Prognostic value of the miR-200 family in bladder cancer: a systematic review and meta-analysis

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Research

Keywords: miR-200 family, bladder cancer, prognosis, meta-analysis

Posted Date: February 25th, 2020

DOI: <https://doi.org/10.21203/rs.2.24463/v1>

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Version of Record: A version of this preprint was published at Medicine on November 20th, 2020. See the published version at <https://doi.org/10.1097/MD.00000000000022891>.

Abstract

Introduction : The association between the miR-200 family and the prognosis of patients with bladder cancer remains controversial. The aim of this study is to evaluate the prognostic value of the miR-200 family in patients with bladder cancer.

Methods : Electronic databases were searched to identify the studies that had assessed the association between the miR-200 family and prognosis in patients with bladder cancer. Hazard ratios (HRs) and 95% confidence interval (CI) for overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS) from eligible studies were used to calculate combined hazard ratios. The heterogeneity across the included studies was assessed by Cochrane's Q test and I² statistic. The Begg's funnel plot and Egger's linear regression tests were used to evaluate the potential publication bias. The meta-analysis was performed with RevMan 5.3 and Stata SE12.0 according to the PRISMA guidelines.

Results : A total of 1152 patients from 8 studies were included in this meta-analysis. The results showed that the high expression of the miR-200 family was associated with better OS (pooled hazard ratio: 0.50, 95% confidence interval: 0.40-0.62), CSS (pooled hazard ratio: 0.36, 95% confidence interval: 0.22-0.59) and RFS (pooled hazard ratio: 0.48, 95% confidence interval: 0.36-0.65). Both Begg's funnel plots test and Egger's test verified that there was no publication bias within the included cohorts.

Conclusion : This study suggests that the high expression of the miR-200 family is significantly associated with better prognosis in patients with bladder cancer.

Introduction

MicroRNAs (miRNAs) are a class of small non-coding RNAs, approximately 18–22 nucleotides in length that regulate gene expression by inhibiting translation and reducing the stability of their target mRNAs [1]. By affecting protein translation, miRNAs have been recognized as powerful regulators of key cellular processes including proliferation, differentiation, apoptosis, stress response and metabolism [2, 3]. miRNAs appear to be key regulators of many diseases, including neurologic disorders, heart disease, vascular diseases, and especially cancers [4]. miRNAs frequently reside in fragile sites and genomic regions involved in various cancers, suggesting that they play a potentially critical and complex role in cancers [5]. Many previous studies have confirmed that the abnormal expression of miRNAs is closely related to the prognosis of many cancers, such as lung cancer [6], gastric cancer [7] and bladder cancer [8]. Therefore, the functional miRNAs could be promising prognostic biomarkers for various human cancers.

miR-200, a family of tumor suppressor miRNAs, consists of miR-200a, miR-200b, miR-200c, miR-141 and miR-429. Those five highly homologous members can be divided into two gene clusters based on the fact that they are expressed by two different polycistronic transcripts. The miR-200b/a/429 cluster is located on chromosome 1p36, and the miR-200c/141 cluster is located on chromosome 12p13 [9]. The miR-200 family is a key inhibitor of epithelial to mesenchymal transition (EMT) through regulation of E-cadherin expression via suppression of ZEB1 and ZEB2 [10]. Many studies have demonstrated that the miR-200 family is dysregulation in a variety of human cancers and is closely related to the prognosis of those tumors, such as colorectal cancer [11], ovarian cancer [12] and breast cancer [13].

Bladder cancer is the second most common cancer in urology with respect to the prevalence and incidence. In 2018, the estimated number of new cases and deaths of bladder cancer in USA were 81,190 and 17,240, respectively [14]. About 75% of newly diagnosed bladder cancer cases are non-muscle invasive bladder cancer (NMIBC), and the rest are muscle invasive bladder cancer (MIBC). For NMIBC, patients suffer from a high rate of recurrence and progression. The 5-year recurrence rate of NMIBC range from 50–70%, and the rate of progression to MIBC in 5 years range from 10–30% [15]. For MIBC, the key clinical concern is metastasis and the high rate of mortality despite the improved systemic therapy. Some markers are currently used to predict the prognosis of bladder cancer, such as oncogenes, cell adhesion molecules, cell cycle regulatory proteins, tumor-associated antigens, etc. [16]. However, better and more reliable prognostic biomarkers are still needed to better understand the occurrence and evolution of the disease and to help predict the prognosis.

Numerous previous studies to date have explored the prognostic value of the miR-200 family in patients with bladder cancer. However, their findings remain controversial. Therefore, a meta-analysis based on existing literatures is needed to assess the prognostic value of the miR-200 family in bladder cancer.

Methods

Systematic search strategy

We conducted a systematic search of electronic databases, including PubMed, Embase, Web of Science and the Cochrane Library (updated on December 10, 2019) to identify all relevant studies. The studies were searched using the terms “bladder cancer OR carcinoma OR tumor” AND “miR-200 OR miR-200a OR miR-200b OR miR-200c OR miR-141 OR miR-429” AND “prognosis OR survival OR outcomes”. In cases of multiple reports from the same series, we used the latest one. We also searched the lists of eligible articles. Two investigators independently completed all the work of the search strategy and filtered the titles and abstracts of all articles based on the following eligibility criteria.

Eligibility criteria

The eligibility criteria of studies included in this meta-analysis were listed as: (1) the subject of the studies were limited to human beings; (2) the language of publication was limited to English; (3) studies focused on the value of the miR-200 family in predicting prognosis in patients with bladder cancer; (4) hazard ratios (HRs) and 95% confidence intervals (CIs) for prognosis outcomes should be reported in the articles or have enough information to calculate them.

Data extraction

The data was extracted by two investigators and the other two were responsible for checking. All authors have discussed the disagreements until a consensus was reached. A standardized form was created and used to extract available data from all eligible publications including the first author's name, publication year, region, study period, the number of patients, duration of follow-up, age, gender (male/female), HRs, 95% CIs and its p value. If multiple HRs were presented in the original articles, we extracted the estimates from the largest adjusted model to reduce the risk of possible unmeasured confusion.

Quality assessment

Two investigators independently assessed the quality of all included studies. The Newcastle-Ottawa Scale (NOS) system was designed to evaluate the quality of non-randomized studies in meta-analysis [17]. It assessed study quality by 3 classifications including selection, comparability and outcome with a total of 9 stars. Studies with a total score of ≤ 5 stars, 6–7 stars, and 8–9 stars were considered to be of low quality, intermediate quality, and high quality respectively. All included studies had an intermediate or high quality according to NOS.

Statistical analysis

We performed a formal meta-analysis of overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS). HRs with 95% CIs from each study were used to calculate combined HRs. Cochrane's Q test and Higgins I^2 statistic were used to assess the heterogeneity across the studies. The studies with $p > 0.1$ and $I^2 < 50\%$ were considered indicative of significant heterogeneity. If no significant heterogeneity was found, a pooled estimate was calculated with a fixed effect model; or, a random effect model was used. The Begg's funnel plot and Egger's linear regression tests were used to evaluate the potential publication bias. A sensitivity analysis was performed to evaluate the stability of the results and to reduce the effect of individual studies on final conclusions. Two-tailed value of $p < 0.05$ was considered statistically significant. The meta-analysis was performed with RevMan 5.3 and Stata SE12.0 (Stata Corp LP, College Station, TX, USA) according to the PRISMA guidelines [18].

Results

Studies retrieved and characteristics

A total of 1152 articles were identified from electronic databases (PubMed, Embase and the Cochrane Library) and 3 additional studies were identified from reference lists. 81 duplicate articles were removed. After a careful review of titles and abstracts, 978 articles were excluded for not relevant, other urinary cancer, laboratory studies, reviews, letters and comments. After assessing the full text of the remaining 96 articles, 88 articles were excluded for some specific reasons, including not evaluate the association between the miR-200 family and prognosis outcomes, not available hazard ratio, not human studies, not English articles and duplicate data. Finally, 8 cohort studies were included in the following meta-analysis. Figure 1 shows the full screening procedure.

The characteristics of the included studies are shown in Table 1. These 8 articles were published between 2011 and 2018. Among them, 4 were published before 2015 and 4 were published in the past 3 years. 4, 3 and 1 studies were conducted in Asian, Europe and America, respectively. Sample size of included studies ranged from 40 to 403 patients, and a total of 1150 patients were included. The mean (median) age of the subjects ranged from 60.1 to 73.0 years, and the percentage of included males ranged from 66.7–83.1%. 6 articles reported OS, 2 articles reported CSS and 5 articles reported RFS.

Table 1
Characteristics of included studies.

Study	Region	No. of patients	Study period	Follow-up (median, months)	Age (years)	Gender (male/female)	miRNA	Survival
Wszolek 2011	USA	57	1990–2005	92	66.4 (34–90)	38/19	141, 200	CSS
Yun 2012	Korea	207	2006–2012	41.3	63.5 ± 12.6	165/42	200	RFS
Ratert 2013	Germany	40	1998–2009	17	69 (50–92)	32/8	141	OS
Pignot 2013	France	166	2001–2005	30.5	70 (31–91)	138/28	200	OS, RFS
Wang 2015	China	114	NA	42.9	70.0 ± 10.1	86/28	141	OS, CSS, RFS
Martínez-Fernández 2015	Spain	87	2009–2012	28.8	73.0 (49–90)	68/19	200	OS, RFS
Liu 2018	China	403	NA	41.6	60.1 (34–90)	297/106	141, 200	OS
Wu 2018	China	76	2002–2006	36.5	NA	57/19	429	OS, RFS
Abbreviations: CSS: cancer-specific survival; RFS: recurrence-free survival; OS: overall survival; NA: not available.								

Table 2
The Newcastle-Ottawa Scale scores for included studies.

Items	Wszolek 2011	Yun 2012	Ratert 2013	Pignot 2013	Wang 2015	Martínez- Fernández 2015	Liu 2018	Wu 2018
Selection 0000	0000	000	000	000	0000	000	000	0000
Representativeness of the exposed cohort	0	0	0	0	0	0	0	0
Selection of the non-exposed cohort	0	0	0	0	0	0	0	0
Ascertainment of exposure	0	0	0	0	0	0	0	0
Outcome of interest was not present at start of study	0	NA	NA	NA	0	NA	NA	0
Comparability 00	00	00	00	00	0	00	0	0
Outcome 000	000	00	000	000	000	00	00	00
Assessment of outcome	0	0	0	0	0	0	0	0
Follow-up time was long enough for outcomes to occur	0	NA	0	0	0	NA	0	NA
Adequacy of follow-up of cohorts	0	0	0	0	0	0	NA	0
Total scores	9	7	8	8	8	7	6	7
Abbreviation: NA: not available.								

Survival outcomes

Prognostic outcomes, including OS, CSS and RFS, were quantitatively synthesized. The impact of the miR-200 family on OS was investigated in 6 studies including 886 patients with bladder cancer. The forest plot shows that high expression of the miR-200 family was associated with better OS (pooled HR: 0.50, 95% CI: 0.40–0.62). The Cochrane Q test ($\text{Chi}^2 = 2.34$, $p = 0.89$) and I^2 test ($I^2 = 0\%$) did not show significant heterogeneity (Fig. 2).

The impact of the miR-200 family on CSS was investigated in 2 studies including 171 patients with bladder cancer. The forest plot shows that high expression of the miR-200 family was associated with better CSS (pooled HR: 0.36, 95% CI: 0.22–0.59). The Cochrane Q test ($\text{Chi}^2 = 0.15$, $p = 0.93$) and I^2 test ($I^2 = 0\%$) did not show significant heterogeneity.

The impact of the miR-200 family on RFS was investigated in 5 studies including 650 patients with bladder cancer. The forest plot shows that high expression of the miR-200 family was associated with better RFS (pooled HR: 0.48, 95% CI: 0.36–0.65). The Cochrane Q test ($\text{Chi}^2 = 0.14$, $p = 1.00$) and I^2 test ($I^2 = 0\%$) did not show significant heterogeneity.

Subgroup analysis

Table 3 summarizes the results of subgroup analysis according to study setting, year of publication and NOS score. Pooled HRs for survival outcome stratified by study setting revealed that Asian studies associated with better RFS (pooled HR: 0.46, 95% CI: 0.31–0.69; $p = 0.0001$, $I^2 = 0\%$) but worse OS (pooled HR: 0.54, 95% CI: 0.40–0.74; $p = 0.0001$, $I^2 = 0\%$) than European studies. Pooled HRs for survival outcome stratified by the NOS score showed that better RFS (pooled HR: 0.46, 95% CI: 0.31–0.69; $p = 0.0001$, $I^2 = 0\%$) in studies with an NOS score of 7. Due to the small number of literatures, no further subgroup analysis can be conducted on the studies that focus on CSS.

Table 3
Subgroup analysis for the association between the miR-200 family and the survivals

Subgroup analysis	OS					RFS				
	No. of	Pooled	p	Heterogeneity		No, of	Pooled	p	Heterogeneity	
	studies	(95% CI)	value	I ² (%)	p	studies	(95% CI)	value	I ² (%)	p
Overall	6	0.50 (0.40–0.62)	< 0.01	0	0.89	5	0.48 (0.36–0.65)	< 0.01	0	1.00
Study setting										
Asia	3	0.54 (0.40–0.74)	< 0.01	0	0.85	3	0.46 (0.31–0.69)	0.01	0	0.98
Europe	3	0.46 (0.34–0.62)	< 0.01	0	0.61	2	0.51 (0.33–0.78)	< 0.01	0	0.90
Year of publication										
Before 2015	2	0.47 (0.27–0.79)	< 0.01	0	0.32	2	0.49 (0.32–0.74)	< 0.01	0	0.74
After 2015	4	0.51 (0.40–0.64)	< 0.01	0	0.87	3	0.48 (0.32–0.72)	< 0.01	0	0.99
NOS score										
6	1	0.59 (0.41–0.85)	< 0.01	0	0.79	-	-	-	-	-
7	2	0.45 (0.32–0.63)	< 0.01	0	0.75	3	0.46 (0.31–0.69)	< 0.01	0	0.98
8	3	0.48 (0.31–0.72)	< 0.01	0	0.61	2	0.51 (0.33–0.78)	< 0.01	0	0.90
Abbreviations: OS: overall survival; RFS: recurrence-free survival; HR: hazard ratio; CI: confidence interval; NOS: Newcastle-Ottawa Scale.										

Publication bias

Begg's funnel plots test and Egger's test were used to assess the publication bias in this meta-analysis (Fig. 3). The outcomes of Begg's and Egger's test are shown in Table 4. Both Begg's funnel plots test and Egger's test

verified that there was no publication bias within the included cohorts.

Table 4
Outcomes of Begg's and Egger's test

Test	Begg test			Egger test		
	OS	CSS	RFS	OS	CSS	RFS
p value	0.368	0.296	0.624	0.413	0.205	0.244
Abbreviations: OS: overall survival; CSS: cancer-specific survival; RFS: recurrence-free survival.						

Sensitivity analysis

Sensitivity analysis was performed to evaluate the stability of the results and to reduce the effect of individual studies on final conclusions. The included studies were sequentially omitted to assess whether any single study could have an impact on OS, CSS and RFS. The test suggested that the pooled results did not tend to alter when a study was excluded (Fig. 4).

Discussion

There is increasing evidence that miRNAs play important roles in tumorigenesis and cancer progression, which are closely related to many pathways such as cell cycle, angiogenesis, invasion, metastasis and innate and adaptive immune responses [19]. To date, significant differences in miRNAs expression have been observed in a variety of cancers analyzed by profiling and next generation sequencing technologies [20]. Therefore, the miRNAs have been considered as novel potential biomarkers for cancer.

The miR-200 family is one of the hottest miRNAs to be studied recently. Recent studies have shown that members of the miR-200 family have been involved in cancer progression and invasion. Cancer progression is closely related to the dynamic process of EMT, during which epithelial cells lose their cell polarity and cell-cell adhesion and acquire migration as well as invasion properties by down-regulating E-cadherin and up-regulating vimentin expression [19]. It has been reported that members of the miR-200 family regulate EMT by targeting ZEB1 and ZEB2, resulting in a dysregulation of the cell-cell adhesion molecule E-cadherin [21]. In addition, members of the miR-200 family also target-regulate EMT regulators, which also plays an important role in tumor progression [22]. The miR-200 family is known as a key transcriptional regulator of EMT and maintains less invasive and aggressive epithelial phenotypes by targeting ZEB1 and ZEB2 [23]. The miR-200 member inhibits ZEB at the post-transcriptional level by binding to a highly conserved target site in the 3'-UTR. The functional relationship between the ZEB factors with the miR-200 family in the double negative feedback loop is called the ZEB / miR-200 feedback loop road [24]. Several other tumor suppressor genes have also been reported to be potential targets for the miR-200 family, including BRD7, BAP1, GATA, CLOCK and PTPN12 [25, 26]. In addition, the miR-200 family inhibits self-renewal and differentiation of cancer stem cells, regulates cell division and apoptosis, and reverses chemoresistance [27].

Many previous studies have focused on the relationship between the miR-200 family and tumor prognosis, especially in ovarian cancer. A meta-analysis performed by Shi and Zhang included seven ovarian cancer-related studies [12], and they found that high expression of the miR-200 family was associated with improved OS (HR =

0.34, 95% CI 0.20–0.58, $p < 0.01$) and progression-free survival (PFS) (HR = 0.64, 95% CI 0.50–0.82, $p < 0.01$). Another meta-analysis by Shi et al. also found that high expression of the miR-200 family predicts better ovarian cancer prognosis (OS: HR = 0.78, 95% CI 0.64–0.94, $p = 0.01$) [28]. Li et al. evaluated the relationship between the miR-200 family and the prognosis of various malignant tumors in humans. Their findings showed that high expression of the miR-200 family was associated with unfavorable OS (HR = 1.32, 95% CI 1.16–1.49, $p < 0.001$), but not significantly associated with RFS (HR = 1.02, 95% CI 0.96–1.09, $p = 0.47$) and PFS (HR = 0.96, 95% CI 0.54–1.70, $p = 0.88$).

To the best of our knowledge, our study is the first meta-analysis to pool available data to evaluate the prognostic value of the miR-200 family in bladder cancer. There is no significant heterogeneity in this meta-analysis. Our results are in line with most of the former studies and suggest that low expression of the miR-200 family may predict improved survival in patients with bladder cancer. Subgroup analysis and sensitivity analysis showed that the results of this study were stable and reliable. The protective effect of the miR-200 family on the prognosis of bladder cancer may be explained by the potential inhibitory effect of the miR-200 family on malignant tumors by targeting ZEB1 and ZEB2 (members of the zinc-finger E-box binding homeobox family) [21, 29, 30]. Therefore, patients with bladder cancer may benefit from a better understanding of the protective role of the miR-200 family in bladder cancer.

There are some limitations in our meta-analysis. First, all the included studies in this meta-analysis were retrospective, which may lead to selection bias. High-quality prospective researches needed to further investigation in this field. Second, the sample size of partial eligible was relatively small. The large-scale studies are necessary to achieve more credible results in the future. Finally, the potential heterogeneity might still exist. Although heterogeneity was not significantly from the results of meta-analysis and subgroup analysis, but the cut-off values across the included studies were not completely consistent, which might lead to unknown heterogeneity. Therefore, more uniform standards should be established to increase homogeneity between the studies.

To conclude, the present meta-analysis demonstrates that the high expression of the miR-200 family may significantly predict better prognostic outcomes in patients with bladder cancer. Therefore, the expression of the miR-200 family may play an important role in the management of those patients. However, in order to better evaluate the prognostic value of the miR-200 family in patients with bladder cancer, additional prospective and large-scale clinical studies will be needed in the future.

Declarations

Acknowledgment

Not applicable.

Statement of Ethics

All the procedures performed were in full accordance with the ethical standards of the appropriate national and institutional committees on human experimentation and with the World Medical Association Declaration of

Helsinki. This study was approved by the institution Ethics Commission of Qilu Hospital of Shandong University. The need for consent to participate was waived by Ethics Commission of Qilu Hospital of Shandong University.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by Medical and Health Science and Technology Development Project of Shandong Province (grant no.2017WS687).

Author contributions

YDF and YHM designed this study; YHM and JBZ searched electronic databases and selected studies; PX and CL extracted the data; YHM and PX were responsible for checking the extracted data; JBZ and CL performed the quality assessment; JBZ and YDF analyzed the data; YHM and CL wrote the manuscript. All authors reviewed and approved the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Figures

Figure 2

Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram: search and study selection process for this review.

A

B

C

Figure 4

Forest plot showing the effects of the miR-200 family on (A) overall survival (B) cancer-specific survival and (C) recurrence-free survival in patients with bladder cancer.

Figure 6

Funnel plots based on overall survival (A) Begg's test (B) Egger's test; cancer-specific survival (C) Begg's test (D) Egger's test; and recurrence-free survival (E) Begg's test (F) Egger's test.

Figure 7

Sensitivity analysis in this meta-analysis. (A) Sensitivity analysis for overall survival; (B) sensitivity analysis for cancer-specific survival; and (C) sensitivity analysis for recurrence-free survival.