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RESEARCH ARTICLE

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Expression of KIF2A, NDC80, CDK1, and CCNB1 in breast cancer patients: Their interaction and linkage with tumor features and prognosis

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Abstract

Background: Kinesin family member 2A (KIF2A), nuclear division cycle 80 (NDC80), cyclin-dependent kinase 1 (CDK1), and cyclin B1 (CCNB1) exhibit a complex interrelation, which promote cancer progression via multiple ways, whereas their interaction and clinical implications in breast cancer are obscure. Hence, this study aimed to evaluate the correlation among KIF2A, NDC80, CDK1, CCNB1, and their linkage with clinicopathological features and prognosis in breast cancer patients.

Methods: 195 breast cancer patients underwent surgical resection were analyzed. KIF2A, NDC80, CDK1, and CCNB1 expressions were determined by immunohistochemical (IHC) assay and scored by a semiquantitative IHC score or positive cell percentage.

Results: KIF2A expression positively associated with NDC80, CDK1, and CCNB1 expressions (all $p < 0.01$). In terms of tumor features: KIF2A high expression linked with increased T stage ($p = 0.011$), N stage ($p = 0.014$), and TNM stage ($p = 0.009$) but not tumor differentiation ($p = 0.651$). NDC80 high expression only related to higher N stage ($p = 0.010$); CDK1 high expression only connected with elevated N stage ($p = 0.035$) and TNM stage ($p = 0.023$). In aspect of prognosis, high expression of KIF2A was correlated with worse disease-free survival (DFS) ($p = 0.031$), while NDC80 high ($p = 0.329$), CDK1 high ($p = 0.276$), and CCNB1 positive ($p = 0.063$) expressions only showed trends to link with poor DFS (without statistical significance). Furthermore, high expression of KIF2A ($p = 0.063$), NDC80 ($p = 0.939$), CDK1 ($p = 0.413$) and positive expression of CCNB1 ($p = 0.296$) did not relate to overall survival.

Conclusion: KIF2A correlates with NDC80, CDK1, CCNB1, and may link with advanced tumor stages and poor prognosis in breast cancer patients.

KEYWORDS
breast cancer, cyclin B1, cyclin-dependent kinase 1, kinesin family member 2A, nuclear division cycle 80

1 | INTRODUCTION

Breast cancer, worldwide, affects approximately 2.1 million newly diagnosed cases in 2018, taking up nearly 1 in 4 cancer cases among women.[1,2] Although breast cancer treatments continue to evolve, it is still the main cause of cancer-related mortality in women globally, and the overall morbidity among Asian women is progressively increasing.[3–5] Hence, breast cancer is still a hot topic in clinical research, and actively investigating potential biomarkers for monitoring progression in breast cancer patients is vital.[6–8]

Kinesin family member 2A (KIF2A) is a member of the kinesin-13 family that is a conserved class of microtubule-dependent motor proteins,[9,10] which participants in the processes of tumor growth and metastasis in cancers (including breast cancer,[11] gastric cancer,[12] and squamous cell carcinoma of the oral tongue [SCCOT]).[13] Based on existing evidence from Protein–Protein Interaction (PPI) network by String Database (https://string-db.org/),[14] KIF2A has a multiple regulation relationship with nuclear division cycle 80 (NDC80), cyclin-dependent kinase 1 (CDK1), and cyclin B1 (CCNB1). Meanwhile, NDC80, CDK1, and CCNB1 have been clarified as important roles in pathological processes in breast cancer: such as regulating breast cancer growth and invasion, etc.[15–17]

Hence, our study aimed to evaluate the correlation among KIF2A, NDC80, CDK1, CCNB1, and their relationships with clinicopathological features and prognosis in breast cancer patients.

2 | METHODS

2.1 | Patients

This retrospective study was permitted by the Institutional Review Board of Cancer Hospital of China Medical University. In the study, we reviewed clinicopathological data of 195 breast cancer patients who received surgical resection between January 2016 and December 2019. The inclusion criteria were (1) pathological diagnosis of breast cancer, (2) age above 18 years, (3) treated by surgical resection, and (4) without neoadjuvant therapy. The exclusion criteria were (1) clinical and follow-up data missing and (2) no formalin-fixed paraffin-embedded (FFPE) tumor specimen. The written informed consents from patients or their guardians were obtained.

2.2 | Data collection and specimen acquisition

The main clinicopathological data of patients were abstracted from the medical documents, which included patients' age, pathological differentiation, tumor size, lymph node (LYN) metastasis status, T stage, N stage, TNM stage, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epithelial growth factor receptor-2 (HER-2) status. Survival data of patients were collected from follow-up records, which were used for estimation of disease-free survival (DFS) and overall survival (OS). DFS was estimated from the surgery to disease relapse or the death of patients. OS was estimated from the surgery to the death of patients. The median follow-up duration was 33 months (min-max: 12–60 months). The FFPE tumor specimens of patients were acquired from the specimen library with approval.

2.3 | Immunohistochemical (IHC) assay

The IHC assay was performed to evaluate the expression of KIF2A, NDC80, CDK1, and CCNB1 in the breast cancer specimens. In brief, 5-μm sections were sliced from FFPE specimens, then were deparaffinated in xylene and hydrated in ethanol gradient solution. After that, the sections were treated by 3% H_2O_2, followed by antigen retrieval in citrate buffer under heating conditions. Next, the sections were immersed in unlabeled blocking serum solution, subsequently, the sections were incubated with primary antibody overnight at 4°C. KIF2A Polyclonal Antibody (dilution 1:50), NDC80 (HEC1) Polyclonal Antibody (dilution 5 μg/ml), CDK1 Polyclonal Antibody (dilution 1:200), and CCNB1 Polyclonal Antibody (dilution 1:200) were purchased from ThermoFisher Scientific (ThermoFisher Scientific, Waltham, Massachusetts, USA). After washing with buffer, the sections were incubated with horseradish peroxidase (HRP)-conjugated secondary antibody (ThermoFisher Scientific, Waltham, Massachusetts, USA) at 37°C for 60 min. Following that, the sections were detected with 3,30-diaminobenzidine (DAB) and counter-stained with hematoxylin. Finally, the sections were examined under the light microscope. The quantification analysis of KIF2A, NDC80, and CDK1 expression was conducted referring to previously published methodology.[18] In brief, the IHC staining intensity was scored from 0 to 3 (0 = no staining, 1 = weak, 2 = middle, and 3 = strong), and the density (percent positive stroma in the visual field) was scored from 0 to 4 (1 = 0%~25%, 2 = 26%~50%, 3 = 51%~75%, and 4 = 76%~100%). The IHC score was the product of both intensity score and density score, and the IHC score > 3 was considered as high expression.[19] Specifically, CCNB1 expression was quantified using positive cell percentage (%). Two independent pathologists reviewed the IHC staining images and scored them.

2.4 | Statistical analysis

Statistical analysis was completed using SPSS 22.0 (IBM, Chicago, Illinois, USA). Graph plotting was carried out using GraphPad Prism 7.01 (GraphPad Software Inc., San Diego, California, USA). Descriptive analysis for data was carried out using number with percentage or mean with standard deviation (SD). Spearman's rank correlation test was performed for correlation analysis. Kaplan–Meier method was applied for constructing the survival curve, and the Log-rank test was used to examine the survival curve. Cox's proportional hazards regression analysis was also performed. p value < 0.05 indicated there was statistical significance.

3 | RESULTS

3.1 | Breast cancer patients' clinical features

The mean age of 195 breast cancer patients was 53.6 ± 11.9 years. There were 40 (20.5%), 138 (70.8%) and 17 (8.7%) patients at well, intermediate and poor pathological differentiation. Besides, the mean tumor size was 3.5 ± 1.7 cm, and 85 (43.6%) patients had LYN metastasis. As to TNM stage, 27 (13.8%), 125 (64.1%) and 43 (22.1%) patients were at TNM stage I, TNM stage II and TNM stage III, respectively. Furthermore, there were 113 (57.9%) ER positive status and 82 (42.1%) patients at ER negative status, 103 (52.8%) patients at PR positive status and 92 (47.2%) patients at PR negative status, 65 (33.3%) patients at HER-2 positive status and 130 (66.7%) patients at HER-2 negative status (Table 1).

TABLE 1 Clinical features of patients

Items	Breast cancer patients (*N* = 195)
Age (years), mean ± SD	53.6 ± 11.9
Pathological differentiation, No. (%)	
Well	40 (20.5)
Intermediate	138 (70.8)
Poor	17 (8.7)
Tumor size (cm), mean ± SD	3.5 ± 1.7
LYN metastasis, No. (%)	85 (43.6)
T stage, No. (%)	
T1	42 (21.6)
T2	128 (65.6)
T3	25 (12.8)
N stage, No. (%)	
N0	110 (56.4)
N1	47 (24.1)
N2	34 (17.4)
N3	4 (2.1)
TNM stage, No. (%)	
I	27 (13.8)
II	125 (64.1)
III	43 (22.1)
ER status, No. (%)	
Negative	82 (42.1)
Positive	113 (57.9)
PR status, No. (%)	
Negative	92 (47.2)
Positive	103 (52.8)
HER-2 status, No. (%)	
Negative	130 (66.7)
Positive	65 (33.3)

Abbreviations: ER, estrogen receptor; HER-2, human epithelial growth factor receptor-2; LYN, lymph node; PR, progesterone receptor; SD, standard deviation.

3.2 | KIF2A, NDC80, CDK1, and CCNB1 expressions in breast cancer patients

The examples of KIF2A, NDC80, CDK1, and CCNB1 expressions in breast cancer tissues assessed by IHC assay were shown in Figure 1A. The KIF2A IHC score, NDC80 IHC score, CDK1 IHC score, and CCNB1 positive cell percentage were 4.9 ± 2.6, 5.7 ± 2.6, 4.8 ± 2.3 and 5.0 ± 7.3, respectively (Figure 1B). Besides, there were 118 (60.5%) KIF2A high expression patients and 77 (39.5%) KIF2A low expression patients, 149 (76.4%) NDC80 high expression patients and 46 (23.6%) NDC80 low expression patients, 124 (63.6%) CDK1 high expression patients and 71 (36.4%) CDK1 low expression patients, as well as 135 (69.2%) CCNB1 positive expression patients and 60 (30.8%) CCNB1 negative expression patients.

3.3 | Association among KIF2A, NDC80, CDK1, and CCNB1 in breast cancer

Protein–protein interaction (PPI) network by STRING Database (https://string-db.org/) showed a complex mutual regulation relationship of KIF2A with NDC80, CDK1, and CCNB1 (Figure 2A). In addition, KIF2A IHC score was positively associated with NDC80 IHC score ($p < 0.001$), CDK1 IHC score ($p < 0.001$) and CCNB1 positive cell percentage ($p = 0.001$) (Figure 2B–D). Also, NDC80 IHC score was positively correlated with CKD1 IHC score ($p = 0.004$), but not CCNB1 positive cell percentage ($p = 0.237$) (Figure 2E,F). Meanwhile, CCNB1 positive cell percentage was positively related to CDK1 IHC score ($p = 0.002$) (Figure 2G). Subsequently, we cut KIF2A, NDC80, CDK1 expression as high expression/low expression with cut-off value of IHC = 3, respectively; then cut CCNB1 expression as positive expression and negative expression with 1% positive cells. And we further discovered that KIF2A high expression was associated with NDC80 ($p < 0.001$), CDK1 ($p < 0.001$), and CCNB1 ($p < 0.001$) positive expressions. In addition, NDC80 high expression was also correlated with CCNB1 ($p = 0.012$) positive expression. Meanwhile, CDK1 high expression was related to CCNB1 ($p = 0.048$) positive expression (Table 2). These data further showed the close relationships among KIF2A, NDC80, CDK1, and CCNB1 in breast cancer.

3.4 | Association of KIF2A, NDC80, CDK1, and CCNB1 with tumor features in breast cancer patients

High KIF2A was associated with raised T stage ($p = 0.011$), increased N stage ($p = 0.014$), and enhanced TNM stage ($p = 0.009$). Besides, high NDC80 was correlated with increased N stage ($p = 0.010$).

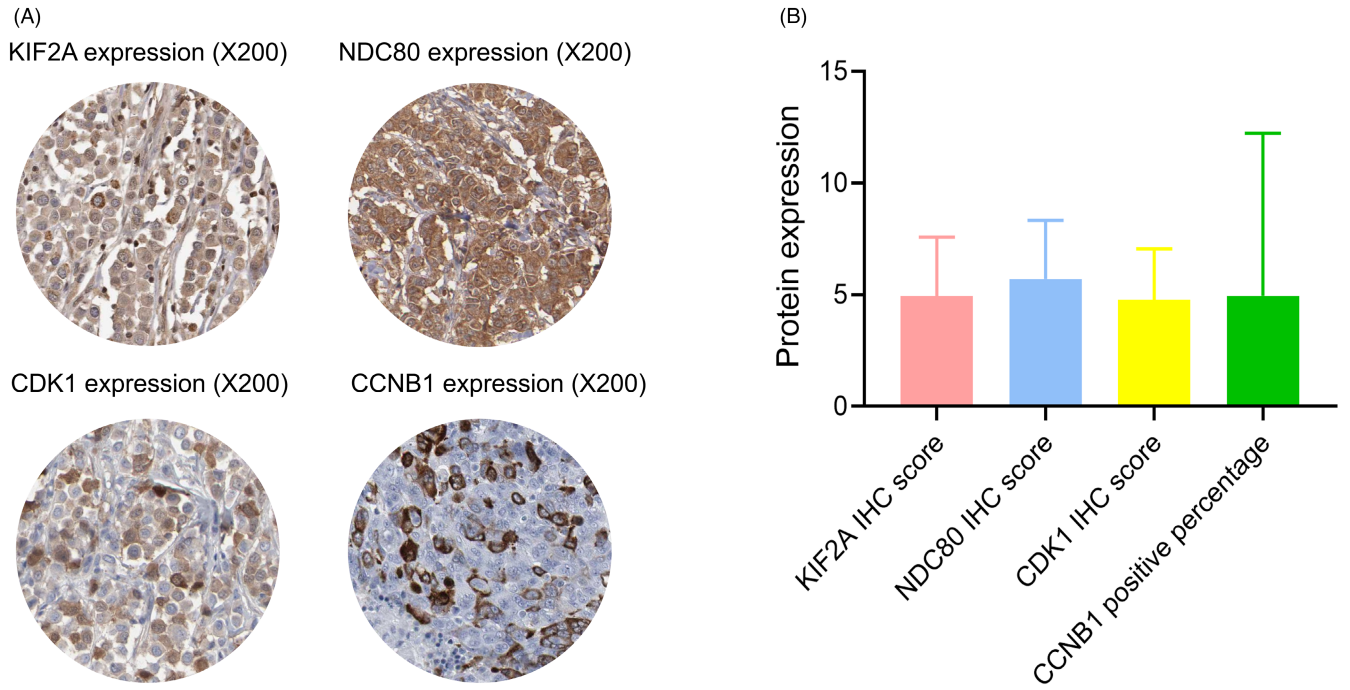

FIGURE 1 KIF2A, NDC80, CDK1, and CCNB1 expressions. The examples of KIF2A, NDC80, CDK1, and CCNB1 expressions assessed by IHC assay (A); The protein quantification of KIF2A, NDC80, CDK1, and CCNB1 (B)

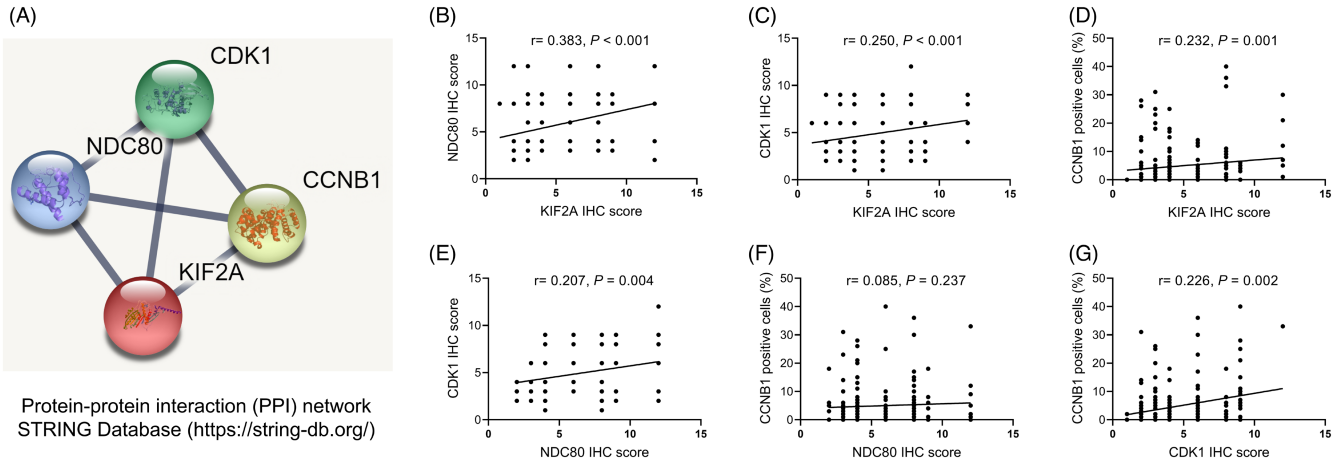

FIGURE 2 Correlation among KIF2A, NDC80, CDK1, and CCNB1 protein expression. A mutual regulation relationship of KIF2A with NDC80, CDK1, and CCNB1 from protein–protein interaction network by STRING Database (A). Correlation of KIF2A IHC score with NDC80 IHC score (B), CDK1 IHC score (C), and CCNB1 positive cells (%) (D). Correlation of NDC80 IHC score with CKD1 IHC score (E) and CCNB1 positive cells (%) (F). Correlation of CCNB1 positive cells (%) with CDK1 IHC score (G)

Meanwhile, high CDK1 was related to raised N stage ($p = 0.035$) and enhanced TNM stage ($p = 0.023$) (Table 3).

3.5 | Association of KIF2A, NDC80, CDK1, and CCNB1 with survival profiles in breast cancer patients

High expression of KIF2A was correlated with worse DFS ($p = 0.031$), while high/positive expression of NDC80 ($p = 0.329$), CDK1 ($p = 0.276$), and CCNB1 ($p = 0.063$) only showed a trend to link with poor DFS (without statistical significance) (Figure 3A–D). Furthermore, high/positive expression of KIF2A ($p = 0.063$), NDC80 ($p = 0.939$), CDK1 ($p = 0.413$), and CCNB1 ($p = 0.296$) did not relate to OS (Figure 4A–D). Besides, Cox's proportional hazards regression analysis showed similar results as K-M curves did (Table 4).

4 | DISCUSSION

According to PPI network by String Database (https://string-db.org/), KIF2A, NDC80, CDK1, and CCNB1 exert multiple complex relationships. Furthermore, KIF2A, NDC80, CDK1, and CCNB1 are

TABLE 2 Correlation among KIF2A, NDC80, CDK1, and CCNB1

	NDC80		CDK1		CCNB1	
Proteins	**Low**	**High**	**Low**	**High**	**Negative**	**Positive**
KIF2A						
Low	37 (19.0)	40 (20.5)	40 (20.5)	37 (19.0)	39 (20.0)	38 (19.5)
High	9 (4.6)	109 (55.9)	31 (15.9)	87 (44.6)	21 (10.8)	97 (49.7)
r	**0.465**		**0.261**		**0.348**	
p value	**<0.001**		**<0.001**		**<0.001**	
NDC80						
Low	–	–	22 (11.3)	24 (12.3)	21 (10.8)	25 (12.8)
High	–	–	49 (25.1)	100 (51.3)	39 (20.0)	110 (56.4)
r	–	–	0.132		**0.179**	
p value	–	–	0.066		**0.012**	
CDK1						
Low	–	–	–	–	22 (11.3)	49 (25.1)
High	–	–	–	–	24 (12.3)	100 (51.3)
r	–		–	–	**0.142**	
p value	–		–	–	**0.048**	

Note: The bold value means statistical significance.

involved into the pathological processes in breast cancer.[11,15–17] However, no study investigating the relationships among KIF2A, NDC80, CDK1, and CCNB1 in breast cancer patients. In this study, we discovered that KIF2A was positively associated with NDC80, CDK1, and CCNB1. Also, NDC80 and CDK1 were positively correlated with CCNB1.

KIF2A, NDC80, CDK1, and CCNB1 are considered as important roles in cancer patients. For example, a recent study reveals that KIF2A high expression is associated with increased TNM stage and lymph node metastasis in gastric cancer patients.[20] In addition, CDK1 high expression has reported to be related to advanced pathological grades and enhanced TNM stage in hepatocellular carcinoma patients.[21] Despite of that the role of KIF2A, NDC80, CDK1, and CCNB1 in cancer patients has been illustrated, while the clinical implications of these four genes in breast cancer patients have not been explored. In this study, we found that KIF2A was positively related to raised T stage, N stage and TNM stage; NDC80 was positively correlated with N stage; Also, CDK1 was positively associated with raised N stage and TNM stage. The probable explanations were as follows: (1) KIF2A interacted with multiple genes or pathways to promote cell proliferation, invasion and migration (for example, as its role in ovarian cancer to bind with miR-206,[17] as its role in gastric cancer to interact with protein kinase B (Akt) signaling pathway,[21] and as its role in squamous cell carcinoma of the oral tongue to promote the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway), subsequently accelerated tumor growth and metastasis, thereby caused raised T stage, N stage and TNM stage in breast cancer patients. (2) NDC80 might interact with never in mitosis gene A-related kinase 2 (NEK2) and centrosomal protein 250 (CEP250) to expedite lymph node metastasis, thereby positively related to N stage in breast cancer patients.[22] (3) CDK1 bound with fibroblast growth factor receptor 1 (FGFR1) to affect cell proliferation, invasion and migration, subsequently impact lymph node metastasis and tumor metastasis, eventually related to raised N stage and TNM stage in breast cancer patients.[23]

Existing evidence show that KIF2A overexpression relates to short 5-year survival in ovarian cancer patients,[17] associates with poor 5-year survival in gastric cancer patients,[20] correlates with worse DFS in esophageal squamous cell carcinoma patients,[24] and is responsibility for undesirable 5-year survival in colorectal cancer patients.[25] Besides, previous data reveals that CCNB1 increased expression correlates with poor DFS and OS in hepatocellular carcinoma patients.[21] In this study, our results showed that high expression of KIF2A was related to poor DFS, then NDC80, CDK1, and CCNB1 only exhibited a trend to relate to poor DFS, but without statistical significance; besides, they were all not correlated with OS. The possible explanations were (1) KIF2A not only correlated with advanced tumor features (above-mentioned), thereby indirectly caused poor DFS in breast cancer patients; but also might interact with multiple genes or pathways to affect chemotherapy drug' resistance to result in adjuvant treatment efficacy, eventually causing short DFS in breast cancer patients. (2) NDC80, CDK1, and CCNB1 could bind with multiple genes (including NEK2,[22] forkhead box protein M1 [FOXM1],[26] or miR-6884-3p)[27] to promote cell growth and invasion, thereby affected tumor progression, then caused poor DFS in breast cancer patients. Whereas owning to relatively sample size of this study, the statistical power was relatively poor.

There were several limitations existing in this study as follows: (1) this single-center study might lead to selected bias, hence, further validation from multicenter study is essential. (2) Follow-up duration was relatively short with median value of 33 months (min-max: 12–60 months), the long-term effect of KIF2A, NDC80, CDK1, and

TABLE 3 Correlation of KIF2A, NDC80, CDK1, and CCNB1 with tumor features

	KIF2A		NDC80		CDK1		CCNB1	
Proteins	**Low**	**High**	**Low**	**High**	**Low**	**High**	**Negative**	**Positive**
Pathological differentiation, No. (%)								
Well	15 (37.5)	25 (62.5)	7 (17.5)	33 (82.5)	17 (42.5)	23 (57.5)	10 (25.0)	30 (75.0)
Intermediate	58 (42.0)	80 (58.0)	35 (25.4)	103 (74.6)	50 (36.2)	88 (63.8)	44 (31.9)	94 (68.1)
Poor	4 (23.5)	13 (76.5)	4 (23.5)	13 (76.5)	4 (23.5)	13 (76.5)	6 (35.3)	11 (64.7)
r	0.033		−0.058		0.092		−0.066	
p value	0.651		0.420		0.202		0.362	
T stage, No. (%)								
T1	20 (47.6)	22 (52.4)	9 (21.4)	33 (78.6)	16 (38.1)	26 (61.9)	13 (31.0)	29 (69.0)
T2	54 (42.2)	74 (57.8)	32 (25.0)	96 (75.0)	50 (39.1)	78 (60.9)	38 (29.7)	90 (70.3)
T3	3 (12.0)	22 (88.0)	5 (20.0)	20 (80.0)	5 (20.0)	20 (80.0)	9 (36.0)	16 (64.0)
r	**0.181**		−0.002		0.084		−0.022	
p value	**0.011**		0.976		0.241		0.760	
N stage, No. (%)								
N0	51 (46.4)	59 (53.6)	34 (30.9)	76 (69.1)	45 (40.9)	65 (59.1)	39 (35.5)	71 (64.5)
N1	17 (36.2)	30 (63.8)	6 (12.8)	41 (87.2)	20 (42.6)	27 (57.4)	13 (27.7)	34 (72.3)
N2	8 (23.5)	26 (76.5)	6 (17.6)	28 (82.4)	5 (14.7)	29 (85.3)	8 (23.5)	26 (76.5)
N3	1 (25.0)	3 (75.0)	0 (0.0)	4 (100.0)	1 (25.0)	3 (75.0)	0 (0.0)	4 (100.0)
r	**0.177**		**0.185**		**0.151**		0.127	
p value	**0.014**		**0.010**		**0.035**		0.076	
TNM stage, No. (%)								
I	13 (48.1)	14 (51.9)	7 (25.9)	20 (74.1)	11 (40.7)	16 (59.3)	9 (33.3)	18 (66.7)
II	55 (44.0)	70 (56.0)	33 (26.4)	92 (73.6)	52 (41.6)	73 (58.4)	41 (32.8)	84 (67.2)
III	9 (20.9)	34 (79.1)	6 (14.0)	37 (86.0)	8 (18.6)	35 (81.4)	10 (23.3)	33 (76.7)
r	**0.186**		0.100		**0.163**		0.075	
p value	**0.009**		0.165		**0.023**		0.296	

Note: The bold value means statistical significance.

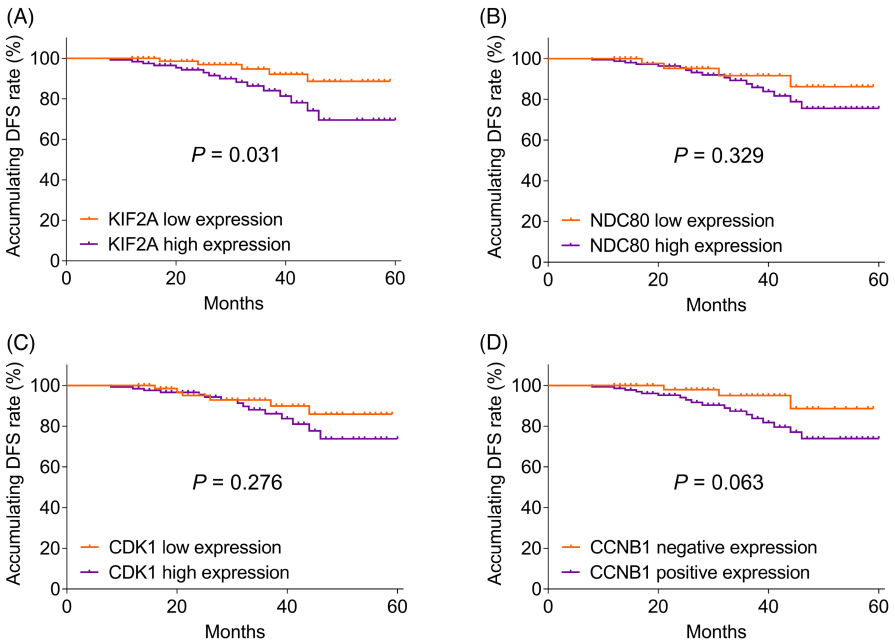

FIGURE 3 Correlation of KIF2A, NDC80, CDK1, and CCNB1 with DFS. K-M curve analysis regarding the correlation of KIF2A (A), NDC80 (B), CDK1 (C), and CCNB1 (D) with DFS in breast cancer patients

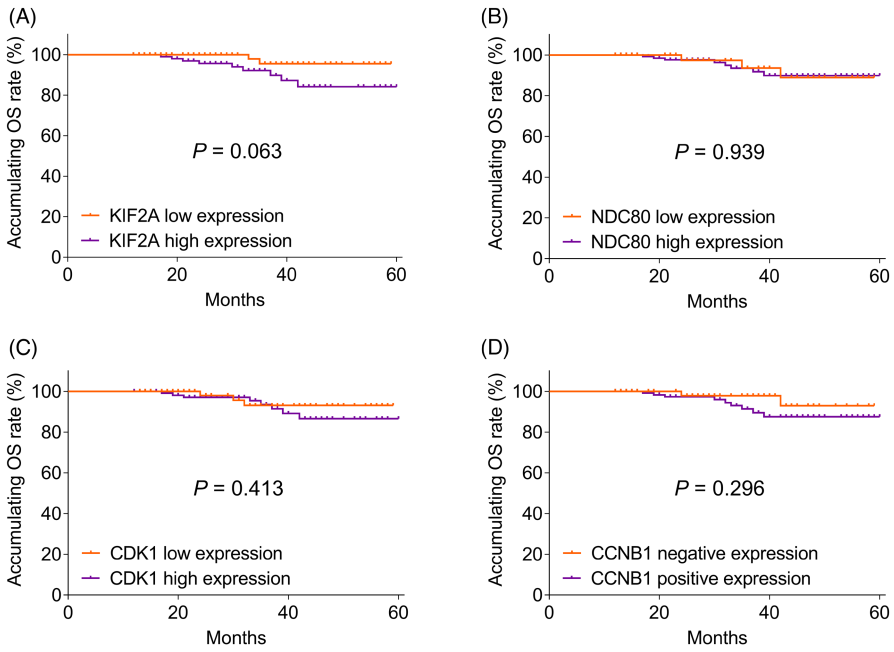

FIGURE 4 Correlation of KIF2A, NDC80, CDK1, and CCNB1 with OS. K-M curve analysis regarding the correlation of KIF2A (A), NDC80 (B), CDK1 (C), and CCNB1 (D) with OS in breast cancer patients

TABLE 4 Cox's proportional hazards regression analysis

Items	*p* value	HR	95%CI	
			Lower	Upper
DFS				
KIF2A high (vs. low)	**0.039**	2.894	1.054	7.942
NDC80 high (vs. low)	0.335	1.711	0.574	5.103
CDK1 high (vs. low)	0.282	1.685	0.652	4.354
CCNB1 positive (vs. negative)	0.078	3.006	0.885	10.212
OS				
KIF2A high (vs. low)	0.084	3.867	0.833	17.946
NDC80 high (vs. low)	0.939	1.053	0.279	3.979
CDK1 high (vs. low)	0.418	1.730	0.459	6.529
CCNB1 positive (vs. negative)	0.309	2.217	0.479	10.266

Note: The bold value means statistical significance.

CCNB1 on survival profiles was still unclear. Hence, further relevant study is needed. (3) The regulated mechanism among KIF2A, NDC80, CDK1, and CCNB1 should be further explored in vivo and in vitro experiments. (4) As this was a retrospective study, it presented some inherent limitations such as patients' selection bias.

In conclusion, KIF2A correlates with NDC80, CDK1, CCNB1, and may link with advanced tumor stages and poor prognosis in breast cancer patients.

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None.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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