

Clinical and *In silico* Evaluation of Cholesterol and Triglyceride Dysregulation and Its Regulatory Targets in Hepatocellular Carcinoma Patients with Metabolic Disorders

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Abstract

Background: Metabolic alterations in hepatocellular carcinoma (HCC) focus on lipid pathway disruption, driving tumor proliferation and immune evasion alongside demographic risk factors via specific genetic and enzymatic targets. The significance of total cholesterol (TC) and triglyceride (TG) levels in HCC patients with metabolic disorders in Maysan, Iraq, considering patient sex and residence area. **Methods:** This study analyzed 510 participants (255 HCC patients with metabolic disorders and 255 healthy controls) using serum measurements of TC and TG levels, logistic regression, Analysis of Variance (ANOVA), and AutoDock Vina molecular docking simulations for Atorvastatin, Rutin, Orlistat, Avsimibe, and Cholic Acid. **Results:** Elevated TG levels correlated with increased HCC risk (odds ratio [OR] = 1.082, $P < 0.001$), while higher TC levels were inversely related (OR = 0.966, $P < 0.001$), highlighting peripheral “cholesterol trapping.” Three-Way ANOVA showed lipid alterations were associated with disease status ($P = 0.001$) but did not vary by sex or residence ($P = 0.901$). Preliminary docking results identified Atorvastatin as the strongest, redocking-validated binder, with Rutin a closely comparable candidate meriting further exploration; Cholic Acid’s predicted binding could not be similarly validated. **Conclusion:** A reliable, demographically stable biomarker for HCC is peripheral dyslipidemia. Although extrapolation to cholic acid or clinical application awaits additional validation, Rutin’s binding design suggests it may be worthy of further research for regulating lipid pathways in HCC.

Keywords: Biomarkers, cholesterol, hepatocellular carcinoma, liver neoplasms, metabolic diseases, molecular docking simulation

INTRODUCTION

Abnormalities in lipid metabolism are currently recognized as one of the critical metabolic traits that contribute to cancer development, metastasis, and immune evasion.^[1] Similar to noncancerous cells under resting conditions, cancer cells exhibit significant alterations in their metabolism to meet their constant demands for the synthesis of cellular membranes, signaling molecules, and biomass.^[2] Dyslipidemia, the condition of having abnormal levels of total TC and TG in the blood, has been shown to play a dual function in cancer development.^[3,4] The mevalonate pathway, which is mediated by the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), is the main biosynthetic pathway for the production of cholesterol and isoprenoids in the body.^[5] Overexpression of HMGCR in cancer cells has been found to contribute to lipid accumulation within

these cells, which subsequently activates small Guanosine Triphosphatases (GTPases) that are critical for their survival.^[6,7] Furthermore, (TG) levels in the blood provide an external source of energy for cancer cells.^[8] Cancer cells utilize the lipids stored within the lipid droplets in the cell and the free fatty acids released through lipolysis of (TG) to enable them to perform beta-oxidation to resist metabolic, oxidative, and hypoxic stress caused by the growth of these cancer cells [Figure 1].^[9]

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How to cite this article: Al-Hameedawi AK, Mohammed IM, Al-Yasiri MJ, Al-Fartosy AJ. Clinical and *in silico* evaluation of cholesterol and triglyceride dysregulation and its regulatory targets in hepatocellular carcinoma patients with metabolic disorders. Biomed Biotechnol Res J 2026;10:343-51.

Submitted: 20-May-2026;

Revised: 22-Jun-2026;

Accepted: 24-Aug-2026;

Published: 28-Sep-2026.

Access this article online

Quick Response Code:



Website:
<https://journals.lww.com/BBRJ>

DOI:
10.4103/bbrj.bbrj_110_26