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Review Article

Potential diagnostic value of circulating miRNA for multiple myeloma: A meta-analysis

Shuai-Shuai Gao[a,b], Yan-Jun Wang[a], Guo-Xun Zhang[b], Wen-Ting Zhang[b,*]

[a] Department of Traumatology and Orthopedic Surgery, Xi'an Daxing Hospital, Shaanxi, China
[b] International Doctoral School, University of Seville, Spain

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ABSTRACT

Background: Multiple myeloma (MM) is the second incurable hematological malignancy. In recent years, due to the rise of microRNA (miRNA), many scholars have participated in the study of its value in the diagnosis of MM, and have obtained good but inconsistent results. Therefore, in order to determine the role of miRNA in the early diagnosis of MM, we performed this *meta*-analysis.

Methods: We searched for related studies including PubMed, Web of Science, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI) and Wanfang Database as of July 20, 2020 to conduct this *meta*-analysis. To improve the accuracy, the quality assessment of Diagnostic Accuracy Study 2 (QUADAS-2) was used. We also applied random effects models to summarize sensitivity and specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and area under the curve (AUC) to measure diagnostic values, and subgroup analysis used to discover potential sources of heterogeneity.

Results: We finally collected 32 studies from 15 articles that included a total of 2053 MM patients and 1118 healthy controls in this *meta*-analysis. The overall sensitivity, specificity, PLR, NLR, DOR and AUC were 0.81, 0.85, 5.5, 0.22, 25 and 0.90, respectively. Subgroup analysis shows that the down-regulation of microRNA clusters with larger samples size of plasma type could carry out a better diagnostic accuracy of MM patients. In addition, publication bias was not found.

Conclusions: Circulating miRNA could be a potential non-invasive biomarker for early diagnosis of MM. However, multi-center, more rigorous, and larger-scale studies are needed to verify our conclusions.

1. Introduction

Multiple myeloma (MM) is a malignant proliferative disease of plasma cells mediated by B lymphocytes, characterized by excessive proliferation of abnormal plasma cells in the bone marrow, bone damage, and immune deficiency[1]. The disease is still the second incurable hematological malignancy, accounting for about 1% of all types of human cancers and 13% of all hematological malignancies. It is more common in middle-aged and elderly people over 40 ages[2], and the survival time of the patient ranges from several months to several years [3], and the incidence of MM has gradually increased in recent years [4,5]. The onset of MM is a gradual evolutionary process, from the initial monoclonal gammopathy of undetermined significance (MGUS) to smoldering MM, intramedullary MM, and finally to non-bone marrow MM / plasma cell leukemia (PCL)[6,7]. Despite the advent of multiple targeted new drugs such as immunomodulatory drugs (IMiDs) [8] and proteasome inhibitors (PI)[9], which have greatly improved the quality of life of patients with MM, some patients have been affected by cytogenetic abnormalities and changes in the bone marrow microenvironment, and malignant transformation of plasma cells has occurred, causing MGUS to progress to MM[10]. As the traditional gold standard for diagnosing MM, bone marrow biopsy may not be accepted by all patients, because of its invasive injury that causes pain for patients, and the condition may have reached an advanced stage. There is an urgent need to find a more sensitive, convenient and non-invasive biomarker for early clinical diagnosis of MM.

MicroRNAs, a class of small non-coding RNAs (comprising 18 to 22 nucleotides), which regulates gene expression, affects a variety of cell

Abbreviations: MM, Multiple myeloma; microRNA, miRNA; QUADAS-2, Quality Assessment of Diagnostic Accuracy Study 2; SE, Sensitivity; SP, Specificity; PLR, Positive likelihood ratio; NLR, Negative likelihood ratio; DOR, Diagnostic odds ratio; AUC, Area under the curve; CI, confidence interval; MGUS, Monoclonal gammopathy of undetermined significance; PCL, Plasma cell leukemia

* Corresponding author at: Plaza Comunidad Castilla la Mancha, No.6, 41008, Seville, Spain.
E-mail address: 724521882@qq.com (W.-T. Zhang).

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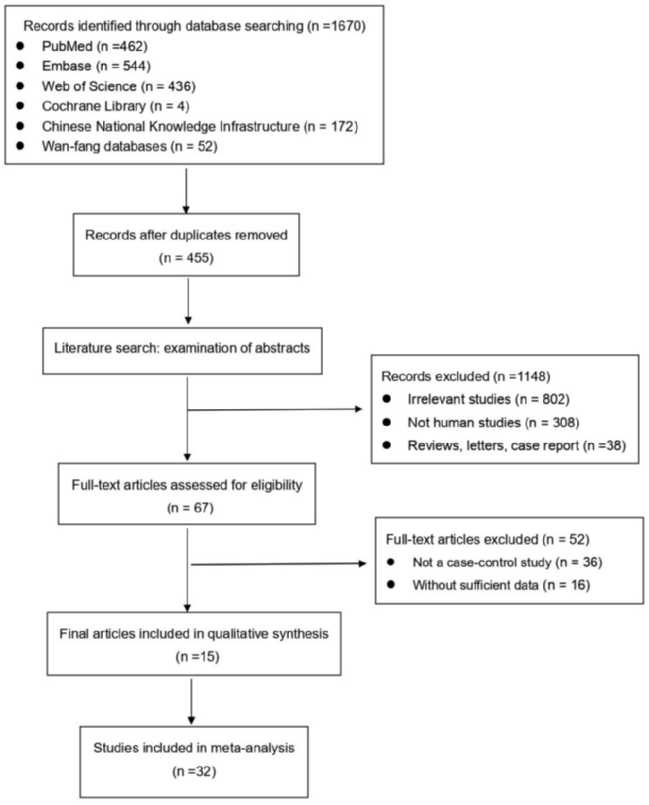

Fig. 1. Flow chart of the meta-analysis.

biological processes and linked to cancer development[11,12]. Circulating miRNA have been put forward as attractive diagnostic tools [13,14] due to its strong specificity, high accuracy and stability[15]. During the formation and evolution of MM cells, many miRNAs related to the pathogenesis of MM were abnormally expressed, suggesting that miRNAs may also play an important role in the occurrence and development of MM[16]. Studies have found that in the bone marrow tissues of patients with MM, the expression of miRNA-181a was increased, and the expression of miRNA-373 was decreased. The expressions of the two were negatively correlated and jointly participate in the occurrence and development of tumors, and proved that the expression levels of these two miRNAs were related to the age, clinical stage, degree of differentiation, and lymph node metastasis of MM patients[17]. Therefore, the study of miRNA expression profiles and gene regulatory networks related to MM can help to understand the mechanism of MM and which has opened up new possibilities for improving the early diagnosis and treatment of MM.

With the rise of miRNAs in recent years, many studies have shown that the accuracy of circulating miRNAs in the early diagnosis of MM is satisfactory but inconsistent[18–20]. This may be caused by factors such as different detection technologies, platforms, standards, and insufficient clinical samples. Therefore, we carried out this *meta*-analysis to evaluate the worth of circulating miRNA in the early diagnosis of MM patients.

2. Materials and methods

2.1. Search strategy and literature selection

Two investigators independently searched the PubMed, Web of Science, EMBASE, Cochrane Library, China National Knowledge

Table 1
Characteristics of the included studies.

Author	Year	Country	microRNAs	Regulation mode	Sample size		Speci-men	Diagnostic power		
					MM	Healthy		Sen (%)	Spe (%)	AUC
Single miRNA										
Kubiczkova, L.[23]	2014	Czech Republic	let-7d	Downregulated	103	30	Serum	0.641	0.867	0.804
Kubiczkova, L.[23]	2014	Czech Republic	let-7e	Downregulated	103	30	Serum	0.888	0.633	0.829
Li, J.[24]	2020	China	miR-15a-5p	Upregulated	23	18	Serum	0.870	0.610	0.804
Li, F.[25]	2015	China	miR-16–1	Downregulated	90	19	Plasma	1.000	0.730	0.864
Hao, M.[26]	2015	China	miR-19a	Upregulated	108	56	Serum	0.773	0.897	0.910
Qiu, X. Y.[27]	2013	China	miR-20a	Downregulated	40	20	Plasma	0.63	0.85	0.74
Sevcikova, S.[28]	2013	Czech Republic	miR-29a	Upregulated	91	30	Serum	0.880	0.700	0.832
Xu, Y. N.[29]	2017	China	miR-29a	Upregulated	40	20	Serum	0.815	0.722	0.763
Kubiczkova, L.[23]	2014	Czech Republic	miR-34a	Upregulated	103	30	Serum	0.777	0.700	0.790
Yoshizawa, S.[19]	2012	Japan	miR-92a	Downregulated	62	133	Plasma	0.919	0.991	0.981
Hao, M.[26]	2015	China	miR-92a	Upregulated	108	56	Serum	0.724	0.869	0.830
Jiang, Y.[30]	2018	China	miR-125b-5p	Upregulated	35	20	Plasma	0.860	0.960	0.954
Kubiczkova, L.[23]	2014	Czech Republic	miR-130a	Downregulated	103	30	Serum	0.575	0.900	0.722
Li, J.[24]	2020	China	miR-134-5p	Upregulated	23	18	Serum	0.870	0.667	0.812
Hao, M.[26]	2015	China	miR-135b-5p	Upregulated	108	56	Serum	0.667	0.833	0.810
Nidhi Gupta.[21]	2019	Germany	miR-143	Upregulated	30	30	Serum	0.767	0.767	0.854
Nidhi Gupta.[21]	2019	Germany	miR-144	Upregulated	30	30	Serum	0.733	0.733	0.784
Xie, L. L. [31]	2018	China	miR-148a	Upregulated	50	30	Serum	0.760	0.700	0.791
Xu, Y. N.[29]	2017	China	miR-155	Downregulated	40	20	Serum	0.800	0.722	0.862
Nidhi Gupta.[21]	2019	Germany	miR-199	Upregulated	30	30	Serum	0.800	0.800	0.90
Nidhi Gupta.[21]	2019	Germany	miR-203	Upregulated	30	30	Serum	0.833	0.833	0.930
Jiang, Y.[30]	2018	China	miR-490-3p	Upregulated	35	20	Plasma	0.600	0.850	0.866
Cai, L.[32]	2019	China	miR-497	Downregulated	63	50	Serum	0.860	0.960	0.933
Jones, C. I.[33]	2012	UK	miR-720	Upregulated	24	13	Serum	0.872	0.923	0.911
Kubiczkova, L.[23]	2014	Czech Republic	miR-744	Downregulated	103	30	Serum	0.728	0.667	0.715
Jones, C. I.[33]	2012	UK	miR-1308	Downregulated	24	13	Serum	0.821	0.923	0.892
Hao, M.[26]	2015	China	miR-4254	Upregulated	108	56	Serum	0.793	0.985	0.920
Shen, X.[34]	2017	China	miR-4449	Upregulated	71	64	Serum	0.789	0.913	0.885
miRNA cluster										
Hao, M.[26]	2015	China	miR-19a + miR-4254	Upregulated	108	56	Serum	0.917	0.905	0.950
Liu, B.[35]	2015	China	miR-21/miR-199b-5p	Upregulated	24	30	Serum	0.960	1.000	0.990
Xu, Y. N.[29]	2017	China	miR-29a/miR-155	Upregulated	40	20	Serum	0.808	0.833	0.874
Kubiczkova, L.[23]	2014	Czech Republic	miR-34a + let-7e	Upregulated	103	30	Serum	0.806	0.867	0.898

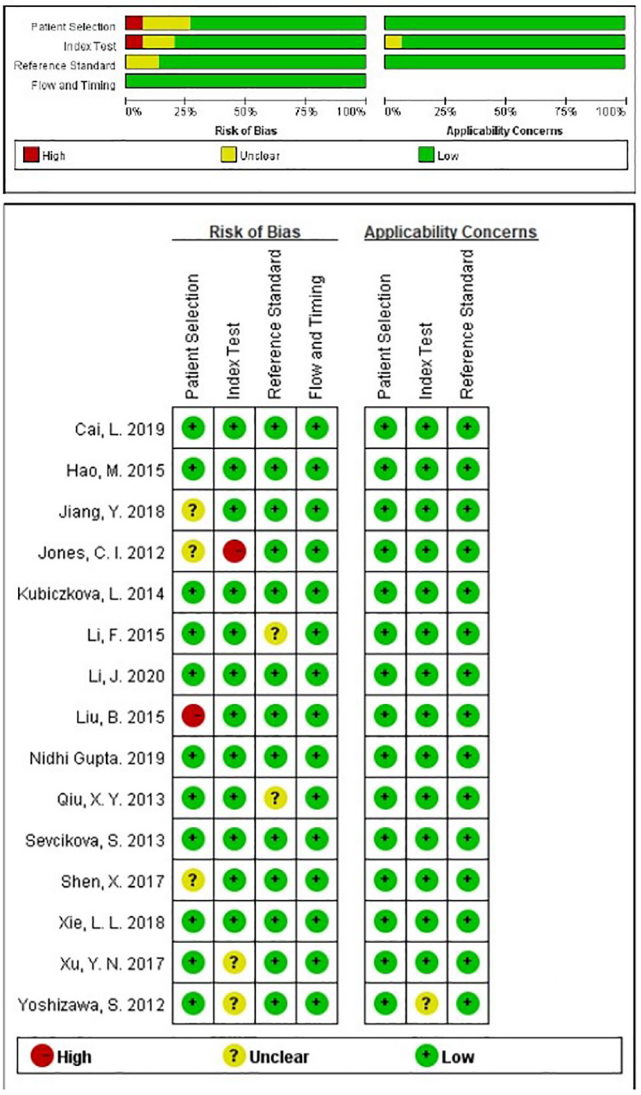

Fig. 2. Overall methodological quality assessments of included articles based on QUADAS-2 tool.

Infrastructure (CNKI) and Wanfang database without language restrictions. The search MeSH terms were used as follows: “multiple myeloma” and “ miRNA ” or “ microRNA ”. The searches were confined to publications involving human subjects, and the last search was conducted on 20/07/2020.

2.2. Inclusion and exclusion criteria

The inclusion criteria: (a) All studies involved newly diagnosed multiple myeloma patients and healthy controls; (b) The obtained miRNA is derived from serum or plasma specimens; (c) The literature contained relevant statistics such as sensitivity, specificity, and AUC value.

The exclusion criteria: (a) Duplicated information; (b) The literature were letters, comments, case reports or reviews; (c) The microRNA obtained is not derived from peripheral circulating blood, such as animal experiments, cell lines or biopsy; (d) Lack of sufficient data.

2.3. Data collection and study assessment

Two researchers separately extracted the following data from the full text and corresponding supplementary information of eligible articles: the name of the first author, country/region, year of publication,

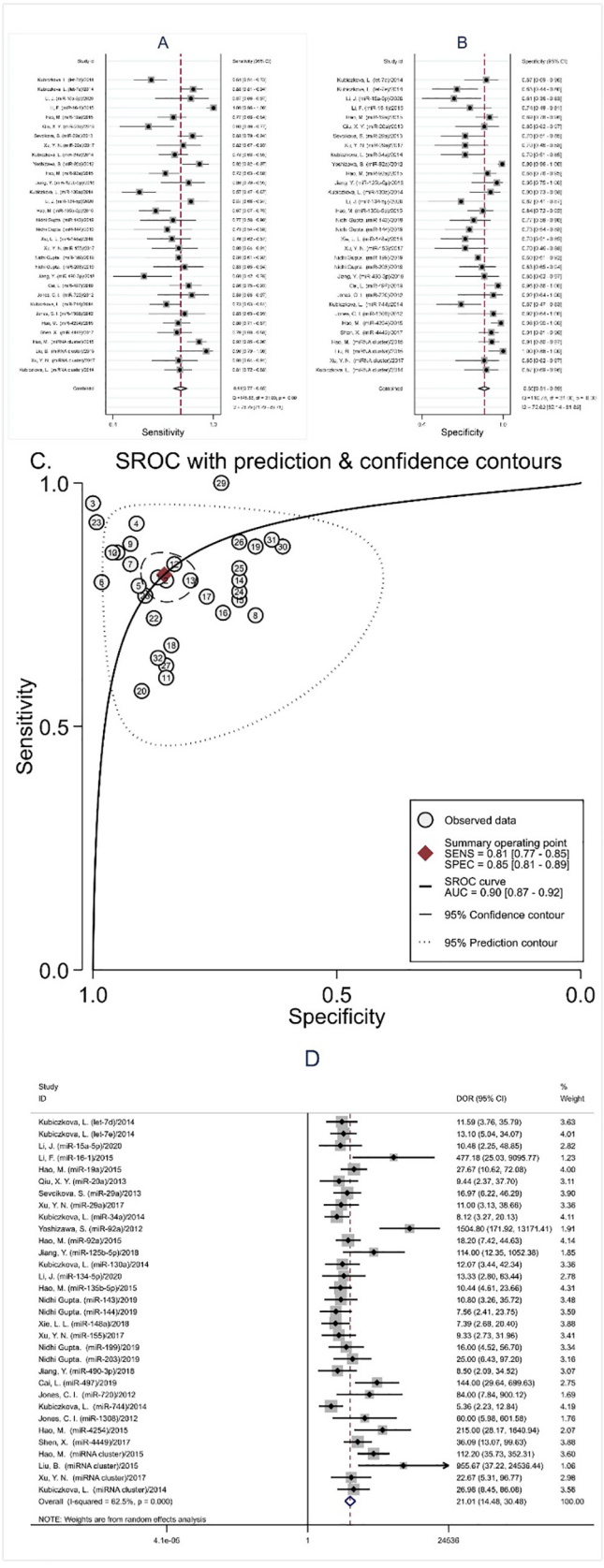

Fig. 3. Diagnostic value of microRNAs in MM patients from healthy controls in all studies. (A) Sensitivity; (B) Specificity; (C) AUC; (D) DOR.

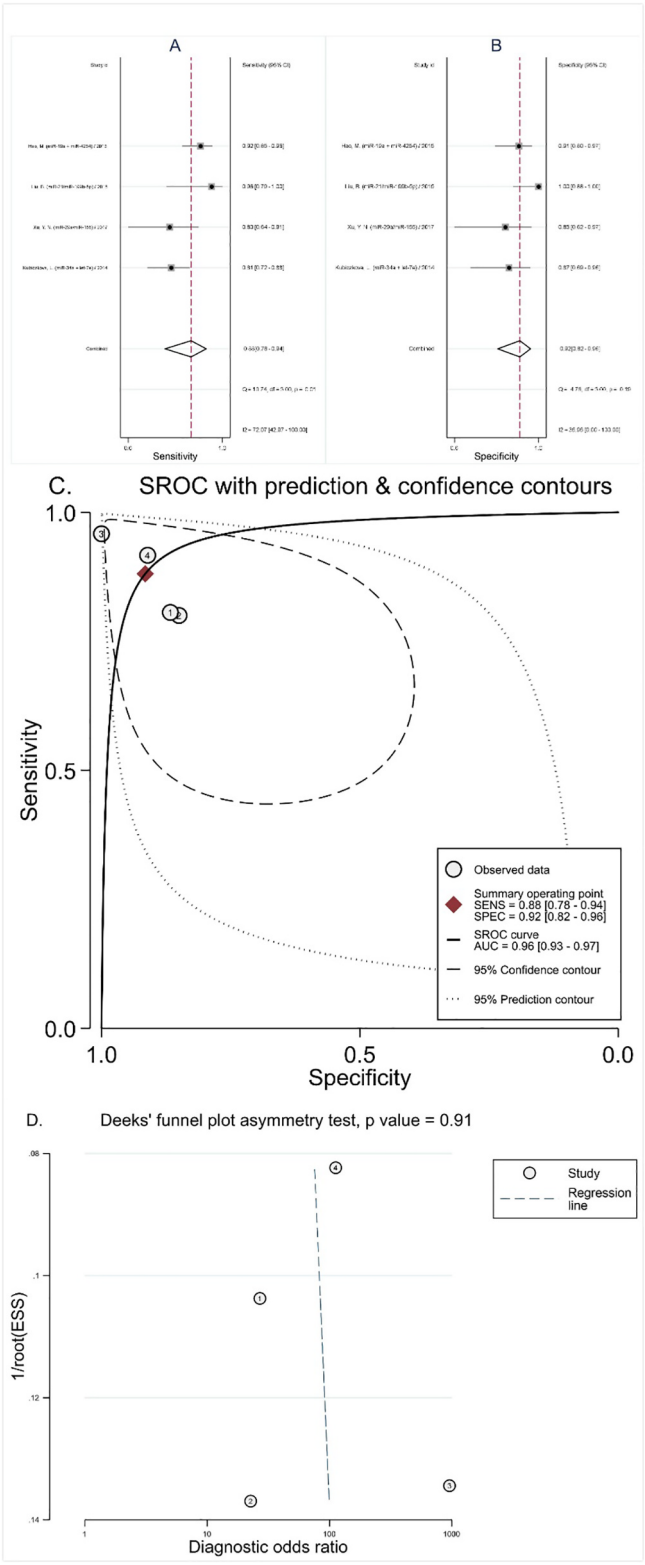

Fig. 4. Diagnostic value of miRNA cluster in diagnosing MM patients from healthy controls. (A) Sensitivity; (B) Specificity; (C) AUC; (D) Funnel plot.

miRNA type (single or cluster), gene expression (up-regulation or down-regulation), sample size (number of patients with MM / healthy people), type of specimen (serum or plasma), as well as relevant statistical data and methodological quality information. The quality of included studies were assessed independently by two investigators using diagnostic accuracy studies-2 (QUADAS-2) criteria[22]. If two investigators disagreed, consulted the third investigator (WTZ) and reached a consensus.

2.4. Statistical analysis

All statistical analyses were done by Review Manager 5.2 and version 13.0 of STATA. The Higgins's inconsistency index (I^2) statistic was used to assess the heterogeneity between these studies. If the I^2 value was over 50%, it considered that there was obvious heterogeneity, and then the random effects model was conducted. We also combined sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and the area under the curve (AUC), and the corresponding 95% CI was calculated the overall and subgroup analysis. In addition, subgroup analysis was performed to explore the heterogeneity. At last, we used Deeks' funnel plot analysis to explore the potential publication bias.

3. Results

3.1. Article screening flowchart

Two investigators independently searched databases, including PubMed, Web of Science, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and Wan-fang databases, a total of 1670 articles. After excluding irrelevant, duplicates, reviews, letters, case report, and not human studies, 67 articles were left. We read these articles carefully to assess eligibility and screening based on inclusion and exclusion criteria, 15 articles (32 studies) were finally included in this *meta*-analysis. (Fig. 1)

3.2. Basic characteristics and quality assessment of included literature

The main characteristics of the 32 studies were shown in Table 1, ranging from 2012 to 2020. Refer to the QUADAS-2 tool to evaluate the quality of all the included literature. The evaluation results show that the overall quality of the studies included in this *meta*-analysis was high. (Fig. 2)

3.3. Diagnostic accuracy of circulating microRNAs in MM patients from healthy controls

We included in the pooled analysis a total of 32 studies involving 3,171 participants (2,053 MM and 1,118 healthy controls). Significant heterogeneity was found in our *meta*-analysis, as demonstrated by the results (I^2 = 78.75% for sensitivity and I^2 = 72.02% for specificity, respectively). Thus, the random-effect model was used in our *meta*-analysis. Overall, the pooled sensitivity was 0.81 (95% CI: 0.77–0.85), specificity was 0.85 (95% CI: 0.82–0.89), PLR was 5.5 (95% CI: 4.1–7.5), NLR was 0.22 (95% CI: 0.18–0.27), DOR was 25 (95% CI: 16–39), and AUC was 0.90 (95% CI: 0.87–0.92). (Fig. 3) The above results suggest that miRNA can be served as an adjuvant tool in differentiating MM patients from healthy controls.

3.4. Diagnostic value of miRNA cluster in MM patients

There were 4 studies focused on miRNA clusters. As shown in Fig. 4, the pooled sensitivity was 0.88 (95% CI: 0.78–0.94), specificity was 0.92 (95% CI: 0.82–0.96), NLR was 0.13 (95% CI: 0.07–0.26), PLR was 10.4 (95% CI: 4.4–24.8), DOR was 80 (95% CI: 19–336), and AUC was 0.96 (95% CI: 0.93–0.97). The results manifested that microRNAs cluster had a relatively high diagnostic accuracy in early diagnosis of MM patients.

3.5. Subgroup analysis

Since the above methods proved that there was heterogeneity

Table 2
Summary estimates of diagnostic power and their 95% confidence intervals.

Subgrupo	Se (95% CI)	Sp(95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
miRNAs profiling						
Single miRNA	0.80 [0.76–0.84]	0.84 [0.79–0.88]	5.1 [3.7–6.9]	0.24 [0.19–0.29]	21 [14–33]	0.89 [0.86–0.91]
Multiple miRNAs	0.88 [0.78–0.94]	0.92 [0.82–0.96]	10.4 [4.4–24.8]	0.13 [0.07–0.26]	80 [19–336]	0.96 [0.93–0.97]
Regulation modo						
Upregulated	0.80 [0.77–0.83]	0.84 [0.79–0.88]	5.2 [3.8–6.9]	0.23 [0.19–0.28]	22 [14–34]	0.88 [0.85–0.91]
Downregulated	0.83 [0.70–0.91]	0.87 [0.76–0.94]	6.5 [3.2–13.1]	0.20 [0.11–0.36]	33 [11–97]	0.92 [0.89–0.94]
Sample size						
≥100	0.82 [0.75–0.87]	0.88 [0.82–0.92]	6.7 [4.2–10.7]	0.21 [0.15–0.29]	32 [17–64]	0.92 [0.89–0.94]
< 100	0.80 [0.75–0.84]	0.81 [0.75–0.86]	4.2 [3.1–5.9]	0.25 [0.19–0.32]	17 [10–29]	0.87 [0.84–0.90]
Specimen types						
Serum	0.80 [0.76–0.83]	0.84 [0.79–0.88]	4.9 [3.7–6.4]	0.24 [0.20–0.29]	20 [14–30]	0.88 [0.85–0.90]
Plasma	0.89 [0.60–0.98]	0.92 [0.78–0.98]	11.7 [3.9–35.6]	0.12 [0.03–0.52]	98 [14–675]	0.96 [0.94–0.98]
Etnia						
Asian	0.83 [0.77–0.88]	0.88 [0.82–0.93]	7.2 [4.5–11.6]	0.19 [0.14–0.27]	38 [19–74]	0.92 [0.89–0.94]
European	0.78 [0.72–0.83]	0.78 [0.73–0.83]	3.6 [2.9–4.5]	0.28 [0.23–0.35]	13 [9–18]	0.85 [0.81–0.88]

Se: sensitivity, Sp specificity, PLR: positive likelihood ratios, NLR: negative likelihood ratios, DOR: diagnostic odds ratio, AUC: area under the curve, CI: confidence interval.

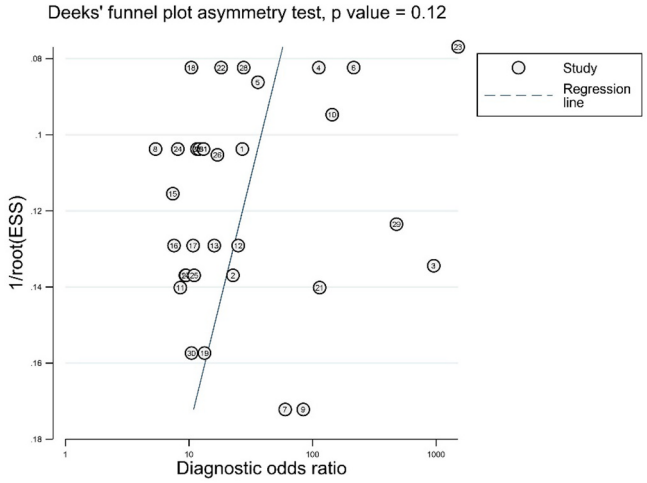

Fig. 5. Deeks' linear regression test of funnel plot asymmetry.

between the included study results, further subgroup analysis was performed according to specimen types, regulation mode, miRNAs profiling, sample size and ethnicity. The relevant statistic for each subgroup analysis were demonstrated in Table 2. It showed that using miRNA clusters to diagnose MM had more advantages than single miRNA: sensitivity (0.88 vs. 0.80), specificity (0.92 and 0.84) and AUC (0.96 and 0.89). Furthermore, down-regulated miRNAs have better diagnostic accuracy than up-regulated miRNAs: sensitivity (0.83 vs. 0.80), specificity (0.87 vs. 0.84) and AUC (0.92 vs. 0.88). In addition, compared with serum, the sensitivity, specificity and AUC of miRNA testing in plasma were higher, 0.89 vs. 0.80, 0.92 vs. 0.84, and 0.96 vs. 0.88, respectively. Moreover, the larger sample size showed higher accuracy: sensitivity (0.82 vs. 0.80), specificity (0.88 vs. 0.81) and AUC (0.92 vs. 0.87). Finally, the analysis based on ethnicity demonstrated miRNA yield a better diagnosis accuracy in the Asian race populations than European.

3.6. Publication bias

Stata 13.0 was used to evaluate publication bias and draw a Deeks funnel chart. As demonstrated in Figs. 5 and 4D, the pooled Deeks test result of all studies was P = 0.12, the pooled Deeks' test result of microRNA clusters was P = 0.91, which indicated that no found publication bias in this *meta*-analysis.

4. Discussion

As a common malignant tumor in clinical practice, MM has always been a hot spot for scholars. The emergence of targeted new drugs has greatly improved the quality of life of MM patients. However, for the early diagnosis of MM, that is, after the patient has bone pain, clinicians obviously cannot make a timely and accurate diagnosis based on traditional imaging examinations, which leads to the development of the patient's condition and delays the treatment[36]. Bone marrow biopsy is the traditional gold standard for diagnosis, but it is an invasive test that is very painful for patients. Therefore, we need a more accurate and advanced noninvasive biomarker for the early diagnosis of MM. According to the latest research, miRNA had strong specificity and sensitivity in diagnosing the occurrence and metastasis of malignant tumors[13,37], and can be used as a new method for early diagnosis and monitoring of tumors. Several studies had analyzed the accuracy of circulating miRNAs in diagnosing MM. For instance, Cai[32] and Nidhi [21] et al. pointed out that the sensitivity and specificity of miR-497 and miR-199 in diagnosing MM were 86.0% and 96.0%, 80.0% and 80.0%, respectively. According to reports by Yoshizawa[19], the sensitivity and specificity of miRNA-92a were 91.9% and 99.1%, respectively, and its diagnostic accuracy was satisfactory. However, Hao et al. [26] found that the sensitivity and specificity of miRNA-92a were low, 72.4% and 86.9%, respectively. It can be seen that even the same miRNA has different accuracy due to different specimens, sample sizes and detection techniques. In addition, it had been shown that miRNA clusters (miR-21, miR-199b-5p) can separate MM patients from healthy peoples with a high sensitivity and specificity (96.0% and 100%)[35], which were more reliable than the results of a single miRNA.

Therefore, we carried out this *meta*-analysis to evaluate the value of circulating miRNAs in the early diagnosis of MM. The overall results of showed that the pooled sensitivity, specificity, PLR, NLR, and DOR of circulating miRNA detection in the diagnosis of MM were 0.81 (95% CI: 0.77–0.85), 0.85 (95% CI: 0.82–0.89), 5.5 (95% CI: 4.1–7.5), 0.22 (95% CI: 0.18–0.27), 25 (95% CI: 16–39), and 0.90 (95% CI: 0.87–0.92), respectively. AUC is a measure of the diagnostic accuracy test method: the closer the AUC is to 1, the greater the diagnostic value[38]. In addition, the pooled DOR showed that the probability of correctly diagnosing MM individuals was 25 times higher than the false negative diagnosis of healthy individuals. All of the results proved that circulating miRNAs showed relatively high accuracy in the diagnosis of MM.

In this *meta*-analysis, subgroup analysis was performed to find probable sources of heterogeneity. We found that down-regulation of microRNA clusters with larger samples size of plasma type could carry out a better diagnostic accuracy of MM patients. The expression of a single miRNA in serum or plasma lacks specificity in cancer detection,

and it might fluctuate in other diseases[37]. However, miRNA clusters with complex molecular mechanisms can reflect the occurrence and development of tumors in many ways, forming a more stable and reliable network diagnostic structure[39]. According to reports, more proteins could be retained in plasma for co-isolation of miRNAs[40], and it had more clinical applications, which was consistent with our results. Our research also found that there was a difference between the down-regulation and the up-regulation of miRNA, this was consistent with Hui's research results[41], this difference may be due to the number of miRNAs analyzed, the type and size of samples contained, the design statistical methods, and the different platforms used for microarray technology. Finally, the diagnostic value of miRNA for Asian races was higher than that for European. This may be related to the morbidity and sensitivity of race, and more multi-center genetic studies are needed to explain the reasons.

To the best of our knowledge, this *meta*-analysis was the latest, most comprehensive, objective and credible on the diagnostic value of miRNA in multiple myeloma. However, there were still some limitations. Although a comprehensive search strategy is used in our literature search, some valuable research may be lost. In addition, individual studies included relatively few patients, which limited the strength of our *meta*-analysis conclusions. Finally, in recent years, the microRNA has been widely used as a potential biomarker in different clinical settings, however, the diagnosis of MM in clinic using only circulating miRNAs still needs to be solved, and even other auxiliary examinations are needed.

5. Conclusion

In short, with the gradual deepening of research on circulating miRNAs, it had shown great advantages in the early diagnosis of MM. This method not only had high sensitivity and strong specificity, but also had non-invasive and no radiation risks. It is worth continuing to optimize its practicality. In the future, multi-center, more rigorous, and high-quality case-control studies are still needed in clinical practice to improve the efficacy of circulating miRNA in the early diagnosis of MM.

6. Ethics Committee

The data comes from literature search and does not require any ethics committee approval and patient informed consent.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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