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A Bioinformatics Analysis of FAM3A to Identify its Potential Role as a Biomarker in Liver Hepatocellular Cancer

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Abstract: Liver hepatocellular cancer (LIHC) is positioned as the third cancer with the highest mortalities worldwide, and high mortalities are associated with late diagnosis and recurrence. This study advances bioinformatics analysis of FAM3A expression in LIHC to evaluate its potential as a prognostic, diagnostic and therapeutic biomarker. Bioinformatics tools such as UALCAN, GEPIA2, KM plotter, TIMER2 and cBioPortal are employed to conduct analysis. Initially, the expression analysis revealed up-regulation of FAM3A in LIHC based on various variables. Further, the study observed that FAM3A methylation regulates expression as variation in methylation level of FAM3A was assessed in LIHC. Moreover, this over-expression of FAM3A results in poor overall survival (OS) in LIHC patients. All of these proposed that FAM3A has a role in the progression and development of LIHC. While examined association of FAM3A expression and infiltration level of $CD8^+$ T cells in LIHC patients using TIMER2 revealed that FAM3A has a positive correlation with purity in LIHC that highlights the molecular landscape. Analysis of genetic alteration revealed minute role of FAM3A in LIHC still provides valuable insight. Overall, our findings reveal that FAM3A has potential as diagnostic, therapeutic and prognostic biomarkers in LIHC.

Keywords: Liver hepatocellular cancer (LIHC); FAM3A expression; Bioinformatics analysis; Biomarker

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1. Introduction

Cancer is a fatal disease with millions of cases globally. In 2022, about 20 million cases and 9.7 million cancer-related mortalities were recorded worldwide. There is various type of cancer, identified by their origin and specific attributes [1-3]. Liver cancer is the sixth most common cancer and 3rd cancer with high mortality worldwide, with 757,948 deaths recorded in 2022 [2]. Liver hepatocellular carcinoma (LIHC) is the most prevalent type of liver cancer, accounting for 80–90% of cases [4,5]. Liver infection, hepatitis B virus (HBV) and hepatitis c virus (HCV) infection, alcohol consumption, obesity, diabetes and smoking are the leading determinants of LIHC [4,6,7]. Moreover, in Asia and Africa, LIHC cases are higher compared to Europe. However, LIHC cases are increasing in developed countries due to high rates of diabetes, obesity and hepatitis [7,8]. Surgery, radiation, therapy, target

therapy, hepatectomy, chemotherapy and liver transplantation are major therapies used for LIHC [9,10]. However, the mortality rate in LIHC is quite high due to recurrence and diagnosis at higher stage. LIHC is diagnosed at advanced stages due to lack of symptoms. LIHC patients have poor survival rates at advanced stages, and at early stages, recurrence is high even after treatment [11–14]. Therefore, it is a compelling necessity to identify efficient prognostic, therapeutic and diagnostic biomarkers for LIHC.

FAM3A (FAM3 metabolic regulating signaling molecule A) is a member of the FAM3 family and encodes cytokine-like proteins. ATP production is amplified in the liver and other tissues by FAM3A. It is a mitochondrial protein where mitochondrial respiration is enhanced in hepatocytes, neuronal cells and vascular smooth muscle cells by FAM3A. FAM3A plays a significant role in inhibiting gluconeogenesis and lipogenesis [15-19]. FAM3A plays a crucial role during skeletal muscle repair by promoting mitochondrial respiration [20]. FAM3A inhibits gluconeogenesis. Insulin resistance or insulin insufficiency is enhanced due to overexpression of gluconeogenesis genes in the liver, resulting in type 2 diabetes mellitus [21-23]. FAM3A arouses adipogenesis, optimizes endoplasmic reticulum (ER) stress in various cell types and protects the liver against ischemia or injury [24-26]. Previous studies stated that FAM3A is overexpressed in Lynch syndrome and results in poor prognosis [27]. LICH increases the risk of colorectal cancer, endometrial cancer, ovarian cancer and stomach cancer.

Overall, these data suggest that FAM3A has an important function in the liver and that changes in the expression of FEM3A lead to liver abnormalities. The study intended to conduct a bioinformatics analysis of FAM3A in LICH. The study assessed the expression, mutation and survival analysis of FAM3A utilizing bioinformatics tools. There is no such analysis has been conducted to investigate the potential of FAM3A in LICH.

2. Material and Method

2.1. UALCAN

UALCAN is a web tool that is comprehensively used for expression profiling of specific genes in cancers [28]. The study analyzed the expression and methylation level of FAM3A in LIHC using UALCAN. The analysis was run using the default setting of FAM3A. UALCAN is also used to evaluate the expression and methylation profiling of FAM3A in LIHC based on different parameters.

2.2. Kaplan-Meier Plotter

Kaplan-Meier (KM) Plotter is a web-based tool that is for evaluating the survival rate of the concerned gene in various subtypes of cancer [29]. In the present study, the prognostic value of FAM3A was examined in LIHC. While Hazard ratio and 95% confidence intervals were displayed, P-value < 0.05 is set as significant.

2.3. GEPIA2

GEPIA2 is an online tool based on the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx). It evaluates the expression profiling and prognostic value of desired genes in various cancer subtypes [30]. The study employed GEPIA2 to conduct a comprehensive expression analysis and survival analysis of FAM3A in LIHC.

2.4. cBioPortal

cBioPortal is an easy-to-use online database that is employed to assess genetic alteration in different human cancers [31]. In this study, cBioPortal is employed to investigate assess the genetic alteration of FAM3A in LIHC.

2.5. Timer2

Timer2 is a widely used database to investigate the immune infiltrate in various cancer subtypes thoroughly [32]. The study harnessed TIMER2 to evaluate the Spearman correlation between the FAM3A expression and $CD8^+$ T immune cells in LIHC.

3. Results

3.1. Analyzing the FAM3A expression in LIHC

The study investigated the expression of FAM3A in LIHC in contrast with a normal sample using UALCAN. The study assessed that the expression of FAM3A is significantly up-regulated in the LIHC samples as compared to normal samples (**Figure 1**). Previous studies have stated that gene overexpression is associated with the progression of cancer [33,34]. Therefore, significant up-regulation illustrated that FAM3A plays a role in the progression of LIHC.

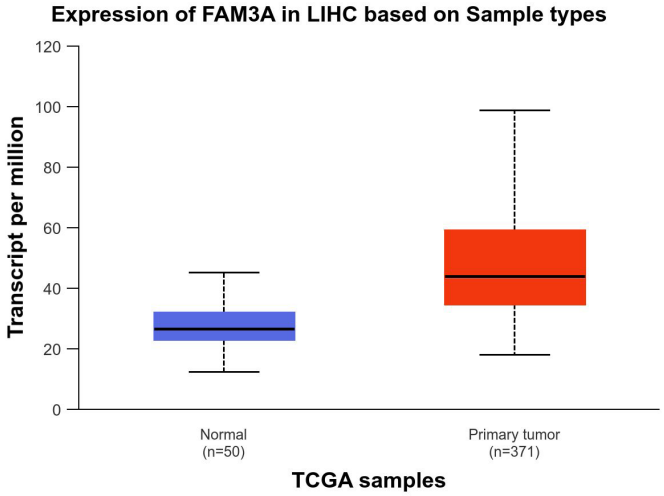

Figure 1. Sample-based expression analysis of FAM3A in LIHC using UALCAN.

3.2. Assessment of FAM3A expression in LIHC based on various parameters

The study harnessed the UALCAN database to assess the expression of FAM3A in LIHC and evaluated significant overexpression in observed parameters. In the pathological stage, the study observed up-regulation but variation in the expression of FAM3A in LIHC, as FAM3A was highly overexpressed in stage 2 as compared to other stages (**Figure 2A**). Next, an analysis in LIHC revealed up-regulation in FAM3A expression, but FAM3A was highly up-regulated in males as compared to females (**Figure 2B**). Similarly, analysis of LIHC patient's age and race also revealed significant overexpression of FAM3A (**Figure 2C–D**). All of this data suggested that up-regulation of FAM3A expression is associated with the progression of LIHC.

3.3. Investigating promoter methylation level of FAM3A in LIHC and normal samples

Previous studies have stated that methylation of the gene has a role in the regulation of gene expression [35,36]. Therefore, the study analyzed the promoter methylation level of FAM3A in LIHC using UALCAN. FAM3A in LIHC samples was significantly hypomethylated in contrast with normal samples (**Figure 3**). This observed hypomethylation of FAM3A suggested up-regulation of the FAM3A of expression in LIHC. Altogether, these findings explain the role of FAM3A in the progression of LIHC.

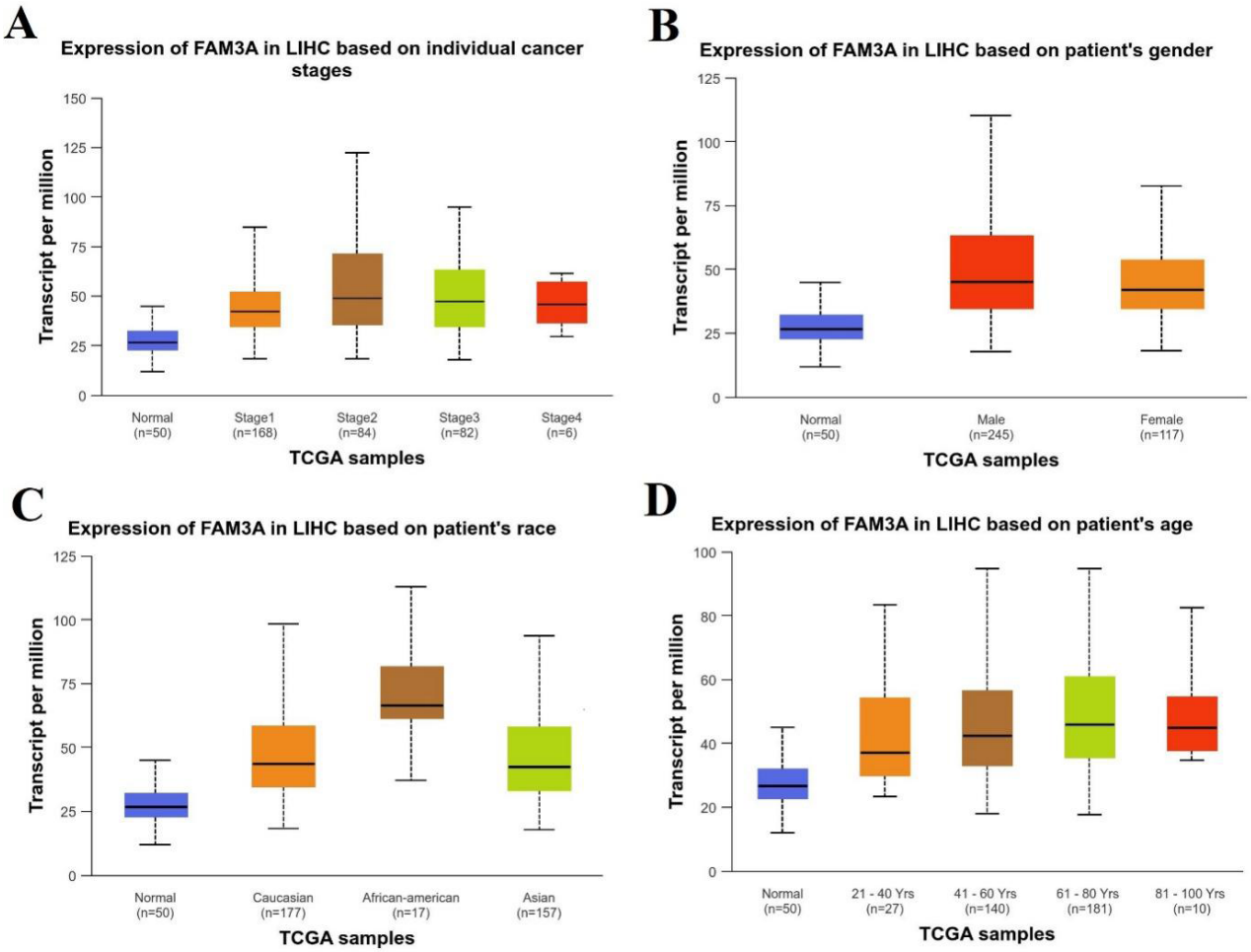

Figure 2. Analysis of FAM3A expression in various parameters. (A) Expression of FAM3A in pathological stages of LIHC. (B) Expression of FAM3A in the LIHC patient's gender. (C) Expression of FAM3A in the LIHC patient's race. (D) Expression of FAM3A in the LIHC patient's age.

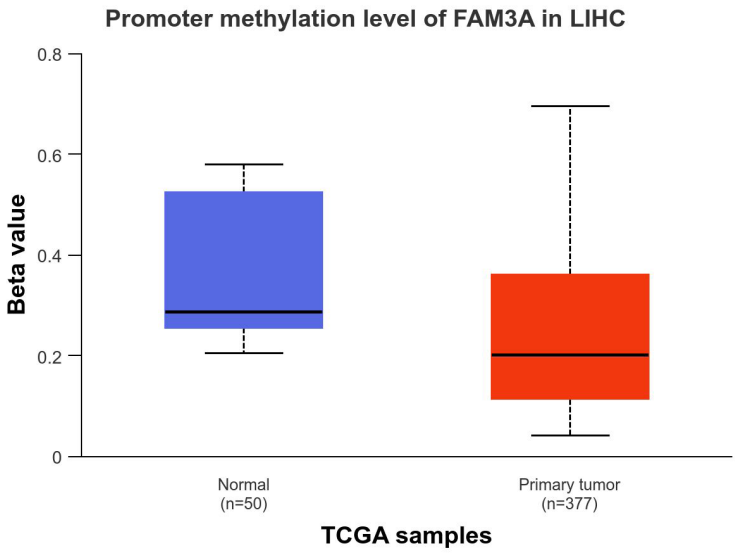

Figure 3. Analysis of promoter methylation level of FAM3A in LIHC and Normal control samples.

3.4. Analysis of the promoter methylation level of FAM3A in LIHC segmented by multiple variables

Simultaneously, the study evaluated promoter methylation level of FAM3A in LIHC segmented by multiple variables like patient's age, gender, race and cancer stages. At first, the study reviewed promoter methylation levels in LIHC cancer stages and evaluated that FAM3A was hypomethylated at these stages except stage 4 (**Figure 4A**). FAM3A was hypermethylated in LIHC stage 4, which explains the diversity in methylation level. Similarly, the study analyzed FAM3A promoter methylation levels in LIHC patients' gender samples and noted variations in methylation levels (**Figure 4B**). The study assessed that FAM3A was significantly hypomethylated in male samples and hypermethylated in female samples. However, investigation based on LIHC patient's age and race revealed that FAM3A is hypomethylated in both of these samples (**Figure 4C–D**). All of these findings highlight the multifaceted role of FAM3A methylation level in the regulation of FAM3A expression and in the progression of LIHC.

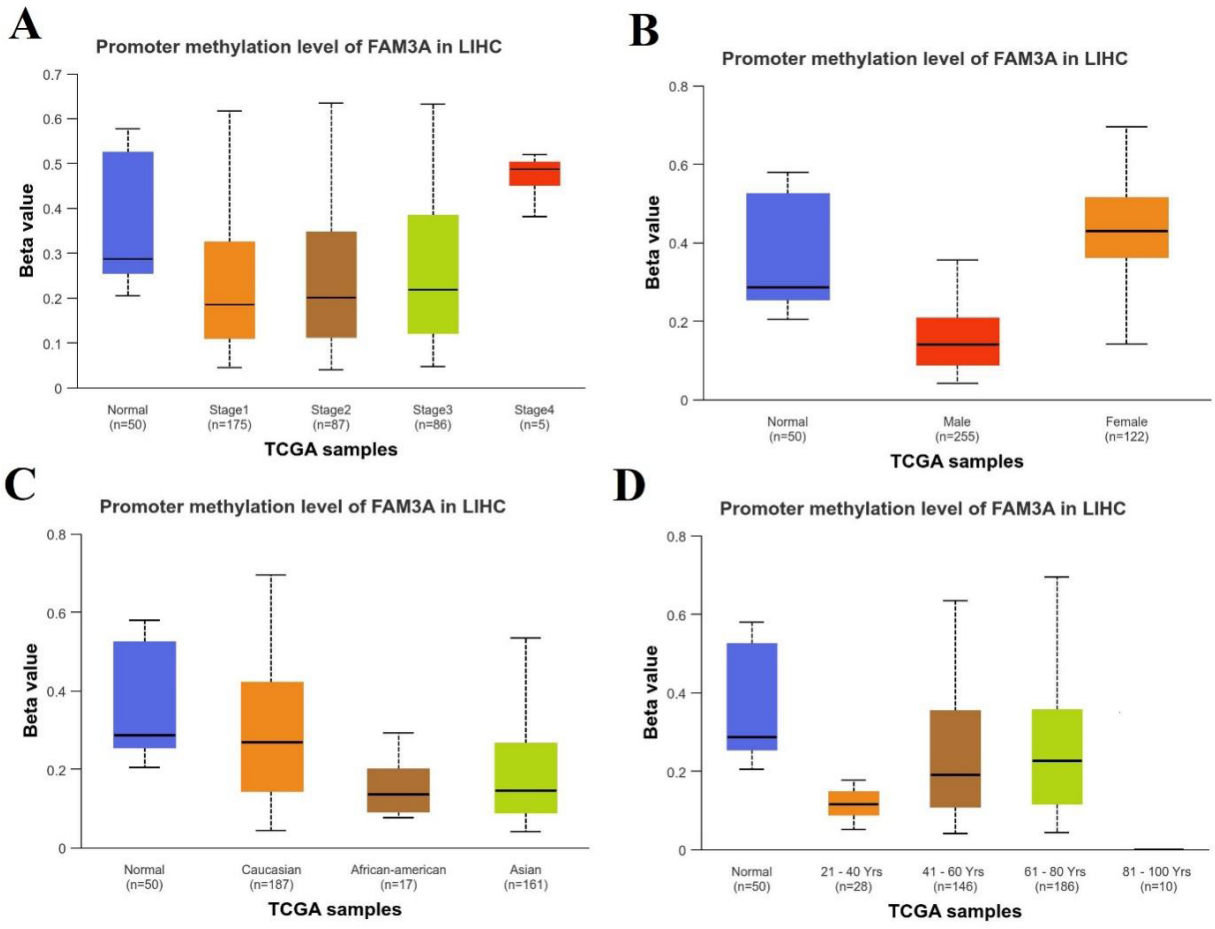

Figure 4. Investigation of FAM3A Promoter methylation level in different parameters. (A) Promoter methylation level of FAM3A in pathological stages of LIHC. (B) Promoter methylation level of FAM3A in LIHC patient's gender. (C) Promoter methylation level of FAM3A in LIHC patient's race. (D) Promoter methylation level of FAM3A in LIHC patient's age.

3.5. Prognostic analysis of FAM3A in LIHC

The study harnessed a Km plotter to conduct a prognostic analysis of FAM3A in LIHC. This curve demonstrated that overexpressed FAM3A in LIHC has a poor survival rate, while low-expressed FAM3A in LIHC has a better survival rate (**Figure 5**). The calculated hazard ratio is 1.49, which indicates that patients with overexpressed

FAM3A have 1.49 times more risk of death as compared to lower-expressed patients. In addition, both values have statistical differences, as the examined *P*-value is 0.025. This result illustrated that overexpressed FAM3A plays a role in the progression of LIHC.

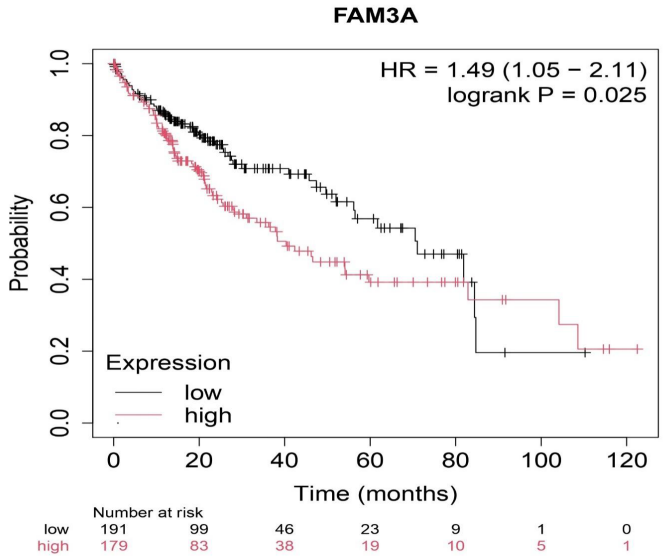

Figure 5. Prognostic analysis of FAM3A expression in LIHC employing KM plotter.

3.6. Expression and prognostic analysis of FAM3A in LIHC using GEPIA2

The study used GEPIA2 to conduct expression and prognostic analysis of FAM3A in LIHC to validate its findings. Initially, sample-based expression analysis of FAM3A was performed in LIHC using GEPIA2 and assessed that FAM3A was overexpressed in LIHC samples (**Figure 6A**). Next, the study utilized the stage plot module of GEPIA2 and examined the expression of FAM3A in different stages of LIHC. The study assessed that expression does not statistically differ in these stages, and the calculated *p*-value of 0.168 supports it (**Figure 6B**). These findings coincide with the previous result that FAM3A is overexpressed in LIHC and plays a role in the development and progression of LIHC.

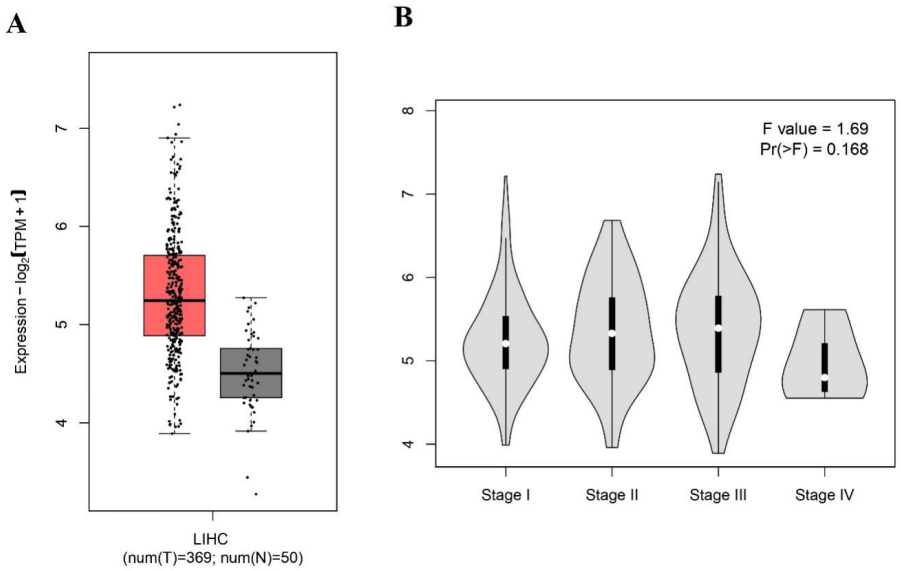

Figure 6. (A) Expression analysis of FAM3A in LIHC and normal control sample employing GEPIA2. (B) Analyzing FAM3A expression in individual cancer stages employing GEPIA2.

Following this, the study examined the impact of FAM3A expression on the overall survival (OS) of LIHC patients employing the survival module of GEPIA2. The result indicated varying survival results (**Figure 7**). It can be observed that elevated FAM3A expression has poor OS in LIHC in comparison with lower expressed FAM3A expression. However, the difference between the two values is not significant, as the calculated log-rank *P*-value is 0.2. These results suggest that FAM3A overexpression is linked with poor OS of LIHC patients and that FAM3A has a role in LIHC progression.

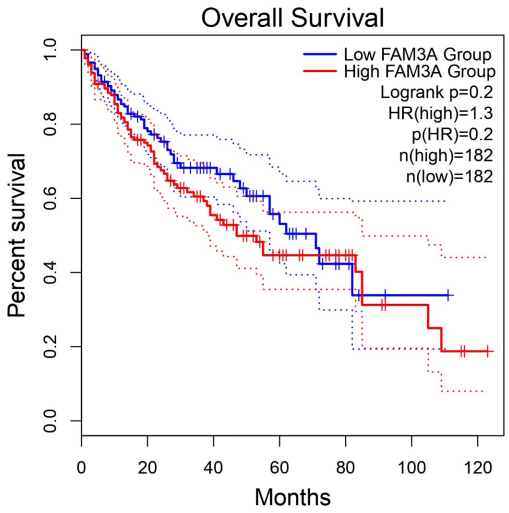

Figure 7. Prognostic analysis of FAM3A expression in LIHC using GEPIA2.

3.7. FAM3A expression and infiltration level of cd8+ t cells in LIHC patients

The study utilized the TIMER2 database to analyze the association of FAM3A expression level with purity and $CD8^+$ T immune cells in LIHC. Previous studies discuss immunity and tumor development as strongly associated [37], while the proportion of cancer cells in tumor samples is called purity [38]. The left-scattered plot highlights the positive association between FAM3A expression level and purity (**Figure 8A**). The evaluated association is significant as the calculated *p*-value is 0.00334. Further, there is a noted weak association between FAM3A expression level and $CD8^+$ T immune cells, as shown in the right scattered plot (**Figure 8B**). The calculated *p*-value is 0.127, indicating that the association is not statistically significant.

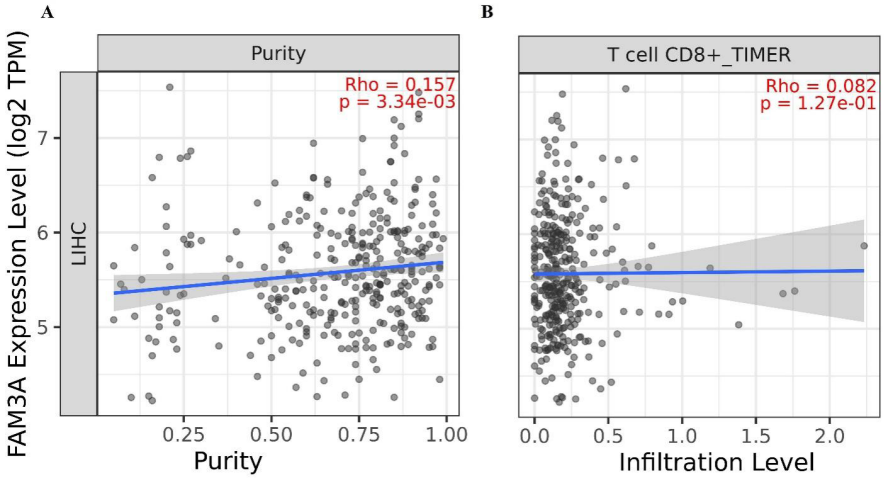

Figure 8. Assessment of FAM3A expression level association with purity and CD^{8+} T immune cells in LIHC using TIMER2.

3.8. Genetic alteration of FAM3A in LIHC

The study examined the genetic alteration of FAM3A in LIHC by employing cBioPortal. 2.3% of genetic alteration of FAM3A was observed in LIHC. Amplification, deep deletion and missense mutation are the examined mutation of FAM3A in LIHC (**Figure 9**). These findings suggest that genetic alteration in LIHC have minute contribution in regulation of FAM3A expression.

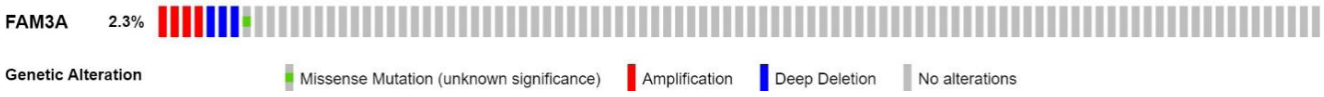

Figure 9. Genetic alteration of FAM3A in LIHC using cBioPortal.

4. Discussion

Cancer is described by poor prognosis and poor medical consequences worldwide [30]. Liver cancer is the sixth most common cancer, with thousands of deaths worldwide. While liver hepatocellular carcinoma (LIHC) accounts for 80–90% of cases, LIHC is diagnosed at a higher stage and recurrence rate, leading to high mortalities [40,41]. Therefore, it is crucial to diagnose new diagnostic, therapeutic and prognostic biomarkers. The study performed a bioinformatics analysis of FAM3A in LIHC to evaluate its potential as an efficient biomarker. FAM3A inhibits hepatic gluconeogenesis, protects cognitive functions, have a role in vascular pathology and metabolic processes [42–44].

First, the study analyzes the expression of FAM3A in LIHC and noted that FAM3A was significantly up-regulated in LIHC. *P*-value < 0.05 indicated significant overexpression than normal samples. The study examined the expression of FAM3A characterized by various variables such as LIHC patient's age, gender, race and pathological stages. The study evaluated significant up-regulation of FAM3A expression based on these variables. These results show that FAM3A has a role in the progression of LIHC. Following this, the study assessed promoter methylation levels of FAM3A in LIHC. The study examined hypomethylated FAM3A methylation levels in LIHC. This demonstrated up-regulation of expression as methylation and expression are reversely associated.

Moreover, to further evaluate the role of FAM3A methylation in LIHC, the study conducted analysis segmented on multiple variables like LIHC patient's age, gender, race and pathological stages. The study observed variations in methylation levels in LIHC pathological stages. FAM3A was hypomethylated in stages 1–3. However, in stage 4, FAM3A was hypermethylated. Subsequently, analysis based on gender revealed that FAM3A is significantly hypomethylated in male samples and hypermethylated in female samples. However, assessment based on age and race demonstrated hypomethylation in FAM3A promoter methylation level. These variations illustrated that FAM3A methylation level regulates FAM3A expression and results in the progression and development of LIHC.

Furthermore, the study investigated the impact of FAM3A expression on the OS of LIHC patients utilizing a KM plotter. The study identified that overexpressed FAM3A have poor OS and lower expressed FAM3A have better OS in LIHC patients. This highlights that FAM3A has a role in the progression of LIHC and high mortalities. After that, to validate the results of FAM3A expression analysis and survival analysis, the study employed GEPIA2. The outcomes from the expression and survival analysis conducted with GEPIA2 accord with earlier results. This illuminates the role of FAM3A in the development and progression of LIHC.

Simultaneously, the study analyzes the genetic alteration of FAM3A in LIHC using cBioPortal. The study evaluated 2.5% of mutation of FAM3A as amplification, deep deletion and missense mutation. This revealed the

minute role of FAM3A mutation in LIHC yet brings deep insight. Moreover, the study analyzed the association of FAM3A expression level with purity and CD^{8+} T immune cells in LIHC. This revealed that FAM3A is positively associated with purity and negatively associated with $CD8^{+}$ T immune cells. This indicates that FAM3A has a role in tumor growth by altering immune cells in the microenvironment. Overall, these highlight the significance of FAM3A as a therapeutic, diagnostic and prognostic biomarker in LIHC.

5. Conclusion

In conclusion, the study performed bioinformatics analysis of FAM3A expression, methylation level, genetic alteration and prognostic rate in LIHC. It can be observed that up-regulated FAM3A contributes to the development and progression of LIHC. In addition, these findings suggested that FAM3A is a unique prognostic, therapeutic and diagnostic biomarker in LIHC. Nevertheless, extensive research is essential before practical implementation.

Disclosure statement

The author declares no conflict of interest.

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