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Prognostic value of cyclin B1 and cyclin B2 expression in breast cancer

A systematic review and updated meta-analysis

Jeongwan Kang, MD[a], Hera Jung, MD[a], Hyunchul Kim, MD[a,*]

Abstract

Background: Cyclin B1 and cyclin B2 are key regulators of cell cycle progression and have been implicated in the prognostic significance of various cancers. This meta-analysis aimed to evaluate the prognostic value of cyclin B1 and B2 expression in breast cancer.

Methods: A comprehensive literature search was conducted on Pubmed, Embase, MEDLINE, Web of Science, and Cochrane library. Studies with survival data and clinicopathological parameters associated with cyclin B1 and B2 or CCNB1 and CCNB2 genes were included. Survival data and clinicopathological parameters associated with cyclin B1 and B2 expression were extracted. Pooled hazard ratios and odds ratios with 95% confidence intervals were calculated. Subgroup analysis was conducted to assess heterogeneity. Publication bias was evaluated.

Results: A total of 23 studies were included in the analysis. High expression of cyclin B1 was significantly associated with worse overall survival (hazard ratio [HR] = 1.69, $P < .01$), disease-specific survival (HR = 1.71, $P < .01$), and disease-free survival (HR = 2.01, $P = .01$). High expression of cyclin B2 was associated with worse disease-specific survival (HR = 2.46, $P = .02$). Clinicopathological parameters did not show significant associations with cyclin B1 and B2 expressions. When data on cyclin B1 and B2 were combined, a significant age-related difference was found (odds ratio = 0.62, $P = .04$).

Conclusions: This meta-analysis provides evidence supporting the prognostic significance of cyclin B1 and B2 expression in breast cancer. High expression of cyclin B1 and B2 is associated with worse survival, indicating their potential as prognostic markers in breast cancer.

Abbreviations: DFS = disease free survival, DSS = disease specific survival, HR = hazard ratio, NOS = Newcastle-Ottawa scale, OR = odds ratio, OS = overall survival.

Keywords: biomarker, breast cancer, cyclin B1, cyclin B2, prognosis

1. Introduction

Breast cancer is the most prevalent female cancer in the United States with approximately 280,000 new cases and over 40,000 deaths a year.[1] Continuous efforts are being made to develop new treatment methods to improve the survival rates of breast cancer patients.[2] Biomarkers are being studied for prognostic and predictive applications in breast cancer patients.[3]

Cyclin B1, and B2 proteins, along with their coding genes CCNB1, and CCNB2 are among such prognostic biomarkers for breast cancer.[4] Cyclin B1 and B2 are members of the cyclin family and play important roles in controlling the cell cycle by interacting with other cell cycle-regulating molecules.[5,6] They form complexes with CDK1 to promote mitosis, particularly playing significant roles in G2/M transition.[7,8] The expression of cyclin B1 and B2 has been associated with the prognosis and clinicopathological parameters of breast cancer.[4] However, conflicting results have been reported in different studies.[9–19] A meta-analysis conducted in 2017 found significant associations between high expression of cyclin B1 and B2 proteins and worse prognosis and several clinicopathological parameters.[4] Since then, contradictory reports have emerged.[20–30] Therefore, we performed an updated meta-analysis using recent protein and mRNA data, different analysis methods, and strict study selection criteria to evaluate cyclin B1 and B2 separately.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study is a meta-analysis that does not involve ethical norms and there is no need for ethical approval.

[a]Department of Pathology, CHA Ilsan Medical Center, Goyang-si, Gyeonggi-do, Republic of Korea.

** Correspondence: Hyunchul Kim, Department of Pathology, CHA Ilsan Medical Center, 1205 Jungang-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do 10414, Republic of Korea (e-mail: hyunchulk@chamc.co.kr).*

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2. Methods

2.1. Study design and literature search

A literature search was performed on Pubmed, Embase, Web of Science, MEDLINE, and Cochrane library on December 5th, 2022. The following combination of keywords was used for the search: (cyclin B1 OR CCNB1 OR cyclin B2 OR CCNB2) AND (breast cancer). Additionally, studies from the reference list of the previous study were manually searched.[4] Two authors (H.J. and H.K.) reviewed the search results independently. This study was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[31]

2.2. Literature selection

Studies evaluating associations between prognosis or clinicopathological parameters and expression of CCNB1, and CCNB2 genes or their protein products, cyclin B1 and cyclin B2 were selected. Studies with Kaplan–Meier curves with or without hazard ratios (HRs) were selected for prognostic information. The following exclusion criteria were applied: (1) obviously irrelevant articles. (2) Review articles, case studies, letters, or errata. (3) Non-English articles. (4) Cell line experiments, and animal studies. (5) Article with insufficient or irrelevant data. (6) Newcastle-Ottawa scale (NOS) 5 or less. Only the most informative article was selected when multiple articles used the overlapping patient population.

Two authors (H.J. and H.K.) applied NOS for to assess the quality of the studies included in the analysis. Any disagreements were resolved through discussion.

2.3. Extraction of data

Two authors (H.J. and H.K.) independently extracted the following information: authors, year of publication, target molecule, survival data of Kaplan–Meier curve (type of survival data—overall survival [OS], disease-free survival [DFS], and disease-specific survival [DSS]; HRs, standard error, *P*-value, and the number of patients of control and experimental groups), and clinicopathological parameters (age, tumor stage, tumor size, tumor grade, lymph node status, tumor histology, and estrogen receptor status).

When specific data from the Kaplan–Meier curve were not presented, HRs were calculated using data extracted with the Engauge Digitizer software, version 12.1, following the method by Irvine et al.[32] When HR and confidence interval with a *P*-value was given, the standard error was calculated.[11] Any disagreements were resolved through discussion.

2.4. Statistical analysis

Statistical analyses were performed with R, version 4.3.0, and the "meta" package, version 6.2.1.[33,34] The odd ratios (ORs) with 95% confidence were pooled to estimate the association between cyclin B1 (CCNB1), and cyclin B2 (CCNB2) and clinicopathological parameters. The HRs with standard errors were pooled to estimate the prognostic significance of cyclin B1 (CCNB1), and cyclin B2 (CCNB2) expression. The random effect model was applied for this analysis. Subgroup analysis was conducted for pooled estimate with high heterogeneity. Egger test, Begg test, and funnel plot for HRs were performed in analysis with more than 7 studies to detect publication bias. A *P* values <.05 were considered statistically significant.

3. Results

3.1. Characteristics of the included studies

The literature selection process is shown in Figure 1. Out of the 3366 initially retrieved studies, 1610 duplicate articles were removed. One thousand six hundred eighty-one obviously irrelevant articles were removed from the remaining 1756 studies. The full-text review was conducted for 75 articles, then 58 studies were removed (45 contained irrelevant data, 9 were cell line or animal experimental studies, 3 articles used overlapping populations, and 1 was a review article.) A total of 17 studies (11 studies from the search,[20–30] and 6 studies which were included in the previous meta-analysis[10,12,13,15,18,19]) were used for this meta-analysis.

The previous meta-analysis included 10 articles, but 4 studies had to be removed. (Two studies did not specify the target molecule in detail; they only described the target molecule as cyclin B.[14,17] One article did not specify the number of patients in Kaplan–Meier curve.[9] And 1 article was non-English.[16])

Table 1 shows a summary of the studies included in this meta-analysis. 13 studies reported on cyclin B1 (CCNB1) expression, while 4 studies reported on cyclin B2 (CCNB2). The study populations were from Argentina, Korea, China, Japan, Sweden, and Croatia. Protein expression was reported in 11 studies using the immunohistochemistry method. mRNA expression was analyzed in 7 studies. For survival data, 9 studies reported OS, 9 reported DFS, and 6 reported DSS. Clinicopathological parameters from 6 studies could be used for this study. NOSs of the studies were 7 or higher.

3.2. Prognostic significance of cyclin B1, and B2 expression

OS, DFS, and DSS were combined for cyclin B1 expression, and DSS for cyclin B2. There were significant associations between worse OS (HR = 1.69, 95% CI = 1.35–2.12, $P < .01$) with no significant heterogeneity ($I^2 = 23\%$, $P = .25$) (Fig. 2A), DSS (HR = 1.71, 95% CI = 1.37–2.13, $P < .01$) with no significant heterogeneity ($I^2 = 0\%$, $P = .82$) (Fig. 2B), and DFS (HR = 2.01, 95% CI = 1.18–3.42, $P = .01$) with significant heterogeneity ($I^2 = 73\%$, $P < .01$) (Fig. 2C) and high cyclin B1 (CCNB1) expression.

The combined DSS showed similar significant association with high cyclin B2 (CCNB2) expression (HR = 1.81, 95% CI = 1.22–2.68, $P < .01$) with significant heterogeneity ($I^2 = 88\%$, $P < .01$) (Fig. 2D).

The overall results of the analysis of prognostic data are summarized in Table 2.

Correlation between cyclin B1, and B2 expression and clinicopathological parameters.

The combined ORs in association with clinicopathological parameters did not show statistically significant results in any of them.

There was no significant association between cyclin B1 expression and age (Fig. 3) (2 studies with 148 patients, OR = 0.61, 95% CI = 0.31–1.12, $P = .15$), tumor stage (2 studies with 245 patients, OR = 0.78, 95% CI = 0.29–2.12, $P = .63$), tumor grade (4 studies with 374 patients, OR = 1.29, 95% CI = 0.42–3.97, $P = .67$), tumor histology (2 studies with 148 patients, OR = 0.68, 95% CI = 0.24–1.91, $P = .47$), and estrogen receptor status (2 studies with 146 patients, OR = 1.12, 95% CI = 0.52–2.43, $P = .78$).

There was no significant association between cyclin B2 expression and age (Fig. 4) (2 studies with 186 patients, OR = 0.64, 95% CI = 0.34–1.20, $P = .16$), tumor size (2 studies with 186 patients, OR = 1.81, 95% CI = 0.73–4.45, $P = .19$), tumor grade (2 studies with 186 patients, OR = 0.74, 95% CI = 0.39–1.41, $P = .36$), lymph node status (2 studies with 186 patients, OR = 0.71, 95% CI = 0.38–1.33, $P = .29$).

To compare the result of the previously reported meta-analysis, we also used a similar approach by analyzing clinicopathological data of cyclin B1 and B2 together. The available data from the studies we selected were age and tumor grade. There was a statistically significant association between younger

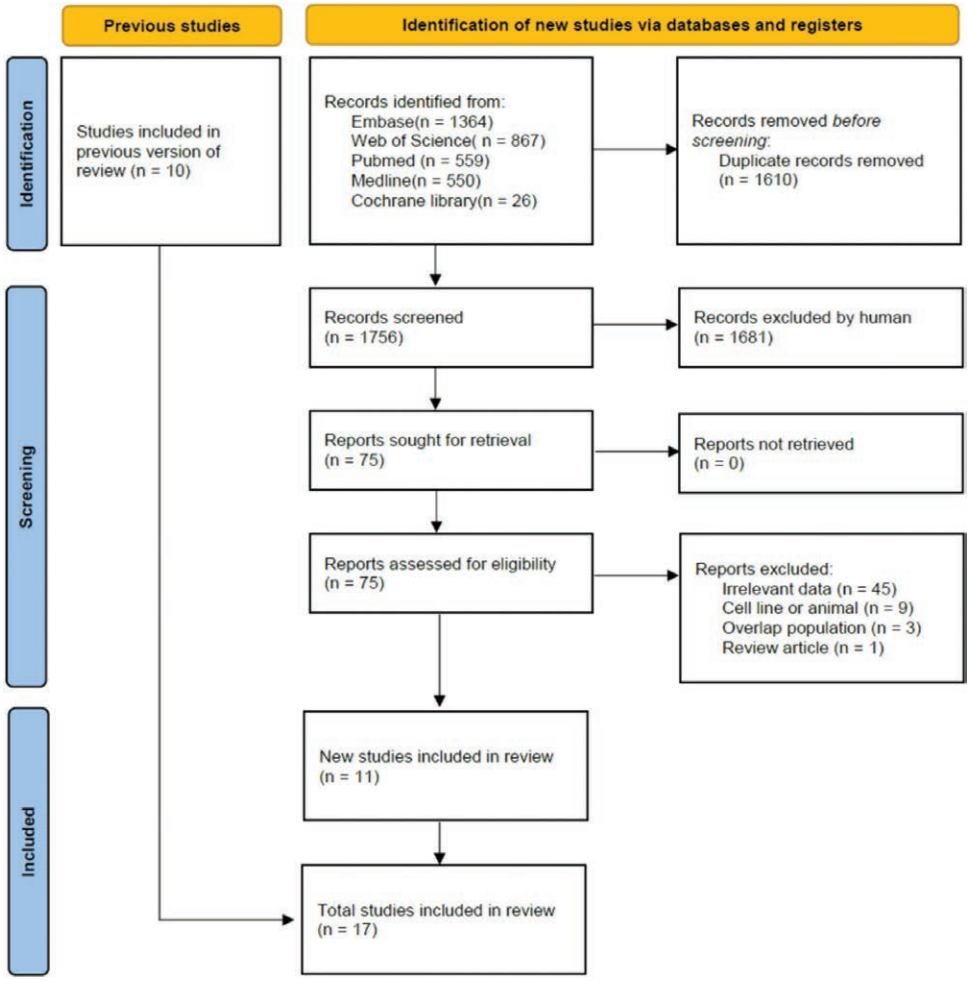

Figure 1. Flow diagram of literature selection.

Table 1

Characteristics of studies included in this meta-analysis.

Studies	Country	Target molecule	Sample type	Number of patients	Clinicopathological parameter
2004 Peters	Argentina	Cyclin B1	Protein	56	Age, grade, stage, tumor size, lymph node, histology, ER
2007 Suzuki	Japan	Cyclin B1	Protein	109	N/A
2010 Koliadi	Sweden	Cyclin B1	Protein	41	Grade, tumor size
2011 Chae	Korea	Cyclin B1	Protein	98	Age, grade, tumor size, lymph node, histology, ER
2013 Klintman	Sweden	Cyclin B1	Protein	222	N/A
2013 Nilsson	Sweden	Cyclin B1	Protein	197	N/A
2013 Plavetic	Croatia	Cyclin B1	Protein	215	N/A
2013 Shubbar	Sweden	Cyclin B2	Protein	80	Age, grade, tumor size, lymph node
2017 Fredholm	Sweden	Cyclin B1	Protein	887	N/A
2021 Wu	China	Cyclin B2	mRNA	114	Age, grade, tumor size, lymph node
2022 Aljohani Metabric	N/A	Cyclin B1	mRNA	1980	N/A
2022 Aljohani TCGA	N/A	Cyclin B1	mRNA	854	N/A
2022 Aljohani Metabric	N/A	Cyclin B2	mRNA	1508	N/A
2022 Aljohani TCGA	N/A	Cyclin B2	mRNA	853	N/A
2022 Aljohani Nottingham	UK	Cyclin B2	Protein	2759	N/A
2022 Wang	China	Cyclin B1	Protein	195	Grade, stage
2014 Ding GSE47561	N/A	Cyclin B1	mRNA	125	N/A
2014 Ding GSE2845	N/A	Cyclin B1	mRNA	226	N/A
2018 Li KMplotter without TNBC	N/A	Cyclin B1	mRNA	1402	N/A
2019 Jin KMplotter	N/A	Cyclin B2	mRNA	5143	N/A
2019 Liu KMplotter	N/A	Cyclin B1	mRNA	5143	N/A

N/A: not available.

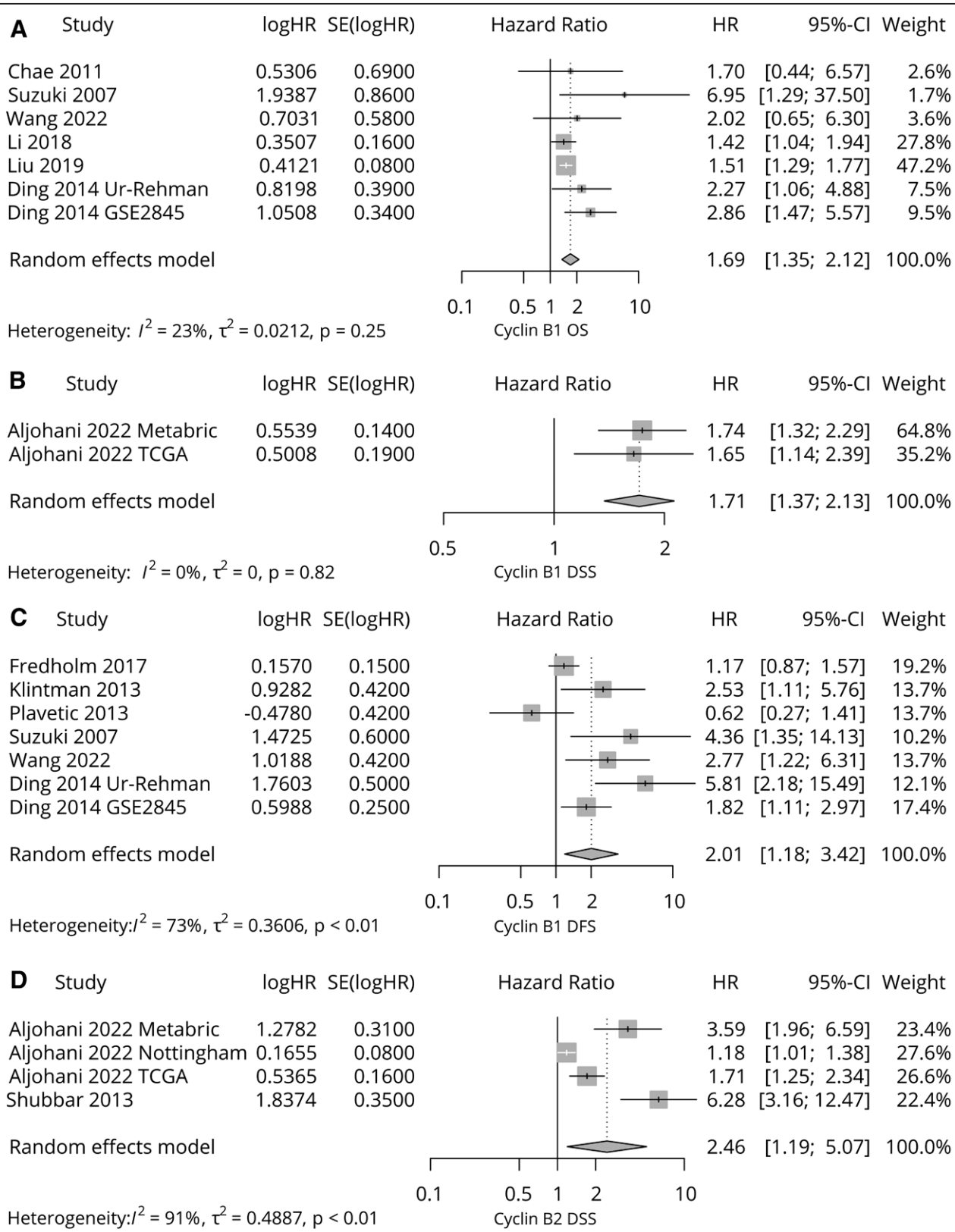

Figure 2. Forrest plots of HRs of survival data. (A) OS of cyclin B1, (B) DSS of cyclin B1, (C) DFS of cyclin B1, and (D) DSS of cyclin B2. DFS = disease free survival, DSS = disease specific survival, OS = overall survival.

Table 2

The summary of prognostic data meta-analysis.

Target molecule	Survival type	Number of Studies	Hazard ratio	Confidence interval	*P* value of HR	I^2	*P* value of I^2
Cyclin B1	OS	7	1.69	1.35–2.12	<.01	23%	.25
	DSS	2	1.71	1.37–2.13	<.01	0%	.82
	DFS	7	2.01	1.18–3.42	.01	73%	<.01
Cyclin B2	DSS	4	2.46	1.19–5.07	.02	91%	<.01

DFS = disease free survival, DSS = disease specific survival, OS = overall survival.

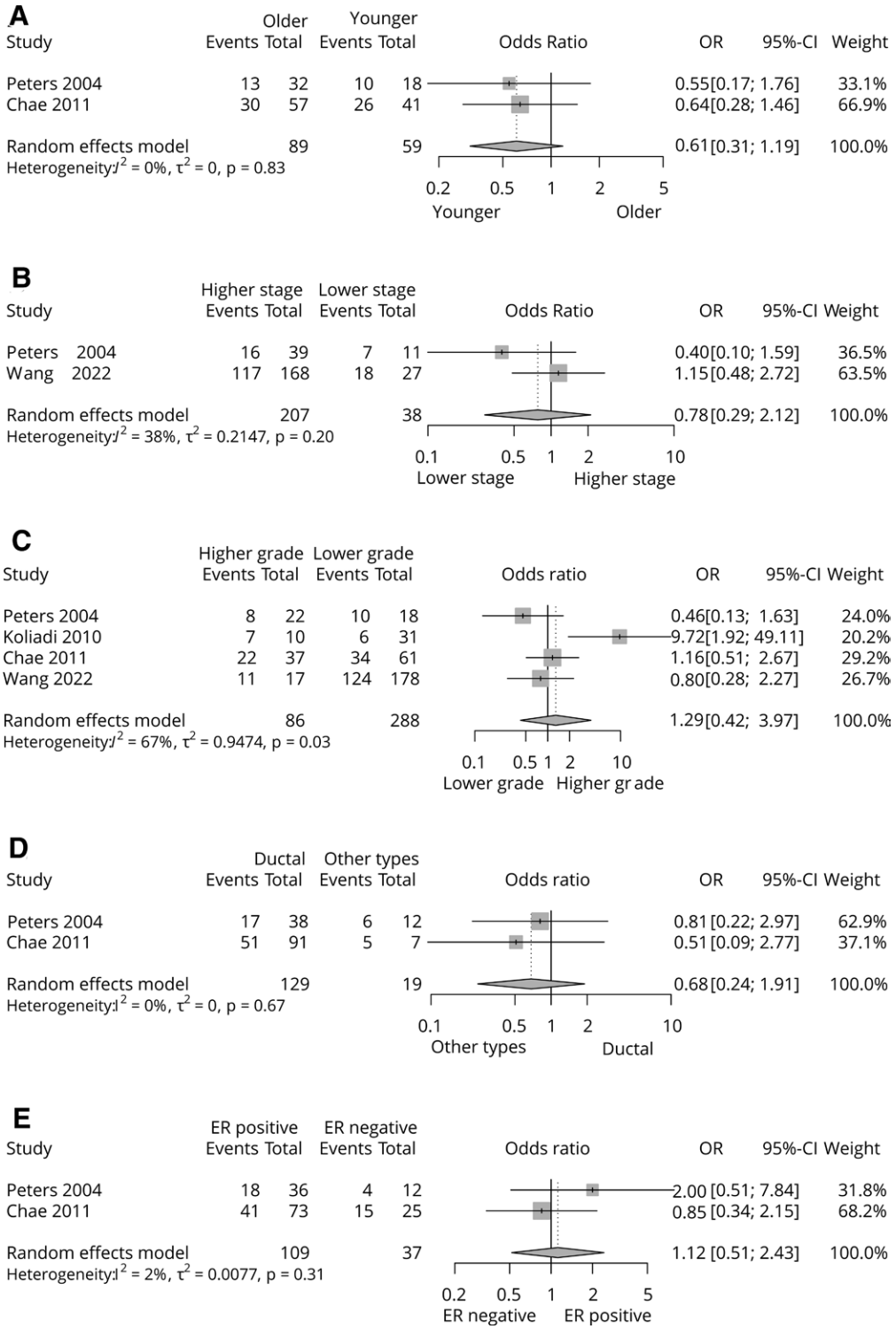

Figure 3. Forest plots of clinicopathological parameters associated with cyclin B1 expression. (A) age, (B) stage, (C) tumor grade, (D) tumor types, and (E) estrogen receptor status.

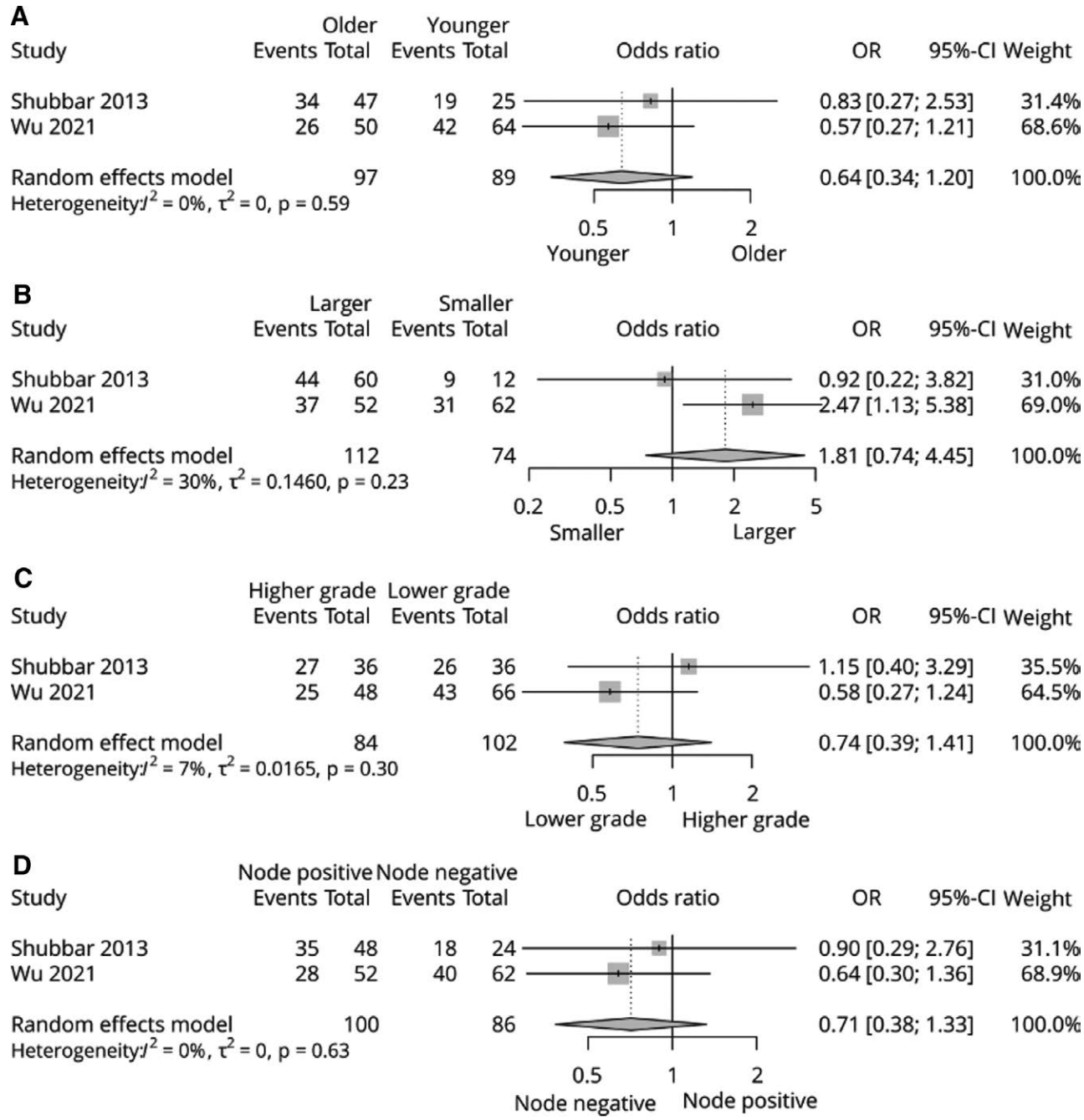

Figure 4. Forest plots of clinicopathological parameters associated with cyclin B2 expression. (A) age, (B) tumor size, (C) tumor grade, and (D) lymph node status.

age and high cyclin B1 and B2 expression (4 studies with 334 patients, OR = 0.62, 95% CI = 0.39–0.99, P = .04), but the tumor grade data did not show a significant result (6 studies with 560 patients, OR = 1.02, 95% CI = 0.55–1.89, P = .95) (Fig. 5).

The overall results of the analysis of clinicopathological parameters are summarized in Table 3.

3.3. Subgroup analysis

Subgroup analysis was conducted for DFS of cyclin B1 expression studies and DSS of cyclin B2 expression. The data were divided into 2 groups according to their types of target molecule, which are protein and mRNA. The subgroup analysis of cyclin B1 DFS showed heterogeneity in both groups (protein group: I^2 = 70%, P < .01; mRNA group: I^2 = 77%, P = .04). The subgroup analysis of cyclin B2 DSS did not show significant heterogeneity in both group (protein group: I^2 = 95%, P < .01; mRNA group: I^2 = 78%, P = .03).

3.4. Publication bias

The tests for publication bias were conducted for HRs of OS and DFS in cyclin B1 (CCNB1) expression studies. Statistically significant publication bias was suggested in Egger test for OS in cyclin B1 expression studies (P = .049) and Begg test for DFS in cyclin B1 expression studies (P = .03). Statistically significant publication bias was not seen in Egger test for DFS in cyclin B1 expression studies (P = .12) and Begg test for OS in cyclin B1 expression (P = .29). The funnel plots are shown in Figure 6.

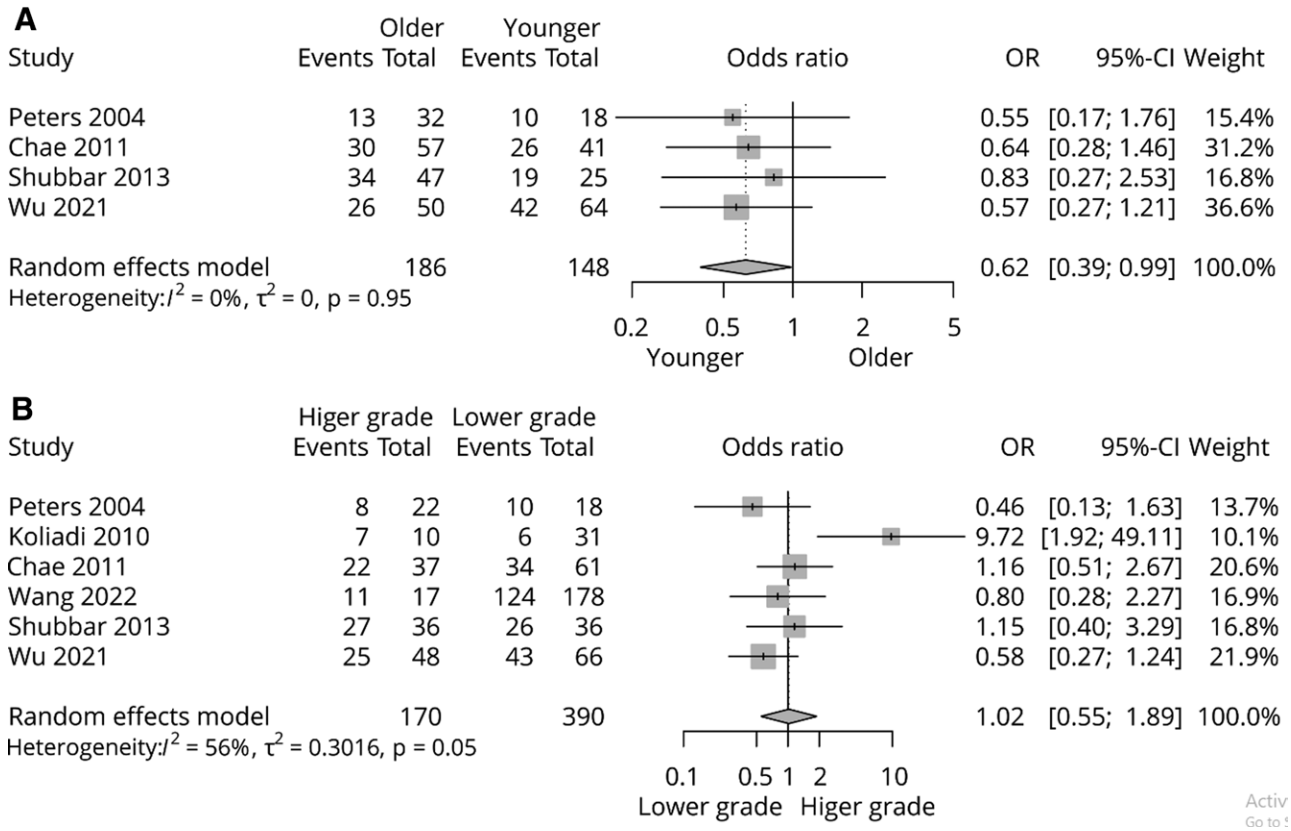

Figure 5. Forest plot of clinicopathological parameters associated with cyclin B1, and B2 expression. (A) Age and (B) tumor grade.

4. Discussion

We conducted a meta-analysis on cyclin B1 and B2 and their coding genes CCNB1 and CCNB2 with updated data, and different analyzing approaches. Our analysis revealed that the expression of cyclin B1 and B2 is associated with a worse prognosis, while no significant associations were found between clinicopathological parameters and the expression of these molecules. These findings are consistent with previous studies,[4] but some slight differences and additional findings warrant further detailed discussion.

In this study, significant associations were observed between the expressions of cyclin B1 and its coding gene CCNB1 with OS, DSS, and DFS. The individual studies on the prognostic significance of cyclin B1 and CCNB1 showed an association between worse prognosis and their expression with varying statistical significance.[10,12,13,15,19,21–23,25–29] The significant prognostic impact of cyclin B1 expression is consistent with previous findings.[4] Interestingly, the OS and DSS showed statistically significant results with no heterogeneity, while the DFS showed significant considerable heterogeneity. Subgroup analysis was conducted to explore the source of heterogeneity but failed to provide a conclusive explanation. It is possible that factors other than the type of target molecule contribute to this heterogeneity; however, due to the lack of detailed information for subgroup analysis, further investigation was not feasible. Incorporating data on both cyclin B1 protein and CCNB1 gene, our study postulates significant results. Cyclin B1 and CCNB1 appear to exert their prognostic effects by upregulating cell cycle and mitosis in breast cancer cells.[35,36] Notably, the inhibition of cyclin B1 has been shown to increase chemosensitivity in in vitro studies, suggesting that cyclin B1 and CCNB1 may serve as prognostic markers and potential treatment targets.

Our analysis also demonstrated significant prognostic significance in cyclin B2 and CCNB2 expression. Due to limited data availability, only DSS data were included, combining 2 mRNA studies and 2 protein studies. Significant heterogeneity was observed in DSS, and subgroup analysis based on the type of target molecule was performed. However, the subgroup analysis failed to explain the heterogeneity with the target molecule data. Additional subgroup analysis could not be done due to a lack of information. Cyclin B2 has been shown to promote breast cancer cell proliferation and lead to a worse prognosis,[18,30] which aligns with previous study findings.[4]

The analysis of the association between cyclin B1 and B2 expression and various clinicopathological parameters did not yield significant results. To apply more scientifically strict analytic conditions, we separately analyzed cyclin B1 and B2 data. However, when available, we also analyzed cyclin B1 and B2 data together with the available parameters, revealing a significant association between age and cyclin B1 and B2 expression. Age-dependent expression of cyclin A1 and D1 has been observed in normal and cancer cells,[37,38] and the age association found in our analysis suggests the possibility of similar age-related differential expressions of cyclin B1 and B2. However, we approach this possibility tentatively, as it is based on the combined analysis of cyclin B1 and B2 data.

This meta-analysis has limitations, despite of the application of strict selection and analysis criteria. Firstly, studies reporting protein data utilized the immunohistochemistry method, which is subjective in determining the results and can be influenced by factors such as the type of antibody used, cutoff values for interpretation, and the equipment employed for staining. Secondly, some parts of our meta-analysis exhibited significant heterogeneity. We attempted to explain the heterogeneity through subgroup analysis but were unable to clarify and perform further investigation. Thirdly, certain HRs were extracted from Kaplan–Meier curves, and despite employing a recently developed method, limitations in accuracy are inevitable. Fourthly,

Table 3

The summary of meta-analysis of clinicopathological parameters associated with cyclin B1, and B2 expression.

Target molecule	Clinicopathological parameter	Number of studies	Odds ratio	OR in favor of	Confidence interval	*P* value of OR	I^2	*P* value of I^2
Cyclin B1	Age	2	0.61	Younger age	0.31–1.19	.15	0 %	.83
	Tumor stage	2	0.78	Lower stage	0.29–2.12	.63	38 %	.2
	Tumor grade	4	1.29	Higher grade	0.42–3.97	.66	67 %	.03
	Histologic type	2	0.68	Other types	0.24–1.91	.47	0 %	.67
	Estrogen receptor	2	1.12	ER positive	0.51–2.43	.78	2 %	.31
Cyclin B2	Age	2	0.64	Younger age	0.34–1.2	.16	0 %	.59
	Tumor size	2	1.81	Larger size	0.74–4.45	.19	30 %	.23
	Tumor grade	2	0.74	Lower grade	0.39–1.41	.36	7 %	.3
	Node status	2	0.71	Node negative	0.38–1.33	.29	0 %	.63
Cyclin B1 and B2	Age	4	0.62	Younger age	0.39–0.99	.04	0 %	.95
	Tumor grade	6	1.02	Tumor grade	0.55–1.89	.95	56 %	.05

OR: odds ratio.

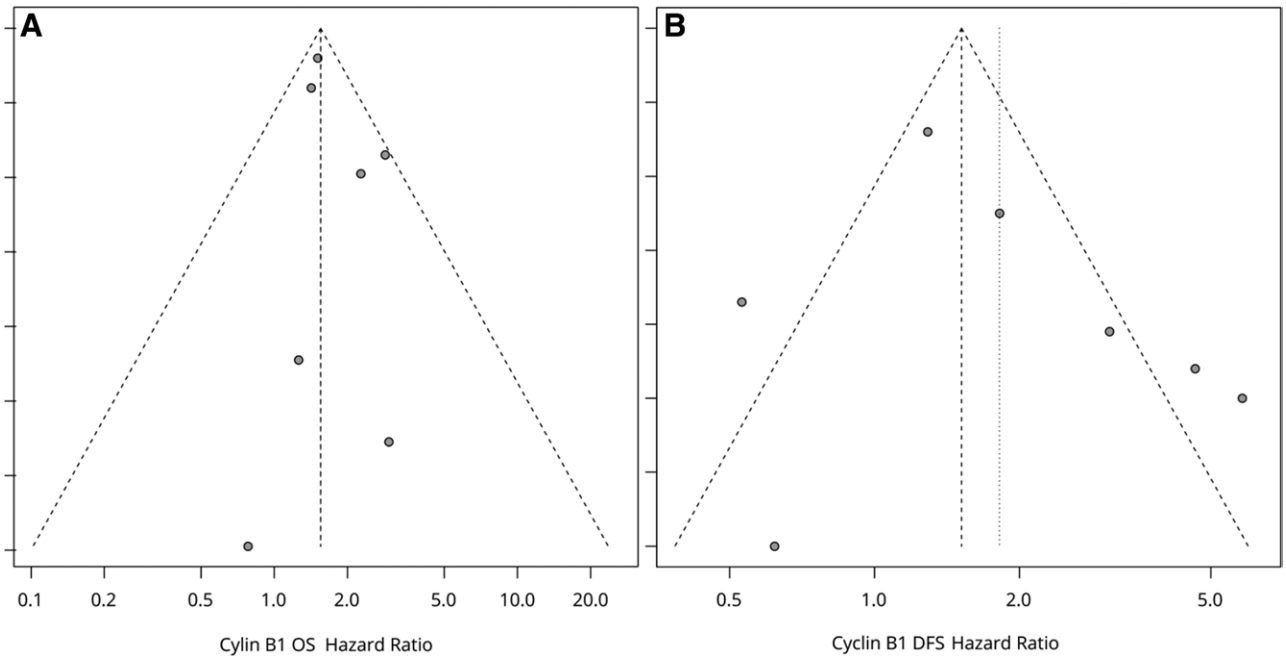

Figure 6. Funnel plots of HRs of survival data. (A) OS of cyclin B1, and (B) DFS of cyclin B1. DFS = disease free survival, OS = overall survival.

there was a potential risk of bias, as some tests for bias yielded significant results. And the relatively small number of studies included in the analysis limits the robustness of bias testing, and the funnel plot displayed slight asymmetry.

In conclusion, our study highlights the potential of cyclin B1 and B2, along with their coding genes CCNB1 and CCNB2, as prognostic markers in breast cancer. We also observed a potential age-related expression of cyclin B1 and B2 in breast cancer. The prognostic significance of cyclin B1 and B2 suggests their potential as therapeutic targets. Further research is needed to validate these findings and explore the underlying mechanisms.

Author contributions

Conceptualization: Hyunchul Kim.
Data curation: Hyunchul Kim.
Formal analysis: Hyunchul Kim.
Investigation: Hyunchul Kim.
Methodology: Hyunchul Kim.
Project administration: Hera Jung.
Resources: Hyunchul Kim.
Software: Hyunchul Kim.
Supervision: Hera Jung.
Validation: Hyunchul Kim.
Visualization: Hyunchul Kim.
Writing – original draft: Jeongwan Kang.
Writing – review & editing: Hyunchul Kim.

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