Evaluation of Lipid Metabolism Reprogramming Markers (Star Related Lipid Transfer Domain Containing 3 (STARD3), Apolipoprotein C1 (APOC1), Sterol Regulatory Element Binding Protein 2 (SREBP2) In Progression of Hepatitis C Virus-Induced Hepatocellular Carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is considered one of the most common cancers globally. Reprogramming of lipid metabolism including increased cholesterol has been linked to the progression of various cancer types. **Objective:** The present study aimed to evaluate expression of STARD3, APOC1, SREBP2 in HCV- associated HCC and adjacent non-tumorous tissue and to examine their relationship with other prognostic indicators.

Patients and methods: The current retrospective study was conducted upon 55 cases of selected HCV-associated hepatocellular carcinoma to examine STARD3, APOC1, SREBP2 expression by immunohistochemistry.

Results: STARD3, APOC1, and SREBP2 showed a highly significant expression in HCV - induced HCC compared to adjacent non tumorous tissue **(P< 0.001)**. STARD3 high expression revealed statistically significant association with tumor grade **(P < 0.001)**, TNM stage **(P < 0.001)**, BCLC staging **(P < 0.001)**, tumor multiplicity **(P < 0.05)** and portal vein invasion **(P < 0.05)**. A statistically significant linear relation was found between APOC1 high expression and TNM stage **(P < 0.001),** BCLC staging **(P < 0.001),** tumor grade **(P < 0.05)**, tumor size **(P < 0.05)** and portal invasion **(P< 0.05).** High SREBP2 expression revealed statistically significant association with tumor grade **(P < 0.001)**, TNM stage **(P < 0.001)** and BCLC staging **(P < 0.001)**, tumor size **(P < 0.05)**, portal vein invasion **(P < 0.05)** and multiplicity **(P < 0.05). Conclusion:** The levels of STARD3, APOC1, and SREBP2 were statistically significantly increased in hepatocellular carcinoma. High expression of these markers was closely linked to poor prognostic factors, including high tumor grade and advanced cancer stage.

Keywords: HCC, APOC1, STARD3, SREBP2.

INTRODUCTION

Hepatocellular carcinoma (HCC) is currently the fifth most commonly diagnosed cancer in the world and also a leading cause of mortality related to malignant tumors worldwide [(1)]. In Egypt, HCC represents a major public health challenge, being the fourth most common type of cancer. This high incidence is largely attributed to the widespread prevalence of Hepatitis C virus (HCV) infection among the Egyptian population [(2)].

Lipid metabolism reprogramming in cancer is an emerging and critical area of cancer biology, as tumor cells often modify their normal metabolic pathways to meet the excessive energy needs for cancer cell rapid growth and survival. Investigating the mechanisms behind lipid metabolism reprogramming in cancer could provide critical valuable insights for developing potential therapeutic strategies. However, identification of complexity of lipid metabolism in cancer biology remains a challenge [(3)].

STARD3 (STAR-related lipid transfer domain 3) is a protein that plays a crucial role in lipid trafficking within cells, especially related to the transport of cholesterol. Overexpression of STARD3 has been informed to enhance cholesterol synthesis through enhancing the expression of cholesterol synthesis enzymes [(4)]. Cholesterol metabolism is frequently altered in cancer cells to facilitate rapid cell growth and the synthesis of new cells. Overexpression of STARD3 has been observed in breast cancer, especially in HER2-positive types. This increased expression is linked to greater tumor aggressiveness, enhanced metastatic potential, and a poorer prognosis [(5)]. Apolipoprotein C1 (APOC1), found on chromosome 19, is a key member of the apolipoprotein family, playing a crucial role in lipid transport and metabolism. Fatty acid oxidation is critical for metabolic reprogramming of malignant cells to achieve the accelerated energetic demands. APOC1 has been shown to significantly enhance fatty acid oxidation. APOC1 has been recognized as a potential biomarker and therapeutic target in variable malignant tumors [(6)]. The sterol response element binding proteins (SREBPs) is group transcription factors that play crucial role in regulating lipid metabolism. The SREBPs family is composed of two genes, SREBF1 and SREBF2 [(7)]. SREBP2 has been documented to activate transcription of mevalonate kinase (MVK) gene which is involved in cholesterol synthesis. Cholesterol is responsible for preservation of the structure of cell membrane. Additionally, cholesterol is required for maintaining signal transduction and cell polarization in cancer cells through formation of the lipid rafts [(8)].

The potential role of lipid reprogramming markers STARD3, APOC1, and SREBP2 expression in HCV-associated HCC hasn't been entirely elucidated. Thus, the present study was designed to evaluate the immunohistochemical expression of STARD3, APOC1, and SREBP2 in HCV-related HCC tissues and adjacent non-cancerous tissues and assess also relation with different clinicopathological parameters as tumor stage and portal invasion.

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PATIENTS AND METHODS

The current retrospective study involved 55 cases of HCC with previous history of HCV infection. The study materials consisted of formalin-fixed, paraffin blocks collected from the Department of Pathology of the Benha Faculty of Medicine.

These samples were processed between 2013 and 2018. The different clinicopathological parameters were obtained from pathology reports and hospital records. The Barcelona Clinic Liver Cancer (BCLC) staging system was assessed for all cases.BCLC A (The early stage) includes patients with one hepatic nodule < 5 cm or three nodules each one < 3 cm and is appropriate for curative therapy strategies. BCLC B (The intermediate stage) includes asymptomatic patients with large or multifocal tumors restricted to the liver. The advanced stage (BCLC C) describes patients with cancer symptoms, macrovascular invasion, or extrahepatic spread. BCLC D (the terminal stage) includes patients in the terminal stage presenting with a poor performance status and receive only supportive care [(9)].

Histopathological analysis: The pathological diagnosis and grading of HCC were independently confirmed by two blind experienced pathologists on sections stained by conventional hematoxylin and eosin (H&E).

Immunohistochemical study: For immunohistochemical (IHC) staining, 10% formalin-fixed, paraffin-embedded, 4-micron tissue sections were prepared and immunostained for the primary antibodies according to the manufacture instructions. The explanatory data for the used primary antibodies are detailed in table 1. The Negative control for previous markers was performed by omitting the investigated antibodies. The staining of sections were blindly assessed and scored by two independent pathologists.

Table (1): The primary antibodies, their clone, and positive control.

Anti-body	Company	Clone	Dilution	Positive control	Staining pattern
STARD3	Abcam	Mono-clonal ab3478	1:50	Adrenal Gland	Cyto-plasmic
APOC1	Thermo Fisher Scientific	Mono-clonal 2E2-1A3	1:100	Sub-cutaneous fat	Cytoplasmic
SREBP2	Thermo Fisher Scientific	Mono-clonal 1580	1:100	Adrenal Gland	Nuclear /cytoplasmic

Interpretation of immunohistochemical staining:

STARD3: STARD3 staining was observed in the cytoplasm. The extent of staining of cells was graded as follows: 0 (negative), 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100%). Grades for staining intensity were 0 (no staining), 1 (weak staining), 2, and 3 (strong staining).). The final scores were calculated by multiplying these two scores. A total score of ≥ 6 was considered as high STARD3 expression while scores below this threshold were considered low expression [(10)].

APOC1: The staining was cytoplasmic. The percentage of stained cells was categorized as 0≤10%, 1=11–25%, 2=26–50%, 3=51–75%, and 4>75%. The intensity was scored as 0 (negative), 1 (weak), 2 (moderate), or 3 (strong). The final immunoreactive score was calculated by multiplying these two values. A final score >1 was defined as high expression; otherwise, it was detected as low expression [(11)].

SREBP2: The expression was nuclear and cytoplasmic. Percent of stained cells was scored as: 1=0–25%, 2=26–50%, 3=51–75% and 4>75%. The staining intensity was assessed as 1 (weak), 2 (medium), 3 (strong) and 4 (very strong). The final score was determined by multiplying these two values. The final score more than 6 was considered high expression. The other scores less than 6 represented low expression [(12)].

Ethical consideration: This study was given the approval by the Ethical Committee at Faculty of Medicine, Benha University (Code number: RC 4-1-2025). Throughout its implementation, the study was complied with Helsinki declaration.

Statistical analysis: Software called SPSS version 16.0 was used to analyze the data. Quantitative data were presented as mean ± standard deviation (SD) and range. Qualitative data were presented as frequency and percentage and were compared using X^2-test. The established threshold for significance was set at 0.05, with $P < 0.05$ being deemed significant and $P \leq 0.01$ being deemed highly significant.

RESULTS

The current retrospective study was conducted on a cohort of 55 Egyptian cases diagnosed with HCC, with prior history of HCV infection. Among these patients, 43 (78.2%) were males, while 12 (21.8%) were females. The mean age of cases was 55.70 ± 4.97 years, with ages ranged from 39 to 70 years. Regarding the grading of HCC, 10 cases (18.2%) were grade 1, 26 cases (47.3%) were grade 2 and 19 cases (34.5%) were considered grade 3. 24 cases (43.6%) presenting tumors were ≤ 5 cm in size, while 31 cases (56.4%) exhibited tumors exceeding 5 cm. Regarding tumor multiplicity, 31 cases (56.4%) showed solitary tumor and 24 cases (43.6%) exhibited multiple tumors. Concerning tumor staging, stage I included 6 cases (10.9%), stage II included 18 cases (32.7%), stage III included 17 cases (30.9%) and stage IV included 14 cases (25.5%). Additionally, 22 patients (40.0%) demonstrated evidence of portal vein invasion. Regarding BCLC staging, stage A included 13 cases (23.6%), stage B included 14 cases (25.5%), stage C included 19 cases (34.5%), while stage D included 9 cases (16.4%).

STARD3 Immunohistochemical Results:STARD3 high expression was detected in 35/55 (63.6 %) of HCC cases however, STARD3 staining was seen in 15/55 (27.3%) of adjacent non tumorous tissue with statistical high significant difference. In HCC cases, STARD3 high expression revealed high statistically significant association with high tumor grade, TNM stage and BCLC staging. High STARD3 expression showed statistically significant association with tumor multiplicity and portal vein invasion. These data were detailed in table 2 and figure 1.

Table (2): Statistical relations of STARD3 with clinicopathological features of HCC:

Clinicopathological variables			STARD3		Test of significance
			Low	High	
Sex	Male	43	14 (32.6%)	29 (67.4%)	X^2=.237 P = 0.526
	Female	12	6 (50.0%)	6 (50.0%)	
Tumor size	≤ 5cm	24	10(41.7%)	14(58.3%)	X^2= .129 P = 0.629
	>5cm	31	10(32.3%)	21(67.7%)	
Grade	G1	10	9 (90.0%)	1(10.0%)	X^2=14.89 P < 0.001**
	G2	26	8 (30.8%)	18(69.2%)	
	G3	19	3 (15.8%)	16 (84.2%)	
Multiplicity	Solitary	32	15(46.9%)	17(53.1%)	X^2=4.65 P < 0.05*
	Multiple	23	5(23.7%)	18(78.3%)	
TNM stage	I	6	6 (100.0%)	0 (0%)	X^2=12.65 P < 0.001**
	II	18	7 (38.9%)	11 (61.1%)	
	III	17	5 (29.4%)	12 (70.6%)	
	IV	14	2 (14.3%)	12 (85.7%)	
Multiplicity	Solitary	32	15(46.9%)	17(53.1%)	X^2=4.65 P < 0.05*
	Multiple	23	5(23.7%)	18(78.3%)	
Portal vein invasion	Absent	33	17(51.5%)	16(48.5%)	X^2=5.76 P < 0.05*
	Present	22	3(13.6%)	19(86.4%)	
BCLC	A	13	11 (84.6%)	2 (15.4%)	X^2=15.87 P < 0.001**
	B	14	6 (42.9%)	8 (57.1%)	
	C	19	2 (10.5%)	17 (89.5%)	
	D	9	1 (11.1%)	8 (88.9%)	
Total		55	20 (36.4%)	35 (63.6%)	

*: Significant, **: Highly significant.

APOC1 Immunohistochemical Results

APOC1 high expression was detected in 34/55 (61.8% %) of HCC cases while was seen in only 10/55 (18.2%) of adjacent non tumorous tissue with statistical high significant difference. In HCC cases, a statistically significant association was found between APOC1 high expression and TNM stage, BCLC staging **(**high tumor grade, tumor size, and portal invasion). These findings are outlined in table 3 and figure 2.

Table (3): Statistical relations of APOC1 with clinicopathological variables of HCC:

Clinicopathological variables			APOC1		Test of significance
			Low	High	
Sex	Male	43	16(37.2%)	27(62.8%)	X^2= .987 P = .654
	Female	12	5(41.7%)	7(58.3%)	
Tumor size	≤ 5cm	24	13(54.2%)	11(45.8%)	X^2=6.23 P < 0.05*
	>5cm	31	8(25.8%)	23(74.2%)	
Grade	G1	10	8(80.0%)	2(20.0%)	X^2= 4.56 P < 0.05*
	G2	26	8(30.8%)	18(69.2%)	
	G3	19	5 (26.3%)	14(73.7%)	
TNM stage	I	6	5 (83.3%)	1(16.7%)	X^2= 15.07 P < 0.001**
	II	18	7 (38.9%)	11(61.1%)	
	III	17	5(29.4%)	12(70.6%)	
	IV	14	4(28.6%)	10(71.4%)	
Multiplicity	Solitary	33	15(45.5%)	18(54.5%)	X^2=.546 P = .384
	Multiple	22	6 (27.3%)	16(72.7%)	
Portal vein invasion	Absent	33	15(45.5%)	18 (54.5%)	X^2= 5.87 P < 0.05*
	Present	22	6 (27.3%)	16 (72.7%	
BCLC	A	13	9(69.2%)	4(30.8%)	X^2= 21.07 P < 0.001**
	B	14	6 (42.9%)	8(57.1%)	
	C	19	5(26.3%)	14(73.7%)	
	D	9	1(11.1%)	8(88.9%)	
Total		55	21(38.2%)	34(61.8%)	

*: Significant, **: Highly significant.

SREBP2 Immunohistochemical Results:
SREBP2 high expression was detected in 32/55 (58.2%) of HCC cases while in 12/55 (21.8%) of adjacent non-cancerous tissue with statistical high significant difference. In HCC cases, high SREBP2 expression revealed high statistically significant association with tumor grade, TNM stage and BCLC staging. High SREBP2 expression showed statistically significant association with tumor size, portal vein invasion and multiplicity as detailed in table 4 and figure 3.

Table (4): Statistical relations of SREBP2 with clinicopathological variables of HCC

Clinicopathological variables			SREBP2		Test of significance
			Low	High	
Sex	Male	43	19 (44.2%)	24 (55.8%)	X^2= 0.242
	Female	12	4 (33.3%)	8 (66.7%)	P = .509
Tumor size	≤ 5cm	24	14 (58.3%)	10 (41.7%)	X^2=4.89
	>5cm	31	9 (29.0%)	22 (71.0%)	P < 0.05*
Grade	G1	10	9 (90.0%)	1 (10.0%)	X^2=15.07
	G2	26	9 (34.6%)	17 (65.4%)	P < 0.001**
	G3	19	5 (26.3%)	14 (73.7%)	
TNM stage	I	6	5 (83.3%)	1(16.7%)	
	II	18	7(38.9%)	11(61.1%)	X^2=12.89
	III	17	7(41.2%)	10(58.8%)	P < 0.001**
	IV	14	4 (28.6%)	10(74.4%)	
Multiplicity	Solitary	31	18 (56.2%)	14 (43.8%)	X^2=8.26
	Multiple	24	5 (21.7%)	18 (78.3%)	P < 0.05*
Portal vein invasion	Absent	33	18 (54.5%)	15 (45.5%)	X^2=5. 54
	Present	22	5 (22.7%)	17 (77.3%)	P < 0.05*
BCLC	A	13	11 (84.6%)	2 (15.4%)	
	B	14	6 (42.9%)	8 (57.1%)	X^2=10.89
	C	19	4 (21.1%)	15(78.9%)	P < 0.001**
	D	9	2 (22.2%)	7(77.8%)	
Total		55	23 (41.8%)	32 (58.2%)	

*: Significant, **: Highly significant

Statistical relation between STARD3, APOC1 and SREBP2 in the studied HCC cases:
High statistically significant association was found between STARD3 and APOC1. Similarly, significant high statistical association between STARD3 and SREBP2 was detected. Additionally, positive high statistically significant association was noted between APOC1 and SREBP2.

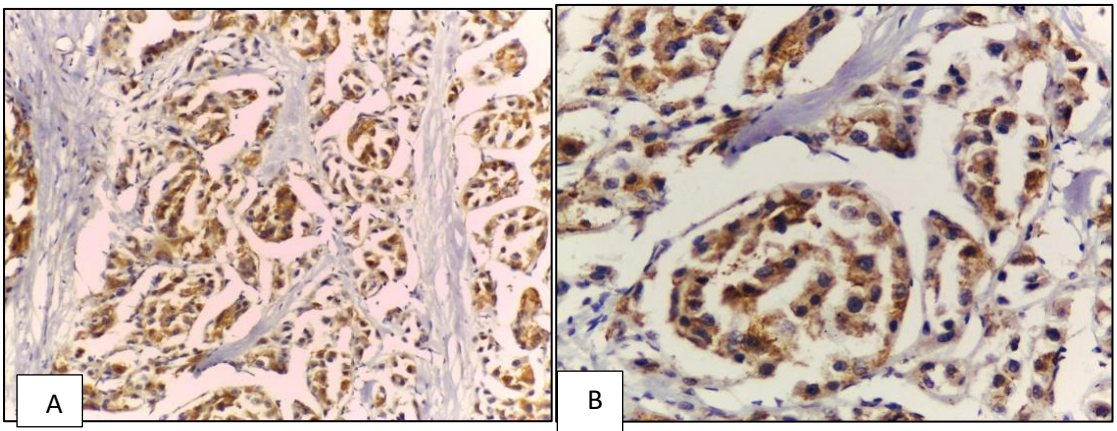

Figure (1): (A) High STARD3 cytoplasmic expression in hepatocellular carcinoma (immunostaining×200). (B) High STARD3 cytoplasmic expression in hepatocellular carcinoma (immunostaining×400).

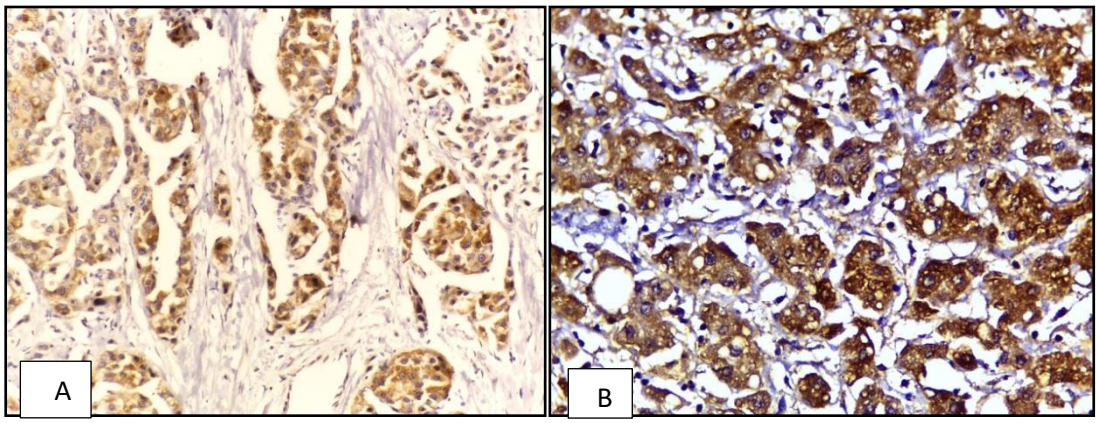

Figure (2): (A) High APOC1 cytoplasmic expression in well differentiated hepatocellular carcinoma (immunostaining × 200). (B) High APOC1 cytoplasmic expression in high grade hepatocellular carcinoma (immunostaining×400).

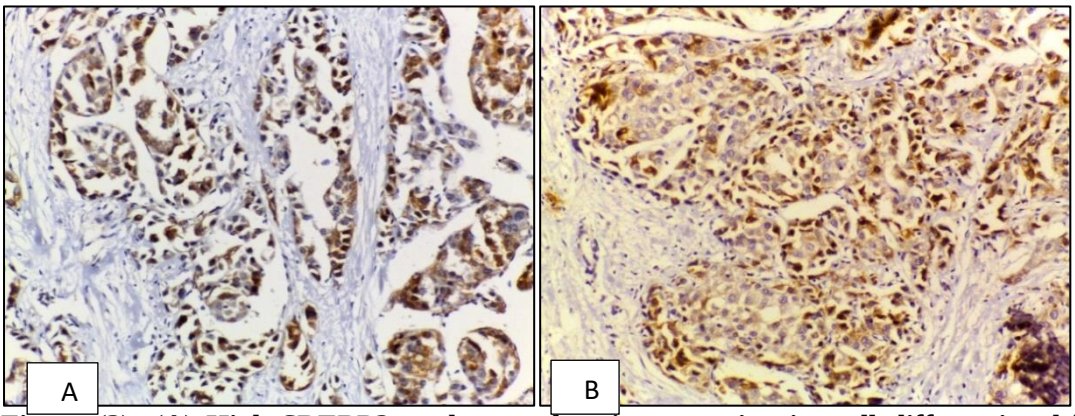

Figure (3): (A) High SREBP2 nucleocytoplasmic expression in well differentiated hepatocellular carcinoma (immunostaining× 200). (B) High SREBP2 nucleocytoplasmic expression in high grade hepatocellular carcinoma (immunostaining× 200).

DISCUSSION

Hepatocellular carcinoma (HCC) represents a major public health concern in Egypt, standing as one of the foremost contributors of cancer-related morbidity and mortality in the country. Egypt has one of the highest incidences of HCC worldwide primarily attributed to the high incidence of chronic hepatitis C virus (HCV) infection, which is the main contributing factor for the development of liver cirrhosis and HCC [(13)]. HCC remains a significant challenge, and ongoing efforts are needed to enhance early detection and improve treatment options. Currently, the available treatment modalities for HCC remain insufficient, and the identification of critical molecular drivers behind the progression of HCC persists as a focal area of research [(14)]. The potential role of lipid metabolism reprogramming in development of different cancers has gained increasing attention in recent years .

Cancer cells often undergo metabolic changes to meet the increased energetic and biosynthetic demands of rapid cell growth and proliferation. Lipid metabolism is one of the altered pathways in cancer cells, and this reprogramming significantly impacts various aspects of tumorigenesis. Lipid metabolism reprogramming can influence many cellular processes such as membrane synthesis, energy production, signaling pathways all of which are essential for cancer cell proliferation, survival, and invasion [(15)].

The current study aimed to explore the immunohistochemical expression of lipid metabolism reprogramming markers STARD3, APOC1, and SREBP2 in HCC induced by HCV infection and explore their association with various clinicopathological parameters.

The current study demonstrated that STARD3 showed statistically highly significant expression in HCC compared to adjacent non tumorous hepatitis or cirrhosis (P <0.001). This suggests that STARD3 might have potential oncogenic role in carcinogenesis of HCC. In addition, the current work showed that the overexpression of STARD3 in HCC cases showed statistically significant linear association with higher tumor grade (p< 0.001), advanced stage (p<0.001), BCLC staging (p< 0.001), tumor multiplicity (P<0.05) and portal vein invasion (P <0.05). These observations may suggest a potential role of STARD3 in promoting aggressiveness and accelerating the progression of HCC. In fact, limited studies had handled STARD3 expression in HCC. However, numerous studies have reported findings similar to ours in other cancer types. **Wang *et al.*** [(3)] explained that STARD3 expression was high in breast cancer compared to normal tissue with high significant difference and that poor prognostic parameters as histological grade and tumor size have been associated with high STARD3 level. **Binh *et al.*** [(16)] reported that STARD3 expressed with HER2 protein and both were linked to poor outcomes in breast cancer. Additionally, STARD3 was exposed to downregulate p27 and increase cyclin D1, thereby promoting faster cell cycle progression.

In prostatic carcinoma, high STARD3 expression was associated with metastasis, local recurrence, and reduced overall survival. STARD3, in combination with CYP17, plays a synergistic role in enhancing steroidogenesis and androgen biosynthesis by promoting the transfer of cholesterol to the mitochondria [(17)].

STARD3 is considered a transmembrane protein that has a crucial role in cholesterol transport. Furthermore, STARD3 facilitates steroidogenesis by facilitating the transfer of lysosomal cholesterol to mitochondria. Several studies have approved that elevated mitochondrial cholesterol levels can inhibit apoptotic cell death in different cancers, thereby triggering tumor progression [(18).] Increased cholesterol levels, which are notably prevalent in the mitochondria membrane of cancer cells, decrease membrane fluidity. This change repress mitochondrial permeability transition and prevents the release of pro-apoptotic molecules like cytochrome c, allowing cancer cells to resist apoptosis and continue to survive [(19)].

Regarding APOC1, The present work revealed that APOC1 high expression was detected in (61.8% %) of HCC cases with highly significant difference from expression in non-cancerous hepatitis tissue (P<0.001). In HCC study cases, high expression of APOC1 was statistically correlated with TNM stage (P <0.001) and BCLC staging (P < 0.001), tumor size (P < 0.05), tumor grade (P< 0.05) and portal vein invasion (P < 0.05).

In the same literature, **Yang *et al.*** [(20)] reported that APOC1 was upregulated in ovarian carcinoma where it was linked to promotion of proliferation and invasion of ovarian cancer cells. **Guo *et al.*** [(21)] observed that upregulation of APOC1 in esophageal carcinoma was significantly associated with higher stage, histological grade and reduced patients survival.

Gu *et al.* [(22)] confirmed that APOC1 is highly expressed in gastric carcinoma and is correlated with poor prognostic parameters as high grade and advanced cancer stage. Their study further revealed that APOC1 enhance cancer cell invasion and migration and involved in the WNT pathway and immune regulation. **Li *et al.*** [(23)] reported that APOC1 can induce metastasis of renal clear cell carcinoma through activation of STAT3 pathway. Additionally, **Tang *et al.*** [(24)] demonstrated elevated APOC1 expression in colorectal carcinoma tissues and its correlation with advanced cancer stages, lymph node involvement, and poorer prognostic outcomes.

Gao *et al.* [(25)] confirmed the upregulation of APOC1 in diffuse large B-cell lymphoma additionally; they noted that APOC1 knockdown led in increased apoptosis and reduction in cancer cell proliferation, invasion, angiogenesis plus inhibition of PI3K/AKT/mTOR signaling pathway. **Liu *et al.*** [(26)] explained that APOC1 silencing significantly inhibits the MAPK/ERK kinase signaling pathway and reduces

NF-κB activity, leading inhibition of growth and metastasis in breast cancer. Furthermore, **Jiang *et al.*** [27] highlighted that APOC1 plays a role in progression of renal cell carcinoma through modulation of the WNT3 signaling pathway.

Regarding SREBP2, the current work detected that SREBP2 high expression was detected in (58.2%) of HCC cases while (21.8%) of adjacent non-cancerous tissue. The statistical difference was significantly high (P< 0.001). In HCC cases, high SREBP2 expression showed high statistically significant association with tumor grade, TNM stage and BCLC staging (P< 0.001) and also tumor size, tumor multiplicity, and portal vein invasion (P < 0.05).

This is consistent with the findings of **Li *et al.*** [28]**,** who observed that SREBP2 expression was significantly increased in HCC compared to adjacent non tumorous tissues and that SREBP2 expression regulated by LINC00618. Furthermore, the upregulation of SREBP2 encouraged cell proliferation, epithelial-mesenchymal transition and caused inhibition of cell apoptosis. Similarly**, Codenotti *et al.*** [29] proposed that SREBP2 plays a crucial role in the growth, migration of rhabdomyosarcoma, primarily by maintaining sufficient cholesterol levels to ensure proper intracellular signaling.

Mok *et al.* [30] highlighted that cholesterol biosynthesis driven by SREBP2 is required for the proliferation of liver cancer stem cells. The deletion of SREBP2 enhanced sensitivity to tyrosine kinase inhibitors, indicating that it plays a role in the control of acquired drug resistance in hepatocellular cancer. Mechanistically, caspase-3 (CASP3)-mediated cleavage of SREBP2 from the endoplasmic reticulum stimulates cholesterol production, which leads to chemotherapy resistance by activating the sonic hedgehog pathway. **Wang *et al.*** [31] found that the SREBP2-driven cholesterol metabolism pathway is important in the development and progression of bladder cancer.

SREBP2 is considered as basic organizer of the process of cholesterol biosynthesis through activation of the expression of genes involved in cholesterol synthesis like HMGCR. Cholesterol is an essential lipid for maintaining cell growth and membrane integrity. In cancer cells, enhanced cholesterol metabolism is mandatory for synthesis of plasma membranes and also required for facilitating rapid cell growth. Cholesterol can promotes cell proliferation and migration through stabilization of lipid rafts cells through TLR7. Additionally, activation of the classic tumorigenic Hedgehog signaling pathway may be maintained by increased cholesterol level [32]**.**

High statistical significant association was found between STARD3 and APOC1 (p < 0.001). Similarly, significant high statistical association between STARD3 and SREBP2 (p < 0.001) was detected. Additionally, positive high statistical significant association was noted between APOC1 and SREBP2 (p < 0.001).

Both APOC1 and SREBP2 are influenced by the activation of MAPK/ERK and PI3K/AKT pathways, respectively. Therefore, the interaction between them could be explained by the cross-talk between MAPK/ERK and other parallel signaling pathways as PI3K/AKT and Wnt pathways. These pathways are crucial in driving abnormal sustained cell proliferation and contributing to resistance to therapy [33]. Regarding the relation between STARD3 and SERBP2, it may be clarified by that in StARD3 overexpressing cells; the levels of the precursor and the mature form of SREBP2 were increased [34]**.**

Based on the preceding findings, this research may emphasize the role of STARD3, APOC1 and SREBP2 in HCC highlighting the potential impact of lipid metabolism reprogramming on development and progression of HCC.

CONCLUSION

The current study detected that lipid metabolism reprogramming markers STARD3, APOC1 and SREBP2 were significantly higher in hepatocellular carcinoma. Their high expression was correlated with poor prognostic characters as high grade and advanced stage. This may give additional confirmation that STARD3, APOC1 and SREBP2 are linked to the development and progression of cancer. Our results may highlight that previous markers may provide potential prognostic indicators and promising therapeutic targets for HCC patients.

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