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COMPREHENSIVE ANALYSIS OF COL1A1 EXPRESSION, METHYLATION, AND GENETIC ALTERATIONS IN LIVER HEPATOCELLULAR CARCINOMA

Zainab lanjar[1], Rohma Fatima[2], Maryam Saddiqa[3], Muhammad Khizer Hayat[4], Imtiaz Ali Soomro[5], Tayyaba Riaz[6], Umair Younas[7], Qaiser Akram[8], Muhammad Ahsan Naeem[9], Muhammad Adnan Aslam[10], Rizwana Sultan[11*]

[1]Department of Veterinary Microbiology, SBBUVAS, Pakistan
[2]Shahida Islam Medical College Lodhran, Pakistan
[3]Department of Livestock & Dairy Development Narowal, Pakistan
[4]Center for Animal Diagnostics, Chughtai Lab, Lahore, Pakistan
[5]Department of Surgery, Peoples University of Medical and Health Sciences Nawabshah, Pakistan
[6]Faculty of Biosciences, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur, Pakistan
[7]Department of Livestock Management, Faculty of Animal Production and Technology (FAPT), Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan
[8]Department of Pathobiology (Microbiology), University of Veterinary & Animal Sciences, Lahore, Pakistan (Narowal Campus 51600), Pakistan
[9]Department of Basic Sciences (Pharmacology), University of Veterinary and Animal Sciences, Lahore, Pakistan (Narowal Campus 51600)
[10]Deputy Director Oric, UVAS, Lahore, Pakistan
[11*]Department of Pathology, Faculty of Veterinary and Animal Sciences, Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan

***Corresponding Author:** Rizwana Sultan,
*Department of Pathology, Faculty of Veterinary and Animal Sciences, Cholistan University of Veterinary and Animal Sciences, Bahawalpur, Pakistan.
Email address: rizwanasultan@cuvas.edu.pk

Abstract

Liver hepatocellular carcinoma (LIHC) is a prevalent and deadly form of liver cancer characterized by significant genetic and epigenetic alterations. This study focuses on the role of COL1A1, a gene implicated in various cancers, by analyzing its expression, promoter methylation, and genetic mutations in LIHC. Using the UALCAN database, we observed a significant upregulation of COL1A1 in LIHC samples compared to normal controls, suggesting its involvement in cancer progression. This finding was corroborated by GEPIA2 analysis, which also showed elevated COL1A1 expression in LIHC. Further analysis using UALCAN revealed that COL1A1 expression was consistently upregulated across different cancer stages, races, ages, and genders of LIHC patients, indicating its broad role in tumor development. Validation with GEPIA2 confirmed these observations at individual cancer stages. Methylation analysis showed that COL1A1 was hypomethylated in LIHC samples relative to normal controls, a factor known to enhance tumor development. Interestingly, stage-specific analysis indicated hypermethylation of COL1A1 in stage

4 LIHC, reflecting its complex regulatory mechanisms. Survival analysis using KM plotter and GEPIA2 indicated that higher COL1A1 expression was associated with lower overall survival (OS) rates in LIHC patients, although the results were not statistically significant. Genetic alteration analysis via cBioPortal identified a low mutation frequency (3%) in COL1A1, suggesting limited impact on LIHC through genetic mutations alone. In conclusion, our comprehensive analysis highlights COL1A1 as a potentially significant player in LIHC progression through its aberrant expression and methylation, although its direct genetic mutations appear to have minimal effect. These findings underscore the need for further research to fully elucidate COL1A1's role and therapeutic potential in LIHC.

Keyword: LIHC, COL1A1, Diagnosis, Treatment

Introduction

Cancer is a paramount health and economic burden worldwide. Cancer is the most common cause of death across the globe with approximately 19,292,789 cancer cases and 9,958,133 cancer deaths in 2020 (1-3). Where diagnostic and therapeutic delay is one of major reason of high mortality and cancer growth (4-6). Liver Hepatocellular Carcinoma (LIHC) is the 6^{th} most common cancer and rated as 2^{nd} cancer in high mortality (7-9). In 2022, approximately 865,269 new LIHC cases and 757,948 LIHC deaths were recorded (10). It is more frequent in male as 5^{th} most common cancer and 9^{th} most common in female (11-15). Smoking, alcohol consumption, obesity, hepatitis and poor lifestyle are some of major risk factor linked with LIHC. Mostly LIHC is diagnosed at advanced staged that why it has high mortality rate (16-18). So, it's essential to discover new diagnostic and therapeutic biomarker.

Collagen type 1 alpha 1 (COL1A1) codes for type 1 Collagen, a triple-helix composed of two alpha 1 and one alpha 2 chain. Collagen mutation is associated with Ehlers-Danlos syndrome, Caffey diseases, and osteogenesis imperfect diseases.(19-22). Recently, it has been reported that COL1A1 is associated with many tumors and COL1A1 high expression increase tumor metastasis (23-28). It is said that high expression of COL1A1 is related to metastasis of colorectal cancer, gastric cancer, breast cancer and lung cancer (29-32). Previous studies show that increased COL1A1 expression is associated with changed immune level and poor prognosis this indicates its potential as immunological biomarker (33, 34). It is also been reported that COL1A1 plays role in LIHC progression, as it is also overexpressed in LIHC samples and associated with poor prognosis(35, 36). Thus, COL1A1 have role in tumor progression and it is vital to further investigate its diagnostic and therapeutic role.

In this study, we performed systematic analysis to evaluate the role of COL1A1 as diagnostic and therapeutic biomarkers in LIHC. In this matter we utilized inline tools like UALCAN database, GEPIA2, KM Plotter and cBioPortal. By using these tools we analyzed COL1A1 mutation, expression, overall survival and function in LIHC.

Materials and Methods

UALCAN

UALCAN is a web based tool, applied for expression analysis and to analyze methylation. This tool is based on TCGA (the cancer genome atlas) and provide analysis (37).in this study we used this public database to analyze COL1A1 expression as well as methylation level in LIHC. We also analyzed expression and promotor methylation based on different parameters like patient's individual stage, patient's age, patients gender and patients race.

GEPIA

GEPIA is online tool uses RNA sequence data and provides analysis (38). We utilized this tool in our study to analyze expression analysis of COL1A1 in LIHC and survival analysis, where p-value set at 0.05.

cBioPortal

To analyze the genetic alteration an online tool is used known as cBioPortal (39). In our study to analyze and anticipate the genetic mutation of COL1A1 in LIHC we used cBioPortal.

Kaplan-Meier plotter

Kaplan-Meier Plotter (KM Plotter) is the best available tool to evaluate prognostic value or overall survival (OS) (40). We used km plotter to OS rate of COL1A1 in LIHC patients. This helps us to evaluate COL1A1 role as biomarkers.

Results

Expression analysis of COL1A1 in LIHC and normal samples

We started our research by analyzing COL1A1expression LIHC samples and normal control samples, in this regard we employed UALCAN database. We observed that COL1A1 was significantly upregulated in LIHC samples as compared to normal control samples (Figure 1). This overexpression predicts that COL1A1 have role in LIHC progression.

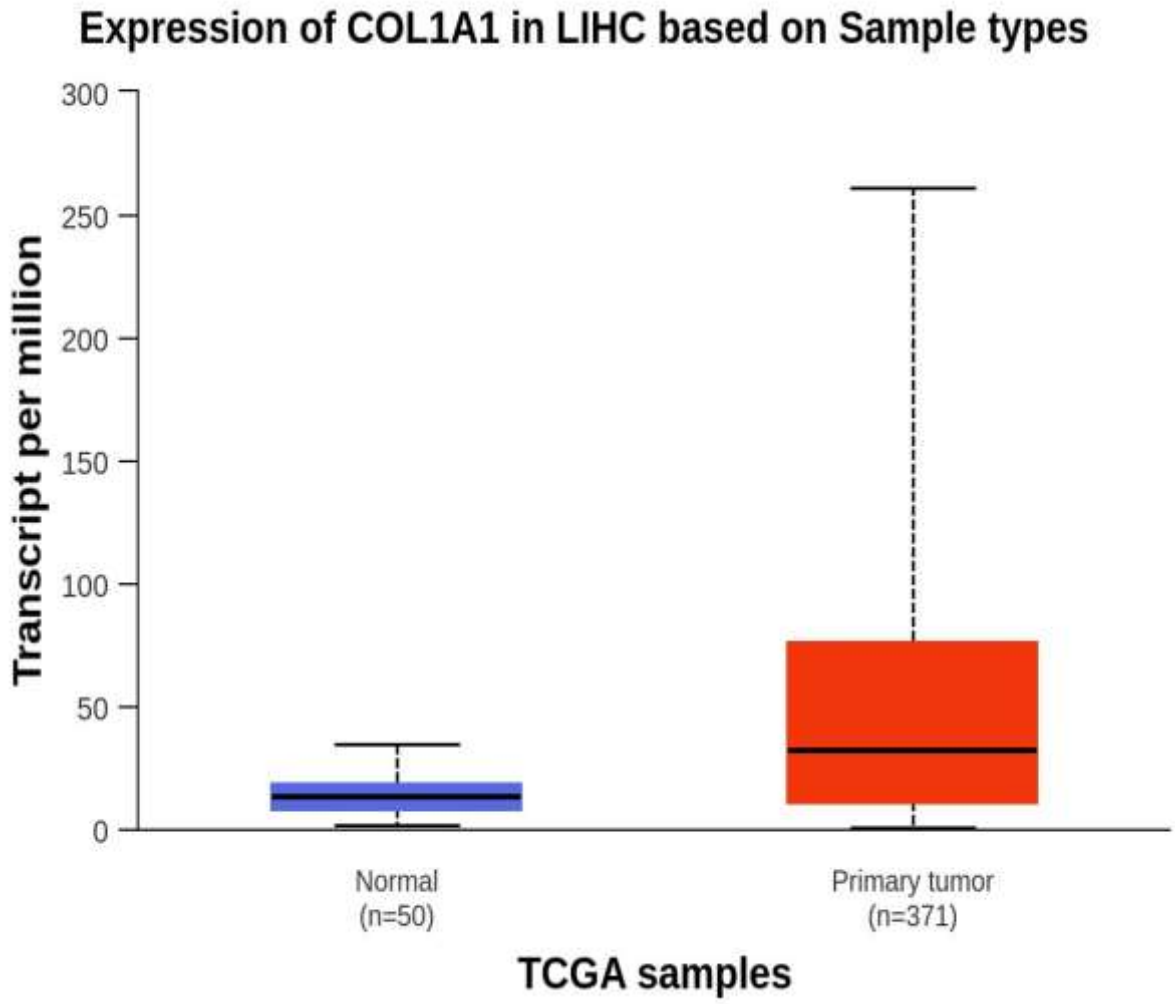

Figure 1: Expression analysis of COL1A1 in LIHC using UALCAN

Ratification of expression analysis of COL1A1

We validated expression of COL1A1 in LIHC utilizing GEPIA2 tool. The analysis revealed that the COL1A1 was significantly upregulated in LIHC samples in contrast to normal samples (Figure 2). So this is evident that COL1A1 have role in proliferation of LIHC.

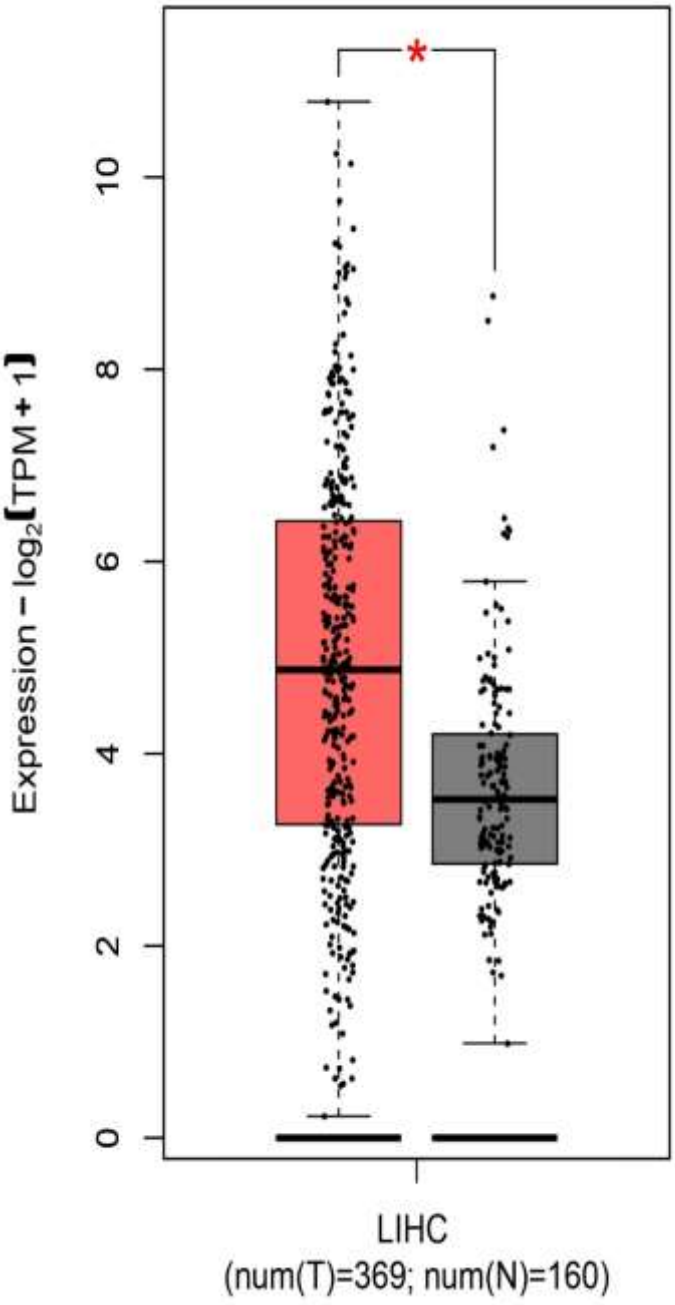

Figure 2: COL1A1 expression in LIHC using GEPIA2

Analysis of COL1A1 expression in LIHC divided based on various elements

Advancing our evaluation we analyzed expression analysis in different elements using UALCAN. Firstly, we investigated COL1A1 expression in LIHC based on individual cancer stages. We assessed that COL1A1 expression was upregulated at each stages (Figure 3A). Next we analyzed COL1A1 expression in LIHC patient's race, patient's age and patient's gender (Figure 3B-D). We analyzed that there was variation in COL1A1 expression but it was upregulated in all these variables. So these results points that COL1A1 have somewhat involvement in LIHC progression.

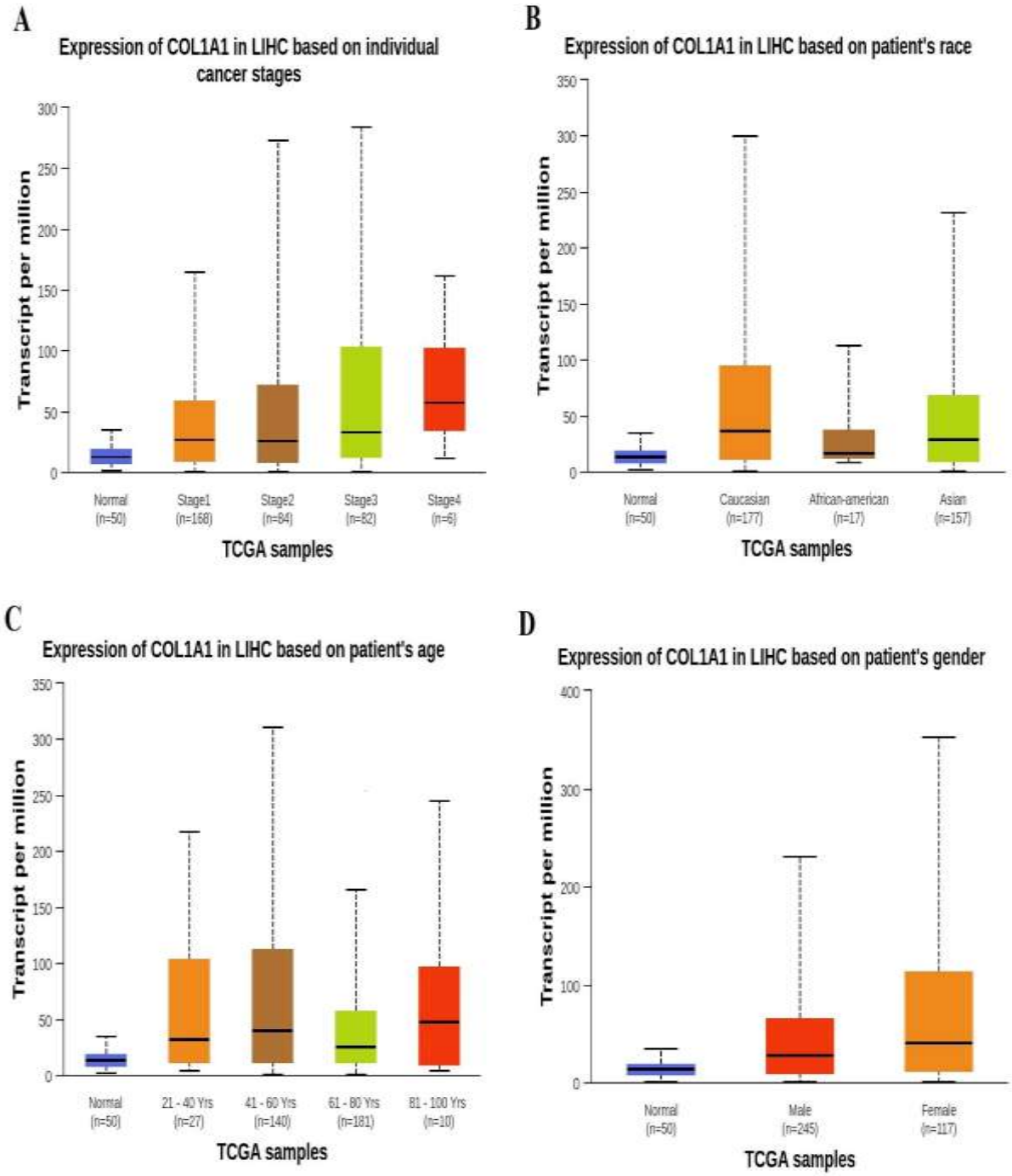

Figure 3: Analysis of COL1A1 expression in LIHC based on different variables using UALCAN database.

Validation of COL1A1 expression analysis in LIHC individual stage

Earlier, we analyzed COL1A1 expression in LIHC at individual cancer stage. So, we used expression analysis module of GEPIA2 database to ratify expression analysis. We investigated that COL1A1 was upregulated in LIHC samples (Figure 4). So this is evident that COL1A1 have role in LIHC progression.

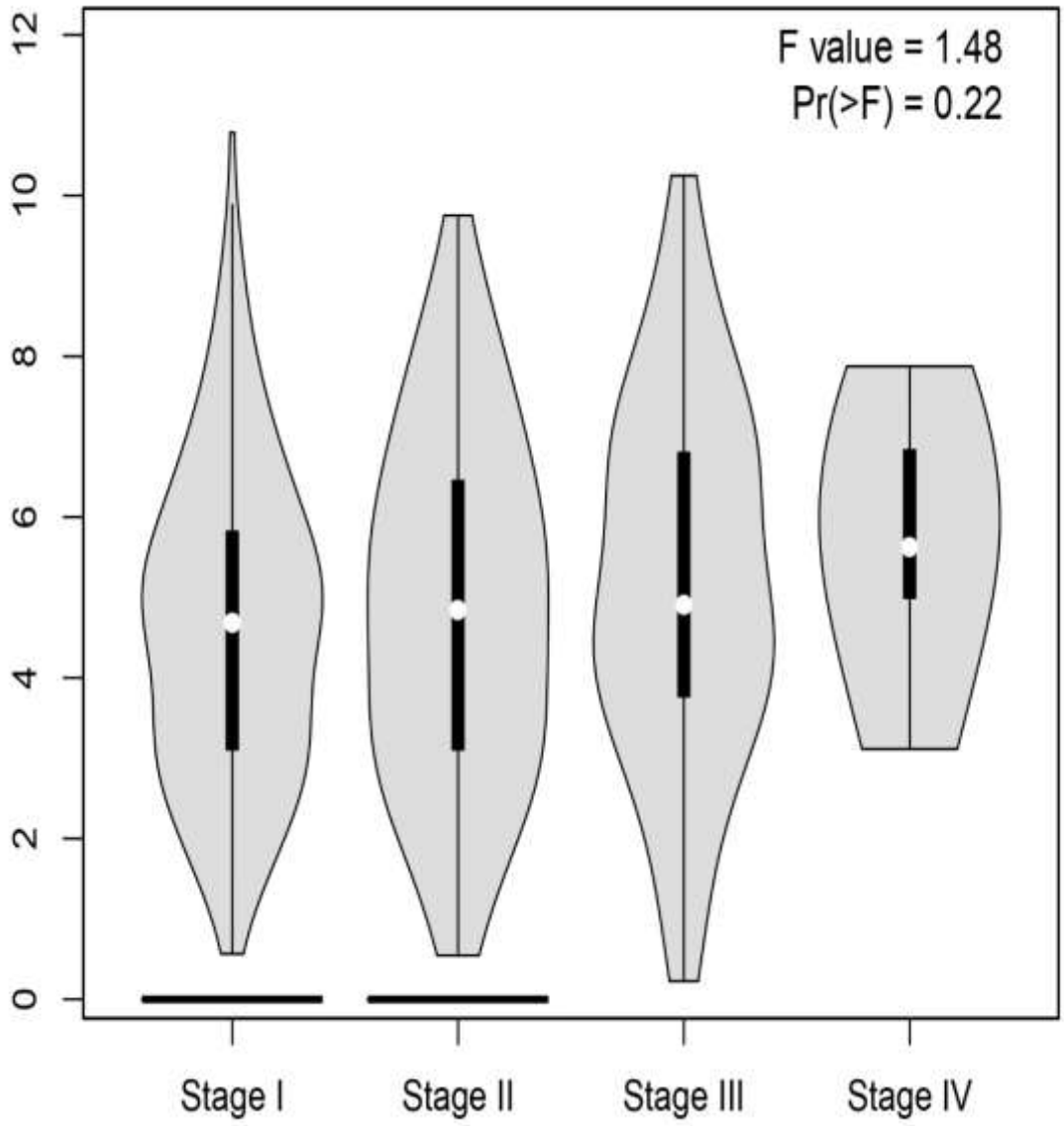

Figure 4: Expression analysis of COL1A1 in LIHC individual stage using GEPIA2

Promotor methylation level of COL1A1 in LIHC and normal control samples

We investigated promotor methylation level of COL1A1 in LIHC sample in comparison with normal control samples utilizing UALCAN database. We examined that COL1A1 was hypo-methylated in LIHC sample in contrast with normal control samples. As previous studies revealed that variation in methylation level increases tumor development. So, hypo-methylated COL1A1 have negative correlation with expression and have in LIHC progression.

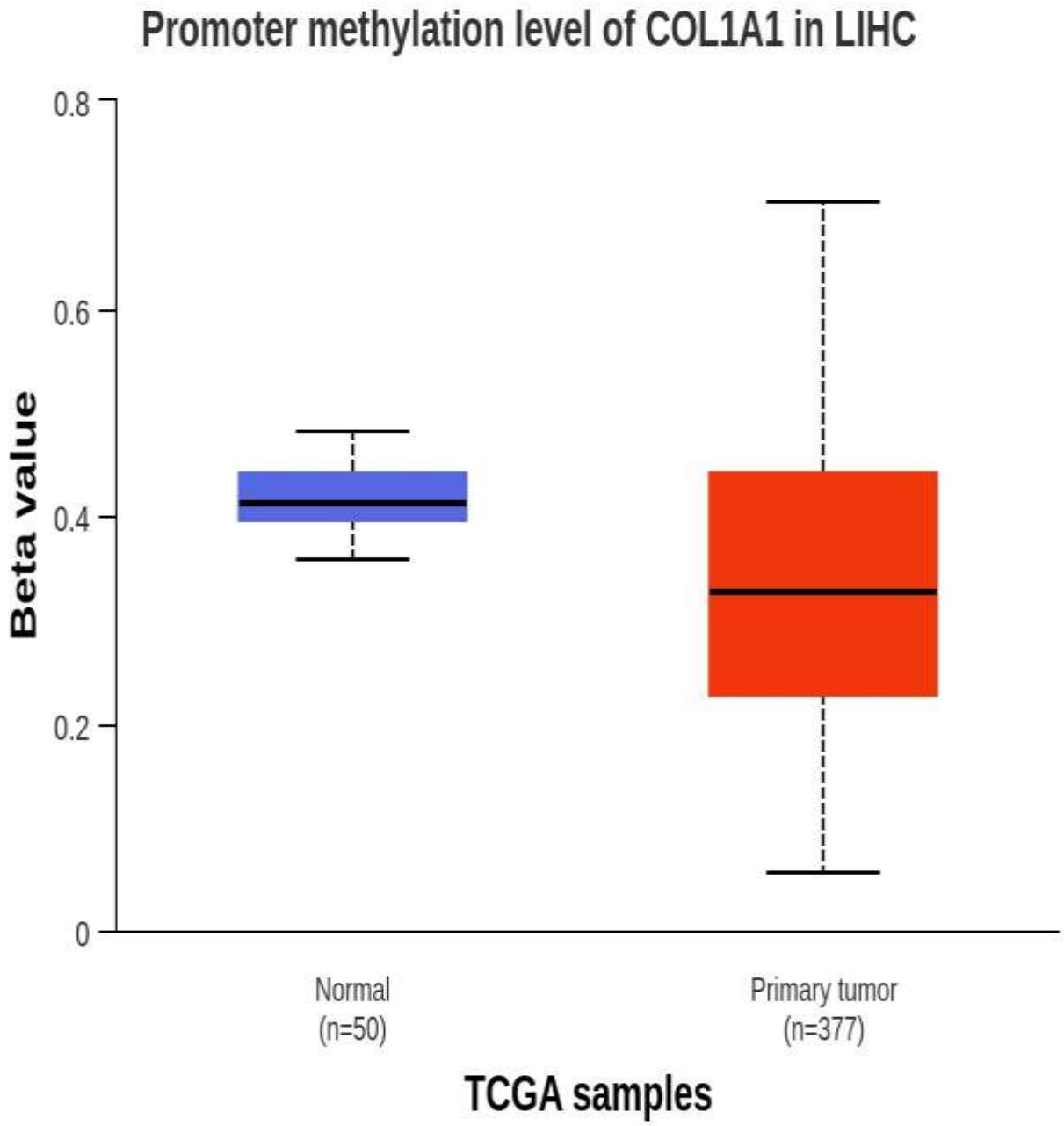

Figure 5: Promotor methylation level of COL1A1 in LIHC compared to normal control samples**.**

Analysis of Promotor methylation level of COL1A1 in LIHC based on different variables
Continuing our research, methylation of COL1A1 is analyzed in LIHC based on different variables as individual cancer stages, patient's age, patients gender and patients race. We evaluated that COL1A1 was hypo-methylated in LIHC based on each of these variables (Figure 6A-D). However in individual stages COL1A1 was hyper-methylated in stage 4 of LIHC (Figure 6A). These findings explains erratic behavior of COL1A1 and its role in LIHC proliferation.

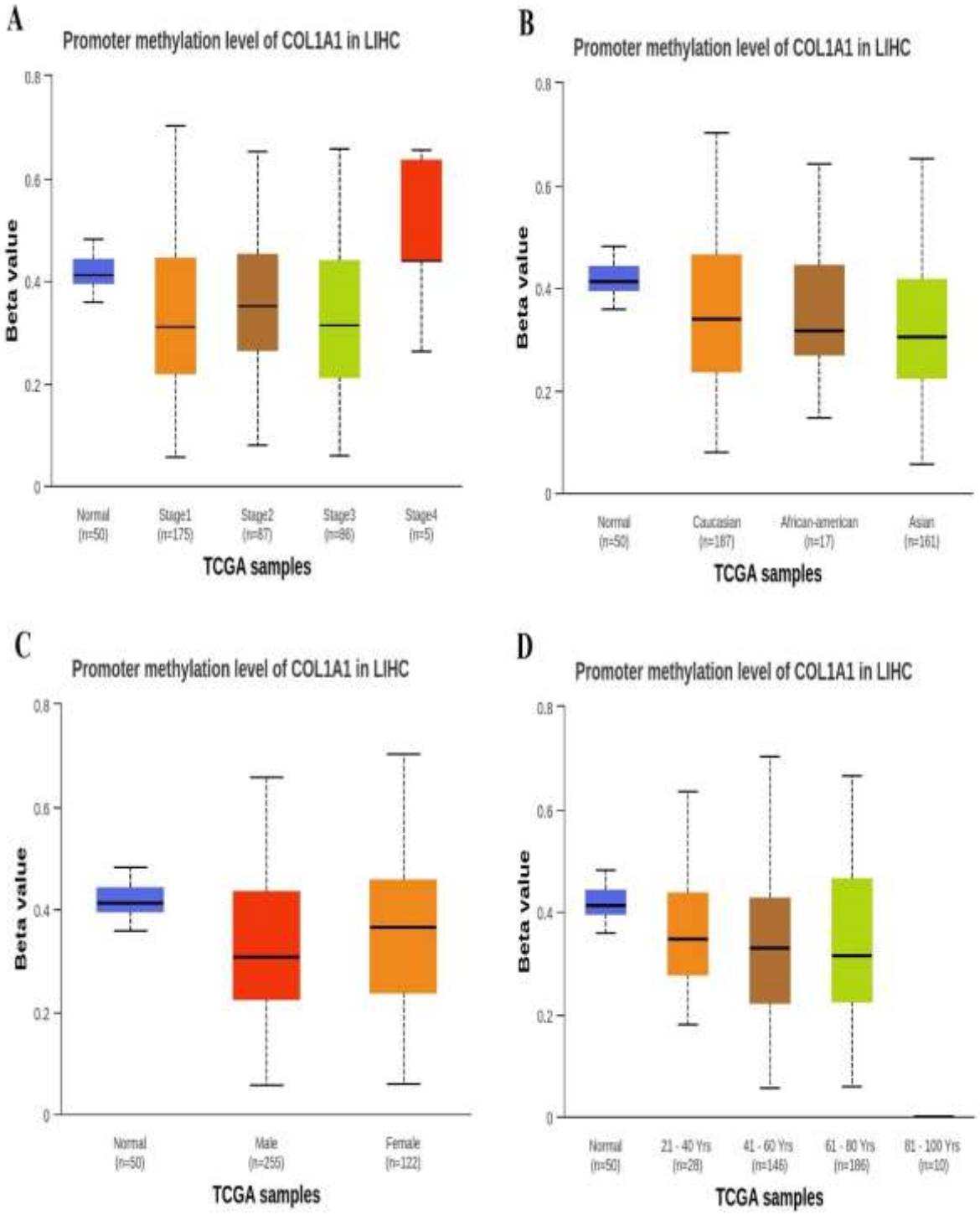

Figure 6: Promotor methylation level of COL1A1 in LIHC divided based on different variables.

Survival analysis of COL1A1 in LIHC

Survival analysis is process which helps us to evaluate overall survival (OS) or prognostic value of patients in cancer. So, we used KM plotter to asses OS rate of LIHC patients with respect to expression of COL1A1. We analyzed that patients have low OS rate with higher COL1A1 expression compared to lower expression (Figure 7). But as the evaluated P-value is 0.06 there is insignificant difference.

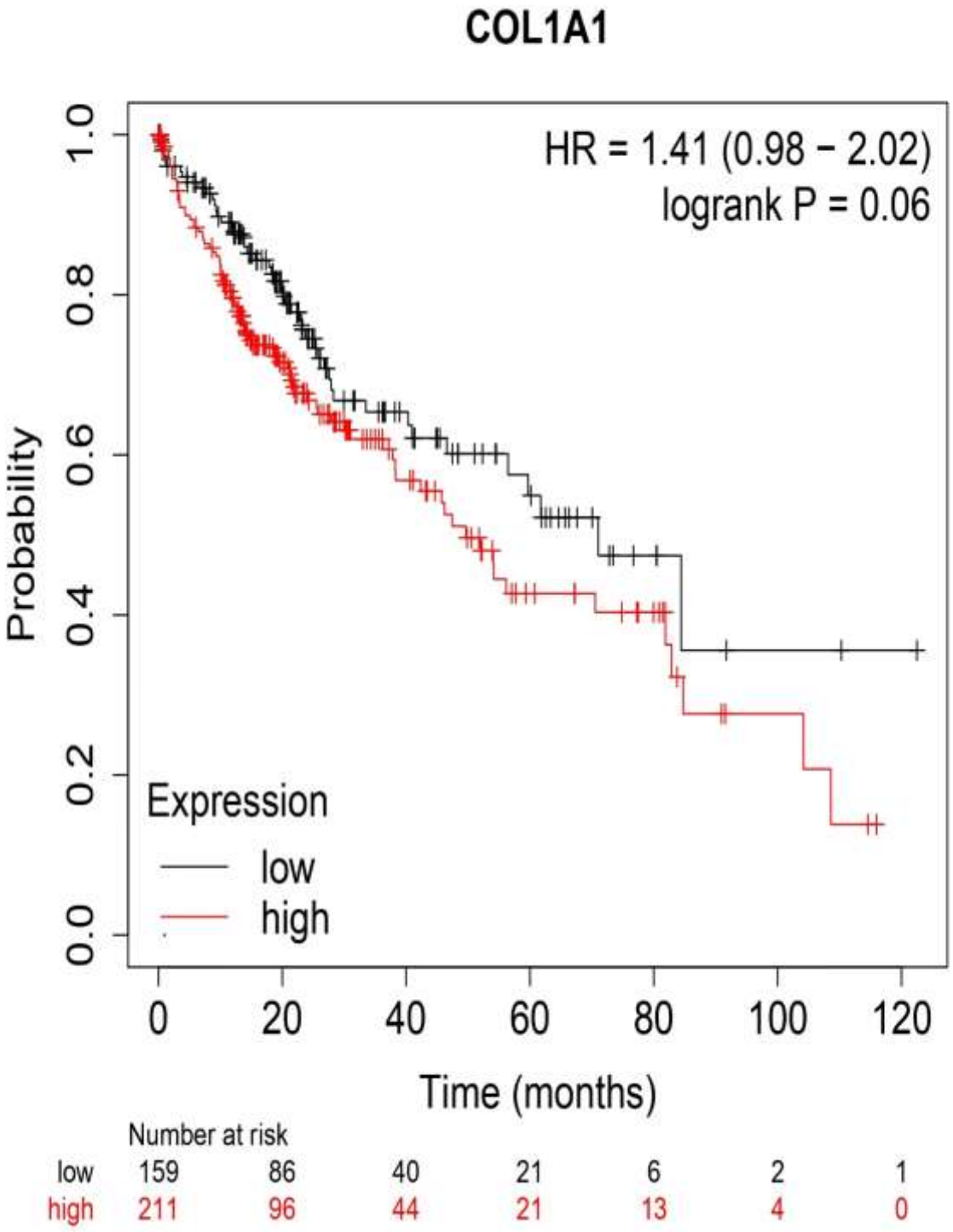

Figure 7: Survival analysis of COL1A1 expression in LIHC.

Further we utilized GEPIA2 to validate survival analysis. The results explains that higher expression of COL1A1 have lower OS rate and lower expression have better OS rate (Figure 8). However the P-value is 0.19 which suggests that expression of COL1A1 not significantly affects OS rate.

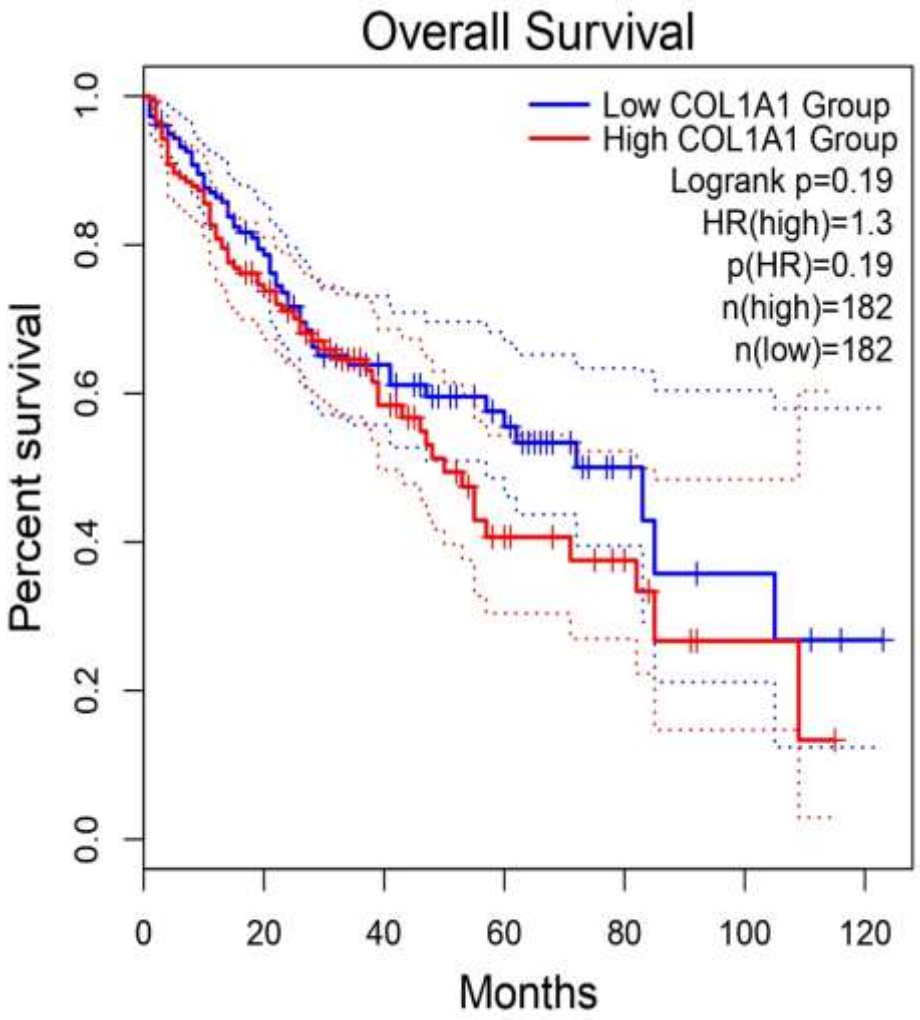

Figure 8: role of COL1A1 expression in overall survival of LIHC patients using GEPIA2.

Genetic alteration of COL1A1 in LIHC

We investigated genetic alteration of COL1A1 in LIHC with the help of cBioPortal. The evaluated mutation are just 3% with amplification, Truncating mutation and missense mutation (Figure 9). These findings suggest that genetic mutation of COL1A1 have little impact in LIHC.

Figure 9: This figure shows genetic mutation of COL1A1 in LIHC.

Discussion

Although many studies have been conducted in past to understand the pathogenesis and metastasis of LIHC, still LIHC patients have severe mortality(41, 42). 14% to 40% times LIHC metastasized in patient after surgery (41, 43, 44). It is demanding but tough to evaluate specific diagnostic, prognostic biomarker for LIHC. That's how we analyzed COL1A1 gene to evaluate its role as diagnostic and prognostic biomarker. As COL1A1 encodes collagen 1 which strengthens muscles, regulates intracellular adhesion and encoded extracellular matrix (ECM) collagen protein have role in tumor progression and development (45, 46). In our study we performed bioinformatics analysis

of COL1A1 in LIHC with best available bioinformatics tools as UALCAN, GEPIA2, KM plotter and cBioPortal.

Primarily we investigated COL1A1 expression in LIHC using UALCAN database. We analyzed that COL1A1 upregulated in LIHC samples as compared to normal control samples. So to verify this result we analyzed expression of COL1A1 in LIHC using GEPIA2 and the evaluated same result as COL1A1 was upregulated in LIHC samples. Further we selected different parameters like individual cancer stage, patient's age, patient's gender and patients race to analyze COL1A1 expression. We examined that COL1A1 was upregulated in cancer samples. As previous studies shows that COL1A1 was highly expressed in different cancers and have role in progression (19, 47-49). This over expression points that COL1A1 have role in development, metastasis and progression of LIHC.

We also studied, promotor methylation of COL1A1 in LIHC with utilizing UALCAN. We analyzed that COL1A1 was hypo-methylated in LIHC samples then in normal samples. As per studies COL1A1 methylation have correlation with poor clinical outcomes of LIHC (50). After that we investigated promotor methylation of COL1A1 in LIHC based on different parameters and the result was same as COL1A1 was hypo-methylated. So overexpression of COL1A1 is have negative correlation with methylation. Moreover we analyzed survival analysis, as COL1A1 is affiliated with overall survival of cancer. We examined that high expression of COL1A1 have poor OS value and lower expression have better OS value. We also validated our result by performing analysis using GEPIA2. So these findings states that COL1A1 have potential as prognostic biomarker. Further we also examined genetic mutation of COL1A1 in LIHC using cBioPortal. It was revealed that COL1A1 have minimal mutation of just 3% in LIHC that explains genetic mutation have nominal role in regulation.

Altogether, these findings emphasis that overexpression of COL1A1 have association with LIHC progression. So this data correlates with previous studies. These analyzed overexpression, hypo methylation and prognostic value explains COL1A1 potential as diagnostic and prognostic biomarker.

Conclusion

With bioinformatics analysis, we examined that COL1A1 can be used as diagnostic, prognostic and therapeutic biomarker in LIHC. COL1A1 was overexpressed, hypomethylated and have association with poor overall survival in LIHC. We used UALCAN, GEPIA2, cBioPortal and KM plotter to analyze COL1A1 in LIHC. These finding present directions for new research and will be helpful to develop new anti-cancer strategies to tackle LIHC.

Acknowledgement

None

Conflict of interest

None

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