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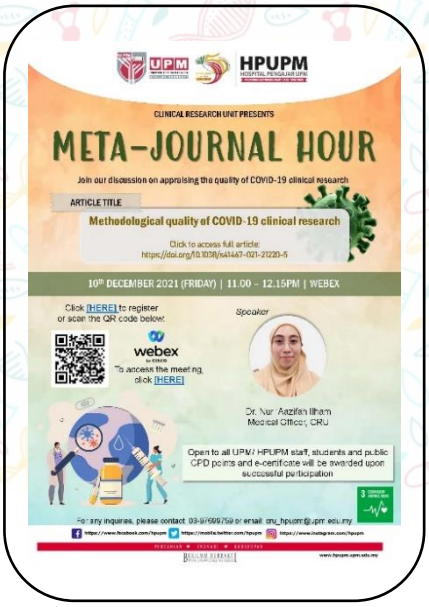
Appraisals in Meta-journal Hour 4

By Aazifah Ilham, Nurul Iman Hafizah and BH Chew

The paper:

Methodological quality of COVID-19 clinical research. doi: 10.1038/s41467-021-21220-5.



Why was this study conducted?

The COVID-19 pandemic began in early 2020 with major health consequences and substantial impact on economy as well. Due to the pandemic, there was an exponential increase in scientific publications related to COVID-19 in order to rapidly elucidate the natural history and identify diagnostic and therapeutic tools related to the disease [1]. The scientific rigor in the published reports is of paramount concern due to increased needs to rapidly disseminate information to the medical community, government agencies and general public.

Therefore, a systematic review was conducted to:

1. Evaluate the methodological quality of COVID-19 using established tools and checklist.
2. Evaluate the methodological quality of COVID-19 study by stratification of median time to acceptance, geographical regions as well as impact factors.
3. Compare methodological quality of research on COVID-19 to match control (historical control).

How was it done?

The systematic review was conducted on May 14, 2020 and was registered with PROSPERO and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The search was created in MEDLINE by a medical librarian with expertise in systematic review using a combination of key items. The search was conducted in the MEDLINE, EMBASE and Cochrane Centre Register of Controlled Trial with the search were limited to English only publications.

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Study selection

All types of COVID-19 clinical studies, including case series, observational studies, diagnostic studies and RCTs were included. Studies that were exploratory or pre-clinical in nature (i.e. in vitro or animal studies), case reports or case series of <5 patients, studies published in a language other than English, reviews, methods or protocols, and other coronavirus variants such as the Middle East respiratory syndrome were excluded from the study selection.

Data extraction

First and corresponding authors' names, date of publication, title of manuscript and journal of publication were collected for all included full-text articles. Journal impact factor was obtained from the 2018 InCites Journal Citation Reports from Clarivate Analytics. Submission and acceptance dates were collected in manuscripts where available. Other information collected include study types, prospective or retrospective study designs, sex reporting, sample size calculation, method of SARS-CoV-2 diagnosis and ethics approval. Methodological quality assessment was conducted using the Newcastle–Ottawa Scale (NOS) for case–control and cohort studies [2], QUADAS-2 tool for diagnostic studies [3], Cochrane risk of bias for RCTs [4] and a score derived by Murad et al. for case series studies [5].

Identification of historical control from identified COVID-19 articles

Following the completion of extraction of COVID-19 articles, a historical control group was obtained by identifying reports matched in a 1:1 fashion. From the eligible COVID-19 article, historical controls were identified by searching the same journal in a systematic fashion by matching the same study designs ("case series", "cohort", "case control" or "diagnostic") in the same journals 12 months prior to the COVID-19 articles publication on the publisher website (i.e. COVID-19 article published on April 2020, going backwards to April 2019) and proceeding forward (or backward if a specific article type was not identified) in a temporal fashion until the first matched study was identified following abstract screening by two independent reviewers. If no comparison article was found by either reviewer, the corresponding COVID-19 article was also excluded from the comparison analysis.

Data synthesis and statistical analysis
Continuous variables were reported as mean (SD) or median (IQR) as appropriate, and categorical variables were reported as proportions (%). Continuous variables were compared using Student t-test or Mann–Whitney U-test and categorical variables including quality scores were compared by $\chi 2$, Fisher's exact test, or Kruskal–Wallis test.

What was the finding?

Article selection
A total of 14787 COVID-19 papers were identified as of May 14, 2020 and 4892 duplicate articles were removed. In total, 9895 titles and abstracts were screened, and 9101 articles were excluded due to the study being pre-clinical in nature, case report, case series <5 patients, in a language other than English, reviews (including systematic reviews), study protocols or methods, and other coronavirus variants with an overall inter-rater study inclusion agreement of 96.7% ($\kappa = 0.81$; 95% CI, 0.79–0.83). A total number of 794 full texts were reviewed for eligibility. Over 108 articles were excluded for ineligible study design or publication type (such as letter to the editors, editorials, case reports or case series <5 patients), wrong patient population, non-English language, duplicate articles, wrong outcomes and publication in a non-peer-reviewed journal. Ultimately, 686 articles were identified and included with an inter-rater agreement of 86.5% ($\kappa = 0.68$; 95% CI, 0.67–0.70).

COVID-19 literature methodological quality
Most studies originated from Asia/Oceania with 469 (68.4%) studies followed by Europe with 139 (20.3%) studies, and the Americas with 78 (11.4%) studies. Of included studies, 380 (55.4%) were case series, 199 (29.0%) were cohort, 63 (9.2%) were diagnostic, 38 (5.5%) were case–control, and 6 (0.9%) were RCTs. Most studies (590, 86.0%) were retrospective in nature, 620 (90.4%) reported the sex of patients, and 7 (2.3%) studies excluding case series calculated their sample size a priori. The method of SARS-CoV-2 diagnosis was reported in 558 studies (81.3%) and ethics approval was obtained in 556 studies (81.0%). Finally, journal impact factor of COVID-19 manuscripts was 4.7 (IQR, 2.9–7.6) with a time to acceptance of 13.0 (IQR, 5.0–25.0) days.

Overall, when COVID-19 articles were stratified by study design, a mean (SD) case series score (out of 5) was 3.3 (1.1), mean NOS cohort study score (out of 8) was 5.8 (1.5), mean NOS case–control study score (out of 8) was 5.5 (1.9), and low bias present in 4 (6.4%) diagnostic studies. Furthermore, in the 6 RCTs in the COVID-19 literature, there was a high risk of bias with little consideration for sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

For secondary outcomes, rapid time from submission to acceptance (stratified by median time of acceptance of <13.0 days) was associated with lower methodological quality scores for case series and cohort study designs but not for case–control nor diagnostic studies. Low journal impact factor (<10) was associated with lower methodological quality scores for case series, cohort, and case–control designs. Finally, studies originating from different geographical regions had no differences in methodological quality scores with the exception of cohort studies. When dichotomized by high vs. low methodological quality scores, a similar trend was observed with rapid time from submission to acceptance (34.4% vs. 46.3%, $p = 0.01$, low impact factor journals (<10) were associated with lower methodological quality score (38.8% vs. 68.0%, $p < 0.0001$). Finally, studies originating in either Americas or Asia/Oceania was associated with higher methodological quality scores than Europe.

Methodological quality score differences in COVID-19 versus historical control
539 historical control articles were matched to 539 COVID-19 articles from the same journal with identical study designs in the previous year for a final analysis of 1078 articles. Overall, 554 (51.4%) case series, 348 (32.3%) cohort, 64 (5.9%) case–control, 106 (9.8%) diagnostic and 6 (0.6%) RCTs were identified from the 1078 total articles. Differences exist between COVID-19 and historical control articles in geographical region of publication, retrospective study design, and sample size calculation. Time of acceptance was 13.0 (IQR, 5.0–25.0) days in COVID-19 articles vs. 110.0 (IQR, 71.0–156.0) days in control articles ($p < 0.0001$). Case-series methodological quality score was lower in COVID-19 articles compared to the historical control (3.3 (1.1) vs. 4.3 (0.8); $n = 554$; $p < 0.0001$). Furthermore, NOS score was lower in COVID-19 cohort studies (5.8 (1.6) vs. 7.1 (1.0); $n = 348$; $p < 0.0001$) and case–control studies (5.4 (1.9) vs. 6.6 (1.0); $n = 64$; $p = 0.003$;). Contrastingly, lower risk of bias in diagnostic studies was noted in 12 COVID-19 articles (23%; $n = 53$) compared to 24 control articles (45%; $n = 53$; $p = 0.02$). A similar trend was observed between COVID-19 and historical control articles when dichotomized by good vs. low methodological quality scores.

How much can we take out from this research/paper?
Strengths of this review include very relevant and important objectives, acceptably good search strategy, selection and data extraction process. However, papers published in journals not indexed by the databases could potentially yield worse quality issues. No pre-clinical studies and systematic reviews were included in this review, only English papers and published before May 2020. Methodological quality was assessed with widely used and validated tools but over

parts of the domains. Trained reviewers were conducting the study but uncertain influence of biases from no-blinding to the geographical region and author. Prejudice of time to acceptance and methodological quality could affect the assessment of the latter.

Assuming all the aforementioned have minimal impact on the methodological quality of the included papers, the review informs us that scientific papers on COVID-19 related areas across all types of study design suffered lower quality than those in the immediate pre-pandemic periods. The immediate questions come to mind will be are poor reporting equivalent to poorly conducted research? Were investigators taking 'shortcuts' in researches? Did longer peer-reviewing really improve the quality of the reporting? Could better editorial process be in place for short time to publication and yet maintain the quality of the research papers?

As the authors rightly indicated that poor science that is manifested during this pandemic endanger the public trust in 'modern' science and the whole scientific research enterprise. This has been quite thin for many recent years. A more responsible conducts in research has been 'preached' but hope cannot be high in the researchers but should be there among the editors of journals. Other safety mechanisms include educating the evidence users in critical appraisals of scientific papers. This may cover some very basic and key areas of scientific study appraisals such as about relevancy of the problem studies and the team who carry out the study, credibility of the methods and usefulness of the outcome measures. Doubtful reports should be further assessed when fuller data is available, and should not be propagated or pursued in further studies. If this fortress is reliably presence in many, then the speed of report and dissemination during the urgent period such as that of the pandemic COVID-19 is preferred not slow sharing of information. Surviving always take precedent over enjoying quality of life because losing the former none is left of the latter

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