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# Prediction of differentially expressed microRNAs in blood as potential biomarkers for Alzheimer's disease by meta-analysis and adaptive boosting ensemble learning

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## Abstract

**Background:** Blood circulating microRNAs that are specific for Alzheimer's disease (AD) can be identified from differentially expressed microRNAs (DEmiRNAs). However, non-reproducible and inconsistent reports of DEmiRNAs hinder biomarker development. The most reliable DEmiRNAs can be identified by meta-analysis. To enrich the pool of DEmiRNAs for potential AD biomarkers, we used a machine learning method called adaptive boosting for miRNA disease association (ABMDA) to identify eligible candidates that share similar characteristics with the DEmiRNAs identified from meta-analysis. This study aimed to identify blood circulating DEmiRNAs as potential AD biomarkers by augmenting meta-analysis with the ABMDA ensemble learning method.

**Methods:** Studies on DEmiRNAs and their dysregulation states were corroborated with one another by meta-analysis based on a random-effects model. DEmiRNAs identified by meta-analysis were collected as positive examples of miRNA–AD pairs for ABMDA ensemble learning. ABMDA identified similar DEmiRNAs according to a set of predefined criteria. The biological significance of all resulting DEmiRNAs was determined by their target genes according to pathway enrichment analyses. The target genes common to both meta-analysis- and ABMDA-identified DEmiRNAs were collected to construct a network to investigate their biological functions.

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**Results:** A systematic database search found 7841 studies for an extensive meta-analysis, covering 54 independent comparisons of 47 differential miRNA expression studies, and identified 18 reliable DE miRNAs. ABMDA ensemble learning was conducted based on the meta-analysis results and the Human MicroRNA Disease Database, which identified 10 additional AD-related DE miRNAs. These 28 DE miRNAs and their dysregulated pathways were related to neuroinflammation. The dysregulated pathway related to neuronal cell cycle re-entry (CCR) was the only statistically significant pathway of the ABMDA-identified DE miRNAs. In the biological network constructed from 1865 common target genes of the identified DE miRNAs, the multiple core ubiquitin-proteasome system, that is involved in neuroinflammation and CCR, was highly connected.

**Conclusion:** This study identified 28 DE miRNAs as potential AD biomarkers in blood, by meta-analysis and ABMDA ensemble learning in tandem. The DE miRNAs identified by meta-analysis and ABMDA were significantly related to neuroinflammation, and the ABMDA-identified DE miRNAs were related to neuronal CCR.

**Keywords:** Alzheimer's disease, Meta-analysis, MicroRNAs, ABMDA, Biomarkers, Neuroinflammation, Neuronal cell cycle re-entry

## Background

Alzheimer's disease (AD) is subcellularly characterized by the presence of extracellular amyloid-beta ( $A\beta$ ) plaque deposition and intracellular neurofibrillary tangles of hyperphosphorylated tau proteins [1]. The aberrant protein aggregates are accompanied by activation of neuroinflammation, and loss of synaptic functions [2]. In the progression of AD, irreversible loss of neurons and synaptic functions gradually develops over decades before the manifestation of cognitive symptoms [3]. Because the root causes of pathological  $A\beta$  accumulation and hyperphosphorylated tau proteins are not clear, drug development for AD often fails and current AD treatments alleviate symptoms only. The failure of most clinical trials in AD has been partially attributed to the lack of sensitive biomarkers to identify potential AD [4], which can identify and enroll patients at the early stage of AD, as it may be too late to rescue the dysfunction present in advanced stages of the disease.

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed that the diagnosis of AD should be dependent on biomarkers rather than solely dependent on clinical symptoms [5, 6]. Aberrant levels of  $A\beta$  and tau proteins in cerebrospinal fluid (CSF) and blood have been evaluated as biomarkers for AD diagnosis [7, 8], specifically, increased levels of total and hyperphosphorylated tau proteins, and decreased levels of  $A\beta$  in CSF. CSF levels of total and hyperphosphorylated tau proteins are correlated with neurofibrillary tangle load, and CSF levels of  $A\beta$  are inversely correlated with amyloid load [9]. However, a review concluded that these CSF biomarkers are more useful for ruling out AD, than for indicating a definite diagnosis [10]. To avoid the side

effects of invasive CSF sampling, such as positional headache, Fei et al. [11] have proposed the use of peripheral blood  $A\beta$  detection, such as the ratio of  $A\beta_{42}/A\beta_{40}$ . However, another review has reported that lower plasma  $A\beta_{42}/A\beta_{40}$  ratios might not be associated with increased AD risk [12]. The plasma phosphorylated tau 217 is proposed to distinguish AD from non-AD neurodegenerative individuals, since its level increases more steeply in non-demented individuals with amyloid positivity than those without amyloid positivity [13]. The limitations to use  $A\beta$  or tau proteins as biomarkers in blood might be due to several reasons. First,  $A\beta$  in both CSF and blood tends to self-aggregate [14], masking epitopes for detection and reducing the correlation with AD. Second, the entrance of  $A\beta$  and tau proteins into body fluid is hindered by the extent of blood-brain barrier (BBB) leakage [15]. Thus, there is a need to identify other potential non-invasive biomarkers to aid the diagnosis of AD. An ideal AD biomarker would allow for mass screening to identify patients at high risk of developing AD in the presymptomatic stage with adequate reliability.

MicroRNAs (miRNAs) are a class of single-stranded non-coding RNAs that are 18–25 nucleotides in length and bind to the 3' untranslated region of target mRNAs to modify the target mRNAs' expression in a post-transcriptional manner [16]. Each miRNA simultaneously targets hundreds of mRNAs, and over 2500 mature miRNAs have been recorded in the latest version of the miRBase database [17]. Out of all recorded miRNAs, 300 have been associated with neurodegenerative diseases and 131 miRNAs are specific for AD [18]. Down-regulated expressions of miR-29a/b-1, miR-29c, and miR-339-5p have been reported to upregulate the expression of *BACE1* in AD brain, thereby increasing  $A\beta$  production [19–21]. The expression of miR-15/107 in

cerebral cortical gray matter is correlated with amyloid plaque density [22]. The AD-dysregulated miRNAs in brain have been associated with neuroinflammation and cell cycle regulation [23, 24] and may be released into peripheral blood through the BBB [25] and transported by lipoproteins in circulation for stability [26]. These stable AD-dysregulated miRNAs in blood may reflect the composition of dysregulated miRNAs in brain, suggesting that they may be potential biomarkers of AD. The dysregulated miRNAs were found in plasma and serum of AD patients [27, 28], e.g., the expression of miR-125b in serum of AD patients is correlated with Mini-Mental State Examination (MMSE) scores [29]. Compared with biomarkers in brain or CSF, blood circulating biomarkers are preferable for their higher accessibility. However, before establishing any miRNAs as AD biomarkers, it is necessary to first evaluate their reliability and consistency among different studies of differentially expressed miRNAs (DEmiRNAs) in AD patients, and their biological significance to understand their roles in the pathogenesis of AD.

Thus far, the development of blood circulating DEmiRNAs as AD biomarkers has been hindered by inconsistent and unreliable studies. For example, Denk et al. [30] and Wu et al. [31] conducted similar studies using quantitative real-time polymerase chain reaction (qRT-PCR) to quantify the expression of miRNAs in serum, and found 22 and 9 DEmiRNAs, respectively. Only one DEmiRNA, miR-146a-5p, was common between the two studies. Further, the studies reported the same miR-146a-5p to have opposite directions of dysregulation in AD. This inconsistency can be attributed to differences in the AD patients recruited for the trials, including the presence of other disease conditions that might influence the levels of biological molecules in blood, and the stages of disease progression [32, 33]. A meta-analysis of these inconsistent DEmiRNA results may resolve discrepancies and enhance generalizability of the results. Takousis et al. [34] conducted a meta-analysis to identify DEmiRNAs in brain, blood, and CSF from expression profiling studies of AD. They applied Stouffer's method to integrate the *P* values of every DEmiRNA from each independent study and found 32 statistically significant DEmiRNAs in blood. However, Stouffer's method does not include information about dysregulation states of DEmiRNAs and its use of *P* values is outdated in terms of the methodology of meta-analysis; thus, the results were probably biased by the number of studies reporting the same DEmiRNAs. Hu et al. and Zhang et al. [35, 36] also conducted meta-analyses independently and reported that the sensitivity (86% and 80%, respectively) and specificity (87% and 83%, respectively) of blood-based miRNAs are comparable with those of fluorodeoxyglucose-positron emission

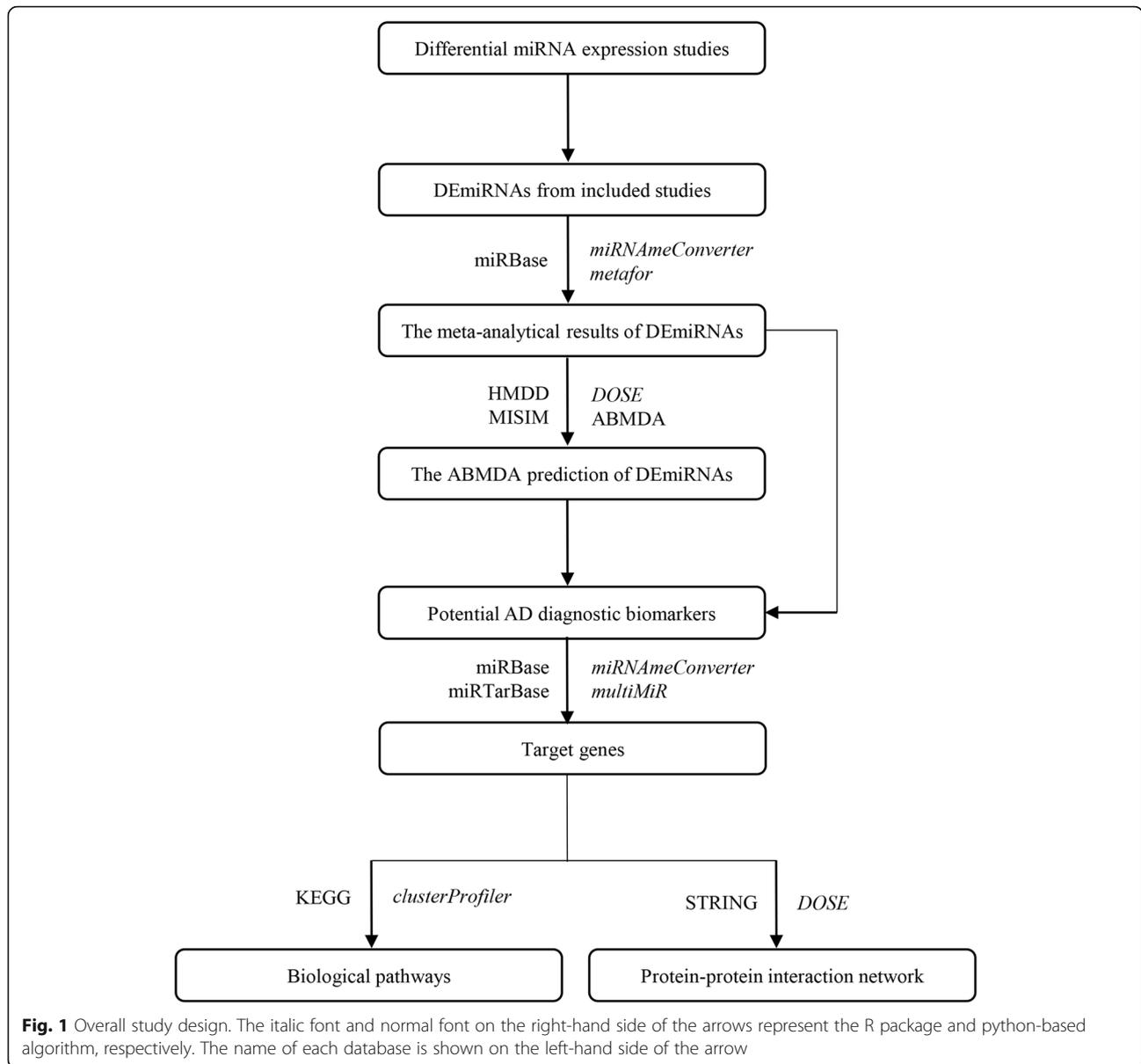
tomography (FDG-PET; sensitivity: 91%, specificity: 86%) [37] for AD diagnosis. The results of these meta-analyses demonstrate that some blood circulating DEmiRNAs may be useful for AD diagnosis, but there has not been extensive identification of DEmiRNAs that may serve as AD biomarkers.

Structural and functional patterns of similar DEmiRNAs can be identified by machine learning, which has been applied to the identification of AD biomarkers. Studies using different machine learning techniques have identified different DEmiRNAs for AD diagnosis with up to 89% accuracy [38–40]. Until recently, machine learning mainly focused on fine tuning the set of DEmiRNAs identified from differential miRNA expression profiling studies to obtain a smaller panel of miRNAs for AD diagnosis. As an emerging trend, machine learning is being used to predict potential DEmiRNAs as AD biomarkers based on DEmiRNAs identified from differential expression profiling studies. For example, Zhao et al. [41] used the adaptive boosting for miRNA disease association (ABMDA) ensemble learning method to identify miRNAs that are associated with a disease. ABMDA is a supervised learning approach with validation against the Human MicroRNA Disease Database (HMDD) [42]. Its clustering algorithm is based on *k*-means distance, and its boosting technique combines classifiers by their corresponding weights to form a stronger classifier. The ABMDA ensemble learning method relies upon the initial set of DEmiRNAs to predict additional DEmiRNAs. In the present study, we used meta-analysis to enhance the reliability of the initial DEmiRNAs and augment the prediction performance of the ABMDA ensemble learning method.

This study aimed to identify blood circulating DEmiRNAs as potential AD biomarkers by augmenting the DEmiRNAs identified by meta-analysis with the ABMDA ensemble learning method. The meta-analysis was conducted under the guidance of the PRISMA statement [43], with the adjustment in the risk of bias assessment.

## Methods

The present meta-analysis was mainly conducted using R and Python packages and is illustrated in Fig. 1. If an included study contained several comparisons, the DEmiRNAs from each comparison were collected independently. The sample sizes of control and AD groups, and DEmiRNAs and their dysregulated states from each independent comparison were extracted. The names of all reported DEmiRNAs were standardized based on the miRBase database [17] before the meta-analysis. A meta-analysis for the DEmiRNAs was performed when more than one comparison reported the same DEmiRNA. Statistically significant DEmiRNAs from the meta-analysis



were collected as positive miRNA–AD associations for the ABMDA ensemble learning method to further increase the number of positive miRNA–AD associations. The ABMDA-identified miRNAs with scores higher than the predefined criteria, together with the DEmiRNAs identified by the meta-analysis, were treated as potential AD biomarkers in blood. The biological significance of the identified DEmiRNAs was studied by a biological pathway enrichment analysis and network analysis of their corresponding target genes. The combination of meta-analysis and ABMDA ensemble learning might be beneficial to resolve the existing inconsistencies and perform systematical predictions based on reliable results.

**Differential miRNA expression studies selection**

Differential miRNA expression studies were collected from PubMed from inception until January 10, 2020, from ScienceDirect and Web of Science between 1993 and 2019. The search strategy is shown below:

For PubMed, (“Alzheimer’s disease” [MESH Terms] OR “Alzheimer’s disease” [All Fields] OR “alzheimer\*” [MESH Terms] OR “alzheimer\*” [All Fields]) AND (“microRNA\*” [MESH Terms] OR “microRNA\*” [All Fields] OR “miRNA\*” [MESH Terms] OR “miRNA\*” [All Fields])

For ScienceDirect and Web of Science, (microRNA OR miRNA) AND Alzheimer

After the search, two authors (SCY and XNL) screened all titles, abstracts, and full texts independently

according to the eligibility criteria. Disagreements between the authors were resolved by discussion with the other authors.

The case-control studies reporting differential miRNA expression in blood from AD and healthy participants were included. The included studies had to report the differential expression profiling methods, sample sizes of the disease and control groups, and statistical significance for each DE miRNA. Studies were excluded if they (1) were not AD research (i.e., focused on other dementia disease conditions); (2) reported irrelevant effects on differential miRNA expression profiles (i.e., demonstrated treatment effects on the differential miRNA expression); (3) did not report the blood DE miRNAs for AD and healthy participants (i.e., were not controlled studies, or recruited AD participants suffering from other diseases); (4) did not report DE miRNAs and their corresponding dysregulation states (i.e., up or down) as outcomes; or (5) did not obtain DE miRNAs by a validation method (i.e., qRT-PCR).

### Meta-analysis

For each study, the following data were extracted for the meta-analysis: (1) comparison ID (PubMed ID with blood elements or disease stages); (2) blood elements; (3) differential miRNA expression profiling method; (4) number of AD cases; (5) number of control cases; and (6) DE miRNAs and their dysregulated states. For studies that reported both screening and validation results of differential miRNA expression, only the results from validation methods were collected. The names of extracted DE miRNAs were standardized using the *miRNAmeConverter* [44] package for R software with the miRBase database [17]. For each DE miRNA that was reported by more than one comparison, a meta-analysis was performed using the *metafor* [45] package for R software. The meta-analysis was conducted for each qualified DE miRNA, independently, under a random-effects model. For each qualified DE miRNA from independent comparisons, that was reported as binary dysregulation (i.e., upregulation or downregulation) in AD group compared with healthy control group. The effect sizes of binary data were calculated as  $\log_e$  odds ratios (logORs) based on the number of dysregulation events in both disease and control samples. The heterogeneity of each DE miRNA was reported as tau square ( $\tau^2$ ) based on the restricted maximum-likelihood estimator and  $I^2$  statistics. The outcomes were logORs with a 95% confidence interval (CI),  $P$  values,  $\tau^2$ , and  $I^2$ . For each DE miRNA in the  $i$ th study, the effect size ( $\theta_i$ ) based on the numbers of dysregulation events in both AD and control samples was calculated according to the formula,  $\log\left(\frac{A_i * D_i}{B_i * C_i}\right)$ , where  $A_i$  and  $B_i$  ( $C_i$  and  $D_i$ ) represent the number of

upregulated and downregulated cases in the disease (control) group, respectively. Then the overall effect was computed according to formula,  $\frac{\sum W_i \theta_i}{\sum W_i}$ , where  $W_i$  is the weight and is equal to  $1/(v_i + \tau^2)$ , where  $v_i$  is the sample variance. A larger sample size has more weight on the overall effect size. The  $P$  values were adjusted by false discovery rate (FDR), and DE miRNAs with FDR-adjusted  $P$  values less than 0.05 were regarded as statistically significant. Statistically significant DE miRNAs with logORs above or below 0 were considered upregulated or downregulated, respectively, in AD compared with healthy controls.

Subgroup analysis was conducted based on the DE miRNAs collected from the included differential miRNA expression studies. The DE miRNAs were split into four different subgroups based on the blood sample sources, i.e., whole blood, plasma, serum, and peripheral blood mononuclear cell (PBMC).

### ABMDA identification of DE miRNAs

ABMDA ensemble learning was used to identify potential miRNA–disease associations. The original miRNA–disease associations with significant dysregulation in the “circulation\_biomarker\_diagnosis” category were extracted from HMDD, in which the associations are experimentally verified. DE miRNAs identified in the meta-analysis with adjusted  $P$  values less than 0.05 were input into the ABMDA ensemble learning method as positive miRNA–AD associations to further increase the number of positive miRNA–AD associations. In addition to initial miRNA–disease associations, ABMDA ensemble learning also requires disease–disease similarity and miRNA–miRNA functional similarity. The disease–disease similarity was determined using the *DOSE* [46] package for R software. The miRNA–miRNA functional similarity was retrieved from the database MISIM [47]. The ABMDA-identified DE miRNAs were sorted by their prediction scores, and the DE miRNAs with top prediction scores were collected until the first predicted DE miRNA that was reported statistically insignificant in the meta-analysis. The names of predicted DE miRNAs were standardized using the *miRNAmeConverter* package for R software with the miRBase database [17]. The ABMDA-identified DE miRNAs with the top prediction scores, together with the meta-analysis DE miRNAs were considered potential AD biomarkers.

### Biological significance of DE miRNAs from meta-analysis and ABMDA by independent and synergic biological enrichment analysis

Each miRNA regulates a large number of genes to exert a profound influence on genetic expression in specific cellular functions, and the primary function of each

miRNA can be understood by identifying its target genes. The target genes of the DE miRNAs from the meta-analysis and ABMDA identification were obtained using the *multiMiR* [48] package for R software based on the database miRTarBase [49]. The target genes of two DE miRNA categories were collected separately to conduct two independent enrichment analyses and were also combined to conduct a synergic enrichment analysis. The biological enrichment analysis was conducted using the *clusterProfiler* [50] package for R software based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) [51]. The pathways with FDR-adjusted *P* values less than 0.05 were considered statistically significant.

#### Collaborative biological function of DE miRNAs from meta-analysis and ABMDA by network analysis

The target gene semantic similarity measurements of the DE miRNAs identified from the meta-analysis and ABMDA were computed using the *DOSE* package for R. The target genes with semantic similarity over 0.95 were treated as common target genes in the two DE miRNA categories. The DE miRNAs and common target genes of the two DE miRNA categories were used to construct a DE miRNA–gene network based on the data from STRING (version 11) [52] to investigate the collaborative function of the DE miRNAs identified from the meta-analysis and ABMDA. Only interactions with the highest confidence (0.9) were kept from the STRING.

#### Risk of bias

The risk of bias for each included study was evaluated according to the Minimum Information for Publication of Quantitative Real-time PCR Experiments (MIQE) [53]. This guideline is designed to assess the quality of qRT-PCR data and describes the minimum information required to ensure that experimental results can be comprehensively interpreted and independently verified. In the present study, the guideline was used to assess the quality of the expression profiling analysis of the included studies, including experimental design, sample annotation, experimental procedure, data processing pipeline, and result presentation. The evaluation was performed by two authors (SCY and XNL), independently. Disagreements between the authors were resolved by discussion with the other authors. Items with low risk were counted +1, suggesting high reproducibility; items with unclear risk were counted 0, suggesting ambiguous reproducibility; and items with high risk were counted –1, suggesting low reproducibility.

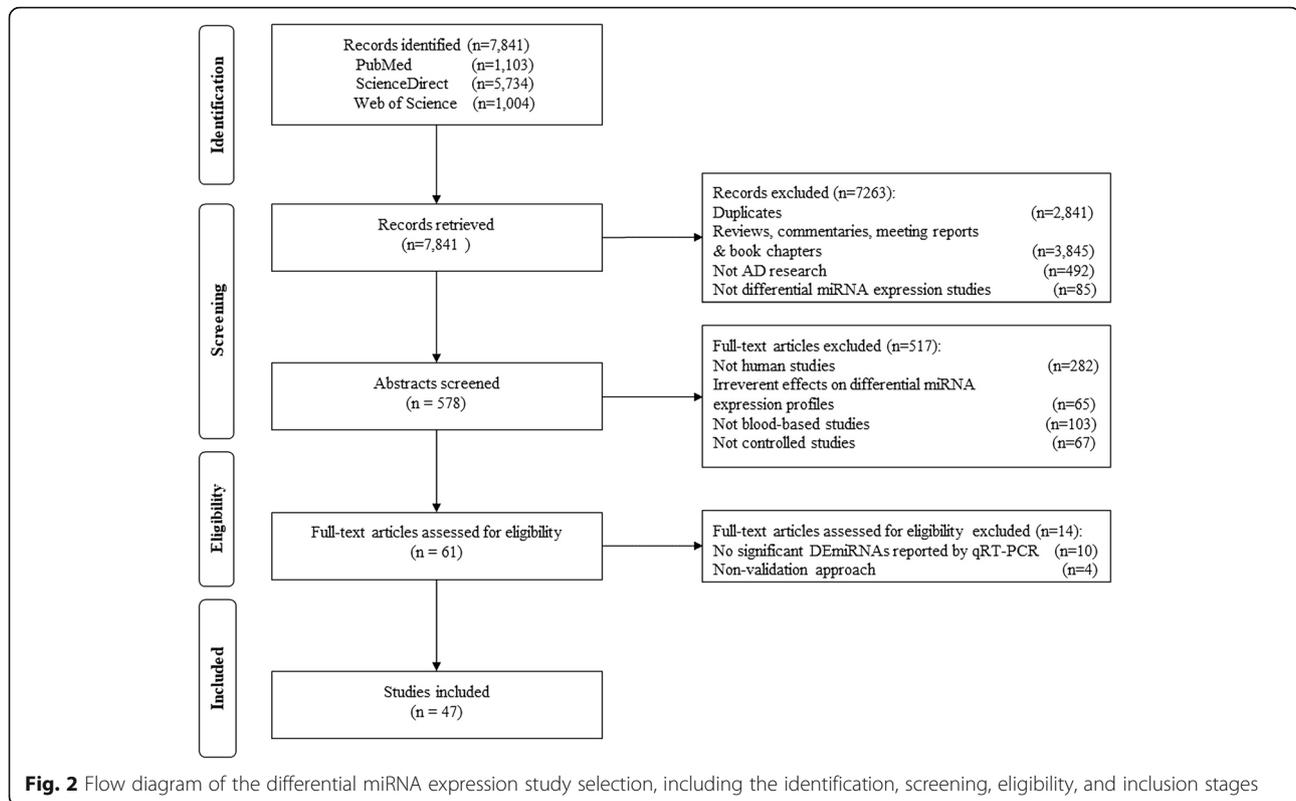
## Results

### Differential miRNA expression studies included in the analysis

The selection process of the differential miRNA expression studies is shown in Fig. 2. A total of 7841 studies were initially identified from PubMed, ScienceDirect, and Web of Science. After a systematic search, 47 studies met the eligibility criteria and were included in the present study [23, 27–31, 39, 40, 54–92]. The characteristics of the included studies are shown in Table 1. The studies mainly focused on four blood elements: serum, plasma, whole blood, and peripheral blood mononuclear cells. Serum ( $n = 19$ ) was the most extensively studied, followed by plasma ( $n = 16$ ).

### Identification of DE miRNAs from meta-analysis

After DE miRNA name standardization, there were 115 DE miRNAs reported in 54 independent comparisons of 47 differential expression studies that compared AD blood samples with healthy blood samples. Eight-eight DE miRNAs were found in one blood element, 25 DE miRNAs were found in two blood elements, two DE miRNAs were found in three blood elements, and no DE miRNAs were found in all four blood elements. The most frequently reported DE miRNAs in AD blood were miR-146a-5p and miR-26a-5p, which were dysregulated in five independent comparisons (Table 2). Of the 115 DE miRNAs, 43 (37.4%) were reported in at least two independent comparisons; dysregulation of 18 of them was reported consistently in the same direction, whereas dysregulation of 25 of them was reported in different directions. Based on the currently available data, none of the inconsistent DE miRNA results were resolved in this meta-analysis. In the meta-analysis of 43 dysregulated miRNAs, 18 DE miRNAs were found to be statistically significant (Table 3; Additional file 1); 7 and 11 DE miRNAs were upregulated and downregulated, respectively. Among the 18 DE miRNAs identified in this study, 6 of them (let-7d-5p, miR-107, miR-128-3p, miR-191-5p, miR-29c-3p, and miR-93-5p) were also found statistically significant in a previous meta-analysis [34]. The discrepancy could be due to that we only included the literature with qRT-PCR as validation results, and we treated comparisons independently even that those comparisons were from the same literature. Meanwhile, 13 DE miRNAs of our meta-analytical results (let-7d-5p, miR-106b-3p, miR-107, miR-126-5p, miR-148b-5p, miR-181c-3p, miR-191-5p, miR-200a-3p, miR-22-3p, miR-483-5p, miR-486-5p, miR-502-3p, and miR-93-5p), were reported contributing the AD diagnostic values in sensitivity and specificity in Hu et al. and Zhang et al. [35, 36]. The most significantly downregulated DE miRNA was miR-107, which was identified in four independent comparisons. MiR-106b-39 was the most significantly



upregulated DEmiRNA among four independent comparisons. Downregulation of miR-107 has been reported to increase *BACE1* expression [93] and influence cell cycle protein expression [94]. The dysregulation of miR-106b-3p is negatively correlated with MMSE score [66] and modulates A $\beta$  metabolism [95]. Most DEmiRNAs identified in the meta-analysis were associated with mediating A $\beta$  generation, tau protein phosphorylation, and neuronal functions maintenance.

For subgroup analysis, among 54 comparisons, 7, 17, 23, and 7 comparisons investigated the DEmiRNAs in whole blood, plasma, serum, and PBMC, respectively. The statistically significant DEmiRNAs from the subgroup meta-analysis are shown in Table 4. MiR-107 was consistently found in two subgroups, whole blood and plasma. Two miRNAs, miR-103a-3p in plasma and miR-181c-5p in serum, were found statistically significant in the subgroup analysis, but not in the meta-analysis. MiR-103a-3p is recently reported to be related to AD progression via regulating *NPAS3* expression [96], while low level of miR-181c-5p in serum is suggested to be an indicator for cerebral vulnerability in AD [97].

#### Identification of potential biomarkers by the ABMDA ensemble learning method

A total of 1751 known miRNA–disease associations between 413 miRNAs and 227 diseases were obtained from

the “circulation\_biomarker\_diagnosis” category in HMDD, including 17 known miRNA–AD associations. Identification of miRNA–disease associations by meta-analysis increased the number of positive miRNA–AD associations by 15 for the ABMDA identification after removing duplicates. The eleventh miRNA from the ABMDA results was determined to be statistically insignificant in the meta-analysis. Therefore, the first 10 miRNAs with prediction scores ranging from 9.45 to 7.88 were collected (Table 5; Additional file 2). Most of these 10 miRNAs have been associated with multiple types of cancer as diagnostic or prognostic biomarkers [98–104]. Only one miRNA, miR-155, has been reported as a biomarker in AD for mediating neuroinflammation [105].

MiR-339-5p is upregulated to alleviate neuroinflammation by inhibiting *HMGB1* [106]. *HMGB1* encodes high mobility group box 1 to produce proinflammatory cytokines by binding to receptors for advanced glycation end products (RAGE) [107] and inhibiting IKK- $\beta$  and IKK- $\gamma$ , which are key elements of NF- $\kappa$ B signaling [108]. NF- $\kappa$ B signaling can also be modulated by the identified DEmiRNAs through multiple mechanisms. Both miR-203a-3p and let-7b-5p target *IGF1R*, which encodes insulin-like growth factor 1 receptor, to alleviate tumor necrosis factor (TNF)-induced activation of NF- $\kappa$ B [109, 110]. MiR-155 and miR-625-5p decrease the expression of *SHIP* and *AKT2*, which encode Src homology 2-

**Table 1** Characteristics of the included differential miRNA expression studies

PubMed ID	Comparison ID	Blood elements	Differential miRNA expression profiling methods (screening method/validation method)	Number of control case	Number of AD case	Number of upregulated miRNA	Number of downregulated miRNA
31857133	31857133_Ser	Serum	qRT-PCR	93	108		1
31811079	31811079_Ser	Serum	qRT-PCR	51	32	9	3
31849573	31849573_Pla	Plasma	microRNA microarray/qRT-PCR	31	16		2
31809862	31809862_WB	Whole blood	qRT-PCR	214	145	1	1
31766231	31766231_Pla	Plasma	microRNA microarray/qRT-PCR	29	23	1	
31691877	31691877_Ser	Serum	qRT-PCR	30	30	4	
31592314	31592314_Pla	Plasma	RNA deep-sequencing/qRT-PCR	11	10		6
31572518	31572518_Ser	Serum	qRT-PCR	98	105		1
31420923	31420923_Pla	Plasma	qRT-PCR	120	120		2
31092279	31092279_Pla	Plasma	qRT-PCR	14	56	3	
30914454	30914454_Pla	Plasma	qRT-PCR	385	385		5
30328325	30328325_Pla	Plasma	qRT-PCR	20	20	1	
29966198	29966198_Pla	Plasma	qRT-PCR	10	10	2	
29746584	29746584_Ser	Serum	qRT-PCR	38	47	14	8
29635818	29635818_Pla	Plasma	qRT-PCR	20	20	1	
29606187	29606187_Ser	Serum	qRT-PCR	107	228	2	1
29036829	29036829_WB	Whole blood	microRNA microarray/qRT-PCR	17	21		3
29036818	29036818_Ser_Mild	Serum	RNA deep-sequencing/qRT-PCR	86	31	1	5
	29036818_Ser_Mod	Serum	RNA deep-sequencing/qRT-PCR	86	52	3	5
	29036818_Ser_Sev	Serum	RNA deep-sequencing/qRT-PCR	86	38	4	5
28934394	28934394_Ser	Serum	microRNA microarray/qRT-PCR	18	11	1	
28849039	28849039_Ser_Mil	Serum	microRNA microarray/qRT-PCR	30	30		1
	28849039_Ser_Mod	Serum	microRNA microarray/qRT-PCR	30	30		1
28626163	28626163_Ser	Serum	RNA deep-sequencing/qRT-PCR	40	45	5	4
28179587	28179587_Pla_AD2	Plasma	qRT-PCR	9	13	4	3
	28179587_Pla_MCI-AD2	Plasma	qRT-PCR	9	8	4	
28137310	28137310_Ser	Serum	RNA deep-sequencing/qRT-PCR	22	36		1
27545218	27545218_Ser	Serum	qRT-PCR	40	48	1	
27501295	27501295_WB	Whole blood	qRT-PCR	109	172		4
27446280	27446280_WB	Whole blood	qRT-PCR	25	25		1
27277332	27277332_WB	Whole blood	qRT-PCR	30	30	1	
27239545	27239545_PBMC	Peripheral blood mononuclear cells	qRT-PCR	36	36	3	
27027823	27027823_Ser	Serum	qRT-PCR	62	84	1	3
26973465	26973465_Pla	Plasma	microRNA microarray/qRT-PCR	40	40		3
26497032	26497032_PBMC	Peripheral blood mononuclear cells	microRNA microarray/qRT-PCR	41	45	2	1
26078483	26078483_Ser	Serum	RNA deep-sequencing/qRT-PCR	75	79		4
25955795	25955795_WB	Whole blood	qRT-PCR	30	30		1

**Table 1** Characteristics of the included differential miRNA expression studies (Continued)

PubMed ID	Comparison ID	Blood elements	Differential miRNA expression profiling methods (screening method/validation method)	Number of control case	Number of AD case	Number of upregulated miRNA	Number of downregulated miRNA
25742200	25742200_Pla	Plasma	qRT-PCR	81	97		1
25667669	25667669_Ser	Serum	qRT-PCR	42	26		1
25152461	25152461_Ser	Serum	microRNA microarray/qRT-PCR	30	38		2
24827165	24827165_Pla	Plasma	qRT-PCR	7	7		1
	24827165_Ser	Serum	qRT-PCR	7	7		1
24577456	24577456_Ser	Serum	RNA deep-sequencing/qRT-PCR	155	158		6
24550773	24550773_Pla	Plasma	qRT-PCR	27	25	1	
	24550773_PBMC	Peripheral blood mononuclear cells	qRT-PCR	27	25	1	
24157723	24157723_Pla	Plasma	qRT-PCR	10	10		2
24139697	24139697_Ser	Serum	qRT-PCR	155	105	1	2
24064186	24064186_PBMC_Mon	Monocytes	qRT-PCR	37	34	1	
	24064186_PBMC_Lym	Lymphocytes	qRT-PCR	37	34	1	
23922807	23922807_Pla_C2	Plasma	microRNA microarray/qRT-PCR	17	20		6
23895045	23895045_WB	Whole blood	RNA deep-sequencing/qRT-PCR	21	94	5	7
23435408	23435408_PBMC	Peripheral blood mononuclear cells	qRT-PCR	25	28		1
22155483	22155483_Ser	Serum	qRT-PCR	7	7		5
19936094	19936094_PBMC	Peripheral blood mononuclear cells	microRNA microarray/qRT-PCR	5	5	2	

containing inositol phosphatase and RAC-beta serine/threonine-protein kinase, respectively, to attenuate NF- $\kappa$ B-dependent inflammation [111, 112]. Additionally, miR-495 targets *NOD1*, which encodes nucleotide-binding oligomerization domain-containing protein 1, to reduce high glucose-induced inflammation in diabetic complications [113], whereas its mature form, miR-495-3p, has recently been reported to regulate inflammatory molecules by targeting *IL5RA* [114]. The mature forms of miR-128-2, let-7a-2, miR-103a-2, and miR-16-2 have not been reported in the miRBase database at the time of this study; however, their family members exhibit inflammatory properties. MiR-128 and let-7a regulate gene expression in response to oxidative stress [115, 116]. MiR-16 and miR-103-3p target *ADORA2A* and *SNRK*, which encode the adenosine A2a receptor and sucrose non-fermentable-related serine/threonine-protein kinase, respectively, to attenuate NF- $\kappa$ B-dependent inflammation [117, 118]. Current literature suggests that NF- $\kappa$ B might be the main downstream effector for the DE miRNAs identified by ABMDA in the present study.

#### Enrichment analysis

There were 3496 and 2938 target genes in total for 18 and 10 DE miRNAs from the meta-analysis and ABMDA

results, respectively (Additional file 3). These target genes were subjected to two independent enrichment analyses based on KEGG to obtain the functional annotations of the DE miRNAs (Fig. 3A, B). Most pathways targeted by the meta-analysis and ABMDA DE miRNAs were commonly found in the two independent enrichment analyses, even though the DE miRNAs in the two categories were not identical. This indicated that multiple DE miRNAs target either common or different mRNA transcripts that functionally converge on the same pathways. Most dysregulated pathways in the enrichment analysis were involved in AD development via modulation of neuroinflammation, including the AGE-RAGE signaling pathway in diabetic complications, cell cycle, cellular senescence, Hippo signaling pathway, and FoxO signaling pathways. In addition, multiple cancerous pathways were also implicated. Compared with the two independent enrichment analyses, the synergic enrichment analysis unifying the two categories of DE miRNAs might provide better insight for AD development. In the synergic enrichment analysis, the dysregulated pathways were more statistically significant (Fig. 3C). Also, the pathways that were found in only one independent enrichment analysis (such as the Hippo signaling pathway from the meta-analysis and cell cycle from

**Table 2** DE miRNAs reported by the included differential miRNA expression studies. The bold DE miRNAs were reported by at least two independent comparisons and were qualified for the subsequent meta-analysis

Comparison ID	MiRNAs	Dysregulated direction	P value
31857133_Ser	miR-193a-3p	Down	< 0.001
31811079_Ser	miR-346	Up	0.0013
	miR-345-5p	Up	0.0239
	miR-122-3p	Up	0.0001
	miR-1291	Up	0.0052
	miR-640	Up	0.0004
	miR-650	Up	0.0035
	miR-1285-3p	Up	0.0032
	miR-1299	Up	0.0003
	miR-1267	Up	0.0055
	miR-208b-3p	Down	0.0006
	miR-206	Down	0.0004
31849573_Pla	<b>miR-132-3p</b>	Down	0.0333
	miR-212-3p	Down	0.001
31809862_WB	miR-532-5p	Up	$4.8 \times 10E-30$
	miR-1468-5p	Down	$6.2 \times 10E-12$
31766231_Pla	miR-206	Up	< 0.025
31691877_Ser	miR-22-5p	Up	$\leq 0.005$
	miR-23a-3p	Up	$\leq 0.05$
	miR-29a-3p	Up	$\leq 0.05$
	miR-125b-5p	Up	$\leq 0.005$
31592314_Pla	miR-451a	Down	< 0.0005
	miR-21-5p	Down	< 0.005
	miR-23a-3p	Down	< 0.005
	let-7i-5p	Down	< 0.05
	miR-126-3p	Down	< 0.005
	miR-151a-3p	Down	< 0.05
31572518_Ser	miR-133b	Down	< 0.001
31420923_Pla	miR-103a-3p	Down	< 0.001
	<b>miR-107</b>	Down	< 0.001
31092279_Pla	miR-92a-3p	Up	0.0442
	miR-181c-5p	Up	0.0024
	miR-210-3p	Up	0.0006
30914454_Pla	miR-101-3p	Down	< 0.001
	miR-153-3p	Down	< 0.001
	miR-144-3p	Down	< 0.001
	miR-381-3p	Down	< 0.001
	miR-383-5p	Down	< 0.001
30328325_Pla	<b>miR-128-3p</b>	Up	< 0.05
29966198_Pla	miR-146a-5p	Up	< 0.05
	miR-933	Up	< 0.05
29746584_Ser	miR-103a-3p	Up	< 0.05
	miR-142-3p	Up	< 0.05

**Table 2** DEmiRNAs reported by the included differential miRNA expression studies. The bold DEmiRNAs were reported by at least two independent comparisons and were qualified for the subsequent meta-analysis (*Continued*)

Comparison ID	MiRNAs	Dysregulated direction	P value
	miR-20a-5p	Up	< 0.05
	miR-29b-3p	Up	< 0.05
	let-7b-5p	Up	< 0.05
	let-7 g-5p	Up	< 0.05
	miR-106a-5p	Up	< 0.05
	miR-106b-5p	Up	< 0.05
	miR-18b-5p	Up	< 0.05
	miR-223-3p	Up	< 0.05
	miR-26a-5p	Up	< 0.05
	miR-26b-5p	Up	< 0.05
	miR-301a-3p	Up	< 0.05
	miR-30b-5p	Up	< 0.05
	<b>miR-132-3p</b>	Down	< 0.05
	miR-146a-5p	Down	< 0.05
	miR-15a-5p	Down	< 0.05
	<b>miR-22-3p</b>	Down	< 0.05
	miR-320a-3p	Down	< 0.05
	miR-320b	Down	< 0.05
	miR-92a-3p	Down	< 0.05
	miR-1246	Down	< 0.05
29635818_Pla	miR-1908-5p	Up	< 0.05
29606187_Ser	miR-135a-5p	Up	< 0.05
	miR-193b-3p	Down	< 0.01
	miR-384	Up	< 0.05
29036829_WB	miR-144-5p	Down	0.03
	miR-374a-5p	Down	0.034
	miR-221-3p	Down	0.042
29036818_Ser_Mild	<b>miR-106b-3p</b>	Up	< 0.001
	miR-26a-5p	Down	< 0.001
	<b>miR-181c-3p</b>	Down	< 0.001
	<b>miR-126-5p</b>	Down	< 0.001
	<b>miR-22-3p</b>	Down	< 0.001
	<b>miR-148b-5p</b>	Down	< 0.001
29036818_Ser_Mod	<b>miR-106b-3p</b>	Up	< 0.001
	miR-1246	Up	< 0.001
	miR-26a-5p	Down	< 0.001
	<b>miR-181c-3p</b>	Down	< 0.001
	<b>miR-126-5p</b>	Down	< 0.001
	<b>miR-22-3p</b>	Down	< 0.001
	<b>miR-148b-5p</b>	Down	< 0.001
29036818_Ser_Sev	<b>miR-106b-3p</b>	Up	< 0.001
	miR-1246	Up	< 0.001
	miR-660-5p	Up	< 0.001

**Table 2** DE miRNAs reported by the included differential miRNA expression studies. The bold DE miRNAs were reported by at least two independent comparisons and were qualified for the subsequent meta-analysis (*Continued*)

Comparison ID	MiRNAs	Dysregulated direction	P value
	miR-26a-5p	Down	0.007
	<b>miR-181c-3p</b>	Down	< 0.001
	<b>miR-126-5p</b>	Down	< 0.001
	<b>miR-22-3p</b>	Down	< 0.001
	<b>miR-148b-5p</b>	Down	< 0.001
28934394_Ser	miR-455-3p	Up	0.007
28849039_Ser_Mil	<b>miR-222-3p</b>	Down	< 0.05
28849039_Ser_Mod	<b>miR-222-3p</b>	Down	< 0.05
28626163_Ser	miR-146a-5p	Up	< 0.05
	<b>miR-106b-3p</b>	Up	< 0.05
	miR-195-5p	Up	< 0.05
	miR-20b-5p	Up	< 0.05
	miR-497-5p	Up	< 0.05
	<b>miR-29c-3p</b>	Down	< 0.05
	<b>miR-93-5p</b>	Down	< 0.05
	miR-19b-3p	Down	< 0.05
	miR-125b-3p	Down	< 0.05
28179587_Pla_AD2	<b>miR-486-5p</b>	Up	< 0.001
	<b>miR-483-5p</b>	Up	< 0.0001
	<b>miR-502-3p</b>	Up	< 0.0001
	<b>miR-200a-3p</b>	Up	< 0.01
	miR-151a-5p	Down	< 0.001
	miR-30b-5p	Down	< 0.01
	miR-103a-3p	Down	< 0.01
28179587_Pla_MCI-AD2	<b>miR-486-5p</b>	Up	< 0.001
	<b>miR-483-5p</b>	Up	< 0.001
	<b>miR-502-3p</b>	Up	< 0.01
	<b>miR-200a-3p</b>	Up	< 0.05
28137310_Ser	miR-501-3p	Down	0.002
27545218_Ser	miR-613	Up	< 0.01
27501295_WB	miR-9-5p	Down	0.001
	miR-106a-5p	Down	0.001
	miR-106b-5p	Down	0.008
	<b>miR-107</b>	Down	0.001
27446280_WB	miR-135b-5p	Down	< 0.01
27277332_WB	miR-206	Up	< 0.001
27239545_PBMC	miR-27b-3p	Up	< 0.05
	<b>miR-128-3p</b>	Up	< 0.05
	miR-155-5p	Up	< 0.05
27027823_Ser	miR-125b-5p	Down	< 0.001
	miR-223-3p	Down	< 0.001
	miR-29	Down	< 0.01
	miR-519	Up	< 0.001

**Table 2** DE miRNAs reported by the included differential miRNA expression studies. The bold DE miRNAs were reported by at least two independent comparisons and were qualified for the subsequent meta-analysis (*Continued*)

Comparison ID	MiRNAs	Dysregulated direction	P value
26973465_Pla	miR-10b-5p	Down	0.022
	miR-29a-3p	Down	0.041
	miR-130b-3p	Down	0.002
26497032_PBMC	miR-425-5p	Up	< 0.001
	miR-339-5p	Up	0.003
	miR-639	Down	0.04
26078483_Ser	miR-31-5p	Down	< 0.0001
	<b>miR-93-5p</b>	Down	< 0.0001
	miR-143-3p	Down	< 0.0001
25955795_WB	miR-146a-5p	Down	< 0.0001
	<b>miR-29c-3p</b>	Down	0.0001
	<b>miR-107</b>	Down	< 0.001
25742200_Pla			
25667669_Ser	miR-210-3p	Down	< 0.01
25152461_Ser	miR-135a-5p	Down	< 0.05
	miR-200b-3p	Down	< 0.05
	miR-384	Down	< 0.05
24827165_Pla	miR-384	Down	< 0.05
24827165_Ser	miR-384	Down	< 0.05
24577456_Ser	miR-98-5p	Down	$2.67 \times 10E-4$
	miR-885-5p	Down	$2.8 \times 10E-4$
	miR-483-3p	Down	$1.0 \times 10E-4$
	miR-342-3p	Down	$9.19 \times 10E-16$
	<b>miR-191-5p</b>	Down	$1.54 \times 10E-9$
	<b>let-7d-5p</b>	Down	$1.2 \times 10E-6$
	<b>miR-34c-5p</b>	Up	< 0.01
24550773_Pla			
24550773_PBMC	<b>miR-34c-5p</b>	Up	< 0.01
24157723_Pla	miR-34a-5p	Down	< 0.05
	miR-146a-5p	Down	< 0.05
	miR-125b-5p	Down	< 0.0001
24139697_Ser	miR-181c-5p	Down	< 0.0001
	miR-9-5p	Up	0.0045
	<b>miR-128-3p</b>	Up	< 0.05
24064186_PBMC_Mon			
24064186_PBMC_Lym	<b>miR-128-3p</b>	Up	< 0.05
23922807_Pla_C2	<b>let-7d-5p</b>	Down	0.0001
	let-7 g-5p	Down	0.001
	miR-15b-5p	Down	0.001
	miR-142-3p	Down	0.0001
	<b>miR-191-5p</b>	Down	0.002
	miR-545-3p	Down	0.03
	miR-151a-3p	Up	< 0.05
23895045_WB	let-7d-3p	Up	< 0.05
	miR-5010-3p	Up	< 0.05
	let-7f-5p	Down	< 0.05
	miR-1285-5p	Down	< 0.05

**Table 2** DEmiRNAs reported by the included differential miRNA expression studies. The bold DEmiRNAs were reported by at least two independent comparisons and were qualified for the subsequent meta-analysis (*Continued*)

Comparison ID	MiRNAs	Dysregulated direction	P value	
23435408_PBMc	<b>miR-107</b>	Down	< 0.05	
	miR-103a-3p	Down	< 0.05	
	miR-26b-5p	Down	< 0.05	
	miR-26a-5p	Down	< 0.05	
	miR-532-5p	Down	< 0.05	
	miR-29b-3p	Down	0.002	
	22155483_Ser	miR-137-3p	Down	< 0.05
		miR-181c-5p	Down	< 0.05
		miR-9-5p	Down	< 0.05
		miR-29a-3p	Down	< 0.05
19936094_PBMc	miR-29b-3p	Down	< 0.05	
	miR-34a-5p	Up	< 0.05	
	miR-181b-5p	Up	< 0.05	

ABMDA) were both statistically significant in the synergic enrichment analysis. The synergic enrichment analysis suggested that the two DEmiRNA categories interact functionally and complement each other.

In the synergic enrichment analysis, the AGE-RAGE signaling pathway in diabetic complications was identified as the second most statistically significant. The AGE-RAGE pathway is involved in diabetic microvascular complications. Elevated levels of AGE and RAGE have also been reported in AD patients, and increased RAGE activity has been detected in patients with early AD symptoms [119, 120]. RAGE also interacts with A $\beta$  oligomers to induce BBB leakage [121] and upregulates NF- $\kappa$ B, which induces neuroinflammation [122]. Elevated neuroinflammation increases the expression of secretases for A $\beta$  production [123], reduces A $\beta$  degradation in microglia [124], and induces the aberrant hyperphosphorylation of tau proteins [125]. Elevated levels of proinflammatory cytokines and A $\beta$  increase cell cycle-related kinases, such as PKA, CAMKII, Fyn, and mTORC1, inducing neuronal cell cycle re-entry (CCR) [126, 127]. Aberrant CCR results in neuronal hyperploidy, which alters neuronal circuit function and reduces synaptic activity [128, 129], ultimately inducing neuronal death [130]. Aberrant CCR is also induced by malfunction of PI3K/AKT/mTOR, a cell survival pathway disrupted in both AD and cancer, though in opposite directions [131]. Further, aberrant CCR is a causative factor for the majority of neuronal death in early AD development and might be a potential biological mechanism to link AD and multiple cancerous diseases. Aberrant A $\beta$  accumulation and proinflammatory cytokines from dying neurons further enhance neuroinflammation and oxidative stress, inducing cellular senescence

and dysregulating the Hippo and FoxO signaling pathways. Cellular senescence is a permanent state of cellular rest that is involved in the onset of AD [132], and neuroinflammation and A $\beta$ -mediated toxicity have been reported to upregulate senescence-regulated genes [133–135]. The Hippo signaling pathway is a kinase cascade relevant for cellular homeostasis, and is upregulated by A $\beta$ -mediated neurotoxicity to enhance neurodegeneration with JNK in AD [136, 137]. The FoxO signaling pathway is involved in the relationship between ROS, insulin resistance, and AD pathology [138, 139]. Under persistent oxidative stress, the FoxO signaling pathway increases the transcription of apoptotic proteins [140].

#### Network

In total, 5222 target genes were identified for the DEmiRNAs from the meta-analysis and ABMDA, and 1865 target genes with semantic similarity over 0.95 were identified as common target genes in the two DEmiRNA categories, suggesting an overlap of the two categories in biological functions. The common target genes were used to retrieve the corresponding protein–protein interactions according to STRING and construct a network. The network comprised 1865 common target genes as nodes, and 18750 edges among the common target genes. The DEmiRNAs let-7b-5p and miR-155 identified by ABMDA shared the most common target genes with the DEmiRNAs miR-93-5p and miR-128-3p identified by the meta-analysis. The common target genes *UBC*, *UBB*, and *RPS27A*, which are core members in the ubiquitin-proteasome system (UPS), exhibited the highest connection degree in the network.

The UPS is imperative not just in A $\beta$  clearance [141], but also in neuroinflammation and neuronal CCR. The

**Table 3** Statistically significant DEmiRNAs identified by the meta-analysis

MiRNAs	Comparison ID	Number of upregulated case in AD	Number of downregulated case in AD	Number of control case	Weight	P value	FDR	LogOR	95% CI	$\tau^2$	$I^2$
miR-107	27501295_WB		172	109	25.08%	3.74E-25	1.61E-23	- 10.40	[- 12.36 , - 8.43]	0.00	0.00%
	25742200_Pla		97	81	25.03%						
	23895045_WB		94	21	24.82%						
	31420923_Pla		120	120	25.07%						
miR-106b-3p	29036818_Ser_Mild	31		86	24.98%	1.05E-20	1.53E-19	9.38	[7.41 , 11.35]	0.00	0.00%
	29036818_Ser_Mod	52		86	25.06%						
	29036818_Ser_Sev	38		86	25.01%						
	28626163_Ser	45		40	24.96%						
miR-22-3p	29036818_Ser_Mild		31	86	24.98%	1.07E-20	1.53E-19	- 9.38	[- 11.34 , - 7.41]	0.00	0.00%
	29036818_Ser_Mod		52	86	25.06%						
	29036818_Ser_Sev		38	86	25.01%						
	29746584_Ser		47	38	24.95%						
miR-126-5p	29036818_Ser_Mild		31	86	33.28%	2.06E-16	1.48E-15	- 9.53	[- 11.81 , - 7.26]	0.00	0.00%
	29036818_Ser_Mod		52	86	33.39%						
	29036818_Ser_Sev		38	86	33.33%						
miR-148b-5p	29036818_Ser_Mild		31	86	33.28%	2.06E-16	1.48E-15	- 9.53	[- 11.81 , - 7.26]	0.00	0.00%
	29036818_Ser_Mod		52	86	33.39%						
	29036818_Ser_Sev		38	86	33.33%						
miR-181c-3p	29036818_Ser_Mild		31	86	33.28%	2.06E-16	1.48E-15	- 9.53	[- 11.81 , - 7.26]	0.00	0.00%
	29036818_Ser_Mod		52	86	33.39%						
	29036818_Ser_Sev		38	86	33.33%						
miR-128-3p	27239545_PBMC	30		30	25.02%	4.64E-16	2.85E-15	8.19	[6.21 , 10.17]	0.00	0.00%
	24064186_PBMC_Mon	34		37	25.08%						
	24064186_PBMC_Lym	34		37	25.08%						
	30328325_Pla	20		20	24.82%						
miR-93-5p	26078483_Ser		79	75	50.13%	2.3E-11	1.24E-10	- 9.50	[- 12.28 , - 6.71]	0.00	0.00%
	28626163_Ser		45	40	49.87%						
miR-29c-3p	25955795_WB		30	30	49.88%	1.81E-09	8.65E-09	- 8.56	[- 11.36 , - 5.77]	0.00	0.00%
	28626163_Ser		45	40	50.12%						
miR-132-3p	29746584_Ser		47	38	50.28%	6.67E-09	2.87E-08	- 8.27	[- 11.07 , - 5.48]	0.00	0.00%
	31849573_Pla		16	31	49.72%						
miR-222-3p	28849039_Ser_Mil		30	30	50.00%	8.09E-09	3.16E-08	- 8.22	[- 11.02 , - 5.43]	0.00	0.00%
	28849039_Ser_Mod		30	30	50.00%						
miR-34c-5p	24550773_Pla	25		27	50.00%	2.67E-08	9.58E-08	7.94	[5.14 , 10.74]	0.00	0.00%
	24550773_PBMC	25		27	50.00%						
let-7d-5p	23922807_Pla_C2		20	17	49.74%	8.9E-06	2.73E-05	- 9.39	[- 13.54 , - 5.25]	4.89	54.62%
	24577456_Ser		158	155	50.26%						
miR-191-5p	23922807_Pla_C2		20	17	49.74%	8.9E-06	2.73E-05	- 9.39	[- 13.54 , - 5.25]	4.89	54.62%
	24577456_Ser		158	155	50.26%						
miR-200a-3p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	8.05E-05	6.01	[3.17 , 8.85]	0.00	0.00%
	28179587_Pla_MCI-AD2	8		9	49.74%						
miR-483-5p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	8.05E-05	6.01	[3.17 , 8.85]	0.00	0.00%
	28179587_Pla_MCI-AD2	8		9	49.74%						
miR-486-5p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	8.05E-05	6.01	[3.17 , 8.85]	0.00	0.00%
	28179587_Pla_MCI-AD2	8		9	49.74%						
miR-502-3p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	8.05E-05	6.01	[3.17 , 8.85]	0.00	0.00%
	28179587_Pla_MCI-AD2	8		9	49.74%						

**Table 4** Statistically significant DEmiRNAs identified by the meta-analysis in subgroup analysis

Blood elements	miRNA	Comparison ID	Number of upregulated case in AD	Number of downregulated case in AD	Number of control case	Weight	P value	FDR	LogOR	95% CI	$\tau^2$	$I^2$
Whole blood	miR-107	27501295_WB		172	109	50.26%	1.03E-12	2.06E-12	- 10.12	[- 12.91, - 7.34]	0.00	0.00%
		23895045_WB		94	21	49.74%						
Plasma	miR-103a-3p	28179587_Pla_AD2		13	9	49.64%	0.000266	0.00031	- 8.62	[- 13.26, - 3.99]	7.09	63.36%
		31420923_Pla		120	120	50.36%						
	miR-107	25742200_Pla		97	81	49.96%	5.26E-14	3.68E-13	- 10.67	[- 13.45, - 7.89]	0.00	0.00%
		31420923_Pla		120	120	50.04%						
Serum	miR-200a-3p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	4.72E-05	6.01	[3.17, 8.85]	0.00	0.00%
		28179587_Pla_MCI-AD2	8		9	49.74%						
	miR-483-5p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	4.72E-05	6.01	[3.17, 8.85]	0.00	0.00%
		28179587_Pla_MCI-AD2	8		9	49.74%						
	miR-486-5p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	4.72E-05	6.01	[3.17, 8.85]	0.00	0.00%
		28179587_Pla_MCI-AD2	8		9	49.74%						
	miR-502-3p	28179587_Pla_AD2	13		9	50.26%	3.37E-05	4.72E-05	6.01	[3.17, 8.85]	0.00	0.00%
		28179587_Pla_MCI-AD2	8		9	49.74%						
	miR-106b-3p	29036818_Ser_Mild	31		86	24.98%	1.05E-20	9.08E-20	9.38	[7.41, 11.35]	0.00	0.00%
		29036818_Ser_Mod	52		86	25.06%						
Serum	miR-126-5p	29036818_Ser_Mild	31		86	33.28%	2.06E-16	7.01E-16	- 9.53	[- 11.81, - 7.26]	0.00	0.00%
		29036818_Ser_Mod	52		86	33.39%						
		29036818_Ser_Sev	38		86	33.33%						
	miR-148b-5p	29036818_Ser_Mild	31		86	33.28%	2.06E-16	7.01E-16	- 9.53	[- 11.81, - 7.26]	0.00	0.00%
		29036818_Ser_Mod	52		86	33.39%						
		29036818_Ser_Sev	38		86	33.33%						
	miR-181c-3p	29036818_Ser_Mild	31		86	33.28%	2.06E-16	7.01E-16	- 9.53	[- 11.81, - 7.26]	0.00	0.00%
		29036818_Ser_Mod	52		86	33.39%						
		29036818_Ser_Sev	38		86	33.33%						
	miR-181c-5p	24139697_Ser	105		155	50.39%	0.00354	0.008598	- 8.28	[- 13.84, - 2.71]	11.96	74.29%
		22155483_Ser	7		7	49.61%						
	miR-22-3p	29036818_Ser_Mild	31		86	24.98%	1.07E-20	9.08E-20	- 9.38	[- 11.34, - 7.41]	0.00	0.00%
	29036818_Ser_Mod	52		86	25.06%							

**Table 4** Statistically significant DEmiRNAs identified by the meta-analysis in subgroup analysis (Continued)

Blood elements	miRNA	Comparison ID	Number of upregulated case in AD	Number of downregulated case in AD	Number of control case	Weight	P value	FDR	LogOR	95% CI	$\tau^2$	$I^2$
		29036818_Ser_Sev	38	86	25.01%							
		29746584_Ser	47	38	24.95%							
	miR-93-5p	26078483_Ser	79	45	50.13%	2.30E-11	6.53E-11	- 9.50	[- 12.28, - 6.71]	0.00	0.00%	
		28626163_Ser	30	30	49.87%							
	miR-222-3p	28849039_Ser_Mil	30	30	50.00%	8.09E-09	2.08E-08	- 8.22	[- 11.02, - 5.43]	0.00	0.00%	
		28849039_Ser_Mod	30	30	50.00%							
PBMC	miR-128-3p	27239545_PBMC	30	30	33.28%	3.94E-13	3.94E-13	8.44	[6.16, 10.72]	0.00	0.00%	
		24064186_PBMC_Mon	34	37	33.36%							
		24064186_PBMC_Lym	34	37	33.36%							

**Table 5** AD-related DE miRNAs identified by ABMDA

Disease	miRNAs	Mature miRNAs	Score	Used as biomarkers in diseases
Alzheimer disease	miR-339	miR-339-5p	9.45	Lung cancer
	miR-128-2		8.92	Hepatocellular carcinoma
	miR-203	miR-203a-3p	8.76	
	miR-495	miR-495-3p	8.75	Non-small cell lung cancer
	miR-155	miR-155-5p	8.70	AD
	let-7a-2		8.67	Lung cancer
	miR-103a-2		8.10	
	miR-16-2		8.02	Breast cancer
	let-7b	let-7b-5p	7.93	Non-small cell lung cancer
	miR-625	miR-625-5p	7.88	Malignant pleural mesothelioma

physiological function of the UPS can be adversely influenced by neuroinflammation. Under neuroinflammation, J2 prostaglandins are generated from prostaglandin D2, which is the most abundant prostaglandin in the brain [142]. J2 prostaglandins enhance the expression levels of *COX2* to transition acute neuroinflammation to chronic neuroinflammation and oxidize the UPS units to promote disassembly [143]. The impaired UPS induces ectopic expression of cell cycle-related genes and causes neuronal CCR, as the metabolisms of cyclin and cyclin-dependent kinases are dependent on the UPS. A recent study [144] has reported that the dysregulation of an E3 ubiquitin ligase, Itch, induces neuronal CCR in response to A $\beta$ . A $\beta$ -induced JNK activation phosphorylates Itch to promote the degradation of TAp73, which is important for protein synthesis under oxidative stress, in neurons [145].

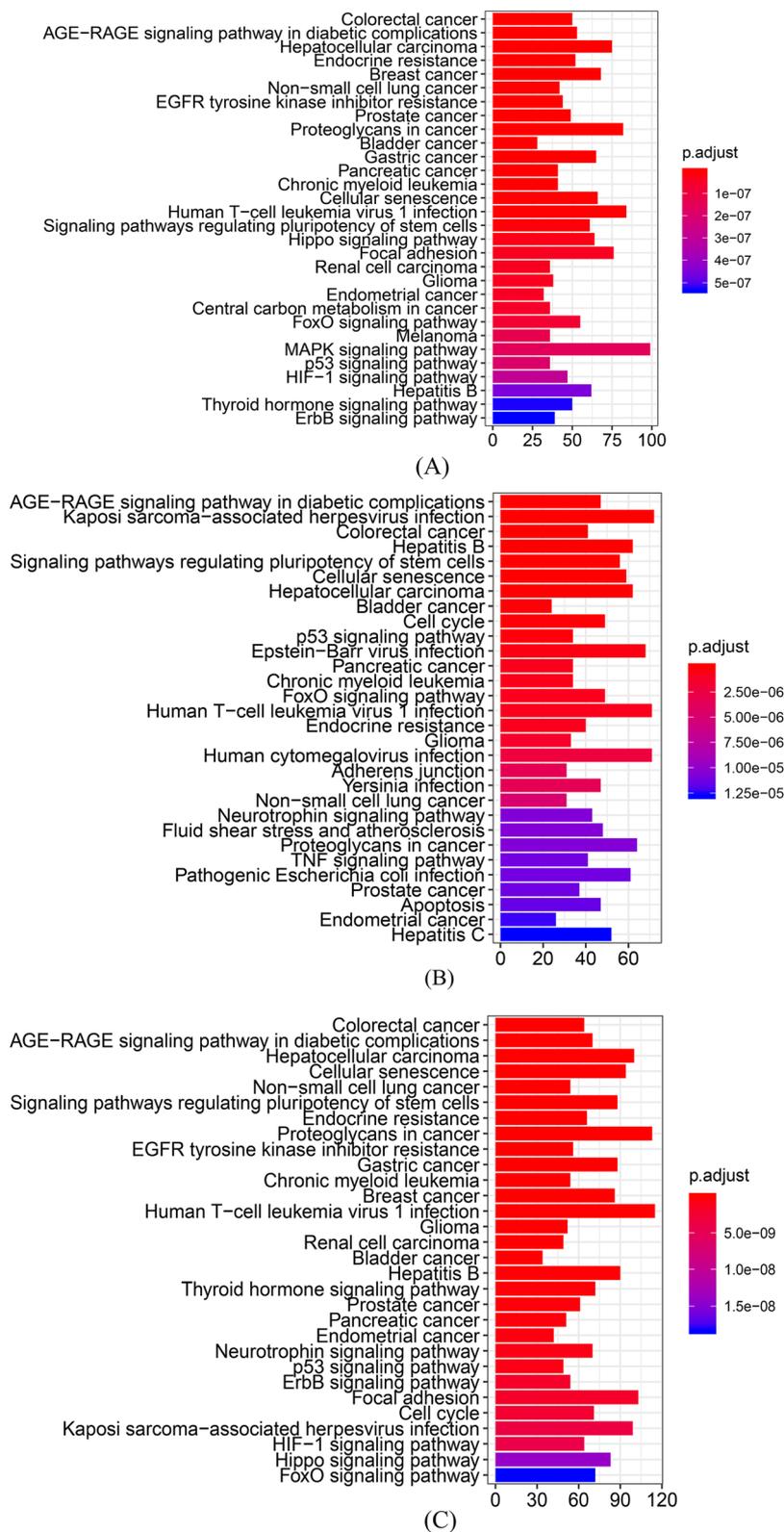
#### Quality assessment of studies

The MIQE guideline was used to assess the expression profiling analysis of the included studies. The results of the quality assessments were shown in Fig. 4. Among the 47 expression profiling studies, miR-39 and U6 RNAs were frequently used as internal normalization controls for qRT-PCR. Around 85% of the included studies provided sufficient information about data processing, including statistical analysis and quantification methods. About 70% of the included studies provided sufficient information about sample annotation, but 16 studies did not provide details of the storage or extraction methods of serum or plasma. Approximately 60% of the included studies did not provide the number of replicates in the experimental design, and 77% did not provide the quantification cycle value in the actual data processing. The parameters of qRT-PCR methods were missing in 14 studies. For the annotation of PCR, most studies provided the full details of reference miRNAs for quantification, but primer information was missing in 19 studies.

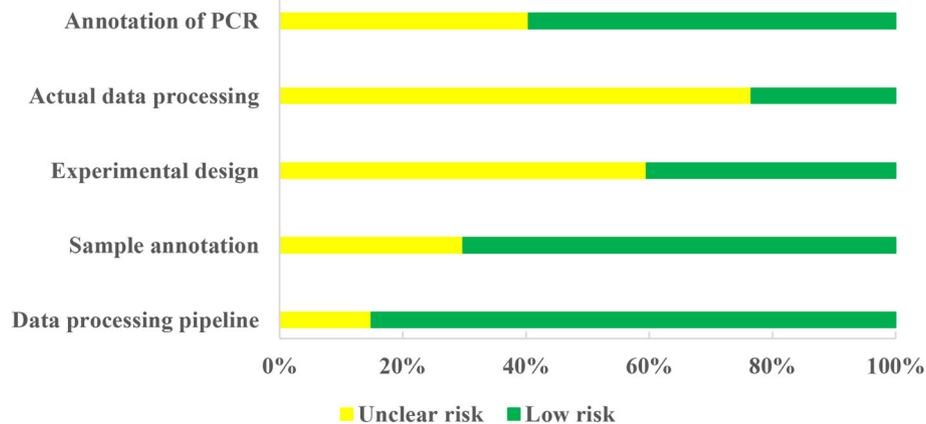
#### Discussion

There is a need for blood circulating biomarkers that can be mass screened accurately and conveniently to identify high risk individuals of AD. The identification of DE miRNAs as biomarkers from differential miRNA expression studies has been successful in cancers [146] and is thought to have potential for AD. DE miRNAs associated with AD pathology, such as A $\beta$  production and neuroinflammation, are potentially important biomarkers because the presence of A $\beta$  and proinflammatory cytokines are considered to be key factors for predicting whether patients with mild cognitive impairment are progressing to AD [147–149]. In this study, we used a meta-analysis approach based on differential miRNA expression studies from blood to identify reliable miRNA–AD associations. The associations were subsequently used for the prediction of potential AD biomarkers using the ABMDA ensemble learning method. We identified 28 DE miRNAs (18 and 10 from meta-analysis and ABMDA, respectively) as potential AD biomarkers in blood.

The DE miRNAs identified with the meta-analysis involved in A $\beta$  metabolism, including *APP* expression, A $\beta$ -production enzyme regulation, and A $\beta$  clearance, tau protein phosphorylation, and also contribute to neuronal function during AD progression, including pathogenic neuroinflammation, apoptosis, mitochondrial oxygen chain activity, and neuronal microtubule maintenance. The meta-analytical results of DE miRNAs mediate A $\beta$  synthesis via several targets, and some of them are also involved in tau protein phosphorylation and neuronal functions. MiR-107 is negatively correlated with *BACE1* and *ADAM10* expression and is downregulated in the early stage of AD [150, 151]. The downregulation of miR-107 also dysregulates the expression of *CDK5R1*, which is involved in neuronal survival [94]. Downregulation of miR-181c dysregulates the expression of *SPTLC1* [152], to increase A $\beta$  deposition, and increases proinflammatory cytokines [153]. MiR-22-3p and miR-29c also regulate A $\beta$  deposition via targeting *MAPK14* and *BACE1*, respectively [154, 155]. Besides A $\beta$  synthesis, A $\beta$



**Fig. 3** Biological pathway enrichment analysis of the target genes of DEMiRNAs identified by **A** meta-analysis; **B** ABMDA; and **C** both the meta-analysis and ABMDA. The x-axis represents the number of genes in each of the KEGG pathway, the y-axis represents the name of each KEGG pathway, and the color represents the FDR-adjusted statistical significance



**Fig. 4** Overall quality assessment of the miRNA differential expression profiling approach for 47 included studies. Green color represents a low risk of bias, in which the authors clearly provided full details of the methods. Yellow color represents an unclear risk of bias, in which the authors provided methods without full details

clearance is also interfered by the meta-analytical results of DEmiRNAs. MiR-128 and miR-93 are reported to be involved in A $\beta$  phagocytosis and UPS for A $\beta$  clearance by targeting cathepsin and *NEDD4L*, respectively [87, 156]. For A $\beta$ -induced toxicity, upregulation of miR-34c enhances A $\beta$ -induced synaptic failure to suppress the memory formation by targeting *SIRT1* and *VAMP2* [157, 158]. MiR-200a-3p coregulates *BACE1* and *PRKACB* to protect neurons against A $\beta$ -induced toxicity and tau protein hyperphosphorylation [159], while upregulation of miR-200a-3p also interferes the function of mitochondrial oxidative chain [69]. The meta-analytical results of DEmiRNAs were also involved in the tau protein phosphorylation. MiR-132 is consistently downregulated in different brain area, and negatively correlated with Braak stage, suggesting that it has an important role in cognitive capacity and correlated with tau protein phosphorylation [160, 161]. The downregulation of miR-132 is reported to increase the expression of *ITPKB* and *SIRT1* for tau pathology and A $\beta$  generation, respectively [162, 163]. Meanwhile, miR-132 is also involved in caspase 3-dependent apoptosis [164]. MiR-483-5p and miR-106b target *MAPT* and *FYN* for tau protein synthesis and phosphorylation, respectively [69, 165]. For neuronal function, miR-222 targets *CDKN1B* to influence cell cycle and apoptosis [68]; miR-191 targets *TMOD2* and *REST* to regulate axonal guidance and dendritic growth [166]; and both miR-486-5p and miR-502-3p are the regulators of dynactin for neuronal function [69]. The potential mechanisms of miR-126-5p, miR-148-5p, and let-7d in AD are not well known. MiR-126-5p targets JNK-interacting protein 2 to mediate inflammatory response in infectious conditions [167]. The expression of miR-148-5p is reported to be positively correlated with MMSE score [66], and let-7d

is reported to be involved in neuronal cell cycle by regulating enzymatic signaling [168]. Compared with other let-7 family members, let-7d does not significantly trigger the release of TNF- $\alpha$  from microglia [169].

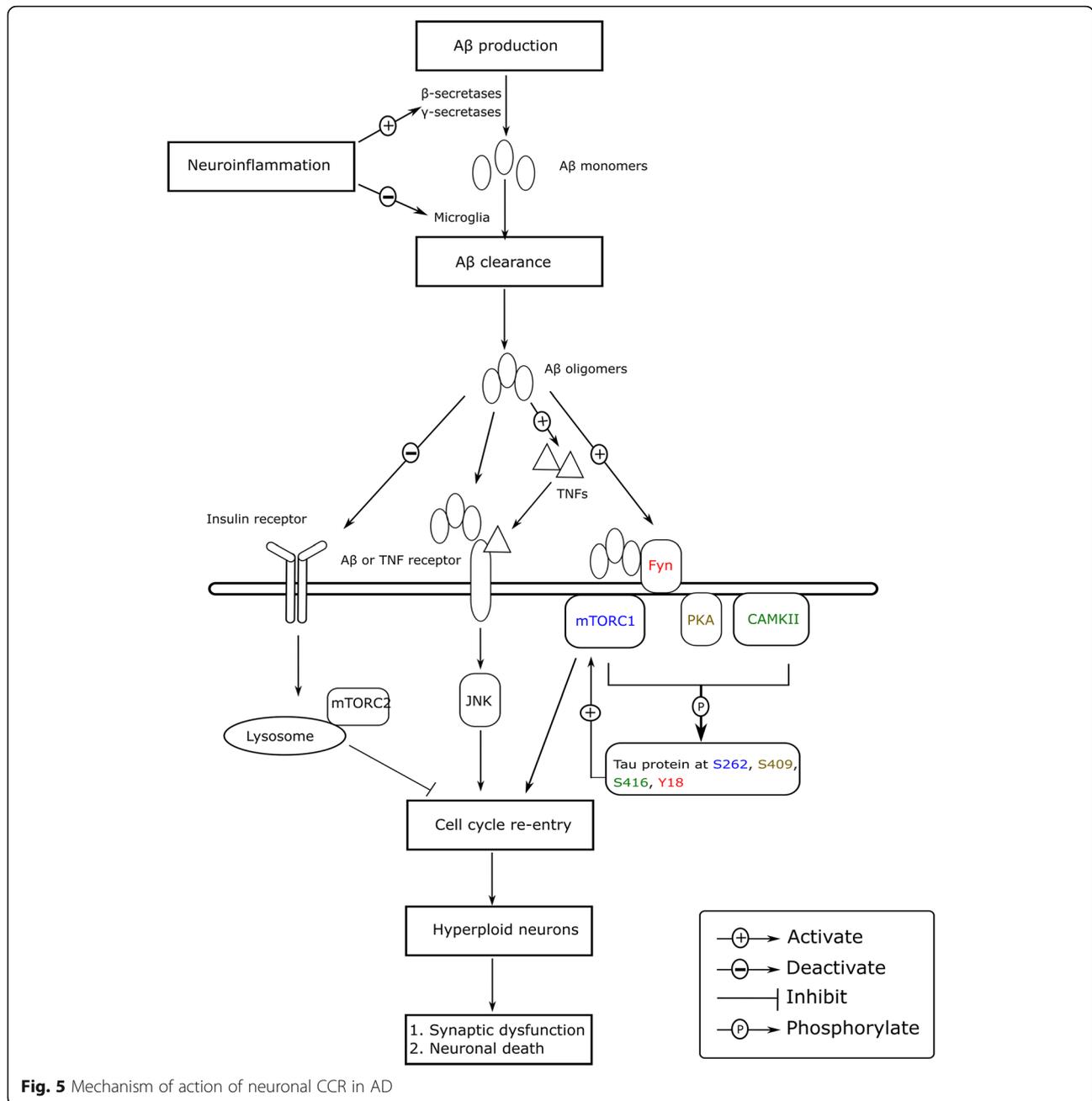
DEmiRNAs from ABMDA also relate to neuroinflammation mainly via modulation of NF- $\kappa$ B. The DEmiRNAs identified in the present study are compatible with the first two differential miRNA expression studies in AD, which reported that the DEmiRNAs are associated with dysregulated inflammation [23, 170]. Independent enrichment analysis in the present study indicated disrupted signaling of AGE-RAGE, cellular senescence, Hippo, FoxO, and cell cycles, and these dysregulated pathways were more statistically significant in the synergic enrichment analysis. The dysregulated pathways were associated with neuroinflammation, in which neuroinflammation increases the production of A $\beta$  by modulation of secretase, suggesting a biological significance of the 28 DEmiRNAs in AD development. The similarity of biological functions of the two DEmiRNA categories fits the ABMDA assumption that the miRNAs associated with the same disease should be functionally related. In the network, 1865 target genes were commonly found from the two DEmiRNA categories, and the highly connected target genes involved *UBC*, *UBB*, and *RPS27A*, which are involved in the neuroinflammatory process and CCR through mediating the UPS.

Comparison of DEmiRNA results from the meta-analysis and ABMDA revealed that the cell cycle pathway was identified as significant only with ABMDA. The majority of neuronal death in AD is due to the dysregulated cell cycle, in which the differentiated neurons in AD-affected brain regions re-enter the cell cycle in the presymptomatic disease [171, 172]. The ectopic expression of developmentally regulated genes in AD links AD

pathophysiology with aberrant CCR and correlates with cognitive decline [173]. CCR markers are expressed in A $\beta$ -cultured neurons within hours, suggesting CCR is an initial event in response to A $\beta$  [174]. These findings indicate that neuronal CCR induces rapid neuronal loss after exposure to A $\beta$ . Neuronal CCR in AD results from A $\beta$ -induced activation of multiple protein kinases at the plasma membrane, and tau protein phosphorylation by these proteins. The absence of  $\beta$ -secretases, or blockage of the A $\beta$  receptor, inhibits CCR [175, 176]. A $\beta$  incorporates into the lipid rafts of neuronal membranes by Fyn-dependent kinase [177] and disturbs the structure of lipid rafts to activate PKA, CAMKII, Fyn, and mTORC1 to phosphorylate tau proteins at S409, S416, Y18, and S262, respectively [126, 127]. The phosphorylated tau proteins subsequently modify mTORC1 activity to induce CCR. A $\beta$  also induces a rapid loss of the insulin receptor in the brain and impairs insulin receptor autophosphorylation to reduce brain insulin signaling [178], decreasing the inhibitory effects of mTORC1 at lysosomes in A $\beta$ -induced CCR [179, 180]. CCR can also be initiated by JNK, which is activated when A $\beta$  binds to receptors, such as RAGE, or by A $\beta$ -induced TNF [144, 181]. Once CCR is initiated, neurons do not complete the cell cycle [171, 174]. The hyperploidy of neurons results in hypertrophy of neuronal cell bodies in AD-affected regions [182, 183]. The number of hyperploidy neurons is higher in preclinical AD individuals than in healthy individuals, and initially increases followed by a gradual decrease in AD development [171]. The hyperploidy gradually decreases the synaptic inputs, which correlates with reduced activity of PSD-95 [129], a scaffold protein for glutamatergic function, suggesting that CCR-induced hyperploidy results in synaptic dysfunction. Further, loss of chromosomal homeostasis induces neuronal death [184], probably via neurotrophins and activation of FOXO1. Neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), elicit prosurvival functions, whereas their precursors, proNGF and proBDNF, elicit apoptotic functions. The levels of neurotrophins and their precursors are downregulated and upregulated in AD, respectively [185, 186], shifting neurotrophic prosurvival functions to apoptotic functions. Additionally, CCR induces dysregulation of cyclin metabolism to activate the transcription factor, FOXO1. The cyclin B-CDK1 complex, which is upregulated in AD, phosphorylates FOXO1 [174] to induce the expression of apoptotic genes [187]. Thus, CCR is a key mechanism to functionally connect A $\beta$  and tau proteins in the early phase of AD development and connects the seemingly unrelated pathologies between AD and cancer, and between AD and insulin signaling impairment [188]. This convergence of pathology points to the importance of CCR in AD development and significance of miRNAs

involved in CCR. Figure 5 summarizes the mechanism of A $\beta$ -mediated CCR in AD, as described above.

Although it remains unclear whether neuroinflammation is the primary cause of AD development or a secondary event to other primary pathologies, neuroinflammation is an imperative and early event for A $\beta$ -mediated toxicity and has been suggested to contribute as much as A $\beta$  in AD pathology [189]. The level of neuroinflammation assessed by microglial activation has been correlated with worse cognitive decline in a PET imaging study of AD participants [190]. Neuroinflammation is progressively increased during AD development, as indicated by elevated levels of proinflammatory cytokines [191]. Proinflammatory cytokines have been identified around amyloid plaques [192], suggesting a role of neuroinflammation in A $\beta$  deposition. Neuroinflammation impairs the microglial A $\beta$  degradation ability [193]. Several genome-wide association studies have reported that immune-related genes are involved in AD pathogenesis [194–197], such as *CD33*, *CRI*, *EPHA1*, and *MS4A6E/MS4A4E*, which regulate the immune system in response to A $\beta$  and activate microglial A $\beta$  degradation. An epigenome-wide association study [198] demonstrated hypermethylation of *ANKK1* in both presymptomatic and AD patients. *ANKK1* encodes Ankyrin 1 to maintain the actin cytoskeleton, and the upregulation of ANK1 in AD microglia has been reported, which supports the significance of the microglial response in AD development [199]. Passamonti et al. [200] reported that cognitive decline is mediated by microglial activation, which is linked to neuroinflammation. The perpetuation of inflammation influences synaptic plasticity and induces neuronal damage, resulting in neurodegeneration [201]. Synaptic loss results primarily from the increased levels of proinflammatory cytokines and activated microglial cells [202]. However, the importance of neuroinflammation in AD has been questioned because of the failure of nonsteroidal anti-inflammatory drugs (NSAIDs) for treating AD. An early AD clinical trial reported the failure of both cyclooxygenase-nonspecific (naproxen) and cyclooxygenase-selective (celecoxib) NSAIDs in cognitive function improvement [203]. Another study [204], which involved long-term follow-up of AD participants who received naproxen or celecoxib, reported that naproxen reduces AD incidence in asymptomatic individuals. The trials suggest that the efficacy of NSAIDs is disease stage dependent and that the choice of NSAID is a determining factor. A COX nonselective NSAID, tarenflurbil, has shown some positive results at a high dosage for individuals with mild symptoms in a post hoc analysis of a phase II clinical trial [205], but no cognitive improvement was observed with the drug in a phase III clinical trial [206]. One possible reason for its failure is the low penetration of the drug



from plasma to CSF. A recent study indicated that intranasal delivery of tarenflurbil can increase the drug concentration in the brain [207], but no clinical trials have yet been carried out with this route of delivery.

The miRNA expression profile in blood is representative of dysregulation in all tissues. The DEMiRNAs could be biased by the presence of multiple comorbidities, although the extent of how specific comorbidities influence DEMiRNAs in AD is not fully known. The miRNAs encapsulated in membrane vesicles can penetrate the BBB [208], suggesting that DEMiRNAs induced by

peripheral complications could also contribute to AD pathology in the brain. Peripheral inflammation interferes with immunological processes in the brain through the entry of activated peripheral immune cells that exacerbate or initiate neuroinflammation. A growing body of evidence supports that peripheral inflammation is a driver of AD. For example, obesity and type 2 diabetes mellitus increase the risk of AD development through mediating neuroinflammation [209], and the gut microbial diversity in obesity patients is associated with increased levels of proinflammatory cytokines in blood

[210]. The AD pathogenetic factor *APOE*  $\epsilon 4$  allele has been reported to impair macrophage efferocytosis, which subsequently induces tissue inflammation and increases the circulating levels of proinflammatory cytokines [211, 212]. Elevated levels of proinflammatory cytokines in the blood of AD patients have been reported in meta-analyses [213, 214], confirming the presence of peripheral inflammation in AD. Peripheral inflammation is positively associated with cognitive decline and could detrimentally impact brain function [215]; specifically, elevated systemic TNF levels have been associated with increased conversion of mild cognitive impairment to AD. Systemic TNFs bind to TNF receptors to alter BBB integrity and allow entry of peripheral immune cells to the brain, inducing neuroinflammation [216, 217]. The entry of peripheral immune cells disrupts synaptic plasticity to induce neuroinflammation, increasing the risk of cognitive decline [215, 218]. Neuroinflammation also releases antigens to activate T cells in CSF. The activated T cells enter the brain and differentiate into effector T cells, which can produce cytokines [219] or induce apoptosis [220]. Abnormalities in T cells have been reported in AD patients compared with controls [221].

### Limitations

Current approaches to diagnose AD (e.g., FDG-PET and CSF-based A $\beta$  and tau protein levels) require sophisticated equipment or lumbar puncture, which could be avoided with the use of blood-based biomarkers. The strength of this study is the integration of meta-analysis and the ABMDA ensemble learning method to identify potential AD biomarkers in blood. However, there are some limitations. First, most of the included miRNA expression studies only conducted qRT-PCR as a validation approach to identify DE miRNAs, and only 17 of the included studies reported both screening and validation approaches. This means that the present identification of DE miRNAs was dependent on those selected by researchers in previous studies, and not an objective manner. This implies that the number of DE miRNAs in AD is likely larger than the number of DE miRNAs identified in the present study. Second, although most DE miRNAs from the meta-analysis and ABMDA identification were associated with neuroinflammation, their function was not distinguishable between acute and chronic neuroinflammation. Acute neuroinflammation is beneficial for microglial clearance of A $\beta$ , whereas chronic neuroinflammation results in neurodegeneration by mediating functional and structural damage to neurons [222, 223]. Third, there were 9 DE miRNAs from the meta-analysis extracted from the independent comparisons of only one study, suggesting that the meta-analytical results might be biased by the unidentified correlation within the recruited population.

Forth, disease stages of AD patients were not fully and consistently provided in most included differential miRNA expression studies, resulting in the performance of subgroup analysis based on disease stage was not currently applicable. Also, the results of original studies might be influenced by the lack of adjustment for the disease stages. Fifth, all the included differential miRNA expression studies were non-longitudinal studies, suggesting that the miRNAs extracted from these studies were not repeated observations over periods of time.

### Conclusion

This study identified 28 DE miRNAs as potential AD biomarkers in blood by meta-analysis and ABMDA ensemble learning in tandem. The DE miRNAs identified by both meta-analysis and ABMDA were related to neuroinflammation, and those identified solely by ABMDA were related to neuronal CCR.

### Abbreviations

AB: Amyloid-beta; ABMDA: Adaptive boosting for miRNA disease association; AD: Alzheimer's disease; AGE: Advanced glycation end product; BBB: Blood-brain barrier; BDNF: Brain-derived neurotrophins; CCR: Cell cycle re-entry; CI: Confidence interval; CSF: Cerebrospinal fluid; DE miRNAs: Differentially expressed microRNAs; FDG-PET: Fluorodeoxyglucose-positron emission tomography; FDR: False discovery rate; KEGG: Kyoto Encyclopedia of Genes and Genomes; logORs: Log odds ratios; miRNAs: MicroRNAs; MIQE: Minimum Information for Publication of Quantitative Real-time PCR Experiments; MMSE: Mini-Mental State Examination; NGF: Nerve growth factor; NIA-AA: National Institute of Aging and Alzheimer's Association; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorder and Stroke and the Alzheimer's Disease and Related Disorders; NSAID: Nonsteroidal anti-inflammatory drugs; PBMC: Peripheral blood mononuclear cell; RAGE: Receptor for AGE; qRT-PCR: Quantitative real-time polymerase chain reaction; TNFs: Tumor necrosis factors; UPS: Ubiquitin-proteasome system;  $\tau^2$ : Tau square

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13195-021-00862-z>.

**Additional file 1.** The meta-analysis results of DE miRNAs.

**Additional file 2.** The ABMDA results.

**Additional file 3.** The target genes of the DE miRNAs identified by meta-analysis and ABMDA.

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### Authors' contributions

SWL and SCY conceived and designed the study. SCY, XNL, HMZ, and YLJ extracted the data. SCY and XNL analyzed the data. SCY, XNL, and SWL wrote the manuscript. HMZ, YLJ, and SWL verified the data and revised the manuscript. SCY and XNL contributed equally to the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

The raw data of this paper are available in the public database, PubMed. The data that support the findings of this paper are available in the published article and its additional files.

#### Declarations

##### Ethics approval and consent to participate

Not applicable. This study is a meta-analysis of published differential miRNA expression study.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare that they have no competing interests.

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