

# Statistical Issues in Malaria Research in Southeast Asia: Systematic Analysis

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## ABSTRACT

This study systematically analyzed the contribution of statistical misuses in the three main malaria research categories published during 2010-2015 from Southeast Asian countries. Related articles were downloaded from the PubMed and Scopus databases using the predefined keywords. The retrieved articles were checked for compliance with the eligibility criteria and stored in EndNote version X7. Finally, 524 articles were included in the analysis. Most of the research involved was conducted in Thailand (263 articles, 50.19%). Intervention and health care research (n =252, 48.09%) was the primary research category. It was also applied to descriptive and inferential statistics (63.49%). The non-parametric test was the most applied statistical analysis approach (28.63%). Only obvious errors were reported as improper use in this article and analyzed based on the available information. Improper use/misuse of statistics was highest in the intervention and health care research category (47.10%). Results of the systematic analysis revealed a high frequency of inappropriate uses/misuse of statistics. In most articles, there was no rationale for selecting the sample sizes. Sampling issues could be considered the main problem of all the malaria research categories (43.15%). The reliability of the articles and the possibility of incorrect interpretations and conclusions should be noted. To decrease the number of errors stemming from inappropriate uses/misuse of statistical analysis, a clear study protocol and statistical analysis plan should be prepared before a study is conducted, and should include the consultation of statisticians.

**Keywords:** Malaria research; Statistical misuse; Southeast Asia

## 1. Introduction

Malaria remains a major global public health problem [1]. The key problem in malaria control is the resistance of

*Plasmodium falciparum* to most of the existing drugs used in treatment [2]. Southeast Asia (SEA) is the hot spot of multi-drug resistant (MDR) *P. falciparum*. This accelerates the

research interests for effective malaria control through research and development of effective alternative antimalarial drugs, vaccines, diagnostic tools, preventive measures, and strategies to improve access to effective antimalarial treatment. Therefore, proper use of statistics is a critical element of integrity in all academic fields of biomedical research, including malaria research. Statistics can, however, be misused through concept or application.

Analysis of the application of statistics as a tool for data analysis and interpretation of a research project is also an issue of importance. As is the same in other research areas, statistics in malaria research requires the appropriate selection to analyze data which is an important issue to assure accurate and reliable conclusions are drawn. Application of statistics in research starts from the beginning when the protocol is designed, i.e., sample size estimation, experimental design, sampling method, randomization, data collection, data verification, quality assurance, data analysis, and interpretation of the results and conclusion. Choosing the wrong statistical methods can make the publication unreliable or even invalid, which causes a waste of time, effort, and research funding.

This study aimed to systematically analyze the impact of statistical misuses in malaria research in SEA published during 2010-2015. The focus was on the three main research categories, i.e., pharmacology, clinical trials, and intervention and health care research and research articles published during the 6-year period to illustrate the issues in statistical analysis. With this information, an accurate perception of the pervasiveness of statistical misuses and reliability of the results and study conclusions would prevent or reduce future errors.

## **2. Materials and Methods**

### **2.1 Search strategy**

Research articles were retrieved from the PubMed and Scopus databases using the 'keywords' summarized in Table 1 [3]. Each was classified into three categories as follows: (i) pharmacological study, (ii) clinical trial, and (iii) intervention or health care research.

### **2.2 Study selection**

The articles were screened based on titles and abstracts, and the full-texts were further evaluated based on the eligibility criteria.

### **2.3 Eligibility criteria**

The articles were included in the analysis following the criteria: (i) articles related to the three main malaria research categories, i.e., pharmacology, clinical trials, and intervention and health care research which were published in PubMed or Scopus databases during the period of January 2010 to December 2015, (ii) full-text articles in English language, and (iii) articles reported from SEA countries. Duplicated and review articles, including letters and editorials were excluded from the analysis. All articles were stored in EndNote version X7.

### **2.4 Data extraction and analysis**

The data were extracted by two independent reviewers, and disparities were resolved by the third reviewer [4, 5]. The information obtained included the first author's name and year of publication, study country, sample size, and research category. Qualitative data are presented as numbers, percentages, and bar diagrams. Most publications presented only summarized data without provision of supplementary raw data, study design, information on data distribution, sample size estimation, etc. Therefore, only obvious errors were reported as improper use in this article and analyzed based on the available information.

**Table 1.** Keywords used to retrieve the articles included in the analysis (adapted from [3]).

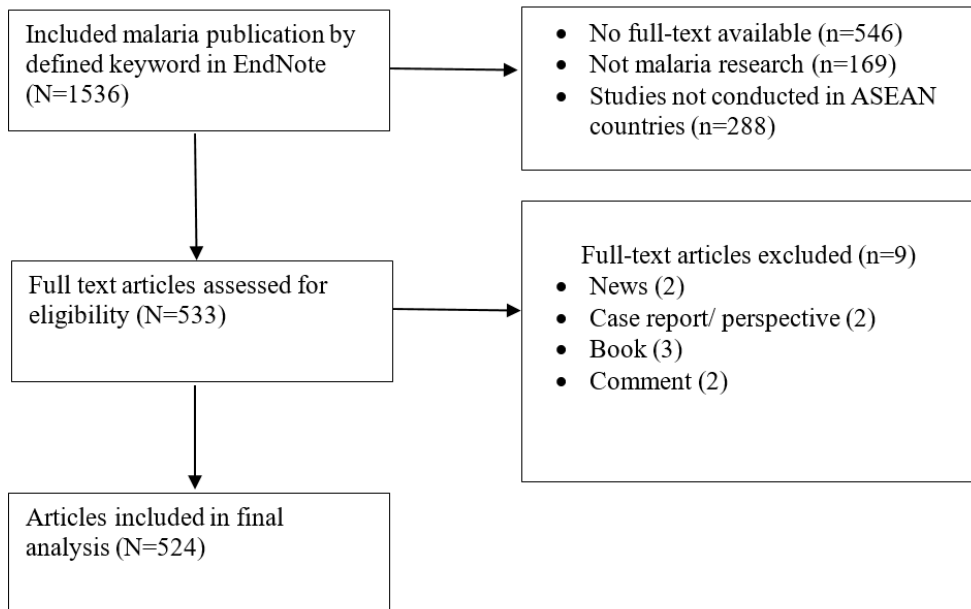
Research category	Keywords
Pharmacology	“malaria” AND “Pharmacology” OR “Pharmacokinetics” OR “In vitro activity: OR “Animal study” OR “Drug metabolism study” OR “Assay methodology” OR “Patient compliance” OR “Drug mechanism of action” OR “Pharmacogenetics.”
Clinical trial	“malaria AND “Clinical trials” OR “Antimalarial drug” OR “Randomized controlled trial (RCT)” OR “Phase 1 clinical trial” OR “Phase 2 clinical trial” OR “Tolerability/Toxicity” OR “Adjunct treatments” OR “Effectiveness” OR “Efficacy” OR “Adherence Efficacy”
Intervention and health care research	“malaria AND “Malaria control” OR “Health promotion” OR “Drug policy” OR “Health system” OR “Private sector access” OR “interventions” or “Early warning system” OR “Political aspects” OR “Mass drug administration” OR “Data sharing” OR “Primary health care” OR “Fever management” OR “Drug supply” OR “Effect of development” OR “Improved nutrition”

### 3. Results and Discussion

#### 3.1 Results

For the analysis, 524 articles out of the 1,536 retrieved articles were finally included (Fig. 1). Table 2 summarizes statistical analysis approaches used for data analysis.

Most articles ( $n = 332, 63.36\%$ ) used both descriptive and inferential statistics for data analysis. In all three of the research categories, the majority or plurality were from Thailand (45.63-63.08%).



**Fig. 1.** Study identification and selection.

**Table 2.** Summary of statistical approaches used in each research category ( numbers and percentages).

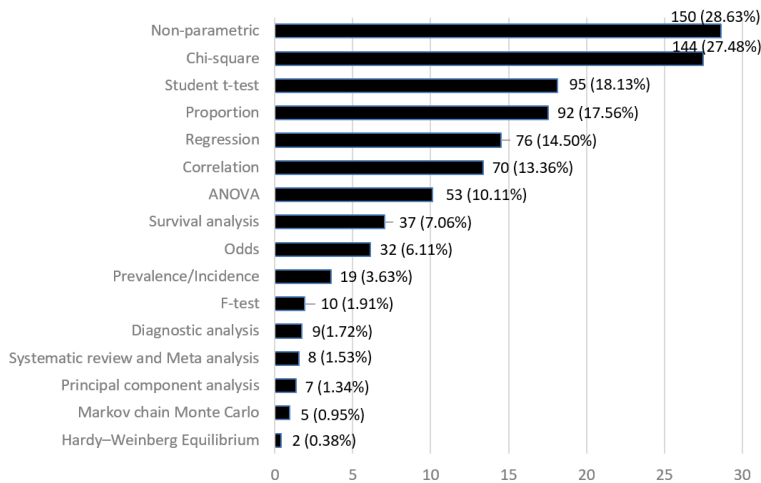
Research category	No statistics or only percentage	Only descriptive statistics	Descriptive and inferential statistics
Pharmacology	42 (20.29)	35 (16.91)	130 (62.80)
Clinical trials	12 (18.46)	12 (18.46)	41 (63.08)
Intervention and healthcare research	67 (26.59)	25 (9.92)	160 (63.49)
<b>Total</b>	<b>120 (22.90)</b>	<b>55 (13.74)</b>	<b>41 (63.36)</b>

Intervention and healthcare research ( $n = 252$ , 48.09%) was the most prominent research category reported from SEA countries during 2010-2015. Data analyses involved non-statistical analysis (26.59%) and descriptive and inferential statistics (63.49%).

Statistical analysis applied for data analysis in the 524 articles is summarized in Fig. 2. The plurality (28.63%) was non-parametric tests for comparison of the difference between groups of non-normally distributed quantitative data (Mann-Whitney U test, Wilcoxon signed-rank test, and Kruskal Wallis test), followed by Chi-square test for qualitative data (27.48%), parametric test for normally distributed quantitative data (student t-test, 18.13%), proportion analysis (17.56%),

regression analysis (14.50%), correlation analysis (Pearson and Spearman correlation tests) (13.36%), ANOVA for comparison of the difference between groups of non-normally distributed quantitative data (10.11%), survival analysis (7.06%), odd analysis (6.11%), prevalence/incidence analysis (3.63%), F-test (1.91%), diagnosis test (sensitivity, specificity, Receiver Operating Characteristic or ROC) (1.72%), systematic review/meta-analysis (1.53%), principal component analysis of PCA (1.34%), Markov chain Monte Carlo (0.95%), and Hardy-Weinberg equilibrium (0.8%).

Table 3 summarizes the types and frequencies of misuse of statistics in different research categories.



**Fig. 2.** Statistical analysis applied in the 524 included articles. ANOVA: analysis of variance; F-test: test of population variances equality.

**Table 3** Summary of misuse of statistics in different research categories (number and percentage).

	Pharmacology	Clinical trials	Intervention trials and health services research	Total number of articles (%)
No information on sample size estimation procedure provided	124	16	68	208 (43.15)
Unclear statistical hypothesis (1-tailed or 2-tailed)	42	15	55	112 (23.24)
Unclear data distribution	38	7	35	80 (16.60)
Inappropriate data presentation	23	5	22	50 (10.37)
Lack of information on the statistical significance level ( $\alpha$ )	21	7	25	53 (11.00)
Application of ANOVA test without information about <i>post-hoc</i> multiple comparisons	3	2	6	11 (2.28)
Use of standard error of the mean (SEM, SE) instead of standard deviation (SD) to present data dispersion	10	1	16	27 (5.60)
Inappropriate use of graphic presentation	1	0	0	1 (0.21)
<b>Total number of articles (N=482)</b>	<b>202 (41.90%)</b>	<b>53 (11.00%)</b>	<b>227 (47.10%)</b>	<b>482 (100%)</b>

Statistical analysis varies among research categories. The lack of information on sample size estimation was the most common issue in all research categories. Inappropriate use of statistics in all types was highest in the intervention and health care research category (47.10%). The most prominent type of misuse of statistical analysis for this research category was the absence of information on sample size estimation (30.71%), followed by unclear statistical hypothesis (23.24%), and then unclear information on data distribution (16.60%).

### **3.2 Discussion**

With the rising number of published articles, inappropriate statistics have been used in all research disciplines [6]. The current study identified and analyzed the “misuse” of statistics in malaria research articles reported from SEA during 2010-2015. The current study focused on the misuse of statistics in the three major research categories, i.e., pharmacology, clinical trials, and intervention and health care research. The frequency of statistical misuse was significantly high (92.31%, 482/524). This is due mainly to poor knowledge of basic statistics, including its application for analyzing different data types. Other contributions include a lack of proper planning and data management and deliberate decisions to achieve a desired statistical result (research misconduct and poor research practices). Research misconduct and poor research practices were reported in about 34% of the published articles [7]. Some of the cases of misuse were due to the nature of research dissemination [8]. Most statistical software does not require basic knowledge of statistics. The statistical analysis approach should be planned and described in detail in the study protocol before conducting the study. Seeking support from statisticians is necessary if the researchers do not have adequate knowledge of the application of statistics to analyze the data sets. It is essential to understand the implications of committing either a type I (false rejection of the null hypothesis when it

is true) or a type II (false acceptance of the null hypothesis when it is false) error. In the present study, however, analyzing the root causes of such statistical misuses was impossible due to the limited or inadequate detailed information in the published articles. Most presented only summarized data without provision of supplementary raw data, study design, information on data distribution, sample size estimation, etc. Therefore, only obvious errors were reported and analyzed based on the available information.

Certain assumptions are required for each statistical test to produce valid results. This requirement should be considered to make accurate and meaningful analysis results and interpretations. In many cases, errors are due to an adherence to the statistical analysis methods from previously published articles with similar study designs [9]. Furthermore, several articles did not report the statistical tests applied for data analysis [10] but instead only stated that the tests were used “where appropriate” [10, 12]. The statistical approaches and tests depend principally on the study objective and data distribution. The complexity of statistical analysis varies according to research types and disciplines [13].

Results of the current study showed that the frequency of each type of inappropriate use of statistics varies with research categories. In general, they were found most with intervention and health care research (e.g., malaria diagnosis) (47.10%), followed by pharmacology (41.9%). It was noted that the frequency of misuses in clinical trial research was relatively low (11.0%). Sample size estimation was the main problem in data analysis of all malaria research categories (43.15%). In most articles, there was no rationale for selecting the sample sizes. Inappropriate sample size may have resulted in the wrong interpretation and conclusion of the study hypothesis. An inadequate sample size does not provide adequate power to detect the difference (type II error). On the other hand, a sample size that is too large would facilitate

false positive detection of the difference (type I error). Sample size estimation approaches depend on the nature of the study. Statistical software was available (e.g., G\*power, OpenEpi, STATA, and n4studies). A priori information about parameters of interest, effect size, confidence level, as well as type I and II error constitutes the key components of sample size estimation.

The second highest frequency of statistical misuse found was unclear data distribution. Data may be skewed and require different statistical tests. This information is required for the selection of appropriate statistical tests, either based on the parametric analysis approach (normally distributed quantitative data) or the non-parametric analysis approach (non-normally distributed quantitative data). Assessment of skewness is not uniformly performed and is rarely reported. As most research articles are aimed at hypothesis testing (e.g., comparison of the difference between two or more than two groups of quantitative data), most (63.36%) used both inferential and descriptive statistics (62.80%, 63.08%, and 63.49% for pharmacology, clinical trials, and intervention and health care research, respectively). The non-parametric analysis approach was the most applied (28.63%) for quantitative data analysis. The Chi-square/Fisher exact test was most used (24.78%) for qualitative data analysis. Misapplication of non-parametric and parametric tests, failure to apply corrections, and disregard for statistical independence are also common [14]. Depending on sample variances, the t-test forms exist for independent quantitative data. A two-sample t-test is appropriate for data with equal variance, while a modified t-test is appropriate for unequal variance. For more than two groups of data, ANOVA should be utilized. For both t-test and ANOVA, multiple comparisons may require adjustment. This study found that the frequency of mistakes due to using the ANOVA test without post-hoc multiple comparisons was about 2.28% for all research categories. More than 50% of all the

articles published in the American Journal of Physiology used unpaired or paired t-tests for data analysis [9]. About 17% did not correctly apply the t-test for multiple comparisons (either by Bonferroni or some other correction methods). In addition, articles that used the ANOVA test did not specify the type of the test (one-way or two-way designs). Furthermore, it has been reported that about 50% of the articles published in the two journals applied a t-test for data analysis when a test for multiple comparisons was required [15].

The unclear direction of statistical hypothesis testing (1-tailed or 2-tailed hypothesis) for inferential statistical analysis ranked the third highest frequency of statistical misuse found in the present study. Although some studies were likely to be 1-tailed hypothesis testing, most arbitrarily applied 2-tailed hypothesis testing. This may result in an incorrect acceptance of the null hypothesis (no significant difference) (type II error). A lack of information about the statistical significance level  $\alpha$  used was found in 11% of all research articles. Setting the statistical significance level ( $\alpha$ ) is important as several elements can influence the p-value such as random error, bias, and confounding. A p-value of 0.051 does not mean any association but means this study cannot detect a statistically significant result. The value of 0.05 is arbitrarily chosen.

The frequencies of other types of statistical misuse in the three malaria research categories were inappropriate data presentation (10.37%), use of standard error of the mean (SEM) instead of standard deviation (SD) to present data dispersion (5.6%), and inappropriate use of graphical presentation (0.21%). It is common to detect misuses of statistics to represent central tendency and dispersion, e.g., using mean and SD instead of the median and range or interquartile range to summarize non-normally distributed data. Furthermore, some researchers use SEM intentionally (to make small data variations) or unintentionally (without knowledge) to present data dispersion from the mean values instead of SD.

#### 4. Conclusion

This systematic study of malaria-related research articles from SEA (pharmacology, clinical trials, and intervention and health care research) published during 2010-2015 revealed a remarkably high frequency of statistics misuse. To reduce the errors, the study protocol and statistical analysis should be planned, with consultations of statisticians, before the study is conducted. The key issues include study objectives, study design, statistical hypothesis (1- or 2-tailed for hypothesis testing), sample size estimation and sampling method, data types (qualitative or quantitative), data collection, data analysis approach (parametric or non-parametric analysis), statistical significance level, data presentation, interpretation and conclusion. Statistical test assumptions must be determined before selecting any statistical test.

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