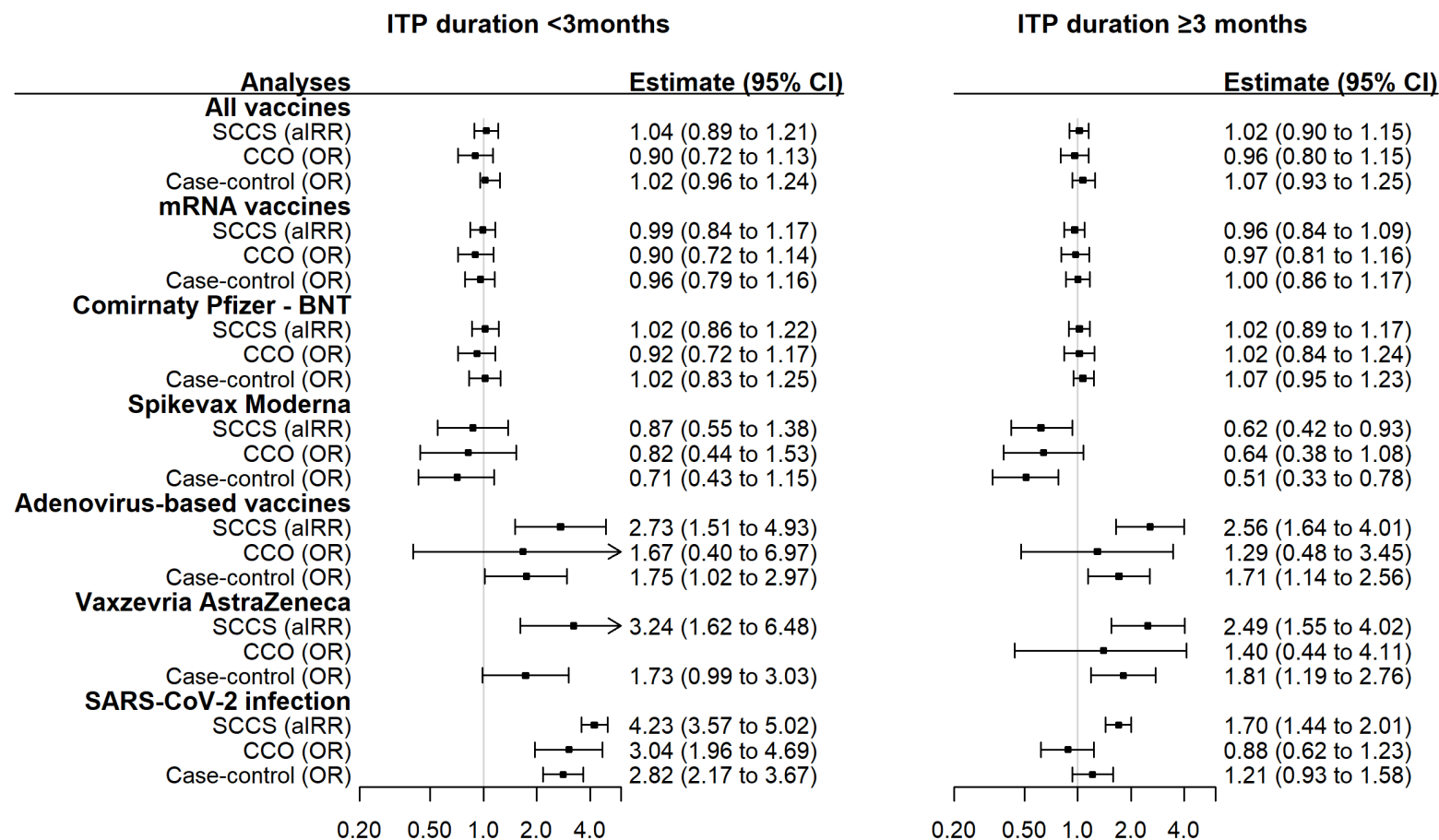
Supplementary Figure



Panel A



Panel B



Panel C.

Figure S1. Associations between COVID-19 vaccination (overall, by vaccine platforms and by vaccines) and immune thrombocytopenia; and association with SARS-CoV-2 infection. Panel A. Subgroup analyses by age. Panel B. Subgroup analyses by sex. Panel C. Subgroup analyses by disease duration.

Abbreviations: aIRR: adjusted incident rate ratio; CI: confidence interval; CCO: case-crossover; COVID-19: coronavirus disease 2019; ITP: immune thrombocytopenia; OR: odd ratio; SCCS: self-controlled case series; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; 95% CI: 95% confidence interval.

Self-controlled cases series (SCCS) analyses were adjusted for seasonality (cut-off points: 31st March, 30th June, 30th September and 31st December) and age (by periods of 20 years).