Systematic Review and Meta-Analysis

Medicine

OPEN

Prognostic and clinicopathological significance of long noncoding RNA SNHG in patients with breast cancer

A systematic review and meta-analysis

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Abstract

Background: Small nucleolar RNA host genes (SNHG), a novel long non-coding RNA is involved in cancer cell proliferation, migration, and invasion. Moreover, there are some reports that SNHG is associated with prognosis in cancer patients and may contribute to diagnosis or prognostic prediction of cancer. This study analyzes the association between SNHGs expression and prognosis and clinicopathological factors in breast cancer.

Methods: Eligible studies were searched through the PubMed, Embase, and Cochrane library until February 14, 2024. Pooled hazard ratio (HR) and odds ratio (OR) with 95% confidence interval (CI) were calculated to elucidate the prognostic and clinicopathological significance of SNHG expression in breast cancer.

Results: Nine studies with a total of 2268 breast cancer patients analyzed. The pooled results proved that high expression of SNHG was associated with unfavorable overall survival (OS) in patients with breast cancer (HR 1.39, 95% CI 1.22–1.59, $P < .001$). High expression of SNHG was significantly correlated with advanced clinicopathological factors, including larger tumor size (OR 2.31, 95% CI 1.42–3.76, $P = .001$), lymph node metastasis (OR 4.02, 95% CI 2.46–6.56, $P < .001$) and tumor-node-metastasis stage (OR 3.47, 95% CI 1.70–7.07, $P = .001$).

Conclusion: High expression of SNHG was associated with unfavorable OS and advanced clinicopathological factors, suggesting that SHNG may be serve as a novel prognostic biomarker in patients with breast cancer.

Abbreviations: CI = confidence interval, HR = hazard ratio, LncRNAs = long noncoding RNAs, ncRNA = noncoding RNA, OR = odds ratio, OS = overall survival, SNHG = small nucleolar RNA host genes, TNM = tumor-node-metastasis.

Keywords: cancer, long noncoding RNA, meta-analysis, prognosis, SNHG

1. Introduction

Breast cancer is the most prevalent cancer and the second leading cause of cancer-related deaths in woman, diagnosing for approximately 1.5 million woman every year worldwide.[1] Classically, clinicopathological features including tumor size, histologic subtype and grade, lymph node metastasis, and lympho-vascular invasion are used to predict the prognosis of patients with breast cancer.[2] However, patients with similar clinical conditions may have different prognosis despite receiving the same treatment.[3] Thus, there is an increasing need for biomarkers that can more accurately predict the prognosis of patients.

Long noncoding RNAs (LncRNAs) are a member of regulatory noncoding RNAs (ncRNAs) longer than 200 nucleotides without functional open reading frames and protein-coding ability.[4] LncRNAs are widely demonstrated vital roles in in cancer development, progression, and metastasis.[4,5] Furthermore, some researchers have reported that lncRNAs could be a biomarker for predicting the prognosis in patients with cancer.[6]

Small nucleolar RNA host genes (SNHGs) are a subclass of lncRNAs and are identified to be involved in cancer cell apoptosis and survival, and cancer progression.[7,8] Many researchers have investigated SNHGs in various cancers.[8] In breast cancer

HMK and NH contributed to this article equally.

This work was supported by a research grant from Jeju National University Hospital in 2022.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Koh HM, Han N, Hyun CL. Prognostic and clinicopathological significance of long noncoding RNA SNHG in patients with breast cancer: A systematic review and meta-analysis. Medicine 2025;104:8(e41668).

Received: 16 February 2024 / Received in final form: 17 November 2024 / Accepted: 7 February 2025

http://dx.doi.org/10.1097/MD.0000000000041668

research, the roles of SNHGs, including SNHG1,[9] SNHG3,[10] SNHG5,[11] SNHG6,[12] SNHG11,[13] SNHG12,[14,15] SNHG15,[16] ang SNHG17,[17] is becoming increasing apparent.[7] Moreover, several SNHGs are identified not only related to the prognosis of breast cancer but also to the progression or inhibition of breast cancer.[18]

Nevertheless, the role of SNHGs as a prognostic factor in breast cancer patients presented in individual studies has not been integrated. In this study, we systematically evaluate the prognostic and clinicopathological significance of SNHGs in breast cancer.

2. Materials and methods

2.1. Literature search

Eligible studies were searched through the PubMed, Embase, and Cochrane library until February 14, 2024 using the following terms: (LncRNA SNHG or long noncoding RNA small nucleolar RNA host gene) and (breast cancer or breast carcinoma) and (prognosis or survival or outcome). Manual search was also performed. This study was based on previously published reports; therefore, ethical approval and informed consent were not required.

2.2. Inclusion and exclusion criteria

The studies that met the following conditions were included: studies investigating the association between SNHG expression and survival, and SNHG expression evaluating in human cancer tissue. Reviews, conference abstracts, non-English articles, and duplicate articles were excluded.

2.3. Data extraction and quality assessment

The required data were collected by 2 authors individually from the included studies. The collected data were as follows: first author, publication year, country, SNHG type, case number, detection method and cutoff value of SNHG expression, follow-up period, survival outcome, and clinicopathological factors. Hazard ratio (HR) and 95% confidence interval (CI) were calculated from Kaplan–Meier plots.

The quality assessment of the included studies was done using Newcastle–Ottawa Scale by 2 authors individually.

2.4. Statistical analysis

Pooled HR or odds ratio (OR) with CIs was calculated using StataSE12 (Stata, College Station). I^2 statistics was used assessing the heterogeneity of the included studies. If the heterogeneity was 50% or more or the P value was <.05, a random model was used, otherwise a fixed model was used. Funnel plot, trim and filled method and Egger's test were performed for checking the publication bias. Sensitivity analysis was done for exploring the robustness of pooled HR. P value < .05 was regarded significant.

3. Results

3.1. Study characteristics

A total 63 studies were reviewed through database searches. Among the studies, 9 studies were selected. The selection process is shown in Figure 1. The characteristics of the included studies are summarized in Table 1. All studies were published in China, and the publication years ranged from 2017 to 2021. A total of 2268 patients with breast cancer were included with case number ranging from 42 to 1764.

3.2. Association between SNHG expression and overall survival in breast cancer

Five studies with a total of 1996 patients with breast cancer evaluated the association between SNHG expression and overall survival (OS). The heterogeneity (I^2 = 0.0%, P = .784) between the included studies was very low that pooled HR was calculated using fixed effects model. The results indicated that high expression of SNHG was associated with unfavorable OS (HR 1.39, 95% CI 1.22–1.59, P < .001; Fig. 2).

3.3. Association between SNHG expression and clinicopathological factors in breast cancer

High expression of SNHG was significantly correlated with larger tumor size (OR 2.31, 95% CI 1.42–3.76, P = .001), lymph node metastasis (OR 4.02, 95% CI 2.46–6.56, P < .001) and tumor-node-metastasis (TNM) stage (OR 3.47, 95% CI 1.70–7.07, P = .001; Table 2, Fig. 3A–C).

3.4. Publication bias

Funnel plot was conducted for checking the publication bias. Egger's test did not demonstrate small-study effects although the funnel plot was slightly asymmetric (P = .053, Fig. 4A). Trim and fill plot was also performed. The pooled HR was significant (HR 1.37, 95% CI 1.20–1.56, P < .001), proving that the pooled results were consistent (Fig. 4B).

3.5. Sensitivity analysis

Sensitivity analysis was implemented for investigating the single-study effects. Pooled HR with 95% CI was the same, which suggested that the pooled results were very significant (HR 1.39, 95% CI 1.22–1.59; Fig. 5).

4. Discussion

NcRNA refers to a member of RNA without coding for protein expression, which can act to control the behavior of cancer by suppressing mRNA transcription and protein function.[19] NcRNA is divided into lncRNA and small ncRNA depending on whether the length is longer than 200 nucleotides or shorter.[19]

LncRNAs are involved in several stages of gene expression, such as transcription, post-transcription, translation, and epigenetic modification.[19] Increasing studies have reported that dysfunction or abnormal expression of lncRNAs is associated with multiple diseases, including cancer.[19,20] LncRNAs may contribute to the cancer pathophysiology and can act as tumor suppressor genes or oncogenes.[20]

SNHGs, a subclass of lncRNA, are identified as a key regulator in cancer development and progression of various cancers.[21] Currently. A sum of 22 members of SNHGs have been identified.[22] Many recent studies have reported that SNHGs were significantly overexpressed in breast cancer tissue or cell lines.[23] Moreover, studies have shown that the upregulation or low expression of SNHGs can be used as prognostic or diagnostic biomarker in breast cancer.[9] The present study systematically investigated lncRNA SNHGs as a prognostic and clinicopathological biomarker.

In this meta-analysis, a total 9 studies with 2268 patients were evaluated. Our results revealed that high expression of SNHG was significantly associated with poor OS and may serve as a prognostic biomarker in patients with breast cancer. Moreover, sensitivity analysis demonstrated that our results were very robust, showing the little impact of individual studies. Furthermore, we assessed the association between SNHG expression and several clinicopathological factors, including tumor size, lymph node metastasis and TNM stage. The pooled

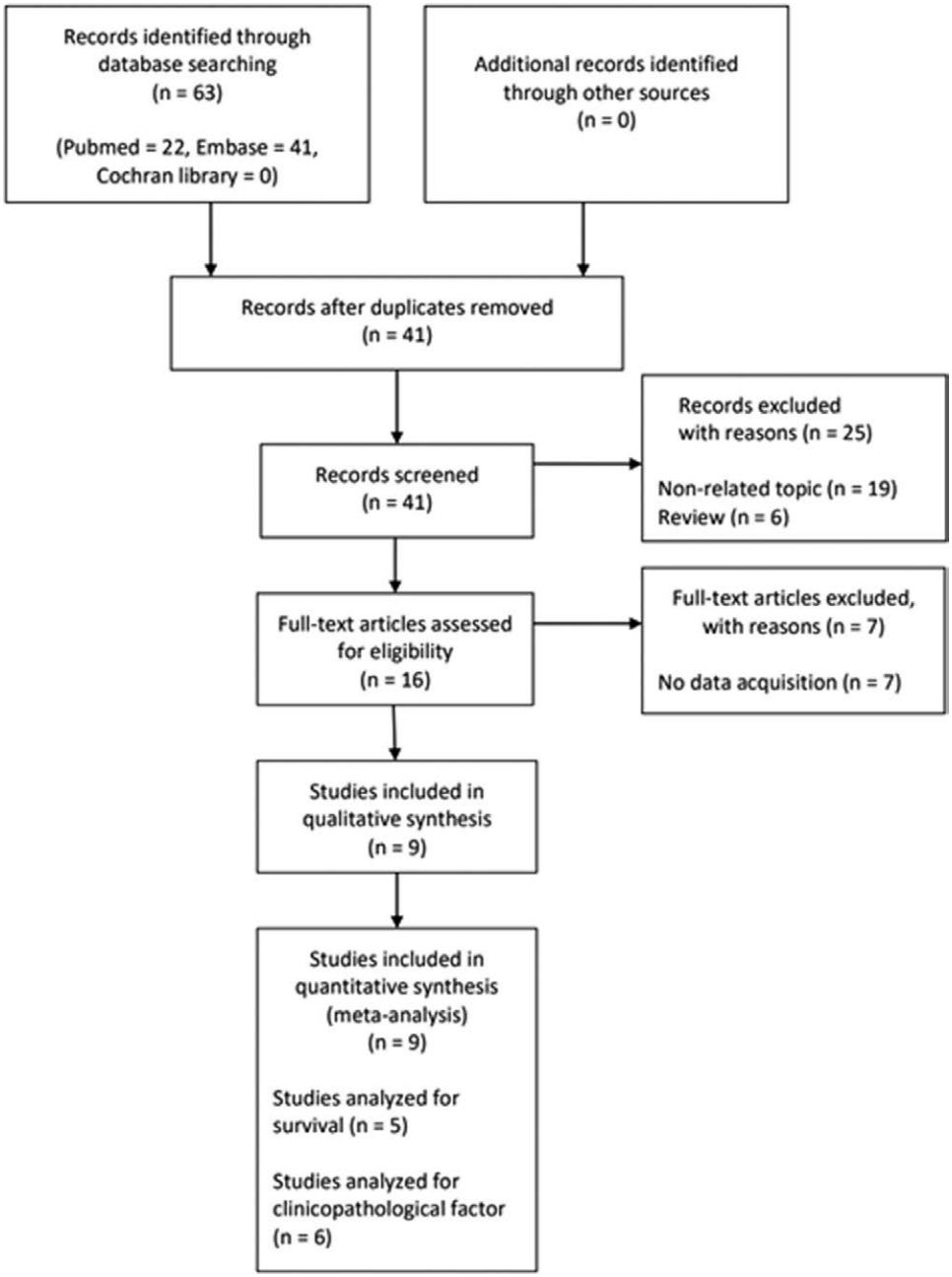

Figure 1. Flow diagram of the study selection.

Table 1

Characteristics of studies included in this meta-analysis.

Study	Country	SNHG type	Case number (high/low)	Stage (case number)	Detection method	Cutoff value	Follow-up (mo)	Survival outcome	Survival analysis	NOS
Yu et al[13]	China	SNHG 11	42 (21/21)	NA	RT-PCR	NR	120	OS	KM	7
Du et al[17]	China	SNHG 17	58 (32/26)	I–II/III–IV (44/14)	RT-PCR	Median	60	OS	KM	7
Mi et al[16]	China	SNHG 15	42 (21/21)	NA	RT-PCR	NR	60	OS	KM	7
Yuan et al[14]	China	SNHG 12	90 (46/44)	I–II/III–IV (30/60)	RT-PCR	NR	60	OS	KM	7
Xiong et al[9]	China	SNHG 1	50 (25/25)	I–II/III–IV (18/32)	RT-PCR	NR	NR	NR	NR	–
Chi et al[11]	China	SNHG 5	1764 (649/1115)	NA	RT-PCR	NR	300	OS	KM	7
Ma et al[10]	China	SNHG 3	60 (37/23)	I/II–III (29/31)	RT-PCR	NR	NR	NR	NR	–
Lv et al[12]	China	SNHG 6	60 (33/27)	I-II/III-IV (35/25)	RT-PCR	Median	NR	NR	NR	–
Wang et al[15]	China	SNHG 12	102 (51/51)	I–II/III–IV (71/31)	RT-PCR	Median	NR	NR	NR	–

KM = Kaplan–Meier, NOS = Newcastle–Ottawa Scale, NR = no report, OS = overall survival, RT-PCR = reverse transcription PCR, SNHG = small nucleolar RNA host gene.

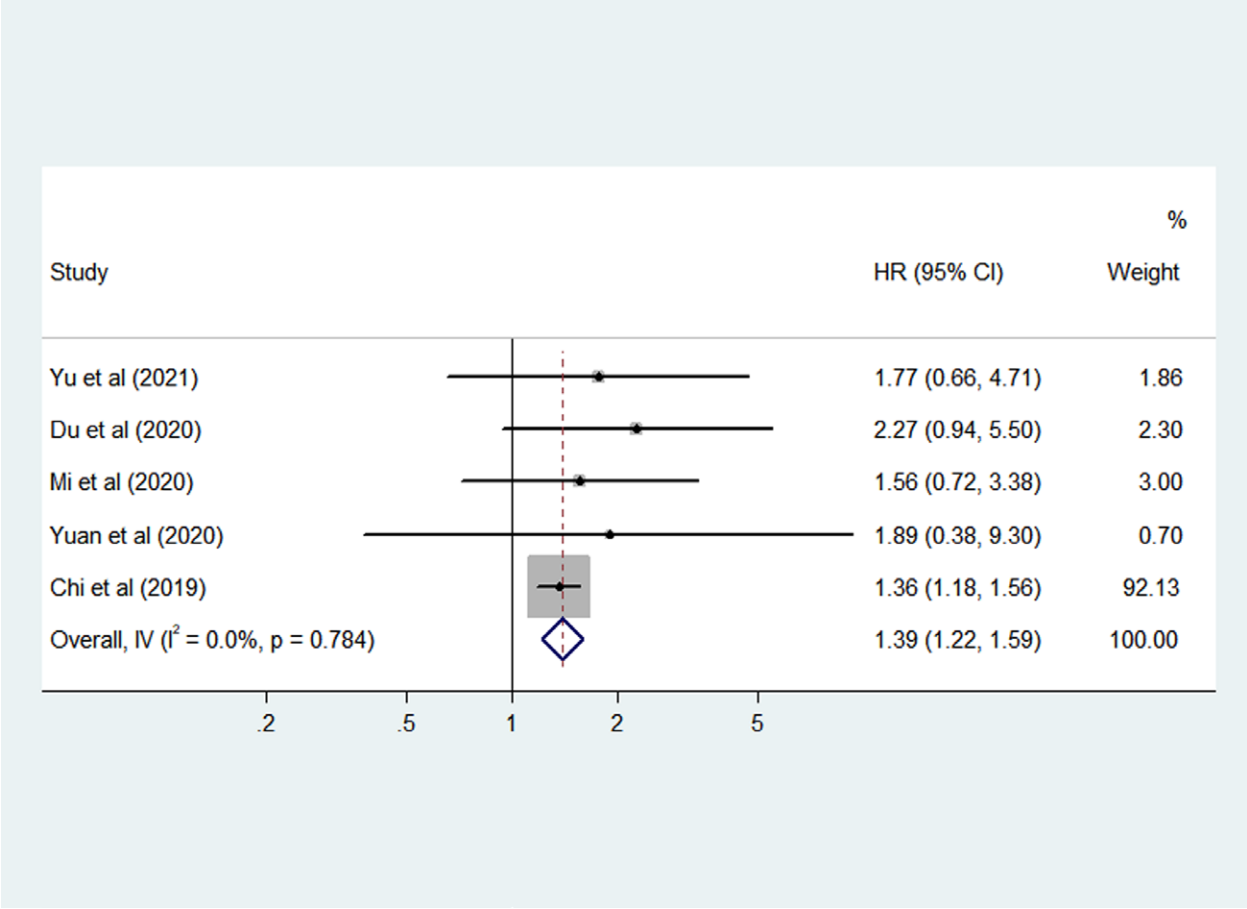

Figure 2. Forest plot of the association between SNHG expression and overall survival in breast cancer. SNHG = small nucleolar RNA host genes.

Table 2

Association between SNHG expression and clinicopathological factors in patients with breast cancer.

Characteristic	Number of studies	Number of patients	Pooled OR (95% CI)	*P* value	Heterogeneity		
					I^2 (%)	*P* value	Model
Age (old vs young)	6	420	1.17 (0.77–1.77)	.457	0.0	.799	Fixed
Tumor size (large vs small)	4	310	2.31 (1.42–3.76)	.001	0.0	.560	Fixed
Tumor grade (high vs low)	2	162	2.00 (0.66–6.09)	.222	61.5	.107	Random
Lymph node metastasis (present vs absent)	5	360	4.02 (2.46–6.56)	<.001	42.8	.136	Fixed
Distant metastasis (present vs absent)	3	252	2.03 (0.95–4.32)	.123	25.9	.259	Fixed
TNM stage (high vs low)	6	420	3.47 (1.70–7.07)	.001	55.9	.045	Random

CI = confidence interval, OR = odds ratio, SNHG = small nucleolar RNA host gene, TNM = tumor-node-metastasis.

results suggested that high expression of SNHG is related to advanced clinicopathological factors.

Mechanically, SNHG is mainly associated with miR regulatory axis and multiple signaling pathway and is reported to play a role as an oncogene in breast cancer.[22] Some researchers showed that high expression of SNHG is associated with unfavorable survival and advanced clinicopathological factors including TNM stage in patients with breast cancer.[22] In previous studies, Yu et al[13] reported that SNHG11 was overexpressed in triple-negative breast cancer tissue and cell lines and activated cancer cell proliferation and migration. Mi et al demonstrated that SNHG15 knockdown overcame the resistance of cisplatin in breast cancer by sponging miR-381 and Xiong et al revealed that SNHG1 acts as a valuable oncogene in breast cancer via SNHG/miR-573/LMO axis, indicating a novel therapeutic target for breast cancer.[9,16] Du et al[17] showed that overexpressed SNHG17 was observed in breast cancer tissue and cell lines and was related to unfavorable prognosis, and also demonstrated that SNHG17 could control breast cancer progression by sponging miR-124-3p. Yuan et al, Lv et al, Chi et al, Ma et al, and Wang et al exhibited that upregulation of SNHG enhances cancer cell proliferation, migration, and invasion via sponging miR regulatory axis in breast cancer.[10–12,14,15]

5. Limitations

There are several limitations in this study. First, since all of the studies included in the analysis were conducted in China, it remains questionable whether it can be a meta-analysis representing the world. Second, because there are SNHG types not

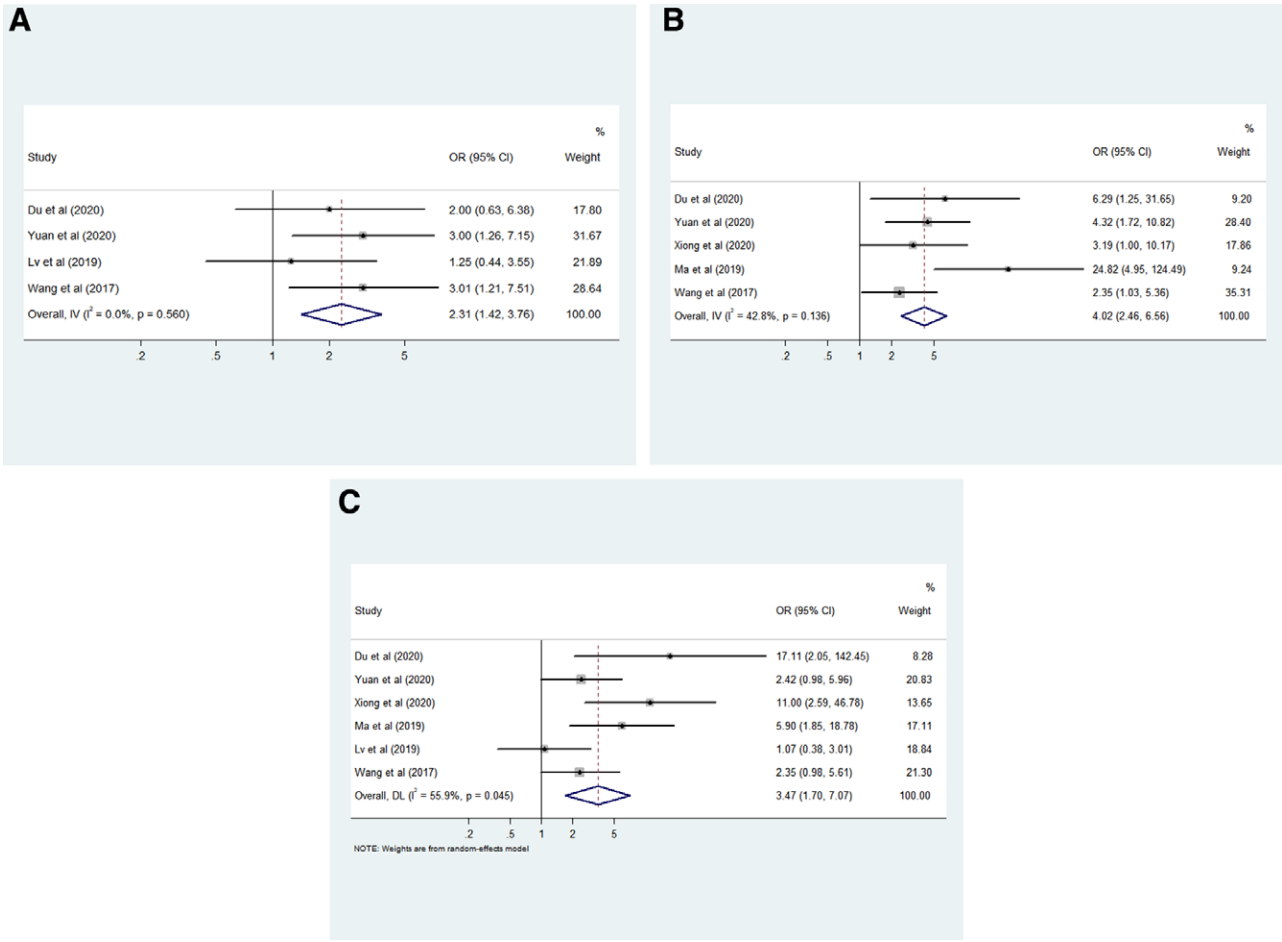

Figure 3. Forest plot of the association between SNHG expression and clinicopathological factors in breast cancer. (A) Tumor size, (B) lymph node metastasis, (C) TNM stage. SNHG = small nucleolar RNA host genes, TNM = tumor-node-metastasis.

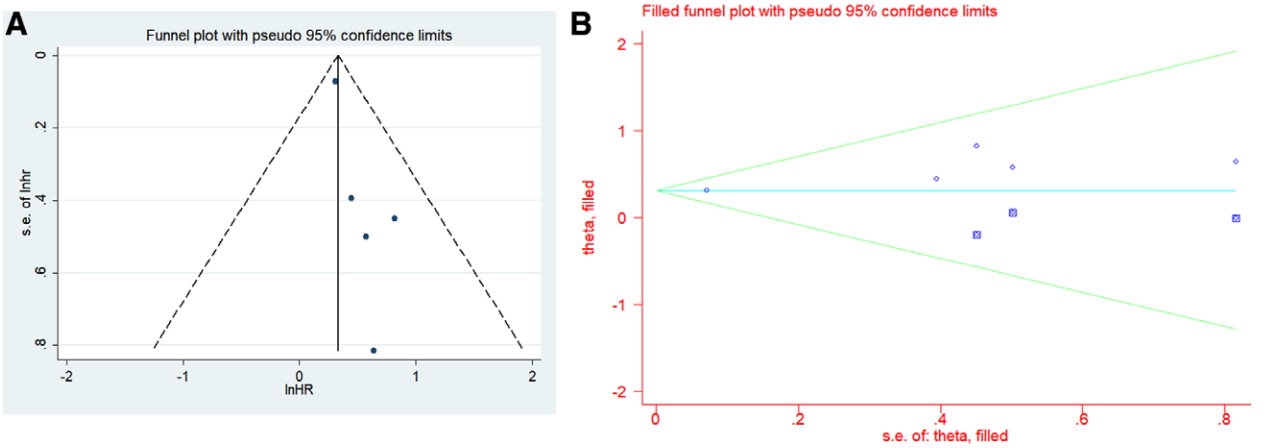

Figure 4. Funnel plot (A) and trim and fill method (B).

included in this analysis, our results may not fully represent the effects of SNHG on breast cancer. Third, since HR with CI was obtained through the survival curve presented in the literature, there may be some numerical inaccuracies.

6. Conclusion

The present study firstly investigated that the prognostic and clinicopathological significance of SNHG expression in patients with breast cancer. High expression of SNHG was correlated with unfavorable OS, as well as larger tumor size, lymph node metastasis, and higher TNM stage in patients with breast cancer. Therefore, SNHG expression may be a biomarker for predicting the prognosis of breast cancer patients.

Acknowledgments

This work was supported by a research grant from Jeju National University Hospital in 2022.

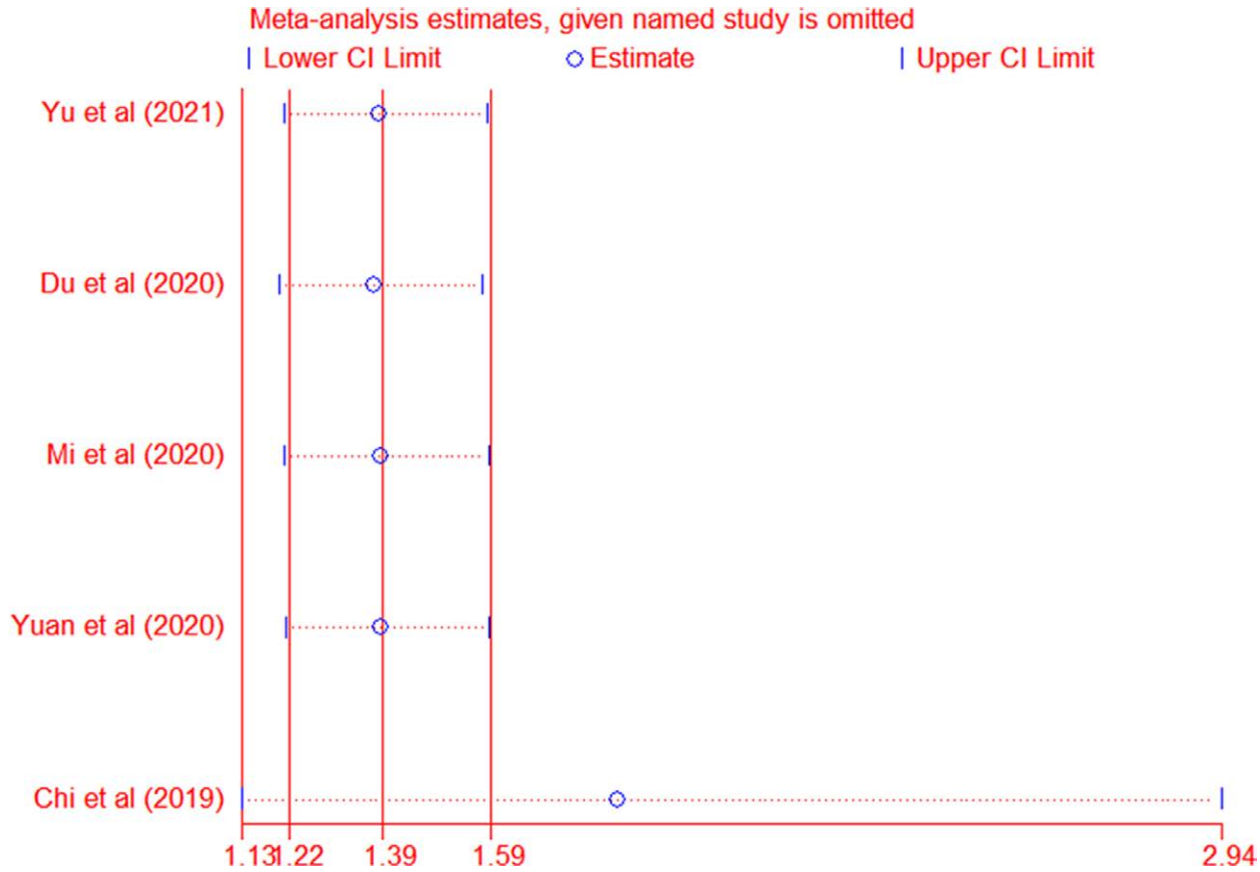

Figure 5. Sensitivity analysis.

Author contributions

Conceptualization: Hyun Min Koh, Nayoung Han, Chang Lim Hyun.
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Supervision: Hyun Min Koh.
Validation: Hyun Min Koh, Nayoung Han.
Writing – original draft: Hyun Min Koh, Nayoung Han.

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