Incidence of breast cancer and methylation of PCDH gene: a single ratio meta analysis of single rate

Type

Research paper

Keywords

Breast Cancer, Gene Methylation, PCDH

Abstract

Introduction
Breast cancer presents one of the highest rates of prevalence. With the development of genetics and biotechnology, we have learned that the occurrence and development of many cancers are closely related to abnormal gene expression. At present, some pieces of literature have reported that there may be a correlation between the expression of PCDH and the occurrence of breast cancer.Therefore, we selected some loci from PCDH gene to explore the correlation between the methylation of PCDH gene and breast cancer.

Material and methods
This research is a systematic review and critical appraisal, make a meta-analysis of prospective and retrospective cohort study. Research was conducted through computer Science, Wanfang and Chinese knowledge network databases PubMed, Embase and Network. In a literature search, seven cohort studies were identified. This I2 statistic is used to quantify heterogeneity. A fixed effect model was used to synthesize the results. Regression tests of linear funnel plot asymmetry were used to estimate potential publication bias.

Results
The methylation rate of PCDH gene in breast cancer with lymph node metastasis was 75%, and that in breast cancer without lymph node metastasis was 70%. The methylation rate of PCDH gene was 75% in breast cancer group with high expression of the Ki-67 gene and 71% in breast cancer group with low expression of Ki-67 gene.

Conclusions
According to previous studies, the positive rate of methylation of PCDH gene in breast cancer tissues is higher than that in adjacent tissues, and there is no obvious statistical difference in the correlation between lymphatic metastasis and Ki-67.

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Incidence of breast cancer and methylation of PCDH gene: a single ratio metaanalysis of single rate

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Abstract

Introduction

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This research is a systematic review and critical appraisal, make a meta-analysis of prospective and retrospective cohort study. Research was conducted through computer Science, Wanfang and Chinese knowledge network databases PubMed, Embase and Network. In a literature search, seven cohort studies were identified. This I^2 statistic is used to quantify heterogeneity. A fixed effect model was used to synthesize the results. Regression tests of linear funnel plot asymmetry were used to estimate potential publication bias.

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keywords

Gene Methylation, PCDH, Breast Cancer

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Introduction

Breast cancer has surpassed lung cancer and become the cancer with the highest incidence of cancer in the world. In 2020, there were 2261419 new cases and 684996 deaths of female breast cancer globally, accounting for 24.5% and 15.5% of the total new cases and deaths of female cancer respectively [1]. At present, more and more studies have shown that the abnormal expression of some genes is related to the occurrence and development of tumors, for example, some genes are abnormally expressed or not expressed after methylation, which accelerates the occurrence and development of tumors or the metastasis of tumors. In addition to some proto-oncogenes and tumor suppressor genes that we are familiar with before, there are many

studies currently exploring the correlation between gene methylation and the occurrence, development and prognosis of diseases. For example, CDX2 methylation predicts the prognosis of lung cancer patients[2], and MGMT promoter methylation is a potential prognosis marker of acute methylation[3]. It has been reported that in the Protocadherin（PCDH） gene family, methylation of PCDH gene will affect many diseases, for example, PCDH10 will affect the progression and pathological types of gastric cancer[4], and PCDH19 will affect the occurrence and outcome of epilepsy[5]. It has been reported that methylation of estrogen receptor promoter gene can lead to benign and malignant changes in breast cells[6].At present, it has been reported that gene methylation is related to the occurrence and development of breast cancer, such as ESR-3 and ERS-1[7].At present, more and more studies have shown that the abnormal expression of some genes is related to the occurrence and development of tumors, for example, some genes are abnormally expressed or not expressed after methylation, which accelerates the occurrence and development of tumors or the metastasis of tumors. In this study, PCDH gene is taken as the breakthrough point[8], PCDH has been reported in the literature, and it is highly expressed in cell signal transduction and signal pathway quotient of tumor cells[9]. DNA methylation is a form of chemical modification of DNA, which changes the genetic expression without changing the DNA sequence. Under the action of DNA methyltransferase, a methyl group is covalently bonded to cytosine 5' carbon position of CpG dinucleotide in genome. Studies have shown that DNA methylation can cause changes in chromatin structure, DNA conformation, DNA stability and interaction between DNA and protein, thus controlling gene expression[10]. This paper started from exploring the correlation between methylation of PCDH gene and breast cancer, and also explored whether there was some correlation between methylation of PCDH gene and lymph node metastasis of breast cancer and expression of Ki-67 gene, which provides more diagnostic evidence in biology for clinical practice[11].

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Materials and methods

The literature retrieval strategy

The methylation of PCDH gene in Pubmed, Embase, Web of science, Cochrane Library and related literatures of breast cancer diagnosis were searched by computer in database. At the same time, Google Scholar and other search engines were used for supplementary search, and the references included in the literature were traced back, and gray documents and conference papers were searched manually. The retrieval time was from the establishment of each database to July 23, 2021. The combination of retrieval strategy and free words was connected with Boolean logic operators and retrieved. English key words: protocadherin, pcdh, cadherins, breast cancer, breast cancer of breast tumor, breast cancer of breast neoplases, Methylation

Inclusion and exclusion criteria

Articles meeting the following criteria were included in meta-analysis: (1) prospective and retrospective cohort study of breast cancer; (2) all patients were pathologically confirmed as malignant breast cancer; (3) at least 20 patients with breast cancer were included in the study; (4) cytological or serological detection of methylation of PCDH gene was selected for these patients; (5) the means and methods of detecting methylation of these patients were described in detail. Exclusion criteria of meta-analysis (1) Exclude all comments, case reports and articles without full text (2) Exclude articles that have not been translated into English or Chinese (3) Exclude studies on benign breast tumors, pathological diagnosis or analysis details after surgery (4) Exclude studies that have not been methylated by PCDH gene (5) Exclude non-clinical experimental

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articles.

The EndNote X9 software is used to eliminate duplicate documents, and the documents are screened based on the titles and abstracts of the documents, and then the potential included documents are read in full.

Data Extraction and Quality Assessment

The following data were extracted from each study: (1) the age range of patients, (2) the types of breast tumors, (3) the number of breast cancers confirmed by pathological biopsy, (4) the number and proportion of methylation of genes detected by methylation histology after diagnosis, (5) the number and proportion of methylation of PCDH genes in serum in some studies, and (6) the staging and grading of tumors in some studies Article Screening and Data Extraction.

The following data were extracted from each study: (1) the age range of patients, (2) the types of breast tumors, (3) the number of breast cancers confirmed by pathological biopsy, (4) the number and proportion of methylation of genes detected by methylation histology after diagnosis, (5) the number and proportion of methylation of PCDH genes in serum in some studies, (6) the staging and grading of tumors in these studiesn order to evaluate the quality of the collected literature, all the included articles were scored by Nos. according to the scoring standard, all the literatures were scored at 7-8. The quality of the included literature was good and met the writing needs of this study（Supplementary Table II）.

Statistical analysis

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Adopt stata15 The heterogeneity of the included literatures was evaluated, and I2<25% meant that there was no heterogeneity, so random effect model was used for combined analysis, whereas fixed effect model was used. Subgroup analysis was performed based on tumor size, tumor lymph node metastasis and tumor Ki-67 expression. Because of the lack of control group in one-arm experiment, according to the formula in the study of Chen Yuehong et al. In the formula,

$$P=X/n$$
$$SE(P)=\sqrt{P(1-P)/n}$$

x is the occurrence number of an event, and n is the total number of observed objects. The used condition n is large enough, and the incidence p is not close to 0 and 1.

Result

According to the search strategy, 424 articles from PubMed, Cochrane Library and Science Network Database were retrieved. No new articles were found after screening references. Among these articles, 29 were excluded because of duplication and 388 were excluded because they did not meet the inclusion criteria: 386 articles were not related to OSNA breast cancer diagnosis; One paper is non-English literature; 1 non-clinical research literature (Figure 1 is about here).A total of 7 experimental studies [12-18] included specimens of breast cancer patients（tableIis about here）, all of whom adopted histological diagnosis methods, and some of them added serological pattern comparison (but this article did not discuss serological gene methylation because of lack of sufficient research quantity). According to the formula and evidence-based medicine of Chen Yuehong et al. According to the formula, we can get P < 0.05 and I2 > 50%. There is no obvious heterogeneity in the meta, so meta-analysis is effective.

PCDH gene methylation and clinical rESponse of breast cancer patients (95% CI 0.47-0.76),

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standard error es is 0.62. All of the seven studies included were force-controlled studies, which showed that the methylation rate of genes in breast cancer tissues was higher than that in normal people or adjacent tissues. The comprehensive Stata showed that ES is 0.62(fig2 and fig3 is about here), which also indicated that the methylation rate of PCDH genes was very high in breast cancer tissues.

Subgroup analysis

1 lymph node metastasis

Methylation forest plot of PCDH gene without lymph node metastasis in breast cancer(fig4 is about here)

Methylation forest plot of PCDH gene without lymph node metastasis in breast cancer(fig5 is about here)

The methylation rate of PCDH gene in breast cancer with lymph node metastasis was 75%, and that in breast cancer without lymph node metastasis was 70%. There is no correlation between methylation of PCDH gene and lymphatic metastasis of breast cancer.

2 The expression of Ki-67[19]

Forest plot of methylation of low-expression PCDH gene in ki-67(fig6 is about here)

Forest plot of methylation of high-expression PCDH gene in ki-67(fig7 is about here)

The methylation rate of PCDH gene was 75% in breast cancer group with high expression of Ki-67 gene and 71% in breast cancer group with low expression of Ki-67 gene.There is no correlation between methylation of PCDH gene and Ki-67 gene expression in breast cancer.

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Dicussion

All the studies are within the confidence interval, and the distribution of all the research points is roughly symmetrical, suggesting that there may be publication bias, however, the results do not suggest obvious publication bias. However, the total data of nine of the seven studies used in this paper are not the same locus of the same PCDH gene, so there is still some heterogeneity. In the direction of the experimental design, the overall thinking of experimental design of each research is the same, but considering the specific operation of experimental design, the specific reagents and instruments, and the problems of manual operation, of course, there are different pathological types of specific experimental tissues, which will lead to certain heterogeneity of the article.

Procadherin (PCDH) is a transmembrane protein and a member of the cadherin superfamily, which plays an important role in cell adhesion and regulation of downstream signaling pathway . At present, studies have shown that PCDH is related to gastric cancer, breast cancer, liver cancer and kidney cancer. Generally, the less PCDH is expressed in water, the worse the differentiation degree of these cancers is, and the greater the recurrence time and probability. δ-PCDHs is often abnormally expressed in human malignant tumors, which may affect the occurrence, progression and prognosis of various malignant tumors by changing cell-cell adhesion and regulating cell signaling pathway. It has been proved that δ-PCDHs plays an inhibitory and carcinogenic role in malignant tumors, and the specific role depends not only on the type of δ-PCDHs, but also on the type of tumor cells. At present, CA153 is the most specific biological test for breast cancer. Therefore, detecting the methylation of PCDH gene as a new biological behavior and better

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applying it in clinical practice should be studied in the future. At the same time, we should pay attention to the correlation and molecular biological mechanism between the expression and deletion of PCDH gene and other tumors.

According to the statistical results, the methylation positive rate of PCDH gene in patients without lymph node metastasis is 70%, and that with lymph node metastasis is 75%. No obvious statistical difference is found, and no obvious gap can be seen, so it is not enough to prove that the methylation of PCDH gene has obvious correlation with lymph node metastasis of breast cancer.

In the aspect of ki-67 gene expression, the positive rate of gene methylation in ki-67 low expression was 71%, and the proportion of ki-67 high expression was 75%. There was no correlation between the methylation of PCDH gene and ki-67 gene expression in tumor. To sum up, it is possible that the relationship between methylation of PCDH gene and lymph node metastasis of breast cancer and Ki-67 gene expression in breast cancer has not been found due to insufficient sample size and tumor classification.

In this analysis, due to the limitation of sample size and technology, all the breast cancer-related influencing factors were not included in the experimental study, for example, the correlation between P53 gene expression[20] and PCDH gene methylation, and whether the tumor marker CA153 of breast cancer is related to PCDH gene methylation, which can be used as a supplementary detection method for CA153[21] and provide a better detection method for clinic. At the same time, it can also study breast。 cancer in the future. To study the different pathological types and methylation of PCDH gene[15, 22], explore the special pathological types of breast cancer, and better help clinicians make preoperative operation plans and better evaluate the prognosis of patients. Can PCDH gene methylation in the clinical work for clinical whether further examination or treatment of a reference standard, at the same time PCDH gene of different location of the specific function should also be a new direction of our further research and

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thinking.

Conclusion

PCDH gene methylation has a certain correlation with the occurrence of breast cancer, but it should be noted that normal breast tissue and adjacent tissues also have a certain proportion of methylation in case-control studies, and have a certain false positive rate.

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n	year	author	country	PCHD	PCHD positive rate	NOS score
1	2020	DE	Chinese	17	81.40	8
2	2019	shan M	Chinese	GB7	80.41	8
3	2018	wentaoliu	Chinese	10	57.65	8
4	2016	yin X	Chinese	17	93.20	8
5	2016	mingshen	Chinese	GB7	55.60	8
6	2008	JS Yu-1	Chinese	8	28.60	8
7	2008	JS Yu-2	Chinese	8	33.30	8
8	2005	gongben-1	Japan	10	33.33	7
9	2005	gongben-2	Japan	GB6	61.90	7

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author	the case determination appropriate	Representation of cases	Selection of control	Determination of control	Comparability of design control 2	Determination of exposure factors	Same method	No response rate	total
DE	1	1	0	1	2	1	1	1	8
shan M	1	1	1	1	2	0	1	1	8
wentaoliu	1	1	0	1	2	1	1	1	8
yin X	1	1	1	1	2	0	1	1	8
mingshen	1	1	0	1	2	1	1	1	8
JS Yu-1	1	1	1	1	2	0	1	1	8
gongben-1	1	1	1	1	0	1	1	1	7

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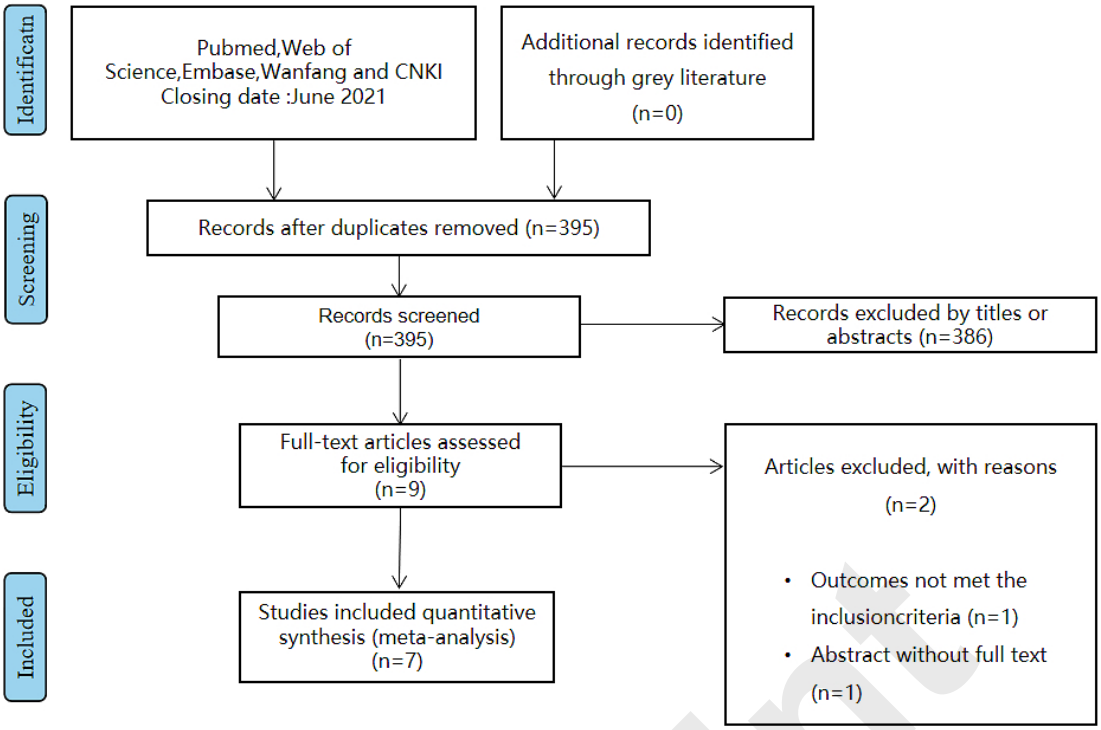
Identificatn
Pubmed,Web of Science,Embase,Wanfang and CNKI Closing date :June 2021
Additional records identified through grey literature (n=0)
Screening
Records after duplicates removed (n=395)
Records screened (n=395)
Records excluded by titles or abstracts (n=386)
Eligibility
Full-text articles assessed for eligibility (n=9)
Articles excluded, with reasons (n=2)
Outcomes not met the inclusioncriteria (n=1)
Abstract without full text (n=1)
Included
Studies included quantitative synthesis (meta-analysis) (n=7)

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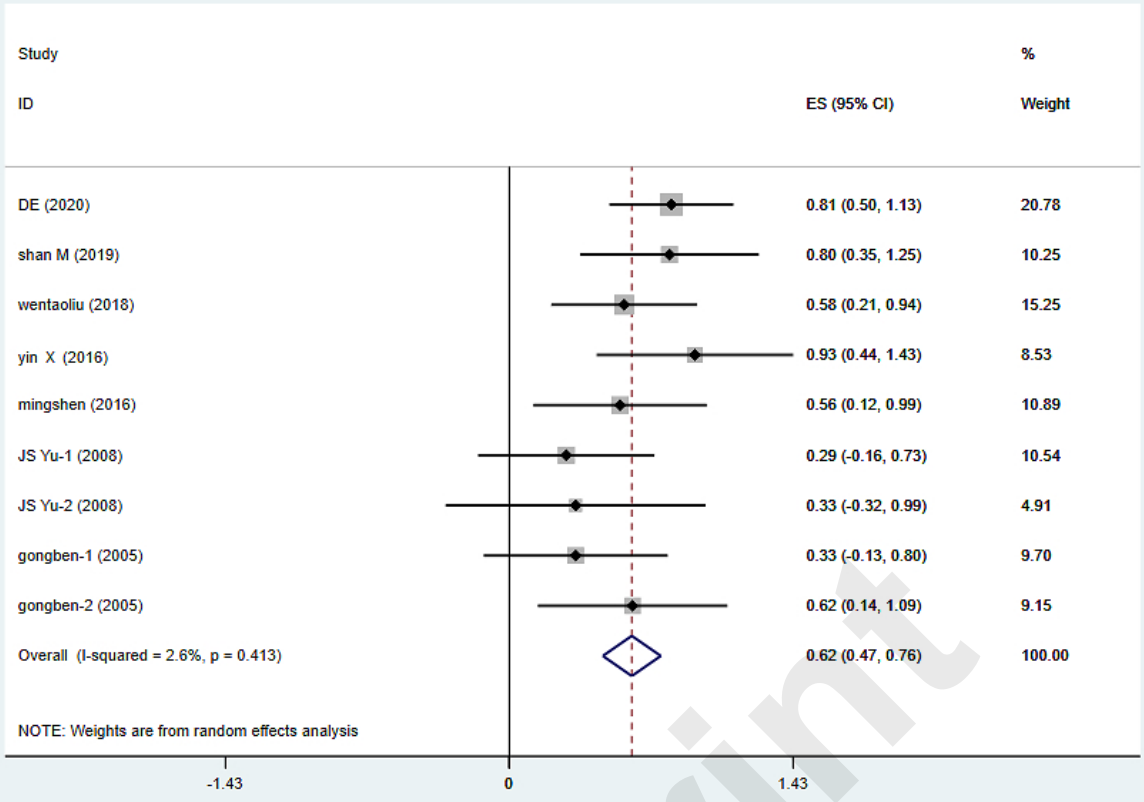
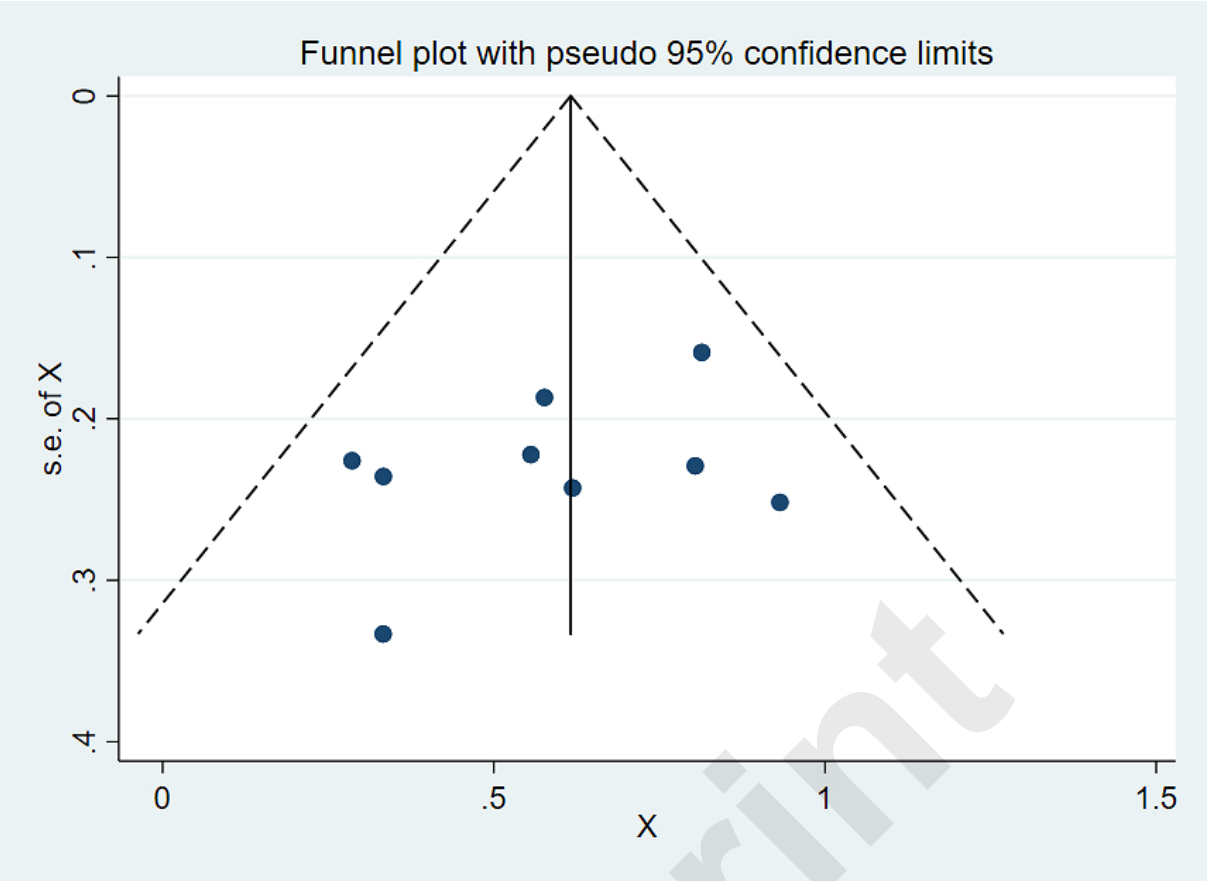

Study
ID
%
ES (95% CI)
Weight
DE (2020)
0.81 (0.50, 1.13)
20.78
shan M (2019)
0.80 (0.35, 1.25)
10.25
wentaoliu (2018)
0.58 (0.21, 0.94)
15.25
yin X (2016)
0.93 (0.44, 1.43)
8.53
mingshen (2016)
0.56 (0.12, 0.99)
10.89
JS Yu-1 (2008)
0.29 (-0.16, 0.73)
10.54
JS Yu-2 (2008)
0.33 (-0.32, 0.99)
4.91
gongben-1 (2005)
0.33 (-0.13, 0.80)
9.70
gongben-2 (2005)
0.62 (0.14, 1.09)
9.15
Overall (I-squared = 2.6%, p = 0.413)
0.62 (0.47, 0.76)
100.00
NOTE: Weights are from random effects analysis
-1.43
0
1.43

Preprint


Funnel plot with pseudo 95% confidence limits
s.e. of X
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.2
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.4
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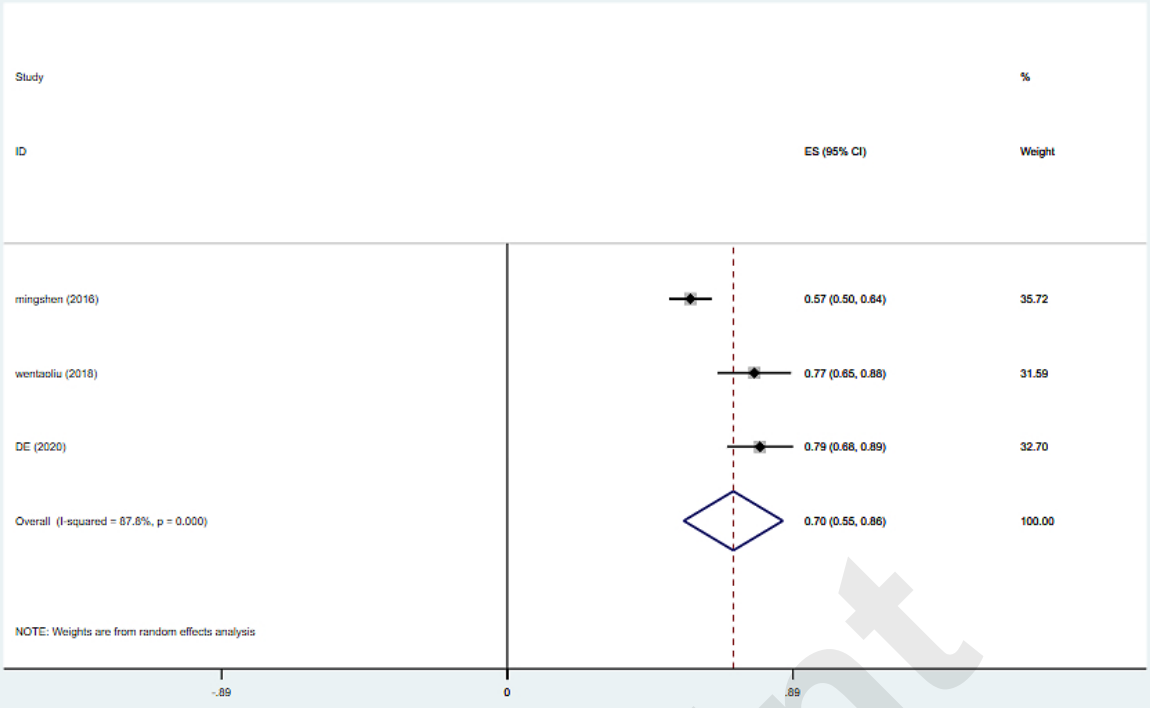
.5
1
1.5
X

Preprint


Study
ID
ES (95% CI)
%
Weight
mingshen (2016)
0.57 (0.50, 0.64)
35.72
wentaoliu (2018)
0.77 (0.65, 0.88)
31.59
DE (2020)
0.79 (0.68, 0.89)
32.70
Overall (I-squared = 87.6%, p = 0.000)
0.70 (0.55, 0.86)
100.00
NOTE: Weights are from random effects analysis
-.89
0
.89

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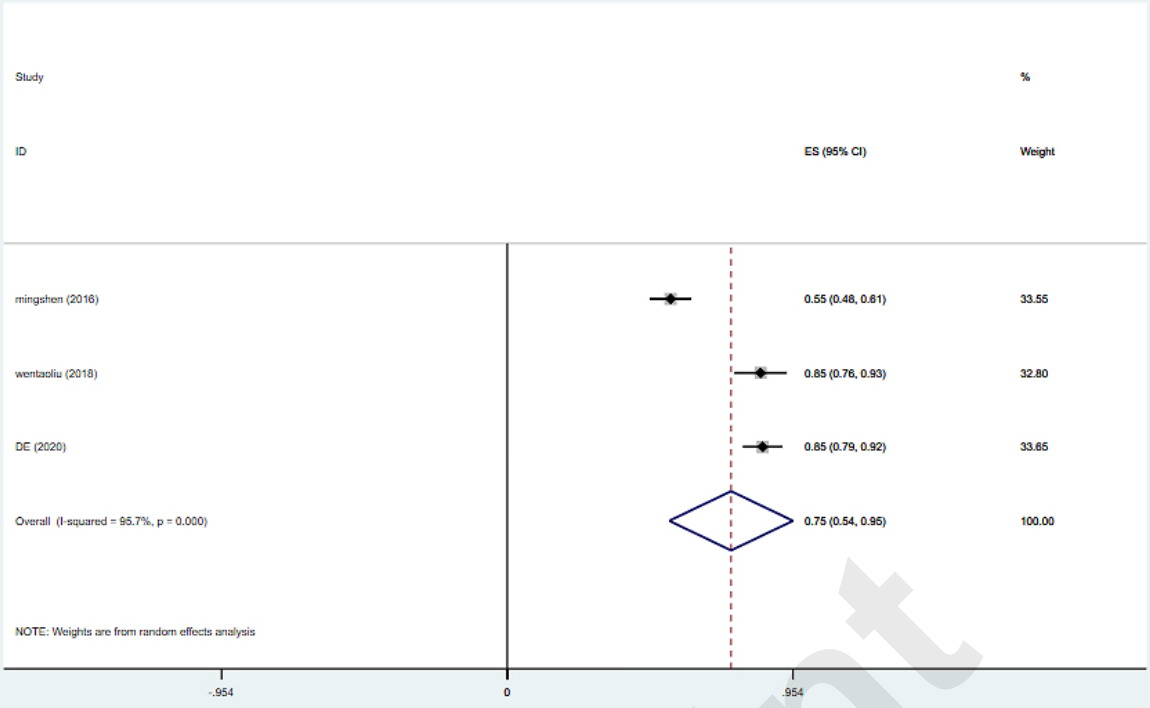
Study
ID
ES (95% CI)
%
Weight
mingshen (2016)
0.55 (0.48, 0.61)
33.55
wentaoliu (2018)
0.85 (0.76, 0.93)
32.80
DE (2020)
0.85 (0.79, 0.92)
33.65
Overall (I-squared = 95.7%, p = 0.000)
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100.00
NOTE: Weights are from random effects analysis
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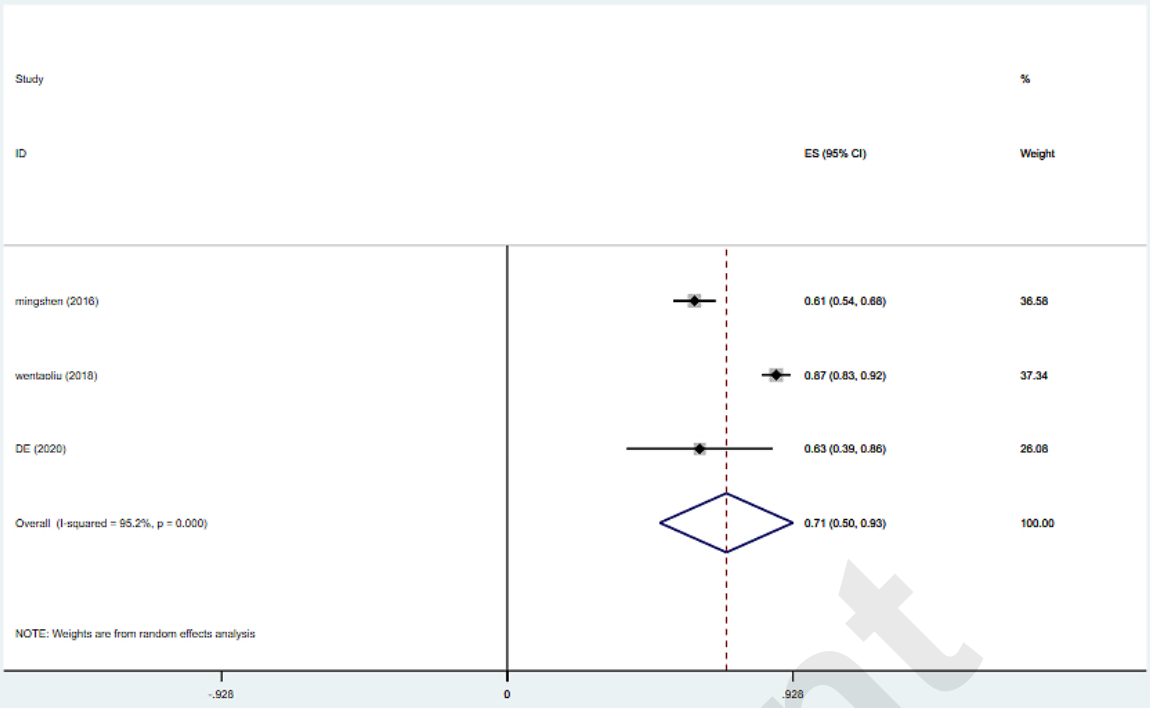
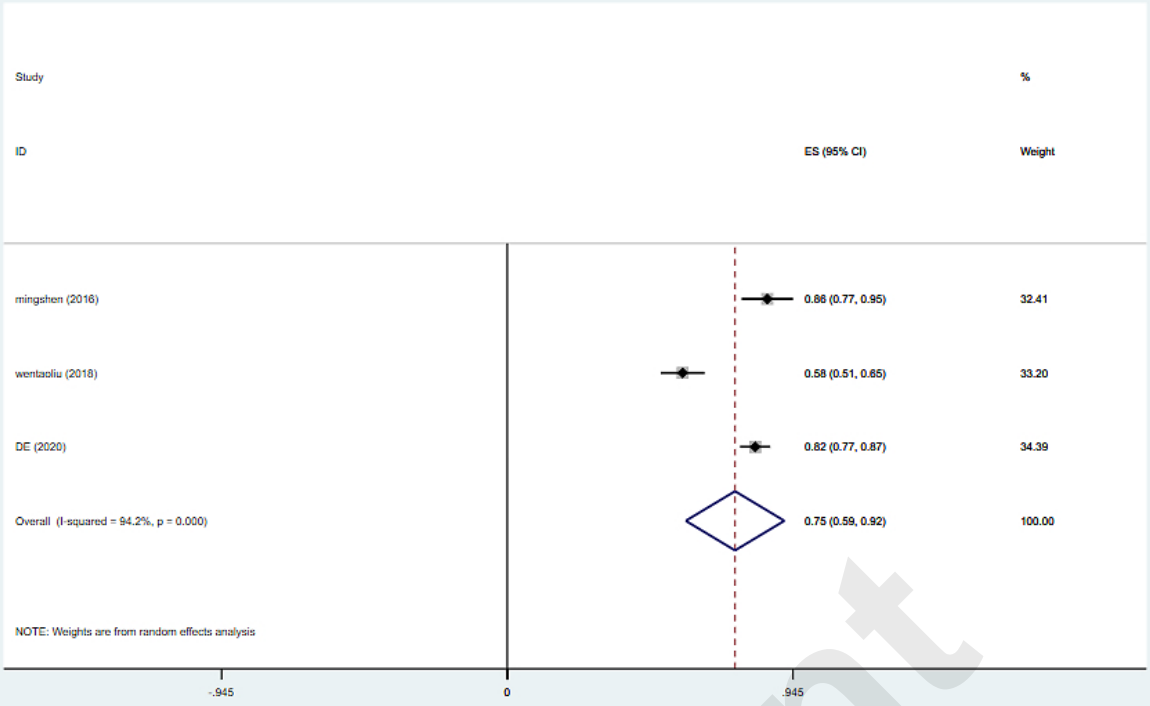

Study
ID
ES (95% CI)
%
Weight
mingshen (2016)
0.61 (0.54, 0.68)
36.58
wentaoliu (2018)
0.87 (0.83, 0.92)
37.34
DE (2020)
0.63 (0.39, 0.86)
26.08
Overall (I-squared = 95.2%, p = 0.000)
0.71 (0.50, 0.93)
100.00
NOTE: Weights are from random effects analysis
-.926
0
.926

Preprint


Study
ID
ES (95% CI)
%
Weight
mingshen (2016)
0.86 (0.77, 0.95)
32.41
wentaoliu (2018)
0.58 (0.51, 0.65)
33.20
DE (2020)
0.82 (0.77, 0.87)
34.39
Overall (I-squared = 94.2%, p = 0.000)
0.75 (0.59, 0.92)
100.00
NOTE: Weights are from random effects analysis
-.945
0
.945

Preprint