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Background rate estimations for thrombosis with thrombocytopaenia: challenges in evaluating rare safety signals following vaccination in real time during a pandemic

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ABSTRACT

Objectives During COVID-19 vaccination programmes, new safety signals have emerged for vaccines, including extremely rare cases of thrombosis with thrombocytopaenia syndrome (TTS). Background event rates before and during the pandemic are essential for contextualisation of such infrequent events. In the literature, most studies do not report an overall TTS event rate. Rather, background rates are mainly reported for subtypes of thrombotic/thromboembolic diagnoses included in the TTS clinical definition mostly by anatomical location, with reported rates for TTS subtypes varying widely. The objective of this study was to report prepandemic TTS background event rates in the general population.

Methods Prepandemic background TTS rates were generated via secondary data analysis using a cohort design in the IBM Truven MarketScan (now Merative MarketScan) US health insurance claims database, from 1 January 2019 to 31 December 2019. Two algorithms were applied: thrombocytopaenia occurring±7 days (algorithm 1) or occurring 1 day prior to ≤14 days after the thrombotic/thromboembolic event (algorithm 2).

Results The study population derived from the MarketScan database analysis included approximately 9.8 million adults (aged ≥18 years; mean age 45 years, 52% females). Using this study population, prepandemic background TTS incidence was estimated as 9.8–11.1 per 100 000 person-years. Event rates were higher in males and increased with age. Similar patterns were observed with both algorithms.

Conclusions This study presents an estimate of aggregate prepandemic background TTS event rates including by type of thrombosis/thromboembolism and age group. The background event rates are dependent on the precision of capturing underlying TTS events in variable data sources, and the ability of electronic health records or insurance claims databases to reflect the TTS clinical definition. Differences between reported event rates demonstrate that estimating background event rates for rare, unprecedented safety events is methodologically challenging.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study presents a prepandemic single background rate for thrombosis with thrombocytopaenia syndrome (TTS), as well as by type of thrombosis/thromboembolism and age group, setting the stage for pandemic background rates.
⇒ Strengths of this study include clearly specified algorithms for defining TTS used in the analysis of the large MarketScan database.
⇒ Limitations include the inherent challenges in defining point estimates for a background event rate, such as the limited epidemiological/observational information about the event, the databases available and their types/nature, the observation periods (prepandemic vs contemporary) and event capture.
⇒ Furthermore, the use of International Classification of Diseases codes only and not recorded platelet count to define TTS may lead to decreased diagnostic specificity.

INTRODUCTION

The current COVID-19 pandemic represents a major public health crisis. As well as causing respiratory illness, COVID-19 is associated with increased risk of serious complications, such as thrombocytopaenia, thrombotic events, myocardial infarction and stroke.[1] Early in the pandemic, efforts were focused on the rapid development of COVID-19 vaccines and global distribution. Less than a year from the start of vaccine deployment, over 6 billion doses had been administered globally.[2] Clinical trials confirmed the efficacy and safety of vaccines in large numbers of participants.[3–5] Postregulatory emergency use or full approval of COVID-19 vaccines, as with all vaccines and medicines, requires monitoring for safety signals and to assess safety in any subpopulations unable to be studied in the clinical study programme.[6]

Table 1 Baseline demographics of adults (aged ≥18 years) included in the study population

	MarketScan database (N=9 850 541)
Age, years, mean (SD)	45.0 (15.5)
Age, years: min, max	18, 117
Age, years, median (IQR)	46 (33–37)
Female, n (%)	5 149 877 (52.3)
US region, n (%)	
Midwest	2 110 497 (23.5)
Northwest	1 870 649 (20.9)
South	3 759 994 (41.9)
West	1 225 657 (13.7)
Payor, n (%)	
Commercial	9 226 611 (93.7)
Medicare	623 930 (6.3)
Age groups, years, n (%)	
18–49	5 656 359 (57.4)
50–59	2 421 415 (24.6)
60–69	1 343 787 (13.6)
70–79	271 762 (2.8)
≥80	157 218 (1.6)

IQR, interquartile range; SD, standard deviation.

Pharmacovigilance uses passive and active surveillance to monitor vaccine safety in the real world. Passive surveillance consists of spontaneous, unsolicited reports of adverse events, such as the Yellow Card system in the UK and the Vaccine Adverse Event Reporting System in the USA.[7 8] To interpret new safety signals, we must be able to understand whether they are related to vaccine administration or occur independently at a rate expected in the general population.

To identify whether a putative signal requires further evaluation, conducting an observed-to-expected analysis can establish if vaccine recipients have a higher event rate than unvaccinated people.[9] This process (called contextualisation) relies on the capture of accurate observed and expected (background) rates for rare events. However, contextualisation is not designed to assign causality to a safety signal.[9 10]

Epidemiological studies that evaluate background event rates (defined by Black *et al* as 'the incidence rate of the event one would observe in a given population in the absence of receipt of the vaccine being tested or any other intervention') provide critical information for vaccine safety signal assessments.[11 12] Such analysis is best accomplished using large, comprehensive datasets to improve precision of event rate estimates and to minimise heterogeneity in event capture (eg, hospital databases may not capture diseases usually diagnosed by primary care and vice versa). A case definition with high specificity and sensitivity that can be feasibly applied (and preferably validated) in large electronic healthcare or insurance databases is also essential.

For thrombosis with thrombocytopaenia syndrome (TTS), the Brighton collaboration has published a TTS diagnosis algorithm[13]; its application to medical records or insurance claims databases can be challenging. For example, while a low platelet count ($<150\times10^9$/L) of new onset is a defining characteristic of TTS, platelet counts are often also below this level in elderly individuals[14] and may not be routinely measured or consistently recorded. However, a possible TTS definition, relying on medical diagnoses rather than on laboratory measures and clinical assessment, can be applied in routinely collected medical records or insurance claims. Some groups have estimated background TTS event rates using different approaches.[10 15] These groups did not report overall TTS rates, but instead reported rates for subtypes of thrombotic/thromboembolic diagnoses, which are included in the TTS clinical definitions, mostly by anatomic location. Background event rates have been used to calculate expected event rates using indirect standardisation to the general population.[15]

This article reports a single prepandemic background event rate for TTS as well as by type of thrombosis/thromboembolism and age group and presents these event rates in the context of published literature.

METHODS

Insurance claims database analysis

We generated prepandemic TTS rates using a descriptive cohort study design in the IBM Truven MarketScan (now Merative MarketScan) database, within the observation period representing the prepandemic era. The main study period was taken from 1 January 2019 to 31 December 2019; additionally, event rates were also reported for two additional calendar years of calculation, from 1 January to 31 December in 2018 and 2017. The MarketScan database contains data on approximately 179 million patients in the USA with employer-sponsored commercial or supplemental Medicare insurance coverage between 2008 and the first quarter of 2020, covering medical and pharmaceutical claims from primary and secondary care facilities. The database includes data on patients from all US states and is broadly representative of a commercially insured population.

Patients were included in the study denominator population if they were enrolled in the dataset on 1 January 2019 (or 1 January 2017 or 2018, respectively, for additional years of calculation) and had ≥24 months of prior continuous enrolment. Patients contributed follow-up time until an event, censoring (eg, end of enrolment) or end of the year (31 December 2019; or 31 December 2017 or 2018 for additional years of calculation), whichever came first. To identify a single prepandemic TTS event rate, two algorithms were implemented that used International Classification of Diseases, 10th Revision (ICD-10) Clinical Modification diagnosis codes recorded in the study

Table 2 Incident and overall* event rates for TTS and by type of thrombosis/thromboembolism in adults aged ≥18 years in the MarketScan database (2019: prepandemic)

Thrombosis type†	Algorithm 1		Algorithm 2	
	Events	Event rate per 100K PY (95% CI)	Events	Event rate per 100K PY (95% CI)
Incident event rates				
All thrombotic/thromboembolic events	902	9.8 (9.2 to 10.4)	1028	11.1 (10.5 to 11.8)
CVST	22	0.2 (0.2 to 0.4)	24	0.3 (0.2 to 0.4)
DVT	613	6.6 (6.1 to 7.2)	715	7.8 (7.2 to 8.3)
Intra-abdominal	124	1.3 (1.1 to 1.6)	129	1.4 (1.2 to 1.7)
PE	363	3.9 (3.5 to 4.4)	408	4.4 (4.0 to 4.9)
Overall event rates				
All thrombotic/thromboembolic events	1783	19.3 (18.4 to 20.2)	1971	21.3 (20.4 to 22.3)
CVST	32	0.4 (0.2 to 0.5)	35	0.4 (0.3 to 0.5)
DVT	1188	12.8 (12.1 to 13.6)	1327	14.3 (13.6 to 15.1)
Intra-abdominal	267	2.9 (2.6 to 3.3)	282	3.1 (2.7 to 3.4)
PE	596	6.4 (5.9 to 7.0)	657	7.1 (6.6 to 7.7)

*Incident event counts exclude patients with thrombosis that occurred in 365 days prior to first thrombosis in 2019. Overall event counts include these patients. The first encounter in 2019 with thrombosis was categorised by subtype. Patients who had more than one subtype during this encounter were counted in each contributing type, but only once in the overall count; hence the counts of events by subtype exceed the overall count.
†All occurring with thrombocytopaenia following the criteria for the algorithm used.
CI, confidence interval; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; PY, person-years; TTS, thrombosis with thrombocytopaenia syndrome.

period (online supplemental figure 1). No single diagnosis code for TTS exists; algorithms based on codes for diagnosis of thrombocytopaenia and thrombotic events were created with the time interval between the diagnoses reflecting observations from the AstraZeneca Global Safety database. Identification of thrombocytopaenia was based on diagnosis codes only for both algorithms, as absolute platelet counts were not routinely recorded. Two algorithms were used due to lack of standardisation in the period used to identify an overlap of thrombotic/thromboembolic events and thrombocytopaenia. For algorithm 1, patients needed to have a diagnosis code for thrombocytopaenia (online supplemental table 1) occurring 7 days prior to, or 7 days after their first thrombotic/thromboembolic event in the study period (online supplemental table 2). This was based on the observation that thrombotic/thromboembolic events and thrombocytopaenia occurred within a few days of each other and was intended to account for possible lag time in recording events in the database. The date of event was defined as the date of this first thrombotic/thromboembolic event. For algorithm 2, patients had a diagnosis code for

Table 3 Incident and overall background TTS event rates by age and sex from the MarketScan database (2019: prepandemic)

Event type and age group	Algorithm 1		Algorithm 2	
	Event rate per 100K PY (95% CI)	Event rate per 100K PY (95% CI)	Event rate per 100K PY (95% CI)	Event rate per 100K PY (95% CI)
	Female	Male	Female	Male
Incident event rates				
0–17 years	0.4 (0.1 to 1.0)	0.5 (0.2 to 1.0)	0.4 (0.1 to 1.0)	0.4 (0.1 to 0.9)
18–49 years	4.5 (3.8 to 5.4)	4.5 (3.8 to 5.5)	4.6 (3.9 to 5.5)	5.4 (4.5 to 6.3)
50–64 years	9.7 (8.3 to 11.3)	15.8 (13.9 to 17.9)	11.4 (9.9 to 13.1)	18.8 (16.7 to 21.1)
≥65 years	31.2 (25.3 to 37.9)	52.6 (44.3 to 62.1)	36.1 (29.9 to 43.3)	56.0 (47.4 to 65.8)
Overall event rates				
0–17 years	1.0 (0.5 to 1.7)	1.7 (1.1 to 2.6)	0.9 (0.5 to 1.6)	1.6 (1.0 to 2.4)
18–49 years	8.1 (7.0 to 9.2)	7.8 (6.7 to 8.9)	8.5 (7.4 to 9.7)	8.7 (7.6 to 9.9)
50–64 years	19.6 (17.6 to 21.8)	33.7 (30.9 to 36.7)	22.1 (19.9 to 24.4)	37.7 (34.7 to 40.8)
≥65 years	61.1 (52.9 to 70.3)	105.3 (93.4 to 118.4)	69.1 (60.4 to 78.8)	112.8 (100.4 to 126.3)

CI, confidence interval; PY, person-years; TTS, thrombosis with thrombocytopaenia syndrome.

Table 4 TTS definitions reported in the literature

Study group/reference	Definite TTS case	Probable TTS case	Possible TTS case
Standard case definition for TTS Brighton Collaboration (11 November 2021)[13]	Thrombocytopaenia (platelets <150×10^9/L, new onset with no recent heparin exposure) *plus* Thrombosis confirmed by imaging, surgical procedure or pathology	Thrombocytopaenia *plus* Thrombosis suggested by clinical presentation with imaging/ laboratory findings to support	Thrombocytopaenia *plus* Thrombosis suggested by clinical presentation without imaging/ laboratory findings
Diagnostic criteria for VITT-associated CVT Perry *et al* (6 August 2021)[21]	Post-vaccine CVT (confirmed by imaging with first symptom <28 days of vaccination) *plus* Thrombocytopaenia (platelets <150×10^9/L or <50% of baseline) *plus* Anti-PF4 antibodies	Post-vaccine CVT *plus* Thrombocytopaenia or anti-PF4 antibodies *plus* Coagulopathy (D-dimer >2000 µg/L or fibrinogen <2.0 g/L with no other explanation) or extracranial venous thrombosis (onset since vaccination with clinical/imaging evidence)	Post-vaccine CVT *plus* Thrombocytopaenia or anti-PF4 antibodies
VITT case definition according to UK expert haematology panel Pavord *et al* (11 August 2021)[22]	Onset of symptoms 5–30 days post vaccination (≤42 days in patients with isolated DVT or PE) *plus* Thrombocytopaenia (platelets <150×10^9/L) *plus* Thrombosis *plus* D-dimer >4000 FEU *plus* Anti-PF4 antibodies	D-dimer level >4000 FEU but one criterion not met (timing, thrombosis, thrombocytopaenia or anti-PF4 antibodies) *or* D-dimer level unknown or 2000–4000 FEU, and all other criteria met	D-dimer level unknown or 2000–4000 FEU with one other criterion not met *or* Two other criteria not met (timing, thrombosis, thrombocytopaenia or anti-PF4 antibodies)

	Criteria	TTS category based on total score from algorithm
Algorithm for TTS classification in spontaneous surveillance reports Laffan *et al* (22 August 2022)[23]	Time to onset 4–40 days of vaccination with thrombosis or platelets <150×10^9/L (2 points) Thrombosis and platelets <150×10^9/L (2 points) CVST or SVT or multiple thromboses (2 points) DVT or PE or single arterial occlusion (1 point) Platelets <50×10^9/L (1 point) D-dimer >4000 FEU (1 point) Anti-PF4 antibodies (2 points)	0: Not TTS 1–2: Unknown 3–5: Possible 6–7: Probable 8–10: Confirmed

CVST, cerebral venous sinus thrombosis; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; FEU, fibrinogen equivalent unit; PE, pulmonary embolism; PF4, platelet factor 4; SVT, splanchnic venous thrombosis; TTS, thrombosis with thrombocytopaenia syndrome; VITT, vaccine-induced immune thrombotic thrombocytopaenia.

thrombocytopaenia (online supplemental table 1) occurring 1 day prior to, or up to 14 days after the index thrombotic/thromboembolic event (online supplemental table 2). This was intended to capture an alternative scenario where thrombocytopaenia would be recorded with a lag time from thrombotic/thromboembolic diagnosis. The date of first event in the observation period was counted.

Thrombotic/thromboembolic events included all venous and arterial thrombotic events and pulmonary embolism (PE) except acute myocardial infarction or overall 'stroke'. Diagnoses included in the overall thrombosis/thromboembolism definition are also reported by subcategories: cerebral venous sinus thrombosis (CVST), deep venous thrombosis, intra-abdominal events and PE

(online supplemental table 2). Only hospitalised events were considered, as primary or secondary care events were deemed unlikely to be of a severity level equivalent to TTS following COVID-19 vaccination.

Event rates were reported as either incident or overall. Incident event rates exclude patients who had previously experienced thrombosis, that is, patients with events that would have occurred in the 365 days prior to first thrombosis in 2019 (or for additional years of calculation, in the 365 days prior to first event in 2017 or 2018). Overall event rates do not exclude these patients. In the case of multiple events within a year of calculation, only the first occurrence within the observation period was counted.

Event rates (with 95% CIs) for each event of interest were calculated by dividing number of observed events by person-time at risk and expressed as event rate per two risk windows: (A) 100K person-years (PYs) and (B) 1 million (1M) persons per 21 days (online supplemental tables 3 and 4). PYs were calculated from date of study period start to date of event, censoring at the end of continuous enrolment or the end of the study period. Event rates were calculated overall for the adult population (≥18 years old at start of study period), and were stratified by sex and age (0–17; 18–49; 50–64; ≥65 years). Event rates per 100K PY are reported for comparison with rates reported in the literature. Event rates per 1M persons per 21 days are also reported in the Supplementary materials, as expressing the rate per 1M persons simplifies the application of these rates to observed numbers of vaccinated patients.

Analyses were performed using R within the Instant Health Data platform (V.4.0.2; Panalgo, Boston, Massachusetts, USA) and verified using a separate implementation on a local server. CIs were calculated using the exact formula for an incidence rate[16] using the implementation in the epiR package (V.2.0.19).[17]

Patient and public involvement

Because the study used only deidentified patient data, patients and the public were not directly involved in this study.

RESULTS

TTS background event rates in insurance claims data

In the analysis of MarketScan data, in 2019, 12 441 377 patients met the inclusion criteria, of whom approximately 9.8 million were adults (≥18 years old). The mean (SD) age of the cohort was 45.0 (15.5) years, 52.3% were female and the majority (93.7%) were insured commercially (table 1).

Incident 2019 prepandemic TTS event rates in adults (95% CI) with algorithms 1 and 2 were 9.8 (9.2 to 10.4) and 11.1 (10.5 to 11.8) per 100K PY, respectively (table 2). When standardised to a 21-day risk window, incident TTS event rates (95% CI) with algorithms 1 and 2 were 5.6 (5.3 to 6.0) and 6.4 (6.0 to 6.8) per 1M persons per 21 days, respectively (online supplemental table 3). Overall 2019 prepandemic TTS event rates in adults (95% CI) with algorithms 1 and 2 were 19.3 (18.4 to 20.2) and 21.3 (20.4 to 22.3) per 100K PY, respectively (table 2).

Event rates stratified by sex and age show that the 2019 prepandemic TTS event rates were typically higher in males than in females and increased with age with both algorithms (table 3). Similar patterns were seen using algorithm 2 and when reporting overall events.

When considering specific type of thrombotic/thromboembolic events (table 2), the most common prepandemic TTS subtypes were deep vein thrombosis (DVT) with thrombocytopaenia (2019 incident event rate (95% CI) using algorithm 1: 6.6 (6.1 to 7.2) per 100K PY) and PE with thrombocytopaenia (3.9 (3.5 to 4.4) per 100K PY) (table 2). CVST with thrombocytopaenia was very rare (0.2 (0.2 to 0.4) per 100K PY).

When considering additional prepandemic years of 2017 and 2018, incident and overall event rates appeared to be decreasing for TTS and most other specific types of thrombotic/thromboembolic events between 2017 and 2019, although 95% CI largely overlapped between 2018 and 2019 (online supplemental table 5).

DISCUSSION

This study presents an estimation of a single prepandemic background TTS event rate, as well as by type of thrombosis/thromboembolism type and age group, expanding on existing data on TTS event rates reported by specific thrombotic/thromboembolic sites in the current literature, and includes the first estimation of a single TTS event rate standardised using a 21-day window. Single TTS event rates are critical in communicating risk with various audiences, such as regulators, clinicians and the public.

Given the initial uncertainty on the definition of TTS and the temporal relationship of the two key diagnostic events of thrombocytopaenia accompanied by thrombosis/thromboembolism, we constructed and implemented two TTS algorithms. Algorithm 1, which most aligned with published background event rates,[10 15] shows that incident TTS events are rare, but not exceptionally rare (ie, occurring with a frequency <1/100 000), with an overall frequency of 9.8 events per 100K PY. Overall event rates are less rare with a frequency of 19.3 events per 100K PY. We observed an increase of prepandemic TTS event rates with increasing age, which was similar to trends reported by published studies on subtype of background TTS event rates.[15] The increase in TTS event rates with age may reflect factors that increase the risk of thrombotic events in older populations such as platelet function changes or use of multiple drugs for treating an increasing number of comorbidities. Prepandemic TTS events were also more frequent among middle-aged and older men than women. This differs from the profile of patients with TTS observed post-vaccination who were reported to be <60 years old and more often female.[18 19] Exploring trends for TTS with additional years of 2017 and 2018 shows heterogeneity in observed event rates

with rates decreasing with increasing calendar years, although 2018 and 2019 differences were within 95% CIs. This level of heterogeneity could have been due to several reasons including possible changes in event coding practice, changes in the included proportion of Medicare (older adult) population in the database, or other underlying population characteristics.

Published event rates for TTS by specific thrombotic/thromboembolic sites show substantial heterogeneity.[10 15] For example, across seven databases from five European countries, Burn *et al* reported prepandemic background rates (per 100K PY) of 1.0–8.5 for DVT with thrombocytopaenia, 0.5–20.8 for PE with thrombocytopaenia, 0.1–2.5 for splanchnic venous thrombosis with thrombocytopaenia and 1.0–43.4 for myocardial infarction or ischaemic stroke with thrombocytopaenia.[15] This heterogeneity may be due to different methods of estimating background event rates between studies and/or differences in diagnostic or recording patterns in selected countries/regions. Variability in case definitions (online supplemental table 6), their coding and time frames covered by the databases used were also likely contributing factors. Neither of these published studies provided an overall TTS event rate, but instead reported individual types of acute thrombosis/thromboembolism in combination with thrombocytopaenia.[10 15] As reported, TTS cases may present with multiple thrombotic/thromboembolic sites, a single case could be counted several times in each of the thrombotic/thromboembolic event analyses, confounding an observed to expected analysis. At an early stage in our understanding of TTS, preliminary estimations of background prepandemic TTS rates were reported as 3.75 (95% CI 3.51 to 4.00) events per 1M persons per 14 days (with TTS defined similarly to algorithm 1 in the present study) and 7.16 (95% CI 6.83 to 7.51) events per 1M persons per 14 days (with TTS defined aligned with algorithm 2 in the present study).[20] This approach was refined in the present study, which reported a single TTS event rate per 21 days to account for a possible 21-day window after vaccination in which patients might experience a TTS event following vaccination.

Limitations of this study include the inherent challenges in defining point estimates for a background event rate. These include the limited epidemiological/observational information about the event, the databases available with sufficiently large population sizes to allow for precise estimation of event rates, the observation periods (prepandemic vs contemporary) and event capture. Furthermore, this analysis is based on adjudicated healthcare claims and no pathology reports were available in the MarketScan database; the use of ICD codes only and not recorded platelet count to define TTS may lead to decreased diagnostic specificity. Analysis of background event rates for newly recognised rare safety signals is also hindered by lack of validated methods to identify events in routinely collected electronic health records or insurance claims. As the definition of the event has evolved over the course of the pandemic (table 4), the estimates of its occurrence in each population will also vary.[13 21–23] For example, thrombocytopaenia observed in reported cases of TTS tends to be more severe (platelet count <50 000 per µL) than thrombocytopaenia observed in elderly patients (platelet count <150 000 per µL).[14 18] Other factors, such as age, sex and the timing of the analysis (eg, seasonal variation), can substantially impact background rates and thus should also be taken into consideration when comparing a background rate with corresponding rates observed with the treatment(s) of interest, such as COVID-19 vaccines.

We reported the challenges involved in determining background event rates of new and extremely rare safety signals. In the case of TTS, there remains a need to align the clinical definitions that will permit a unified approach for studying geographical variations in event rates, especially considering the current lack of an agreed system to code the condition. Postmarketing surveillance is based on self-reported data, usually lacking clinical and laboratory details, limiting application of diagnostic algorithms such as those proposed for TTS. In addition, the algorithms used to study event rates from electronic health records are yet to be validated. Contextualisation of safety events, including estimating background rates, surveillance systems set up to collect high-quality data in real time, and an understanding of benefit-risk analysis are key to sound decision making for vaccination.

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HM, JM, SK, MA, MN, and HGdS are employees of, and may or may not hold stock in, AstraZeneca.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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Data availability statement Data may be obtained from a third party and are not publicly available. The datasets generated and/or analysed during the current study are third-party data available from the proprietary MarketScan Research Database and are therefore not publicly available. The database used for this study may be requested from Merative for a fee, and the ICD-10 codes used for this analysis can be found in supplemental tables 1 and 2. The authors confirm they did not have any special access privileges that others would not have.

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