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HER2 Expression and Nuclear Localization in Clear Cell Renal Cell Carcinoma: Implications for Prognosis and Therapeutic Targeting

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Abstract

Background/Aim: The HER2 oncoprotein is a membrane-associated receptor with tyrosine kinase activity that is overexpressed in several solid tumors and is associated with poor prognosis. However, its role in renal cancer remains unclear. This study aimed to evaluate HER2 expression in renal cell carcinoma and its relationship with prognostic factors.
Materials and Methods: A total of 110 renal epithelial tumor samples were analyzed. Immunohistochemistry and immunofluorescence were performed using antibodies against HER2, hypoxia-inducible factor α (HIF1α), and EPAS1. Associations with clinicopathological parameters were evaluated using the Chi-square test.
Results: Renal cell carcinoma occurred predominantly in males and was associated with larger tumor size. HER2 expression was detected specifically in the clear cell renal cell carcinoma (ccRCC) subtype. Membranous HER2 expression was positive (3+) in 32% of cases and equivocal (2+) in 47%. Nuclear HER2 localization was observed in 33% of tumors. Membranous HER2 expression was associated with EPAS1/HIF2 expression, whereas nuclear HER2 expression was associated with higher Fuhrman nuclear grades (III-IV). Membranous HER2 was detected in both early (stage I) and advanced clinical stages (III-IV).
Conclusion: HER2 expression in ccRCC occurs in both membranous and nuclear compartments. Membranous HER2 is associated with EPAS1/HIF2 signaling, whereas nuclear HER2 localization correlates with higher Fuhrman nuclear grades. These findings suggest that HER2 may represent a potential therapeutic target and that its nuclear localization may serve as a marker of poor prognosis.

Keywords: Clear cell renal cell carcinoma, HER2, nuclear HER2, HIF2/EPAS1, Fuhrman nuclear grade, prognostic biomarkers.

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Introduction

The HER2 receptor is a 185 kDa membrane-associated protein with tyrosine kinase activity and extensive homology to the epidermal growth factor receptor (EGFR). It is involved in tumor cell proliferation, adhesion, apoptosis, differentiation, angiogenesis, and migration. Deregulation, increased expression, or mutation of HER2 has been associated with neoplastic processes (1, 2). These alterations promote receptor dimerization, which activates signaling pathways and triggers specific cellular responses through intracellular signaling cascades (3).

Increased HER2 expression correlates with unfavorable prognosis in several solid tumors and is widely used as a molecular marker (4). Studies in different types of human neoplasia have reported HER2 overexpression in approximately 38% of gastric carcinomas, 20–30% of breast cancers, 20% of cervical cancers, 15% of ovarian cancers, and 18% of colorectal cancers (5-7). In breast cancer, where membranous HER2 is used as a therapeutic target, nuclear localization of HER2 has also been described in HER2-negative tumors, showing strong oncogenic activity and contributing to resistance to treatment (8).

Renal cell carcinoma (RCC) comprises several histological subtypes, of which clear cell renal cell carcinoma (ccRCC) is the most prevalent. RCC is characterized by highly activated angiogenesis associated with alterations in the VHL and BAP1 genes. Loss or mutation of the VHL gene leads to the accumulation of hypoxia-inducible factors (HIFs) and, indirectly, to overexpression of genes such as the erythropoietin receptor, even under normoxic conditions (9-11). Among the epidermal growth factor receptor family members, EGFR has been reported to be expressed in RCC; however, the expression and role of HER2 remain unclear (9, 5, 12, 13).

Although tumor stage is the main prognostic factor in ccRCC, due to the absence of reliable molecular markers, the Fuhrman nuclear grading (FNG) system is commonly used to guide clinical management and patient follow-up (14, 15). This classification system is based on the histological evaluation of nuclear abnormalities and has strong prognostic value in RCC. It stratifies tumors into four Fuhrman grades (FNG 1-4), which correlate with survival, recurrence, and the probability of metastasis, with FNG-4 associated with the worst prognosis (16, 17).

Based on these observations, we hypothesize that the HER2 receptor may be involved in kidney cancer progression and treatment resistance. Therefore, the aim of this study was to evaluate whether HER2 could serve as a molecular marker in kidney cancer by analyzing HER2 expression and its relationship with established prognostic factors.

Materials and Methods

Patient samples. A retrospective study was conducted between 2019 and 2025 on 110 samples of renal epithelial tumors, including normal kidney tissue (non-tumoral), oncocytoma (benign tumor), and RCC. All samples were formalin-fixed and paraffin-embedded and were obtained from the Pathology Departments of J.R. Vidal Hospital and José de San Martín Teaching Hospital, located in Corrientes Province, Argentina. Cases presenting necrosis greater than 30%, extensive hemorrhage, insufficient sample size, or incomplete clinical data were excluded. Epidemiological, clinical, and pathological information was collected using a standardized data collection form.

Ethical considerations. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Research Ethics Committee of Hospital Universitario "J.R. Vidal" – Universidad Nacional del Nordeste (J.R. Vidal University Hospital – National University of the Northeast). The study was approved under the protocol titled "Estudio de los mecanismos moleculares del oncogén ErbB2 en relación a otros ErbBs en el carcinoma de células renales". The committee does not assign numerical reference codes to its approvals. Written informed consent was obtained from all participants in accordance with Argentine Law No. 25,326 on Personal Data Protection. Each participant received the informed consent form for the use of human biological

material and/or clinical data for scientific research prior to sample collection.

Informed consent was obtained from all subjects involved in the study, in accordance with Law No. 25,326 on Personal Data Protection. Each participant received the Informed Consent Form for the Use of Human Biological Material and/or Clinical Data for Scientific Research, and written consent was obtained prior to sample collection.

Immunohistochemical study. Two-micron sections were obtained from formalin-fixed, paraffin-embedded tissue blocks. After deparaffinization and rehydration in xylene and graded alcohols, antigen retrieval was performed using proteinase K (Bio basic PB0451, Markham, Canada) at pH 8 (10 μg/ml). Sections were incubated overnight with the following primary antibodies: ErbB-2 (HER2) 3B5 antibody (Thermo Fisher Scientific, Waltham, MA, USA, Cat# MA5-13675, RRID: AB_10985617), c-erbB-2 oncoprotein antibody (Agilent DAKO, Santa Clara, CA, USA, Cat# A0485, RRID: AB_2335701), HIF1α antibody (Santa Cruz Biotechnology, Dallas, TX, USA, Cat# sc-8711, RRID: AB_2116993), and EPAS-1 antibody (Santa Cruz Biotechnology, Cat# sc-13596, RRID: AB_627525).

Samples were incubated with anti-mouse/anti-rabbit secondary antibodies followed by streptavidin (Vectastain® Elite® ABC Universal Kit PK-7200, Vector Labs, Newark, CA, USA). Signal detection was performed using DAB (substrate kit, Cell Label 957D-20, Cell Marque, Darmstadt, Germany) and sections were counterstained with hematoxylin (GILL II, Biopack solution 9491.07, Buenos Aires, Argentina).

Immunofluorescence (IHF). Sections were incubated with recombinant rabbit anti-mouse IgG secondary antibody Alexa Fluor™ Plus 488 (green) (Invitrogen, Carlsbad, CA, USA). Slides were mounted using ProLong™ Gold Antifade Mountant with DAPI (p36941) Invitrogen, California, USA for nuclear staining. A breast cancer tissue sample was used as a positive control for HER2. Negative controls (without primary antibody) were included in each experiment. Immunostaining was evaluated independently by observers blinded to clinicopathological data. Interobserver agreement was assessed using the kappa coefficient (κ=0.616), indicating good agreement. Discrepancies were resolved by joint review. Each slide was examined under a light microscope at 400× magnification, focusing on areas with the highest proportion of positively stained tumor cells. A minimum of 100 cells per sample was evaluated. Membranous HER2 expression was scored according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines used for breast cancer (18). Nuclear HER2 expression was evaluated using the scoring system described by Schillaci, *et al*. (19).

Table I. *Distribution of renal carcinoma in the study population. Distribution of renal carcinoma 110 cases according to sex, age group, and tumor anatomical location.*

Distribution according to age range and sex			
Age range	Female	Male[a]	*p*-Value
20-29	1	1	>0.5
30-40	2	4[a]	0.01
41-50	6	12[a]	0.01
51-60	10	19[a]	0.01
61-79	15	35[a]	0.01

Distribution according to sex and location				
Sex	No data	Right	Left	*p*-Value
Female	2	19	15	>0.5
Male	3	35	36	>0.5

[a]Statistically significant differences were assessed using a *t*-test (*p=0.01).

Data analysis. Clinical and epidemiological data were analyzed using GraphPad Prism 6 and SPSS software. Associations between variables were evaluated using the chi-square test. A p-value ≤0.05 was considered statistically significant. Microsoft Excel was used for graphical data representation.

Results

The distribution of renal cancer in our population was analyzed. Table I shows a significant difference according

to sex, with renal cancer occurring more frequently in men than in women. The number of cases increased from the 30–40-year age group, with peak frequencies observed in the 51–60 and 61–79-year age groups. Regarding tumor laterality, analysis by sex showed that renal carcinoma occurred in both kidneys in both female and male patients. Poor prognostic factors associated with RCC were analyzed according to sex, including tumor size, FNG, and clinical stage. Figure 1 presents the analysis of these parameters in female and male subgroups. A significant difference was observed for tumor size, with men presenting a higher mean tumor size. No significant differences were observed for FNG or clinical stage between sexes.

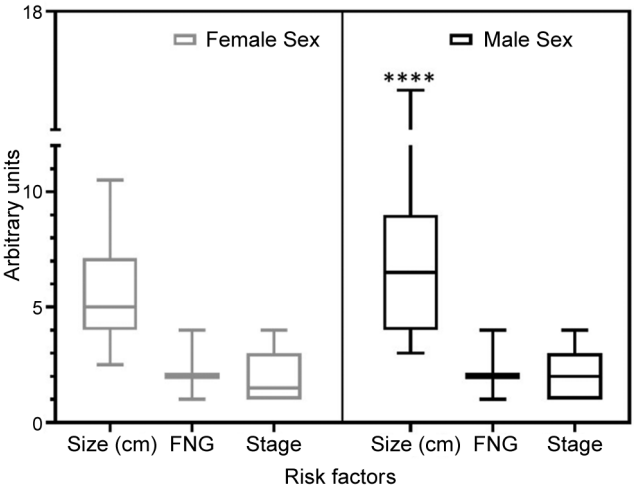


Figure 1. *Clinical characteristics of renal carcinoma in the study population. Comparison of risk factors between female and male patients, including tumor size, Fuhrman nuclear grade (FNG), and clinical stage. A total of 110 samples were analyzed. Associations were analyzed using the chi-square test (****p=0.0001).*

Next, HER2 expression was evaluated in RCC samples of different histological types and compared with normal kidney tissue and benign tumors. Figure 2A (left) shows that HER2 expression was specifically detected in the ccRCC subtype, as confirmed using two different antibodies. Membranous HER2 expression was quantified using the scoring system established by the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP), which is commonly applied for HER2 assessment in breast cancer (Figure 2A, right).

HER2 expression was analyzed in 95 ccRCC cases. Figure 2B (left) shows the distribution of membranous HER2 expression: 32% (31 cases) were HER2-positive (3+), 47% (46 cases) were equivocal (2+), and 21% (20 cases) were negative (0–1+). The distribution between positive and negative groups was statistically significant (*t*-test *p*=0.0001). For diagnostic purposes, equivocal cases (2+) should be confirmed by fluorescence in situ hybridization (FISH). Representative immunohistochemistry images of the four scoring categories are shown in Figure 2B (right).

In addition to membranous expression, HER2 expression was also observed at the nuclear level. As shown in Figure 3A, nuclear HER2 expression was detected in 33% of cases, including strong expression (3+) in 9.3% and moderate expression (2+) in 23.7% of cases, while 67% of cases were negative (0–1+). The immunofluorescence-based scoring is presented in Figure 3B.

Based on these findings, we evaluated whether HER2 expression was associated with HIFs, considering the frequent absence of functional VHL in ccRCC. Figure 4A illustrates the relationship between HER2 and HIF1 expression. In some cases, HER2 expression in the membrane and/or nucleus was accompanied by nuclear HIF1 expression (cases 3 and 4). However, this association was not consistent, as cases with HER2-positive/HIF1-negative expression (case 1) and HER2-negative/HIF1-positive expression (case 2) were also observed. In contrast, a different pattern was observed for HIF2. HER2 expression in the membrane and/or nucleus was associated with nuclear HIF2 expression in several cases (cases 1, 3, and 4), whereas HER2-negative cases showed low (1+) or absent HIF2 expression (case 2). To further investigate this relationship, we analyzed the correlation between HER2 and HIF2 gene expression using data from the TCGA Kidney dataset available in the ONCOMINE database (20). Figure 4B shows the correlation between HER2 mRNA expression (four probes) and HIF2 (probe 1). Similar results were obtained when HER2 probes were analyzed against HIF1. Considering that Pearson's correlation coefficient values between 0 and 1 indicate a

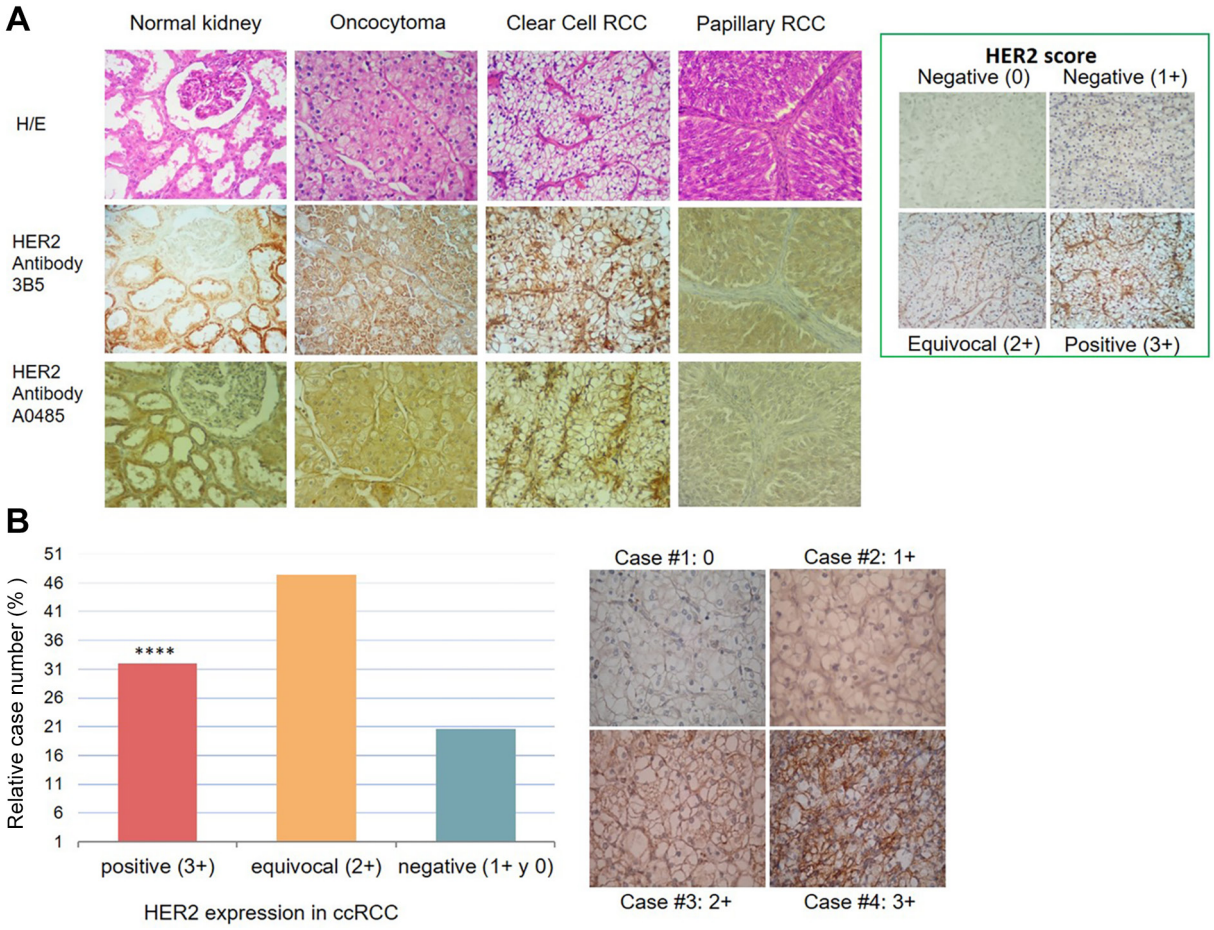


Figure 2. *Membranous HER2 expression in renal cell carcinoma (RCC). (A, left) Representative images of normal kidney (3 cases), oncocytoma (6 cases), and two RCC subtypes (clear cell and papillary). A total of 98 cases were analyzed, the majority of which were of the clear cell RCC subtype. Three cases were removed due to sample exclusion criteria (n=95). The first row shows hematoxylin and eosin (H&E) staining, and the subsequent rows show immunohistochemistry (IHC) using ErbB2 antibodies (3B5, Thermo Fisher and A0485, DAKO). (A, right) Quantification of membranous HER2 expression in RCC using the 3B5 Pierce antibody (400× magnification). (B, left) Graph showing the distribution of membranous HER2 expression across 97 ccRCC cases. (B, right) Representative IHC images under an optical microscope (200× magnification). Statistical analysis was performed using a t-test (****p=0.0001). All described techniques were performed in duplicate for each sample, and microscopic evaluation was conducted by three independent observers.*

positive correlation, our analysis showed a weak positive correlation (Pearson's r=0.053).

Finally, the association between HER2 expression and prognostic factors in ccRCC was evaluated. The relationship between HER2 expression and Fuhrman nuclear grade was analyzed. Membranous HER2 expression was associated with Fuhrman nuclear grade II (Figure 5A), whereas nuclear HER2 expression was associated with higher nuclear grades (III and IV) (Figure 5B). The association between HER2 expression and clinical stage was also evaluated. Membranous HER2 expression was detected in tumors with both early (stage I) and advanced (stages III and IV) clinical stages, but not in intermediate stage II tumors (Figure 5C). In contrast, no significant association was observed between nuclear HER2 expression and clinical stage (Figure 5D).

Discussion

In the present study, we analyzed the distribution of RCC in our cohort and observed a higher frequency and larger

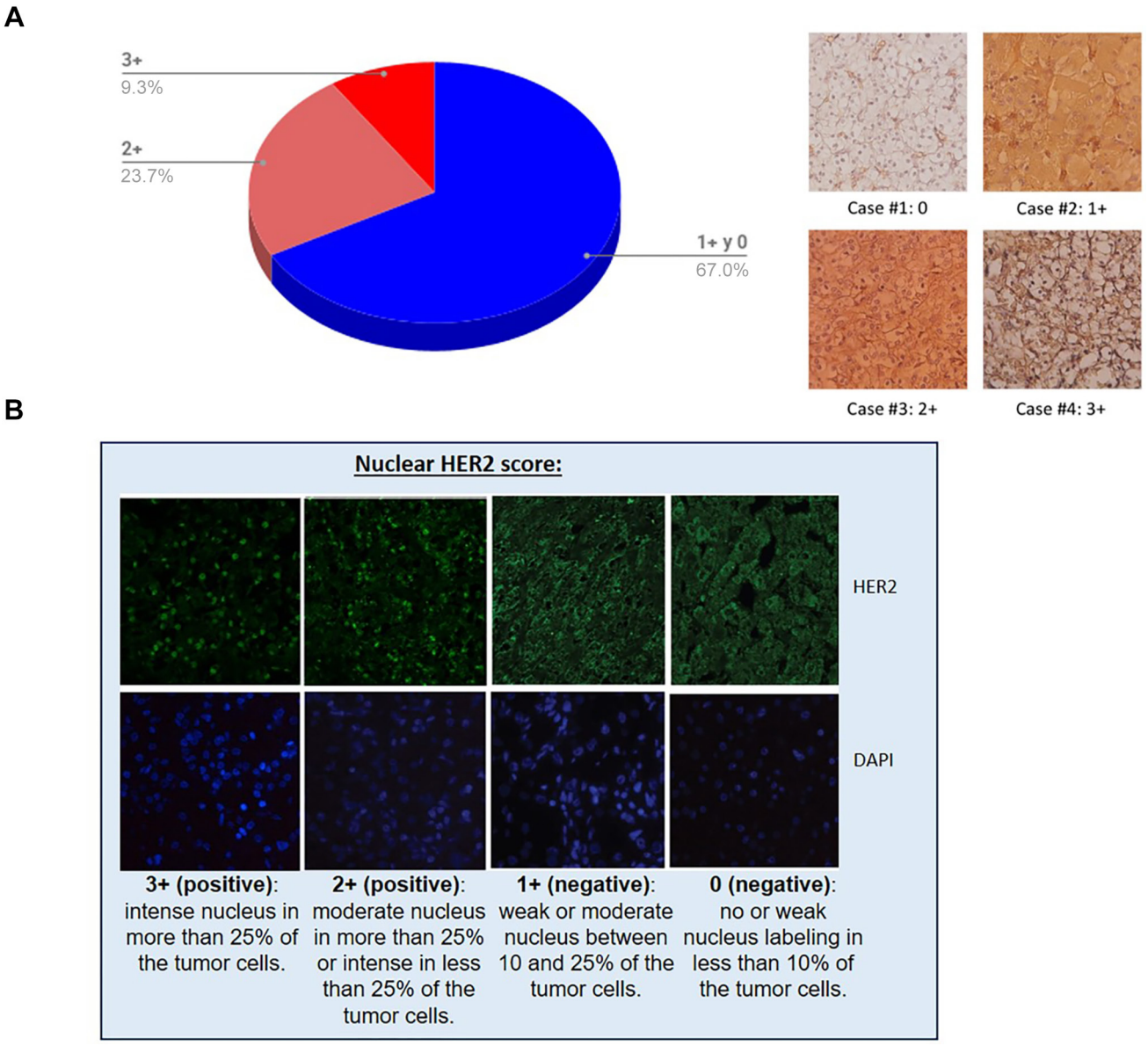
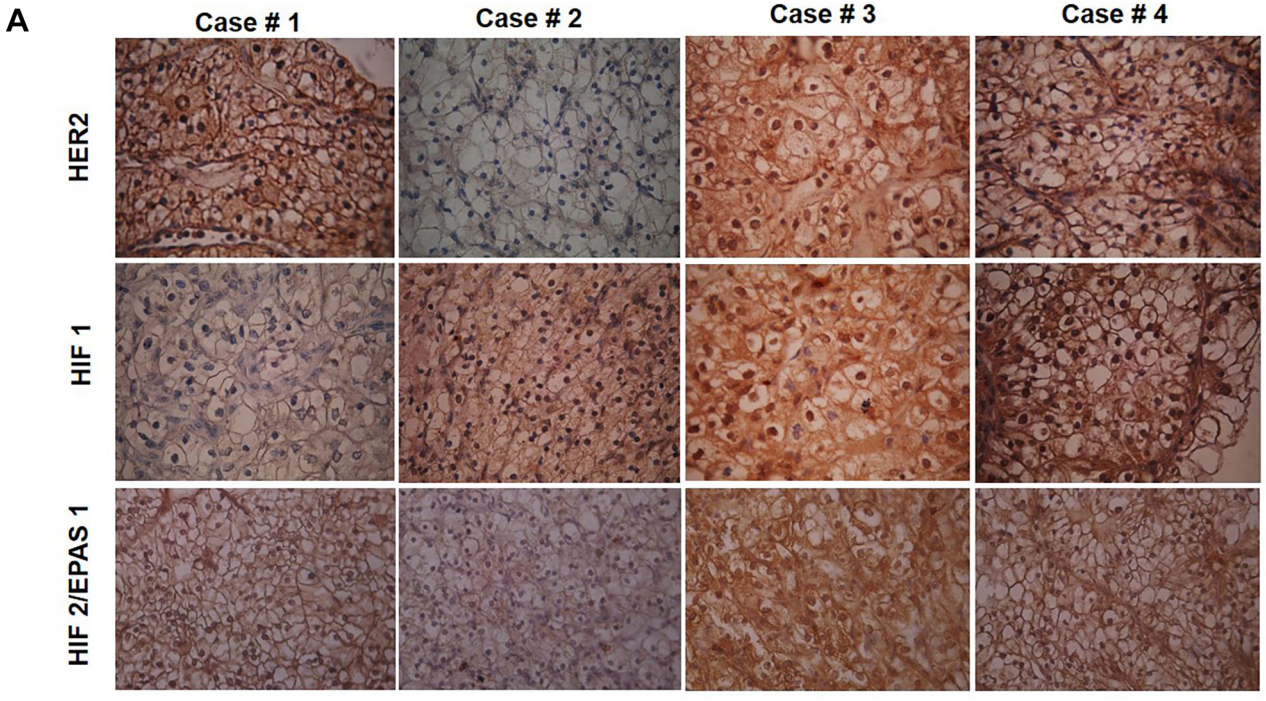


Figure 3. *Nuclear HER2 expression in clear cell renal cell carcinoma (ccRCC). (A) Graph showing the distribution of nuclear HER2 expression across 97 ccRCC cases, with representative immunohistochemistry (IHC) images under an optical microscope (200× magnification) shown on the right. The IHC techniques were performed in duplicate for each sample, and microscopic evaluation was conducted by three independent observers. (B) Validation of nuclear HER2 scoring by immunofluorescence, following the guidelines described in materials and methods.*

tumor size in the male population compared with females. In our population, increased tumor size appeared to be associated with poorer prognosis only in men, whereas the other analyzed parameters did not show significant sex-related differences. The higher incidence and larger tumor size observed in men are consistent with previous reports indicating a higher mortality rate from RCC in males (21, 22).

In the search for oncological markers that may guide therapeutic strategies in renal cancer, we evaluated HER2



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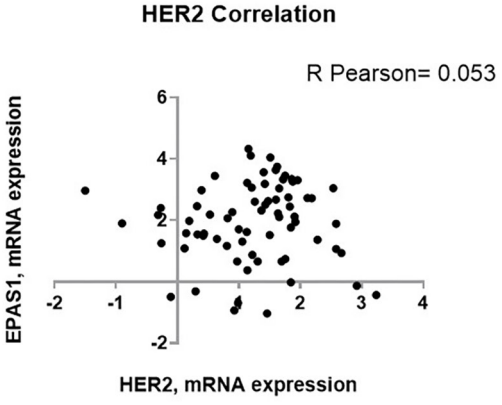

probe 3 HER2 * probe 1 EPAS1 Crosstabulation

Count

		probe 1 EPAS1		
		0	1	Total
probe 3 HER2	0	1	5	6
	1	7	59	66
Total		8	64	72

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Interval by Interval	Pearson's R	0.053	0.138	0.447	0.657[c]
Ordinal by Ordinal	Spearman Correlation	0.053	0.138	0.447	0.657[c]
N of Valid Cases		72			

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the null hypothesis.
c. Based on normal approximation.

Figure 4. *Relationship between HER2 and hypoxia-inducible factor (HIF) expression in clear cell renal cell carcinoma (ccRCC). (A) Representative immunohistochemistry (IHC) images showing HER2, HIF1, and HIF2/EPAS1 expression in four ccRCC cases (400× magnification). The IHC techniques were performed in duplicate for each sample, and microscopic evaluation was conducted by three independent observers. (B) Correlation analysis between HER2 (probe 3) and EPAS1/HIF2 (probe 1) using data from the Oncomine TCGA renal dataset. Pearson's correlation coefficient r=0.053. All other probes available in Oncomine yielded similar correlation results.*

expression in RCC. Our results showed that HER2 is specifically expressed in the membrane of the ccRCC subtype in 32% of cases (3+). Some studies have reported an absence of HER2 overexpression in ccRCC (23), whereas others have demonstrated membranous HER2 expression in this subtype (12). In agreement with our findings, Phuoc *et al.* (24) reported high HER2 expression levels by immunohistochemistry, although they did not find an association with survival. Similarly, Nagasawa *et al.* (25) demonstrated that treatment with a HER2 inhibitor

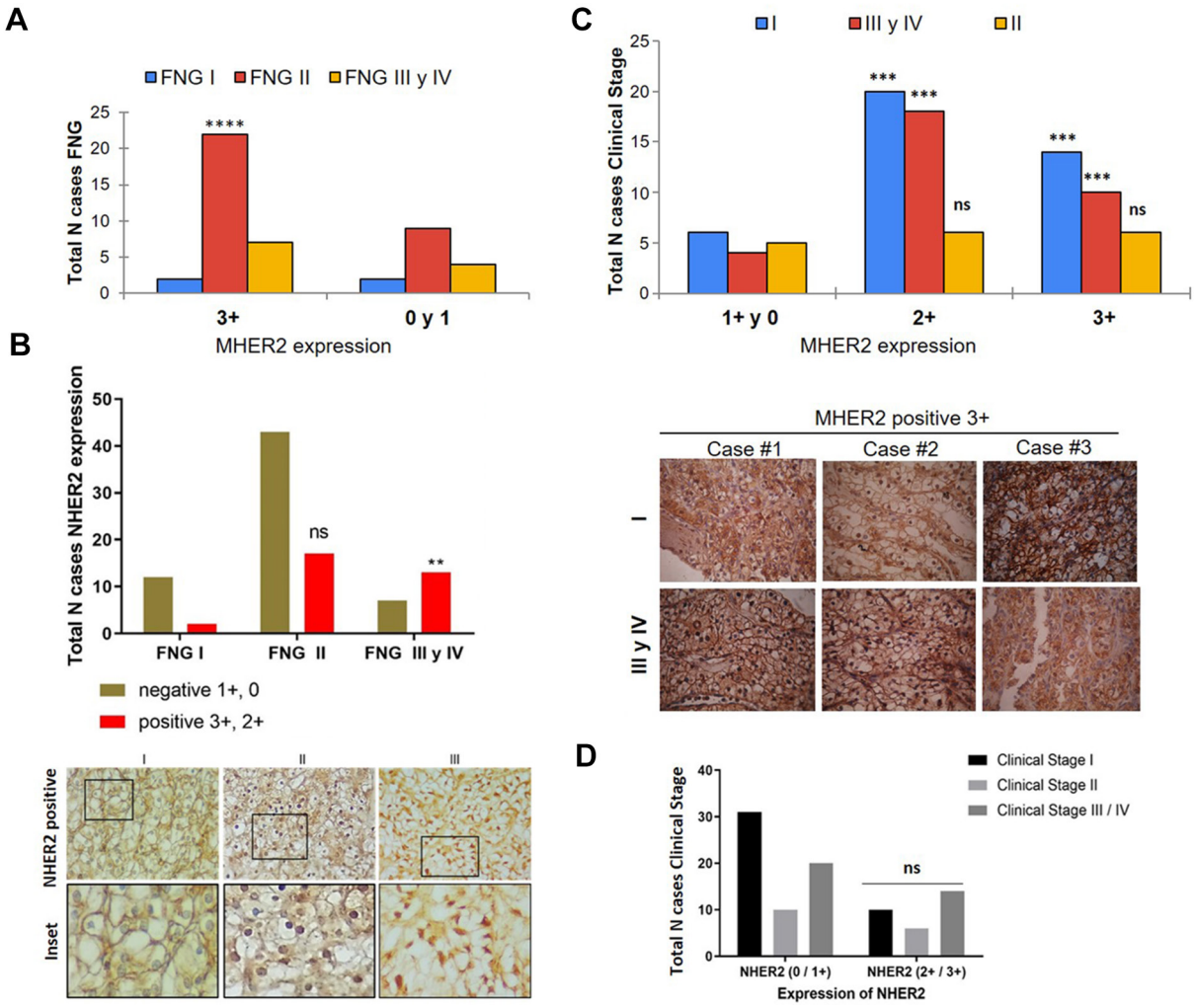

Figure 5. *Association of HER2 expression with prognostic factors in clear cell renal cell carcinoma (ccRCC). (A) Membranous HER2 (MHER2) expression and Fuhrman nuclear grade (FNG). Distribution of membranous HER2 according to FNG: I (blue), II (red), III and IV (yellow). Statistical analysis was performed using Fisher's exact test (****p=0.0001). (B) Nuclear HER2 (NHER2) expression and FNG. Left: Statistical comparison using Fisher's exact test (**p=0.0051). Right: Representative immunohistochemistry (IHC) images of nuclear HER2-positive tumors in FNG I, II, and III (400× magnification). (C) Membranous HER2 expression and clinical stage. Left: Analysis using a t-test (***p=0.001), with stages I (blue), II (yellow), III and IV (red). Right: Representative IHC images of membranous HER2-positive tumors (3+) in clinical stages I and II (400× magnification). (D) Nuclear HER2 expression and clinical stage. Fisher's exact test comparing nuclear HER2-negative and -positive tumors across clinical stages I, II, and III/IV (not statistically significant, p=0.142). The IHC techniques were performed in duplicate for each sample, and microscopic evaluation was conducted by three independent observers.*

reduced the growth of RCC xenograft tumors until their disappearance. Likewise, in patients with upper urinary tract urothelial carcinoma, high HER2 expression was found and was associated with low survival (26). The discrepancies among studies may be explained by differences in detection methods. It has been suggested that the HER2 oncoprotein may accumulate in the cell membrane without a corresponding increase in gene amplification in ccRCC. Consequently, elevated HER2 protein levels may be detected by immunohistochemistry (12, 24) or Western blotting (25) but not necessarily by PCR-based approaches (23). Indirectly, since there is still

no clear connection between HER2 and mitochondrial aconitase 2 (ACO2), it has been reported that mitochondrial ACO2 shows a significant correlation with worse overall survival among patients with RCC. This suggests that HER2 could be promoting this mechanism (27).

In addition to membranous expression, we observed nuclear HER2 localization in 33% of cases. This finding is noteworthy because nuclear HER2 expression has not been extensively investigated in renal cancer. Similar observations have been reported in highly aggressive triple-negative breast cancer, where nuclear HER2 can activate gene transcription (19). Furthermore, nuclear HER2 activity has been associated with resistance to therapy in gastric cancer (28). Based on these observations, it is possible that nuclear HER2 may act as a transcriptional regulator in renal cancer, potentially contributing to tumor progression. The relatively high frequency of HER2 expression in the ccRCC subtype may be partly explained by its association with HIF2, as suggested by our TCGA analysis using the ONCOMINE database.

Regarding prognostic implications, membranous HER2 expression was associated with Fuhrman nuclear grade II, whereas nuclear HER2 expression was associated with higher nuclear grades (III and IV). To our knowledge, few studies have addressed the relationship between HER2 localization and Fuhrman nuclear grade in RCC. These findings suggest that nuclear localization of HER2 may be associated with nuclear dedifferentiation observed in high-grade tumors, which is typically related to poorer prognosis. Similar observations have been reported in breast cancer, where nuclear HER2 localization correlates with worse clinical outcomes (28).

When analyzing the relationship between membranous HER2 expression and clinical stage, we observed HER2 expression in both early (stage I) and advanced stages (III and IV), but not in intermediate stage II tumors. These findings suggest that HER2 may contribute to ccRCC progression through different mechanisms depending on the stage of disease. The presence of membranous HER2 in advanced stages, together with nuclear HER2 expression in high Fuhrman grades, suggests that HER2 may represent both a potential therapeutic target and a marker of poor prognosis associated with its nuclear localization (29). To date, few studies have evaluated the relationship between HER2 expression and clinical stage in RCC. However, similar associations have been described for vascular endothelial growth factor (VEGF), which has been correlated with Fuhrman nuclear grade (30). Overall, the HER2 expression pattern observed in our cohort is of particular interest in ccRCC, as it suggests a possible role for HER2 in nuclear differentiation mechanisms and tumor progression. These findings contribute to the identification of potential therapeutic targets and to a better understanding of the molecular mechanisms involving the HER2 oncogene in renal cancer.

Conclusion

RCC in our cohort was more frequent in males and was associated with larger tumor size. HER2 expression was detected in both the cell membrane and nucleus in the ccRCC subtype. Membranous HER2 expression was associated with EPAS1/HIF2 expression, whereas nuclear HER2 localization was associated with higher Fuhrman nuclear grades (III–IV). Membranous HER2 expression was observed in clinical stages I and III. These findings suggest that HER2 may represent a potential therapeutic target in ccRCC and that its nuclear localization may be associated with markers of poor prognosis.

Conflicts of Interest

The Authors declare that there are no conflicts of interest related to this study.

Authors' Contributions

MA Cortés: Contributed to the experimental design, execution of experiments, data analysis, and manuscript preparation. HM Marín: Contributed to data analysis and manuscript preparation. N Barbás: Contributed to sample collection and data analysis. R Cordo-Ruso: Contributed

to the experimental design and execution of experiments. L Rott: Contributed to sample collection and data analysis. GE Giusiano: Procurement of reagents and manuscript revision. LA Merino: Procurement of reagents and manuscript revision.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

References

1 Baselga J, Swain SM: Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer 9(7): 463-475, 2009. DOI: 10.1038/nrc2656

2 Minner S, Rump D, Tennstedt P, Simon R, Burandt E, Terracciano L, Moch H, Wilczak W, Bokemeyer C, Fisch M, Sauter G, Eichelberg C: Epidermal growth factor receptor protein expression and genomic alterations in renal cell carcinoma. Cancer 118(5): 1268-1275, 2012. DOI: 10.1002/cncr.26436

3 Moasser MM: The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene 26(45): 6469-6487, 2007. DOI: 10.1038/sj.onc.1210477

4 Wang H, Liu C, Han J, Zhen L, Zhang T, He X, Xu E, Li M: HER2 expression in renal cell carcinoma is rare and negatively correlated with that in normal renal tissue. Oncol Lett 4(2): 194-198, 2012. DOI: 10.3892/ol.2012.727

5 Wang Z: ErbB receptors and cancer. Methods Mol Biol 1652: 3-35, 2017. DOI: 10.1007/978-1-4939-7219-7_1

6 Yu S, Liu Q, Han X, Qin S, Zhao W, Li A, Wu K: Development and clinical application of anti-HER2 monoclonal and bispecific antibodies for cancer treatment. Exp Hematol Oncol 6: 31, 2017. DOI: 10.1186/s40164-017-0091-4

7 Bose R, Kavuri SM, Searleman AC, Shen W, Shen D, Koboldt DC, Monsey J, Goel N, Aronson AB, Li S, Ma CX, Ding L, Mardis ER, Ellis MJ: Activating HER2 mutations in HER2 gene amplification negative breast cancer. Cancer Discov 3(2): 224-237, 2013. DOI: 10.1158/2159-8290.CD-12-0349

8 Luo B, Wu XH, Feng YJ, Zheng HM, Zhang Q, Liang XJ, Huang DF, Xu J: Nuclear Her2 contributes to paclitaxel resistance in breast cancer cells. Anticancer Drugs 32(7): 709-716, 2021. DOI: 10.1097/CAD.0000000000001048

9 Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, Heng DY, Larkin J, Ficarra V: Renal cell carcinoma. Nat Rev Dis Primers 3: 17009, 2017. DOI: 10.1038/nrdp.2017.9

10 Luviano-García EH, Sandoval-Pulido JI, González-Pérez R, García-Torres V, Cueva Martínez E, Sierra-Díaz E: TNM vs grado nuclear (OMS-ISUP): supervivencia en pacientes con cáncer renal de células claras. Bol Col Mex Urol 36: 1-5, 2021.

11 Nabi S, Kessler ER, Bernard B, Flaig TW, Lam ET: Renal cell carcinoma: a review of biology and pathophysiology. F1000Res 7: 307, 2018. DOI: 10.12688/f1000research.13179.1

12 Costantini M, Amoreo CA, Torregrossa L, Alì G, Munari E, Jeronimo C, Henrique R, Petronilho S, Capitanio U, Lucianò R, Suardi N, Landi MT, Anceschi U, Brassetti A, Fazio VM, Gallucci M, Simone G, Sentinelli S, Poeta ML: Assessment of HER2 protein overexpression and gene amplification in renal collecting duct carcinoma: therapeutic implication. Cancers (Basel) 12(11): 3345, 2020. DOI: 10.3390/cancers12113345

13 Yorozu T, Sato S, Kimura T, Iwatani K, Onuma H, Yanagisawa T, Miki J, Egawa S, Ikegami M, Takahashi H: HER2 status in molecular subtypes of urothelial carcinoma of the renal pelvis and ureter. Clin Genitourin Cancer 18(4): e443-e449, 2020. DOI: 10.1016/j.clgc.2019.12.003

14 Novara G, Martignoni G, Artibani W, Ficarra V: Grading systems in renal cell carcinoma. J Urol 177(2): 430-436, 2007. DOI: 10.1016/j.juro.2006.09.034
15 Delahunt B, Eble JN, Egevad L, Samaratunga H: Grading of renal cell carcinoma. Histopathology 74(1): 4-17, 2019. DOI: 10.1111/his.13735
16 Delahunt B, Eble JN, Samaratunga H, Thunders M, Yaxley JW, Egevad L: Staging of renal cell carcinoma: current progress and potential advances. Pathology 53(1): 120-128, 2021. DOI: 10.1016/j.pathol.2020.08.007
17 DA Silva Prade J, DE Souza RS, DA Silva D'Avila CM, DA Silva TC, Livinalli IC, Bertoncelli ACZ, Saccol FK, DE Oliveira Mendes T, Wenning LG, DA Rosa Salles T, Rhoden CRB, Cadona FC: An overview of renal cell carcinoma hallmarks, drug resistance, and adjuvant therapies. Cancer Diagn Progn 3(6): 616-634, 2023. DOI: 10.21873/cdp.10264
18 Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF, American Society of Clinical Oncology, College of American Pathologists: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med 138(2): 241-256, 2014. DOI: 10.5858/arpa.2013-0953-SA
19 Schillaci R, Guzmán P, Cayrol F, Beguelin W, Díaz Flaqué MC, Proietti CJ, Pineda V, Palazzi J, Frahm I, Charreau EH, Maronna E, Roa JC, Elizalde PV: Clinical relevance of ErbB-2/HER2 nuclear expression in breast cancer. BMC Cancer 12: 74, 2012. DOI: 10.1186/1471-2407-12-74
20 Rhodes DR, Yu J, Shanker K, Deshpande N, Varambally R, Ghosh D, Barrette T, Pandey A, Chinnaiyan AM: ONCOMINE: a cancer microarray database and integrated data-mining platform. Neoplasia 6(1): 1-6, 2004. DOI: 10.1016/s1476-5586(04)80047-2
21 Álvarez-Sánchez IM, Polo-Rosales Y, Zaragoza-Durañona R, Sánchez-Lorenzo IM: Características clínicas y epidemiológicas de pacientes con adenocarcinoma de células renales tratados con nefrectomía radical. Revista Electrónica Dr. Zoilo E. Marinello Vidaurreta, 45(6), 2020. Available at: http://revzoilomarinello.sld.cu/index.php/zmv/article/view/2335
22 Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, Gore JL, Sun M, Wood C, Russo P: Epidemiology of renal cell carcinoma. Eur Urol 75(1): 74-84, 2019. DOI: 10.1016/j.eururo.2018.08.036
23 Latif Z, Watters AD, Bartlett JM, Underwood MA, Aitchison M: Gene amplification and overexpression of HER2 in renal cell carcinoma. BJU Int 89(1): 5-9, 2002.
24 Phuoc NB, Ehara H, Gotoh T, Nakano M, Yokoi S, Deguchi T, Hirose Y: Immunohistochemical analysis with multiple antibodies in search of prognostic markers for clear cell renal cell carcinoma. Urology 69(5): 843-848, 2007. DOI: 10.1016/j.urology.2007.01.069
25 Nagasawa J, Mizokami A, Koshida K, Yoshida S, Naito K, Namiki M: Novel HER2 selective tyrosine kinase inhibitor, TAK-165, inhibits bladder, kidney and androgen-independent prostate cancer *in vitro* and *in vivo*. Int J Urol 13(5): 587-592, 2006. DOI: 10.1111/j.1442-2042.2006.01342.x
26 Hashimoto M, Fujita K, Tomiyama E, Fujimoto S, Adomi S, Banno E, Minami T, Takao T, Nozawa M, Fushimi H, Yoshimura K, Nonomura N, Uemura H: Immunohistochemical analysis of HER2, EGFR, and Nectin-4 expression in upper urinary tract urothelial carcinoma. Anticancer Res 43(1): 167-174, 2023. DOI: 10.21873/anticanres.16146
27 Jaworski D, Kowalewski A, Durślewicz J, Antosik P, Smolińska M, Grzanka D, Szylberg Ł: The prognostic role of ACO2 in renal cell carcinoma. Anticancer Res 43(4): 1503-1511, 2023. DOI: 10.21873/anticanres.16299
28 Shi W, Zhang G, Ma Z, Li L, Liu M, Qin L, Yu Z, Zhao L, Liu Y, Zhang X, Qin J, Ye H, Jiang X, Zhou H, Sun H, Jiao Z: Hyperactivation of HER2-SHCBP1-PLK1 axis promotes tumor cell mitosis and impairs trastuzumab sensitivity to gastric cancer. Nat Commun 12(1): 2812, 2021. DOI: 10.1038/s41467-021-23053-8
29 Nami B, Wang Z: A non-canonical p75HER2 signaling pathway underlying trastuzumab action and resistance in breast cancer. Cells 13(17): 1452, 2024. DOI: 10.3390/cells13171452
30 Lkhagvadorj S, Oh SS, Lee MR, Jung JH, Chung HC, Cha SK, Eom M: VEGFR-1 expression relates to Fuhrman nuclear grade of clear cell renal cell carcinoma. J Lifestyle Med 4(1): 64-70, 2014. DOI: 10.15280/jlm.2014.4.1.64