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Nota Metodológica

O novo valor de alfa para a significância estatística nas pesquisas clínicas

The new alpha value for statistical significance in clinical trials

El nuevo valor alfa para la significación estadística en ensayos clínicos

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RESUMO

Atualmente a hipótese nula é utilizada para mostrar significância estatística, mas todas as hipóteses do modelo estatístico devem ser utilizadas para divulgar informações mais próximas dos resultados que ocorrem na população. O objetivo deste artigo é descrever as bases para a compreensão do melhor valor de referência para significância estatística a ser adotado em pesquisa clínica. Uma busca manual foi realizada para selecionar artigos no Medline via Pubmed. Apenas artigos em inglês foram considerados. Após a análise da bibliografia selecionada, os achados foram sumarizados para apresentar os resultados. A semelhança dos testes de hipótese estatística com os testes diagnósticos e a avaliação de α e β ao mesmo tempo fornecem uma fórmula para o valor de α. Esta fórmula é: α = poder estatístico – (valor preditivo positivo x poder estatístico)/valor preditivo positivo. O novo valor alfa para interpretação da significância estatística deve ser 0,042 considerando o cálculo do tamanho da amostra com poder estatístico de 0,8 e nível de confiança de 95%. O valor alfa deve ser ajustado se houver variação no poder estatístico.

Palavras-Chave
Bioestatística; Inferência Estatística; Interpretação; Estatística de Dados.

ABSTRACT

Nowadays the null hypotheses is used to show statistical significance, but all the hypotheses of the statistical model must be used to disseminate information closer to the results that occur in the population. The objective of this article is to describe the bases for understanding the best reference value for statistical significance to be adopted in clinical research. A handsearch was conducted to select papers on Medline via Pubmed. Only papers in English were considered. After analyzing the selected bibliography, the findings were sumirized to present the results. The similarity of the statistical hypothesis tests with the diagnostic tests and the evaluation of α and β at the same time provide a formula for the value of α. This formula is: α = statistical power – (positive predicted value x statistical power)/positive predicted value. The new alpha value for the interpretation of statistical significance should be 0.042 considering the sample size calculation with a statistical power of 0.8 and a confidence level of 95%. The alpha value must be adjusted if there is variation in statistical power.

Keywords
Biostatistics; Statistical Inference; Data Interpretation; Statistical.

RESUMEN

Hoy en día se utiliza la hipótesis nula para mostrar significancia estadística, pero se deben utilizar todas las hipótesis del modelo estadístico para difundir información más cercana a los resultados que se dan en la población. El objetivo de este artículo es describir las bases para comprender cuál es el mejor valor de referencia para la significación estadística a adoptar en la investigación clínica. Se realizó una búsqueda manual para seleccionar artículos en Medline a través de Pubmed. Solo se consideraron trabajos en inglés. Luego de analizar la bibliografía seleccionada, se resumieron los hallazgos para presentar los resultados. La similitud de las pruebas de hipótesis estadísticas con las pruebas diagnósticas y la evaluación de α y β al mismo tiempo proporcionan una fórmula para el valor de α. Esta fórmula es: α = potencia estadística – (valor predicho positivo x potencia estadística)/valor predicho positivo. El nuevo valor alfa para la interpretación de la significación estadística debe ser 0,042 considerando el cálculo del tamaño de la muestra con una potencia estadística de 0,8 y un nivel de confianza del 95%. El valor alfa debe ajustarse si hay variación en el poder estadístico.

Palablas Clave
Bioestadística; Inferencia Estadística; Interpretación; Estadística de Datos.

Introduction

Clinical trials have many steps such as planning, protocol registration, participant recruitment and data analysis, but the scientific community seems to prioritize the P value (1). Statistical significance does not represent the biological plausibility or clinical relevance of the findings.

Systematic reviews are studies considered to have a high potential to contribute to decision-making in clinical practice. It values the type of study, the risk of bias, raw data and does not value the P value. Systematic review ignores P value to constructo the evidence.

Statistical significance must take into account all the hypotheses of the statistical model to disseminate information closer to the results that occur in the population (2).

The objective of this article is to describe the bases for understanding the best reference value for statistical significance to be adopted in clinical research.

Methods

This transversal study was carried out using secondary data from papers identified on Medline via Pubmed. The descriptors used for searching were: statistical power analysis, p value significance and statistical tests. A handsearch was conducted to select papers. Only papers in English were considered. After analyzing the selected bibliography, the findings were sumirized to present the results.

Statistical tests of hypotheses

Clinical trials are research designs used to answer a research question. Research questions come from hypotheses. Clinical trials are studies performed with data from a population sample to clarify the hypotheses that generated the research questions (3).

The population is defined as all individuals with the characteristic of interest to the research. The sample is a part of the population selected for data collection. The sample data generate statistics that serve to estimate population parameters (3). The population parameters are unknown, so a statistical hypothesis test is required to estimate the probability of similarity between the sample values and the population parameters.

The statistical hypothesis testing model considers two hypotheses: null hypothesis (*H0*) and alternative hypothesis (*Ha*) (4). *H0* is a statement about the population parameter (4). *H0* is tested without the need to evaluate Ha since they are mutually exclusive values (4). *H0* states that the sample value does not represent the population

value. The hypothesis test analyzes the *H0* generating a value of P. The value of P is the probability that estimates how much the value of the statistic may be similar to parameter (3).

The P value is a probability that varies between 0 and 1. A reference value is needed to verify that the P value is small enough to reject *H0* (4). The reference value is known as the statistical significance level. The significance level represents the probability of rejecting the *H0* when it is true and is also known in the research environment as the symbol α (Table 1). There are other possibilities of probabilities in the decision process for acceptance or rejection of *H0* (Table 1).

Table 1 – Contingency table demonstrating the decision probabilities in the research scenario considering the null hypothesis.

Test results	**Result in the population**	
	True *H0*	**False *H0***
H0 acceptance	Correct decision or true negative (TN)	Type II error (β) or false negative (FN)
H0 rejection	Type I error (α) or false positive (FP)	Correct decision (1-β) or statistical power or true-positive (TP)

The classic interpretation of the P value

Statistical hypothesis tests are performed and their results are interpreted to gain significance in clinical research. Statistical significance is seen in clinical trials when the P value is less than or at least equal to the alpha value, 5% (0.05). The interpretation of the value of $P \leq 0.05$ is that the statistical difference exists between the groups and that there is a 1/20 chance of the result having occurred by chance (2). The P value can be misinterpreted leading to inappropriate conclusions, so some important considerations must be made for the correct interpretation of the results (5):

a) The P value does not say that the test hypothesis is true. The value evaluates the action of chance in the stipulated model. The lower the value of P, the lower the probability of a result having occurred by chance, considering that the other assumptions of the statistical model are correct (Table 1);

b) The action of chance alone cannot be represented by the P value, because a large random error can influence the results and disregarding the assumptions of the model would be inappropriate;

c) High P value does not mean absence of effect or association. Value is related to test hypotheses and not to effect or association. The association or effect may exist irrelevant to clinical practice;

d) Statistical significance does not mean clinical representativeness as statistics refer to a model of hypotheses. Clinical importance can be better assessed using confidence intervals.

Basis for the new alpha value

The classical definition of statistical significance (P ≤ 0.05) does not take into account the probability that *Ha* is true (Table 1) (6). The contingency tables in the 2x2 model are often used in statistics for easy presentation of results and better understanding, so they were used in this article to facilitate the visualization of the reasoning. The similarity of the statistical hypothesis test with the diagnostic tests considering sensitivity, specificity, positive and negative predictive values can help in understanding the new definition of statistical significance (2). The new definition requires the evaluation of α and β at the same time (2).

Table 2 shows the interpretation of the statistical tests as diagnostic tests considering the two hypotheses of the statistical model and the veracity of the results. The introduction of the *Ha* hypothesis and the joint interpretation with *H0* allows for a better perception in the decision making of the results (Table 2).

Table 2 – Contingency table considering the results of the statistical tests, the hypotheses of the statistical model and the relationship with the results in the population.

Test results	**Result in the population**	
	True *Há*	**True *HO***
Statistical significance (P ≤ 0.05)	True positive (TP) or correct result	False positive (FP) or type I error
No statistical significance (P > 0.05)	False negative (FN) or type II error	True negative (TN) or correct result

Table 3 presents the same reasoning including alpha and beta. The population results represent the true results allowing the view of the statistical test as a diagnostic test (2).

Table 3 – Contingency table showing the results of the statistical tests and the alpha and beta presentations.

Test results	**Result in the population**	
	True *Ha*	True *HO*
Statistical significance (P ≤ 0.05)	1 – β (statistical power)	α
No statistical significance (P > 0.05)	β	1 - α

Statistical significance represents the positive result of the statistical test and can best be represented by the positive predictive value (PPV) formula (2). The VPP formula described below takes into account the first line of the contingency table (Table 3).

$$PPV = 1 - \beta \,/\, \alpha \text{ or } PPV = \text{statistical power} \,/\, \alpha$$

The PPV formula considers the results in light of the hypotheses *H0* and *Ha* and can be worked on and reorganized to determine the value of α. The formula for the value of α can be seen below.

$$\alpha = \text{statistical power} - (\text{PPV} \times \text{statistical power}) \,/\, \text{PPV}$$

The new alpha value

The research analyzed under the classical view of statistics considers that the result of statistical tests must be compared to the value of 0.05 to perceive statistical significance.

The value of 0.8 is classically used in clinical research as the statistical power so that in the research planning phase it is used to calculate the sample size (7). It is necessary to have a confidence of at least 95% for the positive result of the hypothesis test to present statistical significance. If we use the alpha value formula considering that the PPV assumes the confidence value and is 0.95, and that the statistical power is 0.8, then the new alpha reference value for the interpretation of significance will be 0.042 (2).

$$\alpha = 0{,}8 - (0{,}95 \times 0{,}8) / 0{,}95$$

$$\alpha = 0{,}042$$

Alpha adjustment for clinical trials

The sample size must be calculated considering the assumptions that the statistical power is 0.8 and the confidence level of 95%, but for statistical significance to occur, the P value calculated by the statistical tests must be less than or equal to 0.042 and not 0.05. The value of statistical power can be greater or less than the reference value suggested for calculating the sample size, so that the alpha value, which will serve as a reference for the statistical tests, must be adjusted to allow adequate interpretation of the results in the research scenario (Table 4).

Table 4 – Adjusted alpha value for statistical tests according to statistical power

Statistical power	α adjusted
0.95	0.050
0.90	0.047
0.85	0.045
0.80	**0.042**
0.75	0.039
0.70	0.037
0.65	0.034
0.60	0.032
0.55	0.028
0.50	0.026
0.45	0.023
0.40	0.021

The research can be completed without performing the sample size calculation and, in these cases, the statistical power must be calculated from the results found. From there, the alpha value adjusted to the statistical power must be calculated.

Conclusion

The new alpha value for the interpretation of statistical significance should be 0.042 considering the sample size calculation with a statistical power of 0.8 and a confidence level of 95%. The alpha value must be adjusted if there is variation in statistical power.

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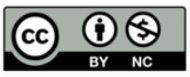	Este é um artigo publicado em acesso aberto (Open Access) sob a licença Creative Commons Attribution, que permite uso, distribuição e reprodução em qualquer meio, sem restrições desde que o trabalho original seja corretamente citado
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