

注:A:利用TIMER2.0数据库分析MBD1在各种肿瘤组织中的表达情况;红色为肿瘤组织,蓝色为正常组织;B:利用UALCAN数据库分析MBD1在LIHC和正常肝组织中的表达情况;C:利用HPA数据库分析MBD1蛋白在LIHC和正常肝组织中的表达;TPM:每千个碱基的转录每百万映射读取的Transcripts;两组间比较,^a $P<0.05$ 。

图1 MBD1在肿瘤和正常组织中的表达情况

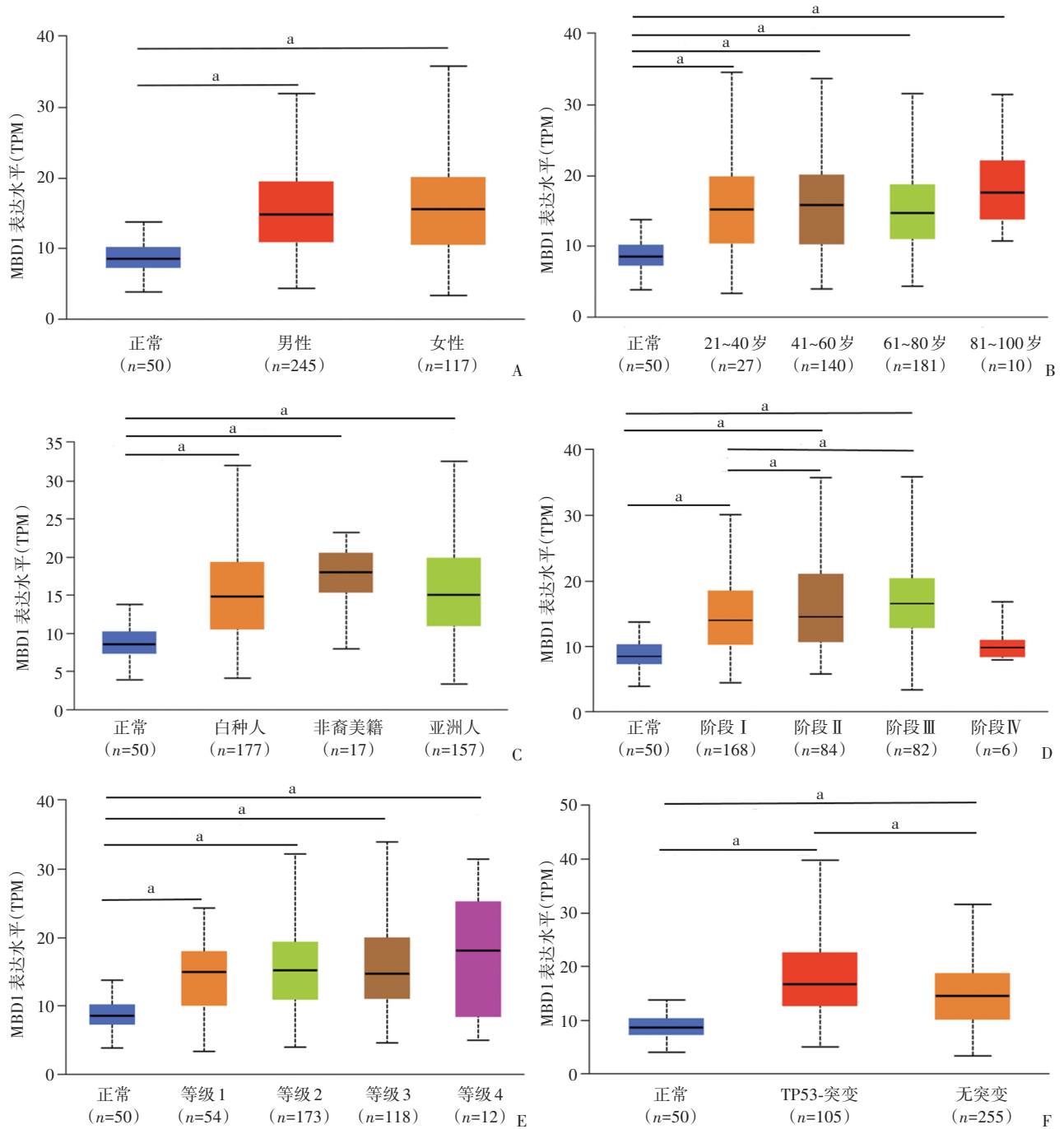
同时对于Ⅱ期或Ⅲ期患者而言,MBD1的表达比Ⅰ期更高,此差异在统计学方面有意义($P<0.05$),见图2D。此外,相较于正常肝组织和无TP53突变的LIHC组织,对于TP53突变的LIHC组织,MBD1明显呈现更高的表达水平,差异有统计学意义($P<0.05$),如图2F。

2.3 MBD1表达水平与LIHC患者预后的相关性

通过对来自TCGA数据库的总共365例样本进行生存分析,结果显示,MBD1高表达组患者生存率低于低表达组患者,差异有统计学意义($P<0.05$),见图3A、B。

2.4 MBD1在LIHC里面的共表达和相关信号通路富集分析

根据LinkedOmics数据库结果分析表明,存在6196个基因和MBD1表达之间是呈正相关的($P<0.05$),而有1946个基因和MBD1的表达关系是呈负相关($P<0.05$),如下图4A。和MBD1表达相关性成最强正向关系的是PIAS2基因,相关系数是0.589;和MBD1表达相关性成最强负向关系的是HEBP2基因,相关系数是-0.328。根据KEGG信号通路富集分析显示,MBD1可能和细胞周期、泛素介导的蛋白水解、核糖核酸转运、调节干细胞多能性、微小核



注:A:性别;B:年龄段;C:种族;D:肝癌临床分期;E:肝癌病理等级;F:TP53突变情况;TPM:每千个碱基的转录每百万映射读取的 Transcripts; 两组间比较,*P<0.05。

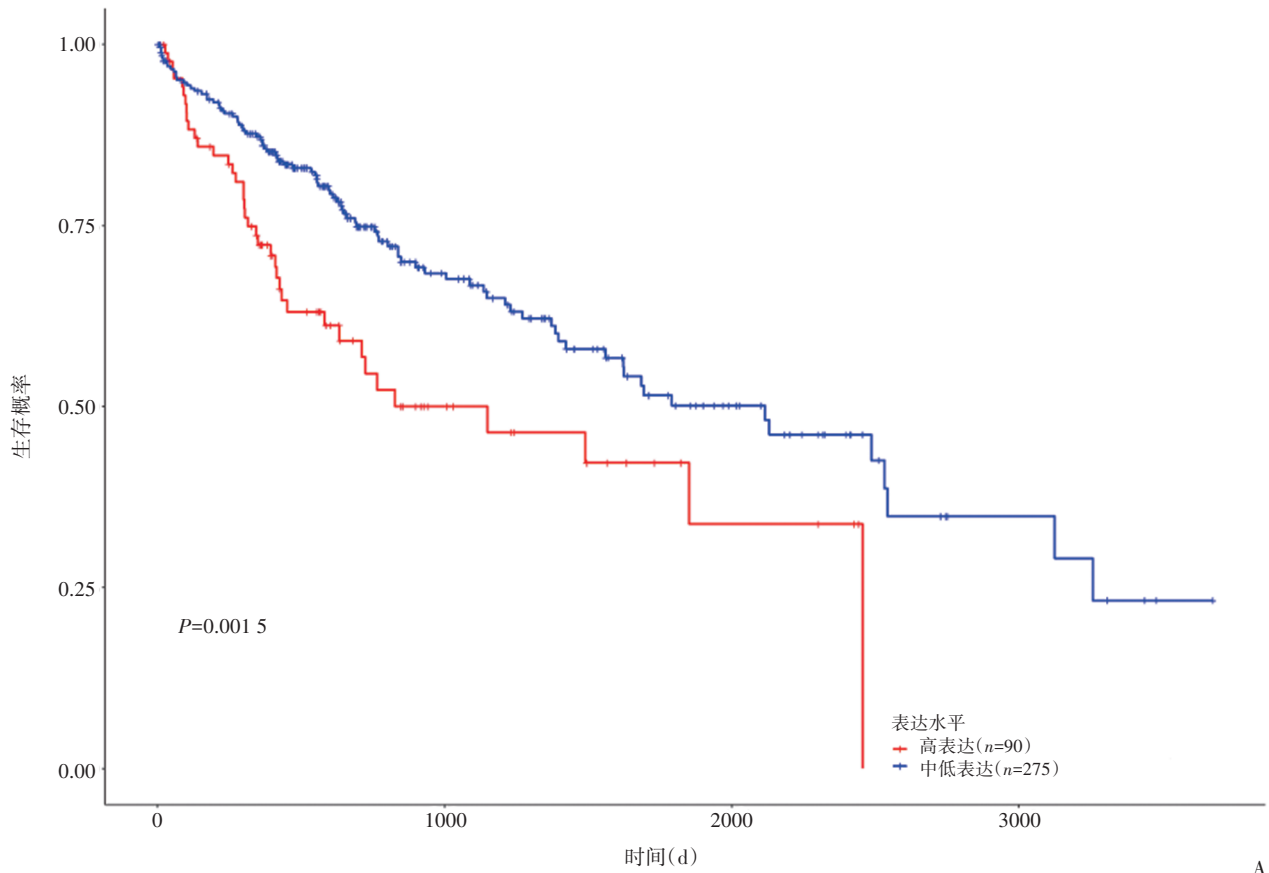
图2 MBD1在不同LIHC组间的表达情况(UALCAN数据库)

糖核酸在癌症中的作用、病毒性致癌、人T细胞白血病病毒1感染等信号通路活化相关,见图4B。

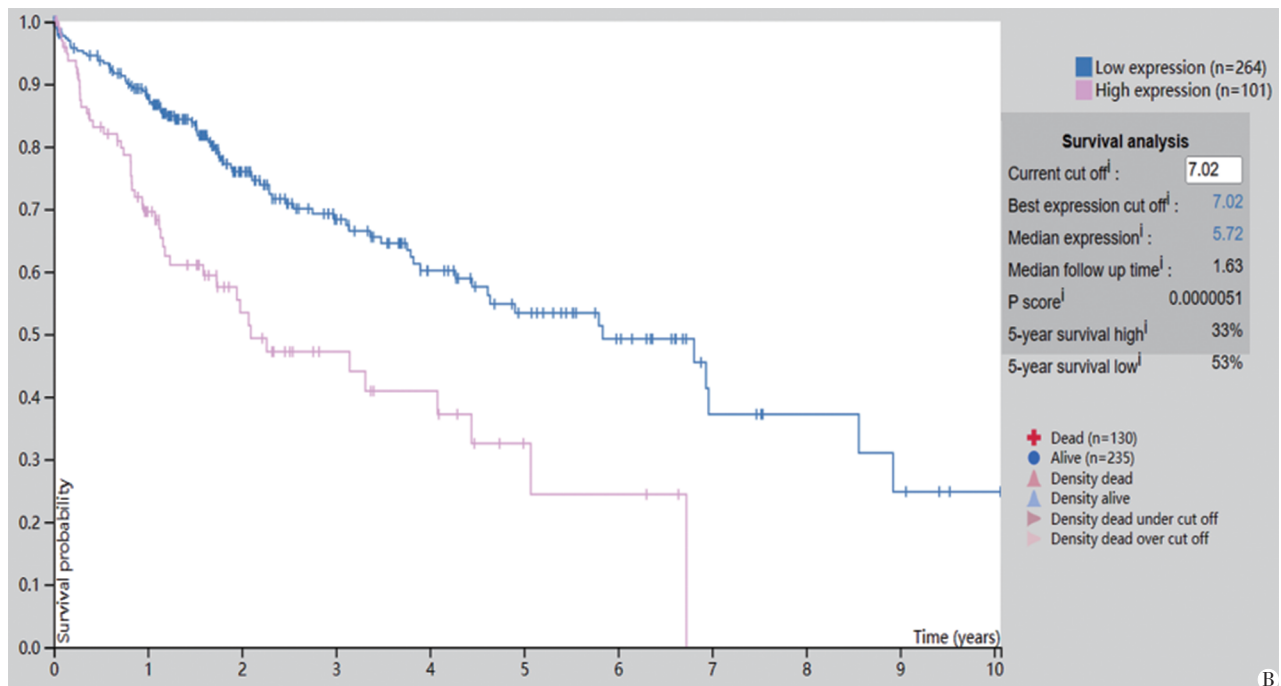
3 讨论

LIHC是世界范围内最常见的胃肠道恶性肿瘤

之一,由于其进展迅速,恶性程度高,预后差,死亡率高,一直受到人们的广泛关注^[9-10]。目前对肝癌的诊断通常借助于特定的生物标志物、影像学、肝组织活检技术等^[11]。甲胎蛋白(Alpha-fetoprotein, AFP)是目前发现最早、应用最广的一种肝脏肿瘤标



A



B

注:A、B:UALCAN、HPA 数据库分析MBD1表达与LIHC患者生存率的相关性。

图3 MBD1表达水平对LIHC患者预后的影响

志物,不过有研究显示,AFP的灵敏性和特异性均不高,这使得LIHC的诊断变得困难^[12]。此外,对于符

合影像学诊断指征的肝癌患者多数已到了中晚期,诊断时间较晚,效果不理想^[13]。对于缺少代表性肝

参考文献

- [1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries[J]. *CA Cancer J Clin*, 2021, 71(3):209-249.
- [2] Lin Q, Huang X, Zhong C, et al. Improved survival with radiotherapy in hepatocellular carcinoma with major vascular invasion: A propensity - matched analysis of Surveillance, Epidemiology, and End Results database [J]. *Cancer Med*, 2019, 8(2):515-526.
- [3] Alqahtani A, Khan Z, Alloghbi A, et al. Hepatocellular Carcinoma: Molecular Mechanisms and Targeted Therapies[J]. *Medicina (Kaunas)*, 2019, 55(9):526.
- [4] 闫伟伟,黄昂,戴广海. MBD蛋白家族研究进展[J]. *传染病信息*, 2017, 30(3):181-185.
- [5] Reese BE, Bachman KE, Baylin SB, et al. The methyl-CpG binding protein MBD1 interacts with the p150 subunit of chromatin assembly factor 1[J]. *Mol Cell Biol*, 2003, 23(9):3226-3236.
- [6] Zhang B, Xu J, Li C, et al. MBD1 is an Epigenetic Regulator of KEAP1 in Pancreatic Cancer[J]. *Curr Mol Med*, 2016, 16(4):404-411.
- [7] Patra SK, Patra A, Zhao H, et al. Methyl - CpG - DNA binding proteins in human prostate cancer: expression of CXXC sequence containing MBD1 and repression of MBD2 and MeCP2 [J]. *Biochem Biophys Res Commun*, 2003, 302(4):759-766.
- [8] Villa R, Morey L, Raker VA, et al. The methyl - CpG binding protein MBD1 is required for PML - RARalpha function[J]. *Proc Natl Acad Sci U S A*, 2006, 103(5): 1400-1405.
- [9] 方国旭,张清华,黄永迎,等. 生物信息学在肝细胞癌风险预测中的应用[J]. *临床肝胆病杂志*, 2022, 38(1): 15-19.
- [10] Chen C, Wang G. Mechanisms of hepatocellular carcinoma and challenges and opportunities for molecular targeted therapy[J]. *World J Hepatol*, 2015, 7(15): 1964-1970.
- [11] 贺庆,刘坤,王超红,等.《原发性肝癌诊疗指南(2022年版)》解读[J]. *西部医学*, 2023, 35(04):474-479.
- [12] Galle PR, Foerster F, Kudo M, et al. Biology and significance of alpha - fetoprotein in hepatocellular carcinoma[J]. *Liver Int*, 2019, 39(12):2214-2229.
- [13] 王文平,季正标,董怡,等. 实时导航超声造影在小肝癌诊断中的应用研究[J]. *中华医学超声杂志(电子版)*, 2016, 13(1):56-60.
- [14] Cong WM, Bu H, Chen J, et al. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update [J]. *World J Gastroenterol*, 2016, 22(42): 9279-9287.
- [15] Bird A. DNA methylation patterns and epigenetic memory [J]. *Genes Dev*, 2002, 16(1):6-21.
- [16] Li L, Chen BF, Chan WY. An epigenetic regulator: methyl-CpG-binding domain protein 1 (MBD1)[J]. *Int J Mol Sci*, 2015, 16(3):5125-5140.
- [17] Du Q, Lu PL, Stirzaker C, et al. Methyl-CpG-binding domain proteins: readers of the epigenome [J]. *Epigenomics*, 2015, 7(6):1051-1073.
- [18] Zhao C, Miao J, Sun R, et al. MBD1/HDAC3-miR-5701-FGFR2 axis promotes the development of gastric cancer [J]. *Aging (Albany NY)*, 2022, 14(14):5878-5894.
- [19] Xu J, Zhu W, Xu W, et al. Up - regulation of MBD1 promotes pancreatic cancer cell epithelial - mesenchymal transition and invasion by epigenetic down - regulation of E-cadherin[J]. *Curr Mol Med*, 2013, 13(3):387-400.
- [20] Dai X, Jiang W, Ma L, et al. A metabolism - related gene signature for predicting the prognosis and therapeutic responses in patients with hepatocellular carcinoma [J]. *Ann Transl Med*, 2021, 9(6):500.

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