Transfer of Statistical Innovations of the 1990s-2000s in Oncology to the Biomedical Literature

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Abbreviations: CRM, Continual Reassessment Method.

ABSTRACT

Introduction Innovations in the fields of clinical studies require time to generate and disseminate new knowledge. We aimed to specifically explore lag times between the introduction and widespread use of innovative statistical methods in oncology using the competing risks and phase I model-based clinical trials settings as examples.

Methods First, we defined a set of closed articles for each setting based on two princeps papers (Gray, Annals of Statistics 1998 for the competing risks setting and O'Quigley et al., Biometrics 1990 for the phase I setting). Secondly, we retrieved from the web of science all citations of the papers included in these sets. Each journal was classified as applied, semi-applied or methodological.

Results A total of 6,727 citations for the competing risks setting and 2,639 citations for the phase I setting were found. Time to reach 25 citations was 6.2 years for the Gray's paper and 4.5 years for the Fine and Gray paper, while it ranged from 3.4 years up to at least 20.1 years and not reached for 6 papers from the competing risks setting. The vast majority (91%) of the citing papers for the competing risks setting originated from applied journals. In contrast, less than half (44%) of the citing papers for the phase I setting were published in applied journals.

Conclusion Statistical innovations in the competing risks setting have been widely diffused in the medical literature unlike the model-based designs for phase I trials, which are still seldom used 30 years after publication.

Introduction

Translational medicine, aiming to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary and collaborative approach, has grown interests in the last decade. Moreover, the commonly accepted delay of 17 years for research evidence to reach clinical practice recently appears to decrease [1] as exemplified by the mapping networks of publications and cross-references. [2] However, most translation gaps between knowledge and clinical application that have been investigated, notably in oncology, concerned translation of biological drivers into therapeutic benefits for patients. [3]

For the advancement of clinical research and eventually of patient care, the translation of innovative statistical methods into practice is also of crucial importance, though the average time elapsed for biostatical innovation to reach medical use is less known. In 1994, Altman showed that, while the key survival paper of Kaplan and Meier achieved only six citations in medical journals in the first 10 years after publication, evidence of decreasing lag times between the introduction and widespread use of innovative statistical methods was expected. [4] More than 2 decades later, we wondered whether the reported above decreasing dichotomy between basic or preclinical and clinical research [2] could be also true in the transfer of innovative statistical methods, confirming the Altman's hypothesis. [4]

We first focused on competing risks methods, the key innovative survival methods of the last decades, [5] common in cancer. Indeed, competing risks exist whenever the probability of the main event (e.g., cancer) is prevented (e.g., by death) or altered (e.g., by transplantation) to occur. In this setting, standard survival methods that ignore the informative censoring of these competing events may result in biased effects of prognostic factors or treatments, [6] illustrating the need for bridging the gap of innovation into practice. Two innovative papers that first proposed a statistical test [7] and a regression model [8] for such data, were selected as the first innovative set.

With the aim of focusing on statistical innovations of potential large expected therapeutic benefits for patients, we secondly considered the setting of phase I clinical trials, which is also of great interest in the oncology area though with a limited diffusion as compared to phase III. [9] We chose as the most influential statistical pioneering approach, the continual reassessment method (CRM) that is, a model-based approach for dose-finding studies where only empiric 3+3 designs (formerly Fibonacci) were long available. We thus included in the second innovative set the original paper of the CRM [10] together with its close proposed modifications (Table 2).

The primary objective of this paper was to assess whether Altman's prediction was fulfilled in the field of oncology using the competing risks and the phase I clinical trials as examples. Secondary objectives were to study the relative importance of the applied and statistical literature in papers citing statistical innovations and to analyze which medical areas the methods are mainly used.

Methods

Selection of articles

Based on our knowledge, we *a priori* included the paper by Gray[7] and that by Fine and Gray [8] in the innovative set for the competing risks setting. For the phase I setting, beside the paper by O'Quigley, [10] because numerous modifications of the initial CRM very similar to the initial paper were published, we jointly considered the set of those articles. Thus, we retrieved all papers citing O'Quigley's paper [10] in the Web of Science on May 9, 2018. We then constructed a co-citations network, where co-citations were defined as links between two papers, both of which cited by the same paper. The relatedness of papers was based on the number of times they have been cited together. This process was used to create the innovative set for the phase I trials setting.

Citation data

For both settings, we retrieved all citations of the innovative set from the Web of Science on July, 23 2018. Citation data were imported into R software (https://www.R-project.org/) using the Bibliometrix package. [12] The information retrieved included the title, abstract, date of publication, journal name and category according to the classification by Incites Journal Citation (https://jcr.incites.thomsonreuters.com). We excluded animal studies by searching animal names (cat, dog, mice, mouse, rat, monkey, primate, macaque) in the title. Each citation article was also segregated to one of the three following categories according to the journal of publication: 1) applied journals, 2) semi-applied journals, and 3) methodological journals (Table 3). For citations of the phase I setting, one investigator (AV) manually reviewed the papers with "phase I" in title to check if they were actual dose-finding phase I clinical trials.

Statistical analysis

Analysis was performed for each setting, separately. Summary statistics were reported, either mean (standard deviation) or median [interquartile range]. We plotted the cumulative number and proportions of "applied", "semi-applied", and "methodological" fractions of citations [5] over time as a percentage of the citations classified in the three categories of journals defined above. We defined translational gap as the time between the publication of the biostatistical paper and the time it reached 25 citations in applied literature, as defined by Altman; [4] estimated cumulative incidence of translational gap was estimated by the Kaplan Meier approach, due to the administrative censoring of the data on 2018.

To obtain further insight into the medical literature citing these innovative statistical tools, we constructed a citation network using the journal as the statistical unit (rather than the paper). Use of this network, together with clustering techniques, allowed us to analyze which medical areas

(using the journal as a proxy) cited the most statistical innovations. VosViewer was used to create maps and clustering analysis. [14]

Ethical Statement

All methods were carried out in accordance with relevant guidelines and regulations. No informed consent or ethics approval was necessary because this study is based on publicly available data and involved no individual patient data collection or analysis.

Results

The innovative sets of papers used for both settings are reported in Table 2. They included 2 articles for the competing risks set, and 28 for the phase I set.

Competing risks set

A total of 6,727 citations (5,863 unique articles), including 2,431 for Gray's article and 4,296 for the Fine and Gray paper, were found (Table 1). Time to translational gap was 6.2 years for the Gray's paper and 4.5 years for the Fine and Gray paper. The vast majority (91%) of the citations originated from applied journals, with a sharp and continuous increase in citations over time (Figure 1); in contrast, the citations from methodological and semi-applied journals represented only small percentages (6% and 2%, respectively) of the citing papers over the entire period. This was confirmed by the representation of the network of these journals (Figure 2).

Beside a methodological cluster, two major clusters confirmed the two main areas of application of competing risks, namely oncology (e.g., Journal of Clinical Oncology, European Journal of Cancer and Hematology) and hematology (e.g., Blood, Haematologica, and Bone Marrow Transplantation). Other clusters represent other areas of application, such as cardiovascular diseases.

Phase I clinical trials set

After excluding books and animal studies, a total of 2,639 citations (1,114 unique papers after removing duplicates) for the phase I innovative set were found. The three most cited papers were published by O'Quigley in 1999 (676 citations), Goodman in 1995 (258 citations) and Babb in 1998 (235 citations). Contrarily to the competing risks setting, the translational gap differed across papers, from 3.4 years up to at least 20.1 years since not reached for 6 papers. Overall, it was reached by 10.7% of the set articles at year-5 and by 47.9% at year-10. Less than one half (44%) of citing articles were published in applied journals, more than one third (36%) in statistics journals, and a fifth (20%) in semi-applied journals, with roughly similar rate of citations over time (Figure 1). When we restricted the citations to those articles with "phase I" in the title, only 415 (37%) articles were selected; of these, only 110 were found to be phase I clinical trials after manual reviewing the titles.

Network of the journals of papers citing one of the phase I set is displayed in Figure 2. The right part of the graph represents the methodological cluster containing, for example, Statistics in Medicine and Biometrics. The left part of the graph represents the large group concerning applications or reviews of the CRM in the most important clinical cancer journals (Journal of Clinical Oncology, Clinical Cancer Research, Annals of Oncology, British Journal of Cancer, and Journal of National Cancer Institute); in contrast, non-cancer journals had published only a few studies.

Discussion

This study aimed to check whether the time lags in the statistical translation process was actually shortened, focusing on two areas with a large potential for clinical research improvements and widely encountered in the oncology literature, namely, the survival methods for competing risks

data and the new designs for phase I clinical trials. The answer was bifid, with a short translational gap, defined by the time to reach 25 citations, [4] of about 5 years for the former, but delayed above 10 years for one half of the later. This could be expected given the two statistical innovative sets are used at different stages of clinical studies, with different levels of complexity. Indeed, the first set of competing risks articles deals with method of data analysis, that can easily be performed using modern statistical software without the need for major expertise - although whether such studies are used, performed and interpreted correctly can be another matter. [15] Therefore, such a lag time of about 5 years for using an innovative data analytic method is in agreement with the time to publication after completion of data collection and analysis recently estimated at about 3 years in six journals with high impact factors. [16] In contrast, the second set of innovative methods concern a change in trial design and logistics; thus, beside the time of analysis and publication, the transfer of innovative clinical trial design into the medical literature is obviously impacted by the additional constraints of patient enrollment time, and the follow-up period for the end point. It moreover requires statisticians to engage since the planning phase, [17] up to the analysis of the data, contrary to traditional methods such as the '3+3' design, which can be used without involving statisticians and computer programs and remains the most common choice among clinicians for phase I dose-escalation oncology trials. [18]

Moreover, difference in complexity of both settings was illustrated in terms of citation patterns. Although the competing risks methodology was widely diffused over the medical (in particular, oncology) community, methodology relating to innovative designs for cancer Phase I trials failed to translate easily into practice, consistent with the results of a previous study that showed a very slow transfer of phase I design improvements into clinical practice. [19]

Nevertheless, the two settings share large implications for clinical research, and researchers trying to apply the statistical innovative methods should not be delayed in using the new

knowledge. This is notably true in the setting of phase I trials in oncology, where improved selection of patients due to improvements in translational medicine should translate into faster and more precise dose determination. [20] Diffusing more widely into the applied literature and the medical community could be achieved in several ways. First, communication between biostatisticians and clinical colleagues should be improved, although many reviews have been published on these methods in the medical literature, as illustrated by the non-negligible fraction of semi-applied and applied papers that are different from the original clinical trials used in our study. This could be driven through key gateway journals, as suggested by the clusters of citation journals where Journal of Clinical Oncology and Statistics in Medicine appear major players (Figure 2). Concerning competing risks analysis, for which adequate modern methods have been integrated into all modern statistical software, a key step may be to educate clinicians to recognize the settings in which competing risks are of concern and to persuade them of the importance of using those methods. For the design of phase I studies, improvements in providing concrete guidance for designing such trials and facilitating their implementation in practice is still mandatory for bridging the gap between statistical innovation and practical implementation. Model-based designs are cited in the US FDA guidance for industries that are related to adaptive clinical trials as “less understood models,” and the FDA highlights some of their disadvantages. [21]

Our study has some limitations. First, we used citations as a measure of the transfer of knowledge between researchers and physicians. Such citation counts, although not a direct measure of the intrinsic significance of a research idea, provide a measure of statistical technology transfer and of its impact. [4] However, in addition to papers that focus on ranking journals and impact factors [22] many others have considered the citations only qualitatively. [23] Second, we segregated articles into three categories of applied, semi-applied and methodological journals, as previously reported. [5] However, this distinction is somewhat simplistic because the applied

fractions of articles published in statistical journals may increase over time; this is reportedly highest for statistical medicine. [5] Third, we focused on two main and distinct topics of biostatistics, and the results might differ for other statistical innovations, such as dynamic prediction modelling, the joint modelling of longitudinal data, and multiple imputation techniques for handling missing data.

Conclusion

In summary, statistical innovations for the competing risks setting have been widely diffused in the medical literature, especially in oncology and hematology, fulfilling Altman's prediction about decreasing lag times, unlike the model-based designs for phase I trials, which are still seldom used 30 years after their first publication. However, for both statistical methods, a translational gap remains that needs to be filled before the oncology community can benefit fully from these modern methods.

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Authors' contributions: SC had the original idea. SC and AV designed the study. AV conducted the literature search, extracted and analyzed data. AV, VL, and SC participated in the interpretation of the data. AV drafted the manuscript. AV, VL, and SC authors reviewed the manuscript and approved the final version.

Availability of data and material: Data used in this study are publicly available data. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1: Number of citations retrieved from Web of Science on July 23, 2018

Setting	*Competing Risks*	*Phase I trials*
No. of articles in the innovative set [a]	2	28
Number of citations		
Mean per year	232	97
Per article: median [IQR]	3,364 [2,897-3,830]	41.5 [28-115.75]
Total	6,727	2,639
Type of journals, [b] *n (%)*		
Applied	6,098 (91)	852 (32)
Semi-Applied	158 (2)	544 (21)
Methodological	471 (7)	1,243 (47)
Time to bridge translation gap		
Cumulative incidence at 5 years	50%	10.7%
Cumulative incidence at 10 years	100%	47.9%
No. of unique citing articles	**5,863**	**1,114**
Type of journals, [a] *n (%)*		
Applied	5,369 (92)	493 (44)
Semi-Applied	134 (2)	218 (20)
Methodological	360 (6)	403 (36)
Mean number of citations per year	232	36

a. The list of journals of each innovative set is presented in Table 2

b. The list of journals of each category is presented in Table 3.

Table 2. List of selected articles for each innovative set.

First Author	Journal	Pub. Year	No. of citations	Time to 25 citations (years)
Competing Risks Setting				
Fine	Journal of The American Statistical Association	1999	4,296	4.5
Gray	The Annals of Statistics	1988	2,431	6.2
Phase I setting				
O'Quigley	Biometrics	1990	676	5.7
Goodman	Statistics In Medicine	1995	258	5.0
Babb J	Statistics In Medicine	1998	235	5.3
Cheung	Biometrics	2000	181	3.4
O'Quigley	Biometrics	1996	170	7.1
Korn	Statistics In Medicine	1994	144	5.5
Ratain	Journal of The National Cancer Institute	1993	136	4.6
Braun	Controlled Clinical Trials	2002	109	5.6
Moller	Statistics In Medicine	1995	85	8.8
Piantadosi	Cancer Chemotherapy And Pharmacology	1998	84	10.4
Chevret	Statistics In Medicine	1993	68	10.3
Whitehead	Journal of Biopharmaceutical Statistics	1998	58	9.8
Mick	Journal of The National Cancer Institute	1993	46	8.4
Tighiouart	Statistics In Medicine	2005	42	9.5
O'Quigley	Biometrics	1992	41	9.5
Reiner	Computational Statistics & Data Analysis	1999	38	13.2
Ishizuka	Statistics In Medicine	2001	37	10.9
O'Quigley	Biostatistics	2002	36	11.8
O'Quigley	Biometrics	2003	35	11.8
O'Quigley	Journal of Biopharmaceutical Statistics	1999	32	16.6
Babb	Statistics In Medicine	2001	29	15.6
Zacks	Statistics & Probability Letters	1998	25	20.1
Rogatko	Clinical Cancer Research	2005	19	Not reached
O'Quigley	Journal of Statistical Planning And Inference	2006	17	Not reached
Doussau	Statistics In Medicine	2013	14	Not reached
Legedza	Controlled Clinical Trials	2000	10	Not reached
Shu	Statistics In Medicine	2008	7	Not reached
Mahmood	Journal of Clinical Pharmacology	2001	7	Not reached

Table 3. List of selected journals for each class.

Applied	Semi-Applied	Methodological
All other journals	1. Trials	1. Stat Med
	2. Contemp Clin Trials	2. Stat Pap
	3. Clin Trials	3. Stat Methods Med Res
	4. Int J Clin Pharm Th	4. J Biopharm Stat
	5. Expert Rev Clin Phar	5. Stat Interface
	6. Invest New Drug	6. Pharm Stat
	7. Neurotherapeutics	7. Biostatistics
	8. Ther Innov Regul Sci	8. Comput Meth Prog Bio
	9. Cancer Chemoth Pharm	9. Commun Stat Appl Met
	10. Expert Opin Drug Met	10. J Am Stat Assoc
	11. Fund Clin Pharmacol	11. Biometrical J
	12. Clin Pharmacol Ther	12. Ann Appl Stat
	13. Control Clin Trials	13. Biometrics
	14. Phytother Res	14. J Stat Softw
	15. Cancer Drug Design And Discovery	15. Comput Stat Data An
	16. Drug Inf J	16. Appl Bioinf Biostat
	17. Pharm Med	17. Adaptive And Flexible Clinical Trials
	18. J Food Drug Anal	18. J Appl Stat
	19. Toxicon	19. Stat Sci
	20. Bmc Med Res Methodol	20. Fundamentals Of Clinical Trials, Fourth Edition
	21. Oncology Clinical Trials	21. Stat Biopharm Res
	22. Brit J Clin Pharmaco	22. J Roy Stat Soc C-App
	23. Expert Opin Drug Dis	23. Handb Stat
	24. Pers Med	24. Wiley Ser Probab St
	25. Drug Discovery And Development - Present And Future	25. J Stat Plan Infer
		26. Biometrika
	26. Cancer Drug Discov D	27. Stat Model
	27. J Pharmacokinet Phar	28. Sequential Anal
	28. Clin Pharmacokinet	29. Stat Sinica
	29. Aaps J	30. J R Stat Soc B
	30. Icsa Book Ser Stat	31. J R Stat Soc C-Appl
	31. Drug Discovery And Development - From Molecules To Medicine	32. Stat Biosci
		33. Environmetrics
		34. Aust Nz J Stat
	32. Re-Engineering Clinical Trials: Best Practices For Streamlining Drug Development	35. Commun Stat-Theor M
		36. Contr Stat
		37. J Chem Inf Model
		38. Stat Pract
	33. Aliment Pharm Ther	39. Commun Stat-Simul C
	34. Pharm Res-Dordr	40. Ch Crc Biostat Ser
	35. Essential Cns Drug Development	41. Stat Biol Health
		42. Can J Stat
	36. Am J Epidemiol	43. J Stat Comput Sim
	37. Therapie	44. Bayesian Anal
	38. Drug Develop Res	45. J Off Stat
	39. Anticancer Therapeutics	46. Stat Probabil Lett
	40. Anti-Cancer Drug	47. Stata J
	41. E Schering Res Fdn W	48. Cr Math
	42. J Clin Pharmacol	49. Springer P Math Stat
	43. J Clin Pharm Ther	50. J Multivariate Anal

44. Drug Discov Today
45. Fundam Clin Pharm
46. Am J Ther
47. Indian J Pharmacol
48. Biopharm Drug Dispos
49. Curr Opin Drug Disc
50. Curr Drug Metab
51. Eur Neuropsychopharm
52. Curr Pharm Design
53. Trends Pharmacol Sci
54. Ther Drug Monit
55. Evaluation Of Biomarkers And Surrogate Endpoints In Chronic Disease
56. Antimicrob Agents Ch
57. Eur J Clin Pharmacol
58. Int J Neuropsychoph
59. Am J Health-Syst Ph
60. Pharmacogenomics J
61. Health Technol Asses
62. J Clin Lipidol
63. J Clin Epidemiol
64. Eur J Epidemiol
65. Pharmacoepidem Dr S
66. J Chemotherapy
67. Pharmacotherapy
68. Soc Sci Med
69. Prog Neuro-Psychoph
70. Value Health
71. Drug Aging
72. Qual Life Res
73. Antivir Ther
74. Rev Saude Publ
75. Toxicol Appl Pharm
76. J Infect Chemother
77. Int J Clin Pract
78. Drug Safety
79. J Epidemiol
80. Bmc Health Serv Res
81. J Antimicrob Chemoth
82. Hiv Clin Trials
83. Pharmacogenomics
84. Rev Epidemiol Sante
51. Stat Ind Technol
52. J Roy Stat Soc A Sta
53. Applied Optimal Designs
54. Med Decis Making
55. Int Stat Rev
56. J Theor Biol
57. Ann I Stat Math
58. Lifetime Data Anal
59. Stat Neerl
60. Pak J Stat Oper Res
61. Bshm Bull
62. Ieee Access
63. R J
64. Comput Biol Med
65. Jmir Med Inf
66. Oxford B Econ Stat
67. Korean J Appl Stat
68. Statistics-Abingdon
69. Internet Res
70. Scand J Stat
71. Expert Syst Appl
72. Jmir Mhealth Uhealth
73. J Eval Clin Pract
74. Ch Crc Handb Mod Sta
75. Annu Rev Stat Appl
76. Electron J Stat
77. Comput-Aided Civ Inf
78. Revstat-Stat J
79. J Biomed Inform
80. Genet Epidemiol
81. Comput Oper Res
82. Theor Biol Med Model
83. Stat Method Appl-Ger
84. Computation Stat
85. J Nonparametr Stat
86. Am Stat
87. J Roy Stat Soc B
88. Bioinformatics
89. Front Artif Intel Ap
90. Int J Biostat
91. Proc Wrld Acad Sci E
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96. 2015 2nd International Conference On Information Science And Security (Iciss)

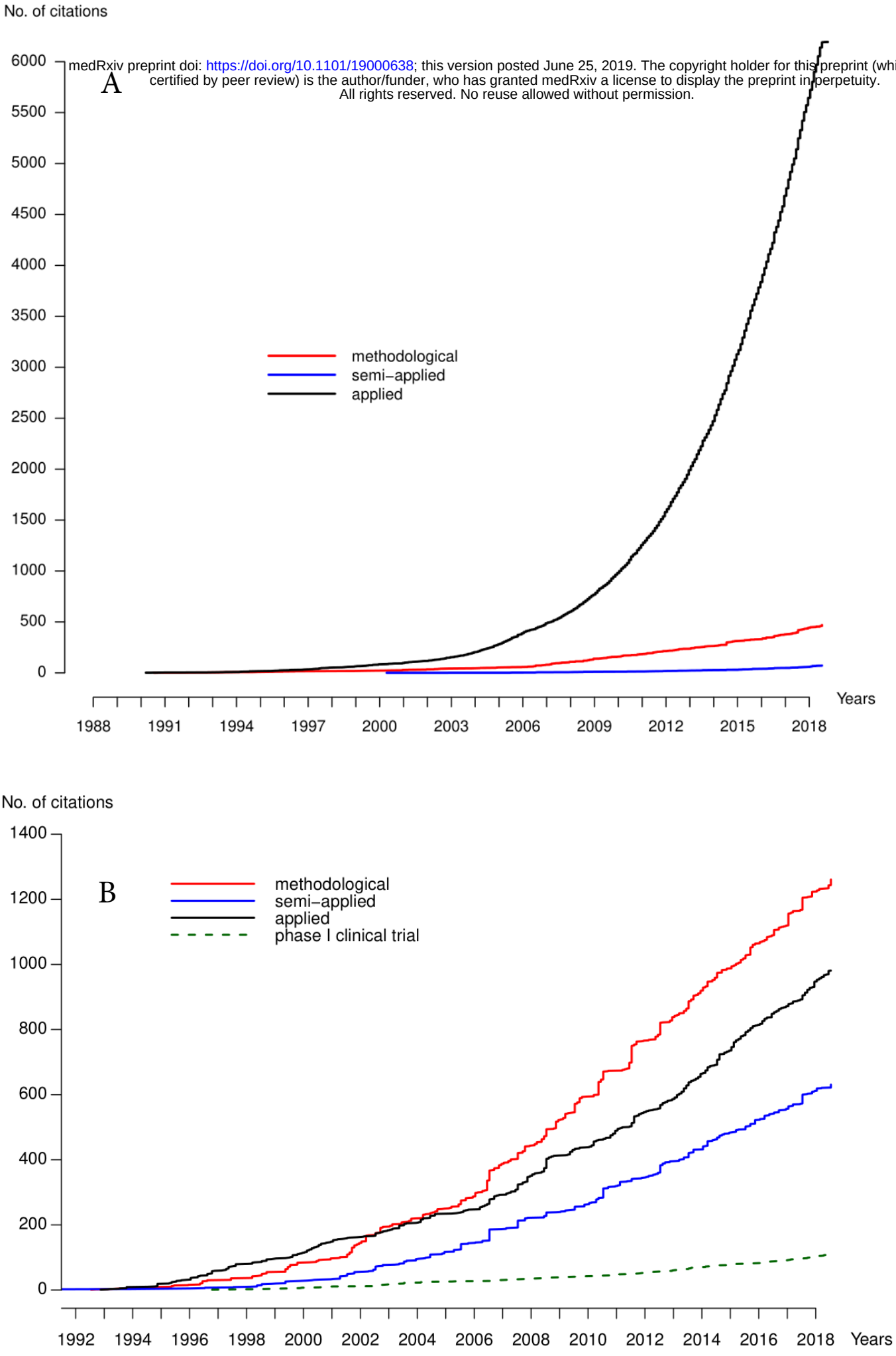
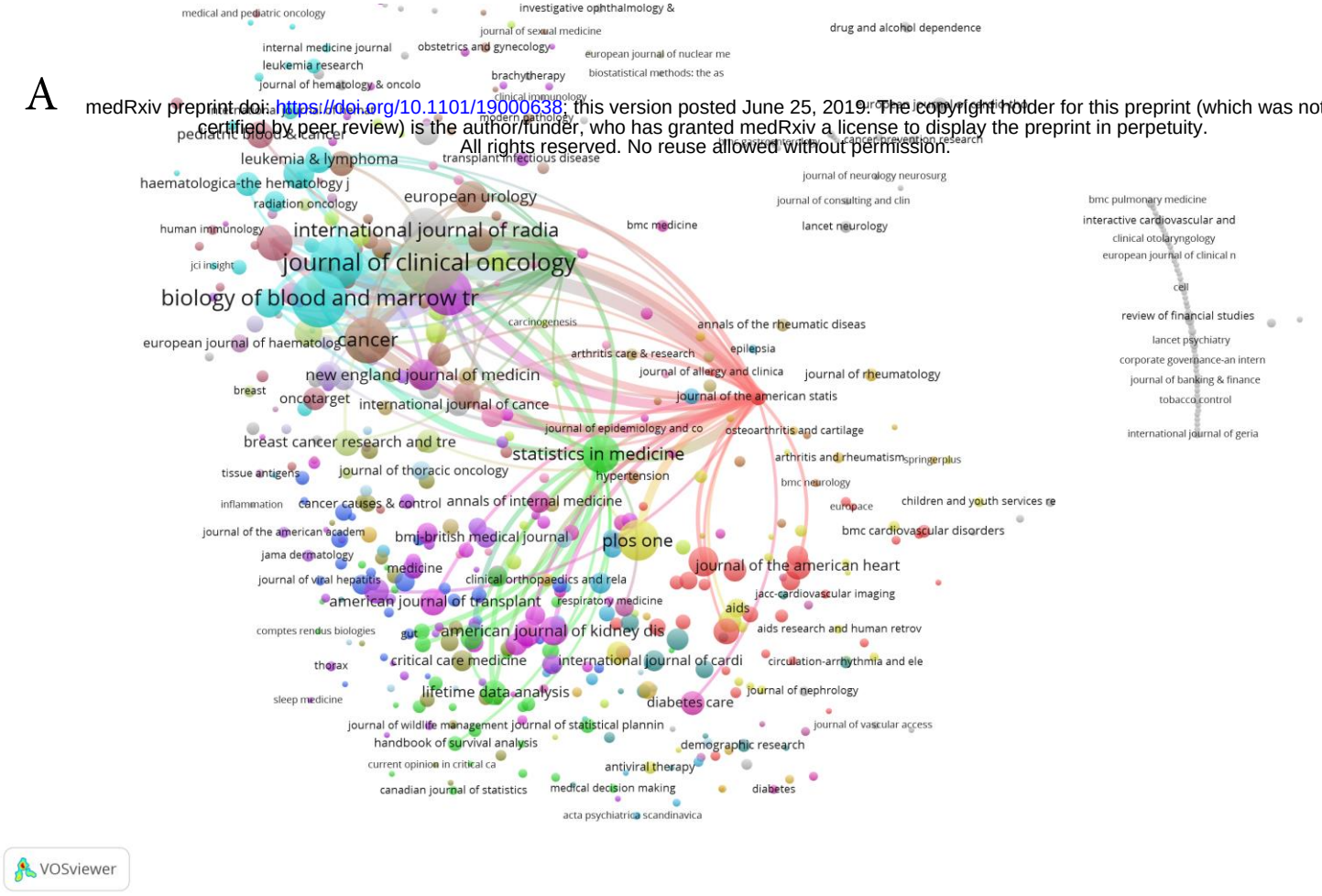


Figure 1. Cumulative number of citations for the competing risks setting (Panel A) and the phase I trials setting (Panel B) retrieved from the Web of Science and classified in each category of journals.

A



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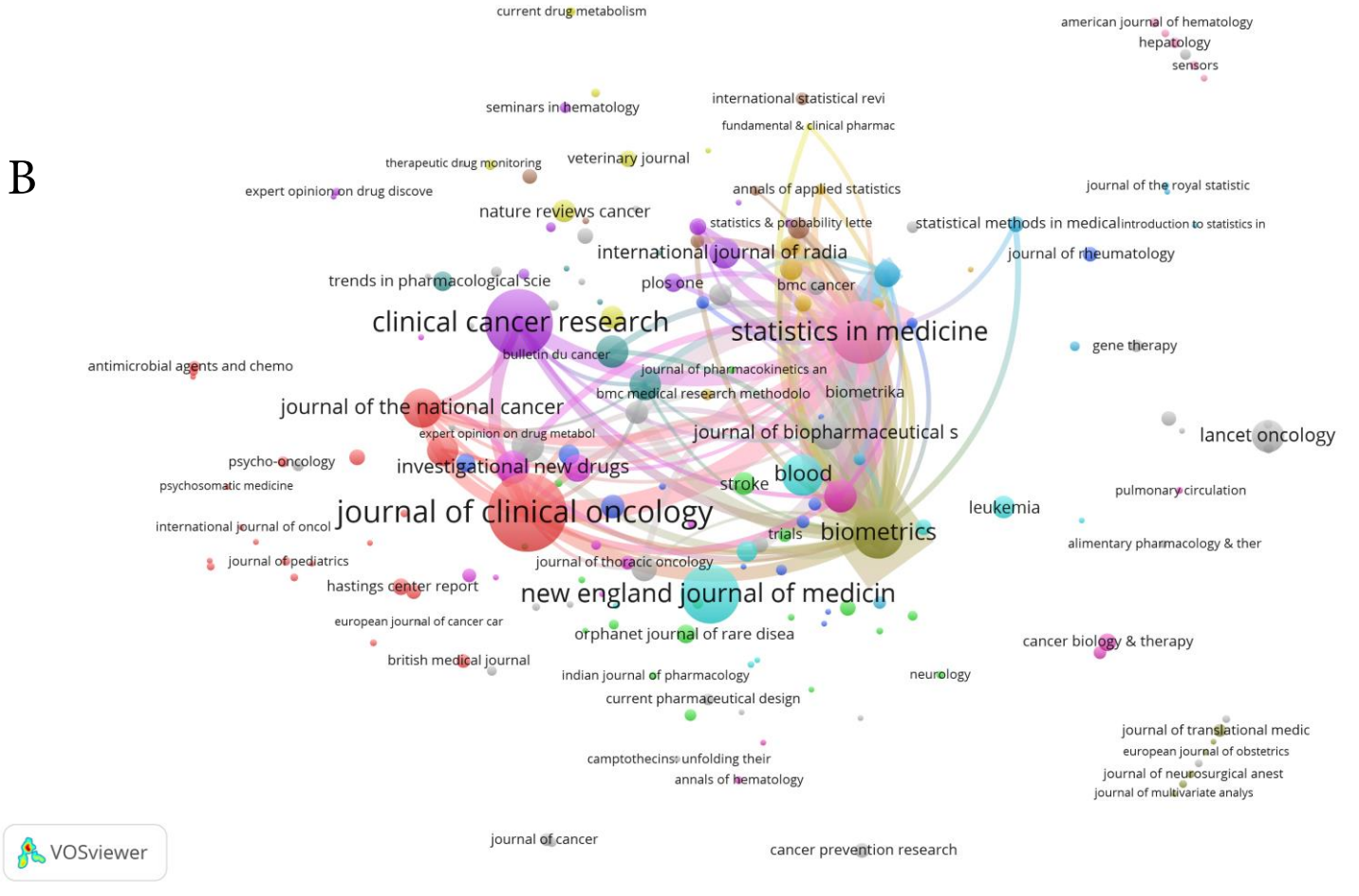

Figure 2. Citation network of journals for the two innovative sets (Competing risks- Fig 2A, Phase I trials- Fig 2B). For clarity, only journals with at least 5 citations are represented.