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Clinicopathological and prognostic significance of GLUT1 in breast cancer

A meta-analysis

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Abstract

Background: Previous studies examining the prognostic value of glucose transporter 1 in breast cancer have yielded inconsistent results. We, therefore, performed a meta-analysis to clarify this issue.

Methods: The research was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Relevant studies were retrieved from PubMed, Web of Science, EMBASE, and Cochrane library.

Results: A total of 7 reports with 1861 patients were finally chosen. GLUT1 overexpression was found to be associated with high histological grade (OR = 3.74, 95% CI = 2.45–5.69, $P < .001$), negative PR status (OR = 0.33, 95% CI = 0.22–0.49, $P < .001$), and negative estrogen receptor (ER) status (OR = 0.27, 95% CI = 0.17–0.42, $P < .001$). However, no significant correlation was seen between GLUT1 levels and presence of lymph node metastasis, tumor size or the status of human epidermal growth factor receptor 2 (HER2). Overexpression of GLUT1 also correlated with a poor overall survival (hazard ratio [HR] = 1.65, 95% confidence interval [CI] = 1.17–2.31, $P = .004$) and disease-free survival (HR = 2.35, 95% CI = 1.4–3.94, $P < .001$). No evidence of significant publication bias was found.

Conclusion: This meta-analysis indicates that GLUT1 expression is associated with poor prognostic and a series of clinicopathological features in breast cancer. GLUT1 might be a potential biomarker and therapeutic target in breast cancer.

Abbreviations: CI= confidence interval, DFS = disease-free survival, ER= estrogen receptor, GLUT1 = Glucose transporter 1, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, OS = overall survival, PR = progesterone receptor.

Keywords: breast cancer, carcinogenesis, GLUT1, meta-analysis, prognosis

1. Introduction

Breast cancer remains the most frequently diagnosed cancer in women worldwide,[1] with a high mortality rate. According to a recent report,[2] published in 2017, 252,710 women will be newly diagnosed and 40,610 women are expected to die of breast cancer in the United States. The therapeutic strategies for breast cancer include surgery, radiotherapy, and systemic treatment including chemotherapy, and endocrine therapy.[3] A series of clinicopathological parameters including tumor stage, histological grade, and biological tumor subtypes are applied to guide the selection of a treatment regimen and to predict survival outcomes.[4] In spite of these efforts, the prognosis of breast cancer remains unsatisfactory. Therefore, there is a pressing need to explore new biomarkers that can provide an accurate prognosis for individual patients.

It is well known that cancer cell growth is an energy-dependent process.[5] As a result, glucose metabolism in cancer cells is typically altered. The metabolic reprogramming of cancer cells is an emerging hallmark of cancer.[6] Altered energy metabolism is observed in many kinds of cancer.[6] Glucose transporter (GLUT1) proteins transport glucose across the plasma membrane and GLUT1 plays an important role in metabolic remodeling in cancer cells. In normal tissues, expression of GLUT1 is limited to the erythrocytes.[7] However, various malignant tumors have shown an overexpression of GLUT proteins, especially GLUT1.[8] The prognostic role of GLUT1 in breast cancer has also been widely investigated; however, the results have been inconsistent. Hussein et al reported that GLUT1 expression did not correlate with the overall survival (OS) ($P = .13$) in breast cancer.[9] However, other investigators have presented significant associations between GLUT1 and a poor prognosis in breast cancer.[10,11] We thus conducted a meta-analysis by pooling data from different studies, with an aim to identify definite correlations between GLUT1, other clinicopathological features, and prognosis in breast cancer.

2. Materials and methods

2.1. Literature search strategy

This study was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA)

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statement.[12] The following electronic databases were thoroughly searched: PubMed, Web of Science, EMBASE, and Cochrane library. The key words used for literature retrieval included: "glucose transporter-1", "GLUT-1", "glucose transporter1", "GLUT1", "breast cancer", and "breast carcinoma". The last search was updated on Jun 2018. References to eligible literature were also manually screened to find potentially relevant studies.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were applied to select eligible studies:

the diagnosis of breast cancer was pathologically proven;

the expression of GLUT1 was detected by immunohistochemical staining (IHC);

correlations between GLUT1 and survival outcomes including OS and disease-free survival (DFS) or clinicopathological factors were reported;

published as full-text articles; and

published in English.

The exclusion criteria included

reviews, letters, and meeting abstracts;

studies with insufficient data for analysis; and

non-human studies.

2.3. Data extraction

Two investigators independently extracted the following information from eligible studies: name of first author, year of publication, country/region, sample size, age, tumor stage, detection method, and cut-off values. Hazard ratio (HR) and 95% confidence interval (CI) for OS or DFS were also extracted if reported in the text. If not, HR and 95% CI were calculated from the survival curves by using Tierney's method.[13] Discrepancies between the 2 investigators were resolved by discussion.

2.4. Statistical analysis

HRs and 95% CIs were used as effective measures to evaluate the associations between GLUT1 and survival outcomes. The correlations of GLUT1 with the clinicopathological characteristics were assessed by using odds ratio (OR) and 95% CI. Heterogeneity among the studies was assessed by using the Cochran Q test and Higgins I^2 statistics. A random-effects or a fixed-effects model was used, and $I^2 > 50\%$ indicated substantial heterogeneity. Publication bias was evaluated by using the Begg test. P value $< .05$ was considered statistically significant. All statistical analyses were performed using the Stata version 12.0 software (Stata Corporation, College Station, TX).

2.5. Ethical approval

All analyses are based on previously-published studies; moreover, this article is of the meta-analysis study design. Therefore, no ethical approval and patient consent are required.

3. Results

3.1. Literature search and study characteristics

The process of the study selection is shown in Figure 1. A total of 839 records were identified through an initial search. After removing the duplicate records, 601 records were screened, of which 538 were excluded by scanning their titles and abstracts. Sixty-three full-text articles were further evaluated. Subsequently, 48 studies were excluded for the following reasons: 41 studies lacked the necessary information, 8 of them were non-English studies, 5 of them were meeting abstracts, 1 was a case report, and 1 was a duplicate study. Finally, 7 studies[9–11,14–17] with 1861 patients were included in this meta-analysis. The baseline characteristics of the included studies are detailed in Table 1. Four studies were conducted in Korea and 1 each in Taiwan, the USA, and Portugal, respectively. All eligible studies were published in English.[9–11,14–17]

3.2. Association of GLUT1 with clinicopathological characteristics

The relationship between GLUT1 and 6 clinicopathological factors was investigated. The 6 clinicopathological parameters were lymph node metastasis, histological grade, progesterone receptor (PR) status, estrogen receptor (ER) status, and human epidermal growth factor receptor 2 (HER2) status and tumor size. The pooled results are summarized in Table 2 and Figure 2. The results demonstrate that GLUT1 overexpression is associated with high histological grade (OR = 3.74, 95% CI = 2.45–5.69, $P < .001$), negative PR status (OR = 0.33, 95% CI = 0.22–0.49, $P < .001$), and negative ER status (OR = 0.27, 95% CI = 0.17–0.42, $P < .001$). However, no significant correlation was seen between GLUT1 levels and presence of lymph node metastasis, tumor size or the status of HER2.

3.3. Correlation between GLUT1, and OS and DFS

Three studies[9–11] with a total of 899 patients reported an association between GLUT1 and OS. The pooled HR and 95% CI of these studies were 1.65 and 1.17 to 2.31, respectively ($P = .004$; Fig. 3), indicating that GLUT1 overexpression predicted poor OS in breast cancer. Another 2 studies[10,11] comprising 376 patients investigated the link between GLUT1 and DFS. The aggregated HR and 95% CI were 2.35 and 1.4 to 3.94, respectively ($P < .001$; Fig. 4). Taken together, these results demonstrate that overexpression of GLUT1 is associated with a shorter OS and DFS in breast cancer.

3.4. Publication bias

The Begg's linear regression model was applied to detect potential publication bias. The P values of the Begg test for OS and DFS were .602 and .41, respectively, indicating no significant publication bias in this meta-analysis.

4. Discussion

A number of studies have evaluated the prognostic significance of GLUT1 in breast cancer, and the results have been conflicting. To address this issue, we conducted a meta-analysis of the available data. The pooled results from 7 studies with 1861 patients showed that elevated GLUT1 expression is associated with high histological grade, negative PR status, and negative ER status. Furthermore, GLUT1 overexpression also correlated with poor OS and DFS. Therefore, GLUT1 has the potential to be a new biomarker indicative of an aggressive and lethal phenotype of breast cancer. To the best of our knowledge, this is the first meta-analysis exploring the prognostic value of GLUT1 in breast cancer.

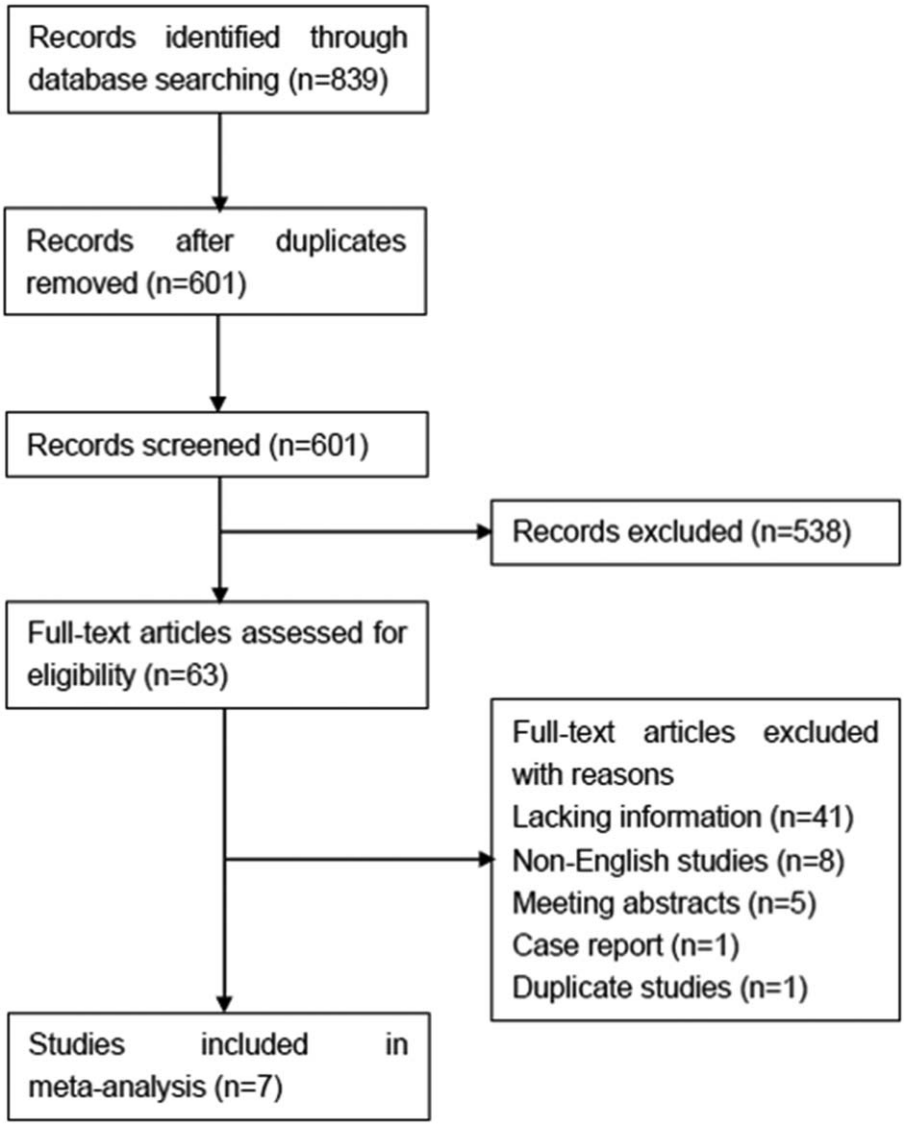

Figure 1. Flow diagram showing literature filtration process.

Cancer cells can reprogram energy metabolism in order to fuel cell growth and proliferation. Reprogramming energy metabolism is a hallmark of cancer.[6] GLUT1 is overexpressed in various tumors to sustain the elevated glucose levels in cancer cells.[18] In addition, GLUT1 is also reported to promote the proliferation, migration, and invasion of tumor cells by activating the EGFR/MAPK pathway as well as the integrinβ/Src/FAK pathway.[18] GLUT1 expression is also associated with 18F-FDG uptake,[19] indicating the potential connection between GLUT1 and tumor progression.

The impact of GLUT1 on the prognosis of different cancers has been previously studied, using a meta-analysis.[20–24] Wang et al pooled data from 26 studies and showed that the overexpression

Table 1

Baseline characteristics of included studies.

Study	Year	Country/Region	No. of patients	Age, mean (range)	Stage	Cut-off value	Method	Language
Choi	2013	Korea	740	49.7	I-III	NR	IHC	English
Hussein	2011	USA	523	56.9 (26–94)	I-III	50%	IHC	English
Jang	2012	Korea	276	50	I-IV	10%	IHC	English
Kang	2002	Korea	100	48.3 (23–74)	NR	10%	IHC	English
Kim	2013	Korea	59	50.8	I-II	10%	IHC	English
Kuo	2006	Taiwan	39	NR	NR	Score 3	IHC	English
Pinheiro	2011	Portugal	124	NR	I-III	5%	IHC	English

IHC = immunohistochemistry, NR = not reported.

Table 2

Summary of the associations between GLUT1 expression and clinicopathological characteristics in breast cancer.

Variables	No. of studies	Effect model	I^2 (%)	P_h	OR (95% CI)	*P*
LN metastasis (+ vs −)	7	Fixed model	22.6	.257	1.15 (0.93–1.42)	.203
Histological grade (III vs I-II)	7	Random model	60.8	.018	3.74 (2.45–5.69)	<.001
PR status (+ vs −)	7	Random model	58.3	.026	0.33 (0.22–0.49)	<.001
ER status (+ vs −)	6	Random model	60.7	.026	0.27 (0.17–0.42)	<.001
HER2 status (+ vs −)	6	Fixed model	24.5	.25	0.91 (0.69–1.19)	.483
Tumor size (>2 cm vs ≤2 cm)	6	Random model	74.8	.001	1.43 (0.86–2.37)	.171

ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.

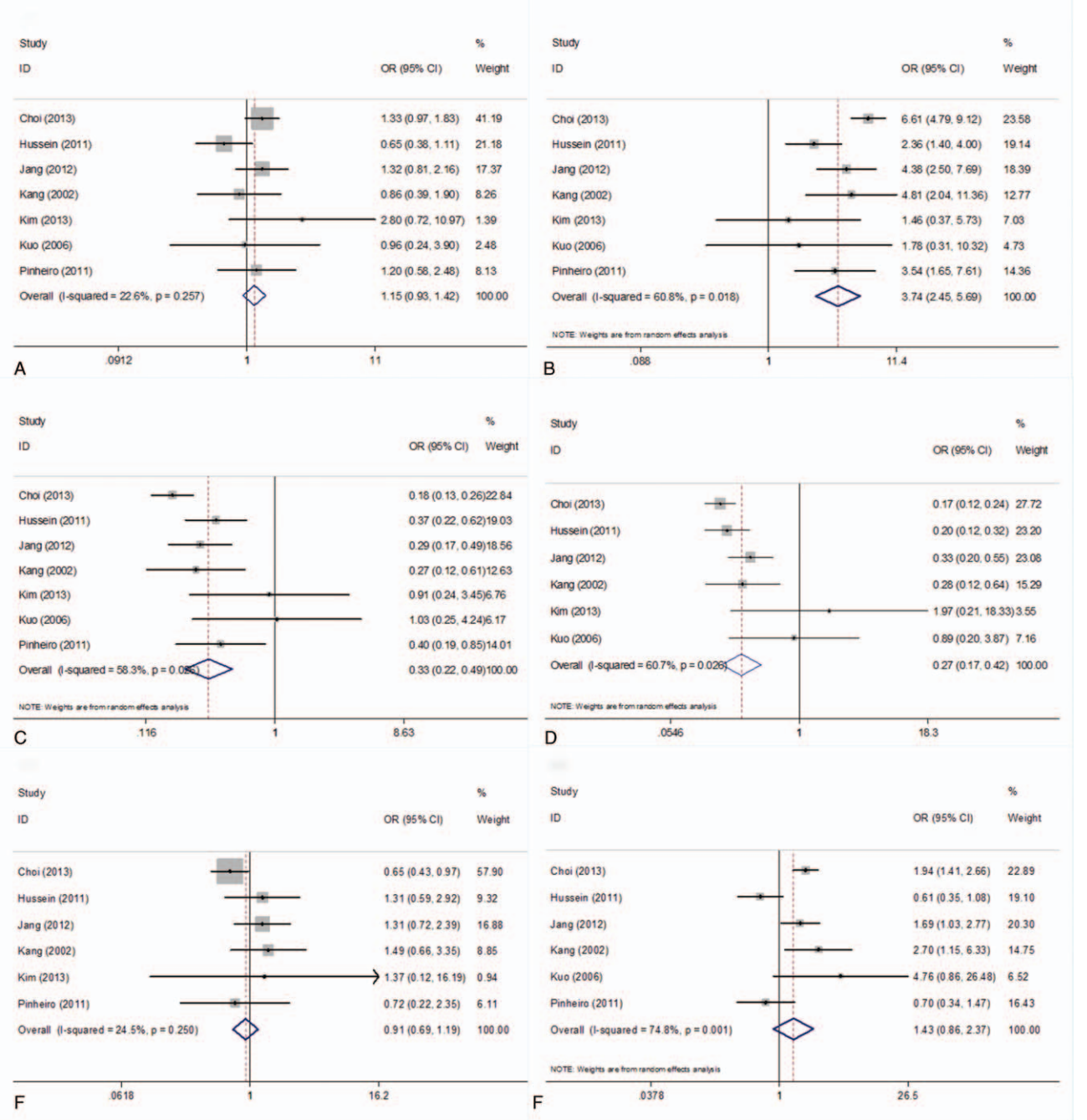

Figure 2. Forrest plot of ORs and 95% CIs for the association of GLUT1 expression with (A) lymph node metastasis, (B) histological grade, (C) PR status, (D) ER status, (E) HER2 status and (F) tumor size in breast cancer patients. CI = confidence interval, = disease-free survival, ER = estrogen receptor, GLUT1 = Glucose transporter 1, HER2 = human epidermal growth factor receptor 2, OR = odds ratio, PR = progesterone receptor.

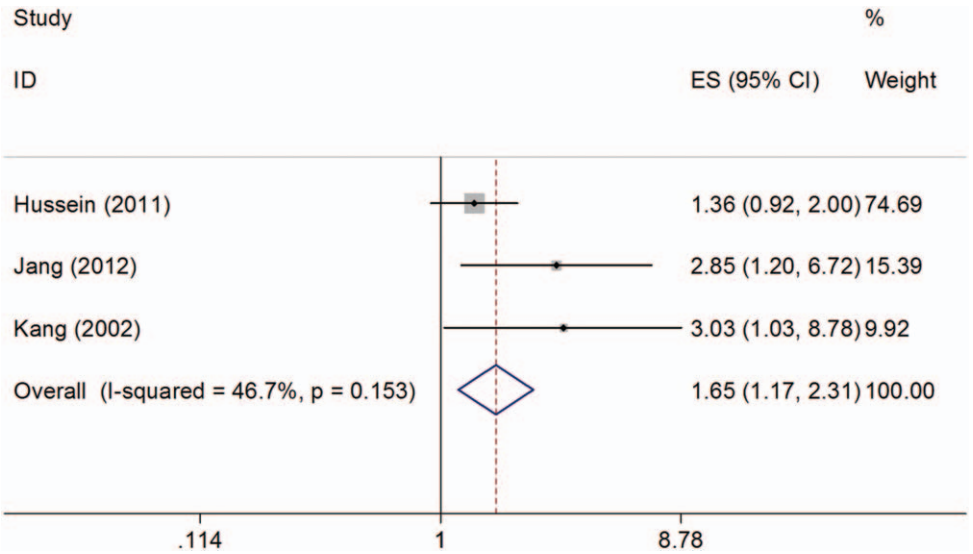

Figure 3. Forrest plot of HR and 95% CI for the association of GLUT1 expression with OS in breast cancer patients. CI = confidence interval, GLUT1 = Glucose transporter 1, HR = hazard ratio, OS = overall survival.

of GLUT1 correlated with poor OS and DFS in solid tumors.[23] Yang and colleagues have reported that GLUT1 is associated with poor DFS in rectal cancer and is also an indicator of aggressive clinical features.[24] In addition, Chen et al reported that the overexpression of GLUT 1 is associated with a poor prognosis in the Asian population [21]. Our results are in line with the results of these previous meta-analyses. Notably, only 4 studies on breast cancer were included in a previous meta-analysis.[23] Our meta-analysis included 15 studies; therefore, it is the most comprehensive study that evaluates the correlation between GLUT1 and breast cancer. Recent studies also indicated that glucose metabolism-related gene GLUT1, and its functional Single Nucleotide Polymorphisms (SNP), might contribute to CRC susceptibility and prognosis in colorectal cancer.[25] Furthermore, Pinheiro's work revealed that GLUT1 overexpression was a promising candidate to predict clinical behavior in pediatric adrenocortical tumors.[26] This study suggests the potential role of GLUT1 in a metabolic remodeling towards a hyperglycolytic phenotype in this malignancy.[26] Therefore, the alteration of tumor metabolism after GLUT1 was up-regulated needs to be further investigated.

There are several limitations of this study. First, most included studies were from Asia, and therefore, the results could be more applicable to Asian patients. Moreover, as only a few studies analyzing the OS and DFS were included, the analysis might be biased.

5. Conclusion

In summary, this meta-analysis indicates that overexpression of GLUT1 is associated with poor prognosis in breast cancer and should be considered as a marker to stratify high-risk patients.

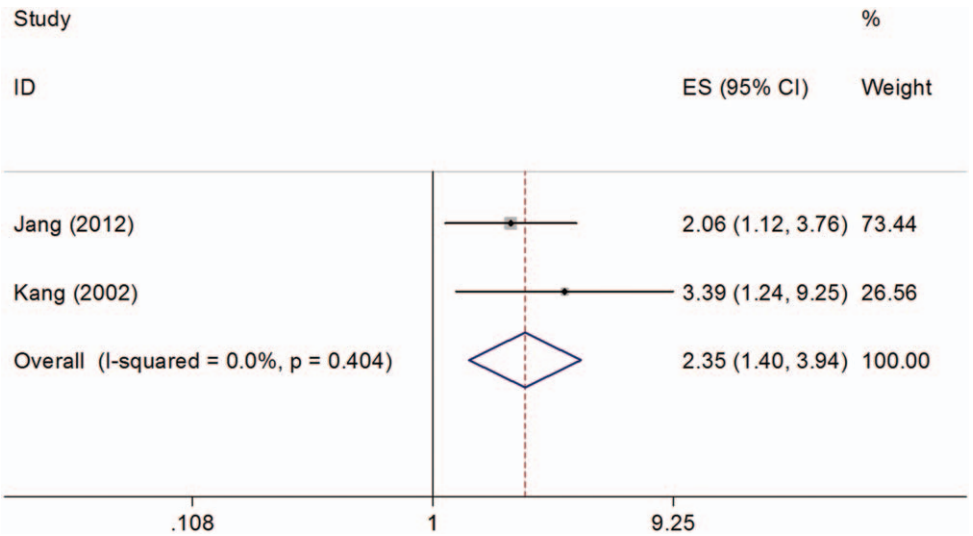

Figure 4. Forrest plot of HR and 95% CI for the association of GLUT1 expression with DFS in breast cancer patients. CI = confidence interval, DFS = disease-free survival, GLUT1 = Glucose transporter 1, HR = hazard ratio.

However, owing to the aforementioned limitations, further large-scale prospective studies on the prognostic value on OS and DFS are needed to verify our results.

Author contributions

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Visualization: Yu Deng, Ting Deng.
Writing – review & editing: Yu Deng, Junying Liu.
Software: Jialing Zou, Weiguo Zhang.
Writing – original draft: Ting Deng.

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