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RAD51, *BRCA1*, and *BRCA2*: Can Be Promising Prognostic Factors and New Therapy Targets for Clear Cell Renal Cell Carcinoma Patients?

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What's known on the subject? and What does the study add?

RAD51 showed increased immunohistochemical (IHC) expression in clear cell renal cell carcinoma (ccRCC), while *BRCA1* and *BRCA2* show reduced IHC expression, suggesting impaired homologous recombination (HR) repair mechanisms in ccRCCs. High *RAD51* expression is associated with poor prognostic factors of ccRCC patients. High *BRCA1/BRCA2* expression is linked to good prognostic factors of ccRCC patients. Expression of these DNA repair proteins may serve as prognostic markers for ccRCC patients, helping to predict cancer aggressiveness and metastasis and detect outcomes. Targeting HR-proficient /deficient ccRCC with DNA repair-targeting therapies, *RAD51* inhibitors or PARP inhibitors could be a promising treatment approach.

Abstract

Objective: Clear cell renal cell carcinoma (ccRCC) is the predominant form of renal cell carcinoma, distinguished by its genetic alterations that affects the tumor's progression and response to treatment. *RAD51*, *BRCA1*, and *BRCA2* are fundamental components of the homologous recombination (HR) DNA repair system, which is vital for preserving genomic stability. Yet, data regarding their expression pattern and potential role in ccRCC development and progression remain unclear. The aim of this work was to study the immunohistochemical expression of *RAD51*, *BRCA1*, and *BRCA2* in ccRCC and to investigate the correlation between their expression levels and the clinical outcomes of patients with ccRCC.

Materials and Methods: Across-sectional study has been performed at Zagazig University's Faculty of Medicine using data from the Pathology Department archives between January 2020 and December 2023 through analyzing 76 ccRCC specimens who underwent either a total (56 cases) or partial nephrectomy (20 cases) to determine the *RAD51*, *BRCA1*, and *BRCA2* immunohistochemical expressions and comparing these with clinicopathologic parameters and survival.

Results: High nuclear expression of *RAD51* was detected in 42.1% of cases and was significantly associated with poor prognostic indicators, including advanced tumor stage, lymphatic spread, distant metastasis, and recurrence. High nuclear expression of *BRCA1*, *BRCA2*, and both proteins was detected in 51.3%, 35.5%, and 27% of cases, respectively, and their immune expression was significantly correlated with favorable prognostic indicators, including early tumor stage and absence of lymphatic spread. High *RAD51* expression showed significant indirect correlations with *BRCA1* expression and with the co-expression of *BRCA1* and *BRCA2*. Using Kaplan-Meier analysis, patients with high *RAD51* and low *BRCA1* expression had shorter disease-free survival and overall survival.

Conclusion: This research emphasizes the significance of *RAD51*, *BRCA1*, and *BRCA2* in the progression of ccRCC. Elevated *RAD51* levels alongside reduced *BRCA1* and *BRCA2* expression are associated with more aggressive tumors, suggesting their potential as immunohistochemical prognostic indicators and providing insights into novel therapeutic approaches for patients with ccRCC.

Keywords: *RAD51*, *BRCA1*, *BRCA2*, clear cell renal cell carcinoma, immunohistochemistry, homologous recombination, prognosis

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Introduction

Renal cell carcinoma (RCC) is a highly prevalent malignancy of the urinary system and one of the ten most frequently diagnosed solid tumors (1). Clear cell renal cell carcinoma (ccRCC) is the predominant histopathological subtype, constituting more than 80% of RCCs (2). While ccRCC generally has a good prognosis when treated in its early stages, up to onethird of cases will metastasize, and 2040% of cases will experience a post-nephrectomy recurrence. ccRCC is notably resistant to chemotherapy, and once recurrence occurs, no further management is effective (3).

Deletion of chromosome 3p and mutations in the *Von Hippel-Lindau (VHL)* gene are prevalent in most ccRCC patients, leading to loss of various tumor suppressor genes, which further enhances genomic instability (4). Moreover, a deficiency in homologous recombination (HR) significantly contributes to genomic instability (5).

HR is recognized as a precise process for the repair of DNA double-strand breaks (DSBs), and any defect in this process can lead to tumorigenesis by enabling the accumulation of chromosomal abnormalities and mutations. In numerous instances, aggressive tumors are characterized by reduced expression of HR proteins, but these tumors also show increased responsiveness to therapeutic interventions, including chemotherapy and radiotherapy. The HR pathway involves important proteins encoded by the *RAD51*, *BRCA1*, and *BRCA2* genes (6).

The *RAD51* gene on human chromosome 15q15.1 encodes the essential HR protein *RAD51*. It has a significant role in DSBs by creating nucleoprotein filaments on single-stranded DNA, enabling strand exchange between single- and double-stranded DNA, and facilitating homologous pairing. When DNA damage occurs, *RAD51* relocates to nuclear foci, where it is believed to recognize and facilitate the repair of broken replication forks (7). Recent research has demonstrated that *RAD51* is a potential prognostic biomarker for various tumors, such as colorectal cancer (8), non-small cell lung cancer (9), and breast cancer (10). Nonetheless, there is a lack of evidence demonstrating the link between *RAD51* and ccRCC, which was the rationale for selecting this marker to be investigated in the current study.

The tumor suppressor gene, *BRCA1*, plays a crucial role in maintaining genome stability. It is frequently impaired in several types of cancer, including breast, ovarian, and pancreatic cancers, leading to the accumulation of genetic defects (11). *BRCA1* forms a complex with *BARD1* to aid DSB repair through HR. The complex formed by *BRCA1-BARD1* interacts directly with *RAD51*, boosting its ability to facilitate recombination. Mutations in *BRCA1* that disrupted the *RAD51* interaction hinder DNA strand invasion and compromise HR (12). Therefore, *BRCA1* serves as a crucial prognostic and therapeutic target for advancing cancer treatment approaches.

BRCA2 protein promotes HR-mediated repair of DSBs by facilitating *RAD51*-dependent DNA strand invasion, pairing, and exchange. The C-terminal recombinase binding (CTRB) domain of *BRCA2* is responsible for loading *RAD51* onto and binding *RAD51* to single-stranded DNA (ssDNA). CTRB alone significantly increases the DNA strand-exchange activity of *RAD51* and enables it to use ssDNA for this activity (13). In human cells, *BRCA2* deficiency leads to HR abnormality, genetic instability, inhibited formation of *RAD51* foci in response to DNA damage, and altered responsiveness to chemotherapy agents (14).

This study is the first to analyze immunohistochemical (IHC) expression of *RAD51*, *BRCA1*, and *BRCA2* in ccRCC and to investigate correlations between their expression levels and the clinicopathological features and clinical outcomes in patients with ccRCC. This research may help identify additional prognostic indicators for ccRCC and inform the development of novel anticancer strategies.

Materials and Methods

This cross-sectional study was conducted at Zagazig University's Faculty of Medicine using data from the Pathology Department archives collected from January 2020 to December 2023. The study included 76 sections from formalin-settled paraffin-inserted tissue blocks diagnosed as primary ccRCC who underwent either a total (56 cases) or partial nephrectomy (20 cases). Patients was selected consecutively. Clinicopathologic information, histopathology reports, and hematoxylin and eosin-stained slides from ccRCC cases were reviewed to confirm the diagnosis. Exclusion criteria were: a history of synchronous or metachronous malignancies; prior antitumor therapy; histological types other than the clear-cell variant; or insufficient tissue for IHC analysis. This work was conducted in agreement with the Helsinki Declaration and written consent was obtained from each member. Moreover, the current study was permitted by the Ethical Committee of Zagazig University according to the Egyptian Ethical Guidelines (approval number: ZU-IRB#11335, date: 12.03.2024).

Immunohistochemistry

The immunostaining method employed a streptavidin-biotin amplification system. The slides were subjected to consecutive steps of deparaffinization, rehydration, and blocking of endogenous peroxidase activity. Antigen recovery was performed by boiling in citrate-buffered saline (pH 6), followed by cooling at room temperature. The slides were then stained with primary antibodies against *RAD51* (rabbit monoclonal Ab; Catalog # EPR4030(3); 1:300 dilution; Abcam, Cambridge, UK), *BRCA1* (rabbit monoclonal Ab; Catalog # EPR19433; 1:400 dilution; Abcam, Cambridge, UK), and *BRCA2* (rabbit polyclonal Ab; Catalog # ab216972; 1:400 dilution; Abcam, Cambridge, UK). The

primary antibody was incubated overnight at room temperature, and then the secondary antibody was applied; diaminobenzidine was used as the chromogen, followed by counterstaining with Mayer's hematoxylin. The *RAD51* positive-control slide used germ cells from healthy testicular tissue. The positive control for *BRCA1* and *BRCA2* was tissue from invasive ductal carcinoma of the breast. Negative control slides were treated without the addition of primary antibodies.

Immunohistochemical Evaluation Criteria

Two independent investigators examined all stained sections by light microscopy; interobserver agreement was achieved. They specifically focused on assessing the nuclear expression of *RAD51*, *BRCA1*, and *BRCA2*. During the pathological annotation process, the assessment involved determining the percentage of positive cells, categorized as follows: 0 for less than 5%, 1 for 5-25%, 2 for 25-50%, 3 for 50-75%, and 4 for 75-100%. Additionally, the intensity of staining was evaluated on a scale where 0 indicates negative, 1 represents weak, 2 denotes moderate, and 3 signifies strong staining. The overall score was derived by multiplying the intensity score by the percentage score. Samples were subsequently classified as either "high expression" or "low expression" based on a cut-off score of 6 (15).

Analysis of Survival Data

For 76 patients with ccRCC between January 2020 and December 2023, the overall survival (OS) time was determined by reviewing the patients' files. Disease-free survival (DFS) and OS were analyzed using the Kaplan-Meier method, and differences among the survival curves were assessed by a log-rank test. A multivariate Cox proportional hazards analysis was employed to determine the independent risk factors influencing survival time.

Statistical Analysis

SPSS 22.0 for Windows and MedCalc Windows were used to perform all analyses. The Mann-Whitney U test was employed to compare two groups of non-normally distributed variables, whereas the Kruskal-Wallis test was utilized for comparisons involving more than two groups of non-normally distributed variables. The proportions of categorical variables were compared using Fisher's exact test or Pearson's chi-square test, as appropriate. A p-value ≤0.05 was considered statistically significant.

Results

Patients' Characteristics

This study included 76 patients with ccRCC. Patients' ages ranged from 48-80 years, with a mean age of 58.66±7.561 years (Table 1). There were 45 (59.2%) male patients and 31 (40.8%) female patients. Tumor size exceeded 7 cm in 54 cases (71.1%). Thirty-nine (51.3%) cases were high grade, while 37 (48.7%) were low grade. Necrosis was detected in 31 (40.8%) cases, while lymphovascular invasion was present in 19 (25%) cases. Seventeen of these 76 patients (22.4%) had stage I disease. On the other hand, 20 ccRCC patients (26.3%) presented with stage IV disease. Nodal metastasis was recorded preoperatively in 25 (32.9%) and distant metastasis in 23 (30.3%) cases as well. The average duration of follow-up was 27.4 months (range: 10-36 months), during which 40 patients (52.6%) remained disease-free. Recurrence occurred in 36 patients (47.4%), while 28 patients (36.8%) died during the follow-up period. The clinicopathological features of the 76 ccRCC patients are detailed in Table 1.

Pattern of *RAD51* Expression in ccRCC and Association with Clinicopathological Parameters

In ccRCC patients, nuclear staining of tumor cells was considered *RAD51*-positive (Figure 1). High *RAD51* expression was observed in 32 patients (42.1%), while 44 patients (57.9%) showed low expression (Table 1). In adjacent non-tumor tissue, no immunostaining for *RAD51* was observed.

Table 1. Clinicopathologic parameters of 76 ccRCC cases

Variable	No (%)
Gender	
Male	45 (59.2)
Female	31 (40.8)
Age	
Mean ± standard deviation	58.66±7.561
Median	57
Range	32
Age	
<50	20 (26.3)
≥50	56 (73.7)
Tumor size	
<7	22 (28.9)
≥7	54 (71.1)
The WHO/ISUP grade	
Grade I-II	37 (48.7)
Grade III-IV	39 (51.3)
Vascular invasion	
Present	19 (25)
Absent	57 (75)
Necrosis	
Present	31 (40.8)
Absent	45 (59.2)
Tumor stage	
T1	17 (22.4)
T2	23 (30.3)

Table 1. Continued

Variable	No (%)
T3	16 (21.1)
T4	20 (26.3)
Tumor stage grouping	
Early stage	40 (52.6)
Advanced stage	36 (47.4)
Nodal stage	
N0	51(67.1)
N1	25 (32.9)
Distant metastasis	
M0	53 (69.7)
M1	23 (30.3)
Relapse	
Absent	40 (52.6)
Present	36 (47.4)
Death	
Alive	48 (63.2)
Dead	28 (36.8)
RAD51	
Low expression	44 (57.9)
High expression	32 (42.1)
BRCA1	
Low expression	37 (48.7)
High expression	39 (51.3)
BRCA2	
Low expression	49 (64.5)
High expression	27 (35.5)
High co-expression of *BRCA1* and *BRCA2*	
Positive	21 (27.6)
Negative	55 (72.4)

ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

High *RAD51* expression was significantly correlated with higher tumor stage, with high expression observed in 4 (23.5%) stage I, 6 (26.1%) stage II, 8 (50%) stage III, and 14 (70%) stage IV ccRCC cases (p=0.009); the correlation was significant (p=0.001). Moreover, high *RAD51* was significantly associated with tumor lymphatic spread (p<0.001 and p=0.000), distant spread (p<0.001 and p=0.000), and tumor recurrence (p=0.024 and p=0.02) (Table 2, Figure 1).

Pattern of *BRCA1* and *BRCA2* Expression in ccRCC and Association with Clinicopathological Parameters

BRCA1 and *BRCA2* showed nuclear staining in cancer cells, with negative immunostaining in the adjacent non-tumor tissue (Figure 2). High immunohistochemical (IHC) expression of *BRCA1*, *BRCA2*, and both proteins were observed in 39 (51.3%), 27 (35.5%), and 21 (27.6%) cases, respectively (Table 1).

BRCA1 immune expression was significantly correlated with early stages of ccRCC, with higher expression observed in 14 (82.4%) stage I cases compared with 8 (40%) stage IV cases (p=0.017); the correlation was significant (p=0.006). Additionally, *BRCA1* expression was significantly associated with cases without lymphatic spread (p=0.028). Similarly, co-expression of *BRCA1* and *BRCA2* was significantly associated with early stages of ccRCC patients (p=0.004; p=0.002), and lack of nodal metastasis (p=0.032; p=0.01), However, *BRCA2* expression is significantly correlated with the early tumor stage (p=0.008) and with the correlation coefficient (p=0.005) (Table 3; Figure 2).

Association Between *RAD51*, *BRCA1*, and *BRCA2* Expression

A significant correlation was detected between positive *RAD51* expression and negative *BRCA1* expression: 30 (68.2%) cases with high *BRCA1* expression showed low *RAD51* expression, whereas 9 (28.1%) of the high *BRCA1* expression cases showed high *RAD51* immunostaining (p=0.001; correlation coefficient p=0.000). No significant correlation was found between *RAD51* and *BRCA2* immune expression (p=0.507); however, co-expression of *BRCA1* and *BRCA2* showed a significant inverse association with *RAD51*. In the correlation between *BRCA1* and *BRCA2*, a significant positive association was detected (p=0.001); 21 cases (27.6%) with high *BRCA2* expression also showed high *BRCA1* expression, and the correlation coefficient was significant (p<0.001) (Figure 3).

Univariate Survival Analysis for Predicting Overall & Disease-free Survival

Univariate analysis of OS and DFS in 76 ccRCC patients using the Kaplan-Meier method (Figure 4) revealed that high tumor grade (p=0.001 and 0.001), advanced stage (p=0.043 and 0.016), presence of nodal metastasis (p=0.004 and 0.003), distant metastasis (p=0.02 and 0.008), and tumor recurrence (p<0.001 and <0.001) were associated with shorter OS and DFS, respectively (Table 4).

High expression of *RAD51* was associated with shorter OS and DFS (p=0.02 and p=0.014, respectively). Cases with a mean OS of 30.93 months exhibited high *RAD51* immunostaining, whereas cases with a longer mean OS of 32.04 months displayed lower *RAD51* expression levels. Conversely, *BRCA1* expression was significantly associated with longer OS and DFS (p=0.04 and p=0.009, respectively). However, *BRCA2* showed no significant correlation with patient survival (Figure 4, Table 5).

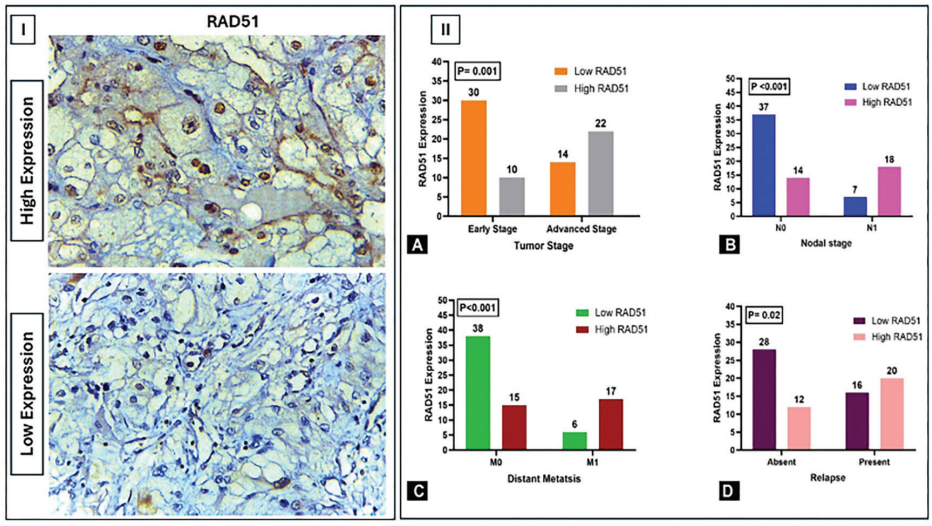

Figure 1. I) High and low *RAD51* immunohistochemical expression in clear cell renal cell carcinoma cases (magnified x400). **II)** High *RAD51* showed a significant association with advanced tumor stage (A), nodal involvement (B), distant metastasis (C), and tumor relapse (D)

Table 2. Correlation between *RAD51* with clinicopathologic parameters of 76 ccRCC cases

Variable	*RAD51* expression		p-value
	Low expression No (%)	High expression No (%)	
Gender			
Male	(28) 62.2%	(17) 37.8%	0.357
Female	(16) 51.6%	(15) 48.4%	
Age			
<50	(13) 65.0%	(7) 35.0%	0.453
≥50	(31) 55.4%	(25) 44.6%	
Tumor size			
<7	(12) 54.5%	(10) 45.5%	0.706
≥7	(32) 59.3%	(22) 40.7%	
WHO/ISUP grade			
Grade I-II	(24) 64.9%	(13) 35.1%	0.231
Grade III-IV	(20) 51.3%	(19) 48.7%	
Vascular invasion			
Present	(10) 52.6%	(9) 47.4%	0.592
Absent	(34) 59.6%	(23) 40.4%	
Necrosis			
Present	(15) 48.4%	(16) 51.6%	0.164
Absent	(29) 64.4%	(16) 35.6%	
Tumor stage			
T1	(13) 76.5%	(4) 23.5%	
T2	(17) 73.9%	(6) 26.1%	**0.009***
T3	(8) 50%	(8) 50%	
T4	(6) 30%	(14) 70%	
Tumor stage grouping			
Early stage	(30) 75%	(10) 25%	**0.001***
Advanced stage	(14) 38.9%	(22) 61.1%	
Nodal stage			
N0	(37) 72.5%	(14) 27.5%	**<0.001***
N1	(7) 28%	(18) 72%	

Table 2. Continued

Variable	*RAD51* expression		p-value
	Low expression No (%)	High expression No (%)	
Distant metastasis			
M0	(38) 71.7%	(15) 28.3%	**<0.001***
M1	(6) 26.1%	(17) 53.1%	
Relapse			
Absent	(28) 70%	(12) 30%	**0.024***
Present	(16) 44.4%	(20) 55.6%	
BRCA1			
Low expression	(14) 37.8%	(23) 62.2%	**0.001***
High expression	(30) 76.9%	(9) 23.1%	
BRCA2			
Low expression	(27) 55.1%	(22) 44.9%	0.507
High expression	(17) 63%	(10) 37%	
High co-expression of *BRCA1* and *BRCA2*			
Positive	(17) 81%	(4) 19%	**0.018***
Negative	(27) 49.1%	(28) 50.9%	

*: Significant, ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

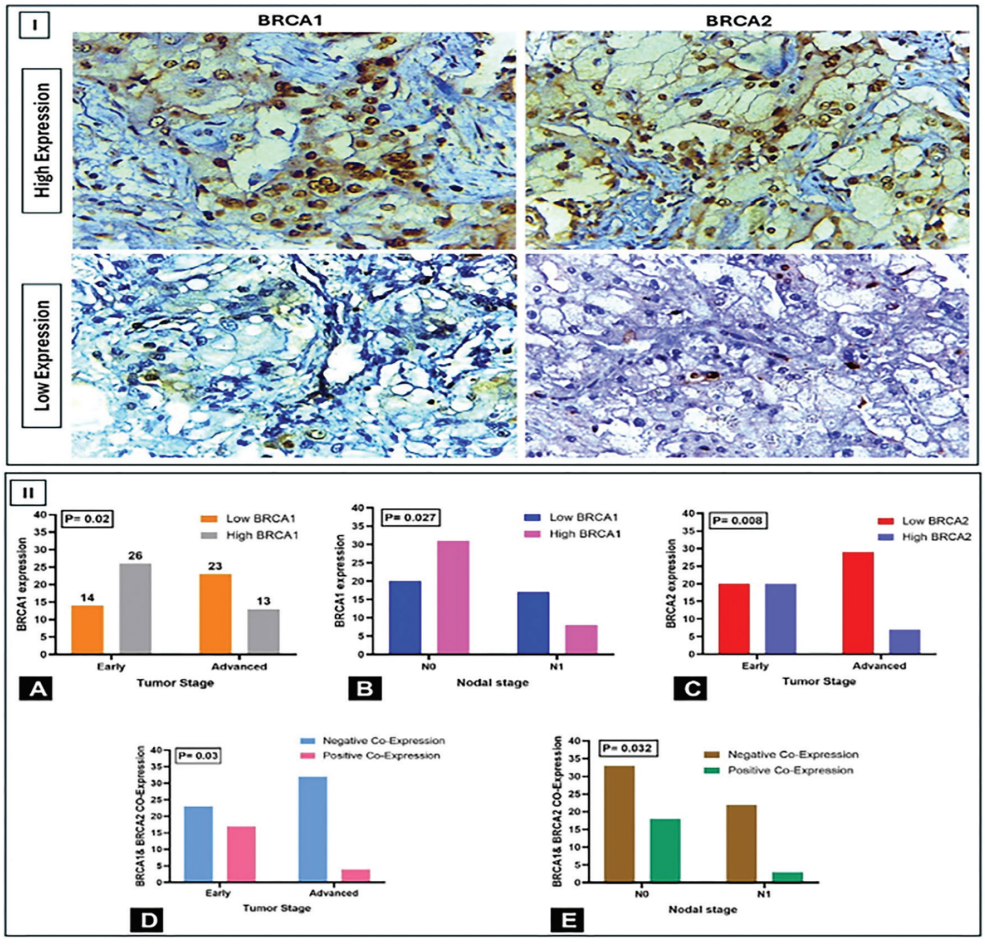

Figure 2. I) High and low *BRCA1* and *BRCA2* immunohistochemical expression in clear cell renal cell carcinoma cases (magnified x400). **II)** High *BRCA1* showed significant associations with early tumor stage (A) and with presence of nodal stage (B); *BRCA2* showed significant association with early tumor stage (C). Co-expression of both showed significant association with early tumor stage (D), and presence of nodal stage (E)

Table 3. Correlation between *BRCA1*, *BRCA2*, and co-expression of both with clinicopathologic parameters of 76 ccRCC cases

Variable	*BRCA1* expression		p-value	*BRCA2* expression		p-value	Co-expression		p-value
	Low expression No (%)	High expression No (%)		Low expression No (%)	High expression No (%)		Negative expression No (%)	Positive expression No (%)	
Gender									
Male	(21) 46.7%	(24) 53.3%	0.672	(26) 57.8%	(19) 42.2%	0.142	(29) 64.4%	(16) 35.6%	0.07
Female	(16) 51.6%	(15) 48.4%		(23) 74.2%	(8) 25.8%		(26) 83.9%	(5) 16.1%	
Age									
<50	(9) 45.0%	(11) 55.0%	0.701	(11) 55%	(9) 45%	0.302	(14) 70%	(6) 30%	0.78
≥50	(28) 50%	(28) 50%		(38) 67.9%	(18) 32.1%		(41) 73.2%	(15) 26.8%	
Tumor size									
<7	(9) 40.9%	(13) 59.1%	0.387	(12) 54.5%	(10) 45.5%	0.248	(15) 68.2%	(7) 31.8%	0.60
≥7	(28) 51.9%	(26) 48.1%		(37) 68.5%	(17) 31.5%		(40) 74.1%	(14) 25.9%	
WHO/ISUP grade									
Grade I-II	(15) 40.5%	(22) 59.5%	0.167	(21) 56.8%	(16) 43.2%	0.171	(24) 64.9%	(13) 35.1%	0.15
Grade III-IV	(22) 56.4%	(17) 43.6%		(28) 71.8%	(11) 28.2%		(31) 79.5%	(8) 20.5%	
Vascular invasion									
Present	(10) 52.6%	(9) 47.4%	0.691	(15) 78.9%	(4) 21.1%	0.128	(17) 89.5%	(2) 10.5%	0.076
Absent	(27) 47.4%	(30) 52.6%		(34) 59.6%	(23) 40.4%		(38) 66.7%	(19) 33.3%	
Necrosis									
Present	(17) 54.8%	(14) 45.2%	0.373	(22) 71%	(9) 29%	0.326	(24) 77.4%	(7) 22.6%	0.41
Absent	(20) 44.4%	(25) 55.6%		(27) 60%	(18) 40%		(31) 68.9%	(14) 31.1%	
Tumor stage									
T1	(3) 17.6%	(14) 82.4%		(7) 41.2%	(10) 58.8%		(10) 58.8%	(7) 41.2%	
T2	(11) 47.8%	(12) 52.2%	**0.017***	(13) 56.5%	(10) 43.5%	**0.03***	(13) 56.5%	(10) 43.5%	**0.021***
T3	(11) 68.8%	(5) 31.2%		(13) 81.2%	(3) 18.8%		(15) 93.8%	(1) 6.2%	
T4	(12) 60%	(8) 40%		(16) 80%	(4) 20%		(17) 85%	(3) 15%	
Tumor stage grouping									
Early	(14) 35%	(26) 65%	**0.021***	(20) 50%	(20) 50%	**0.008***	(23) 57.5%	(17) 42.5%	**0.004***
Advanced	(23) 63.9%	(13) 36.1%		(29) 80.6%	(7) 19.4%		(32) 88.9%	(4) 11.1%	
Nodal stage									
N0	(20) 39.2%	(31) 60.8%	**0.028***	(29) 56.9%	(22) 43.1%	0.07	(33) 64.7%	(18) 35.3%	**0.032***
N1	(17) 68%	(8) 32%		(20) 80%	(5) 20%		(22) 88%	(3) 12%	
Distal metastasis									
M0	(22) 41.5%	(31) 58.5%	0.080	(27) 50.0%	(27) 50.0%	0.098	(35) 66%	(18) 34%	0.09
M1	(15) 65.2%	(8) 34.8%		(10) 45.5%	(12) 54.5%		(20) 87%	(3) 13%	
Relapse									
Absent	(18) 45%	(22) 55%	0.498	(27) 67.5%	(13) 32.5%	0.561	(30) 75%	(10) 25%	0.58
Present	(19) 52.8%	(17) 47.2%		(22) 61.1%	(14) 38.9%		(25) 69.4%	(11) 30.6%	
RAD51									
Low expression	(14) 31.8%	(30) 68.2%	**0.001***	(27) 61.4%	(17) 38.6%	0.507	(27) 61.4%	(17) 38.6%	**0.018**
High expression	(23) 71.9%	(9) 28.1%		(22) 68.8%	(10) 31.2%		(28) 87.5%	(4) 12.5%	

ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

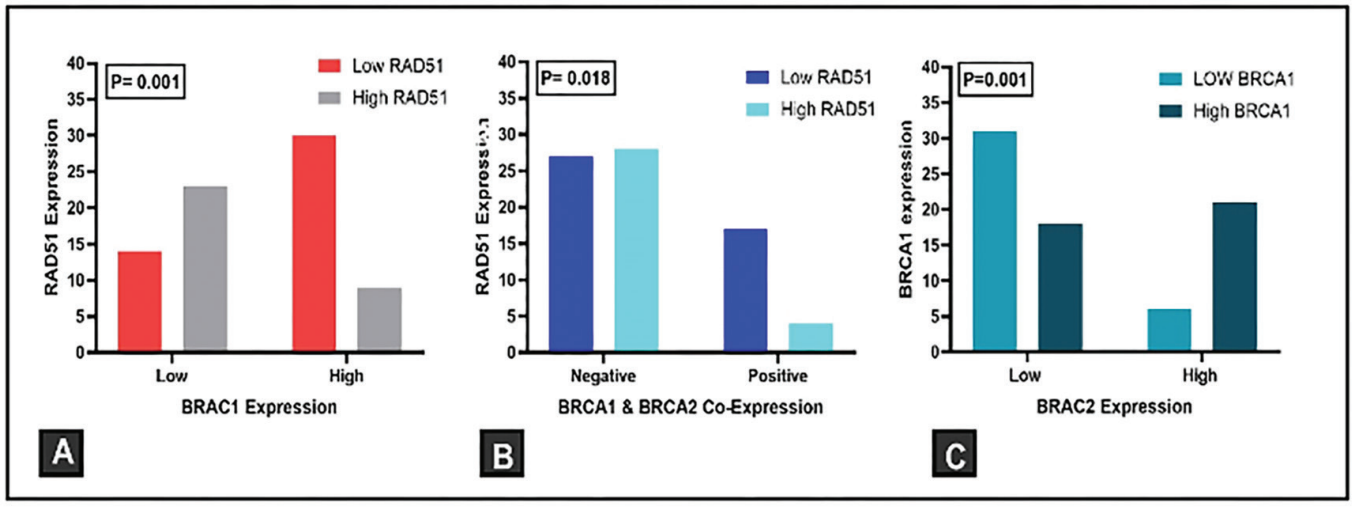

Figure 3. *RAD51* expression showed significantly inverse association with *BRCA1* (A), and co-expression of *BRCA1* & *BRCA2* (B). Direct significant association between *BRCA1* and *BRCA2* (C)

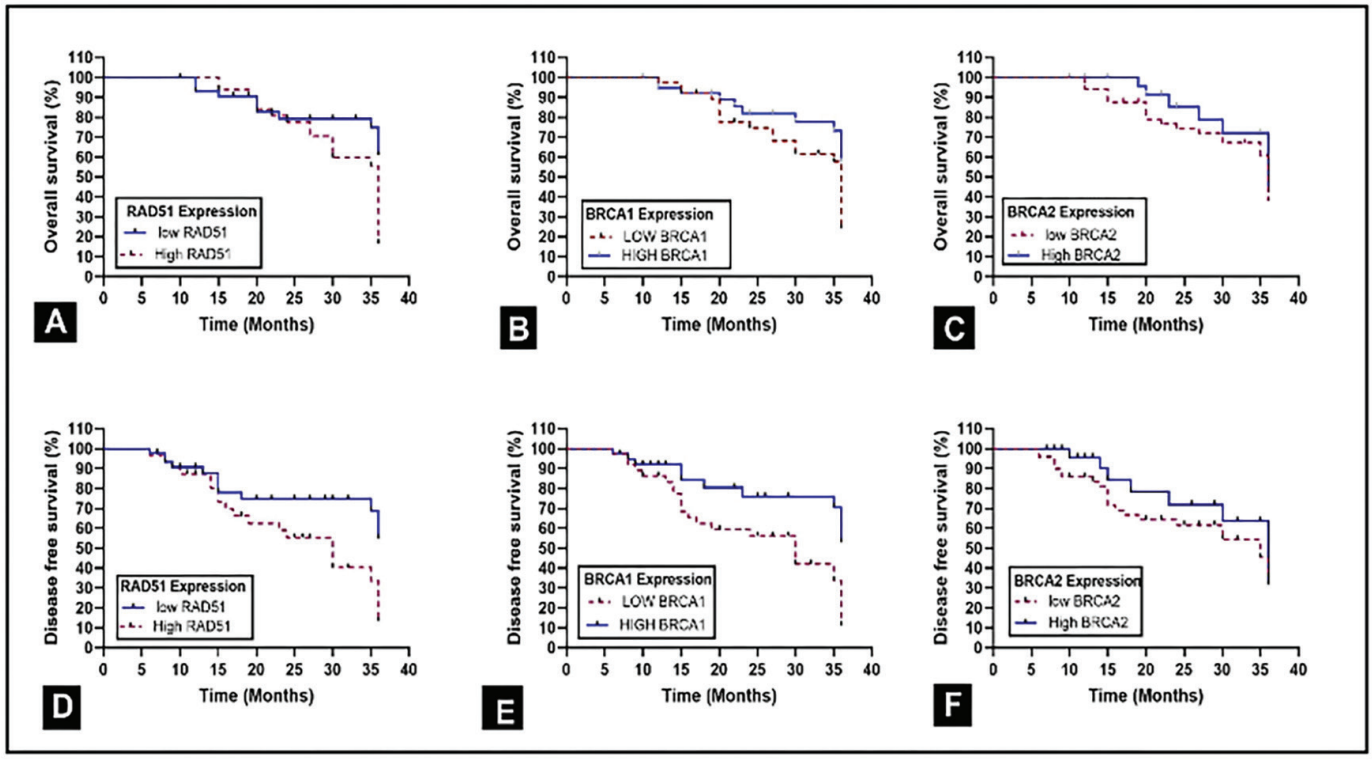

Figure 4. Kaplan-Meier plot, upper panel: Overall survival, lower panel: Disease free survival. (A&F) all studied patient: (A&D) stratified by *RAD51*, (B&E) stratified by *BRCA1*, and (C&F) stratified by *BRCA2*

Table 4. Univariate survival analysis for predicting overall & disease-free survival

Variable	OS			DFS		
	Mean (CI 95%)	Log-rank	p-value	Mean (CI 95%)	Log-rank	p-value
Tumor size						
<7	30.24 (26.09-34.39)	0.132	0.716	27.92 (22.23-33.61)	0.002	0.965
≥7	31.81 (29.79-33.83)			27.80 (24.76-30.84)		
WHO/ISUP grade						
Grade I-II	33.77 (31.58-35.96)	10.78	**0.001***	32.21 (29.17-35.25)	11.46	0.001*
Grade III-IV	29.58 (26.87-32.29)			24.59 (20.87-28.30)		
Vascular invasion						
Present	29.32 (24.57-34.06)	0.668	0.414	26.72 (20.25-33.18)	0.44	0.504
Absent	32.17 (30.34-34.00)			28.28 (25.38-31.17)		
Necrosis						
Present	29.80 (26.76-32.85)	2.8	0.094	24.45 (20.08-28.82)	3.45	0.063
Absent	32.74 (30.58-34.91)			30.39 (27.21-33.57)		
Tumor stage						
T1	31.84 (27.68-36.01)	8.14	**0.043***	29.74 (23.46-36.03)	10.38	**0.016***
T2	33.75 (31.04-36.46)			32.20 (28.42-35.98)		
T3	31.2 (27.49-34.91)			27.46 (21.66-33.29)		
T4	28.92 (24.87-32.98)			22.36 (17.25-27.47)		
Tumor stage grouping						
Early stage	33.10 (30.80-35.40)	7.172	**0.007***	31.37 (28.05-34.70)	8.77	**0.003***
Advanced stage	29.96 (27.22-32.70)			24.74 (20.91-28.57)		
Nodal stage						
N0	32.71 (30.69-34.73)	8.16	**0.004***	30.61 (27.64-33.57)	9.06	**0.003***
N1	29.23 (25.79-32.68)			23.15 (18.62-27.67)		
Distal metastasis						
M0	32.48 (30.47-34.49)	5.35	**0.02***	30.28 (27.33-33.277)	7.01	**0.008***
M1	29.42 (25.79-33.05)			22.97 (18.17-27.78)		
Relapse						
Absent	33.45 (31.26-35.64)	16.05	**<0.001***	32.10 (29.25-34.95)	17.26	**<0.001***
Present	29.30 (26.44-32.16)			23.28 (19.31-27.25)		
RAD51						
Low expression	32.04 (29.49-34.60)	5.27	**0.02***	29.96 (26.40-33.52)	6.02	**0.014***
High expression	30.93 (28.41-33.46)			25.57 (21.67-29.46)		
BRCA1						
Low expression	30.52 (27.91-33.12)	3.93	**0.04***	25.30 (21.56-29.05)	6.86	**0.009***
High expression	32.40 (29.85-34.96)			30.79 (27.23-34.35)		
BRCA2						
Low expression	30.66 (28.25-33.07)	0.72	0.39	26.71 (23.35-30.08)	0.65	0.41
High expression	32.79 (30.12-35.45)			30.03 (25.66-34.41)		
High Co-expression of *BRCA1* and *BRCA2*						
Positive	33.56 (30.69-36.44)	2.70	0.10	32.00 (27.49-36.50)	3.46	0.06
Negative	30.67 (28.46-32.93)			26.399 (23.20-29.59)		

OS: Overall survival, DFS: Disease free survival, CI: Confidence interval, *: Significant, ISUP: International Society of Urologic Pathologists, WHO: World Health Organization, ccRCC: Clear cell renal cell carcinoma

Table 5. Multivariate COX-regression analysis for detection of the most independent prognostic factor affecting patient overall survival

Variable	Multivariate	
	HR (LL-UL CI 95%)	**p-value**
WHO/ISUP grade	0.38 (0.104-1.44)	0.158
Tumor stage	0.069 (0.009-0.52)	0.82
Nodal stage	1.13 (0.37-3.39)	**0.01***
Distal metastasis	13.12 (1.96-87.68)	**0.008***
Relapse	1.32 (0.52-3.33)	0.058
RAD51	0.78 (0.32-1.90)	0.59
BRCA1	0.30 (0.09-1.03)	0.56

HR: Homologous recombination, CI: Confidence interval, LL: Lower limit, UL: Upper limit, *: Significant, ISUP: International Society of Urologic Pathologists, WHO: World Health Organization

Multivariate COX-regression Analysis for Detection of the Most Independent Prognostic Factor Affecting Patient Overall Survival

Nodal metastasis (p=0.01) and distant metastasis (p=0.008) emerged as the most significant independent prognostic factors affecting OS in ccRCC patients in multivariate Cox proportional-hazards analysis.

Discussion

Genomic instability contributes to tumor initiation and advancement, often resulting from defects in DNA damage repair (DDR) (16). HR, a key DDR pathway, maintains genome stability by repairing DNA DSBs. Due to its role in maintaining genome stability, HR is generally considered a pathway that suppresses tumors. In line with this concept, mutations or deficiencies that result in loss of HR function can also lead to genomic instability and tumor initiation (17).

RAD51, *BRCA1*, and *BRCA2* are crucial proteins in the HR pathway (6), and their relevance to ccRCC has received growing attention as understanding of ccRCC genetics and molecular mechanisms advances. Additionally, their function in DNA repair and cancer development is becoming clearer.

RAD51, a crucial participant in HR, is directly responsible for preserving the stability of the genome. *RAD51* encircles a single broken DNA strand with the assistance of auxiliary proteins, then captures the complementary copy of DNA, aligning it with the sequence of the broken strand (18). Since *RAD51* is essential for maintaining genome stability, *RAD51* expression must be tightly regulated in human cells. Inadequate *RAD51* expression could result in accumulation of DNA breaks. Conversely, an increase in *RAD51* expression could stimulate hyper-recombination, which could cause genomic instability (19).

Studies have reported conflicting findings regarding the prognostic significance of *RAD51* across different cancer types. In breast cancer (20) and non-small cell lung cancer (21), low *RAD51* expression has been correlated with an unfavorable prognosis. Conversely, high *RAD51* expression has been linked to a poor prognosis in colon cancer (8), breast cancer (10), and non-small-cell lung cancer (9).

This study focused on *RAD51* IHC expression in ccRCC and revealed *RAD51* overexpression in tumor cells. High nuclear *RAD51* expression was observed in a considerable proportion (42.1%) of cases and was significantly associated with advanced tumor stages, nodal metastasis, distant metastasis, and disease recurrence. Survival analysis revealed an association between high *RAD51* expression and shorter OS and DFS in patients with ccRCC. These findings support the tumor-promoting role of *RAD51* and its potential as a novel predictive biomarker in ccRCC patients.

Consistent with our results, *RAD51* overexpression has been consistently observed in multiple cancer types across several studies and has been linked to aggressive proliferation and increased metastatic potential. In a study involving 70 neuroblastoma cases, *RAD51* expression was notably elevated in stage IV tumors compared with stages I and II, particularly in cases with bone marrow metastases (22). A previous study reported an association between high expression of *RAD51* and breast cancer with lymph node metastases (23). Furthermore, Qiao et al. (9) established *RAD51* expression as a potential prognostic indicator in lung cancer, showing that high *RAD51* expression in tumors predicts poor patient survival.

Lu et al. (18) analyzed *RAD51* expression in various cancers, including ccRCC. They found that the expression of *RAD51* was notably elevated in cancerous cells compared with adjacent tissues. Furthermore, the research indicated a strong association between *RAD51* expression and both advanced pathological stages and DFS. Moreover, the study suggested that the expression of *RAD51* was linked to several important immune checkpoints and immunosuppressive genes, indicating its potential impact on controlling the immune response in tumors through regulation of immune checkpoint activity.

RAD51, despite its vital function in the repair of damaged DNA and its possible role as a tumor suppressor, has been linked to genomic instability and the onset of cancer when overexpressed. Increased *RAD51* expression can lead to accumulation of genotoxic *RAD51* on undamaged chromatin, resulting in reduced HR efficiency (24). Additionally, *RAD51* overexpression can positively regulate cell proliferation, decrease intracellular reactive oxygen species production, and regulate aerobic glycolysis by targeting hypoxia-inducible factor 1α, ultimately contributing to tumor progression (25). *RAD51* is also known to increase the activity of transcription factors, thereby promoting epithelial-mesenchymal transition and production of metalloproteinases (26).

Overexpression of *RAD51* in malignant tissue is linked to a marked rise in HR activity, enhancing tumor cell genetic flexibility. Furthermore, it is believed that it improves the ability to repair DNA breaks, thereby protecting cells from DNA-damaging treatments and conferring resistance to conventional cancer therapies. Consequently, inhibiting *RAD51* to render HR-proficient tumor cells HR-deficient may sensitize them to chemotherapeutic agents. Indeed, some *RAD51* inhibitors have proven effective against certain cancers (27). In ccRCC Liu and Weng (28), 2022 stated that patients with low *RAD51* expression were found to be more likely to respond to immune checkpoint blockade immunotherapy. These findings indicate that *RAD51* protein may serve as a poor prognostic indicator and a potential target for developing anti-tumor strategies for ccRCC patients, necessitating further investigation.

BRCA1 and *BRCA2* are recognized as important tumor suppressor genes that help to prevent tumors by maintaining the stability of the genome. They perform complex tasks in the repair of DNA damage (29). *BRCA1* functions early in HR by detecting DNA damage and facilitating end resection, allowing ssDNA to bind replication protein A (RPA) before RAD51 replaces RPA on the ssDNA. *BRCA2*, aided by *BRCA1* and *PALB2*, displaces RPA and loads *RAD51* onto the resected DNA, forming a *RAD51*-ssDNA filament that is essential for HR and for blocking the detrimental single-strand annealing pathway (30).

Although *BRCA1* and *BRCA2* mutations are mainly linked to ovarian and breast carcinomas (31,32), research on their role in ccRCC remains under active investigation. Understanding these associations could offer valuable insights for improved risk assessment, targeted therapies, and monitoring strategies for affected individuals.

In this study, high IHC expression of *BRCA1*, *BRCA2*, and co-expression of *BRCA1* and *BRCA2* in ccRCC patients were 51.3%, 35.5%, and 27.6%, respectively, and their expression was significantly associated with several favorable prognostic factors, including early tumor stage and absence of lymphatic spread. Furthermore, survival analysis demonstrated an association between high *BRCA1* expression and longer OS and DFS in ccRCC patients. These findings indicate that *BRCA1* and *BRCA2* may play a role in suppressing progression of ccRCC and could be good prognostic indicators for patients with ccRCC.

In 2011, the first report documented a *BRCA1* germline mutation in a Pakistani patient with an aggressive form of ccRCC (33). In the Chinese population, inherited mutations in DDR-related genes, including *BRCA1*, have also been reported in RCC patients (34). A previous study reported a significant association between *BRCA1* alterations and the aggressiveness of ccRCC (35). In contrast, another study found no evidence that *BRCA1* mutations play a role in the development of kidney cancer in Polish individuals (36).

Recognizing VHL as a tumor suppressor gene in RCC (4), Scanlon et al. (37) reported that VHL-deficient cells in RCC had a decreased ability to carry out HR and reduced levels of specific HR genes, such as *BRCA1*. Additionally, VHL loss increased ER-α, which can bind to *BRCA1*, reduce *BRCA1* expression, block *BRCA1-RAD51* interaction, and induce γ-tubulin expression, which is strongly linked to resistance to microtubule-targeted therapy such as Taxol. This may represent a mechanism of drug resistance observed in both RCC and *BRCA1*-deficient cancers.

Diez-Calzadilla et al. (35) found that changes in *BRCA2* were linked to the development of RCC and were strongly associated with aggressive tumors, including higher Fuhrman grades and an increased risk of distant metastasis. Liu et al. (38) suggested that *BRCA2* may be linked to colorectal cancer, ovarian cancer, and RCC by interacting with downregulated BCCIP.

Souza's et al. (39) and Kong et al., (40) indicate that in certain RCCs with a particular morphology, a *BRCA2* mutation may serve as a key mutation. *BRCA2* mutations may contribute to tumor aggressiveness and progression to high-grade RCCs in RCC subtypes such as ccRCC and papillary RCC. Moreover, the chromosomal region containing *BRCA2* is often deleted in sarcomatoid RCC. These findings contradict the conclusions of Złowocka-Perłowska et al. (36), who stated that *BRCA2* does not appear to be associated with the development of kidney cancer. Because of the contradictory information on the involvement of *BRCA2* in RCC.

Mutations in *BRCA1/2* could increase the risk of developing RCC and may have contributed to genomic instability in ccRCC patients; further investigation is required to determine the impact of *BRCA1/2* mutations on ccRCC development.

From a therapeutic standpoint, tumors that harbor *BRCA1/2* germline mutations exhibit biological characteristics resulting in genomic instability, which may make them responsive to DNA-damaging therapies such as platinum-based chemotherapy

and poly (ADP-ribose) polymerase inhibitors (PARPi) (41). It will be interesting to investigate whether patients with ccRCC and *BRCA1/2* mutations could similarly benefit from these treatments.

In this research, we examined the role of *BRCA1* and *BRCA2* as cofactors for *RAD51* and found a significant indirect association between *RAD51* and *BRCA1* expression, suggesting the presence of unknown compensatory mechanisms that allow the maintenance or restoration of *RAD51* recruitment to DNA lesions even when either *BRCA1* or *BRCA2* is absent. Therefore, *RAD51* has a crucial role in the DNA repair mechanisms of most malignant tumors, regardless of whether they have normal or abnormal *BRCA* status (proficient or deficient) (19).

Study Limitations

Median follow-up is 27.4 months, which may be considered relatively short for metastatic ccRCC.

Conclusion

This study highlights the importance of HR proteins, namely *RAD51*, *BRCA1*, and *BRCA2*, in the development and progression of ccRCC. Increased *RAD51* expression and lower expression of *BRCA1* and *BRCA2* are linked to more aggressive tumors and shorter OS and DFS, indicating their potential as significant prognostic markers in IHC analyses and providing insights into novel treatment strategies for ccRCC patients.

Ethics

Ethics Committee Approval: The current study was permitted by the Ethical Committee of Zagazig University according to the Egyptian Ethical Guidelines (approval number: ZU-IRB#11335, date: 12.03.2024).

Informed Consent: Written consent was obtained from each member.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.A.E.M., H.M.A., E.G.A., A.H.H., H.L.M., Concept: A.M.A.E.M., Design: A.M.A.E.M., Data Collection or Processing: A.H.H., H.L.M., Analysis or Interpretation: H.M.A., Literature Search: H.M.A., Writing: A.M.A.E.M., H.M.A., H.L.M.

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