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Research Paper

Expression of Minichromosome Maintenance Proteins (MCM) and Cancer Prognosis: A meta-analysis

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Abstract

Minichromosome maintenance proteins (MCM) played a critical role in replication and cell cycle progression. However, their prognostic roles in cancer remain controversial. Therefore, we performed a meta-analysis to investigate the prognostic value of MCMs in cancers. Totally 31 eligible articles with 7653 cancer patients were included in this meta-analysis. We evaluated the relationship between MCMs expression and overall survival (OS) in various cancer patients by using pooled hazard ratios (HRs) and risk ratios (RRs) with 95% confidence intervals (CIs). The meta-analysis showed that carriers with high expression of MCM5 and MCM7 were significantly associated with short OS for pooled HR (HR=1.04, 95% CI=1.01-1.08, P=0.020, HR=1.78, 95% CI=1.04-3.02, P=0.035, respectively). For pooled RR, individuals with increased MCM2 and MCM7 expression were significantly correlated with poor OS (RR=2.30, 95% CI=1.14-4.63, P=0.019; RR=3.52, 95% CI=2.01-6.18, P<0.001, respectively). The findings suggest that high expression of MCM2, MCM5 and MCM7 might serve as predictive biomarkers for poor prognosis in cancers.

Key words: MCM; meta-analysis; prognosis

Introduction

Based on GLOBOCAN estimates, approximately 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide [1]. Although diagnosis and therapy for cancer has made great progress, the prognosis of most cancers was still poor on account of recurrence, metastasis and chemoradio-resistance [2, 3]. Clinical characteristics, such as stage, grade and histologic type, etc. are the most crucial prognostic factors to predict clinical outcomes [4]. However, individuals with the same classical parameters often end up with various outcomes [5]. In recent years, molecular classification beyond to stage and grade is just unfolding for providing accurate prediction of clinical outcome based on the expression of cancer-related biomarkers, by which treatment could be adjusted according to molecular status[6].

The MCMs are ubiquitously expressed proteins, including MCM1-10. Among these proteins, MCM2-7 form a hexamer called the MCM complex which are all AAA+ ATPases and share partial homologous sequences[7]. MCM complex plays an important role in the initiation of DNA replication. In G1-phase, MCM2-7 replicative helicase binds around double-stranded DNA (dsDNA) in the form of inactive head-to-head dimer. In S-phase, the active MCM2-7 double hexamer (MCM DH) conducts bidirectional DNA synthesis at eukaryotic origins[8]. In addition, the MCM complex contributes to replication elongation, cohesion, condensation, transcription and recombination of DNA molecule[9]. Each member of MCM complex may plays a distinct or similar role in the regulation of cell behavior.

Previous evidence showed that MCM complex subunits have been implicated in cell proliferation, invasion and metastasis [10-12].

Controversial results have been reported among a variety of cancers. A number of studies demonstrated that overexpression of MCMs were found to be significantly correlated to a poor outcome in cancers, such as gastric cancer(GC) [13, 14], non-benign epithelial ovarian tumor [15], breast cancer [16] , glioma [17], non-pure-(BAC)bronchiolo-alveolar carcinoma [18], gallbladder [19], osteosarcoma[20] and muscle-invasive urothelial cancer [21]. High MCMs expression was correlation with high TNM stage, lymph node metastasis and recurrence in above cancers, which suggested increased expression of MCM2 might be associated with increased malignancy of these cancers. However, other studies for ER-positive breast cancer [22], small lung adenocarcinomas [23] and colorectal cancer (CRC) [24] demonstrated the potential role of MCMs overexpression in predicting better prognosis. In ER-positive breast cancer study, Ali et al. pointed out that high MCM2 expression was correlated with human epidermal growth-factor receptor 2 (HER-2)-positive, and HER-2-positive was known as a good biomarker for prognosis of breast cancer [22]. In addition, some researches indicated that MCMs expression was not related with survival of non-small cell lung cancer (NSCLC)[25] and hepatocellular carcinoma (HCC)[26]. The effects of MCMs expression in prognosis of cancers have been investigated but the results have not yet reached a consensus. Up to now, no meta-analysis has investigated the prognosis of various cancers in relation to MCMs expression. To explore whether expression of MCMs was correlated with prognosis of overall cancer and specific cancer subtypes, we performed this meta-analysis.

In our study, 31 studies with 7653 patients were included. Our results indicated that positive or high expression of MCM2, MCM5 and MCM7 may predict worse prognosis of cancers. Our results may be helpful to provide clinical evidence for effective treatment of cancer patients.

Materials and Methods

Search Strategy

Literature search was performed in the electronic platforms of PubMed, Web of Science, Cochrane Library and Embase. The last search date was October 10, 2017. The search strategy was used as: 'MCM2/CDCL1/BM28', 'MCM3/P102/RLF', 'MCM4/CDC21', 'MCM5/P1Cdc46', 'MCM6/Mis5', 'MCM7/CDC47' and 'cancer/carcinoma/neoplasm/neoplasia/tumor/tumour'. Article language was limited to English and Chinese. The references of all relevant articles were manually reviewed to find potentially relevant articles. To evaluate the quality of studies, we used the Newcastle-Ottawa Scale (NOS). We assigned the studies of high quality a scored ≥ 6 stars. The results are shown in Table 1. Two investigators assessed the eligibility of the studies independently and reached agreement by discussion.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) studies concerning the survival outcomes of cancer patients with high/positive MCMs expression versus low/negative MCMs expression; (2) studies with complete information for assessment of hazard ratios (HRs) or risk ratios (RRs) and their 95% confidence intervals (CIs) for overall survival (OS); (3) original articles in English. Exclusion criteria: (1) study without sufficient data; (2) letters, editorials, case reports, reviews, comments or meeting abstracts.

Data Extraction

Two authors (Kaihua Gou and Xue Feng) extracted the data of included studies. The following extracted information was recorded: first author's name, year of publication, number of patient, ethnicity, tumor stage, detection method, cut-off value, analytical method, HRs or RRs with their 95 % CIs for OS and study quality. If the above-mentioned data was not available, items were regarded as 'not reported'.

Statistical Analyses

STATA (Version 11.0; StataCorp, College Station, TX) was used to conduct statistical analysis. Pooled HRs or RRs and their 95% CIs were calculated to measure the impact of MCMs expression on the survival of patients. I^2 test and Q test were performed to assess heterogeneity among the studies ($P<0.10$ indicates significant heterogeneity between studies). A fixed-effect model was used to calculate the pooled HRs or RRs when heterogeneity between studies was not significant. Otherwise, a random-effect model was applied. Sensitivity analysis was carried out to explore heterogeneity when significant heterogeneity was manifested. Subgroup analyses were conducted to explore the effects of source of controls and cancer types. In addition, Egger's test and Begg's test were performed to assess publication bias among included studies. P value<0.05 was considered as statistically significant. We followed the PRISMA statement (S1) to design and report our meta-analysis.

Table 1. Characteristics of eligible studies in this meta-analysis.

Author	Year	Cancer type	Ethnicity	Number	Cutoff	TNM	U/M	Expression	Detection method	Study quality
MCM2										
Cheng, D. D.	2017	Osteosarcoma	Chinese	129	2 scores	NR	M	Protein	IHC	6
Liu, Z.	2016	GBC	Chinese	1060	25%	I-IV	M	Protein	IHC	7
Ali, H. R.	2012	Breast cancer	British	1064	3 scores	NR	U/M	Protein	TMA & IHC	7
Yang, C.	2012	Gastric cancer	Chinese	264	3 scores	I-IV	M	Protein	TMA & IHC	7
Zhao, D. B.	2011	CRC	Chinese	306	51.20%	I-III	M	Protein	TMA & IHC	6
Wojnar, A.	2011	Breast cancer	Polish	117	25%	I-IV	U	Protein	IHC	9
Fujioka, S.	2009	Lung ACs	Japanese	100	14.60%	I	M	Protein	IHC	7
Loddo, M.	2009	Breast cancer	British	182	30%	NR	U	Protein	IHC	7
Kayes, O. J.	2009	Penile carcinoma	British	84	4%	I-IV	M	Protein	IHC	6
Tokuyasu, N.	2008	Gastric cancer	Japanese	43	44%	NR	M	Protein	IHC	8
Gakiopoulou, H.	2007	Ovarian AC	Greek	128	20%	I-IV	M	Protein	IHC	6
Yang, J.	2006	NSCLC	American	128	25%	I-IIIA	U	Protein	IHC & WB	6
Korkolopoulou, P.	2005	UC	Greek	65	18%	II-IV	M	Protein	IHC	6
Gonzalez, M. A.	2004	Breast cancer	British	164	50%	NR	U	Protein	TMA & IHC	7
Hashimoto, K.	2004	Lung AC	Japanese	122	40%	I-III	U	Protein	IHC	7
Kato, H.	2003	OSCC	Japanese	93	62.70%	I-IV	M	Protein	IHC	7
MCM5										
Yu, S. Y.	2014	Oral SCC	Chinese	97	60%	I-IV	M	Protein	IHC	6
Giaginis, C.	2011	Gastric cancer	Greek	66	NR	I-IV	M	Protein	IHC	7
Gakiopoulou, H.	2007	Ovarian cancer	Greek	128	25%	I-IV	M	Protein	IHC	6
MCM7										
Almadori, G.	2017	Laryngeal SCC	Italian	61	50%	I-IV	M	Protein	IHC	6
Karavias, D.	2016	HCC	Greek	111	5 scores	I-IV	U	Protein	IHC	8
Deraco, M.	2015	DMPM	Italian	170	NR	NR	U	Protein	IHC & TMA	6
Zhong, X.	2015	OSCC	Chinese	139	50%	I-IV	M	Protein	IHC & TMA	7
Hua, C.	2014	Glioma	Chinese	59	NR	II-IV	M	Protein & RNA	WB & qPCR	6
Zhong, X.	2014	NSCLC	Chinese	270	50%	I-IV	M	Protein	IHC	8
Liu, Y. Z.	2012	NSCLC	Chinese	494	50% & 10%	I-IV	M	Protein	IHC & ICC	6
Zhou, Y. M.	2012	HCC	Chinese	87	30%	I-IV	M	Protein	IHC	7
Tolonen, T. T.	2011	Prostate cancer	Finnish	292	20%	I-IV	U	Protein	IHC	6
Haruki, T.	2011	Lung AC	Japanese	100	15.60%	NR	M	Protein	IHC	7
Hamamoto, Y.	2010	STS	Japanese	109	17.40%	I-IV	M	Protein	IHC	6
Fujioka, S.	2009	Lung AC	Japanese	100	20.20%	NR	M	Protein	IHC	7
Nishihara, K.	2009	CRC	Japanese	191	58%	I-IV	U	Protein	IHC	7

IHC: immunohistochemistry; TMA: tissue microarray; qPCR: quantitative PCR; WB: western blot; HR: hazard ration; H: high expression; L: low expression; P: positive expression; N: negative expression; TNM: tumor-node-metastasis; M: multivariate analysis; U: univariate analysis; NR: not reported; NSCLC: non-small cell lung cancer; SCC: squamous cell cancer; AC: adenocarcinoma; GBC: gallbladder cancer; CRC: colorectal cancer; Laryngeal SCC: laryngeal squamous cell carcinoma; HCC: hepatocellular carcinoma; DMPM: Diffuse Malignant Peritoneal Mesothelioma; OSCC: oesophageal squamous cell carcinoma; STS: soft tissue sarcomas.

Results

Study Characteristics

In total, 2813 potentially non-duplicated studies were obtained after the initial database searches. After excluding 2546 articles based on title/abstract review, 267 articles were retrieved. Then, another 217 studies were excluded after review of the full texts, including 97 articles of insufficient data, 61 articles of meeting abstract, 23 reviews, 2 article without full text, 1 non-English article and 2 articles quality ≤ 5stars. Finally, 31eligible studies which fulfilled all inclusion criteria were selected in this meta-analysis [13-24, 26-44]. The study selection procedure is outlined in Figure 1. The principal characteristics of the included studies are summarized in Table 1. The overall sample-size added up to 7653 participants. Of the 31 studies, the populations of 17 studies were Asian [13, 14, 17-20, 23, 24, 28-30, 32, 34, 37-40, 44], and the remaining 13 studies were Caucasian [15, 16, 21, 22, 26, 27, 31, 33, 35, 36, 41, 42]. Nine studies investigated the association of MCM2 expression with OS for HR [14-16, 20, 22, 24, 31, 35, 41, 42] and 8 for RR [13, 17-19, 21, 23, 29, 36] separately; 3 articles investigated the association of MCM5 with OS for HR [15, 27, 37]; 6 studies in association with MCM7 were included respectively for HR [26, 30, 38-40, 43] and 7 for RR[17, 23, 28, 33, 41, 44, 45]. The types of cancers included HCC, OSCC, NSCLC and so on. Data concerning different cancers and ethnicity were considered as separate studies in the subgroup analysis.

Association of MCMs with OS

The pooled HR was presented in Table 2. Carriers with increased MCM2 expression were not associated with worse OS compared with decreased expression (HR=1.11, 95% CI=0.98-1.26, P=0.094, Figure 2). However, individuals with high expression of MCM5 and MCM7 were correlated with worse OS compared with low expression (HR=1.04, 95% CI=1.01-1.08, P=0.020; HR=1.78, 95% CI=1.04-3.02, P=0.035, respectively, Figures 4 and 5). As for ethnicity, patients with increased expression of

MCM7 were significantly associated with shorter OS in Asian (HR=2.49, 95%CI=1.93-3.21, P<0.001). In regard to cancer types, the pooled HR of MCM7 high/positive expression was 2.51 in lung cancer (Table 2).

The pooled RR of included studies are presented in Table 3. Patients with increased expression of MCM2 and MCM7 were significantly associated with shorter OS (RR=2.30, 95% CI=1.14-4.63, P=0.019; RR=3.52, 95% CI=2.01-6.18, P<0.001, respectively, Figures 3 and 6). In the subgroup analysis of cancer type, increased expression of MCM2 was related to poor OS of digestive system cancer (RR=2.36, 95% CI=1.57-3.55, P<0.001) but no significant association was found for lung cancer (RR=1.01, 95% CI=0.42-2.41, P=0.992). In the comparison of OS between low/negative and high/positive MCM7 expression, low/negative was significantly associated with a better OS in Asian and Caucasian (HR=3.81, 95%CI=1.84-7.87, P<0.001; HR=2.51, 95%CI=1.57-4.00, P<0.001, respectively). In lung cancer, increased expression of MCM7 were significantly associated with shorter OS (HR=7.84, 95%CI=2.14-28.74, P=0.002).

Table 2. Meta-analysis results of the association between MCMs expression and overall survival for pooled HR.

Categories	Group/subgroup	Data set number	HR(95%CI)	P value	Model	P_{het}	I^2 (%)
MCM2	Overall	10	1.11(0.98-1.26)	0.0941	R	<0.001	75.0%
	Digestive system cancer	2	1.17(0.34-4.02)	0.809	R	<0.001	94.1%
	Breast cancer	5	1.20(0.97-1.48)	0.095	F	0.166	38.2%
	Asian	3	1.31(0.571-3.00)	0.525	R	<0.001	91.4%
	Caucasian	7	1.09(1.00-1.19)	0.061	R	0.030	57.1%
MCM5	Overall	3	**1.04(1.01-1.08)**	**0.020**	F	0.146	48.1%
MCM7	Overall	6	**1.78(1.04-3.02)**	**0.035**	R	<0.001	79.3%
	Digestive system cancer	3	2.17(0.86-5.49)	0.101	R	0.017	75.5%
	Lung cancer	2	**2.51(1.88-3.45)**	**<0.001**	F	0.323	0.0%
	Asian	5	**2.49(1.93-3.21)**	**<0.001**	F	0.169	40.5%

R: random effect model; F: fixed effect model.

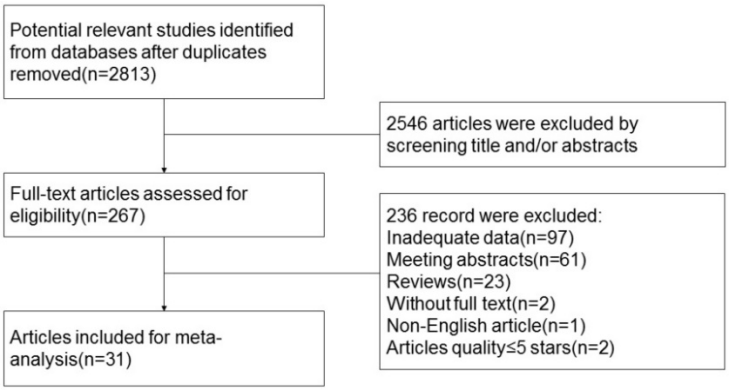

Figure 1. Flow diagram of studies selection procedure

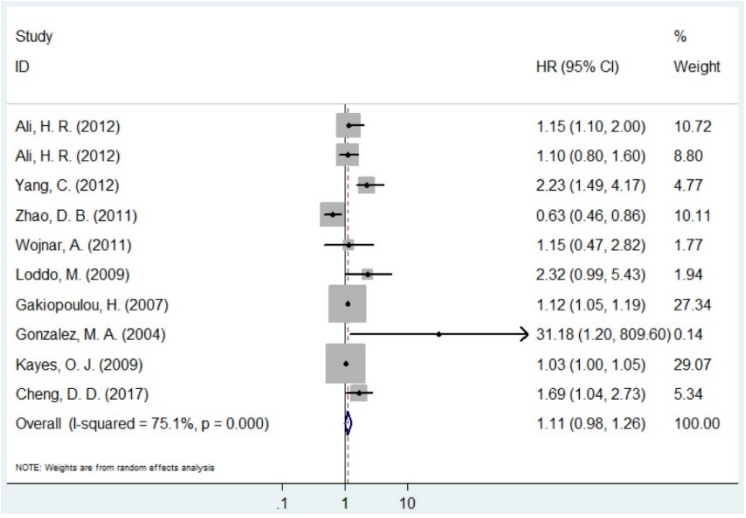

Figure 2. Forest plot of HR for the association between MCM2 and OS (H/P vs. L/N).

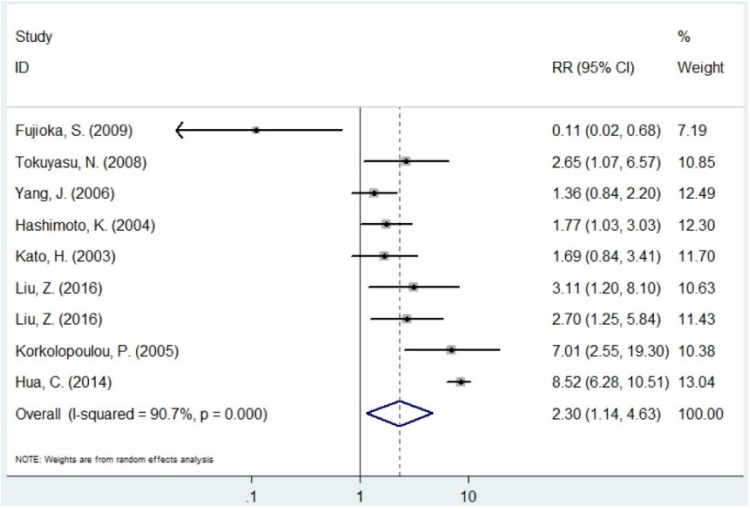

Figure 3. Forest plot of RR for the association between MCM2 and OS (H/P vs. L/N).

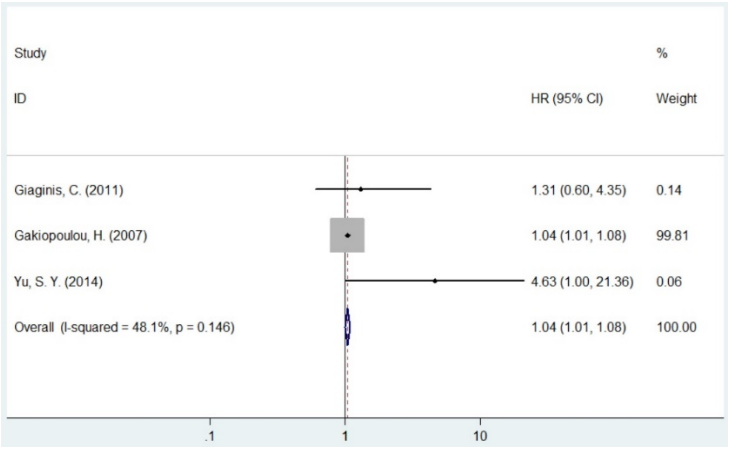

Figure 4. Forest plot of HR for the association between MCM5 and OS (H vs. L).

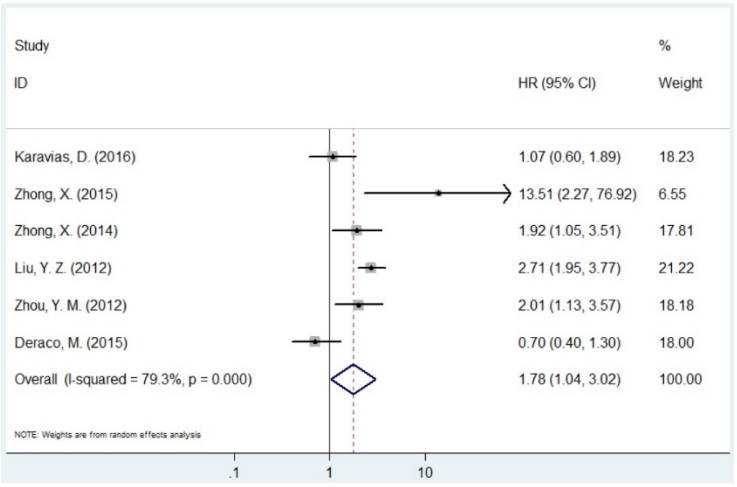

Figure 5. Forest plot of HR for the association between MCM7 and OS (H/P vs. L/N).

Heterogeneity Test, Sensitivity Analysis, and Publication Bias

For MCMs, significant heterogeneity was observed except for MCM5, which could not be completely explained by design or subgroup analysis. Because the numbers of included studies for MCM5 was <5, we did not perform sensitivity analyses. The results of the sensitivity analysis for MCM2 and MCM7 showed that the exclusion of each single study did not change the statistical significance except MCM7 for HR.

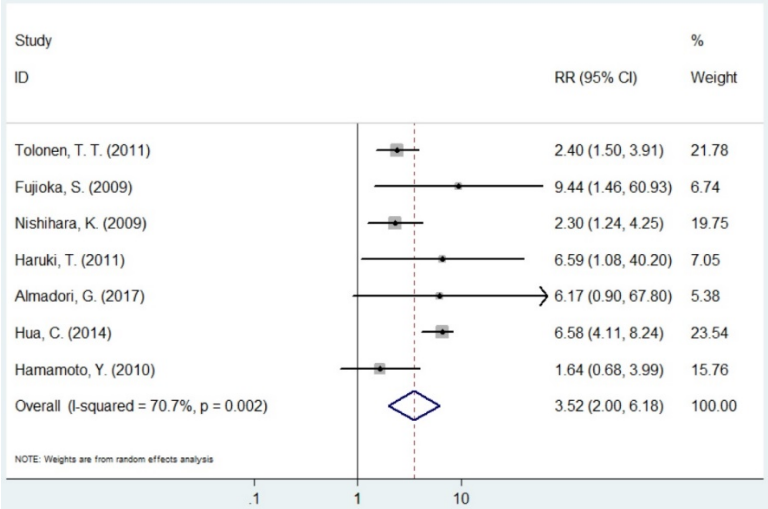

Figure 6. Forest plot of RR for the association between MCM7 and OS (H/P vs. L/N).

Table 3. Meta-analysis results of the association between MCMs expression and overall survival for pooled RR.

Categories	Group/subgroup	Data set number	RR(95%CI)	P value	Model	P_{het}	I^2 (%)
MCM2	Overall	9	**2.30(1.14-4.63)**	**0.019**	R	<0.001	90.7%
	Lung cancer	3	1.01(0.42-2.41)	0.992	R	0.013	77.1%
	Digestive system cancer	4	**2.36(1.57-3.55)**	**<0.001**	F	0.711	0.0%
	Asian	7	2.15(0.96-4.82)	0.064	R	<0.001	90.5%
	Caucasian	2	2.90(0.58-14.40	0.193	R	0.004	87.8%
MCM7	Overall	7	**3.50(2.01-6.18)**	**<0.001**	R	0.002	70.7%
	Asian	5	**3.81(1.84-7.87)**	**<0.001**	R	0.005	73.1%
	Caucasian	2	**2.51(1.57-4.00)**	**<0.001**	F	0.403	0.0%
	Lung cancer	2	**7.84(2.14-28.74)**	**0.02**	F	0.786	0.0%

Table 4. Publication bias.

	z value	P value	t value	P value
HR				
MCM2	0.720	0.474	1.600	0.148
MCM5	1.040	0.296	1.650	0.347
MCM7	1.36	0.175	1.01	0.344
RR				
MCM2	0.730	0.466	-2.430	0.046
MCM7	0.30	0.764	-0.34	0.751

We performed the Begg's and Egger's tests to identify potential publication bias. The detailed results for publication bias test were summarized in Table 4. No significant publication bias was found in this meta-analysis.

Discussion

Since the prognosis significance of MCM family proteins in cancers is controversial, a quantitative meta-analysis is employed in our study. As far as we are concerned, this is the first meta-analysis to evaluate the correlation between expression levels of MCMs and survival of cancer. By analyzing the data extracted from 31 full-text publications, we revealed that high expression of MCM2, MCM5 and MCM7 might be associated with poor OS.

The pooled RR results showed that high MCM2 expression was associated with patients' poor OS. A number of researches have indicated the role of MCM2 in cancer development. Liu et al. reported that positive MCM2 expression was significantly correlation with high TNM stage, large tumor size, lymph node metastasis and invasion in squamous cell (SC)/adenosquamous carcinoma (ASC) and adenocarcinoma (AC) of the gallbladder [19]. Similarly, Giaginis et al. found that MCM2 expression was significantly correlation with the tumors grade, vascular invasion and Dukes' stage in CRC [46]. In addition, MCM2 expression was found to be independent predictors of recurrence in bladder cancer [47]. Mutation of TP53 is associated with a poorer prognosis and this abnormality is common in tumors with high expression of MCM2 and MCM7 [48]. These findings suggested that high MCM2 expression in cancers tends to indicate higher biological malignant aggressiveness, which are consistent with our results.

The present study pointed out that the OS of patients with high expression of MCM5 was significantly shorter than that of patients with low expression. For MCM5, significant correlation was

found between the higher MCM5 expression and OSCCs with larger tumor size, higher clinical stage, higher histological grade, lymph node metastasis and deeper invasion depth [37]. Additionally, the expression levels of MCM5 were also found to be increased in advancing tumor stage of epithelial ovarian adenocarcinoma [15] and muscle-invasive urothelial cancer [21]. Similarly, it has been reported that MCM5 silencing reduced cell proliferation in human anaplastic thyroid cancer-derived cell lines [49]. In human melanocyte cell line, Sox10 inhibited proliferation by down-regulating the expression of MCM5. [50]. Estrogen receptor beta increased cell proliferation and invasion by up-regulating expression of MCM5 in bladder cancer cell lines [51]. Therefore, overexpression of MCM5 might be linked with increased proliferative rate of cancer cells. These results, at least in part, explained the neoplasms with higher level expression of MCM5 own more aggressive biological behaviors. Effective therapeutic target is very essential for the clinical treatment of cancers. Our results would provide useful information about the potential of MCM5 as a therapeutic target.

In the present study, we have found that high MCM7 expression was correlated with poor OS both in HR and RR. We suggest possibly following explanations of why MCM7 expression affected OS. The levels of MCM7 protein expression was higher in Grade II than in Grade I in meningioma [52]. Guan et al. found MCM7 expression was elevated with increased tumor grade in papillary urothelial neoplasia [53]. Feng et al. revealed that MCM7 were associated with the lymph nodes metastasis and the clinical stage in OSCC [54]. However, Ishibashi et al. conducted a study on the correlation between MCM7 expression and clinicopathological characteristics of CRC which was no statistical significance [55]. In vitro, low MCM7 expression significantly inhibited cell proliferation, colony formation and migration in esophageal carcinoma cell lines [56]. Similarly, Qu et al. indicated that MCM7 downregulation reduced proliferation by suppressing the expression of extracellular regulated kinase 2 (ERK2), ERK3, ERK4 and ERK7 which were proteins of MAPK signaling pathway in HepG2 cell line [57]. Cell proliferation, worse clinical tumor stage, positive lymph nodes metastasis and recurrence were all unfavorable cancer parameters. The relations of MCM7 expression with these factors could support our finding of its potential as a prognostic biomarker. As for different populations, the current findings suggested that MCM7 expression might be a useful predictor for prognosis in Asian patients but not in Caucasian patients. The results of different ethnic background should be confirmed by future studies.

Kwok, H. F et al. suggested that MCM2-7 gene may be closely co-regulated by common transcription factors (AML-1a, GATA-1, SRY) in breast cancer [58]. Similar to above result, our study indicated that the pooled HR or RR of MCM2, MCM5 and MCM7 were all >1, although MCM2 pooled HR do not reach statistical significance. Therefore, we point out that MCMs expression may be associated with the prognosis of cancers as a complex. However, contrary to our result, a conclusion that the presence of MCM2 protein disturbs the assembly of MCM4, MCM6, and MCM7 proteins to suppress the DNA helicase activity was draw from study on Hela cells [59]. In that case, high level expression of MCM2 would predict better prognosis. The discrepancy between above publication and our conclusion may be due to the condition that MCM2 protein modification lead to the function change of MCM4, 6 and 7 complex beside the amount of MCM2 protein.

Several limitations should be acknowledged in this meta-analysis. First, the sample size was not sufficiently large for MCM5. Second, all the studies included in the meta-analysis were published in English and Chinese, therefore publication bias might present in our study although the bias test did not show it. Third, the heterogeneity could not be totally eliminated by subgroup analysis and sensitivity analysis. The detecting methods of MCMs expression, cut-off value, source of antibodies, dilution ratios and surgical operation were different, which may cause heterogeneity between the included studies. Finally, the different survival analysis methods might affect the accuracy of outcome, although the most of the studies conducted multivariate analysis in Cox proportional hazards model.

Conclusions

In summary, this meta-analysis found that high expression of MCM2, MCM5 and MCM7 were related with worse survival for cancer patients. However, before MCMs expression are routinely used in patient management, large-scale and well-designed studies on different ethnicities are still needed to validate the results of our meta-analysis.

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Author Contributions

KG. designed the research; KG JL HL XF. conducted the studies; KG JL. analyzed the data and

prepared the manuscript; CX YY. guided the experiments and edited the paper. All of the authors read and approved the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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