

Increased expression of HIST1H1D in esophageal carcinoma predicts poor survival: A study base on TCGA database

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Abstract

Background: Expression level of HIST1H1D, a linker histone H1 gene, was reported to be associated with poor prognosis in some malignant tumors. Online database showed that HIST1H1D was increased in esophageal carcinoma. The current study aimed to evaluate the role of HIST1H1D in esophageal carcinoma using online data from The Cancer Genome Atlas (TCGA).

Methods. Wilcoxon signed-rank test, cox regression analysis and multivariate analysis were used to analyze the relationship between clinical characteristic and HIST1H1D expression level. Kaplan-Meier method was used to analyze the association of HIST1H1D and overall survival. Gene set enrichment analysis (GSEA) was used to identify HIST1H1D-related signaling pathway.

Results. Compared to normal sample, HIST1H1D was significantly increased in esophageal carcinoma sample ($p=0.000$). High HIST1H1D expression was associated with poor survival ($p=0.035$). Univariate analysis showed that high HIST1H1D expression was associated with a poor overall survival (HR:1.19, 95% confidence interval [CI]: 1.05-1.34, $p=0.01$). Multivariate analysis indicated that HIST1H1D remained an independent prognostic predictor of overall survival (HR:1.18, 95% confidence interval [CI]: 1.02-1.36, $p=0.03$). GSEA revealed that alpha linolenic acid metabolism, arachidonic acid metabolism, histidine metabolism, vascular smooth muscle contraction, primary bile acid biosynthesis, phenylalanine metabolism and ether lipid metabolism were enriched in HIST1H1D high expression phenotype.

Conclusions: HIST1H1D may serve as a potential prognostic predictor of poor survival in esophageal carcinoma. Lipid metabolism, histidine metabolism, vascular smooth muscle contraction, primary bile acid biosynthesis, phenylalanine metabolism and ether lipid metabolism may be the key signaling pathway regulated by HIST1H1D.

1. Background

According to a statistics in 2018, there were about 572,000 new cases of esophageal carcinoma and resulted in about 508,000 death, which made esophageal carcinoma the 7th most common carcinoma and the 6th leading cause of cancer-related death(1, 2). There are regional differences in the incidence of esophageal carcinoma. The high incidence areas constitute the “esophageal cancer belt”, which includes the northern Iran, Central Asian republics and northern China(3–5). Tobacco, alcohol, gastroesophageal reflux disease (GERD) and Barrett’s esophagus are the risk factors of esophageal carcinoma(6–10).

For limited stage esophageal carcinoma, surgery is the recommended treatment. For locally advanced disease, surgery combined with radiotherapy and chemotherapy is the treatment choice(11, 12). Targeted therapies have also produced great improvement in esophageal carcinoma. Trastuzumab, Ramucirumab and Pembrolizumab have been approved to be used in advanced esophageal carcinoma in recent year(13–15). Despite the improvements in the treatment of esophageal carcinoma, the outcome remains very poor, with a 5-year survival rate about 10% in non-surgical patients and about 15%-40% in esophagectomy patients(16).

Some genetic factors may associate to the development of esophageal carcinoma, including genes that relate to the cell cycle regulation(17, 18), EGFR or RAS signaling pathway(19, 20), VEGF pathway(20) and epigenetic regulation(21). Identify biomarkers that could predict prognosis may help to find new treatment target and improve the survival of esophageal carcinoma.

Histone H1 is a protein bound to the linker DNA between nucleosomes and it is important in maintaining the normal structure of chromatin(22). In human there are two major loci that contain histone genes. HIST1 is the largest cluster, which locates on the chromosome 6 (6p21-p22)(23, 24). This cluster contains 6 histone H1 genes, HIST1H1A, HIST1H1B, HIST1H1C, HIST1H1D, HIST1H1E and HIST1H1T(25). Researches showed that HIST1H1D expression level was associated with prognosis in some malignant diseases, including acute myeloid leukemia, ovarian cancer, pancreatic ductal adenocarcinoma et al.(26–29). Increased HIST1H1D may contribute to the progression of Fanconi anemia to acute myeloid leukemia. High expression of HIST1H1D was associated with poor prognosis(27). HIST1H1D was downregulated in H3K27me3 HIST1^{high} group of acute myeloid leukemia patients and this group of patients showed better prognosis(26). After searching the GCBI database (<https://www.gcbi.com.cn/gcanalyze/html/generadar/search/singlegene/expressdesc/HIST1H1D>), we found that HIST1H1D expression was also increased in esophageal carcinoma patients (Additional file 1). However, the relation between HIST1H1D and the prognosis of esophageal carcinoma has not been studied.

Thus, we performed the current study to evaluate the prognosis value of HIST1H1D expression level in esophageal carcinoma. The study was based on the TCGA database. To further study the biological pathway related to the HIST1H1D regulation, we also performed the gene set enrichment analysis (GSEA).

2. Methods

2.1 TCGA data download and bioinformatic analysis

The gene expression data and corresponding clinical data of esophageal carcinoma (project ID: TCGA-ESCA) were downloaded from TCGA database (<https://portal.gdc.cancer.gov/>). Expression data of HIST1H1D was extracted. Then the expression difference of HIST1H1D between normal and tumor samples were compared. Clinical information was extracted and patients with incomplete clinical information were excluded. Finally, there were 124 patients were included into cox regression and multivariate cox analysis. The media expression value of HIST1H1D were calculated. Patients with HIST1H1D expression lever higher than media value were distributed to the high expression group and others were distributed to the low expression group. Overall survival in high expression and low expression group were compared. Cox regression and multivariate cox analysis were used to analysis the influence of clinical characteristics on the survival.

2.2 Gene set enrichment analysis

Software GSEA_4.1.0 was used to perform gene set enrichment analysis (GSEA). The expression matrix file and phenotype file were prepared before GSEA. HIST1H1D expression level was used as a phenotype label. Gene set permutations number was set to 1000. Then the expression matrix file and phenotype file were imported and GSEA was performed.

2.3 Statistical analysis

Statistical analyses were conducted by R software (R x64 3.6.2). The comparison of HIST1H1D expression between normal and tumor sample was analyzed by Wilcoxon signed-rank test. Clinical characteristics associated to survival was analyzed by Cox regression and Kaplan-Meier method. To further compare the effect of HIST1H1D expression on overall survival along with other clinical factors, multivariate Cox analysis was performed.

3. Results

3.1 Patient characteristics

Totally 124 tumor samples with gene expression and clinical data were downloaded from TCGA in December 2020. 105 (84.7%) cases were male. 12 (9.7%) patients were with stage I disease, 63 (50.8%) patients were with stage II disease, 41 (33.1%) patients were with stage III disease and 8 (6.4%) patients were with stage IV disease. T1, T2, T3, T4 diseases were found in 23 (18.6%), 35 (28.2%), 63 (50.8%), 3 (2.4%) patients, respectively. 54.1% of the patients had lymph node invasion. Of which, 56 cases were N1 disease, 8 cases were N2 disease, 3 cases were N3 disease. 8(6.5%) patients had distant metastases. Clinical characteristics of patients were shown in Table 1.

3.2 HIST1H1D expression was increased in esophageal carcinoma patients

Data of 159 esophageal carcinoma samples and 10 normal samples with HIST1H1D expression information were downloaded from TCGA database in December 2020. We compared HIST1H1D expression level in normal samples and tumors samples. It was showed that HIST1H1D expression was significantly increased in tumor samples in comparison to normal samples (Fig. 1A).

Table 1
TCGA esophageal carcinoma patient characteristics

characteristic		Total(N = 124)	Percentage(%)
gender	male	105	84.7
	female	19	15.3
stage	I	12	9.7
	II	63	50.8
	III	41	33.1
	IV	8	6.4
T	1	23	18.6
	2	35	28.2
	3	63	50.8
	4	3	2.4
N	0	57	45.9
	1	56	45.2
	2	8	6.5
	3	3	2.4
M	0	116	93.5
	1	8	6.5

3.3 Increased HIST1H1D was associated with poor overall survival

After excluded patients with incomplete survival information, there were totally 158 esophageal carcinoma patients included in the survival analysis. As shown in Fig. 1B, patients with high HIST1H1D expression showed a worse prognosis than patients with low HIST1H1D expression ($p = 0.035$). 1-year, 2-year, 3-year survival in HIST1H1D high and HIST1H1D low group were 75.2% (95% CI: 65.9%-85.9%), 44.7% (95% CI: 31.7%-63.1%), 28.7% (95% CI: 15.5%-53.3%) and 85.6% (95% CI: 77.7%-94.3%), 64.4% (95% CI: 52.1%-79.8%), 50.2% (95% CI: 30.2%-69.6%), respectively (Table 2). Patients with high HIST1H1D showed shorter survival time. We also analyzed the association between HIST1H1D expression and other clinical characteristics. Result showed that HIST1H1D expression was independent of clinical stage, T stage, lymph node invasion or distant metastasis (Additional file 2).

Table 2
Overall survival in HIST1H1D high and low expression patients

	HIST1H1D high expression		HIST1H1D low expression	
	OS (%)	95%CI	OS (%)	95%CI
1-year	75.2	65.9–85.9	85.6	77.7–94.3
2-year	44.7	31.7–63.1	64.4	52.1–79.8
3-year	28.7	15.5–53.3	50.2	36.2–69.6
OS: overall survival				

3.4 HIST1H1D was an independent prognostic factor in esophageal carcinoma

Univariate cox regression analysis revealed that high expression of HIST1H1D correlated significantly with poor survival (hazard ratio [HR]: 1.19, 95% confidence interval [CI]: 1.05-1.34, $p=0.01$) (tab. 3a). HIST1H1D remained associated with survival at multivariate analysis, with a hazard ratio of 1.18 (95% CI: 1.02-1.36, $p=0.03$) (tab. 3b and fig. 2).

Table 3
Association of HIST1H1D and clinical characteristics by univariate cox regression and multivariate analysis

Characteristics	HR (95%CI)	p-value
a. Univariate cox regression analysis		
gender	2.38(0.74–7.70)	0.15
stage	2.61(1.76–3.87)	0.00
T	1.28(0.88–1.85)	0.20
M	4.69(2.14–10.27)	0.00
N	1.78(1.26–2.50)	0.00
HIST1H1D	1.19(1.05–1.34)	0.01
b. Multivariate analysis		
HIST1H1D	1.18(1.02–1.36)	0.03
HR: Hazard Ratio		

3.5 HIST1H1D-related signaling pathway identified by GSEA

We performed GSEA to find out signaling pathways which are differentially activated between low HIST1H1D expression and high HIST1H1D expression data set in esophageal carcinoma. Differences in enrichment of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway (c2.cp.kegg.v7.2.symbols) were analyzed. The enriched pathways were selected according to the normalized enrichment score (NES) (Table 4). As shown in Fig. 3, pathways of alpha linolenic acid metabolism, arachidonic acid metabolism, histidine metabolism, vascular smooth muscle contraction, primary bile acid biosynthesis, phenylalanine metabolism and ether lipid metabolism were enriched in HIST1H1D high expression group.

Table 4
Gene set enriched in HIST1H1D high phenotype

Gene Set Name	NES	NOM p-val
KEGG_ALPHA_LINOLENIC_ACID_METABOLISM	1.84	0.006
KEGG_ARACHIDONIC_ACID_METABOLISM	1.84	0.000
KEGG_HISTIDINE_METABOLISM	1.88	0.004
KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION	1.79	0.017
KEGG_PRIMARY_BILE_ACID_BIOSYNTHESIS	1.74	0.021
KEGG_PHENYLALANINE_METABOLISM	1.71	0.012
KEGG_ETHER_LIPID_METABOLISM	1.51	0.031

NES: Normalized enrichment score; NOM: Nominal. Gene sets with NOM p-val < 0.05 were considered as significant.

4. Discussion

Histones and DNA are the two major components of chromatin. There are two groups of histones, referring as core histones and linker histones(30, 31). Wrapped by DNA on their surfaces, the core histones (H1A, H2B, H3 and H4) constitute the nucleosome core(31). The linker histones H1, locating on the entry and exit sites of the nucleosome core, link the nucleosome cores to form chromatins(32). Histone H1 play a vital role in maintaining the normal structure of chromatins(33). Somatic cell-specific histone H1 can be divided into 6 subtypes, H1.0-H1.5 and H1x. H1.3 gene, also known as HIST1H1D, was located on chromosome 6p21.3-22(34). Some studies indicated that HIST1H1D expression level was increased and was associated with prognosis in some malignant diseases, including acute myeloid leukemia, ovarian cancer, pancreatic ductal adenocarcinoma, et al(26–29). However, whether the prognosis of esophageal carcinoma was dependent on HIST1H1D was unknown. Therefore, we performed the current study to find out whether HIST1H1D was an independent prognostic predictor of esophageal carcinoma.

In this research, RNA-sequencing data and clinical information were downloaded from TCGA database. Bioinformatic analysis indicated HIST1H1D was increased in esophageal carcinoma. Increased

HIST1H1D was associated with poor survival. We further performed GSEA to find out the gene sets enriched in HIST1H1D high expression and low expression phenotypes respectively. It was suggested that increased HIST1H1D expression may serve as an independent predictor of poor prognosis in esophageal carcinoma.

HIST1H1D expression was increased in acute myeloid leukemia, ovarian cancer, pancreatic ductal adenocarcinoma et al (26–29). HIST1H1D promoted Fanconi anemia progressing into acute myeloid leukemia(27). High expression of HIST1H1D was associated with poor prognosis in AML patients(26, 27). In the current study, we found the consistent result in esophageal carcinoma by showing that HIST1H1D was increased in esophageal carcinoma and patients with increased HIST1H1D showed shorter survival time. However, another research showed that HIST1H1D was overexpression in the OVCAR-3 epithelial ovarian cancer cell line and overexpression of HIST1H1D suppressed the growth of ovarian cells by inhibiting the expression of noncoding RNA H19(35, 36).

However, the molecular mechanisms of HIST1H1D affecting the prognosis were poorly understood. In the current study, GSEA showed that alpha linolenic acid metabolism, arachidonic acid metabolism, histidine metabolism, vascular smooth muscle contraction, primary bile acid biosynthesis, phenylalanine metabolism and ether lipid metabolism were enriched in HIST1H1D high expression group.

Some studies have showed that arachidonic acid (AA) metabolism also played a key role in tumorigenesis(37, 38). In fumarylacetoacetate hydrolase (Fah)-deficient mice models, HBV x gene (HBx)-K130M/V131I-mutant variant activated the AKT/FOXO1 pathway and induced stronger inflammation via AA metabolism and promoted hepatocellular carcinoma progression(38). Another research investigated the protein-protein interaction network of enzymes in AA metabolism and found out that most of the key enzymes was increased, including PLA2G4A, ALOX5, LTA4H, PTGS and PTGES3. Increased expression of ALOX5, ALOX5AP, CYP2C8, CYP4F11, PLA2G4A, PTGES2 was related to shorter survival time(37). The correlation of alpha-linolenic acid (ALA) metabolism(39–44), histidine metabolism(45, 46), vascular smooth muscle contraction(47, 48), primary bile acid biosynthesis(49–51), phenylalanine metabolism(52–54) and ether lipid metabolism(55–57) with cancer was also reported. The correlation of HIST1H1D expression and the above pathways was firstly reported in this study and the underlying mechanism needs further exploration.

It should be noted that using mRNA to predict protein was not a perfect method, though an overall positive correlation was observed between protein and mRNA expression level(58). One limitation of our study was that the correlation between HIST1H1D mRNA expression level and protein level could not be assessed. Thus, further study is required.

5. Conclusion

HIST1H1D may serve as a potential prognostic predictor of poor survival in esophageal carcinoma. In addition, alpha linolenic acid metabolism, arachidonic acid metabolism, histidine metabolism, vascular smooth muscle contraction, primary bile acid biosynthesis, phenylalanine metabolism and ether lipid

metabolism, DNA replication and spliceosome pathways maybe the key signaling pathway regulated by HIST1H1D in esophageal carcinoma. Further study is needed to prove the biologic impact of HIST1H1D.

Abbreviations

TCGA, The Cancer Genome Atlas

GSEA, gene set enrichment analysis

GERD, gastroesophageal reflux disease

KEGG, Kyoto Encyclopedia of Genes and Genomes

NES, normalized enrichment score

AA, arachidonic acid

ALA, alpha-linolenic acid

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are available in the TCGA repository, <http://cancergenome.nih.gov/>.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

- SH, HH, ML, MZ and XP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis;

- Study concept and design: XP, MZ, SH, HH, ML, CT, RD, PD
- Acquisition of data: SH, HH and ML
- Analysis and interpretation of data: MZ and XP
- Drafting of the manuscript: SH, HH, ML
- Statistical analysis: MZ and XP
- Administrative, technical, or material support: CT, RD, PD
- Supervision: MZ and XP

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Figures

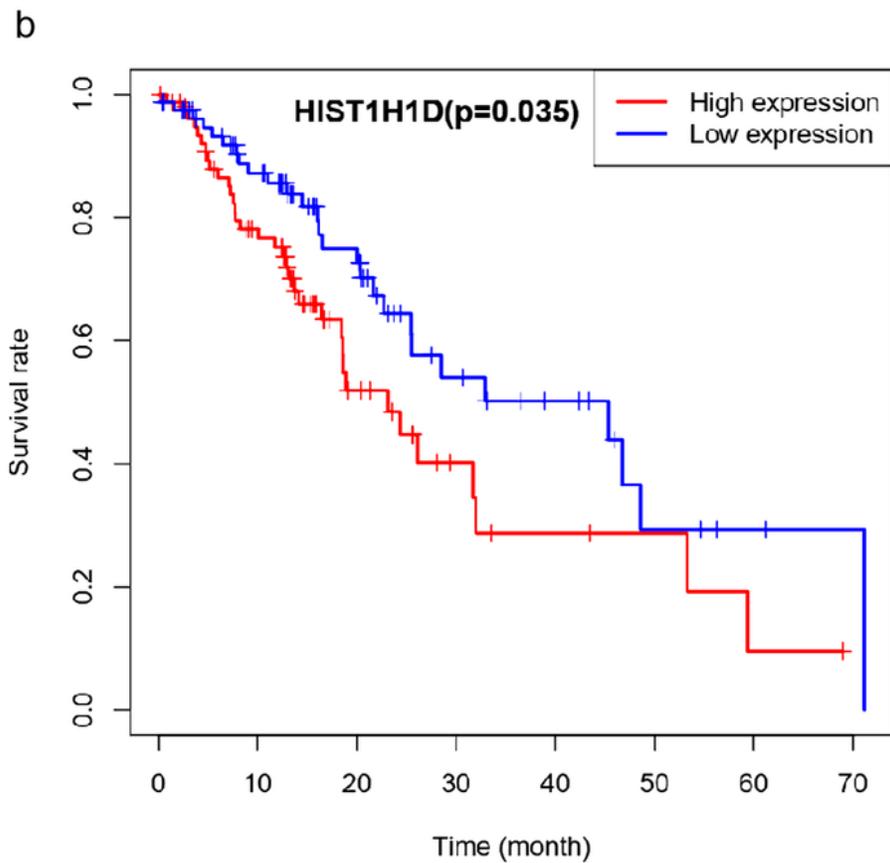
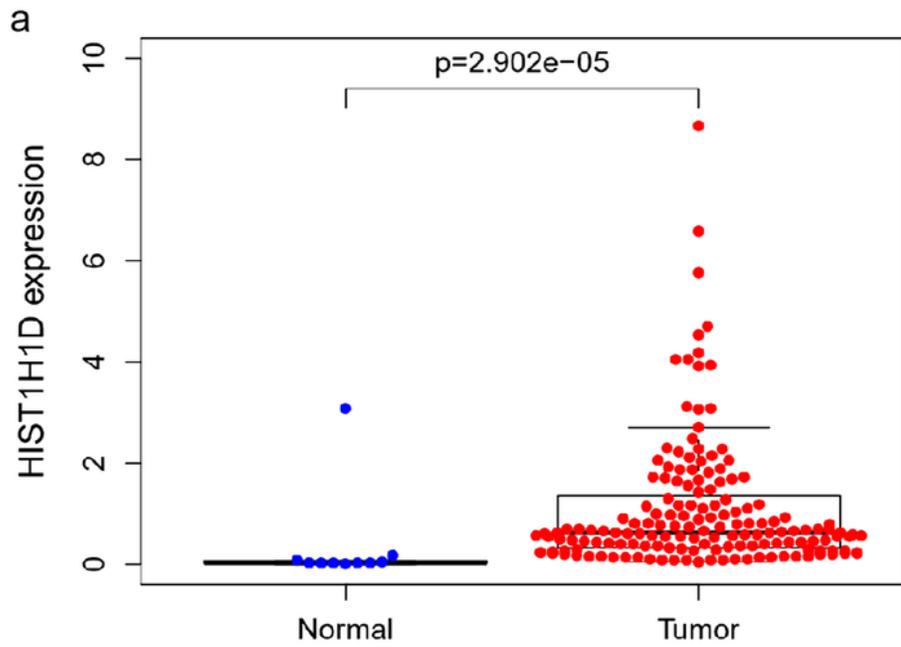


Figure 1

(A) HIST1H1D expression in esophageal carcinoma samples was significantly higher than normal samples (B) Kaplan-Meier analysis indicated that HIST1H1D high expression patients showed worse survival.

Hazard ratio

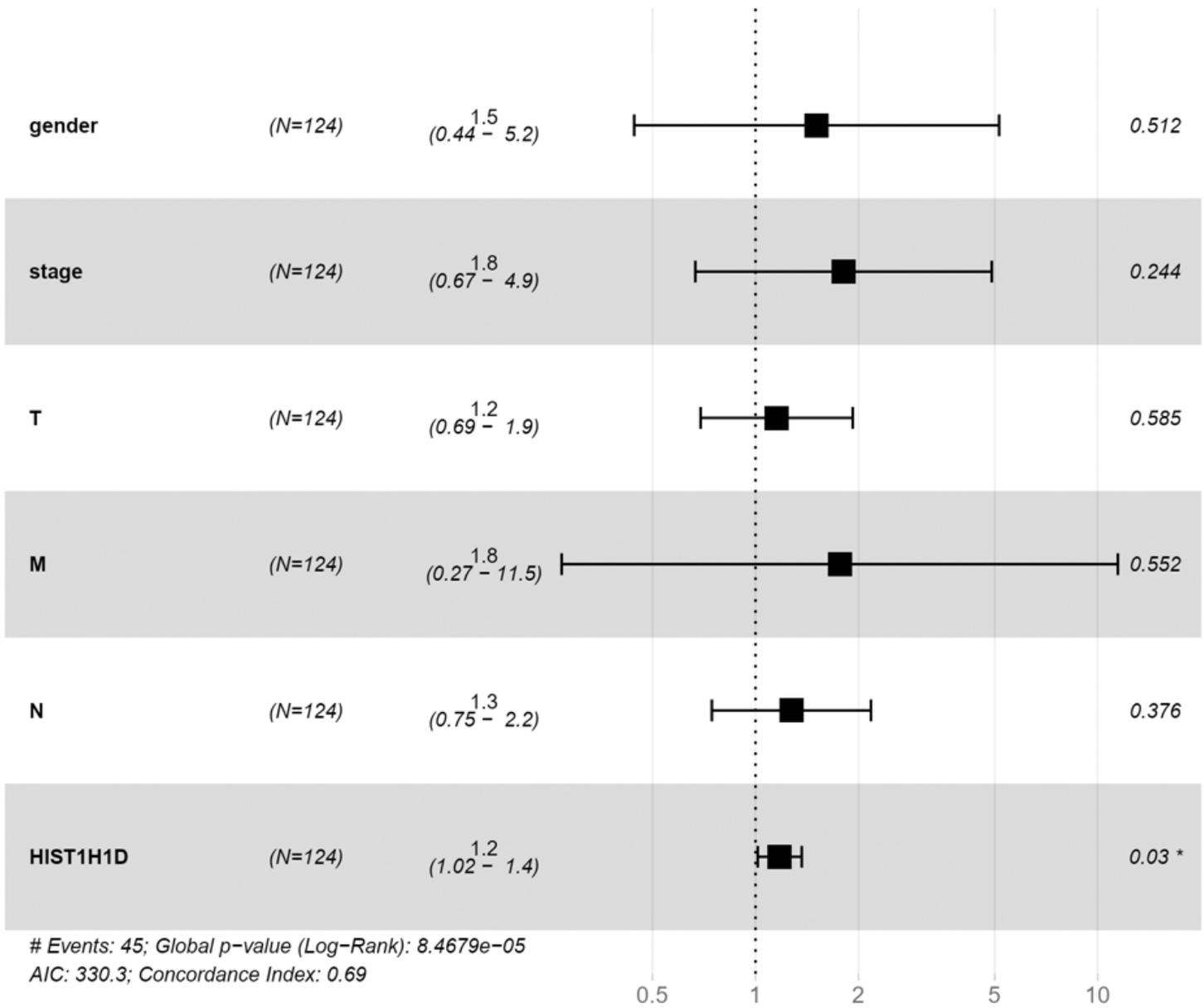


Figure 2

Multivariate analysis showed that high expression of HIST1H1D was an independent prognostic predictor.

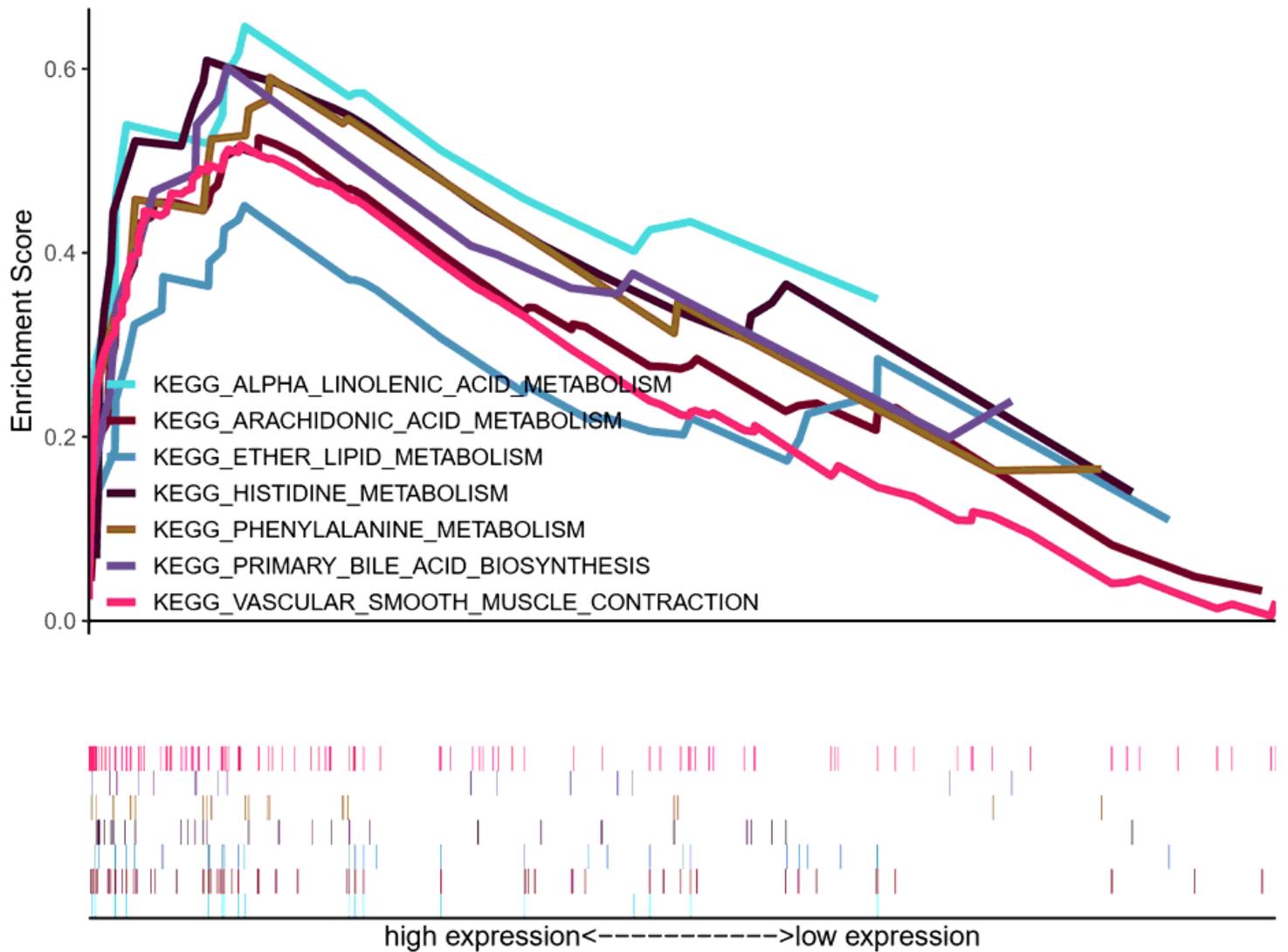


Figure 3

Results of gene set enrichment analysis showed that linolenic acid metabolism, arachidonic acid metabolism, histidine metabolism, vascular smooth muscle contraction, primary bile acid biosynthesis, phenylalanine metabolism and ether lipid metabolism were enriched in HIST1H1D high expression group.

Supplementary Files

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