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Use of the Odds Ratio in Clinical Research

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Abstract

The Odds Ratio is one of several statistics used to assist clinicians determine whether to use a particular treatment in clinical practice. The Odds Ratio fits into the category of effect-size statistics because the larger size of the Odds Ratio statistic, the stronger the relationship between the treatment and the outcome. However, its interpretation is not as clear and direct as that of a correlation. The Odds Ratio is typically used when the outcome of interest is relatively rare. Most Odds Ratio calculations are set up as two by two tables. Therefore, the preferred significance statistic is the Maximum Likelihood Ratio Chi-Square. However, in some circumstances. The Fisher's Exact Probability statistic or Pearson's Chi-Square can also be used. As a simple statistic to calculate, it can be hand calculated in a clinic if necessary to determine the odds of a particular event for a patient at risk for that event. Interpretation of the statistic, and how the Odds Ratio table should be set up require care as misinterpretation can easily occur.

Keywords: Odds Ratio; Health; Epidemiology Studies

Introduction

The statistic, *The Odds Ratio,* is used frequently in research that addresses treatments used by physicians in family and specialty practice. It is one of the best tools to use when the incidence of a particular outcome is relatively low. Due to the fact that the statistic provides information that helps physicians and their patients decide the value of a particular course of treatment, it has increasingly used when incidence of a particular outcome is not rare. However, this use does carry a higher risk of the Odds Ratio overestimating the probability of the disease or condition [1]. One often sees this statistic used in case control studies (Op. Cit.). The odds ratio is used when one of two possible events or outcomes are measured, and there is a supposed causative factor.

The Odds Ratio allows the researcher to examine the odds of one outcome versus another, depending on whether a specific treatment used or not used. Specifically, the odds ratio evaluates whether the odds of a certain event or outcome is the same for two groups that receive different treatments [2]. For example, the medical outcome for a group of patients given a vaccine versus unvaccinated patients. Clinically, that means that the researcher measures the ratio of the odds of a disease occurring, a patient dying, or another outcome of interest happening to the odds of the disease, death, or other outcome not occurring.

The odds ratio is a versatile and robust statistic. It is also easily calculated and thus it is quite useful by clinicians who may need to hand calculate a statistic. In addition to looking at treatments, it is used to calculate the odds of a health outcome given exposure versus non-exposure to a toxic substance or a disaster (or other unique) event [3]. The clinical literature provides many instances of the odds ratio being used in research to estimate reduction in disease or disease complications if patients receive a particular drug or vaccine. Similar to a correlation, the Odds Ratio provides information on the size of the effect. In other words, it provides information on how strong the relationship between treatment type and outcome is [4]. It is an indirect measure, however, as will be seen in the section on interpretation of the statistic (Table 1).

Calculation of the Odds Ratio

The calculation of the odds ratio is quite simple. The formula is as follows:

$$\text{Odds Ratio}^{i} = \frac{PG_1/(1\text{-}PG_1)}{PG_2/(1\text{-}PG_2)}$$

[i]PG = Odds of the outcome happening (given treatment 1) for Group 1

PG = Odds of the outcome happening (given treatment 2) for Group 2

Another way to represent the formula is in table format:

	Standard Treatment	New Treatment
Event Happens	a	b
Event does not happen	c	d

Table 1: Odds Ratio Table Format.

$$\text{Odds Ratio} = \frac{a \div b}{c \div d} \text{ or: Odds ratio} = (ad) \div (bc)(\text{CDC, 2022})$$

Given the algebraic rule of cross products, the second formula will produce the same result as the first formula for odds ratio and is the formula more often reported in research papers.

Significance Tests for the Odds Ratio

The Odds Ratio is often used to test data in a 2 x 2 table. The most powerful statistic for testing the significance of a 2 x 2 table is the Fisher's Exact statistic. If the data are nominal counts, this the best statistic assuming there are no cells where the frequency is very small [5], very small usually means there are less than 5 cases in a cell.. Several significance tests can be used for the Odds Ratio. The most common are the Fisher's Exact Probability test, the Pearson Chi-Square and the Likelihood Ratio Chi-Square.

Fisher's Exact Often, the Odds Ratio dataset takes the form of a 2 X 2 table, and for that situation, a Fisher's Exact Ratio test should be used. The formula for the Fisher's Exact is:

$$p = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{n!a!b!c!d!}$$

Where "*p*" is the Fisher's Exact Probability, "a, b, c, d" represent the counts in the cells, and "n" represents the total sum of the values in all four cells.

Chi-Square When there are more than 4 and at least 80% of the cells have 5 or more values, the Chi-Square test should be used. (Note: Chi-Square can also be used for a 2 X 2 table, but the Fisher's Exact is a more powerful statistic). The Chi-Square (χ^2) assumes that the numbers in the cells represent counts and not proportions or averages, and it assumes that the value of the cell expected values are at least 5 in 80% or more of the cells. (Like Fisher's Exact, χ^2 is not robust with some cells having very few cases. Most statistical computer programs such as Stata and SPSS will calculate the Fisher's Exact and Chi-Square values and provide the significance value of the result. The Chi-Square formula is:

$$\div^2 = \sum \frac{(0-e)^2}{e}$$

Where "o" represents observed frequencies and "e" represents expected frequencies.

Likelihood Ratio Chi-Square. The Likelihood Ratio Chi-Square, is the statistic that should be used to obtain a significance when some cells have very few cases. Like all likelihood ratio statistics this statistic uses a logarithmic formula. In many cases, the likelihood ratio chi-square is the most appropriate test of significance for the Odds Ratio because of the rarity of at least one of the outcomes. Its formula is as follows:

$$G = 2\sum f.\ln\left[\frac{f}{f_i}\right]$$

Where "G" represents the Likelihood Ratio statistic, f represents observed values, f_i represents expected values, and "ln" indicates the log is to be taken.

Standard Error and Confidence Intervals for the Odds Ratio

The odds ratio is not normally distributed (it is skewed), so it is not possible to directly calculate the standard error of the statistic. However, the standard error for the natural logarithm of the odds ratio is quite simple to calculate. It is calculated as follows:

$$SE = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

Then all one needs to do to construct confidence intervals about the natural logarithm is to calculate the standard error using the above formula and add that value (or a multiple of that value) to the log of the Odds Ratio value for the upper

CI and subtract that value (or a multiple of that value) to the log of the Odds Ratio value for the lower CI. More advanced information on direct computation of the confidence intervals for odds ratios can be obtained from the paper published by Sorana Bolboaca, et al. [6], the paper published by Simundic, et al. [7], or Tenny, et al. [1].

It should be remembered that the concept of "no difference" in most statistics refers to a difference of zero and is generally measured through the mean of the variable. The Odds Ratio is different. The "no difference" value for this statistic is 1 and that ratio is expressed as 1:1 and means the odds of a particular outcome are the same for both treatment groups. When a confidence interval includes the value of 1, the researcher or clinician will know that the odds of the measured outcome are the same for both (or all) treatment groups, even without a significance test.

Example of Use of the Odds Ratio

Comparison of Different Effects of Two Different Drugs:

One common use of the odds ratio is to determination if there is a difference in the effectiveness in treating a condition between two drugs, and if there is a difference, how large is that difference. As an example, consider the likelihood of requiring hospitalization for Covid-19 for patients aged 65 and older, considering whether they are vaccinated or not. Let's assume that the hospitalizations for unvaccinated Covid patients aged 65 and over is 1,650 per 100,000 of population. For fully vaccinated people who contract Covid-19 the hospitalization rate is 572 per 100,000.

The question is this: What are the odds of getting so ill that one must be hospitalized for Covid-19 if one is not vaccinated versus if one is fully vaccinated. The odds ratio is a way of comparing whether the odds of needing hospitalization are the same for a person whether vaccinated or not. Or more generally, are the odds of a particular outcome the same for two different groups? (Table 2).

	Unvaccinated	Vaccinated	Odds
Hospitalized	1614 (a)	572 (b)	1614 ÷ 572 = 2.82
Not Hospitalized	98386 (c)	99428 (d)	98386 ÷ 99428 = .9895
Totals	100,000	100,000	2.82/0.9895 = 2.85

Table 2: Results from Fictional Covid-19 Study.

The odds ratio is simply the ratio between the following two ratios: The ratio of hospitalization for the unvaccinated versus the vaccinated, and the ratio of not needing hospitalization for unvaccinated versus vaccinated people.
It is calculated as follows:

$$\text{Odds Ratio} = \frac{a \div b}{c \div d} = \frac{1614 \div 572}{98386 \div 99428} = \frac{2.82}{0.9895} = 2.85$$

The formula can also be presented as ad ÷ bc (this is called the *cross-product*). The result is the same:
Odds Ratio = (1614 X 99428) ÷ (572 x 98386) = (160,476,792 ÷ 56,276,792) = **2.85**.

The result of an odds ratio is interpreted as follows: Unvaccinated people were hospitalized 2.85 times more often than vaccinated people. Based on these results the care provider would recommend to all patients aged 65 and over that if there are no contraindications, these patients should get fully vaccinated.

How the Odds Ratio Statistic is Interpreted

An odds ratio of 1.00 means the two groups had exactly the same outcome, regardless of the difference in their treatment, or a different event experience, or whatever other difference was tested as a potential cause of any difference found [8]. In general, the greater the odds, the stronger the association between the event and the outcome. However, an Odds Ratio is not a correlation and its interpretation is not direct like that of a correlation [4]. In the example, a result of 1.0 would have meant that the two groups were equally likely to be hospitalized. An odds ratio higher than 1 means that the first group (in this case, the unvaccinated group) was *more likely* to experience the event (hospitalization) than the second (vaccinated) group. The statistic indicates how much more likely. When the statistic begins with an integer higher than 1.0, it lets us know how much more likely. The integer means how many times more likely the outcome is. For example, in the example we obtained an Odds Ratio of 2.85. The interpretation is that unvaccinated people were 2.85 times more likely to be hospitalized than vaccinated people. In communicating with a patient, one might say the patient is almost 3 times more likely to get sick enough to need hospitalization if he/she refuses the vaccination and contracts Covid-19.

An odds ratio of less than 1 means that the first group was *less* likely to experience the event [9]. However, an odds ratio value below 1.0 is not directly interpretable. The researcher does not know how much less likely. For example, a result of 0.35 does not mean the first group was .35 times as likely to get sick, or 35% less likely to get sick. All one can say is the first group was less likely to experience the outcome than the second group. The *degree* to which the first group is less likely to experience the event is not available in the odds ratio result. This is why it is extremely important to carefully set up the 2 x 2 table. The researcher should use the first column in the table for the untreated group and the first row for the least desirable outcome. Then the interpretation will allow the researcher to report the odds of the untreated group experiencing the undesirable outcome *relative* to the treated group not experiencing the undesirable outcome.

Epidemiology's Use of the Odds Ratio

In epidemiology studies, the researchers often use the odds ratio to determine after the fact (post hoc) if two different groups had different outcomes on a particular measure. For example, Friese, et al. [10] conducted a study to find out if there were different probabilities for having a larger number of surgeries for breast cancer for women whose initial diagnostic procedures included a needle biopsy versus for women who did not have an initial breast biopsy. Through use of the odds ratio, they discovered that use of the needle biopsy was associated with a reduced probability of multiple surgeries (Table 3). The odds ratio table for this a study would have the following structure:

	Low Number of Surgeries	High Number of Surgeries
No Initial Needle Biopsy	a	b
Initial Needle Biopsy	c	d
Totals	n1	n2

Table 3: Table Format for Epidemiology Study.

In this study, Friese, et al. [10] obtained an odds ratio of .35 and concluded that use of the needle biopsy as an initial diagnostic test reduced the probability of multiple surgeries by .35% for women with breast cancer. (Note: This table should have been changed because an Odds Ratio value of .35 is a bit less interpretable than the value above 1.0 that would have been obtained if they set up their table as follows:

While the statistic result was interpreted to say that women who had an initial needle biopsy had 35% fewer surgeries than women who did not have an initial biopsy, this conclusion is not necessarily correct, and the calculation of a direct percentage should be calculated on the raw data

Conclusion

The great value of the odds ratio is that it is simple to calculate, very easy to interpret, and provides results that both care providers and patients can use to make clinical decisions. It is also useful in epidemiological studies when the data are retrospective. There are a variety of significance statistics that can be used for the Odds Ratio, Furthermore, it is sometimes helpful in clinical situations to be able to provide the patient with information on the odds of one outcome versus another. Patients may decide to accept or forego vaccination (or painful or expensive treatments) if they understand what their odds are for a particular result if they choose one course, and the risks of choosing the alternate course of action. Many patients want to be involved in decisions about their treatment, but to be able to participate effectively, they must have information about what is likely to happen, based on the decision they make. The odds ratio provides information that both clinicians and their patients can use for decision-making.

Odds ratios are one of a category of statistics clinicians might use to make treatment decisions. Other statistics commonly used to make treatment decisions include risk assessment statistics such as absolute risk reduction and relative risk reduction statistics. The Odds Ratio supports clinical decisions by providing information on the odds of a particular outcome relative to the odds of another outcome. In the Covid-19 vaccination example, the risk (or odds) of needing hospitalization if vaccinated is *relative* to the risk (odds) of hospitalization if not vaccinated.

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