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High Tumoral KPNA2 Expression Is a PotentialBiomarker for Poor Prognosis in Advanced Neuroblastoma Patients

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Abstract. *Background/Aim: Karyopherin alpha 2 (KPNA2) has been reported to be associated with cancer aggressiveness and treatment resistance via transporting several cargo proteins into the nucleus, such as cancer-promoting E2F and DNA repair-related MRN complex. Recent studies have highlighted the KPNA2 functions in tumorigenesis and the progression of various cancers. However, the importance of KPNA2 expression has yet to be elucidated in clinical neuroblastoma patients. This study aimed to analyze the clinical impact of KPNA2 expression in neuroblastoma. Materials and Methods: KPNA2 expression in 81 resected neuroblastoma sections was examined using immunohistochemical staining. The significance and prognostic value of tumoral KPNA2 expression were analyzed using our cohort and R2 database. Results: The KPNA2 was expressed in the nucleus of neuroblastoma cells. The expression level of nuclear KPNA2 was not associated with clinicopathological factors in neuroblastoma. Among our cohort (n=81), non-radically resected neuroblastoma patients (n=37) with high KPNA2 expression had poorer prognoses than those with low KPNA2 expression. The R2 database analysis validated that the high KPNA2 expression was related to the poor prognosis in the large-scale neuroblastoma cohort. Conclusion: KPNA2 expression evaluation in neuroblastoma is a promising indicator of prognosis in non-curative resected cases. KPNA2 targeting may be a promising therapeutic strategy against advanced neuroblastoma.*

Neuroblastoma is one of the most common extracranial solid tumors in pediatric patients. Several critical factors, such as MYCN (proto-oncogene BHLH transcription factor) amplification and copy number variations, are essential for diagnosing high-risk neuroblastoma (1, 2). These molecular markers have been pivotal in identifying high-risk patients who require more aggressive treatments (3). However, despite the implementation of multidisciplinary treatment strategies, the prognosis for high-risk neuroblastoma patients remains dismal. Therefore, developing new biomarkers is crucial for diagnosing tumor aggressiveness correctly and selecting a suitable therapeutic strategy against neuroblastoma.

Karyopherin subunit alpha 2 (KPNA2), a nuclear transport protein, has been implicated in cancer aggressiveness of various cancers through the nuclear translocation of several oncogenic proteins (4, 5). Notably, KPNA2 facilitates the nuclear import of cancer-related proteins such as E2F, a crucial regulator of the cell cycle, and the MRN complex (MRE11-RAD50-NBS1), essential for DNA damage response and repair, suggesting the importance of KPNA2 in cancer proliferation and chemotherapy resistance (6). It has been reported that high KPNA2 expression in tumor tissues was associated with tumor aggressiveness, poor prognosis, and therapeutic resistance in several cancers (7-11). These findings indicate that KPNA2 may be a potential biomarker and therapeutic target in different types of primary tumors. However, the importance of the tumoral KPNA2 accumulation as a tumor promotion factor and prognostic biomarker has not been elucidated in clinical neuroblastoma samples.

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This study aimed to clarify the clinical significance and prognostic value of KPNA2 expression in clinical neuroblastoma tumors. Therefore, we evaluated the expression of tumoral KPNA2 in 81 neuroblastoma samples using immunohistochemical staining and analyzed the association of the KPNA2 expression levels with various clinicopathological parameters and survival. Moreover, the prognostic value of tumoral *KPNA2* mRNA expression was validated using a database of large-cohort neuroblastoma cases.

Materials and Methods

Patients and samples. Tumor tissue samples were resected from 102 neuroblastoma-suspected cases who were subjected to surgical biopsy or surgery at Gunma University Hospital and Gunma Children's Medical Center between 1991 and 2020. Preoperative chemotherapy was performed in eleven patients; therefore, they were excluded from further analysis. Among the patients, 81 were pathologically diagnosed with neuroblastoma, nine cases with ganglioneuroblastoma, and one case with ganglioneuroma (Figure 1). Among the 81 neuroblastoma samples, eight cases were MYCN-amplified, and 69 were non-MYCN-amplified. The MYCN status was not analyzed in four cases. In addition, tumors in 44 cases were radically resected, and tumors in 37 were not radically resected. The 81 neuroblastoma cases had the following postoperative complications, such as liver disorder, ileus, renal dysfunction, hearing disorder, chylothorax, sepsis, Horner's syndrome, pseudomembranous enteritis, herpes zoster, and opsoclonus-myoclonus syndrome. This study follows the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Gunma University Hospital (approval number: HS2024-169). Patient consent was obtained by using the opt-out method.

Immunohistochemistry. The staining procedure was carried according to standard methods, as described previously (12). In brief, the deparaffinized specimens (3.5 μm) were incubated in 0.3% hydrogen peroxide in 100% methanol for 30 min at room temperature to block the endogenous peroxidase activity. The antigen retrieval and blocking were performed using an Immunosaver solution (Nishin EM, Tokyo, Japan) and a protein block serum-free reagent (DAKO, Carpinteria, CA, USA). Then, tumor sections were incubated with anti-KPNA2 antibody (1:500; ab84440; Abcam, Cambridge, UK) and anti-Ki67 antibody (1:400; #9027; Cell Signaling Technology, Danvers, MA, USA) in a Dako REAL antibody diluent at 4˚C for 24 h. The primary antibodies were visualized using the Histofine Simple Stain MAX-PO (Multi) Kit (Nichirei, Tokyo, Japan) and 3,3-diaminobenzidine tetrahydrochloride (0.02% in 50 mM ammonium acetate–citrate acid buffer containing 0.005% hydrogen peroxide), and were lightly counterstained with hematoxylin. Negative control sections were not treated with the primary antibodies. Two experienced authors evaluated these slides blinded to the clinical data. The staining score was the average of the two researchers' evaluations.

Evaluation of immunostaining. Immunostaining of KPNA2 was assessed as follows: The positive cell number of nuclear KPNA2 expression was calculated as the percentage of nuclear-stained cells for each section based on 400 neuroblastoma cells and was counted at the four representative positively stained sites in the slide. The neuroblastoma patients were classified as high KPNA2 or low KPNA2 groups based on the receiver operating characteristic (ROC)-derived cut-off value regarding poor prognosis. Accordingly, the KPNA2-positive cell number of ≥98 was defined as the high KPNA2 expression group, and <98 was defined as the low KPNA2 expression group. The immunoreactivity of Ki67 was evaluated as follows: The positive cell number of Ki67 in neuroblastoma tumors was calculated as the percentage of nuclear Ki67 stained cells for each section in 500 neuroblastoma cells. Nuclear Ki67 positive cell number of ≥88 was designated as the high Ki67 expression group, and <88 was designated as the low Ki67 expression group based on the ROC analysis regarding poor prognosis as previously described (12).

On-line microarray database search for KPNA2 mRNA expression in neuroblastoma. We used an online R2 database to validate the relevance of *KPNA2* mRNA expression to overall survival in patients with neuroblastoma (R2 internal identifier: ps_avgpres_dgc2102a786_dgc2102).

Statistical analysis. Statistical differences were analyzed using Chi-square test. The ROC curve analyses were performed to define the cut-off values for KPNA2 and Ki67 scores to predict poor prognosis. Survival curves were calculated using the Kaplan–Meier method, and statistical differences between the curves were analyzed using the log-rank test. These statistical analyses were performed using JMP Pro 14 software (SAS Institute, Cary, NC, USA).

Results

Immunohistochemical staining of nuclear KPNA2 in clinical neuroblastoma tissues. The KPNA2 protein expression was mainly detected in the nucleus of neuroblasts and neuroblastoma cells (Figure 2). The positive rate of nuclear KPNA2 expression was higher in neuroblastoma patients (44.4%, 36/81 cases) than in ganglioneuroma (0%, 0/1 case) and ganglioneuroblastoma (33.3%, 3/9 cases) (Figure 1 and Figure 2). Of the 81 neuroblastoma-diagnosed cases, 58 (71.6%, 58/81 cases) and 23 (28.4%, 23/81 cases) were categorized as the low KPNA2 expression (Figure 2C) and high KPNA2 expression groups (Figure 2D), respectively (Table I).

Association of KPNA2 expression with the clinicopathological features in clinical neuroblastoma patients. The relationship between KPNA2 expression and clinicopathological characteristics is shown in Table I. Unexpectedly, the KPNA2 expression was not related to the factors in the total cohort (n=81) and radically resected cohort (n=44) (Table I, left and middle part). However, high nuclear KPNA2 expression in non-radically resected neuroblastoma patients (n=37) was significantly associated with elder disease onset age (p=0.014) and showed the tendency to be related to the MYCN amplification (p=0.054) and progression of International Neuroblastoma Pathology Classification (INPC) (p=0.062) and International Neuroblastoma Risk Group (INRG) staging system (p=0.057) (Table I, right part).

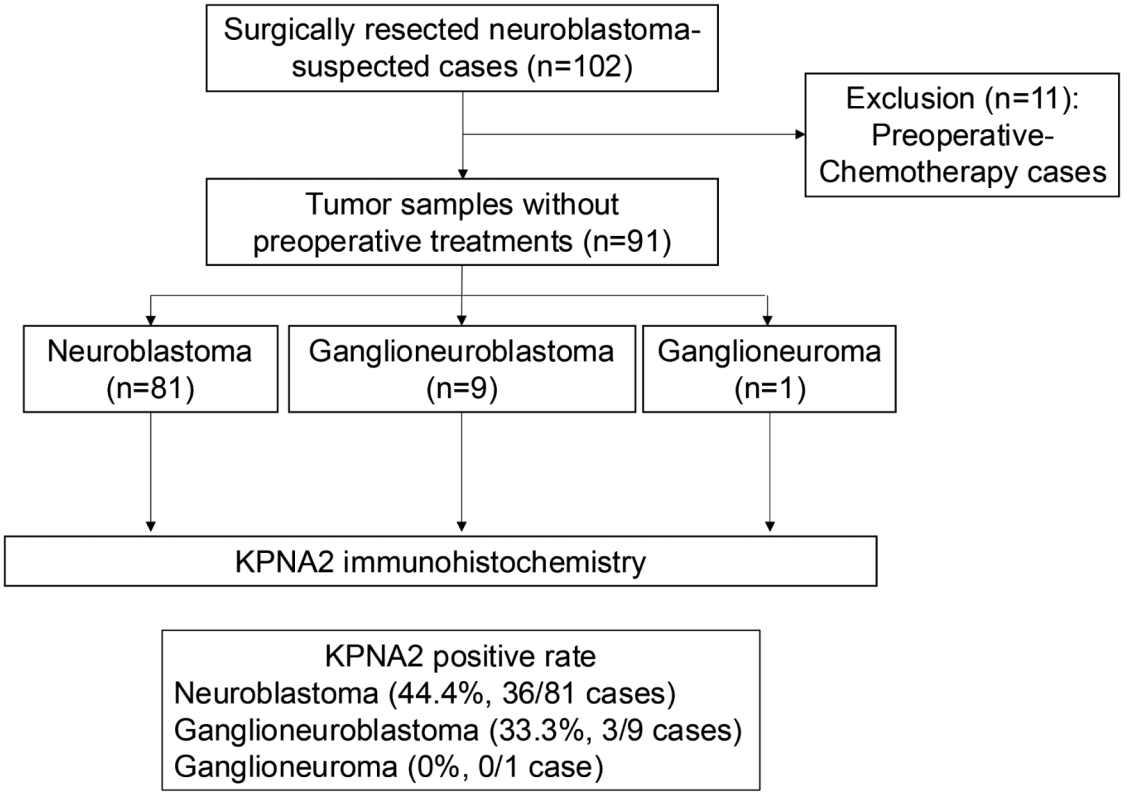

Figure 1. *Eligibility criteria and KPNA2 positive ratio in patients with neuroblastoma, ganglioneuroblastoma, and ganglioneuroma in this study. Among 102 surgically-resected neuroblastoma-suspected cases, 81 patients with neuroblastoma were selected as our cohort to analyze the clinicopathological significance of nuclear KPNA2 accumulation in neuroblastoma cells using immunohistochemistry.*

Prognostic significance of nuclear KPNA2 expression in neuroblastoma patients. Kaplan–Meier analysis in the total cohort (n=81) and radically resected neuroblastoma cohort (n=44) did not show a significant difference between high and low KPNA2 expression groups (Figure 3A, left and middle panel). In contrast to all neuroblastoma and radically resected cases, the high nuclear KPNA2 expression in non-radically resected neuroblastoma patients (n=37) was significantly associated with poor prognosis (p=0.0474, Figure 3A right panel).

This study used the R2 Genomics Analysis and Visualization Platform with prognostic data from 782 neuroblastoma patients to confirm the prognostic value of KPNA2 expression in a larger cohort (R2 internal identifier: ps_avgpres_dgc2102 a786_dgc2102). The results indicated that the neuroblastoma patients with high *KPNA2* mRNA expression had poorer prognosis than those with low expression in not only all cases (n=782, p=8.87e-07, Figure 3B left panel) and non-MYCN-amplified cases (n=629, p=3.39e-04, Figure 3B middle panel) but also MYCN-amplified cases (n=153, p=0.054, Figure 3B right panel); suggesting the significant prognostic value of the KPNA2 expression in patients with neuroblastoma.

Discussion

In this study, we clarified that KPNA2 expression was detected in the nucleus of tumor cells and that high nuclear KPNA2 was associated with high-risk disease conditions and poor prognosis in non-radically resected patients with neuroblastoma. Moreover, the poor prognostic value of high KPNA2 in neuroblastoma was validated using public database analysis.

Numerous studies have indicated that the expression levels of KPNA2 in various tumors were higher than in non-cancerous tissues (5, 13). As anticipated, the positive rate of nuclear KPNA2 expression in neuroblastoma tissues was higher than that in surrounding normal tissues, ganglioneuroma, and ganglioneuroblastoma (Figure 1 and Figure 2). It has been reported that KPNA2 expression is up-regulated by several cancer-promoting factors, such as E2F, the PI3K/AKT pathway, and miR-101 (5, 14-16). Interestingly, the activation and dysregulation of E2F, AKT, and miR-101 were also found to be associated with the aggressiveness of neuroblastoma cells (17-20). Therefore, the expression level of KPNA2 in neuroblastoma is suggested to be regulated by factors such as

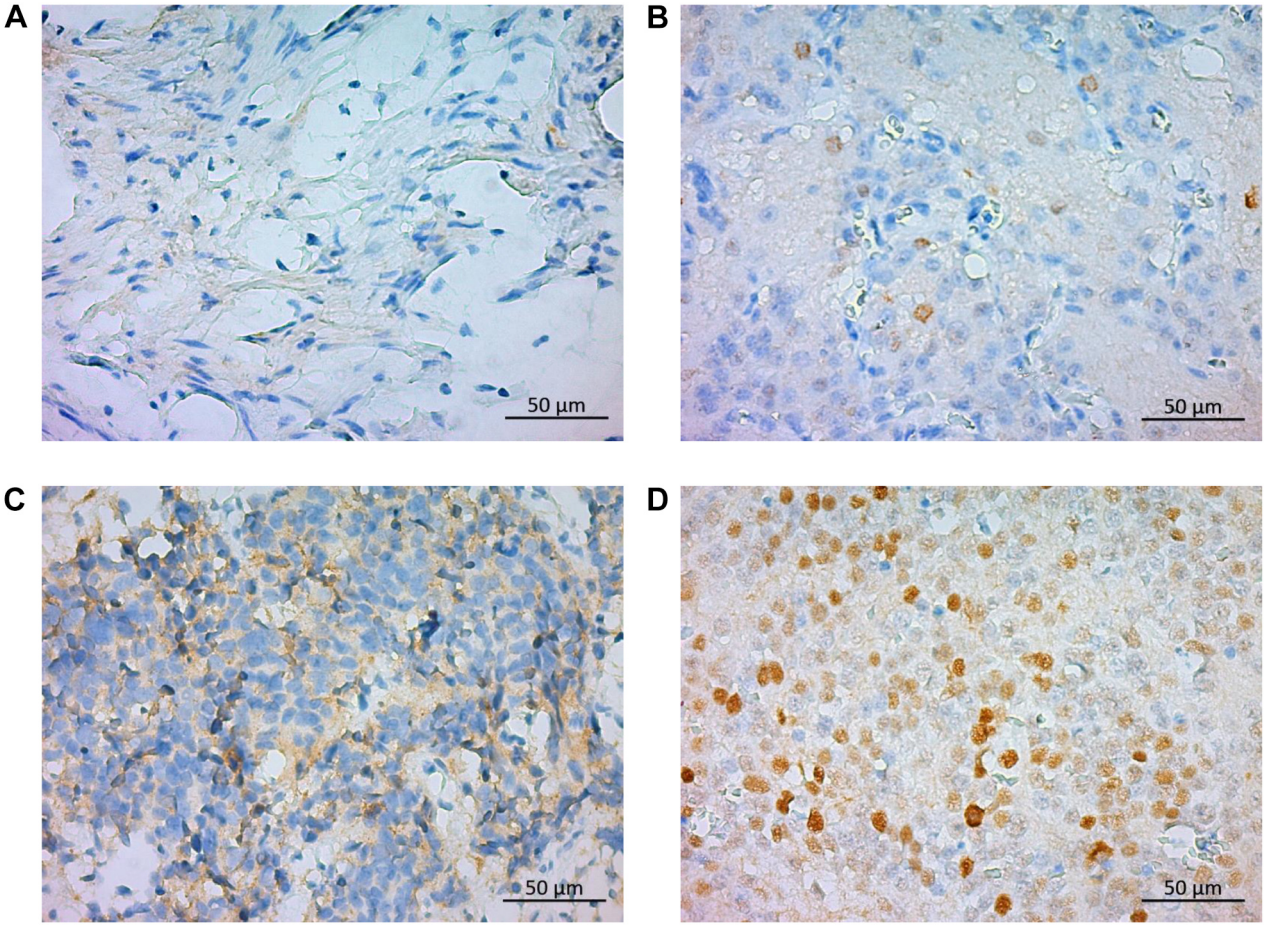

Figure 2. *Immunohistochemical staining of KPNA2 protein in ganglioneuroma, ganglioneuroblastoma, and neuroblastoma samples. Representative sections of (A) ganglioneuroma tissue without KPNA2 expression, (B) ganglioneuroblastoma tissue with low nuclear KPNA2 expression, (C) neuroblastoma tissue with low nuclear KPNA2 expression, and (D) neuroblastoma tissue with high nuclear KPNA2 expression. Scale bar=50 µm.*

E2F, the PI3K/AKT pathway, and miR-101, which are highly expressed and activated in neuroblastoma cells.

Non-radically resected neuroblastoma cases are mainly treated with systemic chemotherapy to prolong the prognosis (1). However, the results of this study showed that high KPNA2 expression was significantly associated with a poorer prognosis in such advanced patients who could not undergo radical resection. These findings suggest that KPNA2 expression may contribute to the treatment resistance to postoperative chemotherapy against residual neuroblastoma cells. In support of this hypothesis, it has been reported that KPNA2 transports the MRN complex into the nucleus, which is critical for DNA double-strand break repair; tumors that express high levels of KPNA2 are not only associated with cancer progression and poor prognosis but also show resistance to chemotherapy and radiation; and suppression of KPNA2 improves sensitivity to anticancer drugs (7, 8, 11, 21, 22). In clinical practice, KPNA2 expression in resected specimens is expected to be a biomarker predicting the risk of postoperative recurrence and treatment sensitivity. Moreover, the KPNA2 targeting strategy may be promising against refractory neuroblastoma by improving chemo-sensitivity. Further research is needed to test these promising hypotheses.

Study limitations. First, this study was performed using retrospectively collected tumor samples from only operated patients without preoperative treatments, not directly linked to the whole neuroblastoma patients. Second, the sample size was small in this study because pediatric neuroblastoma is a rare type of malignant tumor compared to adult solid cancer. Finally, functional analysis of KPNA2 was not performed using cell lines and animal experiment models.

In conclusion, this study showed that KPNA2 was strongly expressed in the nucleus of neuroblastoma cells, and high nuclear KPNA2 expression was significantly associated with poor prognosis in non-radically resected neuroblastoma

Table I. *The relationship between clinicopathological factors and nuclear KPNA2 expression in neuroblastoma patients.*

Factors	All cases (n=81)		*p*-Value	Radically resected cases (n=44)		*p*-Value	Non-radically resected cases (n=37)		*p*-Value
	Nuclear KPNA2 expression			Nuclear KPNA2 expression			Nuclear KPNA2 expression		
	Low n=58	High n=23		Low n=30	High n=14		Low n=28	High n=9	
Sex									
Male	26	11	0.807	16	5	0.273	10	6	0.136
Female	32	12		14	9		18	3	
Age, month									
<18 m	51	16	0.058	30	14	-	21	2	0.014*
≥18 m	7	7		0	0		7	7	
Distant metastasis									
Absent	21	9	0.806	19	9	0.951	2	0	1
Present	37	14		11	5		26	9	
INRGSS									
L1, L2, MS	43	14	0.245	30	13	0.318	13	1	0.112
M	15	9		0	1		15	8	
Radical resection									
No	28	9	0.455	0	0	-	28	9	-
Yes	30	14		30	14		0	0	
INPC									
Favorable	44	15	0.338	27	13	1	17	2	0.062
Unfavorable	14	8		3	1		11	7	
MYCN status (n=77)									
Not amplified	51	18	0.215	27	14	-	24	4	0.054
Amplified	4	4		0	0		4	4	
INRG staging system									
Not high	50	17	0.201	30	14	-	20	3	0.057
High	8	6		0	0		8	6	
Chemotherapy									
No	18	8	0.746	18	8	0.858	0	0	-
Yes	40	15		12	6		28	9	
Ki67 expression									
Low	36	16	0.357	19	13	0.068	17	3	0.250
High	22	7		11	1		11	6	

KPNA2: Karyopherin subunit alpha 2; INRG: International Neuroblastoma Risk Group; INPC: International Neuroblastoma Pathology Classification. *Significant difference at $p<0.05$.

patients. Our data suggested that assessing KPNA2 expression in neuroblastoma is a promising indicator of high-risk cases and that KPNA2 is a promising therapeutic candidate for patients with refractory advanced neuroblastoma.

Conflicts of Interest

The Authors declare no conflicts of interest relevant to this research.

Authors' Contributions

SO, KO and GD contributed equally to this study. SO, KO, and AN collected the samples and analyzed the data. SO, KO, GD, TY, HK, HS, and KS analyzed and interpreted the data. SO, KO, GD, and TY drafted the manuscript. SO, KO, GD, TY, HS, and KS conceptualized the study. All the Authors have read and approved the final version of the manuscript.

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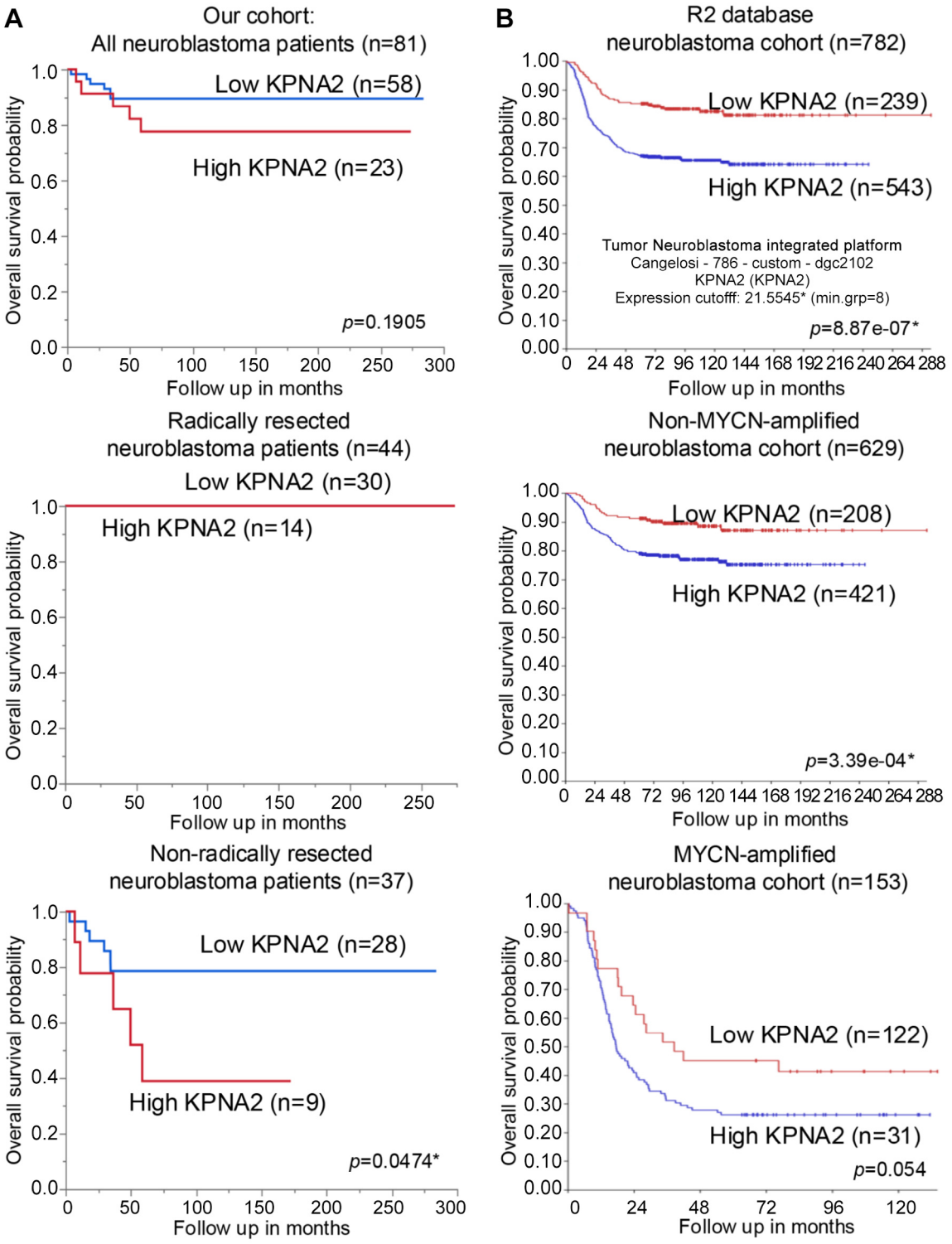

Figure 3. *Kaplan–Meier survival curves of patients with neuroblastoma based on KPNA2 expression. (A) Kaplan–Meier survival analysis based on KPNA2 expression, overall survival in our cohort of all neuroblastoma patients (n=81, p=0.1905, left panel), radically resected (n=44, middle panel), and non-radically resected (n=37, p=0.0474, right panel) neuroblastoma cases. *p<0.05. (B) Prognostic value of KPNA2 expression in neuroblastoma tissues with or without MYCN-amplification. Kaplan–Meier survival analysis based on KPNA2 mRNA expression in the R2 database of all neuroblastoma (n=782, p=8.87e-07, left panel), non-MYCN-amplified (n=629, p=3.39e-04, middle panel), and MYCN-amplified (n=153, p=0.054, right panel) neuroblastoma cases. We used an online R2 Genomics Analysis and Visualization Platform to validate the relevance of KPNA2 mRNA expression to the overall survival of patients with neuroblastoma: R2 internal identifier: ps_avgpres_dgc2102a786_dgc2102. *p<0.05.*

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