

MicroRNAs as potential biomarkers for the diagnosis of traumatic brain injury: a systematic review and meta-analysis

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Abstract

Background: Traumatic brain injury (TBI) is a sudden trauma on the head, commonly associated with death and long-term disability. MicroRNAs (miRNAs) are potential biomarkers of diverse diseases, including TBI. However, few systematic reviews and meta-analyses have been conducted to determine the clinical value of miRNAs expression in TBI patients.

Methods: We did a comprehensive literature search to identify articles that have reported on the diagnostic and prognostic value of miRNAs expression in TBI patients.

Results: Six studies investigating the diagnostic value of miRNA in TBI were analyzed in this study. The overall sensitivity, specificity and area under the curve (AUC) of miRNAs in diagnosis of TBI were 92% [95% confidence interval (CI): 0.87–0.95]; 92% (95% CI 0.78–0.97) and 96% (95% CI 0.94–0.97), respectively. We found that panels of multiple miRNAs could improve the diagnostic accuracy of TBI. Compared to saliva, detected samples like blood and brain tissue could significantly enhance diagnostic accuracy. Besides, the AUC of miRNAs in severe TBI was 0.97, with 92% sensitivity and 92% specificity.

Conclusions: This systematic review and meta-analysis demonstrated that miRNAs could be potential diagnostic markers in TBI patients. MiRNAs detected in blood and brain tissue display high accuracy for TBI diagnosis.

1. Background

Traumatic brain injury (TBI) is a prevalent form of nervous system ailment that inflicts more than 50 million people each year worldwide ^[1]. TBI, particularly severe TBI (sTBI), cause an enormous socio-economic and health care burden because of its associated mortalities and long-term disability among patients. Due to their clinical value in the diagnosis, prognosis and treatment of TBI patients, biomarkers have attracted considerable attention ^[2].

MicroRNAs (miRNAs) are a class of small non-coding RNAs with a length of 19–22 nucleotides. Many studies have found that miRNAs play a significant role in the maintenance and regulation of physiological function in TBI ^[3]. Recently, the expression of miRNAs in TBI has been extensively examined. Many studies have revealed that some miRNAs have diagnostic and prognostic value in TBI. For example, Pietrao et al. showed that miR-425-5p is significantly downregulated in mild TBI (mTBI) and is an ideal diagnostic and prognostic indicator for TBI ^[4]. Also, Redell et al. detected substantial plasma quantities of miR-16, miR-92a, and miR-765 in sTBI patients, and found that the miRNAs have high diagnostic value in sTBI ^[5]. However, meta-analyses of the clinical values of miRNAs in TBI patients are rarely reported. In this study, we conducted a meta-analysis to identify the potential diagnostic and prognostic values of miRNAs in TBI patients.

2. Methods

2.1. Search strategy

Relevant studies published before September 26, 2019 was comprehensively searched through the English databases PubMed, Cochrane Library, Web of Science, and EMBASE. We used "TBI" and "miRNA" as the main key words and the following strategy to search PubMed: (((("Brain Injuries, Traumatic"[Mesh]) OR (((((((((((((((Brain Injury, Traumatic[Title/Abstract]) OR Traumatic Brain Injuries[Title/Abstract]) OR Trauma, Brain[Title/Abstract]) OR Brain Trauma[Title/Abstract]) OR Brain Traumas[Title/Abstract]) OR Traumas, Brain[Title/Abstract]) OR TBI (Traumatic Brain Injury)[Title/Abstract]) OR Encephalopathy, Traumatic[Title/Abstract]) OR Encephalopathies, Traumatic[Title/Abstract]) OR Traumatic Encephalopathies[Title/Abstract]) OR Injury, Brain, Traumatic[Title/Abstract]) OR Traumatic Encephalopathy[Title/Abstract]) OR TBIs (Traumatic Brain Injuries)[Title/Abstract]) OR TBI (Traumatic Brain Injuries)[Title/Abstract]) OR Traumatic Brain Injury[Title/Abstract]))) AND (("MicroRNAs"[Mesh]) OR (((((((((((((((MicroRNA[Title/Abstract]) OR miRNAs[Title/Abstract]) OR Micro RNA[Title/Abstract]) OR RNA, Micro[Title/Abstract]) OR miRNA[Title/Abstract]) OR Primary MicroRNA[Title/Abstract]) OR MicroRNA, Primary[Title/Abstract]) OR Primary miRNA[Title/Abstract]) OR miRNA, Primary[Title/Abstract]) OR pri-miRNA[Title/Abstract]) OR pri miRNA[Title/Abstract]) OR RNA, Small Temporal[Title/Abstract]) OR Temporal RNA, Small[Title/Abstract]) OR stRNA[Title/Abstract]) OR Small Temporal RNA[Title/Abstract]) OR pre-miRNA[Title/Abstract]) OR pre miRNA[Title/Abstract])).

2.2. Eligibility criteria and Data extraction

The inclusion and exclusion strategy for this article were detailed in our previous article ^[6, 7]. The inclusion criteria are as follows: (1) articles provided diagnostic capacity of miRNA for TBI and enough data such as true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN); (2) researches investigated the prognostic correlation between miRNA and TBI. The exclusion criteria are as follows: (1) Non-TBI or miRNAs researches; (2) Non-English Articles; (3) studies without sufficient data; (4) Animal or cell experiment; (5) meeting records, reviews and letters.

The following data were extracted according to our previous protocol: the first author's name; study population, sample sizes and regions; year of publication; and the false and true positives and negatives ^[6].

2.3. Statistical analysis.

The number of TP, FP, FN and TN were extracted independently by two reviewers (Zhou and Yin). Subsequently, these measures were used to calculate the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and corresponding 95% confidence intervals (CIs). The summary receiver operating characteristic (SROC) curve and the area under the SROC curve (AUC) were also calculated to evaluate the pooled diagnostic value of miRNAs. Besides, we tried to calculate pooled hazard ratios (HRs) to analyze the prognostic performance of miRNAs. However, we did not test for the publication bias because only six studies were ultimately included in this meta-analysis. Heterogeneity in this study was assessed by the chi-square and I^2 tests. If $P < 0.1$ or $I^2 > 50\%$, heterogeneity was considered significant and meta-regression, subgroup and sensitivity analyses were

conducted to discover the sources of heterogeneity. All statistical analyses were performed using Stata 12.0 (StataCorp, College Station, TX, USA). We defined $P < 0.05$ as statistically significant.

3. Results

3.1. Study characteristics

We did a search through PubMed, EMBASE, the Cochrane Library and Web of Science and identified a total of 907 records. Among these records, 337 were duplicate studies and were, therefore, excluded. An additional 329 articles were excluded after reading the titles and another 203 publications after reviewing the abstracts. The remaining 38 full-text articles were assessed for relevance according to our pre-determined inclusion and exclusion criteria. Subsequently, 32 studies, including four meetings and 28 without clinical data were excluded, and a two-by-two contingency table was made to calculate HRs. We only extracted enough data to calculate the diagnostic value of miRNAs. Only six diagnostic-related researches were ultimately included in this study [4, 5, 8-11]. A flow chart of the selection process for this study is presented in **Fig.1**.

The included six articles (ranging from the year 2010 to 2018) reported 37 studies, involving a total of 170 TBI patients and 121 controls composed of healthy controls and other diseases (**Table 1**). Among the 37 studies, 23 reported a single miRNA, while the additional 14 discussed a panel miRNAs (**Table 2**). Out of the 37 articles, ten detected miRNA in plasma, five detected miRNA in serum, six detected miRNA in saliva, one identified miRNA in brain-derived extracellular vesicles, and six evaluated the brain tissue. Of the 37 studies, the populations of 35 studies were Caucasian, whereas two studies were Asian. A total of 24 studies were conducted in severe TBI patients, eleven in mild TBI patients, and the remaining two studies focused on TBI patients.

3.2. Diagnosis

The diagnostic value of miRNAs for TBI is shown in **Fig.2**. Forest plots revealed a significant heterogeneity and we, therefore, used the mixed effect model in this meta-analysis. We also summarized sensitivity, specificity, and diagnostic accuracy of all miRNAs in TBI (**Table 3**). The sensitivity, specificity, PLR, NLR, and DOR of overall miRNA for diagnosis of TBI were 0.92 (95% CI: 0.87–0.95), 0.92(95% CI: 0.78–0.97), 11.1 (95% CI: 3.8–32.7), 0.09 (95% CI: 0.05–0.15) and 128 (95% CI: 29–575). Diagnostic accuracy was evaluated by plotting the summary receiver operating characteristic (SROC) curve (**Fig.3a**). The diagnostic accuracy of overall miRNAs was outstanding since the area under the Curve (AUC) was 0.96 (95% CI: 0.94–0.97). We performed subgroup analyses according to ethnicity, detected sample, and miRNA profiling in order to find the heterogeneity (**Fig. 4b**). The diagnostic value of single miRNAs was as follows: sensitivity, 0.91; specificity, 0.90; PLR, 8.9; NLR, 0.10; DOR, 93; and AUC, 0.95. However, miRNA panels have a higher overall diagnostic accuracy: sensitivity, 0.93; specificity, 0.94; PLR, 15.4; NLR, 0.07; DOR, 216; and AUC, 0.97 (**Fig. 5 a, b, and c**). The sensitivity, specificity, PLR, NLR, DOR and AUC of saliva, brain tissue, and blood were 0.73, 0.17, 0.90, 1.59, 0.6 and 0.40; 0.88, 0.87, 6.8, 0.13, 53 and 0.94; 0.99, 0.99, 162, 0.01, 12000 and 1.00, respectively (**Fig. 3 b, c and d**). This result suggested that miRNAs detected in blood have the highest

overall diagnostic accuracy. In the severe TBI patients, the results were 0.92 for sensitivity, 0.92 for specificity, 12 for PLR, 0.09 for NLR, 129 for DOR, and 0.97 for AUC (**Fig. 4a**).

3.3. Sensitivity analysis and meta-regression analysis

The goodness of fit and bivariate normality analyses revealed that the random effects bivariate model was best suited for sensitivity analysis (**Fig. 6a and 6b**). Influence analysis showed that studies of Schober et al., Di Pietro et al., and Yang et al. were the leading researches in weight (**Fig. 6c**). Outlier detection identified that no research would significantly affect the heterogeneity of our meta-analysis (**Fig. 6d**). Considering the bias of miRNAs, ethnicity, and the detected sample, we conducted a meta-regression analysis and found that the detected sample may influence sensitivity and specificity. Results on subgroup analyses indicated that miRNA detected in blood exhibit the highest sensitivity and specificity in the diagnosis of TBI. We further conducted a subgroup analysis according to the type of TBI. In sTBI, there was no apparent heterogeneity because the I^2 value was only 27.07% for sensitivity and 47.04% for specificity. After excluding non-severe TBI studies, the sensitivity and specificity of I^2 value dramatically decreased 59.87% and 41.66% respectively (**Fig. 5d**). We thought that non-severe TBI studies could be the reason for heterogeneity. However, we did not do a subgroup analysis of mTBI studies due to the limitation of the number of mTBI studies.

4. Discussion

As potential biomarkers, miRNAs have been clinically tested for the diagnosis of diverse human diseases. In recent years, more researches have determined the diagnostic value of circulating miRNAs for TBI. However, the diagnostic performance of miRNAs in these studies remains controversial. For example, miR-135b acts as a biomarker in the diagnosis of sTBI, with specificity and sensitivity levels of 75% and 86%, respectively ^[11]. However, the sensitivity and specificity of mir-135b-5p from salivary samples were 73% and 20%, respectively ^[8]. Therefore, the reliability of miRNAs for the diagnosis of TBI remains to be discussed. We conducted this study to systematically assess the accuracy of circulating miRNAs in the diagnosis of TBI.

This meta-analysis involved six articles, including a total of 170 TBI patients and 121 controls. Our results implied that miRNAs had high sensitivity (0.92) and specificity (0.92) in TBI diagnosis. The pooled PLR was 11.3, suggesting that positive miRNA testing improved the diagnostic probability of TBI by 11.3-fold. Besides, the NLR was 0.09, indicating that negative miRNA testing increased the likelihood of TBI by 91%. A DOR of 1 indicates that miRNAs could not distinguish TBI from control, the DOR of 128 in our study indicated that miRNAs are distinguished biomarkers in the diagnosis of TBI.

The most significant role of biomarkers is to help clinicians in clinical decision making. Through likelihood ratios and post-test probabilities, doctors can know the likelihood that a patient has TBI or not. Positive likelihood ratios and negative likelihood ratios were also summarized to assess diagnostic applicability of miRNAs (**Fig. 7a**). $NLR < 0.1$ and $PLR > 10$ imply a high diagnostic accuracy ^[6]. The articles of Schober et al., Di Pietro et al., and Yang et al. revealed that some miRNAs had outstanding diagnostic accuracy,

including single miRNA (miRNA-93, miRNA-425-5p, and miRNA-502) and a panel of miRNAs (miR-138 and miR-744 ; miR-195 and miR-324-5p). When the pretest probability was set at 20%, a positive likelihood ratio improves the post-test probability to 74%. However, when negative likelihood ratio was set at 0.09, the post-test probability for a negative test result is 2% (Fig. 7b).

Notably, ideal biomarkers should be readily measured for accessible samples such as blood and saliva. In our study, miRNAs in blood showed higher diagnostic accuracy, with a sensitivity of 0.95, a specificity of 0.96 and AUC of 0.98. We thought the reason may be that miRNAs can be released from injured brain tissues after TBI in the form of exosomes, which can maintain stability and replicability of miRNA results from human blood [12]. Compared to single miRNA, we demonstrated that multiple-miRNAs have higher diagnostic accuracy for TBI, which was consistent with the findings in other disease conditions [6, 13–15]. Only four of our included articles reported on the diagnostic value of miRNAs in mTBI patients. Since mTBIs, such as concussion, can be easily ignored, we initially evaluated the clinical value of miRNAs expression in mTBI patients. Our results were, however, no conclusive because of the limited number of studies. We suggest that more future researchers could explore the clinical value of miRNAs in mTBI.

This meta-analysis was faced with several limitations. Although heterogeneity was observed in our study, the results of subgroup analysis, such as detected sample and type of TBI, could only find a part of the source of heterogeneity. Second, our meta-analysis had a small sample size. Third, the overall diagnostic accuracy may be expanded because studies with positive results have high possibility of publication. Finally, only studies written in English were included, which may bring some bias to our findings.

5. Conclusion

In conclusion, our meta-analysis is the first to evaluate the clinical value of miRNAs expression in TBI patients. miRNAs have potential diagnostic value for TBI. Besides, subgroup analysis demonstrated that miRNAs in blood could improve diagnostic accuracy. Compared to a single miRNA, panels of multiple miRNAs could more accurately identify TBI patients. However, large-sizes researches should be performed to validate our results and confirm the clinical value of miRNAs in the diagnosis and prognosis of TBI.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare that they have no competing interests" in this section.

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Authors' contributions: YDW and XSZ searched literature databases (PubMed, EMBASE, Cochrane Library and Web of Science) to identify relevant studies. QZ and JY extracted the data from the included studies and QZ was a major contributor in writing the manuscript. ZYH did Statistical analysis. XFY and ZBY was the contributor in designing this study. All authors read and approved the final manuscript.

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Abbreviations

miRNAs: MicroRNAs; **AUC:** area under the curve; **CI:** confidence interval; **CSF:** cerebrospinal fluid; **SROC:** summary receiver operator characteristic; **TP:** true positive; **FP:** false positive; **FN:** false negative; **TN:** true negative
PLR: positive likelihood ratio; **NLR:** negative likelihood ratio; **DOR:** diagnostic odds ratio
TBI: traumatic brain injury **mTBI:** mild traumatic brain injury **sTBI:** severe traumatic brain injury

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Tables

Table 1.Characteristics of studies included in meta-analysis

First author	Publish year	ethnicity	Patients	controls	Patients/controls	miRNAS	Detected sample
Schober	2014	Caucasian	severe TBI	Non-TBI	8/7	miR-138,miR-504,miR-16,miR-376a,miR-195,miR-370,miR-320b,miR-135b miR-744,miR-324-5p,miR-455-3p,let-7a,miR-193b	cerebellar tissue
Di Pietro	2017	Caucasian	mild TBI	healthy volunteers	30/30	miR-425-5p,miR-502,miR-335	serum
Di Pietro	2018	Caucasian	concussion	healthy volunteers	22/10	let-7i-5p,miR-142-3p,miR-107,miR-27b-3p,miR-135b-5p	Salivary
Redell	2010	Caucasian	severe TBI/ mild TBI	healthy volunteers/orthopedic injury patients	18/16	miR-16,miR-92a,miR-765	plasma
Ko	2018	Caucasian	TBI	Healthy controls	16/20	miR-203b-5p, miR-203a-3p, miR-206, miR-185-5p	EV
Yang	2016	Asian	TBI	Healthy controls	76/38	miR-93	serum

TBI: traumatic brain injury; EV: brain-derived extracellular vesicles

Table 2.False and true positives and negatives of total 37 studies from 6 included articles

First author	year	miRNA(s)	TP	FP	FN	TN
Single miRNA						
Schober	2014	miR-138	6	0	2	7
Schober	2014	miR-504	6	1	1	5
Schober	2014	miR-16	8	1	0	3
Schober	2014	miR-376a	8	3	0	4
Schober	2014	miR-195	6	0	2	7
Schober	2014	miR-370	6	0	1	7
Schober	2014	miR-320b	7	3	0	3
Schober	2014	miR-135b	6	1	2	6
Schober	2014	miR-744	7	2	1	5
Schober	2014	miR-324-5p	7	1	1	6
Schober	2014	miR-455-3p	5	0	3	7
Schober	2014	let-7a	7	2	1	5
Schober	2014	miR-193b	7	1	1	6
Di Pietro	2017	miR-425-5p	30	0	0	30
Di Pietro	2017	miR-502	30	0	0	30
Di Pietro	2017	miR-335	30	0	0	30
Di Pietro	2018	let-7i-5p	19	9	3	1
Di Pietro	2018	miR-142-3p	16	8	6	2
Di Pietro	2018	miR-107	15	9	7	1
Di Pietro	2018	miR-27b-3p	15	7	7	3
Di Pietro	2018	miR-135b-5p	16	8	6	2
Yang	2016	miR-93	76	0	0	38
Yang	2016	miR-93	25	0	0	38
miRNA panel						
Schober	2014	miR-138,miR-744	8	0	0	7
Schober	2014	miR-195,miR-324-5p	8	0	0	7
Di Pietro	2018	let-7i-5p,miR-142-3p,miR-107,miR-27b-3p,miR-135b-5p	16	9	6	1
Redell	2010	miR-16,miR-92a	5	1	2	6
Redell	2010	miR-16,miR-765	6	0	1	8
Redell	2010	miR-92a,miR-765	7	0	0	8
Redell	2010	miR-92a,miR-765,miR-16,	7	0	0	8
Redell	2010	miR-16,miR-92a	7	1	0	7
Redell	2010	miR-16,miR-765	7	0	0	8
Redell	2010	miR-92a,miR-765	6	2	1	6
Redell	2010	miR-92a,miR-765,miR-16	7	0	0	8
Redell	2010	miR-16,miR-92a	9	2	2	6
Redell	2010	miR-16,miR-92a	8	6	3	2
Ko	2018	miR-203b-5p,miR-203a-3p,miR-206,miR-185-5p	15	3	1	17

TP: true positive; FP: false positive; FN: false negative; TN: true negative

Table 3.Summary of diagnostic value of miRNAs for diagnosis of TBI

miRNAs	sensitivity	specificity	PLR	NLR	DOR	AUC
overall	0.92(0.87-0.95)	0.92(0.78-0.97)	11.1(3.8-32.7)	0.09(0.05-0.15)	128(29-575)	0.96(0.94-0.97)
Single miRNA	0.91(0.85-0.95)	0.90(0.67-0.97)	8.9(2.4-33.9)	0.10(0.05-0.19)	93(14-610)	0.95(0.93-0.97)
miRNA panels	0.93(0.83-0.98)	0.94(0.71-0.99)	15.4(2.6-91.1)	0.07(0.03-0.20)	216(17-2666)	0.97(0.95-0.98)
blood	0.99(0.91-1.00)	0.99(0.87-1.00)	162(6.5-4029)	0.01(0.00-0.09)	1.2e+04(141-1.1e+06)	1.00(0.99-1.00)
Brain tissue	0.88(0.81-0.94)	0.87(0.77-0.93)	6.8(3.7-12.4)	0.13(0.07-0.22)	53(22-126)	0.94(0.92-0.96)
Salivary	0.73(0.65-0.80)	0.17(0.09-0.28)	0.9(0.8-1.0)	1.59(0.85-3.00)	0.6(0.3-1.2)	0.40(0.36-0.45)
sTBI	0.92(0.85-0.95)	0.92(0.84-0.97)	12(5.6-25.6)	0.09(0.05-0.17)	129(45-374)	0.97(0.95-0.98)

PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve; sTBI: severe traumatic brain injury

Figures



Figure 1

Flow diagram of the study selection for the meta-analysis



Figure 2

Forest plots for studies on overall miRNAs used in the diagnosis of traumatic brain injury (TBI) among 37 studies included in the meta-analysis

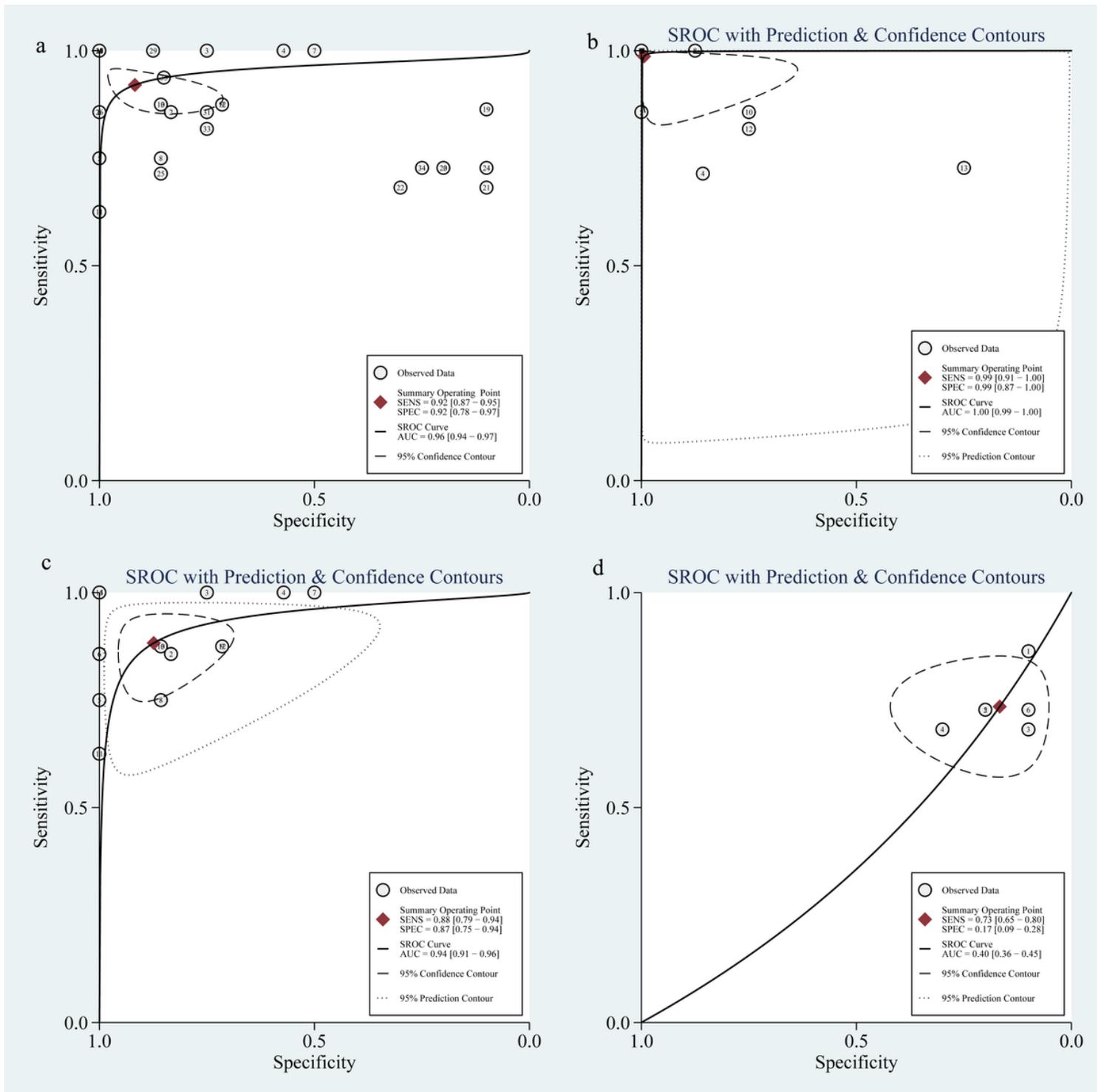


Figure 3

The summary receiver operating characteristic (SROC) curves based on miRNAs (A) all miRNAs, (B) miRNAs detected in the blood sample, (C) miRNAs detected in brain tissue, and (D) miRNAs identified in a salivary sample.

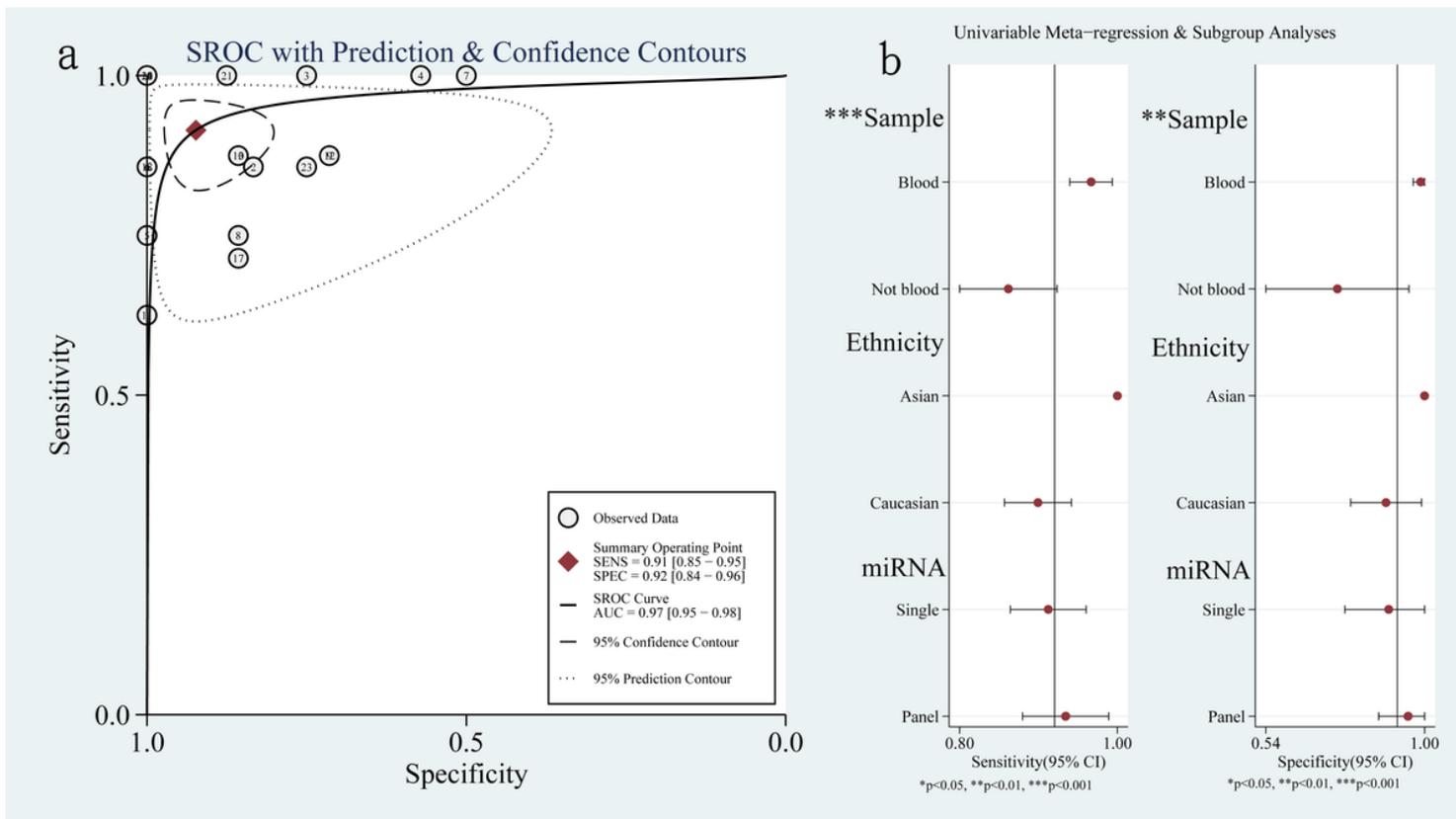


Figure 4

Diagram of (a) The summary receiver operating characteristic (SROC) curves of miRNAs detected in severe traumatic brain injury (TBI) patients, (b) Univariable meta-regression and subgroup analysis for sensitivity and specificity of miRNAs for diagnosis of traumatic brain injury (TBI).

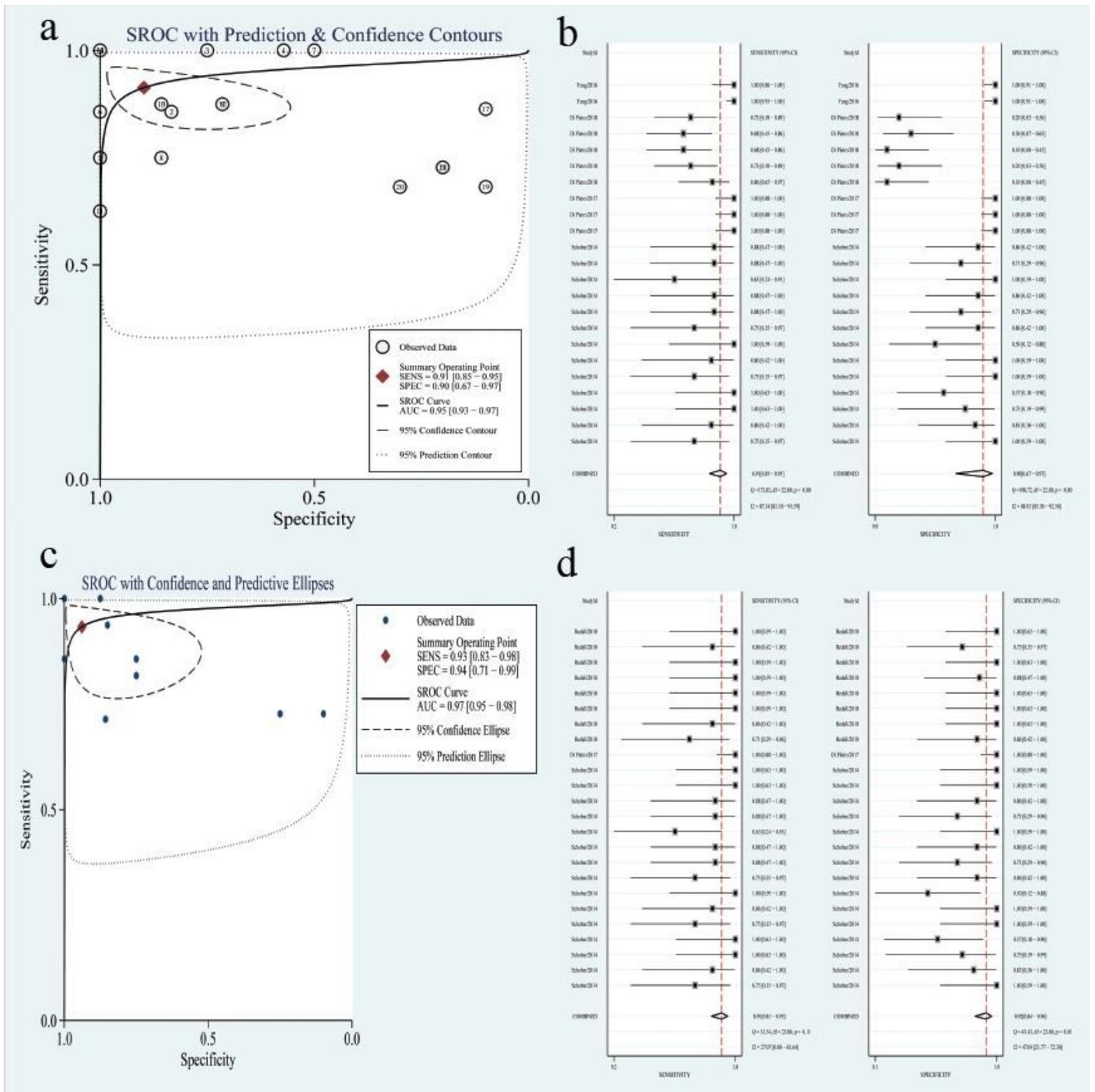


Figure 5

Diagram of (a) The summary receiver operating characteristic (SROC) curves of single miRNAs, (b) Forest plots of individual miRNAs, (c) The summary receiver operating characteristic (SROC) curves of miRNA panels, (d) Forest plots of miRNAs detected in severe traumatic brain injury (TBI) patients.



Figure 6

Diagram of (a) Goodness-of-fit, (b) Bivariate normality, (c) Influence analysis , and (d) Outlier detection
Goodness-of-fit and Bivariate normality showed that random effects bivariate model is suitable. Influence analysis identified that studies of Schober et al., Pietro et al. and Yang et al. were the most dominant studies in weight. Outlier detection implied that no research is the reason for heterogeneity.



Figure 7

Assessment of the clinical applicability of miRNAs for diagnosis (a) Summary of positive likelihood ratio and negative likelihood ratio for diagnosis of traumatic brain injury (TBI), and (b) Fagan nomogram of the miRNAs test for diagnosis of traumatic brain injury (TBI).

Supplementary Files

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