SCIENTIFIC REPORTS

Correction: Author Correction

OPEN

NSAIDs Use and Reduced Metastasis in Cancer Patients: results from a meta-analysis

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This meta-analysis investigated the relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and lymph node/distant metastasis. Relevant sources were identified from MEDLINE, EMBASE, PubMed, and Cochrane Library. Studies that reported the odds ratio (OR)/risk ratio (RR)/ hazard ratio (HR) with 95% confidence intervals (CIs) for the associations of interested outcomes were included. Pooled effect estimates were obtained by using random- or fixed-effect model depending on the heterogeneity across these studies. Sixteen studies involving 202780 participants, including prostate, breast, lung, and colorectal cancer patients, were included. Compared with the reference, generally patients exposed to NSAIDs at pre- and post-diagnosis experienced a significantly reduced risk of distant metastasis (RR 0.708, 95% CI 0.586–0.856 and RR: 0.484, 95% CI: 0.393–0.595, respectively), including prostate cancer (pre-diagnostic use: RR $=$ 0.874, 95% CI, 0.787–0.97; post-diagnostic use: RR $=$ 0.482, 95% CI 0.359–0.647), and breast cancer (pre-diagnostic use: RR $=$ 0.644, 95% CI 0.565–0.735; post-diagnostic use: RR $=$ 0.485, 95% CI 0.362–0.651). However, lymph node metastasis was weakly related with pre-diagnostic use of NSAIDs (RR $=$ 0.949, 95% CI 0.914–0.985). NSAIDs are related to a significantly reduced risk of metastasis development, regardless of pre-diagnostic or post-diagnostic use. However, NSAIDs and lymph node metastasis are weakly associated. Our finding suggested a novel metastasis management.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for patients with coronary heart disease and rheumatoid arthritis. Currently, NSAIDs are becoming necessary in management of cancer patients. One important reason for the use of NSAIDs is that blood coagulation system is often activated in the course of malignancies, and the risk of venous thromboembolism increases with locally advanced or metastatic cancer. Recently, NSAIDs are further recommended as the primary drug for prevention of colorectal cancer[1].

Numerous fundamental studies and clinical trials have focused on the negative correlation between NSAIDs and patients' overall mortality. The protective effect of NSAIDs is widely hypothesized to be attributed to the inhibition of cancer metastasis. However, the lines of evidence supporting the potential of NSAIDs to reduce cancer metastasis are conflicting[2–4]. While some studies found no significant association between NSAID use and cancer metastasis, other studies have demonstrated that NSAIDs are associated with reduced risk of metastasis and even with reduced cancer incidence. Interpretation of this conflicting findings has been complicated by different baseline characteristics of study populations (e.g., men vs. women; aspirin vs. warfarin vs. heparin; pre-diagnostic use vs. post-diagnostic use vs. non-use of NSAIDs; regular use vs. frequent use vs. non-use; lymph node (LN) metastasis vs. distant metastasis; breast cancer vs. lung cancer vs. prostate cancer; early-stage cancer vs. late-stage cancer; long-term follow-up vs. short-term follow-up, and different types of studies (case-control studies vs. cohort studies vs. random-controlled trials (RCT)). To integrate metastatic theory with clinical treatment, as well as provide an indication for treatment with anticoagulant agents to physicians and cancer patients, we conducted a meta-analysis on the impact of pre-diagnostic or post-diagnostic use of NSAIDs on cancer with LN or distant metastasis.

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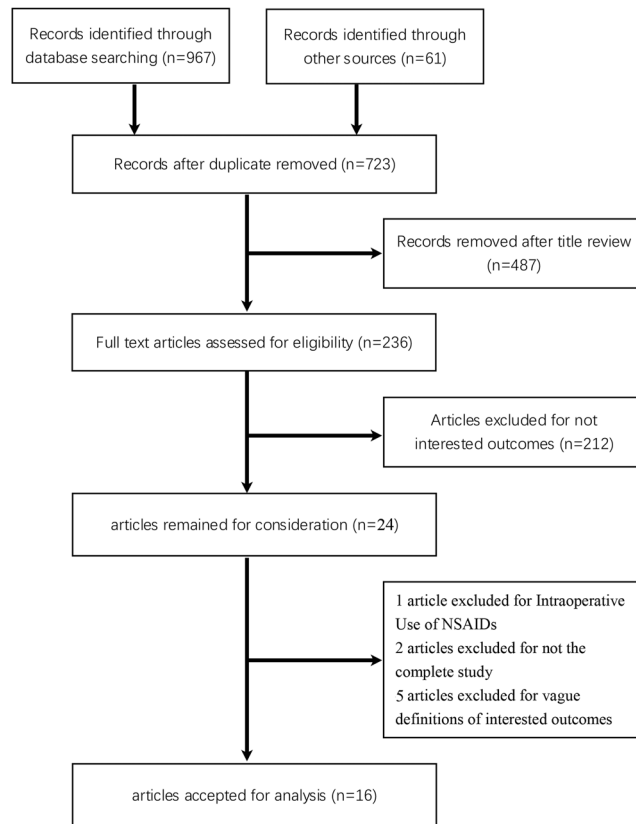
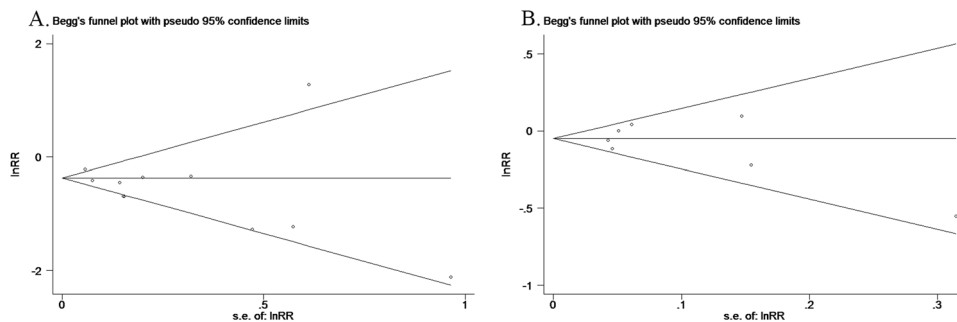**Figure 1.** Flow diagram of study selection.

Figure 2. Public bias assessment of included studies. (**A**) Funnel plots showing association between distant metastasis and NSAID use of patients. (**B**) Funnel plots showing association of lymph node metastasis with NSAID use of patients.

Results

Study Selection and Characteristics.   A total of 962 relevant articles were initially retrieved through literature search engine. Following omissions of duplicated articles and reports without interested outcome, 24 studies were collected for consideration. After full text review, 16 studies were selected for this meta-analysis[5–28] (Fig. 1, Supplementary Dataset 8).

Next, the quality of selected studies was evaluated according to Newcastle-Ottawa Scale (NOS) criterion. The accumulated stars of included case–control studies ranged from 7 to 8, and cohort studies' score ranged from 7 to 9. Therefore, we considered the selected studies were high-quality studies (Supplementary Dataset 9). Besides, Results from Begg's, Egger's and funnel plot's asymmetry tests all showed that there is no evidence of publication bias in both distant metastasis group and lymph metastasis group (Fig. 2).

A total of 202780 patients and at least 45044 events were involved in the 16 eligible studies, including 1 RCT, 11 cohort studies, and 4 case reports. The sizes of these studies ranged from 74 to 78615. Of these primary trails, all had described independent, continuous sampling of their cohort. A total of 10 studies were conducted in USA, 2 in Sweden, and the remaining 4 studies in UK, Canada, Ireland, and Italy. Among these studies, aspirin was the most predominant NSAID given to patients. These studies have investigated many cancers, including breast

cancer (7 studies), prostate cancer (5 studies), colorectal cancer (1 studies), and esophageal cancer (1 study). Moreover, multi-cancers were found in two studies. A total of 10 trials have investigated the association between NSAIDs and distant metastasis, 5 studies explored the connection between NSAIDs and LN metastasis, and one study determined the simultaneous change in distant metastasis and LN metastasis in patients exposed to NSAIDs. Apart from the four trails that have explored the impact of post-diagnostic use of NSAIDs on distant metastasis, the remaining 12 studies investigated the effect of pre-diagnostic use of NSAIDs on distant/LN metastasis. Adjusted HRs/RRs/ORs could be determined in all studies, with 12 studies reporting adjusted estimates (Supplementary Dataset 9).

Association between NSAIDs and Cancer Distant Metastasis.

Eleven studies involving 247,826 patients and more than 40,000 events reported on the risk estimates for cancer distant metastasis in patients exposed to NSAIDs before or after diagnosis. Among the eleven studies, ten studies reported the negative association between NSAIDs and cancer metastasis, although the results from two studies were not statistically significant. The remained study found positive relationship between NSAIDs and cancer metastasis with statistically significance. Overall, compared with the reference group, cancer patients taking NSAIDs showed a significantly reduced risk for metastasis development (RR: 0.623, 95% CI 0.515–0.753, $p < 0.001$) (Supplementary Dataset 1).

A considerable heterogeneity of RRs was observed across the Eleven studies ($I^2 = 69.5\%$). We subsequently stratified these studies based on exposure to NSAIDs. Moderate heterogeneity was detected in the pre-diagnostic NSAID use group (RR: 0.708, 95% CI 0.586–0.856, $p < 0.001$, $I^2 = 63.4\%$), whereas no heterogeneity was detected among trials that employed post-diagnostic use of NSAID (RR: 0.484, 95% CI 0.393–0.595, $I^2 = 0.0\%$) (Supplementary Dataset 1). Therefore, a sensitivity analysis was performed to detect the study that have mainly contributed to this high heterogeneity. After omitting the study of James L. Araujo, the heterogeneity of pre-diagnosis NSAID use group decreased ($I^2 = 48.3\%$) and the inhibition by pre-diagnostic NSAID use slightly increased (RR 0.729, 95% CI 0.671–0.791, $p < 0.001$), although the overall heterogeneity of the studies remained at moderate level ($I^2 = 64.8\%$) (Supplementary Dataset 2).

We subsequently investigated the correlation between NSAID use and the indicated cancer types. In prostate cancer, the summarized results suggested a negative association between NSAIDs and prostate cancer metastasis with a considerable heterogeneity (RR = 0.817, 95% CI 0.74–00.902, $p = 0.006$, $I^2 = 70.9\%$). When we stratified these studies based on the time of exposure to NSAIDs, the risk of metastasis development both in pre-diagnostic and post-diagnostic NSAID use groups decreased (pre-diagnosis: RR = 0.874, 95% CI 0.787–0.97, $p = 0.012$; post-diagnosis: RR = 0.482, 95% CI 0.359–0.647, $p < 0.001$); moreover, heterogeneity was not detected in both groups (pre-diagnosis: $I^2 = 0.00\%$; post-diagnosis: $I^2 = 0.00\%$) (Supplementary Dataset 3). Similar results were obtained in trials that have studied breast cancer (overall use: RR = 0.615, 95% CI 0.546–0.693, $p < 0.001$, $I^2 = 29.3\%$; pre-diagnostic use: RR = 0.644, 95% CI 0.565–0.735, $p < 0.001$, $I^2 = 0.00\%$; post-diagnostic use: RR = 0.485, 95% CI 0.362–0.651, $p < 0.001$, $I^2 = 53.4\%$) (Supplementary Dataset 4). For both lung cancer and colorectal cancer, the pooled RR is consistently less than 1 with a high heterogeneity (Supplementary Dataset 5).

Association between NSAIDs and Cancer LN Metastasis.

We subsequently investigated the relationship between NSAIDs and lymph node metastasis. Six studies involving 110735 participants and approximately 20,000 patients with LN metastasis were recruited in this analysis. All of these studies (predominantly breast cancer and prostate cancer clinical trials) focused on the relationship between pre-diagnostic use of NSAIDs and LN metastasis. Four of these studies found an association between pre-diagnosis use of NSAIDs and a reduced risk of LN metastasis, although only one study reported statistically significant results. However, compared with the referent group, the risk of LN metastasis slightly decreased in the pre-diagnostic NSAID use group (RR = 0.949, 95% CI 0.914–0.985, $p = 0.006$, $I^2 = 36.3\%$) (Supplementary Dataset 6).

In these trails, breast cancer was involved in 5 studies, prostate cancer in 2 studies, colorectal cancer in 1 studies, and lung cancer in 1 study. Therefore, we performed a meta-analysis to determine the relationship between NSAIDs and breast cancer LN metastasis. A negative relationship between NSAIDs and LN metastasis was detected in the summarized studies, although the results were not statically significant (RR = 0.958, 95% CI 0.913–1.004, $p = 0.075$, $I^2 = 34.8$) (Supplementary Dataset 7).

Discussion and Conclusion

Metastasis is a multi-sequential process accounting for most cancer-related deaths. Although the mechanisms regulating cancer metastasis remain incompletely investigated, metastasis is found to be inherently inefficient[29,30]. Even after successful invasion of blood vessels, most cancer cells become dormant because of factors such as anoikis, fluid shear stresses, and immunological surveillance. Therefore, the use of an appropriate intervention for cancer metastasis is a promising strategy to improve the prognosis of cancer patients.

NSAIDs are non-selective or selective COX-1/2 inhibitors, which are wildly prescribed for pain killing, fever reduction, and even anti-inflammation. Nowadays, NSAIDs are used to prevent DVT in cancer patients. Accumulated lines of evidence have confirmed the safety of long-term use of low-dose NSAIDs, the positive association between NSAIDs and improved prognosis[31–33], and the negative association between NSAIDs and carcinogenesis. The reduced mortality of cancer patients exposed to NSAIDs has attracted great attention. Actually, some recent studies have addressed the potential of NSAIDs to inhibit cancer metastasis: study from Huang et al. suggested post-diagnosis NSAIDs use was inversely associated with metastasis[2]; Elwood et al.'s research revealed NSAIDs use reduced metastatic spread[3]; Algra et al. suggested regular use of aspirin was correlated with cancers with distant metastasis[34]. Although all the studies have suggested the benefits of NSAIDs use in cancer patients, some defects may complicate the interpretation of the association. Firstly, the criteria of articles selection are inconsistent among these studies. For example, the data of local and regional relapse is mixed with lymph node metastasis, even distant metastasis. More importantly, the number of included trials is limited and there is a

considerable heterogeneity among these studies. However, the interesting relation between NSAIDs and cancer metastasis revealed by these studies urges us to define the place of NSAIDs in cancer metastasis.

The present meta-analysis, which involves approximately 300,000 participants from 16 studies, has confirmed the antineoplastic effects of NSAIDs in multi-cancer metastasis, regardless of whether NSAIDs is used at pre-diagnosis or post-diagnosis. In terms of LN metastasis, weak inhibition was observed in cancer patients exposed to NSAIDs at pre-diagnosis. Our results have suggested the underappreciated role of NSAIDs in cancer metastasis.

The results showed that both pre- and post-diagnostic use of NSAIDs were related to reduced distant metastasis. However, high heterogeneity was detected in the trials that employed pre-diagnostic NSAID use. The heterogeneity among the pooled studies decreased after omitting the trial performed by James L. Araujo, which we then reviewed. James L. Araujo reported that increased risk of cancer metastatic development was found in patients with pre-diagnosis exposure to NSAIDs, contrary to the conclusion of other studies. Although no defect was found in the study design and in patient enrollment, some flaws may have contributed to the inconsistent results. First, the number of patients involved in this trial was small and the detailed information on NSAID use was subsequently omitted in this study. For example, patients involved in this trial may have intermittently taken NSAIDs, possibly contributing to the confounding results[15,35]. Moreover, to our best knowledge, this study is the only work that focused on the relationship between NSAIDs and esophageal cancer metastasis; therefore, other related information is unavailable. However, multiple studies have demonstrated that NSAID use is associated with reduced incidence of esophageal cancer and reduced esophageal cancer-related mortality, also inconsistent with the conclusion of this study[36,37]. Overall, no conclusion can demonstrate the relationship between NSAIDs and esophageal cancer metastasis until further well-designed studies are performed.

The underlying mechanisms involved in the association between NSAIDs and distant metastasis inhibition remains incompletely investigated. One possible explanation is that NSAIDs inhibit COX2[38]. Abnormally high COX2 expression was observed in multi-cancers. Disordered COX2/PGE pathway is involved in multi-cancer processes, including carcinogenesis, proliferation, and metastatic spread; additionally, inhibition of COX2/PGE pathway with NSAIDs can restrain cancer cell lines and xenograft models. Mutual promotion relationship between cancer metastasis and cancer-associated thrombosis is possibly another one of the underlying mechanisms. Abnormally high constitutive level of tissue factor (TF), one key regulator of hemostasis, is expressed by metastatic cancer cells, cancer microparticles, and cancer-associated monocytes and macrophages; TF can promote thrombosis formation by activating the extrinsic pathway of coagulation cascade[39]; moreover, activated blood coagulation system promotes platelet aggregation, which shields cancer cells in multi-dimensions, including prevention of exposure of tumor cells to NK cells, inhibition of maturation of dendritic cells, promotion of camouflaging of cancer cells as normal cells, reduction of fluid shear stresses by the surrounding platelet, and promotion of cancer cell survival through a COX2-dependent pathway against anoikis. Furthermore, inflammation induced by thrombosis could result in endothelial damage, which may further augment the thrombosis against the anticoagulated system and result in vascular leak, facilitating the escape of cancer cells from blood vessels. Consequently, NSAIDs may disrupt the relationship between cancer metastasis and cancer-associated thrombosis via suppression of platelet function, which is detrimental for the disseminated cancer cells in the bloodstream. Finally, reconstruction of pre-metastasis niche can contribute to metastasis inhibition. By inhibiting the chemotaxis of leukocytes and by restraining the release of bradykinin and aggression of thrombocyte inhibition, NSIADs could suppress inflammation. More importantly, inflammation is one driving force accelerating cancer metastasis[40]. Therefore, NSAIDs may further inhibit the formation metastasis foci by suppressing inflammation of pre-metastatic niche and then transforming the prepared microenvironment into adverse microenvironment for the coming cancer cells.

Noteworthily, inhibition of metastasis in patients with pre-diagnostic exposure to NSAIDs is inconsistent with the conclusions of other clinical studies or meta-analyses[2]. Further analysis of our studies have shown the collective long-term pre-diagnostic use of NSAIDs in these studies (the majority patients used NSAIDs for >1 year, data not shown), although NSAID dosage varied. The prolonged exposure to NSAIDs is possibly one important factor contributing to distant metastasis inhibition given that dissemination of cancer cells is not related to cancer size, and metastasis may occur in an early stage of cancer[41,42]. As mentioned above, by preventing the change in microenvironment during cancer metastasis and pre-metastatic niche, long term pre-diagnostic use of NSAIDs could activate the immune system to kill cancer cells in the blood stream and pre-metastatic niche.

LN metastasis, the most common mechanism of cancer spread, indicates poor prognosis of cancer patients. Although obvious effect of NSAIDs on cancer distant metastasis is observed in many studies, LN metastasis was only weakly inhibited in patients treated with NSAIDs. This finding may be partially attributed to the different mutated genes, disorganized signal pathways, and mechanisms mediating cancer with LN and distant metastases. For example, the antiplatelet property of NSAIDs is widely speculated to contribute to cancer inhibition. However, platelets are absent in the lymphatic system, possibly rendering NSAIDs nonfunctional in the lymphatic system. Moreover, another important factor was the small number of studies acquired in the analysis (multi-cancer: 1 study; prostate cancer: 1 study; breast cancer: 4 studies; lung cancer: 0 study; colorectal cancer: 0 study). This insufficient information significantly limited the determination of the effect of NSAIDs on LN metastasis. Therefore, more well-designed fundamental and clinical studies are warranted to investigate the relationship between NSAIDs and LN metastasis.

Strengths of this meta-analysis lies in its strict inclusion criteria, large number of studies and patients analyzed, and the robustness of the findings in sensitivity analyses. However, our study encountered several limitations. First, the clear and understandable discrepancy in sample sizes lies among the randomized, cohort, and case control studies. Second, different types of studies were included in the primary analysis; heterogeneity of effect magnitude (RR/OR/HR) among studies is anticipated. However, when we performed stratified analyses based on the indicated cancer and the time of NSAID prescription, the heterogeneity among studies became slightly, and

pooled RRs were consistently lower than 1. Moreover, even the intraoperative use of NSAIDs may reduce cancer distant metastasis. All of these lines of evidence have suggested the negative correlation between NSAIDs and cancer metastasis. Third, insufficient studies on the indicated cancers were collected in this study. For example, only two and three studies have investigated the pre-diagnostic use of NSAIDS in colorectal cancer and breast cancer with distant metastasis, respectively. However, heterogeneity was obvious (colorectal cancer: $I^2 = 78.8\%$; breast cancer: $I^2 = 53.4\%$); moreover, the cohort study on esophageal cancer showed that pre-diagnosis use of NSAIDs increases the risk of cancer metastasis, although many analyses have demonstrated the negative relationship between NSAID use and patient mortality. Therefore, this insufficient information limits the analysis of the effect of pre-diagnostic and post-diagnostic use of NSAIDs in indicated cancers, although the results of the pooled analysis consistently showed statistical significance. Fourth, the lack of information on the side effects of NSAIDs, subtype of cancers, and patients' exposure to etiological factors and on the inconsistent spice, dose, and term of usage of NSAIDs, and the varied term of follow up may collectively cause confusion on the use of NSAIDs in management of cancer. Fifth, like all meta-analyses, our study is limited by its being a retrospective analysis.

In conclusion, the results of this meta-analysis suggest the potential of NSAIDs in the management of cancer metastasis, regardless of whether NSAIDs are used at pre-diagnosis or post-diagnosis. However, the acquired information is insufficient to support the recommendation or use of NSAIDs in management of indicated cancer until further large well-designed trials, such as RCTs, are completed. In light of our finding and the confusion in the management of cancer metastasis, our results highlight a novel strategy to manage cancer metastasis.

Method

Search Strategy.   Based on PRISMA guidelines, this meta-analysis of published studies was performed without language restrictions (Supplementary Dataset 9). Relevant studies were extracted from electronic databases, including MEDLINE (published in PubMed from January 1, 1946 to December 1, 2016), EMBASE (January 1, 1980 to December 1, 2016), PubMed (January 1, 1980 to December 1, 2016), and Cochrane Library (January 1, 1980 to December 1, 2016). The combined text and MeSH heading search strategy included "Anti-Inflammatory Agents," Non-Steroidal," "cyclooxygenase 2 inhibitor," "Neoplasms," "lymph node metastasis," and "distant metastasis". Furthermore, the references of all relevant articles were manually scrutinized to supplement our search.

Study Selection.   Relevant studies were considered acceptable based on the following criteria: (1) they were RCTs, cohort studies, or case-control studies (cell lines and animal studies, cross-sectional studies, reviews, meetings, commentaries, and letters were excluded); (2) NSAIDs were taken before or after diagnosis, and the outcomes of interest included LN metastasis and distant metastasis; (3) effect magnitude, including odds ratio (OR), risk ratio (RR), and hazard ratio (HR) and the corresponding 95% confidence interval (CI) (or data used to calculate the effect magnitude) were reported; and (4) studies were independent. When multiple studies based on the same trials were identified, only the most recent or complete study was included.

Methodological Quality Assessment and Data Extraction.   Non-randomized studies (MINORS) were evaluated according to the Newcastle–Ottawa Scale (NOS) criteria, and RCT study was assessed using the Cochrane Collaboration's tool for assessing risk of bias. Disagreements on the quality evaluation of the include papers were resolved by comprehensive discussion. In this analysis, studies awarded seven or more were taken as high-quality studies[43].

Three authors (ZXP, XZ, and LHS) extracted the following information from each study: study characteristics (study design, first author's name, publication year, country, patients, and numbers of events), participants' characteristics (mean age and gender), drug characteristics (species, dosage, and term of usage), and analysis strategy (statistical models, confounders adjusted for, effect sizes, and 95% CIs) (Supplementary Dataset 9).

Publication bias Assessment.   Latent publication bias was determined by Begg's adjusted rank correlation test and Egger's regression asymmetry tests, and also by inspection for a funnel plot' asymmetry tests.

Statistical Analysis.   RRs were taken as the common measure of association across studies. Summary RRs were estimated by pooling study-specific estimates using random- or fixed-effect models according to the heterogeneity among studies. The I^2 statistic was calculated to assess the heterogeneity of reported RRs in all studies[44]. Basically, low, moderate, and high heterogeneity were defined as I^2 of <50%, 50–75%, and >75%, respectively. Sensitivity analysis was performed to assess the effects of the quality of the selected study. All analyses were performed using Stata version 14.0 (Stata Corp), and a p value of <0.05 indicated statistical significance.

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Acknowledgements

Author Contributions

This study was designed by Xiaoping Z. Xiaoping Z., Zhi X. and Haoseng L. conducted the article collection, data extraction and analysis, and discussion of results. Xiaoping Z. and Zhi X. prepared the manuscript. All authors reviewed this manuscript.

Additional Information

Supplementary information accompanies this paper at doi:10.1038/s41598-017-01644-0

Competing Interests: The authors declare that they have no competing interests.

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