MEDS Clinical Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2023.040903
ISSN 2616-1907 Vol. 4 Num. 9

Meta-analysis of the association of ki 67 expression and the clinicopathological features of Triple-negative breast cancer

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Keywords: Triple-negative breast cancer; ki67; Clinicopathological features; Meta-analysis

Abstract: The objective applied in this paper are to evaluate the correlation of the ki67 tumor-proliferation factors and clinicopathological features in patients by Meta-analysis system, and to provide ideas and methods for the diagnosis and treatment of Triple-negative breast cancer. The results of this analysis can provide a reference for the diagnosis and prognosis of Triple-negative breast cancer, and provide a more effective and reasonable treatment plan for patients. The method is using the Internet retrieval system to retrieve English database Pubmed, the Chinese database CNKI, WanFang database, WEIPU data related database, according to certain search methods and keywords, retrieve all the published about three negative breast cancer ki67 expression and clinical pathological characteristics of the literature, by reading the title and abstract, then gradually read the full text, using Review Manager5.4.1 software for Meta analysis. The results are followings: 13 articles were included in this Meta-analysis, including 616 Triple negative breast cancer patients. The positive expression of ki67 was associated with the histological grade of the tumor, and the menstrual status, the difference was statistically significant; It was not associated with tumor diameter, clinical stage, and lymph node metastasis,the difference was not statistically significant. Meta-analysis results: menstrual status (menopausal): OR: 0.8,95%CI was 0.37-1.75, P=0.58; tumor diameter size: OR: 0.77,95%CI was 0.46-1.29, P=0.32; histological grade: OR: 0.24,95%CI was 0.11-0.52, P=0. 0.0003; clinical stage: OR: 0.72,95%CI was 0.30-1.75, P=0.47; lymph node metastasis: OR: 2.03,95%CI is 0.90-4.61, P = 0. 09. Finaly,the conclusions is as the following:among Triple-negative breast cancer, there is no correlation between positive ki67 expression and menstrual status (menopause), tumor size and clinical stage of Triple-negative breast cancer patients, and there is correlation with histological grade and lymph node metastasis.

1. Introduction

Breast cancer is the most common malignant tumor in women. According to the statistics of the National Cancer Center in 2019, the incidence of female breast cancer in China accounts for about 17.1% of all malignant tumors in women, ranking first among female malignant tumors [1]. Triple-negative breast cancer is a subtype of breast cancer that refers to breast cancer where patients with estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are all negative [2].Triple-negative breast cancer is more aggressive and has a worse prognosis than the other subtypes of breast cancer. Without effective therapeutic targets for this subtype of breast cancer, at present, chemotherapy is still used as its main treatment means, and traditional testing indicators such as Estrogen receptor (ER), Progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) have good diagnostic value for conventional Luminal A and Luminal B breast cancer. However, for Triple-negative breast cancer (TNBC) with negative expression of the above indicators, it is difficult to determine the occurrence of such highly heterogeneous tumors[3].Therefore, it is extremely important to find molecular markers that can screen high-risk groups and indicate prognosis for the prevention and treatment of Triple-negative breast cancer[4]. Ki67 is a marker of cell proliferation activity and reflects cell proliferation and division ability [5]. Ki67 is a cell cycle activity-related protein, with good correlation with cell growth fraction and expressed in a variety of malignancies .Ki67 is mainly a division and proliferation-related protein in the nucleus, it is also a nuclear antigen expressed in proliferative active nuclei, containing 15 exons and 14 introns, with molecular structure specificity. Ki67 antigen is phosphorylated and dephosphorylated in mitosis, and is not expressed in the G0 phase of the cell cycle, but to varying degrees in the G1, S, G2 and M phases of the cell cycle. Ki67 changes with the cell cycle within the nucleus, with a complex localization form and obvious specificity. Ki67 has a high sensitivity in the judgment of tumor cell proliferation activity, which can accurately reflect the cell proliferation status, and is related to tumorigenesis, development, and proliferation and metastasis[6]. Through a meta-analysis of previous published articles, this article explores the correlation between ki67 expression and common clinicopathological features, which provides ideas for the diagnosis and treatment of Triple-negative breast cancer and the discussion of prognostic factors.

2. Data and methods

2.1. Inclusion and exclusion criteria

2.1.1. Inclusion criteria

①The expression of ki67 in three-negative breast cancer is major aspects; ② Can retrieve and obtain the full text; ③ Involves relevant clinicopathological features (such as age, menstrual status, tumor size, clinical stage, lymph node metastasis, etc.) and the corresponding data can be extracted; ④ The reading criteria of ki67 are consistent.

2.1.2. Exclusion criteria

①Studies unrelated to the above keywords; ② Review, letters, case reports, conference papers; ③Incomplete data; ④ Animal experiments; ⑤Repeated published documents.

2.1.3. Search strategy

The English database Pubmed was retrieved using the Internet retrieval system, retrieve the

Chinese database CNKI, Wanfang database, WeiPu data and other related databases, according to certain retrieval methods and the retrieval of keywords.The Meta-analysis was performed using the Review Manager5.4.1 software, the extracted data adopts the odds ratio (odds ratio, OR), OR95% confidence interval (confidence interval, CI) to represent. According to the size of heterogeneity, an appropriate effect model was used for statistical analysis, drew forest maps of the analyzed data, discussed whether the correlation between ki67 expression and each clinicopathological characteristics according to the analysis results, and carried out sensitivity analysis of the results to explain whether

2.1.4. Data extraction and analysis

Data from the first author, year of publication, country of publication, total number of samples, source of samples, involved clinicopathological characteristics of the included literature were extracted, and the Excel table was designed to statistically collate the extracted data.As is shown in Table 1.

Table 1: Data extraction and analysis

F	Y	C	T	S	I
HUAMIN LI	2017	China	13	Cancer Tissues	①②③④⑤⑥
JIANHUA WENG	2016	China	43	Cancer Tissues	①③④⑤⑥
XIAOQING GUAN	2015	China	63	Cancer Tissues	①②③④⑤⑥
RUYAN PAN	2013	China	50	Cancer Tissues	④⑤⑥
MENGLIANG SHU	2013	China	45	Cancer Tissues	①③⑤⑥
LV LV	2009	China	30	Cancer Tissues	①②③⑤⑥
YUXIANG ZHU	2010	China	52	Cancer Tissues	①③⑤⑥
JI HAO	2015	China	34	Cancer Tissues	①③⑤⑥
JUNKUO LI	2016	China	111	Cancer Tissues	①③⑤⑥
XIAOXU LI	2014	China	35	Cancer Tissues	①②④⑤⑥
YANAN ZHAO	2014	China	56	Cancer Tissues	①⑤⑥
YANG JUN	2014	China	60	Cancer Tissues	①②③④⑥
HAITAO LI	2015	China	24	Cancer Tissues	① ③⑤⑥

Note: F: first author Y: year of publication C: country of publication T: total number of samples S:source of samples I:involved clinicopathological characteristics

① age ② Menstrual status (menopausal or no) ③ tumor size ④ histological grade ⑤ clinical stage ⑥ whether there is lymph node metastasis

Exacted literature and related clinicopathological features

Document quality evaluation

The quality evaluation of the literature using NOS evaluation criteria with a total score of five stars larger or equal as high quality literature can be included in this Meta-analysis. Through the evaluation, all of the 13 literature masses were more than five stars. As is shown in Table 2.

Table 2: Document quality evaluation.

First author	Year	Selection	Comparability	Exposure	Total scores
HUAMIN LI	2017	☆☆☆	☆	☆☆	☆☆☆☆☆☆
JIANHUA WENG	2016	☆☆☆	☆	☆☆	☆☆☆☆☆☆
XIAOQING GUAN	2015	☆☆	☆	☆☆	☆☆☆☆☆
RUYAN PAN	2013	☆☆☆	☆	☆☆	☆☆☆☆☆☆
MENGLIANG SHU	2013	☆☆☆	☆	☆☆	☆☆☆☆☆☆
LV LV	2009	☆☆☆	☆	☆☆	☆☆☆☆☆☆
YUXIANG ZHU	2010	☆☆☆	☆	☆☆	☆☆☆☆☆☆
JI HAO	2015	☆☆☆	☆	☆☆	☆☆☆☆☆☆
JUNKUO LI	2016	☆☆☆	☆	☆☆	☆☆☆☆☆☆
XIAOXU LI	2014	☆☆☆	☆	☆☆	☆☆☆☆☆☆
YANAN ZHAO	2014	☆☆☆	☆	☆☆	☆☆☆☆☆☆
YANG JUN	2014	☆☆☆	☆	☆☆	☆☆☆☆☆☆
HAITAO LI	2015	☆☆☆	☆	☆☆	☆☆☆☆☆☆

Statistical methods

The Meta-analysis was performed using the Review Manager5.4.1 software, first taking I^2 Testing was performed for homogeneity of each clinicopathological feature, stipulating $P>0.05$, $I^2<50\%$, indicating that the heterogeneity was acceptable, using a fixed effect model (Fixed effects modle, FEM) for analysis, but if $P<0.05$, $I^2>50\%$, indicating the great heterogeneity between the studies, we choose the random effect model (Random effects modle, FEM). Sometimes the heterogeneity comes from a study, so we can properly eliminate a study or combine the data for the analysis again.The effect size of each clinicopathological feature is represented by ratio ratio (odds ratio, OR), 50% credible interval (confidence interval, CI) of OR, and the corresponding forest map and funnel map can be made to analyze whether there is heterogeneity and publication bias.

3. Result

Inclusion of the literatures and the process. As is shown in Figure 1.

Screening process and results.

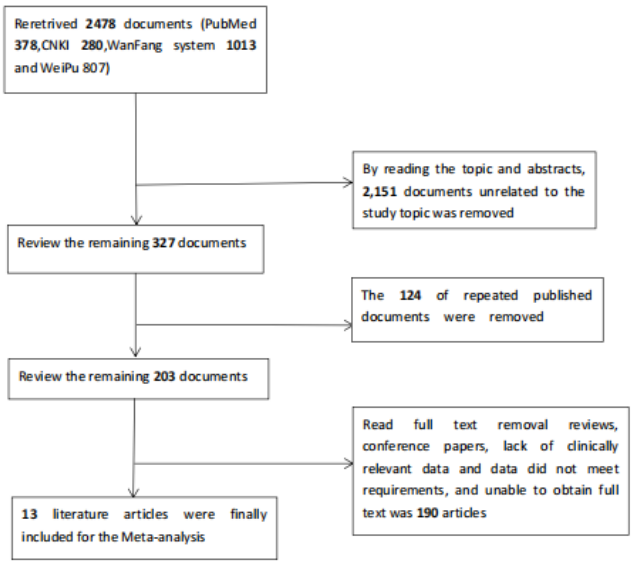

Figure 1: Screening process and results.

3.1. Exacted literature and related clinicopathological features. As follows.

3.1.1 Heterogeneity test

Menstrual status (P=0.58, I^2=0), no heterogeneity; Tumor diameter (P=0.89, I^2=0), no heterogeneity; Histological grade (P=0.79, I^2=0),no heterogeneity; Clinical stage (P=0.15, I^2=35), small heterogeneity; Lymph node metastasis (P=0.001, I^2=62),large heterogeneity.

3.2. Results of the Meta analysis

3.2.1. Relationship between ki67 expression and patient age in Triple-negative breast cancer

Twelve studies analyzed the relationship between ki67 expression and age in Triple-negative breast cancer patients with 566 patients and 470 ki67-positive patients. However, the age demarcation in the 12 studies was not consistent, and the data combination was difficult, so it is not suitable for age analysis.

3.2.2. Relationship between ki67 expression and menstrual status (menopausal status) in Triple-negative breast cancer

A total of five studies analyzed the relationship of ki67 expression and menstrual status in Triple-negative breast cancer with 188 subjects, and 148 patients are positive for ki67 expression, there is homogeneity (P=0.58, I^2=0), a fixed-effect model (FEM) was used to obtain the combined effect size of OR=0.80, 95% CI:[0.37-1.74], P> 0.05, and the difference was not statistically significant, As shown in Figure 2. Using the random effects mode (REM) to do a sensibility analysis to the calculation results, and the OR = 0.80,95%CI:[0.37-1.75] and P>0.05 are basically consistent with the results of the fixed effect model, indicating that the results are stable and the conclusions are accurate and reliable. As shown in Figure 3.

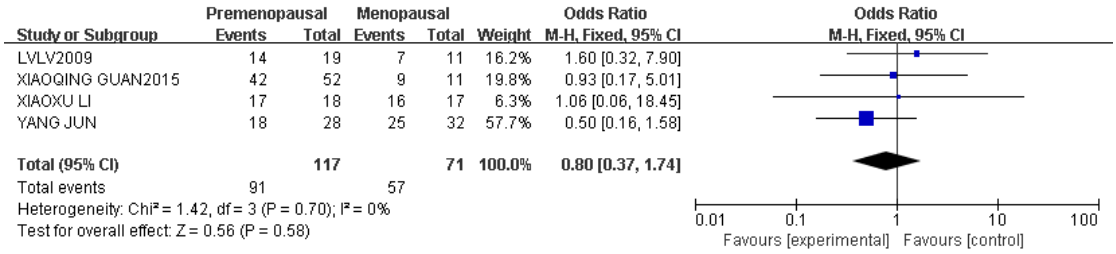

Figure 2: Relationship between k i 67 expression and menstrual status (whether menopausal) in patients with Triple-negative breast cancer.

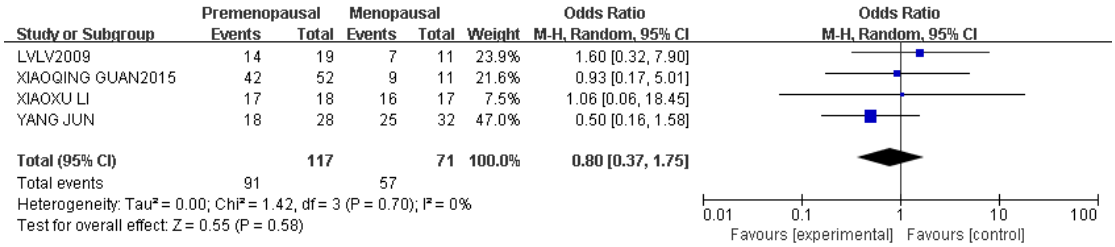

Figure 3: Sensitivity analysis.

3.2.3. Relationship between ki67 expression and patient tumor diameter size in Triple-negative breast cancer

A total of 10 studies analyzed the relationship of ki67 expression and tumor diameter size in Triple-negative breast cancer, with 447 subjects, and 364 subjects are positive for ki67 expression, there is homogeneity (P=0.89, I^2=0), the fixed-effect model (FEM) was used to obtain the combined effect size of OR=0.77,95%CI [0.47-1.29], P> 0.05, and the difference was not statistically significant, as shown in Figure 4. Using the random effects model（REM)to do the sensitivity analysis to the calculation results, and the OR= 0.77,95% CI[0.46-1.29] and P>0.05 are basically consistent with the results of the fixed effect model, indicating that the results are stable and the conclusions are accurate and reliable. As shown in Figure 5.

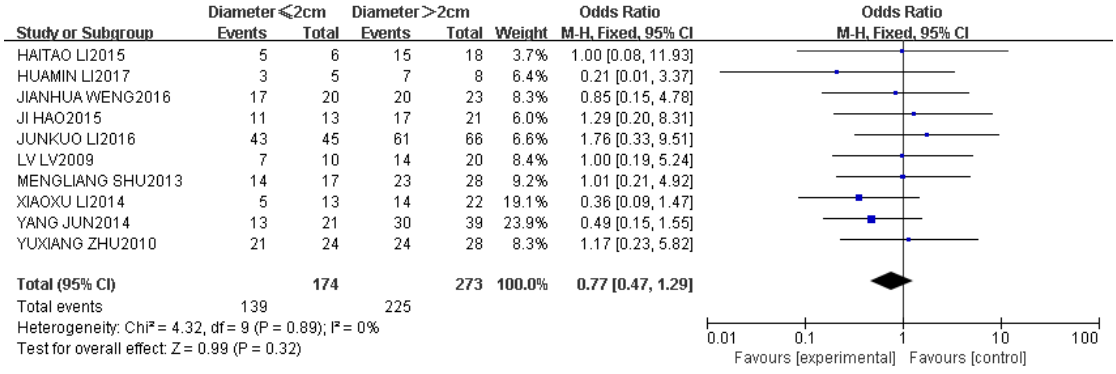

Figure 4: Relationship between ki 67 expression and tumor diameter size in patients with Triple-negative breast cancer.

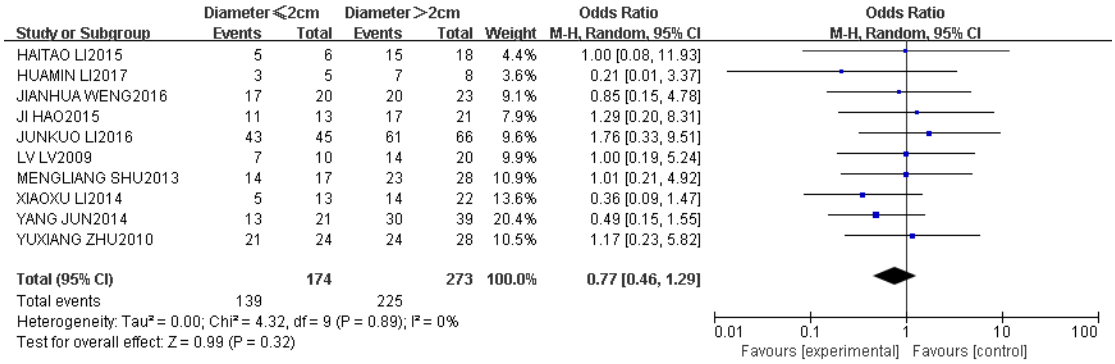

Figure 5: Sensitivity analysis.

3.2.4. Relationship between ki67 expression and patient histological grade in Triple-negative breast cancer

A total of four studies analyzed the relationship between ki67 expression and patient histological grade in Triple-negative breast cancer with 158 subjects, and 97 patients are positive for ki67 expression, there is homogeneity (P=0.79, I^2=0), the fixed-effect model (FEM) was used to obtain the combined effect size of OR=0.23, 95%CI[0.11-0.50], P <0.05, and the difference was statistically significant, as shown in Figure 6. The sensitivity analysis of random effect model (REM) to the calculation results, and the OR=0.24,95%CI[0.11-0.52] and P <0.05 are basically consistent with the results of the fixed effect model, indicating that the results are stable and the conclusions are accurate and reliable. As shown in Figure 7.

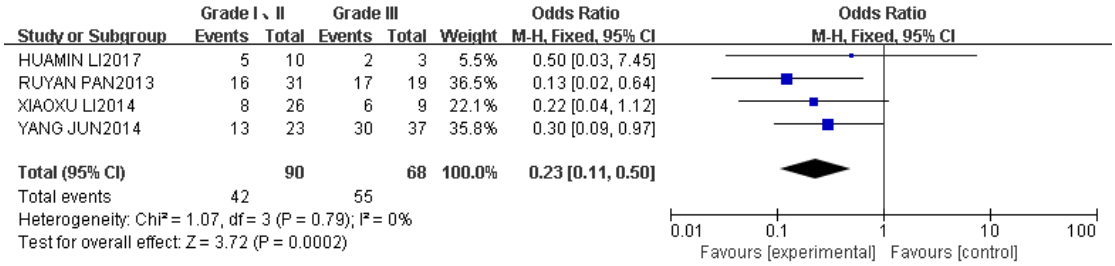

Figure 6: Relationship between ki67 expression and histological grade in patients with Triple-negative breast cancer.

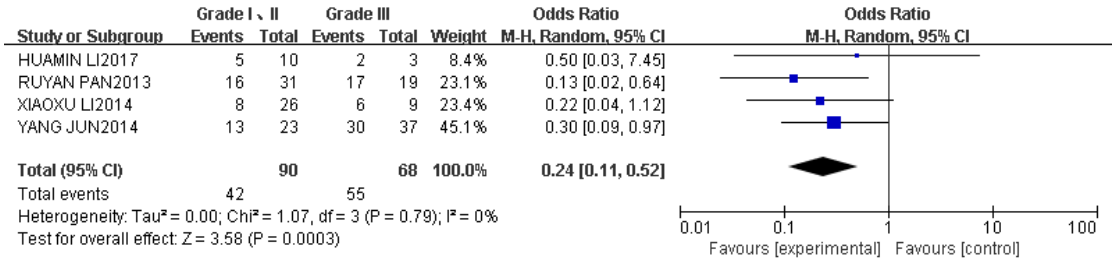

Figure 7: Sensitivity analysis.

3.2.5. Relationship between ki67 expression and patient clinical stage in Triple-negative breast cancer

A total of eight studies analyzed the relationship between ki67 expression and patient clinical stage in Triple-negative breast cancer in 415 subjects and 343 patients with positive ki67 expression, with less heterogeneity (P=0.15, I^2=35), the fixed-effect model (FEM) was used to obtain the

combined effect size of OR=0.51, 95%CI[0.27-0.95], P <0.05, and the difference was statistically significant, as shown in Figure 8.

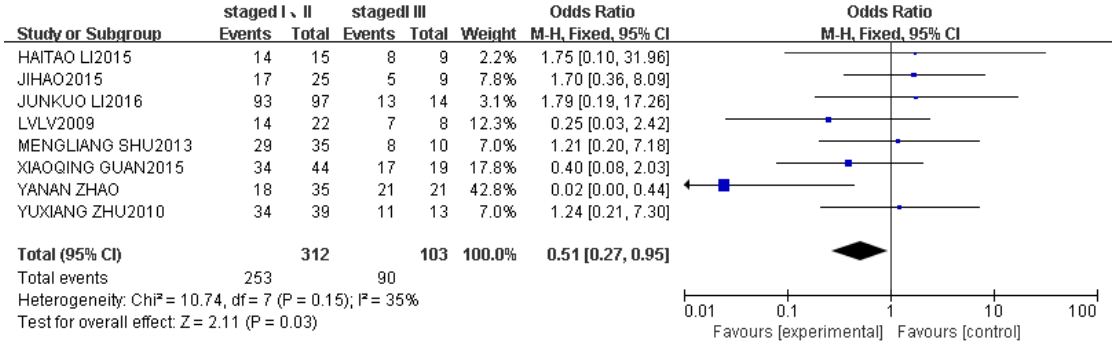

Figure 8: Relationship between ki67 expression and the clinical stage in patients with Triple-negative breast cancer (1).

Using random effect model (REM) to do sensitivity analysis, the results of OR=0.72, 95%CI[0.30-1.75], P>0.05 are not consistent with the results of the fixed effect mode. As shown in Figure 9.

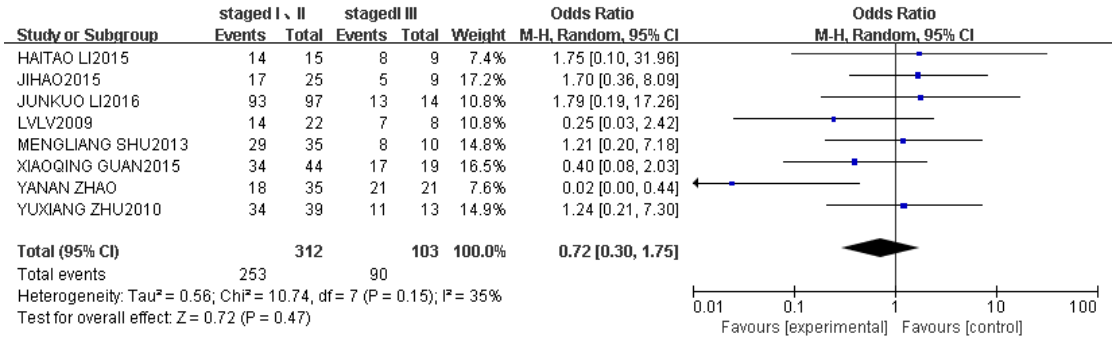

Figure 9: Sensitivity analysis (1).

By cutting them out individually, further exploring the source of the heterogeneity, the heterogeneity came from the Zhao Yanan study, this item was excluded for further analysis, the remaining 7 studies included 359 subjects, a total of 341 subjects have positive ki67 expression, there is homogeneity. Using the fixed effect model (FEM), the combined effect size is obtained with OR=0.87, 95%CI [0.44-1.75], P>0.05, the difference is not statistically significant, as shown in Figure 10.

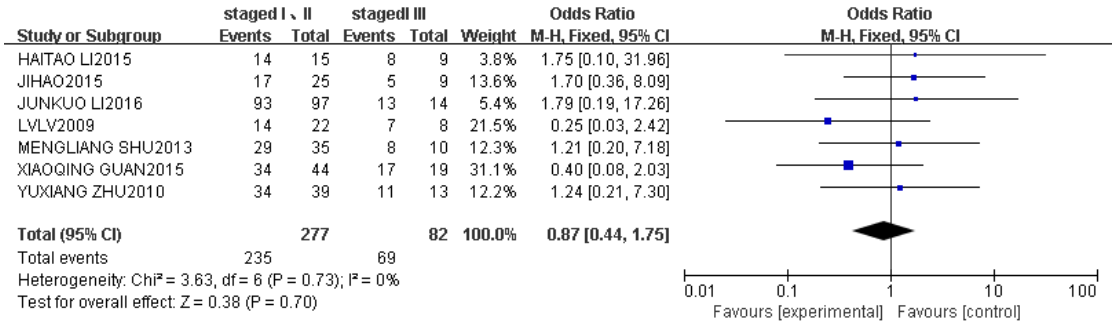

Figure 10: Relationship of ki67 expression and the clinical stage of Triple-negative breast cancer patients (2).

Sensitivity analysis using random effect model (REM), the resulting OR=0.95, 95%CI [0.46-1.96], P>0.05, consistent with the results of the fixed-effect model, indicating that the results

are stable, the conclusions are exact and reliable.As shown in Figure 11.

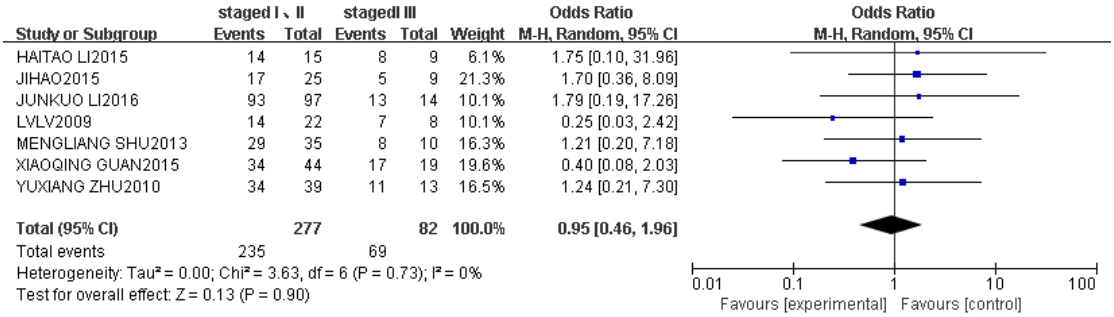

Figure 11: Sensitivity analysis(2).

3.2.6. Relationship between ki67 expression and axillary lymph node metastasis in Triple-negative breast cancer

A total of 13 studies analyzed the relationship of ki67 expression and axillary lymph node metastasis in Triple-negative breast cancer with 629 subjects, and 508 subjects are positive for ki67 expression, there is high heterogeneity (P=0.001, I^2=62), the random effect model (REM) was used to obtain the combined effect size OR=2.03,95%CI[0.90-4.61], P>0.05, and the difference is not statistically significant, as shown in Figure 12.

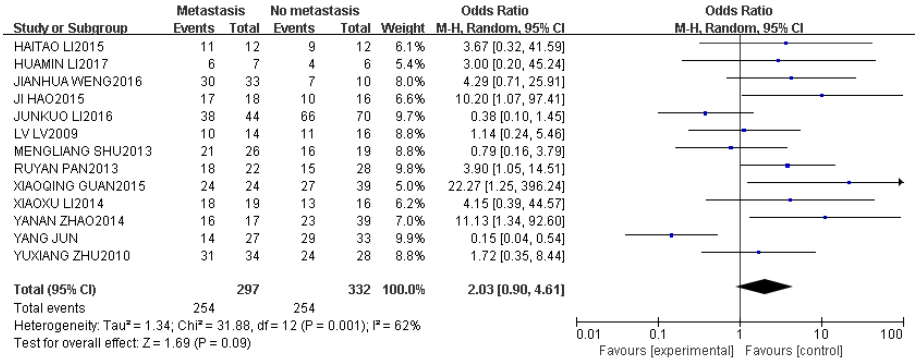

Figure 12: Relations of ki67 expression and axillary lymph node metastasis in patients with Triple-negative breast cancer (1).

The sensitivity analysis of fixed effect model (FEM) to the calculation results, and the OR= 1.70, 95%CI [1.12-26] and P <0.05 are not consistent with the results of the fixed effect model. As shown in Figure 13.

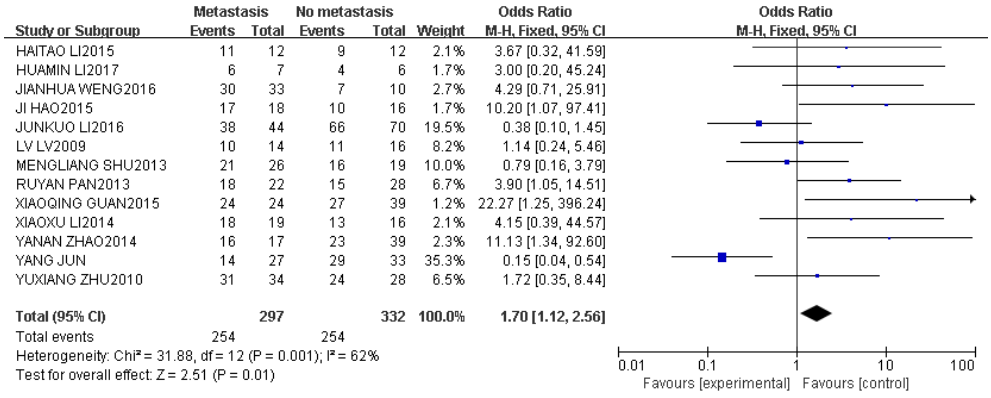

Figure 13: Sensitivity analysis (1).

Further exploring the source of heterogeneity was found from the Yang Jun study. After cutting this study and further analysis, the remaining 12 study subjects included a total of 569 cases, 465 subjects are positive for ki67 expression, (P=0.09, I^2=38), with less heterogeneity, the random effect model (REM) yields the combined effect size of OR=2.54,95%CI[1.59-4.07] and P <0.05. The difference has statistical significance. As shown in Figure 14, apply the fixed effect model (FEM) for sensitivity analysis to the calculation results, the resulting OR = 2.59,95%CI[1.59-4.07] and P <0.05 are consistent with the fixed effect model, indicating that the results are stable and the conclusions are accurate and reliable. As shown in Figure 15.

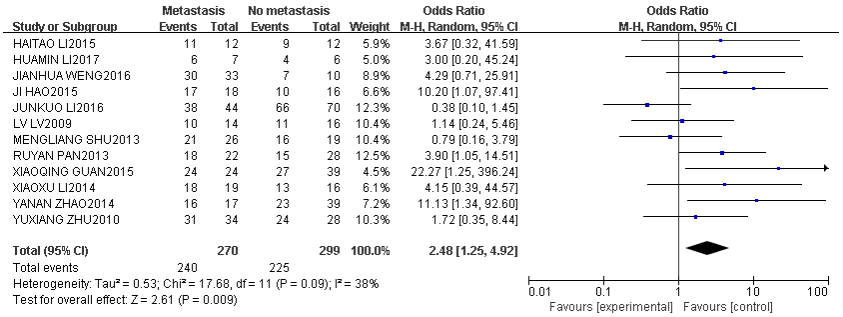

Figure 14: Relationship between ki67 expression and axillary lymph node metastasis in patients with Triple-negative breast cancer (2).

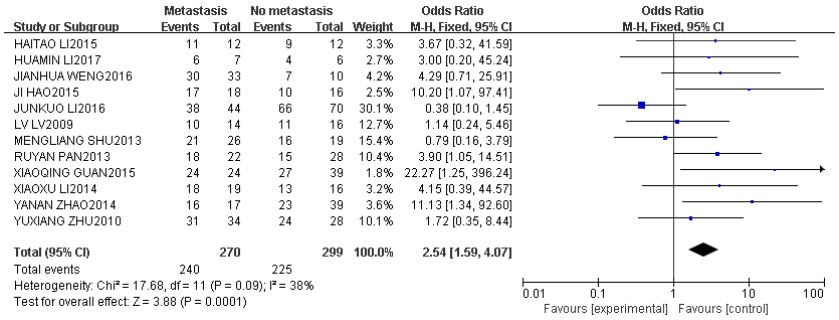

Figure 15: Sensitivity analysis (2).

3.3. Publication bias

The above are the funnel plots drawn by the included literatures. As can be seen from the above figures, some indicators have publication bias, which may be related to the small number of included literatures and the small sample observation volume, which may have a certain impact on the study of the overall data. As shown in Figure 16 to Figure 20.

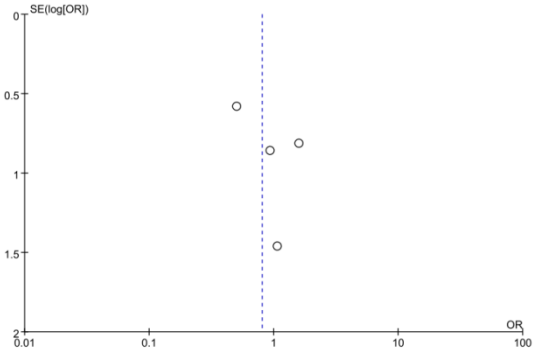

Figure 16: Funnel plot of the menstrual status.

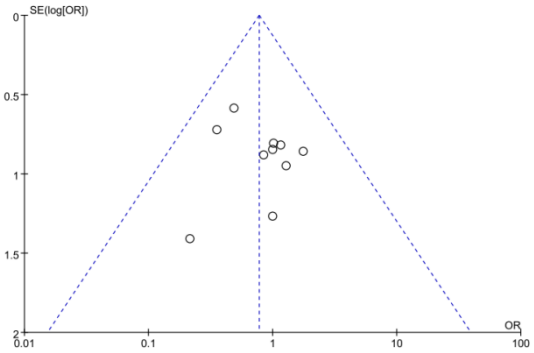

Figure 17: Funnel plot of tumor size.

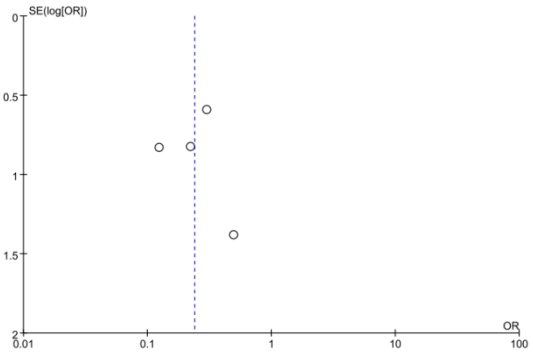

Figure 18: Funnel plot of histological gradet.

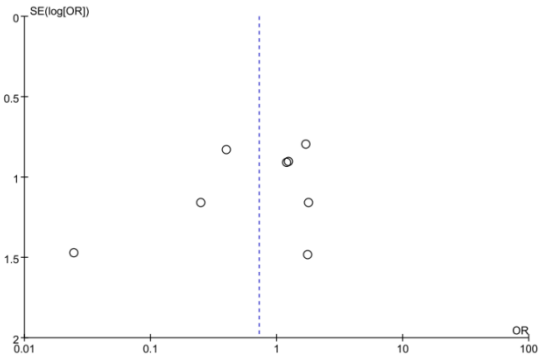

Figure 19: Funnel plot of clinical stage.

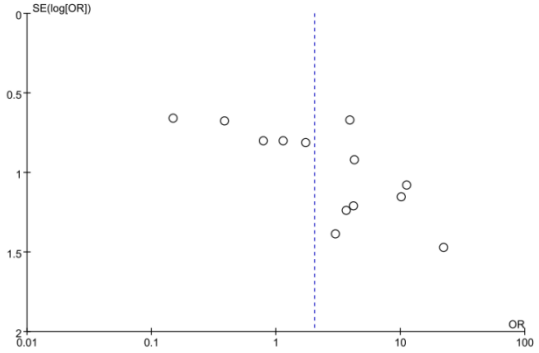

Figure 20: Funnel plot of the lymph node metastasis.

3.4. Discussion

Results analysis

Triple-negative breast cancer refers to breast cancer that are negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) in cancer tissue. According to the GLOBOCAN2018 report released by the World Health Organization International Agency for Research on Cancer (IARC) on the global cancer incidence of cancer, breast cancer ranks first among female tumors (24.2%).The incidence rate of breast cancer in women in China is about 41 / 100,000, and the incidence rate is increasing year by year.Although the incidence of Triple-negative breast cancer is relatively low, representing approximately 15% to 25% of breast cancers[7], however, due to its special pathological characteristics, there has been some controversies in the treatment, which has become a hot topic in recent years[8].The reason why Triple-negative breast cancer is terrible lies in its special pathological type. The three-negative receptor factors make it lack endocrine and anti-HER-2 treatment targets, and has limited treatment methods.There are no other effective systemic treatment measures except chemotherapy.The ki67 is a nuclear protein present in proliferating cells whose expression is closely related to the cell cycle.It is widely used clinically to mark cell proliferative states, and its expression level is correlated with breast cancer prognosis[9] ,and can accurately respond to the proliferative activity of tumor cells[10]. The higher value indicates the worse the tissue differentiation ability, in general, such a tumor prognosis is relatively poor.The ki67 was also present in Triple-negative breast cancer, and this study aimed to investigate the relationship between ki67 expression status and related pathological features in Triple-negative breast cancer, to provide ideas and methods for the diagnosis and treatment of Triple-negative breast cancer.This study included 13 eligible literature, using Review Manager5.4.1 software analyzed five clinicopathological features, including menstrual status, tumor size, histological grade, clinical stage, axillary lymph node features. Through the results obtained by this analysis we can draw the following conclusion: there was no correlation between positive ki67 expression and menstrual status (menopause), tumor size, or clinical stage of triple-negative breast cancer patients, the results are respectively:OR=0.80,95%CI[0.37-1.74], P>0.05; OR=0.77, 95%CI[0.47-1.29], P>0.05;OR=0.87,95%CI[0.44-1.75],P>0.05.There was no correlation between positive ki67 expression and histological grade and lymph node metastasis,the results were respectively: OR=0.23, 95%CI [0.11-0.50], P<0.05; OR=2.54, 95%CI[1.59-4.07], P<0.05. In this Meta-analysis, we verified the relationship between ki67-positive expression and histological grade, yielding grade I, II and III comparisons, OR=0.23,95%CI[0.11-0.50],P<0.05, indicating a higher histological grade of ki67-positive expression in Triple-negative breast cancer, similarly, lymph node metastasis is compared with no lymph node metastasis, OR=2.54,95%CI[1.59-4.07], P<0.05, indicating patients with positive ki67 expression in triple-negative breast cancer are more likely to have lymph node metastasis. But there is no correlation with menstrual status (whether menopause), tumor size, and clinical stage.In addition, ki67 expression in Triple-negative breast cancer may be associated with patient age, but the demarcation of age for age in these 13 studies was inconsistent, resulting in difficult analysis and impossible analysis.

Only the relationship between positive ki67 status and clinicopathological characteristics was analyzed in this analysis, and perhaps there is also a correlation between the value of ki67 and them, which needs to be further explored.

3.4.1. Sources of heterogeneity

In this analysis, in principle, there is too low and too high heterogenicity of the research data, and the reasons may include the following points: (1) the sample size is too small or not representative; (2) the different research follow-up time is different, etc.

3.4.2. Limitations

Due to the permission setting of the database, or some literature is still in publication, leading to part cannot obtain the complete information, and the language only involves Chinese and English, the rest is not included in the analysis, the number of the literature is too little, small data, the analysis results are not representative, there may be publication bias, may have an impact on the analysis results.

4. Conclusion

Among Triple-negative breast cancer, there was no correlation between positive ki67 expression and menstrual status (menopause), tumor size and clinical stage of Triple-negative breast cancer patients, and have correlation with histological grade and lymph node metastasis.

The expression of ki67 indicates the size of the tumor proliferative capacity, which has a certain guiding role in the diagnosis and prognosis of Triple negative breast cancer, and can better develop a reasonable and effective individualized treatment plan for patients.

5. Ethics Statement

The research content in this paper strictly follows the Declaration of Helsinki and the International Ethical Guidelines for Human Biomedical Research witch is published by the World Health Organization and the Council for International Organizations of Medical Sciences (CIOMS).The informed consent of patients has been strictly done to ensure that personal information is not publicly disclosed, and made every efforts to protect the privacy of the interviewee's personal data and information within the scope permitted by law. The manuscript was approved by the Ethics Committee for Medical Research of Dali University.

Acknowledgement

This research was supported by “Li Yunqing Expert Workstation, YunNan” (No.202005AF150014), the Key Laboratory of medical molecular diagnosis in Colleges and Universities of Yunnan Province (NO 36), and the Special fund project for basic research of local undergraduate colleges and universities granted by Department of Science and Technology of Yunnan Province (NO. 202101AN070028).

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