Analysis of Rare Events in Outcomes Research Using Department of Defense Data: Intravenous Immune Globulin Therapy for Bullous Pemphigoid

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Research Article

Keywords: modeling rare events, rare disease, rare therapies, bullous pemphigoid, immune globulin therapy

Posted Date: February 1st, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3879317/v1

Additional Declarations: No competing interests reported.

Abstract

Introduction:

Rare events data have proven difficult to explain and predict. Standard statistical procedures can sharply underestimate the probability of rare events, such as intravenous immune globulin therapy (IVIg) for bullous pemphigoid.

Methods

This retrospective cross-sectional study used Department of Defense TRICARE data to determine factors associated with IVIg therapy among bullous pemphigoid patients. We used prior and weighted correction methods for logit regression to solve rare event bias.

Results

We identified 2,720 individuals diagnosed with bullous pemphigoid from 2019 to 2022, of which 14 were treated with IVIg. Patients who received IVIg therapy were younger (65.07 vs. 75.85, *P* = .0016) and more likely to be female (13 vs. 1, *P* = .0036). The underestimation with the standard regression model for event probabilities ranged from 11–102% using the prior correction method and from 15–107% using the weighted correction method.

Conclusion

Rare events are low-frequency, high-severity problems that can have significant consequences. Rare diseases and rare therapies are individually unique but collectively contribute to substantial health and social needs. Therefore, correct estimation of the events is the first step toward assessing the burden of rare diseases and the pricing of their therapies.

BACKGROUND

In outcomes research data, we deal with rare cases frequently. Currently, about 7,000 rare diseases have been identified, with an estimated 300 million people affected globally [1]. Rare diseases, although individually unique, collectively represent substantial unmet health and social care needs and a significant public health challenge to society as a whole [1]. Definitions of rare diseases vary [1]: under the U.S. Orphan Drug Act, a rare disease is defined as a disease or condition affecting fewer than 200,00 0[2], whereas it is defined as a condition that affects fewer than 5 people per 10,000 population in Europe [1].

It is estimated that 95% of rare diseases have no approved treatment [1, 3]. The treatments for the remaining 5% are frequently expensive and relatively unknown. In addition to the high research and development costs associated with largely limited treatment options, the rather small market for rare diseases is conducive to prohibitive pricing. Rare diseases present a challenge for clinicians in reaching a conclusive diagnosis and determining an appropriate course of treatment due to their low prevalence, heterogenicity, and complexity [1, 4, 5]. Thus, it can be challenging to predict and estimate rare-disease outcomes in a real-world setting.

A rare event is defined as a binary dependent variable characterized by dozens to thousands of times fewer *1*'s (i.e., rare diseases, treatments, newly approved medications) than *0*'s ("nonevents") [6]. There are two main reasons for the difficulty in estimating rare events. First, standard logistic regression can sharply underestimate the probability of events. Therefore, the estimates would be biased. One real-life example is working with data on a rare disease such as bullous pemphigoid (BP), a rare skin condition. It is estimated that BP affects fewer than 50,000 people in the U.S., primarily older people [7]. The most common treatment is prednisone, but long-term use increases the risk of weak bones, diabetes, high blood pressure, high cholesterol, and infection. As an alternative, intravenous immunoglobulin (IVIg) is effective, although optimal use of IVIg is yet to be determined. Most adverse effects of IVIg infusions are transient, infusion-related symptoms that do not have long-term sequelae, although serious adverse events such as thrombosis, renal dysfunction, and acute renal failure have been noted [8]. Additional concerns about IVIg treatment include its potential toxicity and cost. While a single infusion starts at $5,000 to $10,000, treatment usually requires repeated cycles for which insurance coverage is not always covered. Therefore, it is essential to know the probability of using IVIg treatment for a rare disease.

To study the usage pattern of IVIg therapy in BP, we can formulate the model as follows: Let the outcome variable (e.g., whether the patient had IVIg therapy) be y_i and follow a Bernoulli probability function that takes on the value 1 with probability π_i. Let x_i be the vector of explanatory variables such as age, comorbid conditions, gender, or insurance type. Then it can be shown that the variance matrix takes the following form:

$$V\left(\widehat{\beta}\right) = \left[\sum_{\mathrm{i}=1}^{\mathrm{n}} \pi_{\mathrm{i}}\left(1-\pi_1\right) \mathrm{x}_{\mathrm{i}} x_i'\right]^{-1}$$

Rare events have small estimates for π_i observations. Standard logit models that use approximation rather than actual values will usually have larger values for π_i. Thus, $\pi_i(1-\pi_i)$ will be larger for *1*'s than *0*'s, stating that *1*'s are more informative than *0*'s in rare events. Since rare events have small sample sizes (usually < 200 observations), the logit models will yield a suboptimal result [6]. Therefore, logit models need to be adjusted to control this effect.

The second problem is related to how the data are collected. There is a fear among analysts that collecting data sets with no events (and thus with no variation on outcome measures) has led researchers to choose very large data sets with few, and often poorly measured, explanatory variables. For example, to avoid rare events, a researcher could include a broader sample by including a wide variety of International Classification of Disease (ICD) codes, a Healthcare Common Procedure Coding System (HCPCS) Level II alphanumeric code issued by the Center for Medicare and Medicaid Services (J-Codes), or Current Procedural Terminology (CPT) codes rather than specific codes. This technique will cloud the estimates, making it challenging to see the true effect of treatment on an actual targeted sample.

The twofold problem outlined above arises when predicting health outcomes of rare diseases, rare treatments, or small numbers of recently approved medications. The objective of this study is to apply correction methods used in other rare event studies such as major stock market crashes to solve the aforementioned issues in performing research on rare diseases.

METHODS

For this retrospective cross-sectional study, we extracted de-identified patient data for fiscal years (FYs) 2019 to 2022 from the Department of Defense TRICARE data. Each FY (October 1–September 30) is based on the U.S. federal budget calendar. The data from Military Health Services (MHS) has been recognized as a model of equitable healthcare access across socioeconomic and racial groups. The U.S. MHS is a global healthcare network with a diverse population that is more representative of the U.S. population than other data sets, with fewer disparities in healthcare services. The system serves 9.6 million beneficiaries, including active-duty service members, retirees, and family members, on an annual budget of $53 billion. The MHS delivers care through a direct-care/health maintenance organization system for Department of Defense military treatment facilities and a purchased-care/preferred provider organization system for civilian facilities. In addition, the MHS provides universal coverage for its beneficiaries under its TRICARE program. The data do not capture healthcare delivery in combat zones or care received in the Veterans Administrative system. All individuals were in the TRICARE Prime® managed care option.

Patients with BP were identified using the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) diagnosis codes (L12.0). Our outcome variable was the use of IVIg therapy and identified by J codes (J1459, J1554, J1556, J1557, J1561, J1566, J1568, J1569, J1572, J1599). The inclusion criteria used were adults (≥ 18 years), diagnosed with BP and treated with or without IVIg. IVIg date was the index date; the index date for the non-event cohort was randomly assigned between the minimum of IVIg date and maximum of IVIg date.

Patient age, gender, and comorbidities were available in the data sets. We identified the top 10 comorbidities associated with BP: hypertension, hyperlipidemia, pemphigoid, esophagitis reflux, dermatitis, urinary tract infection, limp pain, rash, skin cancer, and dyspnea. A flag was created for patients who had at least three comorbidities prior to treatment to proxy for severity.

For descriptive analysis, we compared the patients with and without IVIg therapy. Numbers and percentages were provided for dichotomous and polychotomous variables. Means and standard deviations were provided for continuous variables. For dichotomous and polychotomous variables, *P* values were calculated according to the chi-square test, and for continuous variables, *t*-tests were used to calculate *P* values. Nonparametric tests (e.g., the Mann-Whitney *U* test, log-rank test, or McNemar test) were applied if there was a deviation from asymptotical assumptions.

Since it is well documented that logit coefficients are biased in small samples, we proposed a correction method to solve the possible "rare event" bias in log estimation. Consider a logit model for outcome variable *y* and set of *k* explanatory variables **x**:

$$[P(y=1\,|x) = G(\beta_0 + \beta_1 x_1 + \cdots + \beta_k x_k)]$$

,

where G is the logistic function:

$$G(z) = exp(z) / [1 + exp(z)]$$

,

which is between 0 and 1 for all real numbers *z*.

To apply the first correction method, we obtained information about the fraction of *1*'s in the population ρ, and then the observed fraction of ones in the sample $\bar{y}$. Then the adjusted coefficient in the logit model is

$$\widehat{\beta_0} - ln\left[\left(\frac{1-\rho}{\rho}\right)\left(\frac{\bar{y}}{1-\bar{y}}\right)\right].$$

Note that prior correction affects only constant terms (therefore, not the odds ratio), but since most of the time interest lies in estimated probabilities:

$$\pi_i = \left(1 - e^{(\beta_0+\beta_1 x_1+\cdots+\beta_k x_k)}\right)^{-1}$$

,

it is necessary to estimate a rare-event bias-adjusted constant term, with the first correction technique, called *prior correction*.

For the second correction technique, we used weights determined by the proportion of *1*'s and *0*'s in the sample to equal the true proportion in the population, letting $w_1 = \frac{\rho}{\bar{y}}$ and $w_o = \frac{1-\rho}{1-\bar{y}}$ be the dependent variable and weighting independent variables by w_1 if $y_i = 1$and w_o if $y_i = 0$. Then, we ran a standard logistic regression of weighted dependent and independent variables.

To solve commonly used data collection biases under rare-event data, King and Zeng propose collecting all (or all available) *1*'s and a small random sample of '*0*s to not avoid losing consistency or even much efficiency relative to the full sample [6].

For the second part of the analysis, we tested differences in predicted probabilities. We proposed nonparametric tests since these tests are most appropriate when the sample sizes are small. The Mann-Whitney *U* test and the Kolmogorov-Smirnov two-sample test were used on predicted probabilities of logit regressions to see whether differences exist.

The analysis uses SAS version 9.4 (SAS Institute Inc.) and STATA 17 (STATA Corp., LLC).

RESULTS

We identified 2720 unique individuals diagnosed with BP in FY 2019-2022. Among these patients diagnosed with BP, 14 were treated with IVIg. The remaining sample was a non-event cohort (n=2706). Overall, 54.19% of individuals were women, and 85% of our sample was 65 years or older (mean, 78 years). We identified the most frequent 10 comorbidities from our sample. According to Table 1, the most frequent comorbidity prior to treatment with IVIg was hypertension (61.32%), followed by hyperlipidemia (37.20%), pemphigoid (34.70%), pain limp (24.15%), dyspnea (23.82%), dermatitis (23.49%), skin cancer (22.31%), urinary tract infection (20.25%), esophageal reflux (19.44%), and rash (16.43%). Within this sample, 54.08% of patients had more than three comorbidities within one year prior to treatment.

BP patients receiving IVIg therapy were younger (65.07 vs. 75.85, *P*=.0016) and more likely to be female (13 vs. 1, *P*=.0036). Overall, patients with IVIg treatment had significantly more comorbidities than patients without IVIg therapy. (78.57% vs. 53.95%, *P*=.0653). Patients receiving IVIg therapy also had a significantly higher likelihood of esophageal reflux (42.85% vs. 19.44%, *P*=.0265), dermatitis (57.14% vs. 23.49%, *P*=.0029), urinary tract infection (50.00% vs 20.25%), *P*=.0055), and rash (42.85% vs, 16.43%, *P*=.0075).

Table 1. Demographic Characteristics of BP Patients With and Without IVIg Therapies

	Total	With IVIg Therapy	Without IVIg Therapy	*P* Value
Sample size (n)	2720	14	2706	
Age, mean (SD)	75.79 (12.72)	65.07 (17.54)	75.85 (12.67)	.0016
Age, median (IQR)	78 (70-85)	72 (54-76)	78 (70-85)	
Female, n (%)	1474 (54.19)	13 (92.85)	14 (53.99)	.0036
Diseases				
Hypertension	1668 (61.32)	11 (78.57)	1657 (61.23)	.1841
Hyperlipidemia	1012 (37.20)	8 (57.14)	1004 (37.10)	.1219
Pemphigoid	944 (34.70)	8 (57.14)	936 (35.58)	.0771
Esophagitis reflux	529 (19.44)	6 (42.85)	523 (19.32)	.0265
Dermatitis	639 (23.49)	8 (57.14)	631 (23.31)	.0029
Urinary tract infection	551 (20.25)	7 (50.00)	544 (20.10)	.0055
Pain limp	657 (24.15)	5 (35.71)	652 (24.09)	.3112
Rash	447 (16.43)	6 (42.85)	441 (16.29)	.0075
Skin cancer	607 (22.31)	5 (35.71)	602 (22.24)	.2275
Dyspnea	648 (23.82)	5 (35.71)	643 (23.76)	.2952
³3 comorbidities	1471 (54.08)	11 (78.57)	1460 (53.95)	.0653

Abbreviations: IQR, interquartile range; IVIg, intravenous immune globulin; SD, standard deviation.

Table 2 shows the coefficients from standard logistic regression, prior correction regression, weighting regression, and reduced non-event sample regression.

Table 2. Coefficient Estimates from Logistic, Rare-Event Corrected Logistic, and Reduced Non-event Sample Regressions

	Coefficient	Standard Error	*P* Value
Standard logistic regression			
Age ³65 years	-1.516914	0.5574599	.007
Male	-2.213399	1.04429	.034
³3 comorbidities	1.427647	0.6653685	.032
Constant	-4.618576	0.6239096	.6239096
Prior correction logistic regression			
Age ³65 years	-1.533331	0.5673812	.007
Male	-1.756653	1.078328	.103
³3 comorbidities	1.307087	0.6505784	.045
Constant	-4.359911	0.6083402	.6083402
Weighting logistic regression			
Age ³65 years	-1.533391	0.5673646	.007
Male	-1.756592	1.078324	.103
³3 comorbidities	1.30694	0.650598	.045
Constant	-4.35976	0.6083932	0
Reduced sample size			
Age ³65 years	-1.145064	0.6302908	.069
Male	-1.863163	1.075973	.083
³3 comorbidities	1.235095	0.7058335	.08
Constant	-1.944585	0.6661061	.004

The correction rate for the prior correction technique assumes that the IVIg rate for BP is 0.00538918 (. This rate is obtained from an open-claims database that covers 330 million patients in the United States. When comparing unadjusted rates for IVIg treatment, our rates were lower (0.00515). There was agreement on the sign of the coefficients across regressions. Older age, male self-identification, and fewer comorbidities decreased the likelihood of BP being treated with IVIg. Coefficients from prior correction logistic regression and standard logistic regression were statistically similar, but both were statistically different from weighting logistic regressions (*P*=.0001). The coefficients from the regression that used the reduced random sample of non-events were also different from standard logistic regression (*P*=.004) (Table 2).

We randomly selected 140 patients from 2706 non-event patients, so the total regression sample was 154, with 10% of the sample in the IVIg cohort (i.e., the rare-event proportion increased from 0.5% to 10%). The reduced random sample increased the event proportion in the regression sample. We calculated event probabilities for each group of patients with respect to age, gender, and comorbidities (Table 3). As expected, standard logistic regression significantly underestimated the event probabilities. The underestimation ranged from 11% to 102% using the prior correction method and from 15% to 107% using the weighting correction method. For example, standard logistic regression predicted that male patients 18 to 64 years old with few comorbidities have a 0.1% probability of receiving IVIg treatment; however, the actual probability was double according to prior correction and weighting correction. Random selection of non-event samples significantly biased the results and found probabilities 10 times larger than corrected probabilities and 20 times larger than probabilities calculated by standard logistic regression.

Rare-event correction affected the constant term the most. Table 3 shows the constant term for each model with its lower and upper confidence intervals.

Table 3. Standard and Corrected Predicted Probabilities for Different Sets of Groups

Age (years)	Gender	Comorbidities	Standard Logistic Regression	Prior Correction Method		Weighting Method		Random Reduction of Non-Event Sample	
				Point Estimate	Underestimation of Probabilities	Point Estimate	Underestimation of Probabilities	Point Estimate	Deviation of Probabilities
18-64	Male	High	0.0044769	0.00831	-85.62%	0.0085	-89.86%	0.0755036	108.82%
³65	Male	High	0.0009856	0.00171	-73.50%	0.0017	-72.48%	0.0156083	102.12%
18-64	Female	High	0.0395085	0.04662	-18.00%	0.04552	-15.22%	0.4761266	364.52%
³65	Female	High	0.0089435	0.00997	-11.48%	0.01031	-15.28%	0.1499854	230.68%
18-64	Male	Low	0.0010776	0.00218	-102.30%	0.00223	-106.94%	0.0230371	102.25%
³65	Male	Low	0.0002366	0.00047	-98.65%	0.00048	-102.87%	0.0045571	100.46%
18-64	Female	Low	0.0097704	0.01253	-28.24%	0.01216	-24.46%	0.2078657	173.60%
³65	Female	Low	0.00216	0.00275	-27.31%	0.0027	-25.00%	0.0484764	100.79%

DISCUSSION

Table 4 lists the top 10 most expensive drugs marketed in United States with annual cost based on length of therapy. The common feature of these medications is that they treat a rare condition. A pair of recently related studies sheds new light on the staggering cost of developing new drugs, an expense that now exceeds $2 billion per therapy on average [9]. To create an incentive for pharmaceuticals to bear the cost of a rare condition, treatment prices for these medications are prohibitive. Therefore, analyzing rare conditions and estimating the event rates correctly has significant importance. All pricing models are based on these estimates. We applied several correction techniques to a rare treatment for BP using a military health data set.

Table 4: Ten Most Expensive Drugs in the United States

Order	Drug	Annual Cost Based on Length of Therapy ($)
1	Zolgensma	2,125,000
2	Zokinvy	1,073,760
3	Danyelza	1,011,882
4	Kimmtrak	975,520
5	Myalept	929,951
6	Luxturna	850,000
7	Folotyn	842,585
8	Brineura	755,898
9	Blincyto	754,720
10	Ravicti	695,970

The overall BP prevalence is 0.012%, or 12 per 100,000 adults in United States[10]. The prevalence of BP among those aged 60 years and older is 0.038%, or 37.7 per 100,000 adults [10]. Studies have shown that BP is mostly a disease of older adults, with a reported onset around 75 years, and a clear female preponderance [11, 12]. Our results supported these statistics, as 85% of our sample was at least 65 years old (median, 78 years) and 54.19% were women.

BP is often associated with various systemic diseases and tends to have a poor prognosis because of limited physical function and low immunity among older people. A notable increase in incidence rates may be related to an aging population, increased drug use, diagnostic sensitivity, and non-bullous presentations, the latter of which have frequently been underdiagnosed [11, 13]. We found that 54% of the population had at least three comorbidities within one year prior to diagnosis. The most frequent comorbidity prior to diagnosis was hypertension (61.32%), followed by hyperlipidemia (37.20%), pemphigoid (34.70%), pain limp (24.15%), dyspnea (23.82%), dermatitis (23.49%), skin cancer (22.31%), urinary tract infection (20.25%), esophageal reflux (19.44%), and rash (16.43%).

Diagnosis is usually made based on clinical features, histological examination, and the quantification of circulating typical autoantibodies [11, 14]. However, especially in the first phases of the disease, typical clinical features may be lacking, resulting in a late diagnosis and consequently delayed

treatment [11].

Glucocorticoid, a systemic corticosteroid, is the first line of treatment for BP[12,16,17]. Oral prednisone (0.5-1 mg/kg/day, progressively, over a period of 6-9 months), the most commonly used treatment for BP, usually controls the disease within 2 weeks. In addition, compared with high-dose glucocorticoids alone, the combination of glucocorticoids and immunosuppressive agents like IVIg or antibiotics have been found reduce mortality because of the synergistic effect of combined therapy and the reduction of adverse reactions caused by glucocorticoids[17] Moreover, due to a higher incidence of this rare disease in elderly patients—a population with a higher frequency of comorbidities—BP treatment and management remain a challenge. Glucocorticoids may be contraindicated as a treatment option in some of these patients due to their comorbidities. For example, a patient with severe hypertension might not be eligible for treatment with corticosteroids. Further, the main problem linked with the use of systemic steroids in elderly patients is the high rate of adverse effects, which may result in higher rates of mortality and adverse outcomes than with topical clobetasol propionate 0.05%[21]. Therefore, alternative treatments like IVIg can play an important role in managing this disease.

IVIg has demonstrated pleiotropic anti-inflammatory effects [15], including increased autoantibody catabolism, and meaningful positive effects in BP in several cases and studies both as monotherapy and in combination with rituximab [16][17, 18]. IVIg may particularly benefit patients (1) who may be recalcitrant or nonresponsive to conventional therapy with oral corticosteroids and/or other adjuvants; (2) who are unable to tolerate such agents; (3) who develop significant side effects to these agents, necessitating their discontinuation; or (4) for whom these agents are contraindicated [18].

Our study indicated that other treatments such as glucocorticoids continue to be predominantly used, as only 14 individuals in our population were receiving IVIg therapy. Those treated with IVIg were younger (65.07 vs. 75.85 years, *P*=.0016), more likely to be female (1474 vs. 13, *P*=.0036), and had significantly more comorbidities than those patients not receiving IVIg (78.57% vs 53.95%, *P*=.0653). This finding might be explained by a recent study that indicates efgartigimod, a monoclonal antibody, has entered clinical trials for BP after promising results in patients with pemphigus and myasthenia gravis [16]. Although we did not investigate myasthenia gravis as a comorbidity, it is well-known that this disease is predominant in women and that one of its treatments is IVIg. This might indicate that the population with BP who will benefit most from IVIg are patients who tend to be younger and female and have other comorbidities. Further research is needed to explore this possible association.

As discussed previously, rare events are difficult to explain and predict because statistical procedures tend to underestimate the probability of rare events or because the data collection strategies are inefficient [6]. As expected, our results yielded that standard logistic regression significantly underestimated the event probabilities. The underestimation in our study ranged from 11% to 102% using the prior correction method and from 15% to 106% using the weighting correction method. For example, in our study, standard logistics regression predicted that male patients 18 to 64 years old, with fewer comorbidities, have a 0.1% probability of receiving IVIg treatment; however, the actual probability was more than double according to prior correction and weighting correction. This discrepancy could give rise to a large margin of error and, ultimately, cost-ineffective decisions.

Furthermore, our study showed that the random selection of non-event samples significantly biased the results. We found the probabilities were 10 times larger than the corrected probabilities and 20 times larger than the probabilities calculated by standard logistic regression. These results support King and Zeng's findings, which indicated that a second, more important common problem in analyzing rare events lies in how data are collected [6]. The reduced sample size in our study demonstrated the most bias, supporting the idea that data collection can greatly influence results.

Other techniques such as meta-analysis have been suggested for rare event bias correction. However, meta-analyses of binary data can be problematic when the proportion of events is low [19, 20]. Meta-analyses of binary data are frequently performed using the standard inverse-variance fixed-effects model, based on large-sample normal approximation, or fixed-effects methods, based on exact distributional theory such as the Mantel–Haenszel (MH) or Peto model, or the standard random-effects DerSimonian-Laird (DL) model [20]. These methods, based mostly on large-sample normal approximation (particularly inverse-variance) [20, 21, 22], lack power to investigate the incidence of rare events. Therefore, their statistical properties for estimating treatment effects are often judged as suboptimal either through biased results, inappropriately wide confidence intervals, or insignificant statistical power to detect true differences.

The Cochrane guidelines (Version 6.1, 2020) recommend the use of methods mostly accessible in Review Manager (RevMan), a free-access software developed by the Nordic Cochrane Centre [20, 22]. Its guideline suggests that, at event rates less than 1%, the Peto odds ratio should be utilized [20]. In circumstances where event rates are above 1% and meta-analyses involves many studies with imbalanced treatment groups, the MH odds ratio should be used [20, 23]. However, some of these methods, notably, the MH without continuity correction, logistic regression, and exact methods, are not available in RevMan. Second, meta-analysts often have to revert from inverse-variance weighting to a random-effects DL model to reduce bias in estimation when heterogeneity is present.

Most recently, new methods, including maximum likelihood, profile likelihood, and restricted maximum likelihood or the nonparametric "permutations" methods, have been proposed for improved estimation of variance (τ) [20, 24, 25]. The nonparametric bootstrap of the DL estimator was shown to be a better performer in small meta-analyses that were falsely assumed to be homogenous under the standard DL

model [20]. Although this nonparametric bootstrap of the DL model has now been extended for both the MH and Peto models, little is known about the performances of these methods in meta-analyses involving rare events when heterogeneity is an issue.

LIMITATIONS

This study has several limitations related to the use of administrative data sets and retrospective analysis. Although retrospective studies are an important tool to study rare diseases, manifestations, and outcomes [26], their design has is subject to limitations. Since the analysis was based on claims data not originally designed for research, some information is bound to be missing. Selection, recall, and loss of follow-up biases may affect how representative the data is for the rare event of interest.

Using an administrative database has several strengths, including a large population/base sample size, which provides an established denominator [27]. The data include patient demographics, clinical characteristics, detailed healthcare use, and cost information, allowing treatments and outcomes to be identified and compared across populations included in the data [27]. However, some limitations warrant mentioning. First, like most claims-based data sources, there is a lag between the time when individual receives services and when the files become available for research (typically 2-3 years) [27]. Thus, some information may be missed in processing or reimbursement and the data may not be generalizable to the entire population. Also, the claims to not capture all health data. Therefore, while diagnoses are included, information that may be found in medical records, such as health-related behaviors, anthropomorphic data, and nonprescription medication use, are not captured in the claims. Further, claims for which services were recommended but not yet received would not be captured in the data set. Additionally, administrative claims data do not include information about the decision-making process (e.g., how, why, and by whom the decisions were made; the correlation between planned and received treatment; and why treatment was altered or discontinued) and patient-reported outcomes [27].

Finally, it is important to note that the correction models we applied have not been validated, and further research must be done in different settings.

CONCLUSION

Rare events are low-frequency, high-severity problems that can have significant consequences including major stock market crashes, pandemics, wars, rare diseases, and small counts of recently approved medications. While rare diseases are individually unique, they collectively contribute to substantial health and social care needs. Additionally, rare diseases present a challenge for clinicians in reaching a conclusive diagnosis and determining an appropriate course of treatment due to their low prevalence, heterogenicity, and complexity [1, 4, 5]. Predicting and estimating rare-disease outcomes in a real-world setting can be challenging to researchers and can have significant public health implications.

Therefore, improving statistical techniques to understand rare events is a tremendous analytical challenge that can have major impacts on health care. In technical terms, the maximum likelihood-based logit model can generate heavily biased parameter estimates and is prone to overfitting rare-event data even in low-dimensional models. Such issues have forced scientists to get creative and explore unconventional analytic methods. We have proposed the application of several correction techniques used in public economics to outcomes research studies dealing with rare-event estimation bias from standard logistic regression or inefficient data collection techniques.

Declarations

Author contributions: O.B. provided the supervision, conceptualization, methodology, validation, and visualization of the research and participation in the writing process from the original draft preparation to the reviewing and editing of the manuscript. H.Y. participated in the supervision and participated in the writing process from the original draft to the reviewing and editing of the manuscript. G.S. participated in the project management, supervision, and investigation of the literature review and in the writing process from the original draft preparation to the reviewing and editing of the manuscript.

Acknowledgment: The authors thank Easheta Shah for assistance in editing the manuscript.

Funding: This research received no external funding.

Disclosure: The authors report no competing interest.

Ethics approval and consent to participate: This study used publicly available, de-identified U.S. Department of Defense TRICARE claims data and is exempt from IRB review for human subjects research pursuant to 32 CFR 219.101(b), according to the Department's Human Research Protection Program Office.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analyzed in this study are available through the Military Health System (https://www.health.mil).

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