The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4130-4136

Studying The Expression of RNA-Binding Proteins RBM-Hur, and Lysophosphatidylcholine Acyltransferase 1 (LPCAT1) in Urothelial Carcinoma; Immunohistochemical Study

Emad M Abdelrahman[1], Mona A. Abo Elkheir [2], Kareem Ali ElAttar[3] , Eman A. Saad[2]

[1]General Surgery Department, [2] Pathology Department and

[3]Urology Department, Faculty of Medicine, Benha University, Egypt

Corresponding Author: Emad M. Abdelrahman, Email: emadshan301@gmail.com **and** emad.sarhan@fmed.bu.edu.eg ,Tel: **O1226763986, ORCID** https://www.orcid.org/0000-0001-6066-2215

ABSTRACT

Background: In developed nations, bladder cancer is a main cause of mortality. Urothelial bladder cancer (UBC) makes up the bulk of cases up to (90%) . An important lipid metabolism enzyme called LPCAT1 has been linked to the development of various cancers. HuR is an RNA-binding protein involved in tumor growth, regulates normal cell proliferation and inflammatory responses associated with cancer (13). that regulates the healthy cell proliferation and inflammatory responses associated with cancer. The study aimed to evaluate the significance expression of RBM-HuR and LPCAT1 in UBC.

Methods: The current retrospective study included 50 formalin-fixed, paraffin-embedded blocks for UBC. to examine the expression of both RBM-HuR and LPCAT in UBC was performed using Immunohistochemistry where. anti RBM-HuR and anti LPCAT1 immunostaining were performed using Avidin-Biotin complex technique and correlated to clinicopathological parameters including pT stage and grade of the tumor, lymph node (LN) metastasis, distant metastasis, lympho-vascular invasion, and associated CIS

Results: LPCAT1 expression was negatively correlated with the (pT stage and grade of the tumor, lymph node (LN) metastasis, distant metastasis, lympho-vascular invasion, and associated CIS) ($P < 0.05$). ***However,*** RBM-HuR expression was positively correlated to the same clinicopathological criteria. ($P < 0.05$).

Conclusions: RBM-HuR and LPCAT1 could both be used as potential prognostic indicators in UBC.

Keyword: Urothelial carcinomas, RBM-HuR, LPCAT1.

INTRODUCTION

Bladder cancer is among the top 10 prevalent malignancies. It was anticipated that there were 213,000 fatalities in 2020 [(1)]. Men: Women ratio is 3-4:1, but females are already in advanced stages of the disease when they are discovered, which results in a worse prognosis [(2)].

According to the National Cancer Institute, bladder cancer ranks third among all malignancies in Egypt for both sexes, accounting for 6.9% of all cancer cases [(3)].

More than 90% of bladder cancers are urothelial cell carcinomas (UBC) [(1)]. Smoking cigarettes and occupational exposures are well-established risk factors in the development of UBC [(4)]. The TNM staging and tumor grading, which serve as indicators of a patient's likelihood of having a favorable or bad prognosis, are clinicopathological factors that affect bladder cancer care [(5)]. Many clinic-pathological markers are proposed for the prediction of an recurrence and outcome in patients with UBC[(6)].

According to reports, UBC has a number of metabolic anomalies, and numerous altered metabolic pathways that can contribute tumorogenesis. Phospholipid levels in UC have been reported to be higher [(7)].

Lysophosphatidylcholine acyltransferase 1 (LPCAT1), a crucial enzyme in lipid metabolism, has received a lot of interest recently from academics. The AYTL2 gene produces the LPCAT1 enzyme, which is widely present in healthy tissues [(8)]. This enzyme can move from its primary location at the endoplasmic reticulum in the cytoplasm to the nucleus [(9)]. According to several studies, LPCAT1 when overexpressed can initiate the development of malignancies [(10)].

Several RNA-binding proteins are involved in the regulation and expression of genes [(11)]. Moreover, they have the ability to attach to RNA, which allows them to influence cell growth, invasion, and metastases [(12)].

HuR is an RNA-binding protein involved in tumor growth. HuR regulates normal cell proliferation and inflammatory responses associated with cancer [(13)].

The pathogenic functions, predictive and prognostic utility of both RBM-HuR and LPCAT1expression in UBC patients, however, are still unknown despite having previously been investigated in several malignancies [(6)]. Hence, the purpose of the study was to evaluate the importance of expression of RBM-HuR and LPCAT1 in UBC.

MATERIAL AND METHODS

The current retrospective study was conducted after approval of the ethical and research committee, Benha university (RC 25-3-2023) the study included 50 formalin-fixed, paraffin embedded blocks for UBC that were assessed at the Pathology Department of faculty of

Received: 02/11/2022
Accepted: 04/01/2023

medicine, Benha University for UBC throughout the period from January 2017 till December 2022.

Histopathological study:

Using the conventional hematoxylin and eosin (H& E) stain, Sections of 4-micron thickness were stained for graded cases of low and high-grade UBC and Staged using TNM staging system into pT0-4, . With stage group from 0 to IV considering stage 0 and I as low stage while stages II to IV were described as high stage [13,14].

For immunohistochemical study, anti RBM-HuR and anti LPCAT1 immunostaining were performed using Avidin-Biotin complex technique.

Primary polyclonal antibodies, anti-HuR antibody and Anti-human LPCAT1 with concentration (1:500, SC0093, Santa Cruz Biotechnology Inc., Dallas, TX, USA) was used. Diaminobenzine (DAB) was used as chromogen. Antigen retrival was performed by using 10mmol/1citrate buffer (ph 6.0) and heated for 15 minutes using microwave.

-**Negative control:** removal of the 1ry antibody during staining was used as negative control replaced by saline or phosphate buffer.

-Positive control: human endometrial carcinoma tissues were used as positive control for HuR [11] and Human cerebellar tissue for LPCAT1 [10]**.**

Immunohistochemical assessment:

Cytoplasmic staining of RBM-HuR was done following criteria of ***Boman et al.*** [15] the extent of stain expression was categorized as: 0 (0–1%), 1 (2–25%), 2 (26–75%), 3 (> 75%),while the intensity as 0 (-ve) ,1 (weak), 2 (moderate) and 3 (strong). A combined score was obtained to reach the final scores of 0–9. Scores were categorized as low and high, with cut off point of 4 value.. Expression of LPCAT1 is nuclear with Score 1: **+ve** expression in ≤50% of tumor cells and Score 2: **+ve** expression in >50% [16]**.**

Both variables were combined to assess LPCAT1 score as follows: Pattern A: high nuclear expression was moderate to strong in >50% of tumor cells Pattern B: low nuclear expression was weak in >50% of the tumor cells.

Ethical approval:

The current retrospective study was conducted after approval of the ethical and research committee, Benha university (RC 25-3-2023). This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki).

Statistical analysis

SPSS (version 20) was used for the statistical analysis of the data. Statistics were considered significant if P< 0.05. As AUC 0.7 was regarded as good, the ROC curve was also utilized to calculate the AUC, Sensitivity, and Specificity of all markers.

RESULTS

Clinical and pathological outcomes

The correlation between T stage, tumor size and grade, LN metastasis, distant metastasis, LVI, and associated CIS was very statistically significant (P = 0.0001). Between Pt stage and age or sex, there was no statistically significant association (P>0.05) **Table 1.**

Immunohistochemical results:

There was a statistically significant correlation between RBM-HuR and LPCAT1 expression in the studied cases P < *0.05.*

RBM-HuR expression correlated positively with tumor size (P=0.03), grade (P=0.001), pT stage (P=0.01), LNs metastasis (P=0.003), distant metastasis (P=0.003), and LVI (P=0.003) in a statistically significant way. RBM-HuR expression and CIS presence did not correlate statistically significantly (P = 0.371) **Figure 1,2 and Table 2.**

There was a strong statistically significant negative correlation between the expression of LPCAT1, tumour size, grade, pT stage, distant metastases in radical cystectomy, LVI, and associated CIS (P < 0.005) **Figure 3,4 and Table 2.**

In the cases under study, there was a statistically significant association (P< 0.05) between RBM-HuR and LPCAT1 expression.

By using ROC analysis, LPCAT1 has sensitivity (81.82%) and specificity (67.44%) and RBM-HuR has sensitivity (73.7%) and specificity (57.1%) in diagnosis of bladder urothelial-carcinoma cases **Table 3, Graph 1**.

Table (1) Correlation between clinic-pathological criteria and pathologic T stage (pT) of studied cases:

Clinico -pathological variants		Total	*pT stage*		P Value
			NMI (pTa,T1)	**MI (pT2,pT3,pT4)**	
			NO	**NO**	
Age	**<60 years**	**21**	**8 (38%)**	**13 (62%)**	**P= 0.798 Insignificant**
	≥60 Years	**29**	**10 (35%)**	**19 (65%)**	
Sex	**Male**	**39**	**15 (38%)**	**24 (62%)**	**P= 0.505 Insignificant**
	Female	**11**	**3 (27%)**	**8 (73%)**	
Histopathological variant	**Papillary**	**17**	**15 (88%)**	**2 (12%)**	**P= 0.000 HS**
	non papillary	**33**	**3 (9%)**	**30 (91%)**	
Tumor size	**Up to 5cm**	**21**	**15 (71%)**	**6 (29%)**	**P= 0.000 HS**
	More than 5cm	**29**	**3 (9%)**	**26 (91%)**	
Grade	**Low**	**18**	**15 (83%)**	**3 (17%)**	**P= 0.000 HS**
	High	**32**	**3 (9%)**	**29 (91%)**	
Nodal Metastasis in radical cystectomy cases	**N0**	**7**	**4 (57%)**	**3 (43%)**	**P= 0.01 HS**
Distant Metastasis in radical cystectomy cases	**M0**	**19**	**4 (21%)**	**15 (79%)**	**P =0.282 Insignificant**
	M1	**7**	**0 (0%)**	**7 (100%)**	
Lymph vascular invasion	**Absent**	**20**	**16 (80%)**	**4 (20%)**	**P= 0.000 HS**
	Present	**30**	**2 (7%)**	**28 (93%)**	
Associated CIS	**Absent**	**28**	**17 (60%)**	**11 (40%)**	**P= 0.000 HS**
	Present	**22**	**1 (5%)**	**21 (95%)**	

CIS; carcinoma insitu NO; number

Table (2) Correlation between clinico pathological Variants and RBM-HuR and LPCAT1 Expression in the studied cases*:*

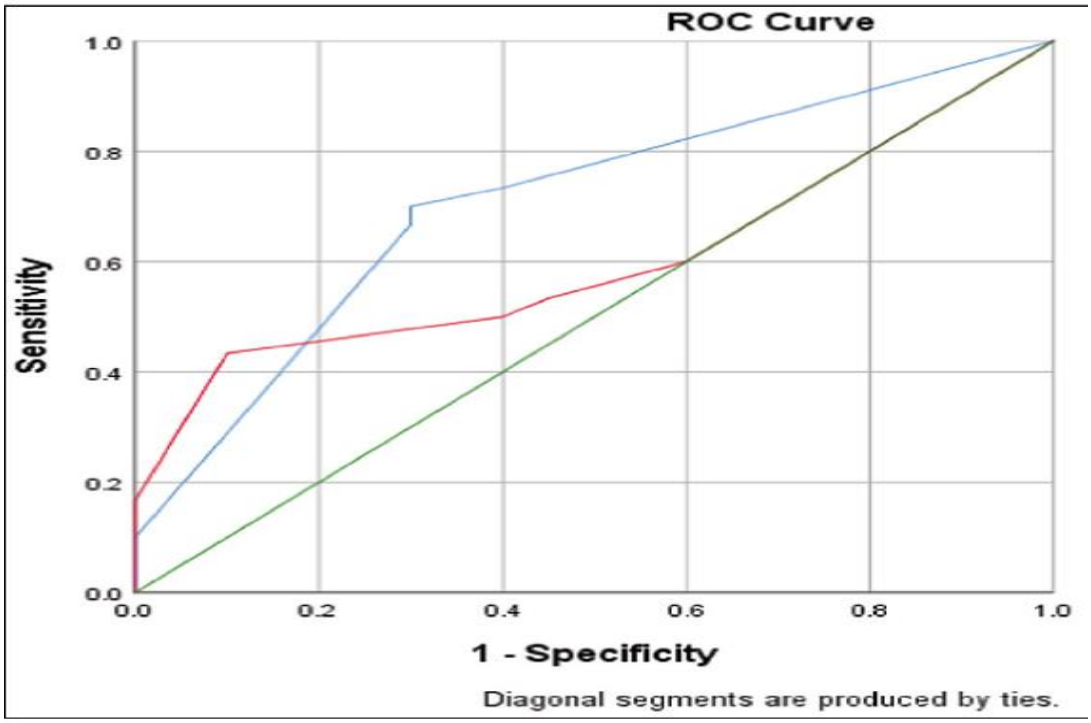
Clinicopathological variants		Total	RBM-HuR expression		P Value	LPCAT1 expression		P Value
			Negative	**Positive**		**low nuclea expression**	**High nuclear expression**	
Histopathological variant	**Papillary**	**17**	**15 *(88%)***	**2 (12%)**	**P= 0.108**	**4 (24%)**	**13 (76%)**	**P=0.000 HS**
	Non-papillary	**33**	**16 (48%)**	**17 (52%)**		**25 (76%)**	**8 (24%)**	
Tumor size	**Up to 3cm**	**21**	**20 (95%)**	**1 (5%)**	**P= 0.03 S**	**7 (33%)**	**14 (67%)**	**P=0.002 HS**
	>3cm	**29**	**11 (38%)**	**18 (62%)**		**22 (76%)**	**7 (24%)**	
Grade	**Low**	**18**	**18 (100%)**	**0 (0%)**	**P= 0.001 HS**	**4 (22%)**	**14 (78%)**	**P=0.005 HS**
	High	**32**	**13 (41%)**	**19 (59%)**		**25 (78%)**	**7 (22%)**	
pT stage	**NMI**	**pTa**	**8** **8 (100%)**	**0 (0%)**	**P= 0.01 S**	**1 (12%)**	**7 (88%)**	**P=0.001 HS**
		pT1	**11** **11(100%)**	**0 (0%)**		**5(45%)**	**6 (55%)**	
	MI	**pT2**	**21** **9 (42%)**	**12 (58%)**		**15 (71%)**	**6 (29%)**	
		pT3	**9** **3 (33%)**	**6 (67%)**		**7 (78%)**	**2 (22%)**	
		pT4	**1** **0 (0%)**	**1(100%)**		**1 (100%)**	**0(0%)**	
Staging group in radical cystectomy cases	**Low-stage (0/I)**	**7**	**7(100%)**	**0 (0%)**	**P=0.006 HS**	**2 (29%)**	**5(71%)**	**P=0.006 HS**
	High stage(II/III /IV)	**19**	**5 (26%)**	**14 (74%)**		**11 (58%)**	**8 (42%)**	
Lymph vascular invasion	**Absent**	**20**	**20 (100%)**	**0 (0%)**	**P= *0.003* HS**	**6 (30%)**	**14 (70%)**	**P=0.001 HS**
	Present	**30**	**11 (36%)**	**19(64%)**		**23 (77%)**	**7 (23%)**	
Associated CIS	**Absent**	**28**	**18 (65%)**	**10 (35%)**	**P= 0.371**	**9 (32%)**	**19 (68%)**	**P=0.000 HS**
	Present	**22**	**13 (59%)**	**9 (41%)**		**20 (91%)**	**2 (9%)**	

S; significant HS; HighlySignificant. CIS; carcinoma insitu NO;number MI; muscle invasive NMI; non muscle invasive

Table 3: ROC analysis for detecting sensitivity and specificity of both markers in diagnosis of the studied cases of urothelial carcinoma:

Marker	AUC	Sensitivity (%)	Specificity (%)	Accuracy	P value
LPCAT1	0.770	81.82	67.44	73.0	0.012
RBM-HUR	0.645	73.7	57.1	58.0	0.04

AUC; Area Under the Curve



Graph 1: ROC analysis for detecting sensitivity and specificity of both markers in diagnosis of the studied cases of urothelial carcinoma:

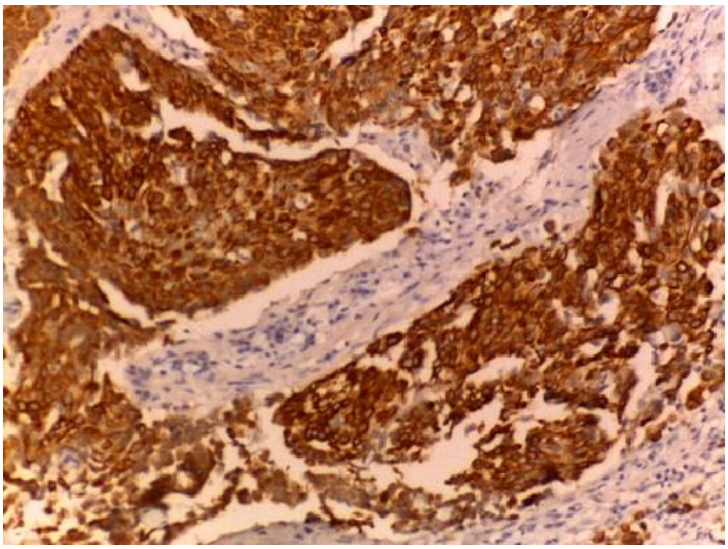


Fig. (1) photomicrograph of a section of bladder urothelial carcinoma, high grade, muscle invasive showing high RBP-HUR cytoplasmic expression, (ABC, X :400).

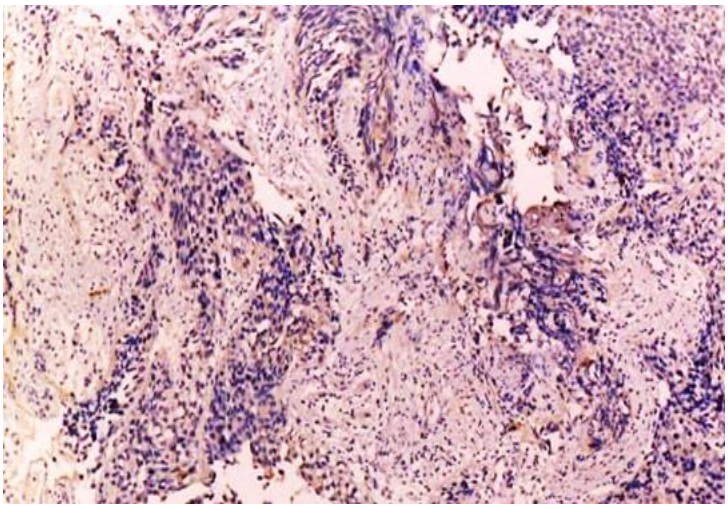


Fig. (2) photomicrograph of a section of bladder urothelial carcinoma, muscle invasive, showing low RBP-HUR cytoplasmic expression, (ABC, X:200).

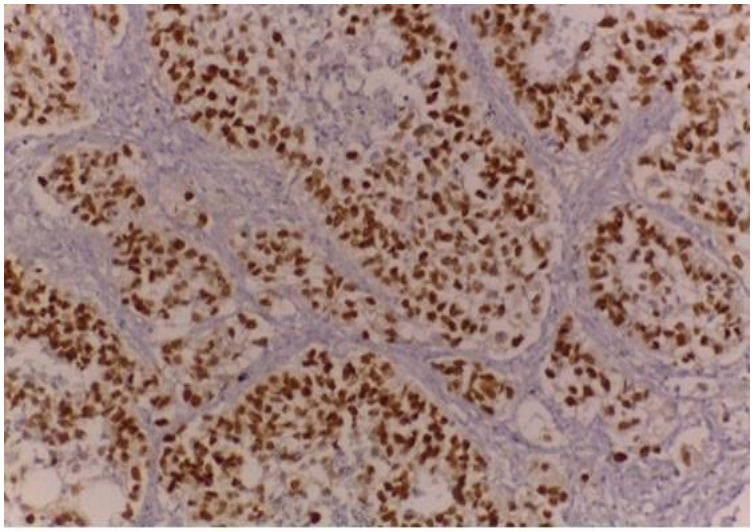


Fig. (3) photomicrograph of a section of bladder urothelial carcinoma, muscle invasive, high grade showing high LPCAT1 nuclear expression (ABC, X :200)

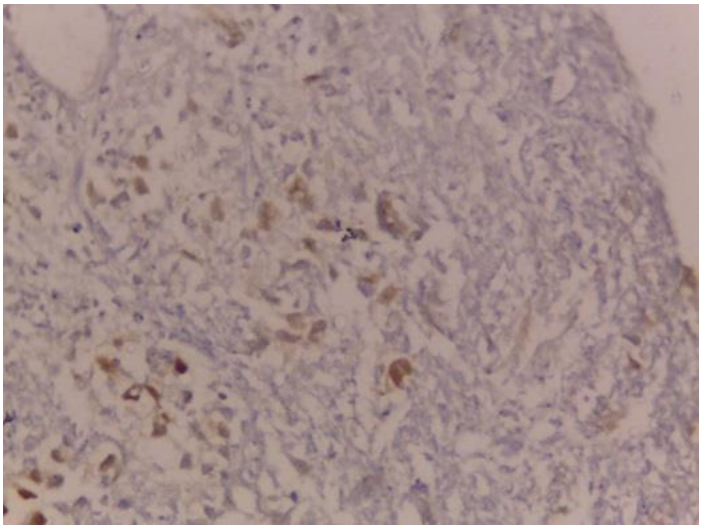


Fig. (4) photomicrograph of a section of bladder urothelial carcinoma, muscle invasive, high grade showing low LPCAT1 nuclear expression (ABC, X:200).

DISCUSSION

One of the more common and prevalent cancers in the globe is bladder cancer. It is the 3rd most prevalent malignancy in in Egypt. [5].

In the current study 50 cases of UBC were examined with M:F ratio of 3.54:1. This is consistent with ***Gunlusoy et al.*** [17], who reported M:F ratio of 3.5:1. This backs up the study conducted by ***Rambau et al.*** [5]. In line with prior research by ***Boman et al.*** [15] UBC in this study included 34% papillary transitional cell carcinoma (TCC) and 66% infiltrating-non TCC [15]. Contrary to a prior research by ***Cumberbatch et al.*** [19], who documented that most tumors were superficial. High-grade cases in the present study were presented (64%) while low-grade cases were presented (36%) and this matched the 2016 WHO grading system. Also, it matched a prior study on UBC conducted by ***Moch et al.*** [4], who presented (32%) as low grade, and (68%) were high grade. While other ~~study~~ studies by ***Barua et al.*** [18], found low grade in (57%) and high grade in (43%).

Muscle invasion was reported in 62% while 38% were non-muscle invasive and this matched the results of ***Amin et al.*** [14], who documented that most of UBC present in an advanced stage. While ***Cumberbatch et al.*** [19], reported non muscle invasive as in most cases.

Difference in the results concerning age, grade, and stage may be explained by the heterogeneity of urothelial carcinoma concerning different genetic basis may play a role. In addition, the different number of studied cases [3].

The cost of treatment of UBC is very high and this is assumed to be due to high rate of recurrence in addition to the invasive nature of the tumor. To improve prognosis and survival, adequate predictive and prognostic markers are necessary [13,20].

It was discovered that inhibiting the RNB protein HuR has anti-metastatic, pro-apoptotic, or antiangiogenic effects, highlighting HuR's uses as a therapeutic target in a wide range of cancer types, such as glioblastoma [21]. In this study, it was found that the innunohistochemical expression of RNA-HuR in UBC was high and this was associated with poor prognostic and clinicopathological behaviors and that was in line with results of ***Shi et al.*** [22] and ***Yu et al.*** [23], who documented upregulation of HuR levels in UBC and its expression indicates poor outcome. However, different results were obtained in breast cancer [24], where its expression didn't indicate poor clinicopathological criteria and its overexpression was associated with good prognosis. This disparity may be caused by different laboratory techniques used for the study as? cell culture and cell transfection techniques.

HuR oncogenic role is assumed to be due to its ability to activate angiogenesis in various cancers [25]. Also, numerous molecules, including (VEGF-A), VEGF-C, and cyclooxygenase 2, were discovered to control and regulate HuR [26].

LPCAT1 expression documented a negative statistically significant association between its expression and tumor grade and size, pT stage and TNM stage in radical cystectomy, and LVI. (P-value< ***0.05***). These findings complemented those of studies by ***Abdelzaher et al.*** [10] and ***Uehara et al.*** [27]. This may indicate a possible function for nuclear LPCAT1 downregulation in the development of UBC as well as in the aggressive phenotype and behavior of these tumors. On the other hand, other investigations by ***Abdelzaher et al.*** [8] and ***Zou et al.*** [28] showed a positive correlation between LPCAT1 overexpression and higher tumor grade and stage in breast and prostatic carcinomas. Similar outcomes were described for colorectal carcinoma and clear cell renal cell carcinoma [29,30].

Wei et al. [31] documented that lung adenocarcinoma with upregulated LPCAT1 had a higher incidence of brain metastasis. The inherent variability of phospholipids in various tumors may be the cause of this discrepancy. Additionally, it might be linked to the various monoclonal antibody clones, immunohistochemical techniques, and scoring systems that were used to detect the expression of LPCAT1 in various studies. [32].

In UBC, the expression RBM-HuR and LPCAT1 are negatively correlated. As far as we are aware, no comparable published evidence about the association between RBM-HuR and LPCAT1 in UBC exists.

CONCLUSION

By using ROC analysis, it was found that LPCAT1 is more sensitive while RBM-HuR is more specific in the diagnosis of UBC. The expression of LPCAT1 and RBM-HuR exhibited a substantial correlation with a variety of clinicopathological parameters and may serve as both diagnostic and independent prognostic markers in BUC. Patients with a poor prognosis who could profit from targeted treatment may also be included.

Conflict of interest: NIL
Financial support and sponsorship: Nil

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