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Review Article

Quality of systematic review and meta-analysis may decide its clinical significance and publication

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Abstract: In this brief review, the authors aim to show the importance of the quality of a systematic review and meta-analysis by illustrating some examples. First, the reliability of systemic reviews' conclusions is largely dependent upon the quality of included studies. Second, the publications are potentially influenced by the quality of systematic reviews. Third, AMSTAR tool should be employed to evaluate the quality of systematic reviews.

Keywords: Systematic review, meta-analysis, publication, quality

Introduction

At present, the clinical significance of systematic reviews and meta-analyses has been increasingly recognized [1, 2]. Generally speaking, the researchers should be strongly encouraged to perform systematic reviews and meta-analyses in their fields. The physicians should also prefer to make their clinical decisions based on the results of systematic reviews and meta-analyses. In the present review, we would like to illustrate some examples to demonstrate how the quality of a systematic review and meta-analysis influence its usefulness in clinical practices and even its final publications.

Reliability of systemic reviews' conclusions is dependent upon the quality of included studies

In 1992, the clinical guidelines counseled that asymptomatic postmenopausal women might use hormone therapy to prevent disease and to prolong life [3]. Evidence from previous meta-analyses suggested that estrogen use could decrease the risk of coronary disease [4, 5]. However, most of included studies were observational and of low-quality. In 1998, a large randomized controlled trial involving 2763 participants demonstrated that estrogen did not protect against the development of overall cardiovascular events [6]. Notably, estrogen significantly increased the incidence of deep vein thrombosis. In 2002, a larger randomized controlled trial involving 16608 participants showed that estrogen plus progestin significantly increased the risk of coronary heart disease, stroke, and pulmonary embolism among generally healthy postmenopausal women [7]. Subsequently, evidence from meta-analyses of high-quality randomized controlled trials supported no benefit of hormone therapy in the secondary or primary prevention of cardiovascular disease events [8]. Indeed, the current recommendations from U.S. Preventive Services Task Force are that a combination of estrogen and progestin should not be used for the prevention of chronic conditions in postmenopausal women [9]. Accordingly, the conclusions of systematic review and meta-analyses would greatly change with the quality of included studies. If the quality of included studies was low, they could not be used in clinical practice.

Publications are associated with the quality of systematic reviews

Clinically significant portal hypertension (CSPH) often represents a clinical challenge in patients with hepatocellular carcinoma (HCC) who un-

Table 1. An overview of systematic reviews regarding the impact of CSPH on the prognosis of HCC after surgery

First author, Journal (Year)	Berzigotti, Hepatology (2015)	Choi, J Hepatobiliary Pancreat Sci (2014)	Tang, Asian Pac J Cancer Prev (2014)
Region	Barcelona, Spain	Seoul, Korea	Chengdu, China
Databases	Medline, (Hand-searching)	PubMed, EMBASE, Cochrane Library	PubMed, EMBASE, CNKI
Last search date	October, 2013	Not reported	December, 2013
Criteria for CSPH	HVPG ≥10 mmHg or PVP ≥20 cm H_2O or standard surrogate criteria: presence of gastro-esophageal varices or PLT <100000/ml and spleen diameter >12 cm	Esophageal varices and/or thrombocytopenia with splenomegaly	Oesophageal varices and/or splenomegaly associated with thrombocytopenia
Inclusion criteria	Clearly presented	Described	Clearly presented
Quality assessment	According to the Quality In Prognosis Studies (QUIPS)	According to the Newcastle-Ottawa Scale (NOS)	Not evaluated
Statistical software	RevMan 5.2	RevMan 5.1, Comprehensive Meta-Analysis software Version 2	RevMan 5.0.24
Heterogeneity	Chi-square test and I^2 statistic	Cochran's Q test	Chi-square test
Statistical model	Only random effects	Only random effects	Fixed or random effects
Data expression	Odds ratio	Odds ratio, hazard ratio	Risk ratio, weighted mean difference
Sensitivity analysis	According to the study quality, method used to estimate the presence of portal hypertension, proportion of patients with preserved hepatic function, tumor burden, and type of surgery	According to the definitions of CSPH	Not reported (but a subgroup analysis was performed in patients with Child-Pugh class A)
Publication bias	Not evaluated	Funnel plot	Funnel plot
No. included papers	11	11	7
No. included patients	1737	2285	1928
Outcomes	3- and 5-year mortality	Operation-related factors	Post-operative liver failure and ascites
	Complications related to cirrhosis	Postoperative mortality, complications	Peri-operative blood transfusion
		Liver-related morbidity or liver insufficiency	Operative mortality
		Prognostic significance of CSPH	1-, 3-, and 5-year overall survival rate

Abbreviations: CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HVPG, hepatic vein pressure gradient; PLT, platelets count; PVP, portal vein pressure.

Table 2. List of references included in the three systematic reviews

Berzigotti (2014)	Choi (2014)	Tang (2014)
Bruix, Gastroenterology 1996	An, Korean J Hepatol 2006	Capussotti, World J Surg 2006
Llovet, Hepatology 1999	Capussotti, World J Surg 2006	Choi, Liver Int 2011
Cucchetti, Ann Surg 2009	Ishizawa, Gastroenterology 2008	Cucchetti, Ann Surg 2009
Capussotti, World J Surg 2006	Cucchetti, Ann Surg 2009	Ishizawa, Gastroenterology 2008
Ishizawa, Gastroenterology 2008	Kawano, Ann Surg Oncol 2008	Ruzzenente, World J Gastroenterol 2011
Ruzzenente, World J Gastroenterol 2011	Choi, Liver Int 2011	Yang, Chinese Hepatology 2012
Boleslawski, Br J Surg 2012	Maithel, J Am Coll Surg 2011	Santambrogio, HPB 2013
Hidaka, Br J Surg 2012	Ruzzenente, World J Gastroenterol 2011	
Llop, J Hepatol 2012	Kondo, Hepatogastroenterology 2012	
Giannini, Liver Int 2013	Giannini, Liver Int 2013	
Santambrogio, HPB 2013	Santambrogio, HPB 2013	

dergo hepatic resection. Recently, there are at least 3 systematic review and meta-analysis papers published to evaluate the impact of CSPH on the outcomes of HCC patients treated with hepatectomy. In April 2014, Tang et al. published the first meta-analysis in the journal *Asian Pacific Journal of Cancer Prevention* (Thomson Reuters 2013 impact factor=1.5) [10]. They concluded that the presence of CSPH (i.e., presence of oesophageal varices and/or splenomegaly associated with thrombocytopenia) was significantly associated with a higher rate of post-operative liver failure and ascites, peri-operative blood transfusion, operative mortality, and 3- and 5-year overall mortality. In addition, the influence of CSPH on the post-operative liver failure and ascites, peri-operative blood transfusion, and 3- and 5-year overall mortality remained statistically significant in the subgroup analysis of patients with Child-Pugh class A.

In September 2014, Choi et al. published the second meta-analysis regarding the same topic in the *Journal of Hepato-Biliary-Pancreatic Science* (Thomson Reuters 2013 impact factor=2.313) [11]. They showed significantly higher rates of postoperative mortality, complications, liver-related morbidity, and liver failure and overall mortality in the CSPH group than in the non-CSPH group.

In February 2015, Berzigotti et al. published the third meta-analysis in the journal *Hepatology* (Thomson Reuters 2013 impact factor=11.19), which is the top one journal in the field of liver diseases [12]. They also demonstrated that the patients with CSPH had a significantly higher risk of 3- and 5-year mortality and of clinical decompensation after surgery than those without CSPH. Additionally, in the paper by Berzigotti et al., the sensitivity analyses were conducted according to the study quality, method used to estimate the presence of portal hypertension, proportion of patients with fully preserved hepatic function, tumor burden, and type of surgery. Importantly, the findings of all sensitivity analyses were consistent with those of the overall meta-analyses. Therefore, the conclusions regarding the negative impact of CSPH on the prognosis of HCC after surgery should be stable and reliable.

The similarities and differences of methods and results sections among the 3 systematic review and meta-analysis papers were summarized in **Table 1**.

First, the quality assessment and sensitivity analyses were more adequately designed in the study by Berzigotti et al. [12]. By comparison, in the study by Tang et al. [10], the quality assessment was lacking, and no sensitivity analysis was performed.

Second, Berzigotti et al. searched only one database (i.e., Medline) in a combination with hand-searching the list of references [12]. By comparison, Tang and Choi searched three databases [10, 11]. Notably, Tang et al. also employed one Chinese-language database (i.e., CNKI, China National Knowledge Infrastructure). And one Chinese-language full-text paper was included.

Third, the number of included references was 7 in the study by Tang et al. [10]. By contrast, the number of included references was higher in the studies by Berzigotti and Choi [11, 12]. Thus, the potential bias of study selection

Table 3. AMSTAR tool list (see the reference by Shea et al. BMC Med Res Methodol. 2007)

Questions:
1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?
Answers:
1. Yes
2. No
3. Can't answer
4. Not applicable

should be clarified. Given that the relevant references should be comprehensively searched in a systematic review [13], another 9 references might be further included to strengthen their findings (**Table 2**).

Collectively, it appears to be reasonable that a high-quality and more methodologically sound systematic review and meta-analysis paper is more likely to be published in high-impact journals. Certainly, other factors that may influence the final publication should never be neglected, such as the academic background of a study team.

AMSTAR tool should be used to assess the methodological quality of systematic reviews

Recently, numerous instruments have been developed to assess the quality of systematic reviews. However, most of them had their potential limitations and weakness. In this paper, we briefly introduced a more popular and valid measurement tool for the "assessment of multiple systematic reviews" (AMSTAR). AMSTAR is constructed by a group of methodological experts [14]. Thirty-seven initially evaluated items are combined based on the quality of reporting of Meta-analyses (QUORUM) [15], the Sacks's checklist [16], the language restriction, the publication bias, and the publication status. Finally, 11 components were identified by factor analysis (**Table 3**) [14]. Subsequently, the internal and external validation studies demonstrated that AMSTAR had satisfactory inter-observer agreement, reliability, construct validity, and feasibility [17, 18]. On May 20, 2015, a total of 171 papers could be identified by a preliminary search strategy with the search items "(AMSTAR) AND (systematic review)" in the PubMed database.

Conclusions

The researchers should pay more attention on improving the quality of systematic reviews and meta-analyses. AMSTAR tool may be a useful reference tool to monitor the quality of systematic reviews and meta-analyses.

Disclosure of conflict of interest

None.

Authors' contribution

Xingshun Qi conceived this work and drafted the manuscript. Zhiping Yang, Ming Bai, and Yongji Wang gave critical comments and revised the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

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