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MiRNAs with prognostic significance in multiple myeloma

A systemic review and meta-analysis

Peipei Xu, PhD, Tian Xia, MD, Yipeng Ling, PhD, Bing Chen, PhD*

Abstract

Background: Multiple myeloma (MM) is a clonal plasma cell malignancy associated with hypercalcemia, bone lesions, and renal failure. The prognostic significance of the mutation of miRNAs, one kind of small noncoding RNA molecules that can modulate gene expression, should be confirmed in non-Hodgkin lymphomas (NHL). This study aimed to identify the prognostic value of miRNAs in patients with MM.

Methods: A meta-analysis was performed to estimate the pooled hazard ratios and their corresponding 95% confidence intervals for the associations between levels of miRNA expression (predictive factors) and outcomes in patients with MM. We systematically searched the PubMed, Web of Science, and China National Knowledge Infrastructure databases (final search conducted January 1, 2018) to identify eligible studies. Eligible studies were included by certain inclusion and exclusion criteria, whose quality was assessed by Newcastle-Ottawa Scale.

Results: After performing the literature search and review, 10 relevant studies, including 1214 cases, were identified. The results of our meta-analysis revealed that upregulated miR-92a level and downregulated miR-16, miR-25, miR-744, miR-15a, let-7e, and miR-19b expression were associated with poor prognosis in MM.

Conclusions: This study identified miRNAs could serve as potential prognostic biomarkers in MM. Given the limited research available, the clinical application of these findings has yet to be verified.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, ISS = International Staging System, MCL = mantle cell lymphoma, MM = multiple myeloma, NHL = non-Hodgkin lymphoma, NOS = Newcastle-Ottawa Scale, OS = overall survival, PFS = progression free survival, R-ISS = Revised International Staging System, TTP = time to progress.

Keywords: biomarker, meta-analysis, microRNA, multiple myeloma, prognosis

1. Introduction

Multiple myeloma (MM) is a malignant clonal proliferative disease of plasma cells, which is characterized by extensive proliferation of pathological plasma cells and infiltration of other

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tissues and organs in the bone marrow, leading to extensive bone destruction, anemia, renal failure, and hypercalcemia. Although MM is currently incurable, patient's overall survival (OS) and progression free survival (PFS) prolonged with the application of new molecule-targeted drugs such as immunomodulatory factors (lenalidomide, pomamide) or proteasome inhibitors (bortezomib, carfilzomib), in which case the prognostic evaluation and risk stratification become extremely critical as they influence the choice of treatment.

Over the past few years, the prognosis of MM has been widely discussed and changed. Numerous parameters have been examined for their value as prognosis features, among which the most widely used prognostic factors in newly diagnosed MM are the International Staging System (ISS)[1] and currently revised ISS (R-ISS) system.[2] As a result, several sophisticated technologies such as interphase fluorescence in situ hybridization and gene-expression profiling analysis should be applied to clinical treatment. Although these examination methods have the advantages in accuracy, they are very complicated and inconvenient to use. Investigators are devoted to finding a specific biomarker that can be easily detected as the outcome indicator for myeloma.

Many advances in in-depth MM-related research on biomarkers, such as microRNAs (miRNAs), have promoted the utility of miRNAs in the prognosis of myeloma. MiRNAs are one kind of small noncoding RNA molecules that are 19 to 25 nucleotides in

length and can modulate gene expression through degrading target mRNAs and/or suppressing their translation by binding to the 3'-untranslated region of target genes.[3] Bioinformatics projections indicate that 30% of all human genes are regulated by miRNAs. Therefore, miRNAs are involved in a variety of biological processes and have the endless potential as biomarkers. In addition to their role in normal biological processes, growing evidence indicates that aberrant expression of miRNAs might be related to the progression of human cancers,[4] including pancreatic ductal adenocarcinoma,[5] renal cell carcinoma,[6] brain tumors[7] and so on. The tissue levels of specific miRNAs correlate well with several hematological malignancies, including MM.[8–12]

Several investigators have paid attention to the prognostic role of miRNAs in MM.[13,14] However, to date, no systematic review or meta-analysis on the role of particular miRNAs in the survival of patients with MM has been performed. In this study, we systematically reviewed relevant studies on the prognostic value of miRNAs in MM and performed a meta-analysis to better understand the prognostic value of miRNAs in MM. The present study aimed to investigate the relationship between the expression of several miRNAs and the outcome of MM disease to provide a rationale for miRNA-based therapeutics.

2. Materials and methods

This meta-analysis was performed following the Meta-analysis of Observational Studies in Epidemiology guidelines.[12]

2.1. Search strategy

Literature searches were conducted using the PubMed, Web of Science, and China National Knowledge Infrastructure databases (final search conducted January 1, 2018). The keyword combinations in the search strategy were "microRNA OR microRNAs OR miR OR miRNA" (all fields), "myeloma OR MM" (all fields), and "prognosis OR prognostic OR survival" (all fields). Searches were limited to English language publications.

2.2. Inclusion and exclusion criteria

Eligible studies included in the meta-analysis met the following criteria:

(1) focused on patients with MM,
(2) assayed type either blood or tissue samples,
(3) investigated the prognostic value of miRNA,
(4) clearly defined the cut-off, and
(5) clearly described the miRNA measurement method.

Studies were excluded if they met one of the following criteria:

(1) single study focused on a miRNA not investigated by another study,
(2) failure to extract the data,
(3) and lack of basic data for aggregate calculation.

2.3. Data extraction and quality assessment

The database search was independently reviewed by 2 authors (T. Xia and X. Liu). Basic information was independently pooled by 2 investigators. We calculated from the available numerical data in the articles by using the methods described by Tierney[15] when the statistical variables were not described. The data from Kaplan–Meier survival curves were read by Engauge Digitizer version 4.1. We sent e-mails to the corresponding authors of eligible articles requesting additional information and original data needed for the meta-analysis. The quality of included studies was assessed by Newcastle-Ottawa Scale (NOS) according to the following categories: selection (descriptions on the derivation of the cohort, derivation of the non-exposed cohort, exposure ascertainment, presence of the outcome of interest at the start of the study), comparability (study controlled the most important factor and other factors), and outcome of interest (description of outcome assessment, adequacy of follow-up of cohorts, follow-up long enough for outcomes to occur).[16] A total of 9 items were extracted, and each item was scored as 1. The total score of NOS ranged from 0 to 9, and studies with a score of at least 6 were considered high quality.

2.4. Statistical analysis

We pooled the hazard ratios (HRs) (95% CIs) extracted from the studies using the Stata 13.0 software (StatCorp, College Station, TX). Statistical heterogeneity was assessed by calculating the I^2 statistic, and assessing the P value.[17,18] An I^2 value exceeding 50% and/or the P value less than .05 indicated the presence of heterogeneity, and a random-effects model was used. An observed HR < 1 suggested a more favorable prognosis in patients with aberrant miRNA, and an HR > 1 indicated a worse prognosis. Egger test was used to assess publication bias.

2.5. Ethical consideration

Ethical approval was not required for this study.

3. Results

3.1. Selection of studies

A flow diagram of the study selection process is shown in Figure 1. A total of 206 publications were identified in the initial search. After reviewing the titles and abstracts of these articles, we identified 15 articles evaluating the use of prognostic miRNA biomarkers in MM. We then carefully reviewed the full texts of these articles and excluded an additional 5 articles. In total, 10 articles (38 studies)[19–28] were eligible for inclusion in this meta-analysis.

3.2. Characteristics of the included studies

A total of 4810 MM patients were assessed in the 10 included articles, with a median sample size of 156 patients (range, 33–234 patients). These studies reported the prognostic values of 32 different miRNAs. The levels of miRNA expression were mainly detected in serum samples. Three studies used bone marrows, and 1 study used purified plasma cells. Six studies did not directly report HR data. Thus, we estimated the HRs using the methods described above (Table 1). In the included articles, increased expression of 7 miRNAs were associated with poor prognosis in MM. Among these miRNAs, 7 were reported by at least 2 studies (Table 2). Thus, we performed this meta-analysis to summarize the effect of these seven miRNAs.
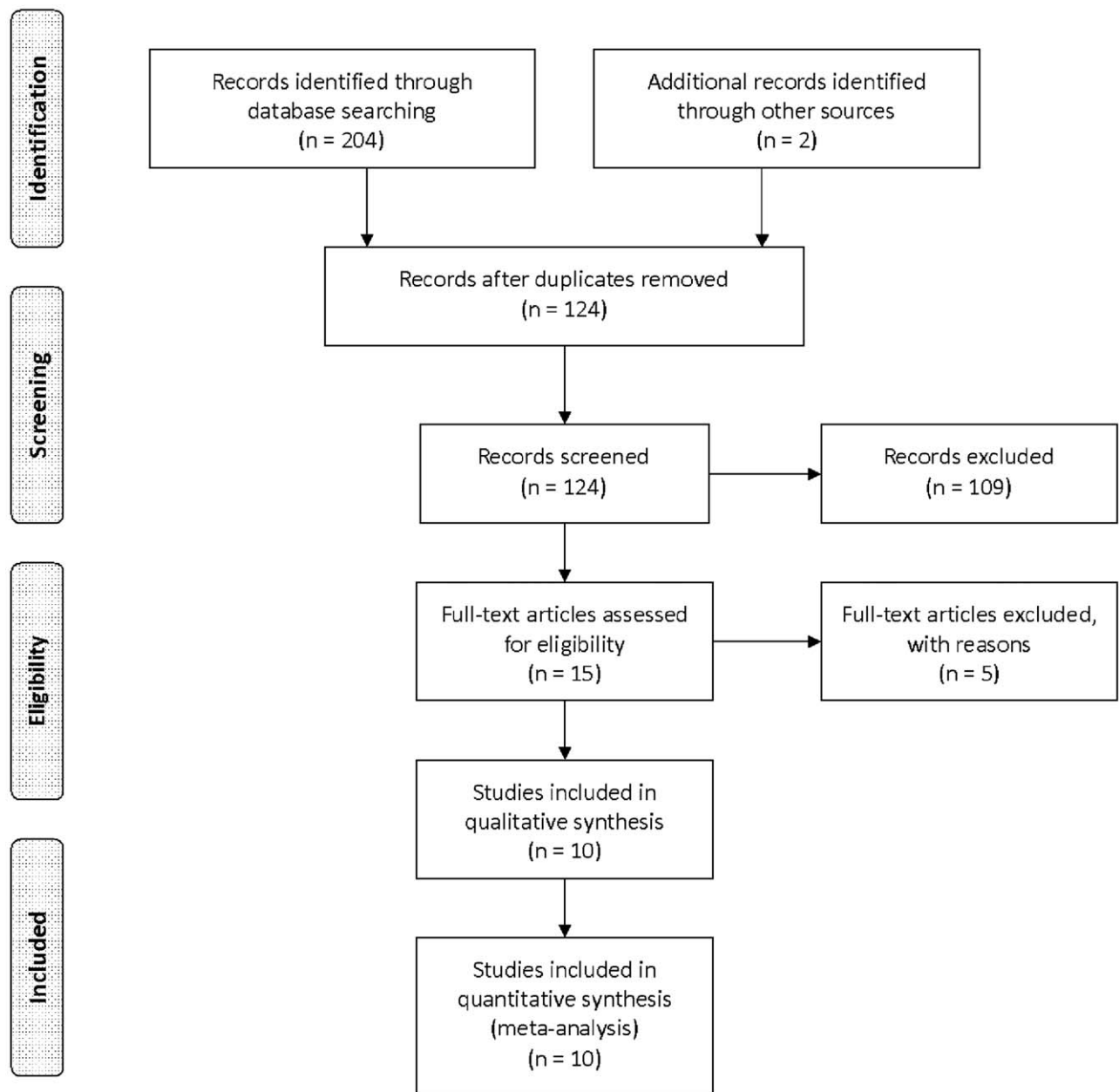
Figure 1. Flow diagram of the study selection procedure.

3.3. Quality assessment

The NOS scores of every study ranged from 7 to 9, with an average of 8.30. The detailed information of NOS scores is shown in Table 3.

3.4. MiRNAs and MM prognosis

3.4.1. MiR-16. Two articles (n = 822) suggested that down-regulation of miR-16 was associated with poor prognosis in patients with MM, both of which reported OS and progression-free survival (PFS) data[25,29] and calculated crude HR for miR-16. The observed interstudy heterogeneity for PFS ($I^2 = 87.6\%$, $P = .005$) and OS ($I^2 = 70.0\%$, $P = .058$) was both significant, and the Egger test results indicated the absence of significant

publication bias ($P = .035$). The fixed-effects model revealed that miR-16 expression was inversely associated with PFS (HR: 1.08, 95% confidence interval (CI): 1.01–1.17) and OS (HR: 1.15, 95% CI: 1.04–1.28) in MM patients (Fig. 2).

3.4.2. MiR-25. Two articles (n = 820) reported the effect of miR-25 on the prognosis of MM patients and OS and PFS data.[19,25] No significant heterogeneity was observed for PFS across studies ($I^2 = 0.0\%$, $P = .629$). However, significant interstudy heterogeneity was observed for OS ($I^2 = 69.0\%$, $P = .073$). The fixed-effects model revealed that miR-25 expression was inversely associated with PFS (HR: 1.09, 95% CI: 1.01–1.19) and OS (HR: 1.25, 95% CI: 1.11–1.40) in MM patients. There was no significant evidence of publication bias (Egger test, $P = .229$) (Fig. 3).

Table 1

Main characteristics of the eligible studies.

No	First Author	Year	Country	miRNA profiled	Expression with poor prognosis	Sample size Total	Sample size Low	Sample size High	Stage I/II/III	Specimen	Cut-off	Follow-up	Outcome
1	Rocci A[19]	2014	USA	16	Low	234	129	105	NA	Serum	Median	NA	PFS/OS
				25	Low	232	104	128	NA	Serum	Median	NA	PFS/OS
				30a	Low	NA	NA	NA	NA	Serum	Median	NA	PFS/OS
				720	Low	NA	NA	NA	NA	Serum	Median	NA	PFS/OS
2	Kubiczkova L[20]	2014	Czech Republic	744	Low	103	43	60	ISS 35/29/39	Serum	ROC curve	NA	OS/TTP
				let-7e	Low	103	52	51	ISS 35/29/39	Serum	ROC curve	NA	OS/TTP
3	Li F[21]	2015	China	33b	Low	58	25	33	ISS 24 (I–II)/16 (III)	Bone marrow	ROC curve	10.5 (3–26.5)	PFS/OS
4	Qu X[22]	2013	China	92a	High	53	26	27	NA	Bone marrow	29.23	13.5 (0.5–72.5)	PFS
5	Hao M[23]	2014	China	19a	Low	103	48	58	ISS 18/39/50	serum	Youden's Index	13.5	PFS/OS
6	Li F[24]	2015	China	15a	Low	86	16	70	D-S 10 (I–II)/76 (III); ISS 37 (I–II)/49 (III)	Bone marrow	ROC curve (2.35)	15 (3.0–55.5)	PFS/OS
7	Seckinger A[25]	2015	Germany	135a	High	53	34	19	NA	Purified plasma cells	8.38	NA	EFS/OS
				135b	High	53	24	29	NA	Purified plasma cells	8.18	NA	EFS/OS
				200a	High	53	39	14	NA	Purified plasma cells	8.42	NA	EFS/OS
				200b	High	53	25	28	NA	Purified plasma cells	8.89	NA	EFS
				596	High	53	28	25	NA	Purified plasma cells	9.61	NA	EFS/OS
8	Manier S[26]	2017	France	let-7b	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				let-7c	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				let-7e	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				106a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				106b	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				106	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				125a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				125b	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				155	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				15a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				16	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				17	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				181a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				18a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				19a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS
				19b	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				20a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				21	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				223	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				25	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				744	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
				92a	Low	156			ISS 63/56/33	Serum	NA	5.4 (4.6–5.8)	PFS/OS
9	Hao M[27]	2016	China	214	High	108	35	73	ISS 23/43/50	Serum	1	16.5	PFS/OS
10	Navarro A[28]	2015	Spain	19b	Low	33	5	28	ISS 17/11/5	Serum	maximally selected log-rank statistics	4 (1–14)	PFS
				331	Low	33	6	27	ISS 17/11/5	Serum	maximally selected log-rank statistics	4 (1–14)	PFS

EFS = Event-Free Survival, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, qRT-PCR = quantitative real-time polymerase chain reaction, Rep = report, SC = survival cunve, TTP = time of tumor progression.

Table 2

Descriptive characteristics and related data from included studies.

Author–year	MiRNAs	OS		PFS		TTP		EFS	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Rocci 2014	16	1.14 (1.03–1.27)	.008	1.06 (0.98–1.14)	.13				
	25	1.23 (1.1–1.39)	.0005	1.09 (1.01–1.19)	.034				
	30a	1.16 (1.03–1.3)	.016	1.03 (0.95–1.11)	.49				
	720	1.15 (0.99–1.32	.06	1.09 (0.99–1.18)	.077				
Kubiczkova 2014	744	1.83 (0.72–4.63)	<.0001			3.11 (1.88–5.13)	<.0001		
	let-7e	2.8 (1.38–5.66)	.001			3.8 (2.27–6.37)	<.0001		
Li 2015	33b	1.17 (0.16–8.5)	.879	2.19 (0.049–9.92)	.308				
Qu 2013	92a			2.549 (1.09–5.89)	.006				
Hao 2014	19a	2.995 (1.167–7.69)	.023	2.787 (1.421–5.468)	.003				
Li 2015	15a	4.97 (1.48–16.69)	.038	3.26 (1.22–8.72)	.008				
Seckinger 2015	135a	2.56 (0.79–8.23)	.03					3.51 (1.58–7.8)	.004
	135b	1.81 (0.33–10.08)	<.001					3.11 (1.42–6.84)	<.001
	200a	3.68 (1.13–11.96)	.02					4.09 (1.9–8.81)	.01
	200b							1.73 (0.85–3.55)	.03
	596	1.72 (0.34–8.69)	.001					1.81 (0.81–4.04)	.02
Manier 2017	let-7b	4.57 (1.9–10.97)	.001	1.78 (1.21–2.6)	.003				
	let-7c	2.28 (1.04–4.99)	.039	1.22 (0.84–1.78)	.302				
	let-7e	2.39 (1.09–5.24)	.03	1.73 (1.19–2.53)	.005				
	106a	2.67 (1.21–5.88)	.015	1.9 (1.3–2.78)	.001				
	106b	2.76 (1.25–6.1)	.012	2.52 (1.72–3.69)	<.001				
	106	1.82 (0.83–3.89)	.133	1.23 (0.85–1.8)	.273				
	125a	2.31 (1.05–5.08)	.037	1.28 (0.88–1.86)	.203				
	125b	1.27 (0.6–2.72)	.533	1.02 (0.7–1.49)	.906				
	155	3.19 (1.42–7.14)	.005	1.64 (1.12–2.4)	.011				
	15a	2.27 (1.02–5.06)	.046	1.37 (0.94–2)	.101				
	16	2.37 (1.09–5.17)	.03	1.86 (1.27–2.72)	.001				
	17	2.21 (1.01–4.83)	.046	1.83 (1.25–2.67)	.002				
	181a	2.15 (1–4.63)	.051	1.45 (0.99–2.12)	.054				
	18a	4.62 (1.85–11.5)	.001	2.01 (1.37–2.94)	<.001				
	19a			0.13 (0.02–0.99)	.049				
	19b	0.48 (0.22–1.03)	.06	0.83 (0.56–1.22)	.335				
	20a	2.91 (1.29–6.54)	.01	2 (1.37–2.92)	<.001				
	21	1.88 (0.88–4.06)	.106	1.53 (1.05–2.23)	.028				
	223	1.77 (0.83–3.76)	.14	1.33 (0.91–1.94)	.147				
	25	2.56 (1.16–5.65)	.02	1.2 (0.82–1.76)	.344				
	744	2.1 (0.97–4.53)	.059	1.32 (0.91–1.93)	.144				
	92a	2.15 (1–4.65)	.051	1.39 (0.95–2.02)	.089				
Hao 2016	214	2.38 (0.76–7.41)	.002	1.76 (0.93–3.32)	.015				
Navarro 2015	19b			9.89 (3.18–30.69)	<.0001				
	331			3.47 (1.39–8.7)	<.0001				

CI = confidence interval, EFS = Event-Free Survival, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, TTP = time of tumor progression.

3.4.3. MiR-744. Two articles (4 studies, n = 259) assessed the association between miR-744 expression and prognosis in MM. Of these studies, 2 provided OS data,[20,25] 1 PFS data[25] and 1 TTP data.[20] For OS, no significant heterogeneity was observed across studies ($I^2 = 0.0\%$, $P = .823$). The fixed-effects model revealed that decreased miR-744 expression was predictive of shorter OS (crude HR: 1.99, 95% CI: 1.10–3.59) (Fig. 4).

3.4.4. MiR-15a. Two articles evaluated the association between miR-15a expression and the prognosis of MM patients (n = 242), both of which reported OS and PFS data.[24,25] For PFS, the observed interstudy heterogeneity was significant ($I^2 = 61.6\%$, $P = .107$). For OS, no significant interstudy heterogeneity was observed ($I^2 = 10.6\%$, $P = .290$). The Egger test results indicated the absence of significant publication bias ($P = .006$). The fixed-effects model revealed that miR-15a expression was inversely associated with PFS (HR: 1.53, 95% CI: 1.08–2.18) and OS (HR: 2.88, 95% CI: 1.48–5.62) in MM patients (Fig. 5).

3.4.5. Let-7e. Two articles describing four studies reported lower let-7e expression to be a predictive factor for poor prognosis of patients with MM using univariate analyses (n = 259). One of them provided PFS data,[25] one TTP data,[20] and 2 OS data.[20,25] No significant heterogeneity was observed across studies (OS, $I^2 = 0.00\%$, $P = .769$). The fixed-effects model revealed that let-7e expression was inversely associated with OS (HR: 2.61, 95% CI: 1.54–4.41) in MM patients (Fig. 6). The Egger test results indicated the absence of significant publication bias ($P = .479$).

3.4.6. MiR-92a. Two articles determined the association between miR-92a expression and prognosis of patients with MM (n = 209), of which one provided PFS data[30] and the other OS and DFS (disease-free survival) data.[25] For PFS, no significant heterogeneity was observed across studies ($I^2 = 38.8\%$, $P = .201$). The fixed-effects model revealed that upregu-

Table 3

Newcastle-Ottawa scale scores.

Study	Selection	Comparability	Outcome	Total
Rocci 2014	4	1*	2†	7
Kubiczkova 2014	4	2	2†	8
Li 2015	4	1*	3	8
Qu 2013	4	2	3	9
Hao 2014	4	2	3	9
Li 2015	4	2	3	9
Seckinger 2015	4	1*	2†	7
Manier 2017	4	2	2‡	8
Hao 2016	4	2	3	9
Navarro 2015	4	2	3	9

Reasons for lost stars:

* Study not controlling other additional factors, such as age, gender, and smoke.

† Inadequacy of follow-up of cohorts.

‡ Follow-up not long enough for outcomes to occur.

lation of miR-92a was predictive of shorter PFS (HR: 1.54, 95% CI: 1.09–2.17) (Fig. 7).

3.4.7. MiR-19b. Two articles determined the association between miR-19b expression and prognosis of patients with MM (n = 189), of which one provided PFS data[28] and the other OS and DFS data.[25] The observed interstudy heterogeneity for PFS was significant ($I^2 = 93.9\%$, $P = .000$). The fixed-effects model revealed that miR-19b expression was not associated with PFS for MM patients (crude HR: 1.08, 95% CI: 0.75–1.56) (Fig. 8).

4. Discussion

A comprehensive systematic literature review was conducted to explore the utility of miRNA biomarkers that can be accurately and robustly evaluated in predicting the prognosis of patients

with MM. Although various miRNAs were found to be associated with the prognosis in MM patients, most of miRNAs were assessed only in a single study. Seven miRNAs were evaluated in at least 2 studies. We, therefore, performed a meta-analysis of the effect of these 7 miRNAs on the survival of MM patients. The results of this study showed that lower expression of miR-15a, miR-16, miR-25, miR-744, and let-7e predicted worse OS in MM patients. Similarly, downregulation of miR-15a, miR-16, and miR-25 and upregulation of miR-92a were associated with shorter PFS.

MiR-15a and miR-16 are clustered at chromosomal location 13q14 and possess similar sequences. They are considered to have similar tumor suppressor functions and to be involved in the regulation of cell differentiation, proliferation, apoptosis, or angiogenesis in several types of human cancer, including MM.[31–35] Xu et al proved that miR-16 may serve as a potential diagnostic biomarker for MM.[36] Roccaro et al[37] identified that miR-15a/16–1 regulates the proliferation of MM cells in vitro and in vivo by inhibiting AKT serine/threonine protein kinase, ribosomal-protein-S6, MAP-kinases, and NF-kB activator MAP3KIP3. Several other studies also revealed that miR-15a/16–1 targets multiple genes that are related to cell cycle, apoptosis, and angiogenesis, such as BCL2, MCL1, CCND1, WNT3A, and VEGF.[38] MiR-15a/16 directly targets calcineurin-binding protein 1 (CABIN1) mRNA and negatively regulates its RNA and protein expression in MM cells. As a result, the downregulation of miR-15a and miR-16 promotes tumor proliferation in MM by increasing CABIN1 expression.[39]

MiR-25 is hosted by the minichromosome maintenance protein-7 gene and is transcribed as part of the mir-106b-25 polycistron.[40] MiR-25 has dual functionality, acting as either an oncogenic miRNA or a tumor suppressor. Previous studies have reported this miRNA to be downregulated in ovarian cancer[41] and upregulated in pediatric brain cancer, medulloblastomas, prostate cancer, hepatocellular cancer, gastric cancer, lung
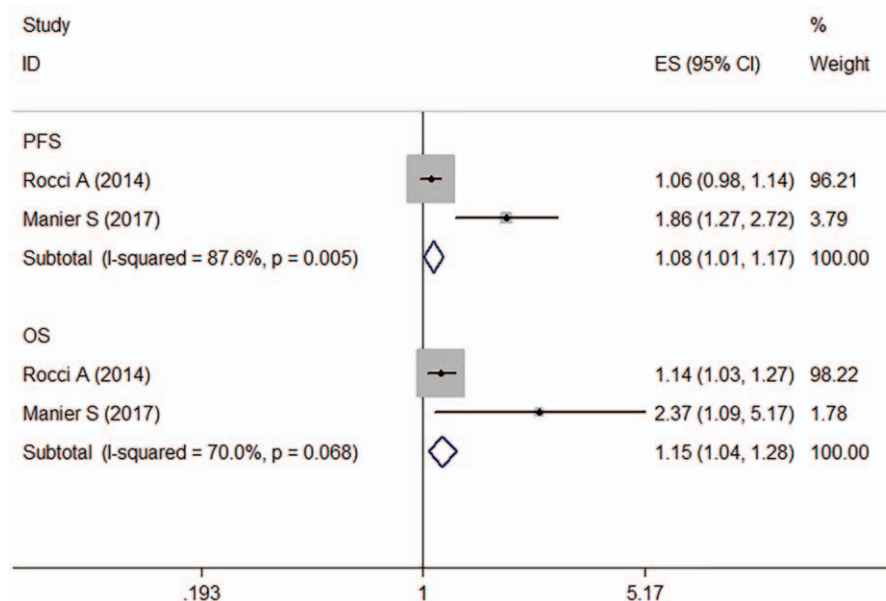

Figure 2. Forest plot of the HRs for the association between miR-16 and MM survival. HR = hazard ratio, OS = overall survival, PFS = progression-free survival.
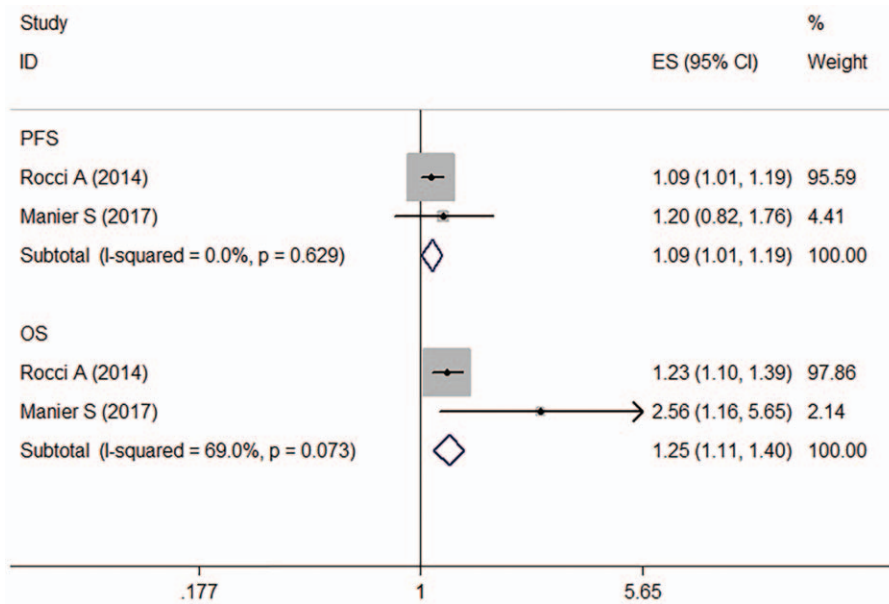
Figure 3. Forest plot of the HRs for the association between miR-25 and MM survival. HR = hazard ratio, OS = overall survival, PFS = progression-free survival.

adenocarcinoma, and colorectal cancer.[42–47] Xiang et al pointed out that hsa-miR-25 is 1 of the key miRNA biomarkers that could be applied in the treatment of MM, indicating its potential function as an outcome predictor.[48]

MiR-92a, a known hypoxia-regulated miRNA, has been found to be upregulated in many cancers. The human myeloid leukemia cell line K562 secretes exosomes containing a large amount of miR-92a that enhances angiogenesis under normoxic and

hypoxic conditions.[49] When it comes to hematology, miR-92a expression plays a crucial role in lymphocyte ontogeny. For instance, Husby et al identified that miR-92a is significantly differentially expressed in patients who died of mantle cell lymphoma (MCL).[50] Furthermore, miR-92a has been proven to be related to MM progression, and Qu et al identified that the effect of miR-92a on the progress of MM may involve the c-Jun pathway.[22]
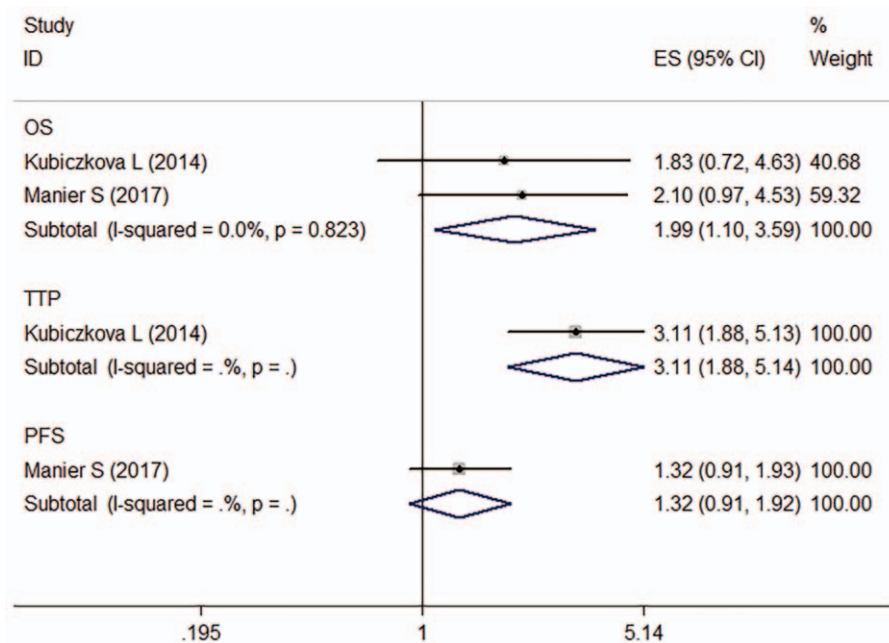

Figure 4. Forest plot of the HRs for the association between miR-744 and MM survival. HR = hazard ratio, OS = overall survival, PFS = progression-free survival, TTP = time of tumor progression.
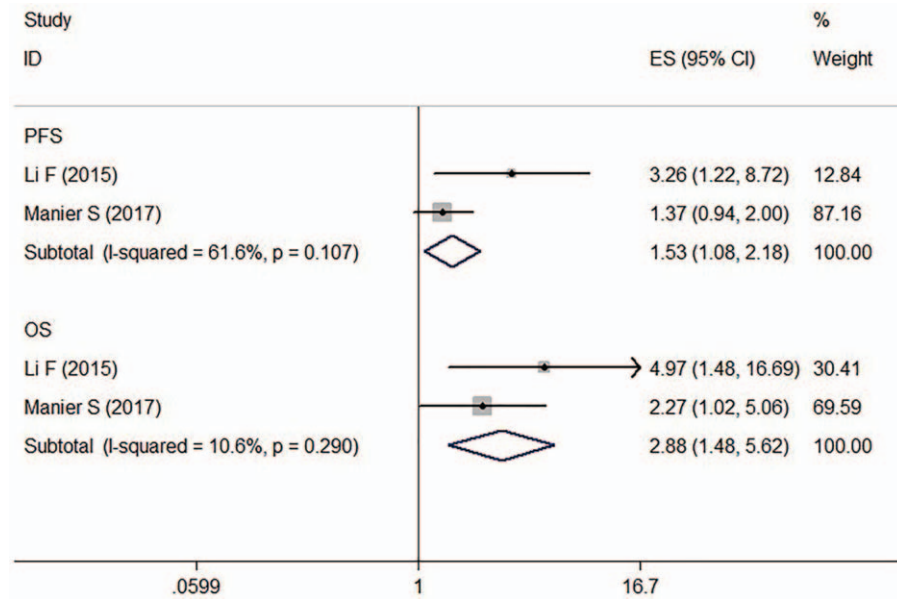
Figure 5. Forest plot of the HRs for the association between miR-15a and MM survival. HR=hazard ratio, OS=overall survival, PFS=progression-free survival.

MiR-744 lies in the 17p12 region, close to the TP53 gene (17p13). Deletions at chromosome 17p13.1 to 17p12 were previously found to be associated with poor prognosis[51] of MM patients. Meanwhile, low TP53 gene expression, which is highly correlated with loss of heterozygosity of the TP53 locus, was associated with shorter event-free survival and OS.[52] Levels of miR-744 and let-7e showed a significant positive correlation with thrombocyte count and albuminlevels and showed a significant

negative correlation with C-reactive protein, creatinine, and beta-2microglobulinlevels.[20] Let-7 is a direct regulator of RAS expression in human cells,[53] which may explain the observation of let-7 downregulation in MM.

The results of the current study are confined by some restrictions. First, the number of studies available was limited. Second, marked heterogeneity observed in some of the analyses were likely identified due to differences in patient characteristics
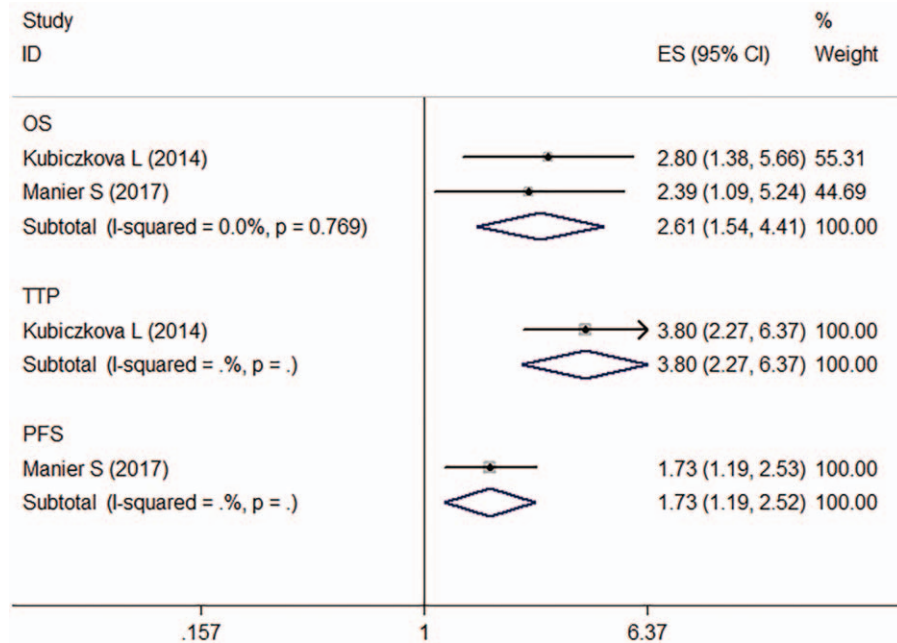

Figure 6. Forest plot of the HRs for the association between let-7e and MM survival. HR=hazard ratio, OS=overall survival, PFS=progression-free survival, TTP=time of tumor progression.
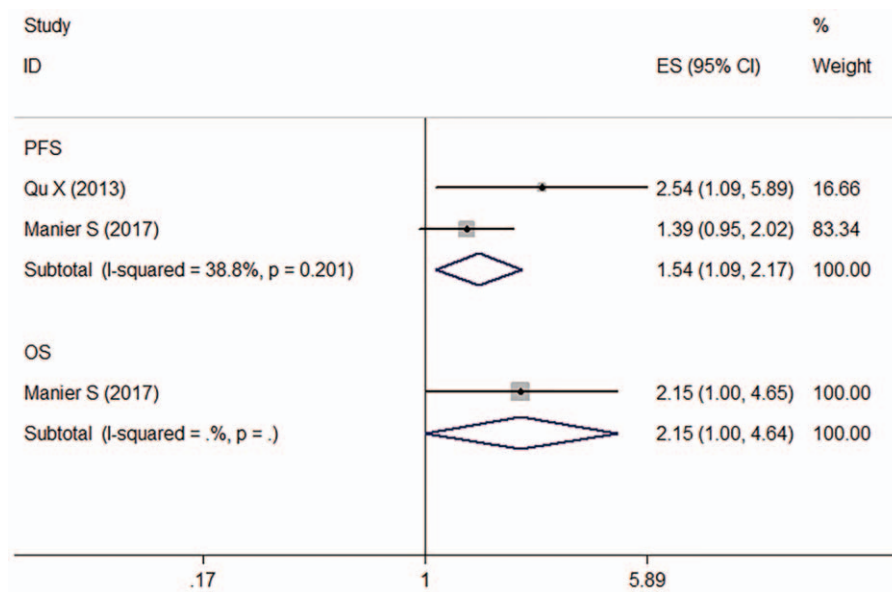
Figure 7. Forest plot of the HRs for the association between miR-92a and MM survival. HR = hazard ratio, OS = overall survival, PFS = progression-free survival.
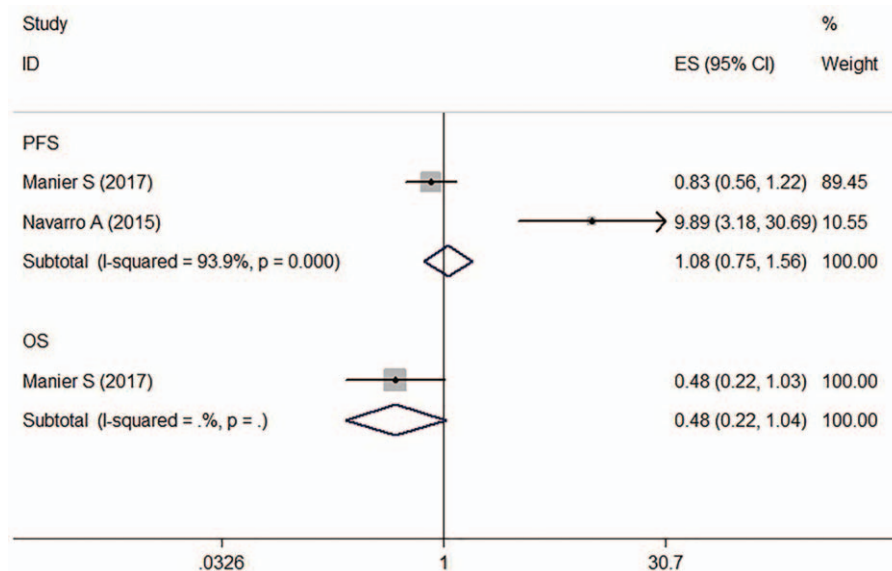
Figure 8. Forest plot of the HRs for the association between miR-19b and MM survival. HR = hazard ratio, OS = overall survival, PFS = progression-free survival.

and assay methods, cut-off values for miRNA expression levels, follow-up durations, and HR extraction methods.

To summarize, miRNAs such as miR-16, miR-25, miR-744, miR-15a, miR-92a, and let-7e are closely related to the outcome of MM, and further studies are needed to understand the molecular mechanism underlying the effect of miRNAs in MM. Future integrated analyses of several RNA signatures will allow further characterization of biology and prognosis in relation to given therapies.

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