ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2024 September 24; 15(9): 1117-1255

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

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Monthly Volume 15 Number 9 September 24, 2024

World Journal of Clinical Oncology

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RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

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https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
September 24, 2024

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World J Clin Oncol 2024 September 24; 15(9): 1188-1197

DOI: 10.5306/wjco.v15.i9.1188

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Clinical and Translational Research

Study on the expression and prognostic relationship of *MYL6B* in liver cancer based on bioinformatics

Hai-Bing Lv, Qing-Yun Wu, Yu-Jiao Zhang, Sheng-Wei Quan, Ning Ma, Yu-Qing Dai, Yan Sun

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade A
Creativity or Innovation: Grade A
Scientific Significance: Grade A

P-Reviewer: Soreq L

Received: May 7, 2024
Revised: July 21, 2024
Accepted: August 2, 2024
Published online: September 24, 2024
Processing time: 113 Days and 16.9 Hours

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Abstract

BACKGROUND

Primary liver cancer is a prevalent and deadly cancer type. Despite treatment advances, prognosis remains poor, with high recurrence rates. Early detection is crucial but challenging due to the disease's insidious nature. Myosin proteins play significant roles in cancer development, influencing cell migration, invasion, and tumor suppression. *MYL6B*, a myosin light chain, is involved in various cellular processes and has been associated with poor prognosis in colorectal adenocarcinoma and potential as a biomarker in breast cancer.

AIM

To investigate the expression of *MYL6B* in liver hepatocellular carcinoma (LIHC) and its impact on prognosis and potential mechanisms of action using bioinformatics methods.

METHODS
The expression of *MYL6B* in pan-cancer and normal tissues was analyzed using the gene expression profiling interactive analysis 2 and tumor immune estimation resource databases. The expression level of *MYL6B* in LIHC tissues and its relationship with prognosis were analyzed, immunohistochemical analysis of *MYL6B* and its effect on immune cell infiltration, and the protein network were further studied.

RESULTS
MYL6B was highly expressed in diffuse large b-cell lymphoma, LIHC, pancreatic adenocarcinoma, skin cutaneous melanoma, thymoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, and lowly expressed in kidney chromophobe, acute myeloid leukemia, testicular germ cell tumors. The expression level of *MYL6B* was significantly different between cancer and normal tissues. It had a significant impact on both overall survival and disease-free survival. *MYL6B* is highly expressed in hepatocellular carcinoma and its expression level increases with cancer progression. High *MYL6B* expression is associated with poor prognosis in terms of overall survival and recurrence-free survival. The immunohistochemical level of *MYL6B* is high in hepatocellular carcinoma tissues, and *MYL6B* has a high level of immune infiltration inflammation. In protein network analysis, *MYL6B* is correlated with *MYL2*, *MYL6*, *MYL9*, *MYLK4*, *MYLK2*, *MYL12A*, *MYL12B*, *MYH11*, *MYH9* and *MYH10*.

CONCLUSION
The expression level of *MYL6B* in LIHC was significantly higher than in normal liver tissues, and it was correlated with the degree of differentiation survival rate, and immune infiltration. *MYL6B* is a potential target for LIHC treatment.

Key Words: *MYL6B*; Liver cancer; Bioinformatics; Prognosis; Expression

Core Tip: In the study, we employed advanced bioinformatics methodologies to meticulously scrutinize the intricate relationship between *MYL6B* and liver hepatocellular carcinoma (LIHC). It entailed a comprehensive analysis encompassing the contrasting expression patterns observed between LIHC and normal tissue samples, coupled with an intricate examination of how *MYL6B* expression levels correlate with the staging of cancer progression and the rates of survival. Furthermore, an exhaustive immunohistochemical investigation was conducted to elucidate the nuances of inflammation across varying levels of *MYL6B* expression in tissue specimens. The findings of this investigation unequivocally underscore *MYL6B*'s pivotal role as a prognostic determinant in hepatocellular carcinoma.

Citation: Lv HB, Wu QY, Zhang YJ, Quan SW, Ma N, Dai YQ, Sun Y. Study on the expression and prognostic relationship of *MYL6B* in liver cancer based on bioinformatics. *World J Clin Oncol* 2024; 15(9): 1188-1197
URL: https://www.wjgnet.com/2218-4333/full/v15/i9/1188.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i9.1188

INTRODUCTION

Primary liver cancer is a common cancer type with a high mortality rate. In 2020, there were 905677 new cases (4.7%) and 830180 deaths (8.3%) from liver cancer worldwide[1]. Different treatment strategies are applied for liver cancer patients at different stages. Early-stage liver cancer patients should undergo curative treatments such as liver resection, transplantation, and radiofrequency ablation, while late-stage patients should receive palliative treatments such as transarterial chemoembolization and chemotherapy[2-5]. Despite significant progress in its diagnosis and treatment in recent years, the prognosis of liver cancer remains unsatisfactory. The 5-year survival rate for liver cancer patients after surgery is 37%-65%, and the recurrence rate is as high as 75%-100%[6-8].

However, the high malignancy and insidious nature of liver hepatocellular carcinoma (LIHC) mean that most advanced or end-stage cancer patients have little chance of surgical cure[9]. LIHC is typically detected in the late stages of the disease, at which point there are few effective treatment options to improve survival rates[10]. Therefore, the search for diagnostic biomarkers is crucial for early diagnosis and personalized treatment of LIHC. Additionally, accurate subtyping aids in providing personalized therapy. Myosin plays a significant role in the development of cancer, as it is involved in cell migration, invasion, and tumor suppression. Genetic and epigenetic modifications of genes encoding myosin heavy chains have been found in many types of cancer. In some cases, changes in myosin expression can serve as prognostic factors for patient survival. Therefore, some members of the myosin superfamily may have potential as cancer biomarkers[11].

Myosin plays an important role in cancer development. Myosin is involved in cancer progression through their roles in cell migration and invasion and their tumor suppressor functions. Genetic and epigenetic alterations of genes encoding

myosin heavy chains have been found in many types of cancer. In some cases, changes in myosin expression can serve as a predictor of patient survival. Therefore, some members of the myosin superfamily have potential as cancer biomarkers [11]. For example, myosin 1e can promote the malignant progression of breast cancer by enhancing tumor cell proliferation and stimulating tumor cell dedifferentiation[12], while the activation of myosin II in cancer cells drives tumor progression through interaction with the secretions of the immune microenvironment[13]. Additionally, The elevated expression of myosin X in tumors contributes to the invasiveness and metastasis of breast cancer[14], myosin Vb can function as a tumor suppressor gene in colorectal cancer[15].

MYL6B is myosin light chain 6B, a protein encoded by the *MYL6B* gene. Myosins are superfamily of motor proteins that have a significant effect on the process of movement, and myosin light chains can regulate Ca^{2+} transduction[16,17]. As an important myosin light chain, *MYL6B* is involved in cell viability, adhesion, migration, and endocytosis, tissue structure, and transportation[18-20].

MYL6B is associated with various cancers. For instance, in colorectal adenocarcinoma, *MYL6B* is correlated with poor prognosis in patients. In vitro functional experiments have validated that knocking down *MYL6B* can inhibit the proliferation, migration, and invasion of colorectal adenocarcinoma cells, while promoting apoptosis[21]. In breast cancer, *MYL6B* is upregulated and serves as a potential biological marker. The expression level of *MYL6B* mRNA in breast tumor tissues is higher than in normal tissues, and in Luminal A type breast cancer, the expression level of *MYL6B* is significantly positively correlated with the expression of miRNA clusters. Similarly, messenger RNA expression promotes the metastasis of Luminal A subtype breast cancer. *MYL6B* is significantly upregulated in the blood of breast cancer patients and can be identified with the highest level of protein certainty in human plasma. Therefore, further exploration of *MYL6B* as a potential blood biomarker for breast cancer is warranted[22].

Therefore, this study used bioinformatics methods to analyze the expression level, staging, and prognostic significance of *MYL6B* in liver cancer. Based on these analyses, this study elucidates the role of *MYL6B* in liver cancer and provides potential therapeutic targets for its progression and diagnosis.

MATERIALS AND METHODS

Comparative analysis of MYL6B expression in cancer tissues and normal tissues

The investigation into *MYL6B* expression profiles involved a meticulous comparison between various cancer tissues and their corresponding normal counterparts, facilitated by the utilization of the gene expression profiling interactive analysis (GEPIA2) database (http://gepia2.cancer-pku.cn/). Furthermore, a comprehensive analysis of *MYL6B* expression across diverse tissue types was undertaken utilizing the tumor immune estimation resource (TIMER) database (http://timer.cistrome.org/). Notably, a rigorous statistical analysis was conducted to discern significant differences in *MYL6B* expression among various cancer types, thereby enriching our understanding of its potential roles in malignancy progression.

Evaluation of survival outcomes associated with MYL6B expression

Survival outcomes associated with *MYL6B* were meticulously evaluated through meticulous scrutiny of data obtained from the Kaplan-Meier plotter database (https://kmplot.com/). This encompassed an in-depth analysis of both overall survival (OS) among a cohort of 364 subjects and recurrence-free survival (RFS) within a subgroup comprising 316 individuals. These survival analyses provided invaluable insights into the prognostic implications of *MYL6B* expression levels in cancer.

Immune infiltration and immunohistochemical staining analysis

Immune infiltration analysis using TIMER database. The exploration of *MYL6B* expression extended beyond mere quantitative assessments, delving into qualitative aspects through immunohistochemical staining analyses. Leveraging the resources provided by the human protein atlas (HPA) database (https://www.proteinatlas.org/), this endeavor involved the meticulous examination of *MYL6B* expression in both high-expression cancer tissues and normal tissue counterparts. The antibody HPA063034 (Sigma-Aldrich) was utilized for immunohistochemical analyses.

Exploration of co-expressed genes associated with MYL6B

Furthermore, a deeper understanding of *MYL6B*'s functional implications was sought through an exploration of its co-expression network. This endeavor was facilitated by the utilization of the LinkedOmic database (https://www.linkedomics.org/), enabling the identification and analysis of genes that exhibit coordinated expression patterns with *MYL6B*. Subsequently, comprehensive analyses of both upregulated and downregulated genes were undertaken, with a focus on the top 50 significantly altered genes. The visualization of these findings was facilitated through the generation of heat maps, enhancing the interpretability and utility of the results.

Additionally, the construction of protein-protein interaction networks surrounding *MYL6B* was undertaken utilizing the resources provided by the STRING database (https://string-db.org/).

Statistical analysis

The statistical analysis was automatically computed based on the above online databases. $^{a}P < 0.05$ indicated a statistically significant difference.

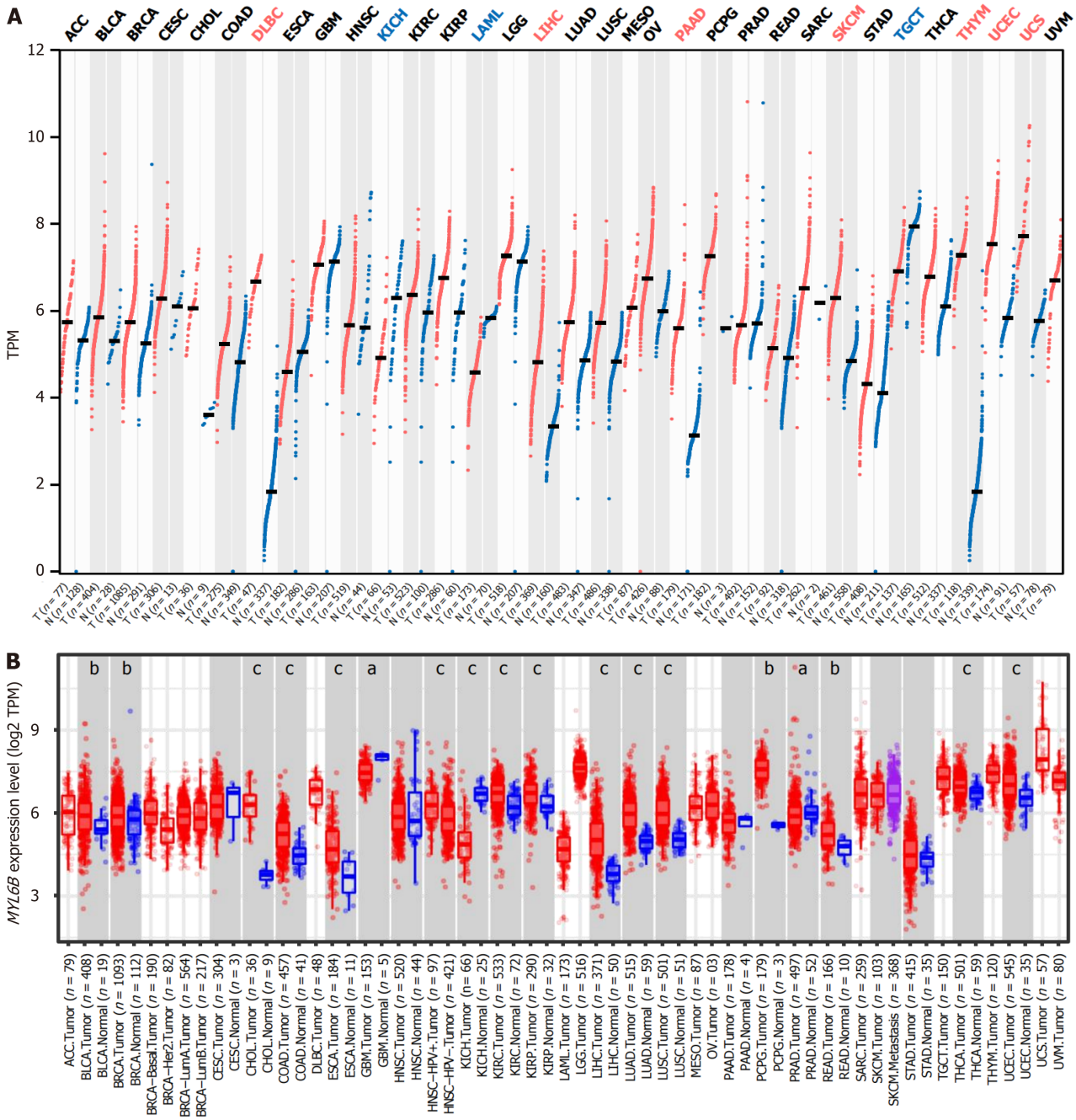


Figure 1 Expression of *MYL6B* across various cancer types. A: Comparison between cancerous tissues and adjacent normal tissues using the gene expression profiling interactive analysis database; B: Comparison of cancer tissues with corresponding normal tissues utilizing the tumor immune estimation resource 2.0 database. Statistical significance is denoted by asterisks. [a]*P* < 0.05. [b]*P* < 0.01. [c]*P* < 0.001. TPM: Transcripts per million; ACC: Adrenocortical carcinoma; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and neck squamous cell carcinoma; KICH: Kidney chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LGG: Brain lower grade glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin cutaneous melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular germ cell tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine corpus endometrial carcinoma; UCS: Uterine carcinosarcoma; UVM: Uveal melanoma.

RESULTS

Expression analysis of MYL6B in various cancers

In multiple cancer tissues, the expression level of *MYL6B* showed variability compared to normal tissues, *MYL6B* expression levels differed significantly between cancer and normal tissues (Figure 1A). GEPIA2 analysis revealed *MYL6B* high expression in diffuse large B-cell lymphoma, pancreatic adenocarcinoma, skin cutaneous melanoma, thymoma, uterine corpus endometrial carcinoma, and uterine carcinosarcoma cancer tissues, while low expression was observed in

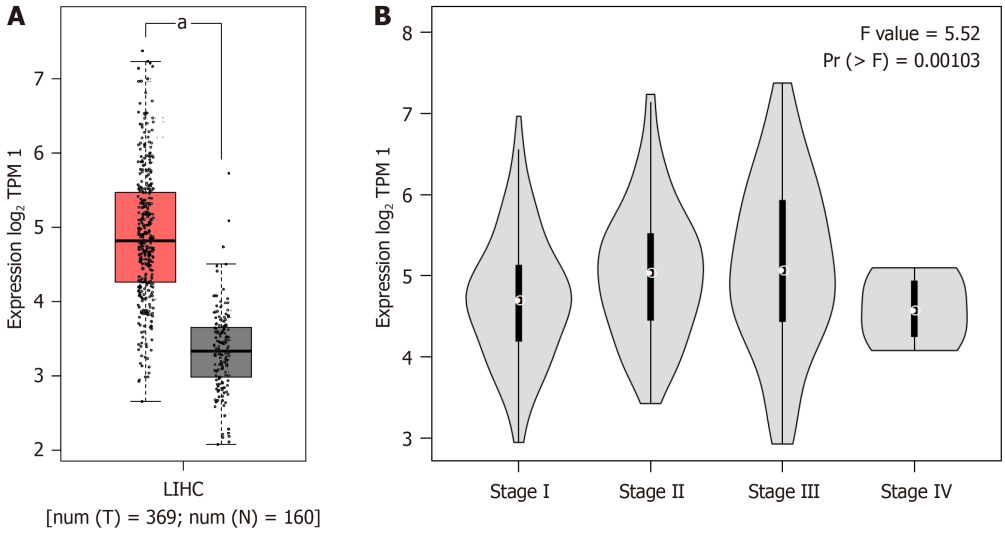


Figure 2 Relationship between *MYL6B* expression and staging in hepatocellular carcinoma. A: Comparison of *MYL6B* expression levels between liver hepatocellular carcinoma (LIHC) and normal tissues; B: Correlation between *MYL6B* expression levels and staging in LIHC. TPM: Transcripts per million; LIHC: Liver hepatocellular carcinoma; T: Tumor; N: Normal.

kidney chromophobe, acute myeloid leukemia, testicular germ cell tumors. Furthermore, in LIHC, *MYL6B* showed high expression in GEPIA2 analysis. Similarly, TIMER analysis showed high expression in LIHC with significant differences (Tumor n = 371, Normal n = 50) (Figure 1B).

High expression of MYL6B in LIHC tissues and its significant correlation with grading and staging

In the context of hepatocellular carcinoma (HCC), *MYL6B* demonstrated significant differences when subjected to comparative analysis (Tumor n = 369, Normal n = 160) (P < 0.05), revealing markedly elevated expression levels specifically within the LIHC samples (as illustrated in Figure 2A). Furthermore, upon scrutinizing *MYL6B* expression vis-à-vis tumor staging, a statistically significant correlation emerged [Pr (> F) = 0.00103], underscoring the close association between *MYL6B* expression levels and unfavorable prognostic indicators in LIHC. Moreover, as the disease progressed, a noticeable upward trajectory was observed in the expression levels of *MYL6B* (as depicted in Figure 2B), suggesting a potential link between *MYL6B* expression dynamics and the evolving pathophysiology of HCC.

High expression of MYL6B associated with poor prognosis in HCC patients

To investigate the correlation between *MYL6B* and LIHC prognosis, Kaplan-Meier plotter database was used to explore the association between high and low expression groups of *MYL6B* with survival rates, patient prognosis, and recurrence risk. Results indicated a close association between high gene expression and shorter OS and progression-free survival. Analysis of OS (n = 364), with low expression group (n = 208) and high expression group (n = 156), showed higher OS in the low expression group compared to the high expression group (logrank P = 0.0057), with median survival times of 70.5 months and 41 months, respectively (Figure 3A). For RFS, with low expression group (n = 235) and high expression group (n = 81), median survival times were 36.1 months and 15.17 months, respectively (Figure 3B).

Higher immune infiltration levels of MYL6B

Through comprehensive immune infiltration analyses, we uncover a compelling association between elevated *MYL6B* expression and heightened immune cell infiltration, particularly characterized by increased activation of CD8 + T cells. This observation, depicted graphically in Figure 4A, underscores the immunomodulatory roles of *MYL6B* within the tumor milieu, potentially shaping the host immune response to cancer. Additionally, immunohistochemical staining images obtained from the HPA database further corroborate these findings, revealing differential *MYL6B* expression patterns between normal and cancer tissues (Figure 4B). Notably, high *MYL6B* expression in cancer tissues correlates with the severity of malignancy, underscoring its potential as a biomarker of tumor aggressiveness and immune modulation.

MYL6B gene expression and protein network

Furthermore, the LinkedOmic database was harnessed to delve into the repertoire of co-expressed genes associated with *MYL6B*. This comprehensive analysis unveiled a diverse array of genes that exhibited either positive or negative correlations with *MYL6B* expression. As depicted in Figure 5A, a heat map visualizes the top 50 co-expressed genes, showcasing downregulated genes such as *SARNP*, *SNRPD2*, *ATP5G2*, *SNRPA*, *PFDN5*, and upregulated genes including *KLHL20*, *NFIC*, *PLB2*, *MTM1*, *LONP2*, among others. This systematic exploration of co-expression patterns provides valuable insights into the potential regulatory networks in which *MYL6B* participates, offering avenues for further investigation into its functional roles in HCC.

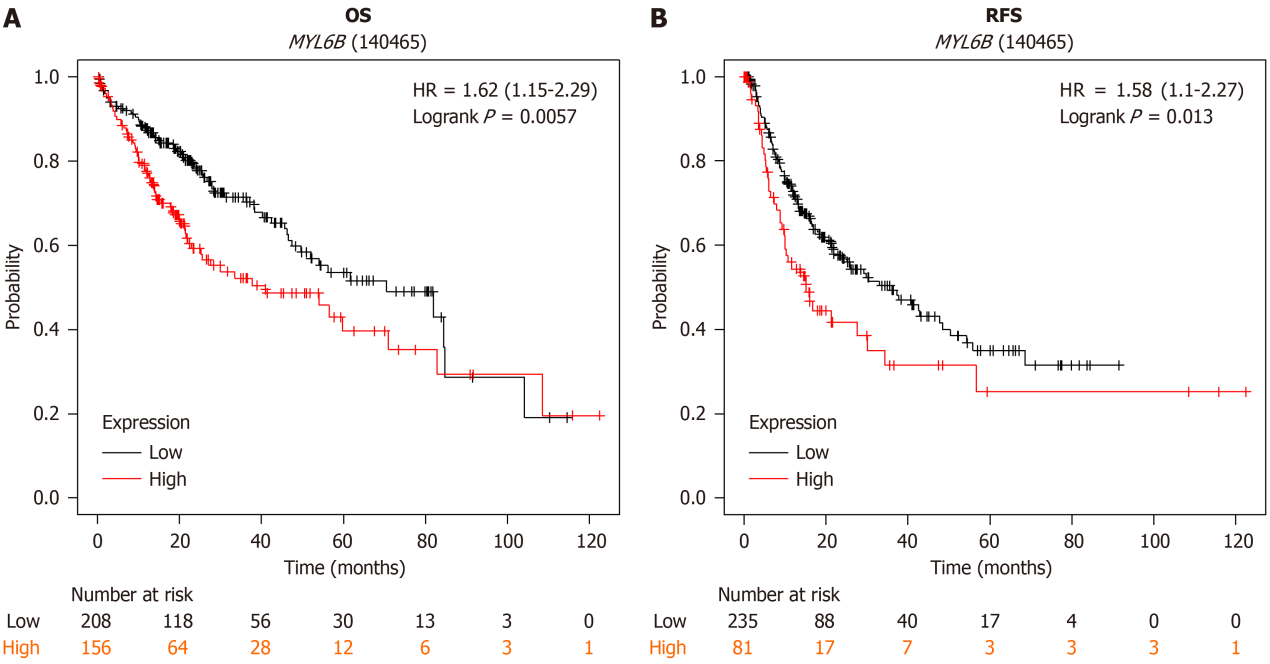


Figure 3 Relationship between *MYL6B* expression levels and prognosis in liver hepatocellular carcinoma. A: Overall survival (n = 316); B: Progression-free survival (n = 370). OS: Overall survival; HR: Hazard ratio; RFS: Recurrence-free survival.

Analysis of the protein interaction network of *MYL6B* using the STRING database revealed correlations with *MYL2*, *MYL6*, *MYL9*, *MYLK4*, *MYLK2*, *MYL12A*, *MYL12B*, *MYH11*, *MYH9*, and *MYH10* (Figure 5B). This facilitated the elucidation of interactions associated with *MYL6B*, thereby offering deeper insights into its molecular mechanisms and functional roles. Furthermore, the identification of top co-expressed protein genes provided valuable context and further enriched our understanding of the biological processes in which *MYL6B* may be implicated.

DISCUSSION

This study employed advanced bioinformatics methodologies to meticulously scrutinize the intricate relationship between *MYL6B* and LIHC. It entailed a comprehensive analysis encompassing the contrasting expression patterns observed between LIHC and normal tissue samples, coupled with an intricate examination of how *MYL6B* expression levels correlate with the staging of cancer progression and the rates of survival. Furthermore, an exhaustive immunohistochemical investigation was conducted to elucidate the nuances of inflammation across varying levels of *MYL6B* expression in tissue specimens. The findings of this investigation unequivocally underscore *MYL6B*'s pivotal role as a prognostic determinant in HCC.

MYL6B, as an exosomal gene, has been studied in relation to HCC. A study focusing on the prognostic, recurrence risk, and immune infiltration prediction models based on two exosomal genes, *MYL6B* and *THOC2*, in HCC revealed that the prognostic and recurrence risk prediction model built upon these two exosomal genes (*MYL6B* and *THOC2*) was confirmed to be an independent predictive factor with superior predictive performance[23]. Some mechanistic studies on *MYL6B* suggest that it can bind to *MDM* and *p53* proteins. Furthermore, it has been indicated that *MYL6B* can promote the binding of *MDM2* to *p53*, thereby enhancing the ubiquitination and degradation of *p53* (wild-type *p53* and Y220C mutant *p53*), exerting its *p53* inhibitory effect. Overexpression of *MYL6B* in HCC is associated with poor prognosis in patients with HCC and several other types of tumors. Additionally, knocking out *MYL6B* may hinder the clonal formation ability of HCC cell lines, upregulate the protein expression levels of *p53* and *BAX*, and increase apoptosis[24].

In this study, bioinformatics techniques alongside other research methodologies were employed to evaluate the expression pattern of *MYL6B* across a spectrum of cancers, with subsequent exploration of its impact on the progression and prognosis of HCC. The findings unveiled a conspicuous upregulation of *MYL6B* expression in HCC tissues, with substantially elevated levels of *MYL6B* expression demonstrating a strong correlation with unfavorable prognosis and advanced tumor staging.

Tumor occurrence is a complex and multi-step process primarily caused by the accumulation of gene mutations associated with organismal growth and development. It is widely believed that genetic and chromosomal instability are the main reasons for gene mutations and potential tumor progression. Subsequently, malignant cells detach from primary tumors and enter the stages of metastasis and invasion. To facilitate this, a series of physiological and metabolic processes need to be altered. These include loss of cell polarity and tissue disintegration, formation of cell protrusions, damage to cell adhesion, and inhibition of apoptosis. The seven classes of myosin superfamily, including myosin I, II, V, VI, VII, IX, and X, have been shown to participate in these processes during tumor occurrence. Additionally, myosins are involved in various factors, pathways, and mechanisms related to tumor progression, and they have specific functions in nuclear

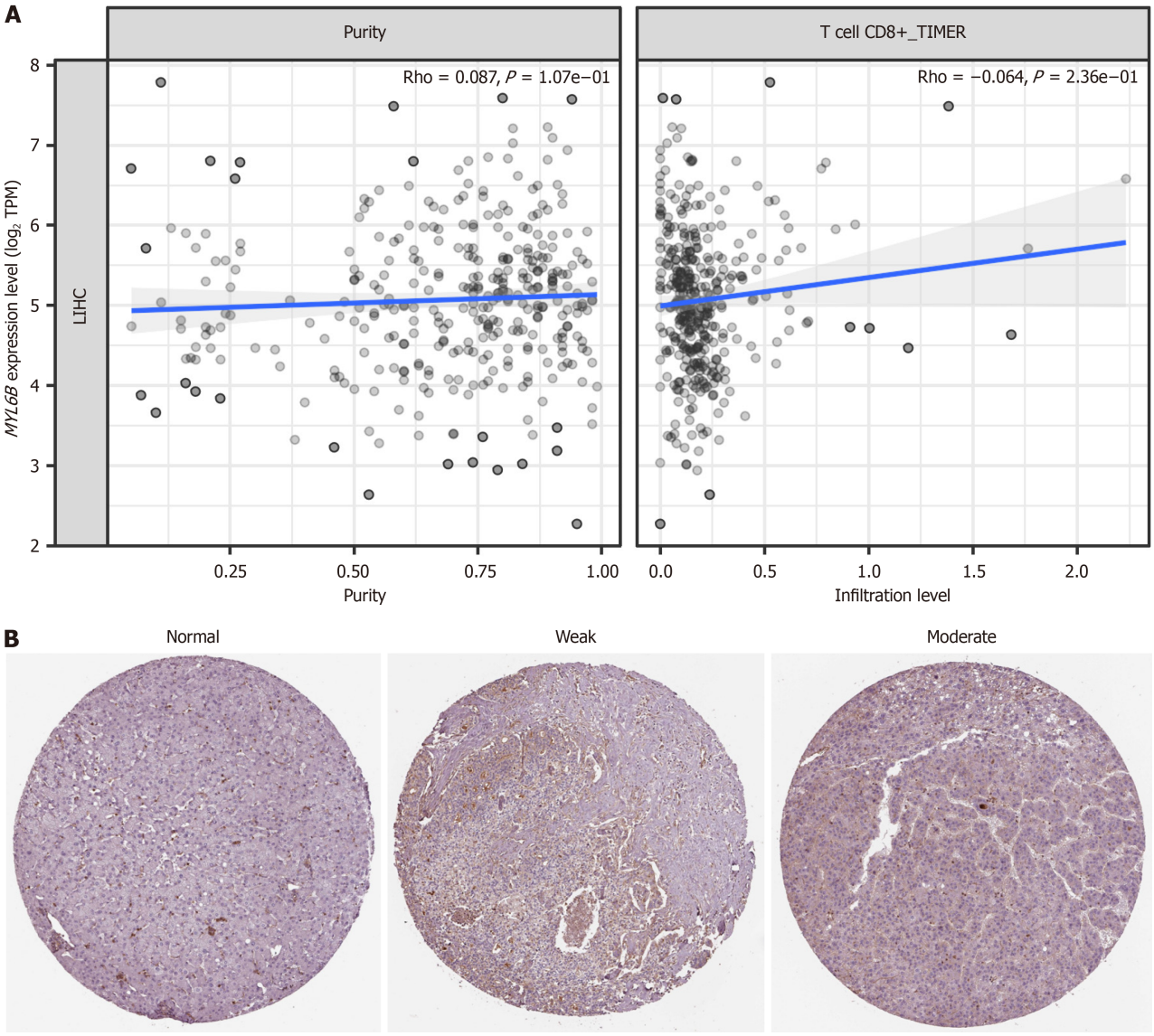


Figure 4 Immune infiltration and immunohistochemical analysis of *MYL6B*. A: Relationship between CD8 + T cell immune infiltration levels and *MYL6B* expression levels; B: Immunohistochemical analysis of *MYL6B* in normal and cancer tissues.

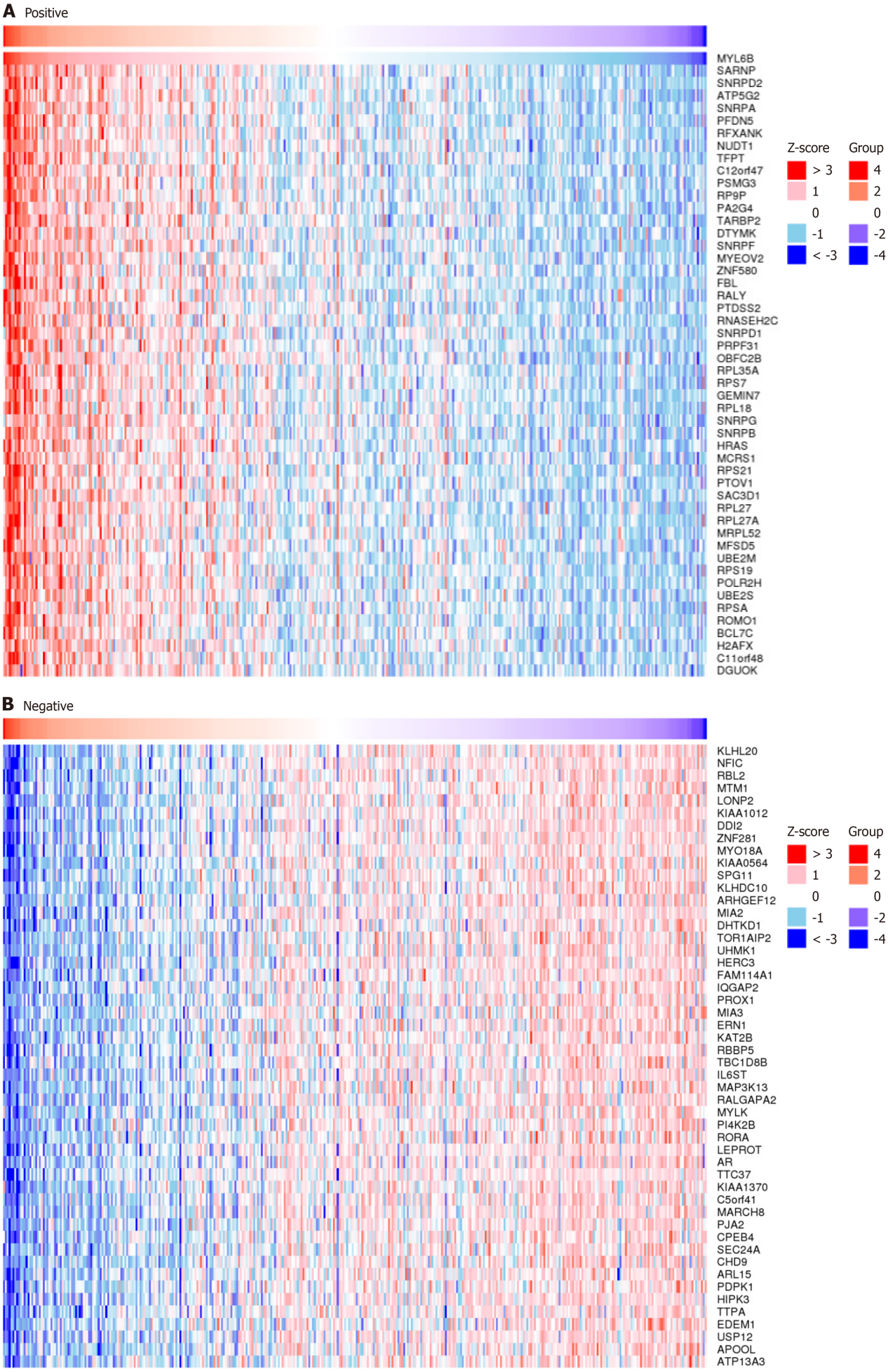
division and myosin superfamily optimization processes[25].

MYL6B, as a myosin, is correlated with cancer development. The modification of the actin cytoskeleton's structure is a fundamental mechanism in the progression of cancer, enabling the proliferation and dissemination of cancerous cells. This intricate process involves a myriad of contributors, with myosin motors standing out as pivotal regulators that oversee numerous stages of tumorigenesis. From orchestrating nuclear transcriptional programs to orchestrating the reshaping of the cellular cortex during cancer cell migration and division, myosin motors exert indispensable control over the intricate dance of cancer progression[11,26].

Hence, *MYL6B* emerges as a versatile prognostic marker across a spectrum of cancer types. Its multifaceted roles encompassing diverse biological functions, modulation of immune infiltration, and orchestration of protein interaction networks position *MYL6B* as a potent facilitator of tumor progression. Delving into its protein interactions unveils a nexus with *MYL2*, *MYL6*, and *MYL9*, underscoring *MYL6B*'s potential as an appealing therapeutic target for addressing LIHC. Within the realm of HCC, *MYL6B* assumes the role of a predictive risk factor of LIHC, offering valuable insights into disease prognosis and management strategies. However, there are several limitations in our study: (1) Some important clinical information (*e.g.*, different ages, tumor sizes) was not considered; (2) Since all data were retrieved from online databases, biological experiments are needed in the future to verify our research results; and (3) More detailed molecular mechanisms need to be elucidated.

CONCLUSION

The expression level of *MYL6B* in LIHC was significantly higher than in normal liver tissues, and it was correlated with


A Positive
MYL6B
SARNP
SNRPD2
ATP5G2
SNRPA
PFDN5
RFXANK
NUDT1
TFPT
C12orf47
PSMG3
RP9P
PA2G4
TARBP2
DTYMK
SNRPF
MYEOV2
ZNF580
FBL
RALY
PTDSS2
RNASEH2C
SNRPD1
PRPF31
OBFC2B
RPL35A
RPS7
GEMIN7
RPL18
SNRPG
SNRPB
HRAS
MCRS1
RPS21
PTOV1
SAC3D1
RPL27
RPL27A
MRPL52
MFSD5
UBE2M
RPS19
POLR2H
UBE2S
RPSA
ROMO1
BCL7C
H2AFX
C11orf48
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KLHL20
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MTM1
LONP2
KIAA1012
DDI2
ZNF281
MYO18A
KIAA0564
SPG11
KLHDC10
ARHGEF12
MIA2
DHTKD1
TOR1AIP2
UHMK1
HERC3
FAM114A1
IQGAP2
PROX1
MIA3
ERN1
KAT2B
RBBP5
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IL6ST
MAP3K13
RALGAPA2
MYLK
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RORA
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TTC37
KIAA1370
C5orf41
MARCH8
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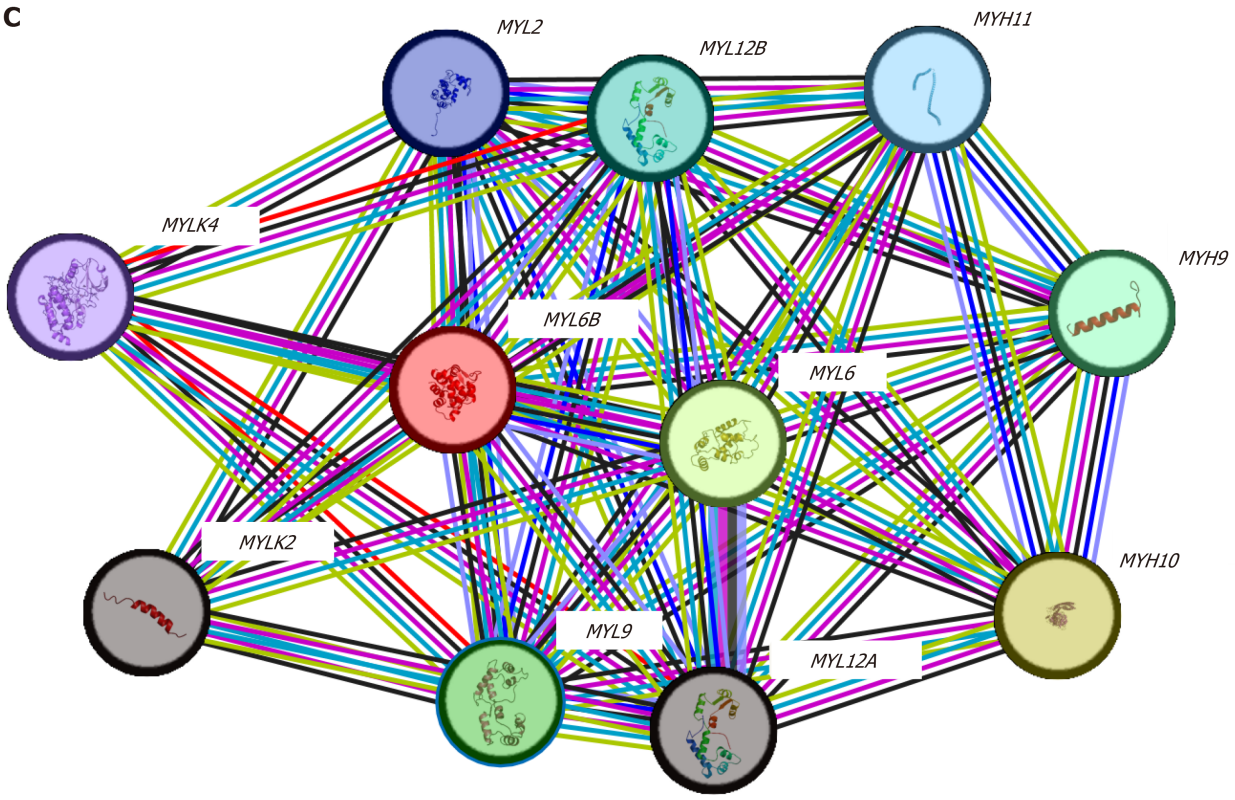

Figure 5 Expression of *MYL6B*-related genes and protein network. A: Analysis of top 50 upregulated and downregulated genes related to *MYL6B* using LinkedOmic data; B: Analysis of *MYL6B* protein network using STRING database.

the degree of differentiation survival rate, and immune infiltration. *MYL6B* is a potential target for LIHC treatment.

FOOTNOTES

Author contributions: Lv HB and Wu QY designed experiments, formal analysis, methodology and writing original draft; Zhang YJ and Quan SW contributed to data curation and methodology; Ma N provided resources; Dai YQ contributed to methodology; Sun Y contributed to conceptualization, project administration, supervision and writing; All authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

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S-Editor: Fan M
L-Editor: A
P-Editor: Xu ZH

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