INTRODUCTION

Colorectal cancer (CRC) ranked third in terms of incidence and second in terms of mortality. It is estimated to have over 1.8 million new cases and cause 881 000 deaths in 2018.\(^1\) Many colorectal carcinomas develop through an adenoma-carcinoma sequence for years,\(^2\) which makes clinical intervention and prognosis improvements possible and meanwhile essential. Nonsteroid anti-inflammatory drugs, especially aspirin, have been shown to reduce both the incidence and the...
mortality of CRC in several studies. However, taking the possible bleeding complications of aspirin and the clinical burden of CRC into account, other attractive chemopreventive agents are warranted.

Statins, the inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, are cholesterol-lowering agents most commonly prescribed worldwide. Besides their lipid-lowering effects, various researches have revealed their unexpected preventive effects on tumor development and progression via HMG-CoA reductase-independent pathway and HMG-CoA reductase-dependent pathway. Underlying mechanisms, including suppression of tumor growth, induction of apoptosis, and inhibition of angiogenesis were engaged.

While many preclinical researches on cells and animals have indicated the positive effects of statins on CRC, such as increasing intracellular oxidative stress, inducing apoptosis and augmenting chemosensitivity, whether statin uses are positively correlated with the survival of CRC patients in clinic is controversial. No consensus concerning the prognostic effects of statins on CRC has been reached so far. Therefore, we conducted this meta-analysis to assess the overall and cancer-specific survival benefits of statin uses on CRC patients. Our results may provide further insights into clinical applications of statins on CRC patients.

2 | METHODS

This systematic review and meta-analysis were performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses. It was registered with the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO, CRD42017074280).

2.1 | Search strategy

We identified related references through searches of PubMed, the Cochrane Library, Web of Science, EMBASE, and SCOPUS from inception to August 2017, using search strategies (Table S1). All references of related articles and relevant reviews were screened manually to further identify potentially relevant studies.

2.2 | Study selection and data extraction

The following criteria for eligibility among studies were set before selection of criteria: (a) the exposure of interest was statin uses before or after diagnosis of CRC, (b) case-control or cohort studies, (c) outcomes of interest were all-cause death or cancer-specific death, (d) articles were published in English, (e) when several articles were published by the same authors or group, the newest or most informative article was selected. Exclusion criteria were the following: (a) no information on all-cause or cancer-specific survival, (b) letters to editor or commentary, reviews, (c) clinical studies reporting odds ratios (ORs) or risk ratios, or only univariate analyses. Two investigators extracted following data from the eligible articles independently: the name of first author, year of publication, origin of the study, follow-up period, patient number, study design, patient characteristics, statin uses, risk estimates and corresponding 95% confidence intervals (95% CIs), and covariates adjusted for in the multivariable analysis. Discrepancies were resolved by consensus, involving a third investigator.

2.3 | Quality assessment and statistical method

The methodological quality of included observational studies was independently determined by the Newcastle-Ottawa scale (NOS), which was based on three aspects of selection, comparability, and exposure/outcome. Two investigators independently completed the quality assessments and considered studies with a score of 7 or greater as high quality. Any disagreements were discussed with a third reviewer. We adopted adjusted hazard ratios (HRs) to calculate summary hazard ratios (HRs) with 95% CIs, using a random-effects model. We defined post-diagnostic statin uses as any use of statins after cancer diagnosis. Statistical heterogeneity across studies was estimated by Cochrane $X^2$ and $I^2$ statistics. A $P$ value of $<0.1$ or $I^2>50\%$ were considered as substantial heterogeneity across studies. In addition, we conducted pre-determined subgroup analyses based on tumor site, tumor stage, baseline therapy, and KRAS mutation status. A two-tailed $P$ value $<0.05$ was considered significantly. All statistical analyses were analyzed by Stata (version 11.0; StataCorp, College Station, TX).

3 | RESULTS

3.1 | Characteristics and quality assessment of included study

The detailed flow chart of study selection process was summarized in Figure 1. Totally, 4317 potentially relevant references were identified from initial search strategy. Four hundred and nineteen articles were excluded after duplication and remaining 3898 were screened based on abstracts and titles. After exclusion of unrelated articles, 47 full-text articles were further reviewed according to preset inclusion and exclusion criteria. Finally, 14 studies involving 130 994 patients met our criteria and were included in this meta-analysis. Detailed characteristics of the included studies were summarized in
Table 1. Generally, six studies involving 86,622 patients reported survival outcomes for patients of pre-diagnostic statin uses, while 11 studies involving 44,322 patients investigated survival outcomes related to post-diagnostic statin uses. Eight studies were conducted in Europe (United Kingdom, Denmark, Netherlands, Germany), four in North America, and two in Asia (China, Korea). Six studies investigated patients with stages I-IV, four with stages I-III, two with stage III, one with stages II-III, one with stage IV cancer. One study only included patients with rectum cancer, four studies only included patients with colon cancer, while the remaining nine studies included patients with both colon cancer and rectum cancer. The methodological quality of all included case-control and cohort studies was summarized (Table S2). The NOS results revealed that 13 of the 14 included studies had a score ≥7 except one study scored 6.

3.2 | Association between pre-diagnostic statin uses and mortality

Six studies reported the association between pre-diagnosis statin use and mortality in CRC patients. One study was excluded as it only reported OR of cancer-specific mortality.
| Year | 1st author | Study design | Tumor site | Statin Uses & No. of Patients | Tumor Stage | Treatment | Study design | Endpoints | Adjusted variables |
|------|------------|--------------|------------|-------------------------------|-------------|-----------|--------------|-----------|-------------------|
| 2009 | Siddiqui    | Retrospective| Colon      | Pre: 1309                     | I-IV        | S+C/R     |              | CSM       | BMI, NSAIDs        |
| 2011 | Ng          | Prospective  | Colon      | Post: 842                     | III         | S+C       |              | ACM       | DFM, RFM          |
| 2012 | Lakha       | Prospective  | Colon      | Pre: 277 Post: 282            | I-IV        | S+CR      |              | ACM       | CSM               |
| 2012 | Nielsen     | Prospective  | Colon      | Pre: 43487                    | I-IV        | C/R       |              | CSM       |                   |
| 2012 | Mace        | Retrospective| Rectum     | Post: 407                     | I-IV        | S+C/R     |              | ACM       | CSM, DFM, RFM     |
| 2014 | Cardwell    | Prospective  | Colon      | Pre: 14026 Post: 7657         | I-III       | S+C/R     |              | ACM       | CSM               |
| 2014 | Krens       | Retrospective| Colon      | Post: 529                     | IV          | C         |              | ACM       | PFM               |
| 2015 | Hoffmeister | Prospective  | Colon      | Post: 2699                    | I-IV        | S+C/R     |              | ACM       | CSM, DFM, RFM     |
| 2015 | Kim         | Retrospective| Colon      | Post: 686                     | III         | S+C/R     |              | CSM       | DFM               |
| 2015 | Shao        | Prospective  | Colon      | Pre: 17115                    | I-III       | S+C/R     |              | ACM       | CSM               |
| 2016 | Gray        | Prospective  | Colon      | Pre: 10408 Post: 8391         | I-III       | S+C/R     |              | ACM       | CSM               |
| 2017 | Gray        | Retrospective| Colon      | Post: 680                     | II-III      | S+C       |              | ACM       | CSM               |
| 2017 | Lash        | NA           | Colon      | Post: 21152                   | I-III       | S+C/R     |              | ACM       | CSM, RFM          |
| 2017 | Voorneveld  | Retrospective| Colon      | Post: 999                     | I-IV        | S+C       |              | ACM       | CSM               |

ACM = All-cause mortality; AJCC = American Joint Committee on Cancer; BMI = Body mass index; C = Chemotherapy; CRC = Colorectal cancer; CSM = Cancer-specific mortality; DFM = Disease-free mortality; HRT = hormone replacement therapy; NA = Not available; NSAIDs = Nonsteroid anti-inflammatory drugs; Post = Post-diagnosis; Pre = Pre-diagnosis; R = Radiotherapy; RCT = Randomized controlled trial; RFM = Recurrence-free mortality; S = Surgery.
3.3 | Pre-diagnostic statin uses and all-cause mortality

For all-cause mortality (ACM), the pooled HR was 0.85 (95% CI, 0.79-0.92) with a minor heterogeneity ($I^2 = 5.7\%, P = 0.346$), indicating that pre-diagnosis statin uses significantly lowered the risk of ACM (Figure 2A). In the subgroup analysis stratified by country, tumor site, tumor stage and therapy, both the heterogeneity and the result of ACM did not markedly alter (data not shown). No evidence of publication bias was observed in any analyses using Begg’s ($P = 1.000$) and Egger’s tests ($P = 0.494$) (data not shown).

3.4 | Pre-diagnostic statin uses and CSM

In terms of CSM, the pooled HR was 0.82 (95% CI, 0.79-0.86) with no heterogeneity ($I^2 = 0.0\%, P = 0.519$), suggesting that pre-diagnosis statin uses were associated with a 18% lower CSM (Figure 2B). In the subgroup analysis stratified by country, tumor site, tumor stage and therapy, both the heterogeneity and the result of CSM did not markedly alter (data not shown). No evidence of publication bias was observed in any analyses using Begg’s ($P = 0.462$) and Egger’s tests ($P = 0.293$) (data not shown).

3.5 | Association between post-diagnostic statin uses and mortality

Eleven studies investigated the association between post-diagnosis statin uses and mortality in CRC patients. One study was excluded due to its risk of immortal time bias. The remaining 10 studies with 44,040 patients were further analyzed.

3.6 | Post-diagnostic statin uses and ACM

For ACM, the pooled HR was 0.86 (95% CI, 0.76-0.98) with a considerable heterogeneity ($I^2 = 75.3\%, P = 0.000$) (Figure 2C). In the subgroup analysis stratified by country, tumor site, tumor stage and therapy, the result of ACM did not markedly alter (data not shown). Subgroup analysis by KRAS mutation status revealed no statistical differences in ACM between statin users and nonusers. For KRAS-mutated CRC patients, the pooled HR of ACM was 0.85 (95% CI 0.61-1.18) (Figure 3A); for KRAS wild-type CRC patients, the pooled HR of ACM was 0.79 (95% CI 0.70-0.89) (Figure 3B).

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**FIGURE 2** Meta-analysis of the association between statin uses and mortality of colorectal cancer (CRC) patients. (A) Pre-diagnosis statin uses and all-cause mortality. (B) Pre-diagnosis statin uses and cancer-specific mortality. (C) Post-diagnosis statin uses and all-cause mortality. (D) Post-diagnosis statin uses and cancer-specific mortality.
was 0.81 (95% CI 0.64-1.03). When stratified by tumor type, the heterogeneity decreased ($I^2 = 57.5\%, P = 0.095$) in patients with colon cancer. In other subgroups, the heterogeneity did not significantly change. No evidence of publication bias was observed in any analyses using Begg’s ($P = 0.251$) and Egger’s tests ($P = 0.053$) (data not shown).

### 3.7 Post-diagnostic statin uses and CSM

In terms of CSM, the pooled HR of eight studies was 0.79 (95% CI, 0.70-0.89) with a significant heterogeneity ($I^2 = 55.3\%, P = 0.028$), suggesting that statin uses reduced the risk of CSM (Figure 2D). In the subgroup analysis stratified by country, tumor site, tumor stage and therapy, the result of CSM did not markedly alter (data not shown). When stratified by tumor type, the heterogeneity decreased ($I^2 = 10.6\%, P = 0.290$) in patients with colon cancer. In other subgroups, the heterogeneity did not significantly change. No evidence of publication bias was observed in any analyses using Begg’s ($P = 0.902$) and Egger’s tests ($P = 0.794$) (data not shown).

### 3.8 Sensitivity analysis

Omitting single study in sensitivity analysis did not markedly alter the overall results of ACM and CSM with pre- and post-diagnosis statin uses (data not shown). However, when calculating CSM with post-diagnosis statin uses, the heterogeneity decreased ($I^2 = 37.8\%, P = 0.141$) after omitting 2015, Hoffmeister. In other subgroups, the heterogeneity did not significantly change (data not shown).

### 4 DISCUSSION

The present meta-analysis demonstrates that statin uses both before and after CRC diagnosis improved the overall and cancer-specific survival for CRC patients. These effects persisted even after subgroup analysis stratified by country, tumor site, tumor stage and therapy. Our results may be important for making further clinical decisions for CRC patients.

Several studies in vitro and vivo have strongly indicated the anticancer effects of statins on CRC. Role of statins as an adjuvant agent for CRC treatment has been suggested in many preclinical animal models. Experiment on colon-26 cell lines model in vivo by Feleszko et al reveals that, combined treatment with lovastatin and doxorubicin resulted in significant retardation of tumor growth, as compared with either of the agents alone.27 In the MIN mice model, it is indicated that atorvastatin was effective in significantly slowing the growth of colon cancer cell xenografts due to increased levels of apoptosis.28 Cho et al shows that, in the colitis-associated colon cancer model, simvastatin inhibited colon cancer development by the induction of apoptosis and the suppression of angiogenesis.29 There are various underlying molecular mechanisms of statins on CRC. Statins are competitive inhibitors of HMG-CoA reductase, the rate-limiting enzyme of mevalonate pathway. The mevalonate pathway produces various end products, including farnesyl pyrophosphate (FPP) and geranyl pyrophosphate (GPP), which are involved in cellular proliferation, angiogenesis, and anti-apoptosis via inducing isoprenylation of the intracellular G-proteins.30 Reduced levels of mevalonate via statins, therefore, results in antiproliferative, proapoptotic, anti-angiogenic, and anti-invasive effects.30 Furthermore, HMG-CoA reductase-independent mechanisms are also indicated. Statins inhibit DNA methyltransferase activity, demethylate bone morphogenetic protein 2 promoters and activate the bone morphogenetic protein pathway, which increases apoptosis and promotes differentiation in CRC cells.31

Besides, several recent researches have suggested the possible synergistic effects of statins and EGFR inhibitors on CRC with KRAS mutations.32,33 KRAS mutations are estimated to account for approximately 30%-40% of CRC patients nonresponsive for monoclonal antibodies targeting EGFR.34 As an essential element of the EGFR signaling pathway, KRAS can acquire activating mutations in exon 2, thus rendering EGFR inhibitors ineffective.35 The activation
of KRAS protein could initiate several downstream signaling cascades, including Raf/MAPK, Rac/Rho, PI3K/PKB, thus promoting cell proliferation, migration and survival.\textsuperscript{36} By inhibiting the production of FPP and geranylgeranyl pyrophosphate (GGP) which are essential for Ras prenylation, statins could interfere with Ras functional localization and thus inhibiting the downstream signaling pathways.\textsuperscript{36} Therefore, in this study, the prognostic effects of statins were analyzed based on KRAS mutation status. Due to limited number, only four studies were included. No improvement on overall survival was observed when stratified by KRAS mutation status for post-diagnosis statin uses. Further studies need to explore the association between KRAS status and survival benefit of statin uses. However, our study does show a possible trend toward a reduction in ACM among KRAS mutant CRC patients using statins after diagnosis.

The beneficial effects of statins on CRC prognosis could be attributed to both its cancer-prevention effects and its potential role on cancer adjuvant therapy. Pre-diagnosis statin uses have been demonstrated to be preventive for colorectal adenoma and CRC. In a retrospective cohort study following 3587 patients with histologically confirmed adenomatous polyps (APs), statin uses were associated with less polyp number, smaller polyp size, lower incidence rate of advanced APs.\textsuperscript{37} A recently conducted meta-analysis involving 13,239 patients showed that, statins did not significantly affect the risk of any adenoma but was inversely correlated with the risk of advanced colorectal adenoma.\textsuperscript{38} Moreover, in a meta-analysis evaluating clinical CRC risk, the pooled results from 42 researches showed a modest reduction of CRC incidence after statin uses.\textsuperscript{39} The role of statins on cancer adjuvant therapy has also been studied in clinical. A retrospective, case-control study from US reported a less advanced tumor stage, a lower frequency of distant metastases, and a higher survival rate for male CRC patients taking statins.\textsuperscript{15} Also, three well-designed retrospective cohort studies all reported improved pathological complete response to neoadjuvant chemoradiation in rectal cancer patients with statin uses.\textsuperscript{19,40,41}

To our knowledge, there were four meta-analysis\textsuperscript{23,42,43} so far that analyzed the association between statin uses and prognosis of CRC. Compared with the previous analyses, our meta-analysis updated some important information, including three new studies involving 22,831 patients, which accounts for over 20% of all patients included. In three former studies,\textsuperscript{42,43} there are several limitations interfering with the conclusion. First, data from several studies\textsuperscript{16,17} recorded in Cai et al\textsuperscript{42} and Ling et al\textsuperscript{43} were inconsistent with original data. Second, the OR in Siddiqui et al\textsuperscript{15} was misused as HR for analysis, and the potential immortal time bias in Lakha et al\textsuperscript{17} was overlooked. Nielsen et al\textsuperscript{18} was calculated twice in Ling et al.\textsuperscript{43} Also, essential data from several studies\textsuperscript{9,15,46} included in Gray et al\textsuperscript{23} have not been publicly published yet, therefore, quality assessment could not be done, and the data accuracy cannot be guaranteed. Hence, these studies were excluded in our meta-analysis.

There are some limitations in our study. Firstly, heterogeneity does not markedly alter in subgroup analysis. Therefore, other potential sources of heterogeneity, such as using of non-steroid anti-inflammatory drugs, statin dose and duration, location of CRC, pathological differentiation, should be further analyzed if data are available. Secondly, owing to the relatively small sample size, some subgroup analysis may contain few studies and conclusions might be less convincing. For instance, in subgroup analysis stratified by KRAS mutation status, only four studies were included. Results may be more stable and reliable with increasing number of studies that could be involved in future. Thirdly, dose-response analysis was not conducted due to insufficient research data in this study. This might be an important confounding factor when estimating the effects of statins. Furthermore, due to the limited relevant researches, disease-free survival and recurrence-free survival were not included in our study. Up until now, available evidence is not sufficient to show any difference in disease-free survival DFS and recurrence-free survival RFS in CRC patients taking statin therapy. Whether statins own cancer-directed benefits or not should be further discussed, and statins prescription should not be a routine for CRC prevention or treatment by now.

5 | CONCLUSIONS

In conclusion, our meta-analysis demonstrates that both pre-diagnosis and post-diagnosis statin uses are associated with reduced ACM and CSM for CRC patients. Considering that statins are low cost and wildly used agents worldwide, we believe our updated meta-analysis can provide new insights into optimizing adjuvant treatment of CRC. Further clinical studies, especially RCTs and basic studies investigating KRAS mutations, are expected to be conducted to confirm the role of statins in CRC treatment.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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