

Guidelines for Reporting of Statistics for Clinical Research in Urology



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IN an effort to improve the quality of statistics in the clinical urology literature statisticians at *European Urology*, *The Journal of Urology*®, *Urology* and *BJUI* developed a set of guidelines to address common errors of statistical analysis, reporting and interpretation. Authors should break any of the guidelines if it makes scientific sense to do so but would need to provide clear justification. Adoption of the guidelines will in our view not only increase the quality of published articles in our journals, but improve statistical knowledge in our field in general.

It is widely acknowledged that the quality of statistics in the clinical research literature is poor. This is true for urology just as it is for other medical specialties. In 2005 Scales et al. published a systematic evaluation of the statistics in papers appearing in a single month in *European Urology*, *The Journal of Urology*®, *Urology* and *BJUI*.¹ They reported widespread errors, including 71% of papers with comparative statistics having at least 1 statistical flaw. These findings mirror many others in the literature, as indicated in the review by Lang and Altman.² The quality of statistical reporting in urology journals has no

doubt improved since 2005 but remains unsatisfactory.

The editors of the 4 urology journals in the review by Scales et al have come together to publish a shared set of statistical guidelines.³ Statistical reviewers at the 4 journals will systematically assess submitted manuscripts using the guidelines to improve statistical analysis, reporting and interpretation by the authors. Adoption of the guidelines will, in our view, not only increase the quality of published papers in our journals but improve statistical knowledge in our field in general. For example, asking an author to follow a guideline about the fallacy of accepting the null hypothesis would no doubt result in a better paper, but we hope it will also enhance the author's understanding of hypothesis tests.

The guidelines are didactic based on the consensus of the statistical consultants to the journals. We avoided making specific analytic recommendations when possible, and focused instead on analyses or methods of reporting statistics that should be avoided. We intend to update the guidelines over time and hence encourage readers who question the value or rationale of a guideline to write to us.

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See Editorial on page 457.

1. The Golden Rule: Break any of the Guidelines if it Makes Scientific Sense to Do So

Science varies too much to allow methodologic or reporting guidelines to apply universally.

2. Reporting of Design and Statistical Analysis

2.1. Follow existing reporting guidelines for the type of study you are reporting, such as CONSORT for randomized trials, ReMARK for marker studies, TRIPOD for prediction models, STROBE for observational studies or AMSTAR for systematic reviews.

Statisticians and methodologists have contributed extensively to a large number of reporting guidelines. The first is widely recognized to be the CONSORT (Consolidated Standards of Reporting Trials) statement on reporting of randomized trials but there are now many other guidelines covering a wide range of different types of study. Reporting guidelines can be downloaded from the Equator Web site (<http://www.equator-network.org>).

2.2. Describe cohort selection fully.

It is insufficient to state, for instance, “the study cohort consisted of 1,144 patients treated for benign prostatic hyperplasia at our institution.” The cohort needs to be defined in terms of dates (for example, “presenting March 2013 to December 2017”), inclusion criteria (“International Prostate Symptom Score greater than 12”) and whether patients were selected to be included (for a research study) vs being a consecutive series. Exclusions should be described one by one, with the number of patients omitted for each exclusion criterion to give the final cohort size (for example, “patients with prior surgery [n=43], allergies to 5-ARIs [n=12] and missing data on baseline prostate volume [n=86] were excluded to give a final cohort for analysis of 1,003 patients”). Note that inclusion criteria can be omitted if obvious from context (for example, no need to state “undergoing radical prostatectomy for histologically proven prostate cancer”). However, dates may need to be explained if their rationale could be questioned (for example, “March 2013 when our specialist voiding clinic was established to December 2017”).

2.3. Describe the practical steps of randomization in randomized trials.

Although this reporting guideline is part of the CONSORT statement, it is so critical and so widely misunderstood that it bears repeating. The purpose of randomization is to prevent selection bias, which can be achieved only if those consenting patients cannot guess treatment allocation of a patient before registration in the trial or change it afterward. This safeguard is known as allocation concealment. Stating merely that “a randomization list was created by a statistician” or that “envelope randomization was

used” does not ensure allocation concealment as a list could have been posted at the nurse’s station for all to see, and envelopes can be opened and resealed. Investigators need to specify the exact logistic steps taken to ensure allocation concealment. The best method is to use a password protected computer database.

2.4. Statistical methods should describe the study questions and statistical approaches used to address each question.

Many statistical methods sections state only something like “Mann-Whitney was used for comparisons of continuous variables and Fisher’s exact for comparisons of binary variables.” These statements say little more than “the inference tests used were not grossly erroneous for the type of data.” Instead, statistical methods sections should lay out each primary study question separately by carefully detailing the analysis associated with each question and describing the rationale for the analytic approach when this is not obvious or if there are reasonable alternatives. Special attention and description should be provided for rarely used statistical techniques.

2.5. Statistical methods should be described in sufficient detail to allow replication by an independent statistician given the same data set.

Vague reference to “adjusting for confounders” or “non-linear approaches” is insufficiently specific to allow replication, a cornerstone of the scientific method. All statistical analyses should be specified in the Methods section, including details such as the covariates in a multivariable model. All variables should be clearly defined when there is room for ambiguity. For instance, avoid saying that “Gleason grade was included in the model” and state instead “Gleason grade group was included in four categories 1, 2, 3 and 4 or 5.”

3. Inference and P-Values

3.1. Don’t accept the null hypothesis.

In a court case defendants are declared guilty or not guilty, and there is no verdict of “innocent.” Similarly, in a statistical test the null hypothesis is rejected or not rejected. If the p-value is 0.05 or greater, investigators should avoid conclusions such as “the drug was ineffective,” “there was no difference between groups” or “response rates were unaffected.” Instead, authors should use phrases such as “we did not see evidence of a drug effect,” “we were unable to demonstrate a difference between groups” or simply “there was no statistically significant difference in response rates.”

3.2. P-values just above 5% are not a trend, and are not moving.

Avoid saying that a p-value such as 0.07 shows a “trend” (which is meaningless) or “approaches

statistical significance” (because the p-value isn’t moving). Alternative language might be, “although we saw some evidence of improved response rates in patients receiving the novel procedure, differences between groups did not meet conventional levels of statistical significance.”

3.3. P-values and 95% confidence intervals do not quantify the probability of a hypothesis.

A p-value of 0.03 does not mean there is a 3% probability that the findings are due to chance. Additionally, a 95% confidence interval should not be interpreted as a 95% certainty the true parameter value is in the range of the 95% confidence interval. The correct interpretation of a p-value is the probability of finding the observed or more extreme results when the null hypothesis is true, and the 95% confidence interval will contain the true parameter value 95% of the time were a study to be repeated many times using different samples.

3.4. Do not use confidence intervals to test hypotheses.

Investigators often interpret confidence intervals in terms of hypotheses. For instance, investigators might claim that there is a statistically significant difference between groups because the 95% confidence interval for the odds ratio excludes 1. Such claims are problematic because confidence intervals are concerned with estimation, not inference. Moreover, the mathematical method to calculate confidence intervals may be different from those used to calculate p-values. It is perfectly possible to have a 95% confidence interval that includes no difference between groups although the p-value is less than 0.05 or vice versa. For instance, in a study of 100 patients in 2 equal groups with event rates of 70% and 50%, respectively, the p-value from Fisher’s exact test is 0.066 but the 95% confidence interval for the odds ratio is 1.03 to 5.26. The 95% confidence interval for the risk difference and risk ratio also exclude no difference between groups.

3.5. Take care interpreting results when reporting multiple p-values.

The more questions you ask, the more likely you are to get a spurious answer to at least one of them. For example, if you report p-values for 5 independent true null hypotheses, the probability that you will falsely reject at least one is not 5% but greater than 20%. Although formal adjustment of p-values is appropriate in some specific cases, such as genomic studies, a more common approach is simply to interpret p-values in the context of multiple testing. For instance, if an investigator examines the association of 10 variables with 3 different end points, thereby testing 30 separate hypotheses, a p-value of 0.04 should not be interpreted the same

way as if the study tested only a single hypothesis with a p-value of 0.04.

3.6. Do not report separate p-values for each of 2 different groups in order to address the question of whether there is a difference between groups.

One scientific question means 1 statistical hypothesis tested by 1 p-value. To illustrate the error of using 2 p-values to address 1 question, take the case of a randomized trial of drug versus placebo to reduce voiding symptoms with 30 patients in each group. The authors might report that symptom scores improved by 6 (standard deviation 14) points in the drug group ($p=0.03$ by 1-sample t-test) and 5 (standard deviation 15) points in the placebo group ($p=0.08$). However, the study hypothesis concerns the difference between drug and placebo. To test a single hypothesis, a single p-value is needed. A 2-sample t-test for these data gives a p-value of 0.8, which is unsurprising given the scores in each group were virtually the same, confirming that it would be unsound to conclude that the drug was effective based on the finding that change was significant in the drug group but not in placebo controls.

3.7. Use interaction terms in place of subgroup analyses.

A similar error to the use of separate tests for a single hypothesis is when an intervention is shown to have a statistically significant effect in 1 group of patients but not another. The approach that is more appropriate is to use what is known as an interaction term in a statistical model. For instance, to determine whether a drug reduced pain scores more in women than in men, the model might be as follows:

$$\{\text{Final Pain Score}\} = \beta_0 + \beta_1\{\text{Baseline Pain Score}\} + \beta_2\{\text{Drug}\} + \beta_3\{\text{Sex}\} + \beta_4\{\text{Drug}\} \times \{\text{Sex}\}$$

It is sometimes appropriate to report estimates and confidence intervals within subgroups of interest but p-values should be avoided.

3.8. Tests for change over time are generally uninteresting.

A common analysis is to conduct a paired t-test comparing, for example, erectile function in older men at baseline with erectile function after 5 years of followup. The null hypothesis is that “erectile function does not change over time,” which is known to be false. Investigators are encouraged to focus on estimation rather than inference, reporting, for example, the mean change over time along with a 95% confidence interval.

3.9. Avoid using statistical tests to determine the type of analysis to be conducted.

Numerous statistical tests are available that can be used to determine how a hypothesis test should be

conducted. For instance, investigators might conduct a Shapiro-Wilk test for normality to determine whether to use a t-test or Mann-Whitney, Cochran's Q to decide whether to use a fixed or random effects approach in a meta-analysis, or use a t-test for between group differences in a covariate to determine whether that covariate should be included in a multivariable model. The problem with these sorts of approaches is that they are often testing a null hypothesis that is known to be false. For instance, no data set perfectly follows a normal distribution. Moreover, it is often questionable that changing the statistical approach in light of the test is actually of benefit. Statisticians are far from unanimous as to whether Mann-Whitney is always superior to t-test when data are non-normal or that fixed effects are invalid under study heterogeneity or that the criterion of adjusting for a variable should be whether it is significantly different between groups. Investigators should generally follow a pre-specified analytic plan, only altering the analysis if the data unambiguously point to a better alternative.

3.10. When reporting p-values be clear about the hypothesis tested and ensure that the hypothesis is sensible.

P-values test specific hypotheses. When reporting a p-value in the Results section, state the hypothesis being tested unless this is completely clear. For example, in the statement "Pain scores were higher in group 1 and similar in groups 2 and 3 ($p=0.02$)" it is ambiguous whether the p-value of 0.02 is testing group 1 vs groups 2 and 3 combined or the hypothesis that pain score is the same in all 3 groups. Clarity about the hypotheses being tested can help avoid the testing of inappropriate hypotheses. For instance, p-values for differences between groups at baseline in a randomized trial are testing a null hypothesis that is known to be true (informally, that any observed differences between groups are due to chance).

4. Reporting of Study Estimates

4.1. Use appropriate levels of precision.

Reporting a p-value of 0.7345 suggests that there is an appreciable difference between p-values of 0.7344 and 0.7346. Reporting that 16.9% of 83 patients responded entails a precision (to the nearest 0.1%) that is nearly 200 times greater than the width of the confidence interval (10% to 27%). Reporting in a clinical study that the mean calorie consumption was 2,069.9 suggests that calorie consumption can be measured extremely precisely by a food questionnaire. Some might argue that being overly precise is irrelevant because the extra numbers can always be ignored. The counter argument is that investigators should think hard about every number

they report rather than just cutting and pasting numbers from the statistical software printout. The specific guidelines for precision are listed below.

- Report p-values to a single significant figure unless the p is close to 0.05 (for example, 0.01 to 0.2), in which case, report 2 significant figures. Do not report "NS" for p-values of 0.05 or above. Low p-values can be reported as $p < 0.001$ or similar. A p-value can be 1, although some investigators prefer to report this as > 0.9 . For instance, $p < 0.001$, 0.004, 0.045, 0.13, 0.3 and 1 are reported to appropriate precision.
- Report percentages, rates and probabilities to 2 significant figures, for example 75%, 3.4% and 0.13%.
- Do not report p-values of zero as any experimental result has a non-zero probability.
- Do not give decimal places if a probability or proportion is 1 (for example, a p-value of 1.00 or a percentage of 100.00%). The decimal places suggest it is possible to have a p-value of 1.05 for instance. There is a similar consideration for data that can only take integer values. It makes sense to state that the mean number of pregnancies was 2.4 but not that 29% of women reported 1.0 pregnancies.
- There is generally no need to report estimates to more than 3 significant figures.
- Hazard and odds ratios are normally reported to 2 decimal places, although this can be avoided for high odds ratios (for example, 18.2 rather than 18.17).

4.2. Avoid redundant statistics in cohort descriptions.

Authors should be selective about the descriptive statistics reported and ensure that each number provides unique information. They should avoid reporting descriptive statistics that can be readily derived from data that have already been provided. For instance, there is no need to state 40% of a cohort were men and 60% were women when you can choose one or the other. Another common error is to include a column of descriptive statistics for 2 groups separately and then the whole cohort combined. For example, if the median age is 60 in group 1 and 62 in group 2, we do not need to be told that the median age in the cohort as a whole is close to 61.

4.3. For descriptive statistics, median and quartiles are preferred over means and standard deviations (or standard errors), and range should be avoided.

The median and quartiles provide all sorts of useful information, such as 50% of patients had values above the median or between the quartiles. The range gives the values of just 2 patients and so is generally uninformative of the data distribution.

4.4. Report estimates for the main study questions.

A clinical study typically focuses on a limited number of scientific questions and generally, authors should provide an estimate for each of the questions. In a study comparing 2 groups authors should give an estimate of the difference between groups and avoid giving only data on each group separately or simply saying that the difference was or was not significant. In a study of a prognostic factor authors should give an estimate of the strength of the prognostic factor, such as an odds ratio or hazard ratio, as well as reporting a p-value testing the null hypothesis of no association between the prognostic factor and outcome.

4.5. Report confidence intervals for the main estimates of interest.

Authors should generally report a 95% confidence interval around the estimates relating to the key research questions but not other estimates given in an article. For example, in a study comparing 2 surgical techniques the authors might report adverse event rates of 10% and 15%. However, the key estimate in this case is the difference between groups, and so this estimate of 5% should be reported along with a 95% confidence interval (for example, 1% to 9%). Confidence intervals should not be reported for the estimates within each group (adverse event rate in group A of 10%, 95% CI 7% to 13%). Similarly, confidence intervals should not be given for statistics such as mean age or gender ratio.

4.6. Do not treat categorical variables as continuous.

A variable such as Gleason grade groups is scored 1 to 5 but it is not true that the difference between groups 3 and 4 is half as great as the difference between groups 2 and 4. Variables such as Gleason grade group should be reported as categories (for example, 40% grade group 1, 20% grade group 2, 20% grade group 3, and 20% grade groups 4 and 5) rather than as a continuous variable (mean Gleason score of 2.4). Similarly, categorical variables such as Gleason should be entered into regression models not as a single variable (a hazard ratio of 1.5 per 1-point increase in Gleason grade group) but as multiple categories (hazard ratio of 1.6 comparing Gleason grade group 2 to group 1 and hazard ratio of 3.9 comparing Gleason grade group 3 to group 1).

4.7. Avoid categorization of continuous variables unless there is a convincing rationale.

A common approach to a variable such as age is to define patients as either old (60 years old or older) or young (younger than 60 years) and then enter age into analyses as a categorical variable reporting, for example, that “patients aged 60 and over had twice the risk of an operative complication than patients aged less than 60.” In epidemiological and marker

studies a common approach is to divide a variable into quartiles and report a statistic such as a hazard ratio for each quartile compared to the lowest (“reference”) quartile. This is problematic because it assumes that all values of a variable within a category are the same. For instance, it is likely not the case that a patient 65 years old has the same risk as a patient 90 years old but a different risk to a patient 64 years old. It is generally preferable to leave variables in a continuous form reporting, for instance, how risk changes with a 10-year increase in age. Non-linear terms can also be used to avoid the assumption that the association between age and risk follows a straight line.

4.8. Do not use statistical methods to obtain cut points for clinical practice.

Various statistical methods are available to dichotomize a continuous variable. For instance, outcomes can be compared on either side of several different cut points, and the optimal cut point chosen as the one associated with the smallest p-value. Alternatively, investigators might choose a cut point that leads to the highest value of sensitivity + specificity, that is the point closest to the top left corner of a receiver operating curve (ROC). Such methods are inappropriate for determining clinical cut points because they do not consider clinical consequences. For instance, the ROC curve approach assumes that sensitivity and specificity are of equal value, whereas it is generally worse to miss disease than to treat unnecessarily. The smallest p-value approach tests strength of evidence against the null hypothesis, which has little to do with the relative benefits and harms of a treatment or further diagnostic evaluation.

4.9. Association between a continuous predictor and outcome can be demonstrated graphically, particularly by using non-linear modeling.

In high school math we often thought about the relationship between y and x by plotting a line on a graph with a scatterplot added in some cases. This relationship also holds true for many scientific studies. For example, for a study on age and complication rates an investigator could plot age on the x axis against risk of a complication on the y axis and show a regression line, perhaps with a 95% confidence interval. Non-linear modeling is often useful because it avoids assuming a linear relationship and allows the investigator to consider questions such as whether risk starts to increase disproportionately beyond a given age.

4.10. Do not ignore significant heterogeneity in meta-analyses.

Informally speaking, heterogeneity statistics test as to whether variations between the results of different studies in a meta-analysis are consistent

with chance or with true differences between studies. If heterogeneity is present, authors need to do more than merely report the p-value and focus on the random effects estimate. Authors should investigate the sources of heterogeneity and try to determine the factors that lead to differences in study results, for example, by identifying common features of studies with similar findings or idiosyncratic aspects of studies with outlying results.

4.11. For time to event variables, report the number but not the proportion of events.

Consider a study that reports “of 60 patients accrued 10 (17%) died.” While it is important to report the number of events, patients entered the study at different times and were followed for different periods, and so the reported proportion of 17% is meaningless. The standard statistical approach to time to event variables is to calculate probabilities, such as the risk of death being 60% by 5 years or the median survival (the time at which the probability of survival first decreases below 50%) being 52 months.

4.12. For time to event analyses, report median followup for patients without the event or the number followed without an event at a given followup time.

It is often useful to describe how long a cohort has been followed. To illustrate the appropriate methods of doing so, consider a cohort of 1,000 pediatric patients with cancer treated in 1970 and followed to 2010. If the cure rate was only 40%, median followup for all patients might only be a few years, while the median followup for patients who survived was 40 years. This latter statistic gives a much better impression of how long the cohort had been followed. Now assume that in 2009 a second cohort of 2,000 patients was added to the study. The median followup for survivors will now be around a year, which is again misleading. An alternative would be to report a statistic such as “312 patients have been followed without an event for at least 35 years.”

4.13. For time to event analyses, describe when followup starts, and when and how patients are censored.

A common error is that investigators use a censoring date that leads to an overestimate of survival. For example, when assessing the metastasis-free survival a patient without a record of metastasis should be censored on the date of the last time he/she was known to be free of metastasis (negative bone scan, undetectable prostate specific antigen [PSA]) and not on the date of last patient contact (which may not have involved assessment of metastasis). For overall survival, date of last patient contact would be an acceptable censoring date because he/she was indeed known to be event-free at that time.

When assessing cause specific end points, special consideration should be given to the cause of death. The end points “disease specific survival” and “disease-free survival” have specific definitions and require careful attention to methods. With disease specific survival, authors need to consider carefully how to handle death due to other causes. One approach is to censor patients at the time of death but this can lead to bias in certain circumstances, such as when the predictor of interest is associated with other cause death and the probability of other cause death is moderate or high. Competing risk analysis is appropriate in these situations. For disease-free survival, evidence of disease (disease recurrence) and death from any cause are counted as events, and so censoring at the time of other cause death is inappropriate. If investigators are specifically interested only in the former and wish to censor deaths from other causes, they should define their end point as “freedom from progression.”

4.14. For time to event analyses, avoid reporting mean followup or survival time, or estimates of survival for those who had the event.

All 3 estimates are problematic in the context of censored data.

4.15. For time to event analyses, make sure that all predictors are known at time zero or consider alternative approaches such as a landmark analysis or time dependent covariates.

In many cases variables of interest vary over time. As a simple example, suppose we were interested in whether PSA velocity predicted time to progression in patients with prostate cancer on active surveillance. The problem is that PSA is measured at various times after diagnosis. Unless they are being careful, investigators might use time from diagnosis in a Kaplan-Meier or Cox regression but use PSA velocity calculated on PSA levels measured at 1 and 2-year followup. As another example, investigators might wish to determine whether response to chemotherapy predicts cancer survival but measure survival from the time of the first dose before response is known. It is obviously invalid to use information only known “after the clock starts.”

There are 2 main approaches to this problem. A “landmark analysis” is often used when the variable of interest is generally known within a short and well-defined period of time, such as adjuvant therapy or chemotherapy response. In brief, the investigators start the clock at a fixed “landmark” (for example, 6 months after surgery). Patients are only eligible if they are still at risk at the landmark (cases of recurrence before 6 months are excluded) and the status of the variable is fixed at that time (a patient who gets chemotherapy at 7 months is defined as being in the no adjuvant group). Alternatively,

investigators can use a time dependent variable approach. In brief, this approach “resets the clock” each time new information is available about a variable. The time dependent variable approach would be the most typically used for the PSA velocity and progression example.

4.16. When presenting Kaplan-Meier figures, present the number at risk and truncate followup when numbers are low.

Giving the number at risk is useful for helping to understand when patients were censored. When presenting Kaplan-Meier figures a good rule of thumb is to truncate followup when the number at risk in any group falls below 5 (or even 10) as the tail of a Kaplan-Meier distribution is unstable.

5. Multivariable Models and Diagnostic Tests

5.1. Multivariable, propensity and instrumental variable analyses are not magic wands.

Some investigators assume that multivariable adjustment “removes confounding,” “makes groups similar” or “mimics a randomized trial.” There are 2 problems with such claims. First, the value of a variable recorded in a data set is often approximate, and so may mask differences between groups. For instance, clinical stage might be used as a covariate in a study comparing treatments for localized prostate cancer. However, stage T2c might constitute a small nodule on each prostate lobe or, alternatively, most of the prostate consisting of a large hard mass. The key point is that if one group has more T2c disease than the other, it is also likely that the T2c tumors in that group will fall towards the more aggressive end of the spectrum. Multivariable adjustment has the effect of making the rates of T2c in each group the same but does not ensure that the type of T2c is identical.

Second, a model only adjusts for a small number of measured covariates, which does not exclude the possibility of important differences in unmeasured (or even unmeasurable) covariates. A common assumption is that propensity methods somehow provide better adjustment for confounding than traditional multivariable methods. Except in certain rare circumstances, such as when the number of covariates is large relative to the number of events, propensity methods give extremely similar results to multivariable regression. Similarly, instrumental variables analyses depend on the availability of a good instrument, which is less common than is often assumed. Often, the instrument is not strongly associated with the intervention, leading to a large increase in the 95% confidence interval or an underestimate of treatment effects.

5.2. Avoid stepwise selection.

Investigators commonly choose which variables to include in a multivariable model by first determining

which are statistically significant on univariable analysis. Alternatively, they may include all variables in a single model but then remove any that are not significant. This type of data dependent variable selection in regression models has several undesirable properties, increasing the risk of overfit and making many statistics, such as the 95% confidence interval, highly questionable. Use of stepwise selection should be restricted to a limited number of circumstances, such as during the initial stages of developing a model, if there is poor knowledge of what variables might be predictive.

5.3. Avoid reporting estimates such as odds or hazard ratios for covariates when examining the effects of interventions.

In a typical observational study an investigator might explore the effects of 2 different approaches to radical prostatectomy on recurrence while adjusting for covariates such as stage, grade and PSA. It is rarely worth reporting estimates such as odds or hazard ratios for the covariates. For instance, it is well known that a high Gleason score is strongly associated with recurrence. Reporting a hazard ratio of say 4.23 is not helpful and a distraction from the key finding, which is the hazard ratio between the 2 types of surgery.

5.4. Rescale predictors to obtain interpretable estimates.

Predictors sometimes have a moderate association with outcome and can take a large range of values which can lead to uninterpretable estimates. For instance, the odds ratio for cancer per year of age might be given as 1.02 (95% CI 1.01, 1.02; $p < 0.0001$). It is not helpful to have the upper bound of a confidence interval be equivalent to the central estimate, and a better alternative would be to report an odds ratio per 10 years of age. This odds ratio is simply achieved by creating a new variable equal to age divided by 10 to obtain an odds ratio of 1.16 (95% CI 1.10, 1.22; $p < 0.0001$) per 10-year difference in age.

5.5. Avoid reporting univariate and multivariable analyses unless there is a good reason.

Comparison of univariate and multivariable models can be of interest when trying to understand mechanisms. For example, if race is a predictor of outcome on univariate analysis but not after adjustment for income and access to care, one might conclude that poor outcome in African Americans is explained by socioeconomic factors. However, the routine reporting of estimates from univariate and multivariable analysis is discouraged.

5.6. Avoid ranking predictors in terms of strength.

It is tempting for authors to rank predictors in a model claiming for instance, “the novel marker was the strongest predictor of recurrence.” Most

commonly, this type of claim is based on comparisons of odds or hazard ratios. Such rankings are not meaningful since, among other reasons, it depends on how variables are coded. For example, the odds ratio for hK2 and, hence, whether it is an apparently “stronger” predictor than PSA will depend on whether it is entered in nanograms or picograms per ml. Furthermore, it is unclear how one should compare model coefficients when both categorical and continuous variables are included. Finally, the prevalence of a categorical predictor also matters. A predictor with an odds ratio is 3.5 but a prevalence of 0.1% is less important than a predictor with a 50% prevalence and an odds ratio of 2.0.

5.7. Discrimination is a property not of a multivariable model, but of the predictors and the data set.

Although model building is generally seen as a process of fitting coefficients, discrimination is largely a property of what predictors are available. For instance, we have excellent models for prostate cancer outcome primarily because Gleason score is strongly associated with malignant potential. In addition, discrimination is highly dependent on how much a predictor varies in the data set. For example, a model to predict erectile dysfunction which includes age will have much higher discrimination for a population sample of adult men than for a group of older men presenting to a urology clinic because there is greater variation in age in the population sample. Authors need to consider these points when drawing conclusions about the discrimination of models. This is also why authors should be cautious about comparing the discrimination of different multivariable models when these were assessed in different data sets.

5.8. Correction for overfit is strongly recommended for internal validation.

In the same way that it is easy to predict last week's weather, a prediction model generally has good properties when evaluated on the same data set used to create the model. This problem is generally described as overfit. Various methods are available to correct for overfit, including crossvalidation and bootstrap resampling. Note that such methods should include all steps of model building. For instance, if an investigator uses stepwise methods to choose which predictors should go into the model and then fits the coefficients, a typical crossvalidation approach would be to 1) split the data into 10 groups, 2) use stepwise methods to select predictors using the first 9 groups, 3) fit coefficients using the first 9 groups, 4) apply the model to the 10th group to obtain predicted probabilities and 5) repeat steps 2 to 4 until all patients in the data set have a predicted probability derived from a model fitted to a data set that did not include that patient's data. Statistics

such as the area under the curve (AUC) are then calculated using the predicted probabilities directly.

5.9. Calibration should be reported and interpreted correctly.

Calibration is a critical component of a statistical model, as the main concern for any patient is whether the risk given by a model is close to the true risk. It is rarely worth reporting calibration for a model created and tested on the same data set, even if techniques such as crossvalidation are used because calibration is nearly always excellent on internal validation. Where a pre-specified model is tested on an independent data set, calibration should be displayed graphically in a calibration plot. The Hosmer-Lemeshow test addresses an inappropriate null hypothesis and should be avoided. Note also that calibration depends on the model coefficients and data set being examined. A model cannot be inherently “well calibrated.” All that can be said is that predicted risk and observed risk are close in a specific data set and representative of a given population.

5.10. Avoid reporting sensitivity and specificity for continuous predictors or a model.

Investigators often report sensitivity and specificity at a given cut point for a continuous predictor (such as a PSA of 10 ng/mL) or they report specificity at a given sensitivity (such as 90%). Reporting sensitivity and specificity is not of value because it is unclear how high sensitivity or specificity would have to be to justify clinical use. Similarly, it is difficult to determine which of 2 tests, one with a higher sensitivity and the other with a higher specificity, is preferable because clinical value depends on the prevalence of disease and the relative harms of a false-positive compared with a false-negative result. In the case of reporting specificities at fixed sensitivity or vice versa it is all but impossible to choose the specific sensitivity rationally. For instance, a team of investigators may state that they want to know specificity at 80% sensitivity because they want to ensure they catch 80% of cases. However, 80% might be too low if prevalence is high or too high if prevalence is low.

5.11. Report the clinical consequences of using a test or a model.

Instead of using statistical abstractions, such as sensitivity and specificity or a ROC curve, authors are encouraged to choose illustrative cut points and then report results in terms of clinical consequences. Consider a study in which a marker is measured in a group of patients undergoing biopsy. If a given level of the marker had been used to determine biopsy, then a certain number of biopsies would have been conducted and a certain number of cancers found and missed.

5.12. Interpret decision curves with careful reference to threshold probabilities.

It is insufficient merely to report that “the marker model had the highest net benefit for threshold probabilities of 35% to 65%.” Authors need to consider whether those threshold probabilities are rational. If the study reporting benefit between 35% and 65% concerned detection of high grade prostate cancer, few if any urologists would demand that a patient have at least a 1-in-3 chance of high grade disease before recommending biopsy. Thus the authors would have to conclude that the model was not of benefit.

6. Conclusions and Interpretation

6.1. Draw a conclusion, don't just repeat the results.

Conclusion sections are often simply a restatement of the results. “A statistically significant relationship was found between body mass index and disease outcome” is not a conclusion. Authors instead need to state implications for research and/or clinical practice. For instance, a conclusion section might call for research to determine whether the association between body mass index is causal or make a recommendation for more aggressive treatment for patients with higher body mass index.

6.2. Avoid using words such as “may” or “might.”

A conclusion that a novel treatment “may” be of benefit would only be untrue if it had been proven that the treatment was ineffective. Indeed, that the treatment “may” help would have been the rationale for the study in the first place. Using words such as may in the conclusion is equivalent to stating, “we know no more at the end of this study than we knew at the beginning,” which is reason enough to reject a paper for publication.

6.3. A statistically significant p-value does not imply clinical significance.

A small p-value means only that the null hypothesis has been rejected, which may or may not have implications for clinical practice. The fact that a marker is a statistically significant predictor of outcome does not imply that treatment decisions should be made on the basis of that marker. Similarly, a statistically significant difference between 2 treatments does not necessarily mean the former should be preferred to the latter. Authors need to justify any clinical recommendations by carefully analyzing the clinical implications of their findings.

6.4. Avoid pseudo limitations such as “small sample size” and “retrospective analysis,” and consider instead sources of potential bias and the mechanism for their effect on findings.

Authors commonly describe study limitations in a rather superficial way, such as “small sample size

and retrospective analysis are limitations.” However, a small sample size may be immaterial if the results of the study are clear. For instance, if a treatment or predictor is associated with a large odds ratio, a large sample size might be unnecessary. Similarly, a retrospective design might be entirely appropriate, as in the case of a marker study with long-term followup, and have no discernible disadvantages compared to a prospective study. Discussion of limitations should include the likelihood and effect size of possible bias.

6.5. Consider the impact of missing data and patient selection.

It is rare that complete data are obtained from all patients in a study. A typical article might report, “of 200 patients 8 had data missing on important baseline variables and 34 did not complete the end of study questionnaire, leading to a final data set of 158.” Similarly, many studies include a relatively narrow subset of patients, such as 50 patients referred for imaging before surgery, of the 500 treated surgically during that timeframe. In both instances it is worth considering analyses to determine whether patients with missing data or who were not selected for treatment were different from those who were included in the analyses. Although statistical adjustment for missing data is complex and warranted only in a limited set of circumstances, basic analyses to understand the characteristics of patients with missing data are relatively straightforward and often helpful.

6.6. Consider the possibility and impact of ascertainment bias.

Ascertainment bias occurs when an outcome depends on a test, and the propensity for a patient to be tested is associated with the predictor. PSA screening provides a classic example when prostate cancer is found on biopsy but the main reason why men are biopsied is because of an elevated PSA. Therefore, a study in a population subjected to PSA screening will overestimate the association between PSA and prostate cancer. Ascertainment bias can also be caused by the timing of assessments. For instance, frequency of biopsy in prostate cancer active surveillance will depend on prior biopsy results and PSA level, which induces an association between those predictors and time to progression.

6.7. Do not confuse outcome with response among subgroups of patients undergoing the same treatment, as patients with poorer outcomes may still be good candidates for that treatment.

Investigators often compare outcomes in different subgroups of patients all receiving the same treatment. A common error is to conclude that patients with poor outcome are not good candidates for that

treatment and should receive an alternative approach. This approach confuses differences between patients for differences between treatments. As a simple example, large tumors are more likely to recur after surgery than small tumors, but that cannot be taken to suggest that resection is not indicated for patients with tumors larger than a certain size. Indeed, surgery is generally more strongly indicated for patients with aggressive (but localized) disease and such patients are unlikely to do well on surveillance.

6.8. Be cautious about causal attribution: correlation does not imply causation.

It is well-known that “correlation does not imply causation” but authors often slip into this error when making conclusions. The introduction and methods section might insist that the purpose of the study is merely to determine whether there is an association between treatment frequency and treatment response but the conclusions may imply that more frequent treatment would improve response rates.

Use and Interpretation of P-Values

That p-values are widely misused and misunderstood is apparent from even the most cursory reading of the medical literature. One of the most common errors is accepting a null hypothesis concluding from a p-value of 0.07 that a drug is ineffective or that 2 surgical techniques are equivalent. This particular error is described in detail in guideline 3.1. The more general problem

is that p-values are often given excessive weight in the interpretation of a study. Indeed, studies are often classed by investigators as positive or negative based on statistical significance. Gross misuse of p-values has led some to advocate banning the use of p-values completely.⁴

We follow the American Statistical Association statement on p-values and encourage all researchers to read either the full statement⁵ or the summary.⁶ We emphasize that the p-value is just 1 statistic that helps interpret a study but it does not determine our interpretations. Drawing conclusions for research or clinical practice from a clinical research study requires evaluation of the strengths and weakness of study methodology, the results of other pertinent data published in the literature, biological plausibility and effect size. Sound and nuanced scientific judgment cannot be replaced by just checking whether one of the many statistics in an article is or is not less than 0.05.

Concluding Remarks

These guidelines are not intended to cover all medical statistics but rather the statistical approaches most commonly used in clinical research papers in urology. It is possible for authors to follow all of the guidelines and yet the study can be statistically flawed or break numerous guidelines while still being statistically sound. On balance, however, the analysis, reporting and interpretation of clinical urological research will be improved by adherence to these guidelines.

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