**Name of journal:** ***World Journal of*** ***Gastroenterology***

**Manuscript NO: 36061**

**Manuscript Type: Letter to the Editor**

**Duplicate publication bias weakens the validity of meta-analysis of immunosuppression after transplantation**

Fairfield CJ *et al*. Duplicate publication bias in meta-analysis

Cameron J Fairfield, Ewen M Harrison, Stephen J Wigmore

**Cameron J Fairfield, Ewen M Harrison, Stephen J Wigmore,** Department of Clinical Surgery, University of Edinburgh, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, United Kingdom

**ORCID number:** Cameron J Fairfield (0000-0001-7635-1868); Ewen M Harrison (0000-0002-5018-3066); Stephen J Wigmore (0000-0002-3614-8002).

**Author contributions:** Fairfield CJ wrote this letter; Harrison EM and Wigmore SJ revised the letter.

**Conflict-of-interest statement:** The authors have no conflict of interest to report.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Cameron J Fairfield, MBChB,** Department of Clinical Surgery, University of Edinburgh, Royal Infirmary of Edinburgh, 51 Little France Drive, Edinburgh EH16 4SA, United Kingdom. [cameron.fairfield@nhs.net](mailto:cameron.fairfield@nhs.net)

**Telephone:** +44-131-2423614

**Received:** August 28, 2017

**Peer-review started:** August 29, 2017

**First decision:** September 13, 2017

**Revised:** September 15, 2017

**Accepted:** September 26, 2017

**Article in press:**

**Published online:**

**Abstract**

Duplicate publication can introduce significant bias into a meta-analysis if studies are inadvertently included more than once. Many studies are published in more than one journal to maximize readership and impact of the study findings. Inclusion of multiple publications of the same study within a meta-analysis affords inappropriate weight to the duplicated data if reports of the same study are not linked together. As studies which have positive findings are more likely to be published in multiple journals this leads to a potential overestimate of the benefits of an intervention. Recent advances in immunosuppression strategies following liver transplantation have led to many studies investigating immunosuppressive regimes including immunosuppression monotherapy. In this letter we focus on a recently published meta-analysis by Lan *et al* investigating studies assessing immunosuppression monotherapy for liver transplantation. The authors claim to have identified fourteen separate randomised studies investigating immunosuppression monotherapy. Seven of the references appear to relate to only three studies which have been subject to duplicate publication. Several similarities can be identified in each of the duplicate publications including similar authorship, identical immunosuppression regimes, identical dates of enrolment and citation of the original publication in the subsequent manuscripts. We discuss the evidence of the duplicate publication inclusion in the meta-analysis.

**Key words:** Liver transplantation; Immunosuppression; Meta-analysis; Duplicate publication; Bias

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The purpose of this letter to the editor is to comment on the potential inclusion of duplicate publications within the meta-analysis titled: “Efficacy of immunosuppression monotherapy after liver transplantation: A meta-analysis”.

Fairfield CJ, Harrison EM, Wigmore SJ. Duplicate publication bias weakens the validity of meta-analysis of immunosuppression after transplantation. *World J Gastroenterol* 2017; In press

**TO THE EDITOR**

We read with interest the article titled “Efficacy of immunosuppression monotherapy after liver transplantation: A meta-analysis” by Lan *et al*[1]. The authors have performed a meta-analysis assessing the use of immunosuppression monotherapy after liver transplantation. The authors claim to have included fourteen randomised studies comparing monotherapy *vs* combination immunosuppression for liver transplanted patients and conclude that calcineurin inhibitor monotherapy is both effective and leads to fewer adverse events than combination therapy. The authors state that the review is the first meta-analysis to include multiple studies assessing the effect of immunosuppression with or without steroids on graft rejection after liver transplantation. Finally, the authors state that the strengths of their review include duplicate study elimination. For the following reasons, we do not agree with their results or their conclusions.

The authors claim to have included fourteen separate randomised studies. On closer inspection, the authors have included seven references relating to only three randomised studies and have not made adequate efforts to eliminate duplicate studies[2-8].

The first of these studies was performed in the United Kingdom and both publications share the same start date, protocol, several co-authors and the same recruitment centres[2,3]. The earlier publication appears to record preliminary results[2]. Lan *et al*[3] appear to have included these preliminary results as a separate study. Furthermore, the main publication relating to this study clearly states that the findings are “similar to those in our preliminary report”. The citation in support of this statement is identical to that included as a separate study in the meta-analysis by Lan *et al*[3].

The second of these studies was performed in Germany and both publications share the same enrolment dates, protocol, several co-authors, recruitment centre and numbers of patients allocated to each intervention arm[4,5]. Furthermore, the publication recording long-term follow-up for patients in this study explicitly states that the authors have previously published their study and that in the publication in 2010 they “present the results of a re-evaluation of our study patients”[5].

The third of these studies was performed in Italy and all three publications share the same enrolment dates, several co-authors, recruitment centre and protocol[6-8]. Furthermore, both duplicate studies with later publication dates explicitly state that the earlier publications are interim reports relating to the same study[6,7].

The authors also claim to have published the first meta-analysis assessing steroid-free immunosuppression in liver transplanted patients. Three meta-analyses[9-11] were published prior to the date of submission by Lan *et al*[1]. Two further meta-analyses have been published since this date[12,13]. In each case where any of the three studies discussed have been included in another meta-analyses the authors have concluded that the studies have been subject to duplicate publication.

The problem with inclusion of duplicated data in meta-analyses is that it creates bias with inappropriate weight being afforded to the duplicate data. The failure in Lan 2014 to adequately avoid duplicate publication bias may mean that the results of this meta-analysis are invalid.

**REFERENCES**

1 **Lan X**, Liu MG, Chen HX, Liu HM, Zeng W, Wei D, Chen P. Efficacy of immunosuppression monotherapy after liver transplantation: a meta-analysis. *World J Gastroenterol* 2014; **20**: 12330-12340 [PMID: 25232269 DOI: 10.3748/wjg.v20.i34.12330]

2 **Samonakis DN**, Mela M, Quaglia A, Triantos CK, Thalheimer U, Leandro G, Pesci A, Raimondo ML, Dhillon AP, Rolles K, Davidson BR, Patch DW, Burroughs AK. Rejection rates in a randomised trial of tacrolimus monotherapy versus triple therapy in liver transplant recipients with hepatitis C virus cirrhosis. *Transpl Infect Dis* 2006; **8**: 3-12 [PMID: 16623815 DOI: 10.1111/j.1399-3062.2006.00124.x]

3 **Manousou P**, Samonakis D, Cholongitas E, Patch D, O'Beirne J, Dhillon AP, Rolles K, McCormick A, Hayes P, Burroughs AK. Outcome of recurrent hepatitis C virus after liver transplantation in a randomized trial of tacrolimus monotherapy versus triple therapy. *Liver Transpl* 2009; **15**: 1783-1791 [PMID: 19938143 DOI: 10.1002/lt.21907]

4 **Moench C**, Barreiros AP, Schuchmann M, Bittinger F, Thiesen J, Hommel G, Kraemer I, Otto G. Tacrolimus monotherapy without steroids after liver transplantation--a prospective randomized double-blinded placebo-controlled trial. *Am J Transplant* 2007; **7**: 1616-1623 [PMID: 17511685 DOI: 10.1111/j.1600-6143.2007.01804.x]

5 **Weiler N**, Thrun I, Hoppe-Lotichius M, Zimmermann T, Kraemer I, Otto G. Early steroid-free immunosuppression with FK506 after liver transplantation: long-term results of a prospectively randomized double-blinded trial. *Transplantation* 2010; **90**: 1562-1566 [PMID: 21048536 DOI: 10.1097/TP.0b013e3181ff8794]

6 **Belli LS**, de Carlis L, Rondinara G, Alberti AB, Bellati G, De Gasperi A, Forti D, Idèo G. Early cyclosporine monotherapy in liver transplantation: a 5-year follow-up of a prospective, randomized trial. *Hepatology* 1998; **27**: 1524-1529 [PMID: 9620322 DOI: 10.1002/hep.510270609]

7 **De Carlis L**, Belli LS, Rondinara GF, Alberti A, Sansalone CV, Colella G, Aseni P, Slim AO, Forti D. Early steroid withdrawal in liver transplant patients: final report of a prospective randomized trial. *Transplant Proc* 1997; **29**: 539-542 [PMID: 9123120 DOI: 10.1016/S0041-1345(96)00255-2]

8 **Romani F**, Belli LS, De Carlis L, Rondinara GF, Alberti A, Sansalone CV, Bellati G, Zavaglia C, Fesce E, Ideo G. Cyclosporin monotherapy (after 3 months) in liver transplant patients: a prospective randomized trial. *Transplant Proc* 1994; **26**: 2683-2685 [PMID: 7940840]

9 **Knight SR**, Morris PJ. Steroid sparing protocols following nonrenal transplants; the evidence is not there. A systematic review and meta-analysis. *Transpl Int* 2011; **24**: 1198-1207 [PMID: 21923805 DOI: 10.1111/j.1432-2277.2011.01335.x]

10 **Segev DL**, Sozio SM, Shin EJ, Nazarian SM, Nathan H, Thuluvath PJ, Montgomery RA, Cameron AM, Maley WR. Steroid avoidance in liver transplantation: meta-analysis and meta-regression of randomized trials. *Liver Transpl* 2008; **14**: 512-525 [PMID: 18383081 DOI: 10.1002/lt.21396]

11 **Sgourakis G**, Radtke A, Fouzas I, Mylona S, Goumas K, Gockel I, Lang H, Karaliotas C. Corticosteroid-free immunosuppression in liver transplantation: a meta-analysis and meta-regression of outcomes. *Transpl Int* 2009; **22**: 892-905 [PMID: 19453997 DOI: 10.1111/j.1432-2277.2009.00893.x]

12 **Gu J**, Wu X, Lu L, Zhang S, Bai J, Wang J, Li J, Ding Y. Role of steroid minimization in the tacrolimus-based immunosuppressive regimen for liver transplant recipients: a systematic review and meta-analysis of prospective randomized controlled trials. *Hepatol Int* 2014; **8**: 198-215 [PMID: 24765218 DOI: 10.1007/s12072-014-9523-y]

13 **Fairfield C**, Penninga L, Powell J, Harrison EM, Wigmore SJ. Glucocorticosteroid-free versus glucocorticosteroid-containing immunosuppression for liver transplanted patients. *Cochrane Database Syst Rev* 2015; **(12)**: CD007606 [PMID: 26666504 DOI: 10.1002/14651858.CD007606.pub3]

**P-Reviewer:** Akamatsu N, Bramhall S, Chiu KW, Rodriguez-Peralvarez ML

**S-Editor:** Gong ZM **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** United Kingdom

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0