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Investigation of the Relationship between Clinical Trial Design of Randomized Controlled Trials and Scientific Influence of the Trial Outcome in Non-small Cell Lung Cancer

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The results of clinical trials are essential for the advancement of evidence-based medicine (EBM). Our previous research using the Relative Citation Ratio (RCR), article-based citation metric developed by the National Institutes of Health (NIH), identified that the outcomes of clinical trials designed to have a high evidence level, such as large sized randomized trials, and those with novel interventions have higher scientific influence. In the present study, aiming to further investigate the factors that improve the scientific influence of clinical study results, we focused on randomized controlled trial (RCT) and evaluated the relationship between study design and RCR of drug intervention RCTs in patients with non-small cell lung cancer (NSCLC). Publications of drug intervention RCTs for NSCLC patients published between 2007 and 2016 were included. Clinical trial design factors were compared among three RCR categories with 50 trials in each: lowest RCR (LOW50), median RCR (50 NIH percentile [50NIH%ile]), and highest RCR (TOP50) group. The numbers of Phase 3, multi-country, for-profit company sponsored/supported, and statistically powered RCTs, which confirmed pre-defined differences between/among interventions, increased by more than 30% from 50NIH%ile to TOP50. The number of novel interventions such as EGFR-TKI and Immune checkpoint inhibitors were also increased as RCR increased. Our results indicate quantitatively that the clinical trial design is an important factor that affects scientific influence of the RCT outcome. RCTs should be sufficiently large to generate statistically confirmatory outcomes, be conducted in multiple countries, and use newer drugs in order to better contribute to the progress of EBM.

Key words —— clinical trial design, randomized controlled trial, bibliometric analysis, non-small cell lung cancer, evidence-based medicine

Introduction

The results of clinical trials provide the best evidence of the efficacy and safety of drugs and are essential to progress evidence based medicine (EBM).[1, 2] Clinical trials have been conducted in large numbers all over the world, and the number is growing every year according to the Clinical-Trials.gov (https://clinicaltrials.gov/ct2/resources/trends, March 25, 2021). Clinical trial design is one of the factors that define the level of evidence. Randomized controlled trials (RCTs) are normally performed to compare efficacy and safety between/among different interventions and are known to have the lowest biases and provide stronger evidence compared to other trial designs.[2, 3]

Some research has investigated the relationship between clinical trial characteristics and scientific influence of the trial outcome by bibliometric approach.[4-7] Bibliometrics is a quantitative analysis of published papers. The Journal Impact Factor (JIF), h-index, and number of citations of the publication are well-known indicators and have been used to assess productivity of researchers/institutions or used for researches assessing scientific influence of published clinical trials.

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Previous evidence using the above indices suggested publications of positive outcome tended to have higher scientific impact, and higher impact factor journals tended to have higher sample size and used lower bias methodologies in clinical trials.[4-7] However, the existing bibliometric indices are not appropriate when assessing individual publications.[8] In order to overcome this disadvantage, NIH developed the Relative Citation Ratio (RCR) in 2015. The RCR is a field-adjusted and time-adjusted index based on the number of citations. RCR is calculated by dividing the number of citations per year by the expected number of citations per year. It has been validated by experts and quantifies the scientific influence of individual publications.[9] Publications from different disciplines can be compared by defining the discipline of the target publications using a new method, named the co-citation network. Articles funded by the NIH Research Project Grant Program R01 (NIH-R01) were benchmarked and RCR = 1.0 is the median RCR of NIH-funded research publications (50 NIH percentile [50NIH %ile]) in any field. Currently, the RCR is used not only in the NIH, but also outside of the NIH.[10-12]

Our previous research, the first research focused on the study design of drug intervention clinical trial including all study phases and assessed the scientific influence of the outcome using the RCR, identified drug intervention clinical trials designed to have a high evidence level, such as large sized randomized trials have higher scientific influence of the outcome, and novel interventions also improve the influence of clinical trial outcomes. However, we could not identify the definitive factors to increase the scientific influence due to a certain degree of correlation between variables.[13] In the present study, aiming to further investigate the factors that improve the scientific influence of clinical study results, we narrowed our focus on RCTs, which is known to provide the most reliable clinical evidence, and evaluated the relationship between study design and RCR of drug intervention RCTs in patients with non-small cell lung cancer (NSCLC) published between 2007 and 2016.

In the previous and present research, we focused on NSCLC to minimize variations in clinical trial design patterns by disease areas. Lung cancer is one of the most common cancers globally and the leading cause of cancer death. In 2020, approximately 1.8 million people died due to lung cancer worldwide.[14] NSCLC accounts for around 85% of all lung cancers. Cytotoxic chemotherapy has been the main treatment option for NSCLC in the last 10 years; however, in recent years, the therapeutic algorithm and treatment options have changed drastically due to emerging molecular-target drugs. Predictive biomarker tests have enabled the identification of highly efficacious treatment options, and the prognosis has been greatly improved compared to chemotherapy.[15] Meanwhile, the unmet medical need remains high because most patients will experience disease progression despite the use of these highly efficacious drugs, and thus, various drug intervention clinical trials are being actively conducted today. NSCLC is, therefore, considered appropriate for this research because there were a significant number of clinical trials due to high unmet medical needs, the EBM was well established, and innovative new drugs have emerged in recent years.

Materials and Methods

1. Publication search

We used PubMed to search for publications on clinical trials for NSCLC because RCR was avail-

able for PubMed indexed publications.[9] On May 6, 2019, we performed a PubMed search by referring the National Comprehensive Cancer Network (NCCN) guideline for NSCLC (https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, March 25, 2021). The search term was "non-small cell lung cancer." The search results were narrowed by "studies in humans" in the Species category, "published in English" in the Language category, and "Clinical Trial," "Clinical Trial Phase 1 to 4," or "RCT" in the Article type category. In addition, the publications were narrowed to "Published from 20070101 to 20161231" in the Publication date category to assess the changes over time during the most recent 10 years, specifically in publications for which the RCR was available at the time of research initiation.[13, 16-18] The PubMed identifier (PMID) of the matched publications were downloaded.

2. RCR and NIH percentile (NIH%ile)

RCR and NIH%ile, percentile rank of each paper's RCR compared to NIH publications, are publicly available in website, named iCite (https://icite.od.nih.gov/analysis, May 6, 2019). We performed an iCite search on May 6, 2019 by using the downloaded PMID, and obtained the RCR and NIH%ile of each publication.

3. Identification of eligible publications

Because the number of PubMed-searched publications exceeded 3,100, we set three categories, each with 50 publications, to investigate the trend between the clinical trial characteristics and the RCR. Fifty publications were used in several bibliometrics analyses to investigate the top influential publications, and thus considered sufficient when comparing the difference of study design factors among the three RCR categories.[19-21] The three categories were: (1) LOW50, 50 publications of the lowest RCR; (2) 50NIH%ile, 25 publications below and above the median RCR; and (3) TOP50, 50 publications in the highest RCR. We screened publications until 50 eligible publications were found for each category. We included original publications that reported the outcome of primary objectives/endpoints of drug intervention RCT in NSCLC patients. A study was defined as an RCT if participants observed in the trial were assigned prospectively to one of two or more interventions using random allocation, as defined by the Cochrane Library (www.training.cochrane.org/handbook, March 25, 2021). We excluded publications reporting: i) trial results including other tumor types/disease other than NSCLC patients; ii) non-drug interventions, procedures, and biomarkers (*eg*, supplements, surgical procedures, radiation, chemoradiation, diagnostic procedures, biomarker assay, and validations); iii) retrospective or Phase 4 trials; iv) non-primary outcomes (*eg*, data updates, sub-analyses, and pooled analyses of multiple trials); v) non-randomized trials; and vi) others (*eg*, study design, conference abstracts, commentaries, reviews, and FDA approval letters).

4. Identification of clinical trials

For all research, we searched corresponding clinical trials in clinical trial registries (ClinTrials.gov, Japan Pharmaceutical Information Center Clinical Trial Information, University Hospital Medical Information Network Clinical Trials Registry, and European Union Drug Regulating Authorities Clinical Trials Database) to find data not provided in the publication, if available. A unique trial name, trial identifier, and/or other study characteristics such as indication, interventions, number of subjects, and study outcomes

were used to identify the matched critical trial.

5. Data extraction

The following data were extracted from the publications or registries: trial phase, blinding status, trial sponsorship/support (for-profit company sponsored/supported or others), trial center (multi-center, single-center, or unknown), trial country (multi-country or single-country, with country name), number of enrolled subjects, primary endpoints (survival-related, disease progression/recurrence-related, response-related, and other), statistical considerations (statistically powered to test the hypothesis of pre-defined differences between/among interventions directly [statistically powered] or not), trial outcome of the statistically powered trial (positive: met primary endpoint; negative: did not meet primary endpoint), and interventions. In terms of trial sponsorship/support, a trial was classified as for-profit company sponsored/supported if: i) explicit acknowledgement of sponsorship/support from a for-profit company was provided in the article or trial registry; or ii) at least one author was an employee of a for-profit company.[22, 23] In cases where the trial center information was not provided in the publication or trial registry, a trial was classified as a single-center trial if all authors belonged to the same affiliation and as a multi-center trial if there were multiple author affiliations and multiple institutional review boards (IRBs) mentioned; otherwise, it was classified as unknown.[13] In cases where the trial country information was not provided in the publication or trial registry, a trial was classified as single-country if all author institutions belonged to a single country; otherwise, a trial was classified as multi-country.

6. Statistical analysis

A Fisher's exact test was used to determine the differences in the proportion of each clinical trial design factor among LOW50, 50NIH%ile and TOP50. A Kruskal-Wallis test was used to determine differences in the number of subjects among LOW50, 50NIH%ile and TOP50. For all analysis, StatsDirect 3 (StatsDirect Ltd, Merseyside, UK) was used, with $P < 0.05$ considered statistically significant.

Results

1. RCR of the publications in the three RCR categories

The flow diagram of the publication selection process is shown in **Fig 1**. Among the 3,100 publications published between 2007 to 2016, a total of 1,021 publications (32.9%) were screened to identify the 50 eligible publications in each category. **Figure 2** shows the relationship between the RCR and NIH%ile of the 3,100 publications and the publications of the three RCR categories. The median RCRs of the LOW50, 50NIH%ile, and TOP50 publications were 0.14, 1.01, and 19.01, respectively.

2. Clinical trial design characteristics

Figure 3 shows the differences in the clinical trial design factors among the three RCR categories. For the trial phase (**Fig 3A**), the number of Phase 3 trials increased from LOW50 (five trials, 10.0%) to TOP50 (42 trials, 84.0%). The number of Phase 2 trials was the same in the LOW50 and 50NIH%ile (33 trials, 66.0%) publications, but decreased from 50NIH%ile to TOP50 (eight trials, 16.0%). In terms of blinding (**Fig 3B**), the number of blinded trials increased from LOW50

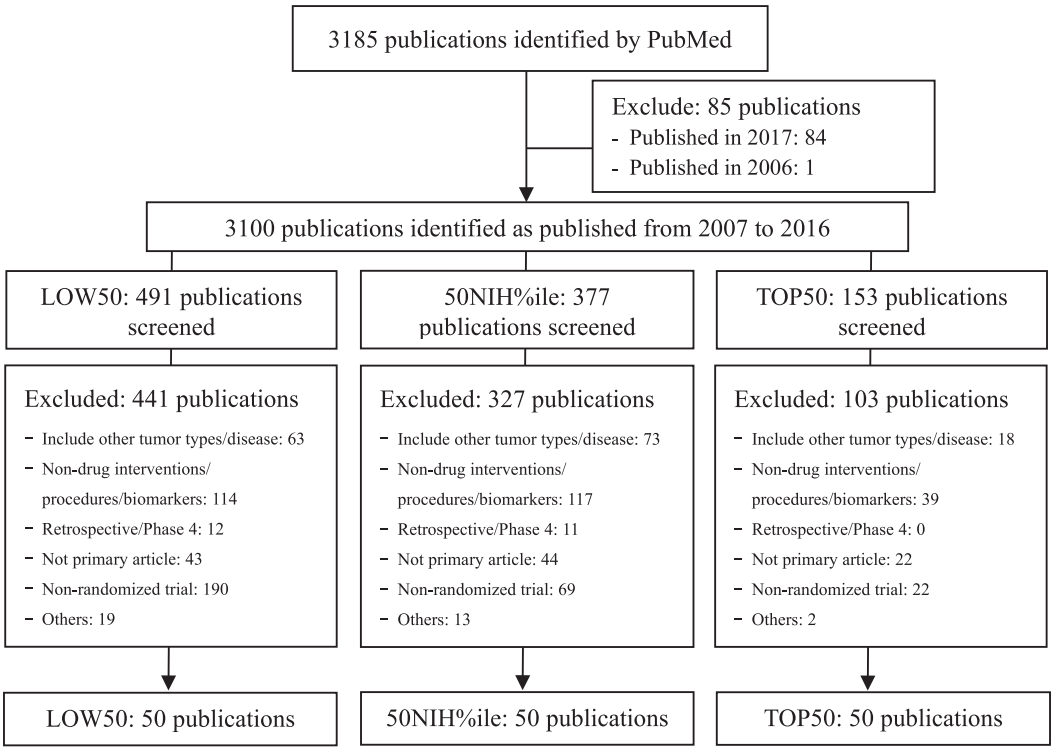

Fig 1 Flow diagram of the publication selection
RCTs for the comparison of three RCR categories.

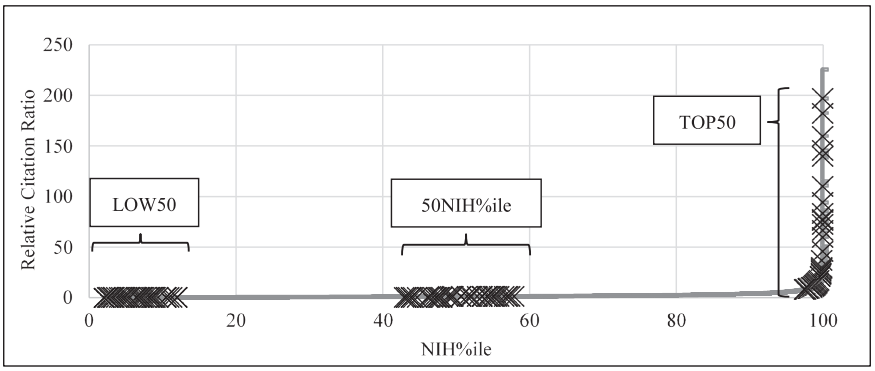

Fig 2 Relative Citation Ratio (RCR) and National Institutes of Health percentile (NIH%ile) of the searched 3,100 publications and the eligible publications for the research
X shows the publications of RCT in the three RCR categories. The gray dot/line shows the publications not included in the three RCR categories.

(three trials, 6.0%) to TOP50 (19 trials, 38.0%). In terms of the number of trial centers (**Fig 3C**), the number of multi-center trials increased as the RCR increased from LOW50 (32 trials, 64.0%) to TOP50 (50 trials, 100%). Regarding the trial country (**Fig 3D**), the number of multi-country trials increased as the RCR increased from LOW50 (four trials, 8.0%) to TOP50 (39 trials, 78%). The number of single-country trial was highest in LOW50 (46 trials, 92%), whilst most of the trials in TOP50 were multi-country trials. For trial sponsorship/support (**Fig 3E**), the number of for-profit company sponsored/supported trials was similar in LOW50 (24 trials, 48.0%)

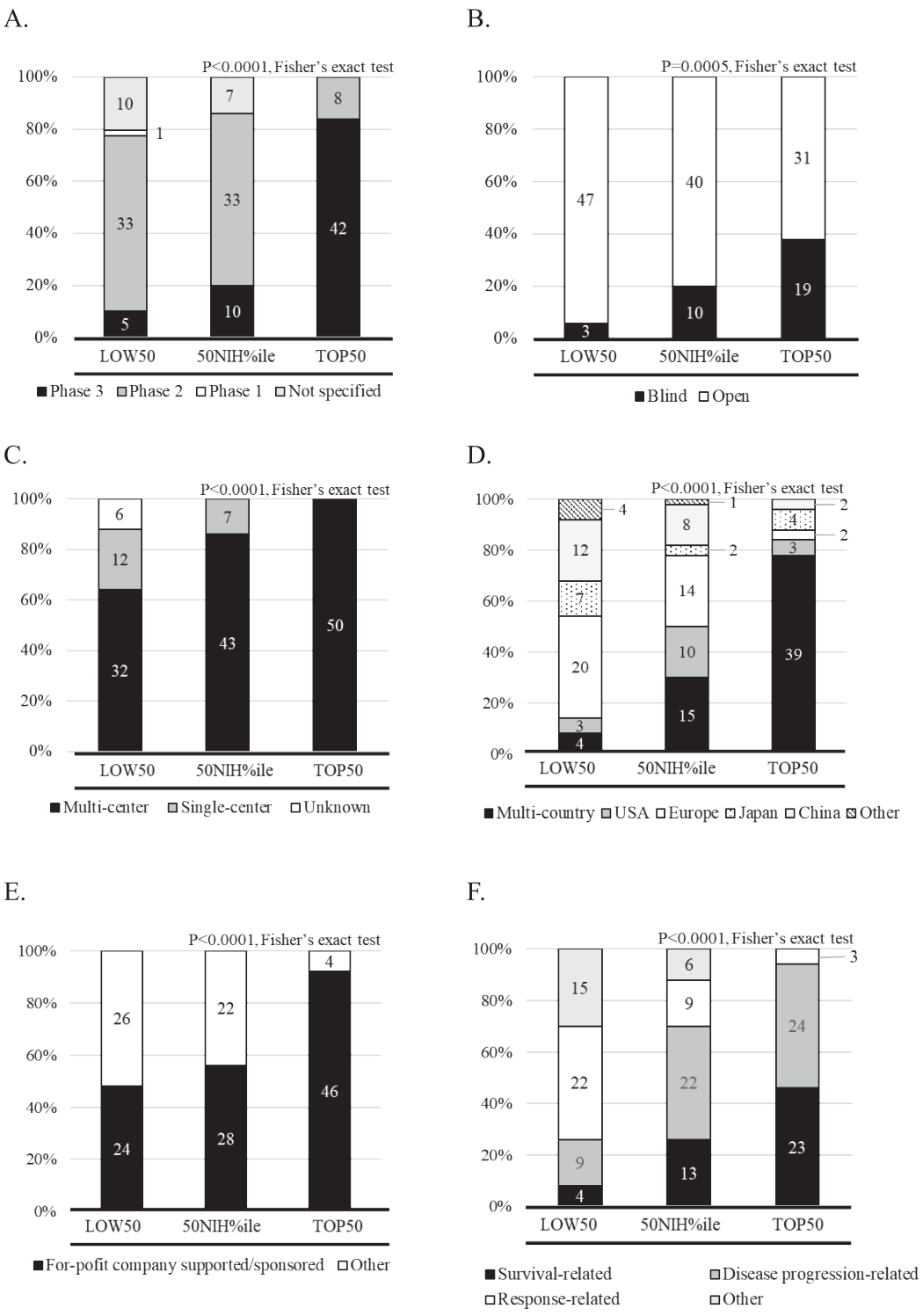

Fig 3 Clinical trial characteristics by the Relative Citation Ratio (RCR) category
A: Trial phase, B: Blinding status, C: Trial center, D: Trial country, E: Trial sponsorship/support, F: Primary endpoint.

and 50NIH%ile (28 trials, 56.0%), and then increased in TOP50 (46 trials, 92.0%). Regarding the primary endpoint (**Fig 3F**), important endpoints for NSCLC treatment, such as survival- and disease progression/recurrence-related endpoints, increased as RCR increased.

Figure 4 shows the subject number for each RCR category. The number of subjects increased as the RCR increased, with a difference of approximately 6-fold between LOW50 (median = 74.5

subjects) and TOP50 (median = 434 subjects).

Figure 5 shows the proportion of statistically powered trials and their study outcomes. The number of statistically powered trials increased as RCR increased. The number of positive trials increased from 50 NIH%ile (six trials, 21.4%) to TOP50 (33 trials, 67.3%), but 16 trials (32.7%) in TOP50 were negative.

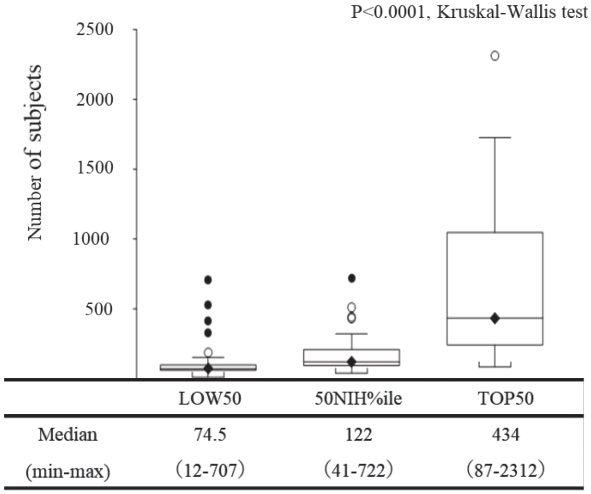

Fig 4 The number of subjects in each Relative Citation Ratio (RCR) category

Box-and-whisker plot: triangle: median, box: 25th–75th percentiles, whiskers: minimum-maximum excluding outliers, ○ outliers above the 75th percentile + 1.5 interquartile range, ● outliers above the 75th percentile + 3.0 interquartile range.

3. Types of intervention

The types of interventions in each RCR category are shown in **Table 1**. The most common intervention in LOW50 was chemotherapy-only (38 trials, 76.0%), and the number of chemotherapy-only trials decreased as the RCR increased from LOW50 to TOP50 (nine trials, 18.0%). The intervention of 39 trials (78.0%) in TOP50 included molecular target drugs for NSCLC, and the number decreased from TOP50 to LOW50 (six trials, 12.0%).

Discussion

It is known that RCTs provide stronger evidence compared to non-randomized trials due to their lower bias.[2,3] In this study, the results showed that the number of non-randomized trials excluded during the publication screening decreased as the RCR increased: LOW50, 190 publications; 50NIH%ile, 69 publications; and TOP50, 22 publications (**Fig 1**). Moreover, the median RCR of LOW50 improved from 0.03 in the previous research, which included both RCT and non-RCTs, to 0.14 in this research only with RCT.[13] These results support that RCTs tend to

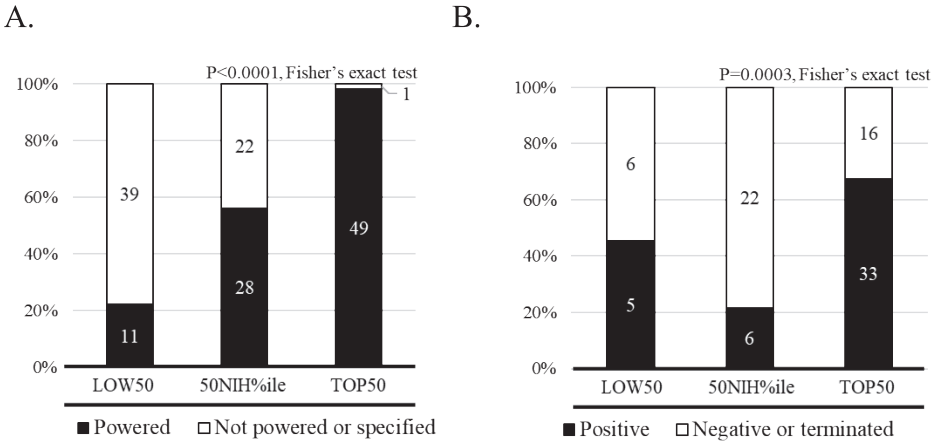

Fig 5 Statistical characteristics by the Relative Citation Ratio (RCR) category

A: Statistical power, B: Outcome of primary endpoint.

Table 1 The type of intervention(s) of the trial in each RCR category

Intervention	LOW50	50NIH%ile	TOP50
Chemotherapy-only	38	15	9
Molecular target drug included*	6	24	39
- EGFR-TKI	3	8	21
- Immune checkpoint inhibitor	0	0	7
- ALK inhibitor	0	0	2
- VEGF/VEGFR-mAb	3	4	3
- EGFR-mAb	0	1	3
- Other	0	14	7
Other	6	11	2

*If multiple type of molecular-target drugs were tested in a trial, each molecular-target drug was counted for each type.Abbreviations: ALK: anaplastic lymphoma kinase, EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor, LOW50: 50 publications with the lowest RCR, mAb: monoclonal antibody, RCR: Relative Citation Ratio, TOP50: 50 publications with the highest RCR, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor, 50NIH%ile: 25 publications just below and just above the median RCR (50 publications in total).

have higher scientific influence compared to non-RCTs because of their stronger evidence.

The present research showed that the proportion of each trial design factor changed as the RCR category changed. Especially, the proportion of Phase 3, multi-country, for-profit company sponsored/supported, and statistically powered RCTs increased more than 30% from 50NIH%ile to TOP50, the subject number increased approximately four-fold from 50NIH%ile to TOP50, and 94% of trials in TOP50 used important primary endpoints (*eg*, overall survival or progression free survival). These observations indicate that the outcome of confirmatory Phase 3 RCTs conducted globally by pharmaceutical companies tend to have higher scientific influence. In new oncology drug development, a Phase 3 trial normally becomes a large-sized trial due to the subject numbers required to confirm statistically pre-defined efficacy differences against standard treatment. Moreover, global collaboration is a key to expediting subject recruitment for early completion, test drugs in diverse populations, and facilitate new drug applications in as many countries/regions as possible.[24] Trial outcomes derived from confirmatory global trials represent the best evidence in many regions for choosing a better treatment option, and thus, the scientific influence of the trial outcome would increase. In addition, molecular target drug interventions increased as RCR increased opposed to chemotherapy-only interventions. Seventy-eight percent of interventions were molecular target drugs in the TOP50, and immune checkpoint inhibitors and ALK/ROS1 inhibitors were tested only in the TOP50. This indicates that newly developed and highly efficacious drugs can increase the scientific influence of the trial outcome.

There were 49 (98.0%) statistically powered trials in TOP 50. Of them, 16 trials did not meet the primary endpoint. This result suggests, from a statistical perspective, that a positive outcome is not always required to gain higher scientific influence. Rather, the statistical power to confirm a pre-defined difference will be equally important or more important to gain higher scientific influence. It is reported that the success rate of oncology RCTs was approximately 30%, and in 82% of negative

trials, the result was due to lack of efficacy.[25-27] Because a negative outcome is not equal to "no evidence," and in fact generates important insights for the next hypothesis, statistical measures that lead to conclusive outcomes will contribute to the progress of drug development and EBM, regardless of outcomes.

In contrast, most of the trials in LOW50 were non-Phase 3 (90.0%), single-country (92.0%), involved non-important endpoints (*eg*, response rate, safety, feasibility: 74.0%), and were not statistically powered for direct comparison between the interventions (78.0%). These RCTs were designed for exploratory purposes, such as to select better doses/regimens, estimate efficacy differences between the interventions for the next confirmatory trials, or just to compare interventions descriptively. While this type of study provides important information to proceed to later phase trials, or answers some clinical questions which physicians may have, they do not provide statistically conclusive results. Thus, the utility of the trial outcome is limited, and that would limit the scientific influence of the outcome.

Most published TOP50 trials were sponsored/supported by pharmaceutical companies, and some other trials were supported by the NIH or led by oncology cooperative trial groups. It has been reported that the proportion of global trials funded by industry is 10-fold higher than non-industry sponsored trials (30.3% and 3.2%, respectively), and the lack of funding is the most critical barrier for academic clinical cancer researchers to conduct clinical research.[28, 29] Funding support from for-profit companies or non-profit organizations will be important for academic researchers to conduct large-sized, confirmatory trials which will lead to highly influential outcomes.

Our research had several limitations. First, while several measures have been taken to enhance the publication of clinical trial results, not all clinical trials publish their results in journals and there is a risk of publication bias.[30, 31] This is an inevitable limitation of bibliometric analysis; however, it is expected that this bias will be smaller in future because advanced efforts to improve the clinical trial transparency including trial registry, result reporting and data sharing are ongoing globally (https://www.jpma.or.jp/basis/rinsyo/lofurc0000001vkc-att/policy18.pdf, December 13, 2021). Second, RCR is one of the citations based bibliometric index, and does not directly indicate the degree of contributions to the progression of EBM. However, RCR is a better available indicator to assess the influence of individual publications compared to JIF or citation numbers. The development of better article-based bibliometric indicator capable of evaluating usefulness of the research outcome and its contribution to the progress of EBM is expected. Third, it was not possible to assess the degree of contribution of each factor to the increase in RCR due to correlations among the study design factors. Rather than our comprehensive analysis, the research focused on more fragmented study design or disease area could reveal definitive factor which impact on the scientific influence of the outcome. Finally, our findings might not be directly applicable to other disease areas or interventions since we focused on drug intervention clinical trials in NSCLC patients to maintain consistency of baseline characteristics of the study design. The research by using our bibliometric approach would be valuable to identify the factors that impact on the scientific outcome of clinical trial in each disease area or intervention.

In conclusion, our research showed quantitatively that the clinical trial design would have ef-

fect on the scientific influence of the RCT outcome. The trial results of large-sized, multi-country, statistically powered confirmatory RCTs with novel interventions have higher scientific influence. Statistical power is an equally important or more important factor than a positive RCT outcome to gain high scientific influence of the outcome. Outcomes of small-sized, exploratory, chemotherapy-only, and single-country RCTs tend to have lower scientific influence. Besides new drug development by pharmaceutical company, use of clinical study collaborative groups capable of conducting multi-center/country studies, acquisition of research funding from the government, and investigator-initiated clinical trial by collaborating with pharmaceutical company are one of the solutions to conduct highly influential trial. Pharmaceutical companies can contribute to the conduct of highly influential trials by developing novel compounds and supporting researchers with funding.

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Conflict of Interests

None of the authors have any conflicts of interest that are directly relevant to this research. Yutaka Noguchi is an employee of Daiichi Sankyo Co., Ltd.

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