Review

Statistics review 3: Hypothesis testing and *P* values

Elise Whitley[1] and Jonathan Ball[2]

[1]Lecturer in Medical Statistics, University of Bristol, Bristol, UK
[2]Lecturer in Intensive Care Medicine, St George's Hospital Medical School, London, UK

Correspondence: Editorial Office, *Critical Care*, editorial@ccforum.com

Published online: 18 March 2002 *Critical Care* 2002, **6**:222-225

Abstract

The present review introduces the general philosophy behind hypothesis (significance) testing and calculation of *P* values. Guidelines for the interpretation of *P* values are also provided in the context of a published example, along with some of the common pitfalls. Examples of specific statistical tests will be covered in future reviews.

Keywords hypothesis testing, null hypothesis, *P* value

The previous review in this series described how to use confidence intervals to draw inferences about a population from a representative sample. A common next step in data analysis is calculation of *P* values, also known as hypothesis testing. Hypothesis testing is generally used when some comparison is to be made. This comparison may be a single observed value versus some hypothesized quantity (e.g. the number of babies born in a single delivery to mothers undergoing fertility treatment as compared with typical singleton birth), or it may be a comparison of two or more groups (e.g. mortality rates in intensive care unit patients who require renal replacement therapy versus those who do not). The choice of which statistical test to use depends on the format of the data and the study design. Examples of some of the more common techniques will be covered in subsequent reviews. However, the philosophy behind these statistical tests and the interpretation of the resulting *P* values are always the same, and it is these ideas that are covered in the present review.

The null hypothesis

A typical research question is most easily expressed in terms of there being some difference between groups. For example, 'In patients with acute myocardial infarction (AMI), does the administration of intravenous nitrate (as compared with none) reduce mortality?' To answer this question, the most appropriate study design would be a randomized controlled trial comparing AMI patients who receive intravenous nitrate with control patients. The challenge then is to interpret the results of that study. Even if there is no real effect of intravenous nitrate on mortality, sampling variation means that it is extremely unlikely that exactly the same proportion of patients in each group will die. Thus, any observed difference between the two groups may be due to the treatment or it may simply be a coincidence, in other words due to chance. The aim of hypothesis testing is to establish which of these explanations is most likely. Note that statistical analyses can never prove the truth of a hypothesis, but rather merely provide evidence to support or refute it.

To do this, the research question is more formally expressed in terms of there being no difference. This is known as the null hypothesis. In the current example the null hypothesis would be expressed as, 'The administration of intravenous nitrate has no effect on mortality in AMI patients.'

In hypothesis testing any observed differences between two (or more) groups are interpreted within the context of this null hypothesis. More formally, hypothesis testing explores how likely it is that the observed difference would be seen by chance alone if the null hypothesis were true.

What is a *P* value?

There is a wide range of statistical tests available, depending on the nature of the investigation. However, the end result of any statistical test is a *P* value. The '*P*' stands for probability, and measures how likely it is that any observed difference between groups is due to chance. In other words, the *P* value is the probability of seeing the observed difference, or

AMI=acute myocardial infarction.

Table 1

Results from six trials of intravenous nitrates in acute myocardial infarction patients

	Number dead/randomized				
Trial	Intravenous nitrate	Control	Odds ratio	95% confidence interval	*P* value
Chiche	3/50	8/45	0.33	(0.09, 1.13)	0.08
Bussman	4/31	12/29	0.24	(0.08, 0.74)	0.01
Flaherty	11/56	11/48	0.83	(0.33, 2.12)	0.70
Jaffe	4/57	2/57	2.04	(0.39, 10.71)	0.40
Lis	5/64	10/76	0.56	(0.19, 1.65)	0.29
Jugdutt	24/154	44/156	0.48	(0.28, 0.82)	0.007

greater, just by chance if the null hypothesis is true. Being a probability, *P* can take any value between 0 and 1. Values close to 0 indicate that the observed difference is unlikely to be due to chance, whereas a *P* value close to 1 suggests there is no difference between groups other than that due to random variation. The interpretation of a *P* value is not always straightforward and several important factors must be taken into account, as outlined below. Put simply, however, the *P* value measures the strength of evidence against the null hypothesis.

Note that the aim of hypothesis testing is not to 'accept' or 'reject' the null hypothesis. Rather, it is simply to gauge how likely it is that the observed difference is genuine if the null hypothesis is true.

Interpreting *P* values

Continuing with the previous example, a number of trials of intravenous nitrates in patients with AMI have been carried out. In 1988 an overview of those that had been conducted at that time was performed in order to synthesize all the available evidence [1]. The results from six trials of intravenous nitrate are given in Table 1.

In the first trial (Chiche), 50 patients were randomly assigned to receive intravenous nitrate and 45 were randomly assigned to the control group. At the end of follow up, three of the 50 patients given intravenous nitrate had died versus eight in the control group. The calculation and interpretation of odds ratios will be covered in a future review. However, the interpretation in this context is that the odds ratio approximately represents the risk of dying in the nitrate group as compared with that in the control group. The odds ratio can take any positive value (above 0); in this context, values less than 1 indicate a protective effect of intravenous nitrate (a reduction in risk of death in patients administered intravenous nitrate), whereas an odds ratio greater than 1 points to a harmful effect (i.e. an increase in risk of death in patients administered intravenous nitrate). An odds ratio close to 1 is consistent with no effect of intravenous nitrate (i.e. no difference between the two groups). Interpretation of the confidence intervals is just as described in Statistics review 2, with the first confidence interval (Chiche) indicating that the true odds ratio in the population from which the trial subjects were drawn is likely to be between 0.09 and 1.13.

Initially ignoring the confidence intervals, five of the six trials summarized in Table 1 have odds ratios that are consistent with a protective effect of intravenous nitrate (odds ratio <1). These range from a risk reduction of 17% (Flaherty) to one of 76% (Bussman). In other words, in the Bussman trial the risk of dying in the nitrate group is about one-quarter of that in the control group. The remaining trial (Jaffe) has an odds ratio of 2.04, suggesting that the effect of intravenous nitrate might be harmful, with a doubling of risk in patients given this treatment as compared with those in the control group.

The *P* values shown in the final column of Table 1 give an indication of how likely it is that these differences are simply due to chance. The *P* value for the first trial (Chiche) indicates that the probability of observing an odds ratio of 0.33 or more extreme, if the null hypothesis is true, is 0.08. In other words, if there is genuinely no effect of intravenous nitrate on the mortality of patients with AMI, then 8 out of 100 such trials would show a risk reduction of 66% or more just by chance. Equivalently, 2 out of 25 would show such a chance effect. The question of whether this is sufficiently unlikely to suggest that there is a real effect is highly subjective. However, it is unlikely that the management of critically ill patients would be altered on the basis of this evidence alone, and an isolated result such as this would probably be interpreted as being consistent with no effect. Similarly the *P* value for the Bussman trial indicates that 1 in 100 trials would have an odds ratio of 0.24 or more extreme by chance alone; this is a smaller probability than in the previous trial but, in isolation, perhaps still not sufficiently unlikely to alter clinical care in practice. The *P* value of 0.70 in the Flaherty trial suggests that the observed odds ratio of 0.83 is very likely to be a chance finding.

Comparing the *P* values across different trials there are two main features of interest. The first is that the size of the *P* value

is related, to some extent, to the size of the trial (and, in this context, the proportion of deaths). For example, the odds ratios in the Lis and Jugdutt trials are reasonably similar, both of which are consistent with an approximate halving of risk in patients given intravenous nitrate, but the *P* value for the larger Jugdutt trial is substantially smaller than that for the Lis trial. This pattern tends to be apparent in general, with larger studies giving rise to smaller *P* values. The second feature relates to how the *P* values change with the size of the observed effect. The Chiche and Flaherty trials have broadly similar numbers of patients (in fact, the numbers are somewhat higher in the Flaherty trial) but the smaller *P* value occurs in the Chiche study, which suggests that the effect of intravenous nitrate is much larger than that in the Flaherty study (67% versus 17% reduction in mortality). Again, this pattern will tend to hold in general, with more extreme effects corresponding to smaller *P* values. Both of these properties are discussed in considerably more detail in the next review, on sample size/power calculations.

There are two additional points to note when interpreting *P* values. It was common in the past for researchers to classify results as statistically 'significant' or 'non-significant', based on whether the *P* value was smaller than some prespecified cut point, commonly 0.05. This practice is now becoming increasingly obsolete, and the use of exact *P* values is much preferred. This is partly for practical reasons, because the increasing use of statistical software renders calculation of exact *P* values increasingly simple as compared with the past when tabulated values were used. However, there is also a more pragmatic reason for this shift. The use of a cut-off for statistical significance based on a purely arbitrary value such as 0.05 tends to lead to a misleading conclusion of accepting or rejecting the null hypothesis, in other words of concluding that a 'statistically significant' result is real in some sense. Recall that a *P* value of 0.05 means that one out of 20 studies would result in a difference at least as big as that observed just by chance. Thus, a researcher who accepts a 'significant' result as real will be wrong 5% of the time (this is sometimes known as a type I error). Similarly, dismissing an apparently 'non-significant' finding as a null result may also be incorrect (sometimes known as a type II error), particularly in a small study, in which the lack of statistical significance may simply be due to the small sample size rather than to any real lack of clinical effect (see the next review for details). Both of these scenarios have serious implications in terms of practical identification of risk factors and treatment of disease. The presentation of exact *P* values allows the researcher to make an educated judgement as to whether the observed effect is likely to be due to chance and this, taken in the context of other available evidence, will result in a far more informed conclusion being reached.

Finally, *P* values give no indication as to the clinical importance of an observed effect. For example, suppose a new drug for lowering blood pressure is tested against standard treatment, and the resulting *P* value is extremely small. This indicates that the difference is unlikely to be due to chance, but decisions on whether to prescribe the new drug will depend on many other factors, including the cost of the new treatment, any potential contraindications or side effects, and so on. In particular, just as a small study may fail to detect a genuine effect, a very large study may result in a very small *P* value based on a small difference of effect that is unlikely to be important when translated into clinical practice.

P values and confidence intervals

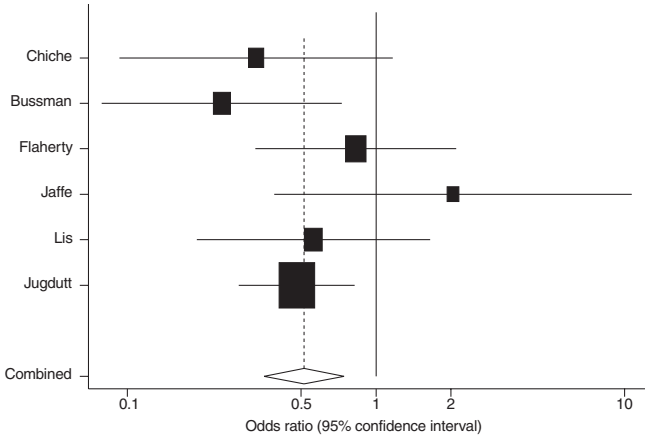
Although *P* values provide a measure of the strength of an association, there is a great deal of additional information to be obtained from confidence intervals. Recall that a confidence interval gives a range of values within which it is likely that the true population value lies. Consider the confidence intervals shown in Table 1. The odds ratio for the Chiche study is 0.33, suggesting that the effect of intravenous nitrate is to reduce mortality by two thirds. However, the confidence interval indicates that the true effect is likely to be somewhere between a reduction of 91% and an increase of 13%. The results from that study show that there may be a substantial reduction in mortality due to intravenous nitrate, but equally it is not possible to rule out an important increase in mortality. Clearly, if the latter were the case then it would be extremely dangerous to administer intravenous nitrate to patients with AMI.

The confidence interval for the Bussman study (0.08, 0.74) provides a rather more positive picture. It indicates that, although the reduction in mortality may be as little as 26%, there is little evidence to suggest that the effect of intravenous nitrate may be harmful. Administration of intravenous nitrate therefore appears more reasonable based on the results of that study, although the *P* value indicates a 1 in 100 probability that this may be a chance finding and so the result in isolation might not be sufficient evidence to change clinical practice.

The overview of those trials was carried out because the results did not appear to be consistent, largely because the individual trials were generally too small to provide reliable estimates of effect. A pooled analysis of the data from all of the nitrate trials shown in Table 1 (and including one other trial with no deaths) was therefore conducted to obtain a more robust estimate of effect (for details of the methods used, see Yusuf *et al*. [1]). The odds ratios and 95% confidence intervals for the individual trials in Table 1 are shown in Fig. 1. The odds ratio for each trial is represented by a box, the size of which is proportional to the amount of statistical information available for that estimate, and the 95% confidence interval is indicated by a horizontal line. The solid vertical line indicates an odds ratio of 1.0; in other words it shows the line of 'no effect'. The combined odds ratio from all six trials is indicated by the dashed vertical line, and its associated 95% confidence interval by the diamond at the bottom.

This pooled analysis resulted in an estimated overall odds ratio of 0.53 with a 95% confidence interval of (0.36, 0.75),

Figure 1



Individual and combined odds ratios and 95% confidence intervals for six intravenous nitrate trials.

suggesting a true reduction in mortality of somewhere between one-quarter and two-thirds. Examination of the confidence intervals from individual studies shows a high degree of overlap with the pooled confidence interval, and so all of the evidence appears to be consistent with this pooled estimate; this includes the evidence from the Jaffe study, which, at first glance, appears to suggest a harmful effect. The *P* value for the pooled analysis was 0.0002, which indicates that the result is extremely unlikely to have been due to chance.

Note that, since that meta-analysis was reported, treatment of AMI patients has changed dramatically with the introduction of thrombolysis. In addition, the Fourth International Study of Infarct Survival (ISIS-4) [2], which randomized over 58,000 patients with suspected AMI, found no evidence to suggest that mortality was reduced in those given oral nitrates. Thus, in practice the indications for intravenous nitrates in patients with AMI are restricted to symptom and blood pressure control.

Specific methods for comparing two or more means or proportions will be introduced in subsequent reviews. In general, these will tend to focus on the calculation of *P* values. However, there is still much to be learned from examination of confidence intervals in this context. For example, when comparing the risk for developing secondary infection following trauma in patients with or without a history of chronic alcohol abuse, it may be enlightening to compare the confidence intervals for the two groups and to examine the extent to which they do or do not overlap. Alternatively, it is possible to calculate a confidence interval for the difference in two means or the difference or ratio of proportions directly. This can also give a useful indication of the likely effect of chronic alcohol abuse, in particular by exploring the extent to which the range of likely values includes or excludes 0 or 1, the respective expected values of a difference or ratio if there is no effect of chronic alcohol abuse, or in other words under the null hypothesis.

Although *P* values provide a measure of the strength of an association, an estimate of the size of any effect along with an associated confidence interval is always required for meaningful interpretation of results. *P* values and confidence intervals are frequently calculated using similar quantities (see subsequent reviews for details), and so it is not surprising that the two are closely related. In particular, larger studies will in general result in narrower confidence intervals and smaller *P* values, and this should be taken into account when interpreting the results from statistical analyses. Both *P* values and confidence intervals have an important role to play in understanding data analyses, and both should be presented wherever possible.

Key messages

A *P* value is the probability that an observed effect is simply due to chance; it therefore provides a measure of the strength of an association. A *P* value does not provide any measure of the size of an effect, and cannot be used in isolation to inform clinical judgement.

P values are affected both by the magnitude of the effect and by the size of the study from which they are derived, and should therefore be interpreted with caution. In particular, a large *P* value does not always indicate that there is no association and, similarly, a small *P* value does not necessarily signify an important clinical effect.

Subdividing *P* values into 'significant' and 'non-significant' is poor statistical practice and should be avoided. Exact *P* values should always be presented, along with estimates of effect and associated confidence intervals.

Competing interests

None declared.

References

1. Yusuf S, Collins R, MacMahon S, Peto R: **Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials.** *Lancet* 1988, **1**:1088-1092.
2. Anonymous: **ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction.** *Lancet* 1995, **345**:669-685.
3. Whitley E, Ball J: **Statistics review 1: Presenting and summarising data.** *Crit Care* 202, **6**:66-71.
4. Whitley E, Ball J: **Statistics review 2: Samples and populations.** *Crit Care* 202, **6**:143-148.

This article is the third in an ongoing, educational review series on medical statistics in critical care. Previous articles have covered 'presenting and summarising data' [3] and 'samples and populations' [4]. Future topics to be covered include power calculations, comparison of means, comparison of proportions, and analysis of survival data to name but a few. If there is a medical statistics topic you would like explained, contact us on editorial@ccforum.com.