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Research Article

Lactate Dehydrogenase B Exhibits Shared Overexpression but Divergent Prognostic Significance in Lung Adenocarcinoma and Lung Squamous Cell Carcinoma

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Abstract

Aim: Lactate dehydrogenase B (LDHB) is a metabolic enzyme increasingly implicated in non-small cell lung cancer (NSCLC), yet its comparative relevance across lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) remains unclear. We evaluated LDHB expression and prognostic value in both subtypes.

Material and Method: The Cancer Genome Atlas (TCGA) RNA-sequencing and clinical data for LUAD and LUSC were analyzed. Tumor-normal and paired comparisons used Wilcoxon tests, and tumor-normal discrimination was assessed by receiver operating characteristic (ROC) analysis. Overall survival (OS) was evaluated using Kaplan-Meier, log-rank, and Cox regression adjusted for age and pathological stage. Supporting analyses used Gene Expression Profiling Interactive Analysis (GEPIA), Encyclopedia of RNA Interactomes (ENCORI/starBase), Lung Cancer Explorer (LCE), Clinical Proteomic Tumor Analysis Consortium data accessed through UALCAN (UALCAN-CPTAC), and the Human Protein Atlas (HPA).

Results: LDHB was significantly upregulated in tumors in both LUAD ($p=6.997\times10^{-8}$) and LUSC ($p=1.687\times10^{-6}$), confirmed in paired samples and supported by external datasets. ROC discrimination was moderate (LUAD AUC 0.714; LUSC AUC 0.703). High LDHB was associated with poorer OS in LUAD (multivariable HR 1.476, 95% CI 1.024-2.127, p=0.0368) but not in LUSC (multivariable HR 0.963, 95% CI 0.692-1.342, p=0.8255). UALCAN-CPTAC showed a significant protein-level increase in LUAD but not LUSC, and the transcriptome-based HPA prognostic annotation classified LDHB as unfavorable in LUAD.

Conclusion: LDHB is a shared transcriptomic alteration across major NSCLC subtypes, but its prognostic and protein-level relevance is more pronounced in LUAD, supporting subtype-specific clinical significance rather than a universal NSCLC biomarker.

Keywords: Lactate dehydrogenase, lung adenocarcinoma, lung cancer, bioinformatics, proteomics

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide, accounting for approximately 2.5 million new cases and 1.8 million deaths in 2022 (1). This burden reflects late diagnosis, biological heterogeneity, treatment resistance, and the limited prognostic accuracy of conventional clinicopathological parameters in certain patient subsets.

NSCLC is the most common form and comprises two major histological subtypes, LUAD and LUSC. Although grouped under the NSCLC umbrella, they differ in cellular origin,

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genomic alterations, smoking-related biology, and therapeutic vulnerabilities (2). A molecular alteration shared at the expression level may therefore have different biological or prognostic implications across subtypes. TCGA confirmed distinct genomic and transcriptomic landscapes for LUAD and LUSC, establishing the basis for subtype-aware molecular interpretation (3,4).

Metabolic reprogramming is a hallmark of malignant transformation (5). In this context, lactate has shifted from a presumed waste product to a central oncometabolite: nutrient-infusion studies in patients show that human lung tumors actively take up and oxidize lactate as a major carbon source for the tricarboxylic acid cycle (6). Within this circuit, LDHB catalyzes the conversion of lactate to pyruvate, fueling mitochondrial oxidative metabolism, in contrast to the LDHA-driven pyruvate-to-lactate flux of the Warburg effect. While LDHA has dominated the glycolysis literature, LDHB supports KRAS-dependent LUAD growth (7). Recent functional studies show that LDHB sustains mitochondrial DNA integrity and nucleotide metabolism. Its silencing impairs tumorigenesis, reduces metastatic capacity by diminishing mitochondrial glutathione catabolism, and sensitizes NSCLC cells to radiotherapy (8-10). These findings position LDHB as a metabolically active, pro-tumor enzyme rather than a passive glycolytic readout.

Despite the growing functional literature, the comparative relevance of LDHB across LUAD and LUSC remains incompletely defined. Most evidence derives from LUAD models, KRAS-driven tumors, or pan-NSCLC cell lines. Histology-dependent prognostic effects of LDHB protein have been reported, and the Human Protein Atlas annotates LDHB as an unfavorable marker in LUAD (11,12). Whether LDHB represents a shared transcriptomic alteration with equivalent clinical meaning or a subtype-restricted prognostic marker remains unresolved, given integrated transcriptomic, proteomic, and survival evidence in both subtypes.

We therefore conducted an integrated bioinformatic analysis of LDHB in LUAD and LUSC, combining TCGA transcriptomic and clinical data, paired tumor-normal comparisons, ROC analysis, Kaplan-Meier and Cox survival modeling, external transcriptomic and survival validation (GEPIA, ENCORI, LCE), proteomic assessment (UALCAN-CPTAC), pathological evidence (HPA). The aim was to determine whether LDHB upregulation is shared across major NSCLC subtypes and whether its prognostic significance differs between LUAD and LUSC.

MATERIAL AND METHOD

This study was conducted exclusively using publicly available, de-identified secondary datasets (TCGA/GDC, GEPIA, ENCORI/starBase, Lung Cancer Explorer, UALCAN-CPTAC, Human Protein Atlas, and GEO). No human participants were recruited, no identifiable personal data were accessed, and no biological specimens were collected. Therefore, institutional ethics committee approval was not required.

Study Design and Data Sources

This integrated bioinformatic study evaluated LDHB expression, tumor-normal discrimination, prognostic relevance, and protein-level support in LUAD and LUSC. Publicly available transcriptomic, clinical, proteomic, and pathology datasets were analyzed using TCGA, GEPIA, ENCORI/starBase, LCE, UALCAN-CPTAC, and HPA. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for observational research (13) and the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) (14). The overall analytical workflow is summarized in Figure 1.

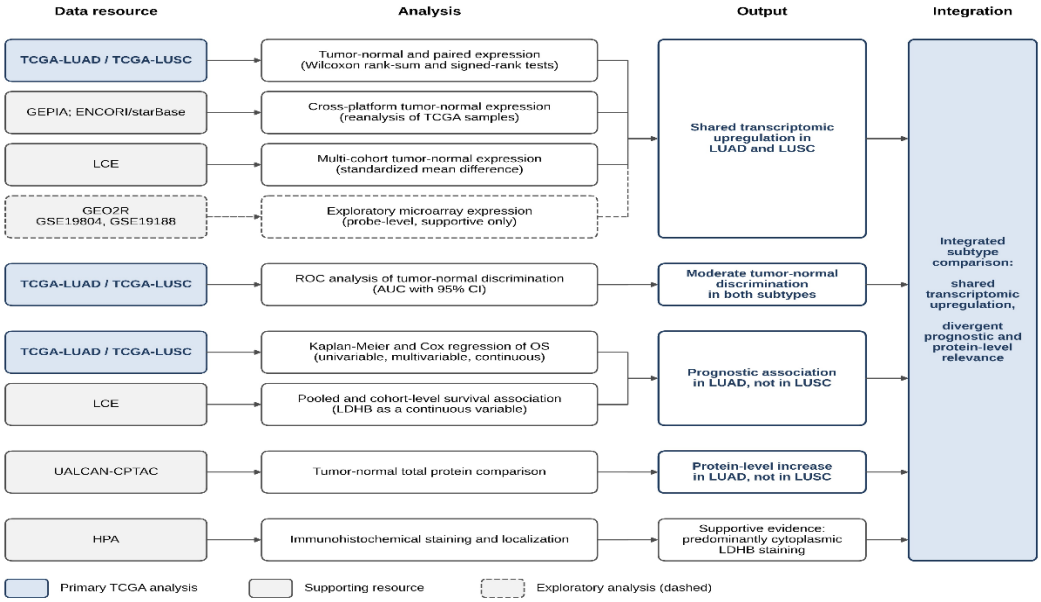

Figure 1. Integrated workflow for LDHB analysis in LUAD and LUSC. Arrows link each data resource to the analyses it supports and to the corresponding outputs. TCGA provides the primary expression, paired tumor-normal, ROC, and survival analyses. GEPIA and ENCORI/starBase provide cross-platform transcriptomic corroboration, and LCE provides multi-cohort expression and survival validation. UALCAN-CPTAC provides the tumor-normal protein comparison, and HPA provides supportive immunohistochemical staining and localization data. Exploratory GEO2R analyses, shown with dashed arrows, provide supplementary expression support. The outputs are integrated to compare LDHB expression and prognostic relevance between the two subtypes.

TCGA Data Acquisition and Preprocessing

RNA-sequencing data and clinical annotations for TCGA-LUAD and TCGA-LUSC were obtained from the Genomic Data Commons using the TCGAbiolinks R/Bioconductor package (15). STAR-counts quantification files were downloaded for primary tumor and solid tissue normal samples. The expression analysis included 540 primary tumor and 59 normal samples for LUAD, and 511 primary tumor and 51 normal samples for LUSC. LDHB expression was extracted from the tpm_unstrand assay and transformed as log2(TPM + 1).

TCGA Tumor-Normal and Paired Expression Analyses

LDHB expression was compared between tumor and normal tissues separately in each subtype using the Wilcoxon rank-sum test. Paired analyses in matched cases used the Wilcoxon signed-rank test; when multiple samples of the same type were available for a patient, mean expression was used. The ability of LDHB expression to discriminate tumor from normal tissue was assessed by ROC analysis with AUC values and 95% confidence intervals (CIs), computed with the pROC package (16). ROC results were interpreted as an effect-size summary rather than evidence of standalone diagnostic utility.

Survival Analysis and Cox Regression

OS was calculated from days_to_death when available and days_to_last_follow_up otherwise, then converted to months; status was coded 1 for deceased and 0 for living. Only primary tumors were used. Patients were dichotomized at the cohort-specific median LDHB value. Kaplan-Meier curves were compared by log-rank test. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% CIs.

Univariate models used high versus low LDHB; multivariate models were adjusted for age at diagnosis and pathological stage. LDHB was additionally modeled as a continuous log2 (TPM + 1) variable. Schoenfeld residuals were used to assess the proportional hazards assumption in the continuous models.

External Transcriptomic and Survival Validation

GEPIA was used to assess LDHB tumor-normal differences in LUAD and LUSC from TCGA and GTEx data (17); because GEPIA uses a separately reprocessed quantification pipeline, its absolute expression values are not directly comparable to the in-house TCGA values and were interpreted by direction and significance only. ENCORI/starBase pan-cancer differential expression provided fold-change, p, and false discovery rate (FDR) values (18). LCE was used to validate tumor-normal standardized expression differences and survival associations, reporting standardized mean difference (SMD), HR, z, and adjusted p values, together with available cohort-level outputs (19).

Exploratory GEO2R analysis (20) of GSE19804 (21) and GSE19188 (22) used Benjamini-Hochberg correction and auto-detected log transformation; because these were probe-dependent and, for GSE19188, of mixed histology, they were treated as supportive only

Protein and Pathology Analyses

Protein-level LDHB was evaluated with UALCAN-CPTAC by comparing normal and primary tumor tissues in LUAD and LUSC, with exploratory LUAD subgroup analyses by stage, grade, and subtype (23). We reviewed HPA for protein evidence, localization, cancer specificity, and staining pattern, and for its prognostic annotation, derived from TCGA RNA-sequencing and survival data (12).

Statistical Analysis and Visualization

TCGA analyses were performed in R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria). Wilcoxon rank-sum and signed-rank tests were used for unpaired and paired comparisons. A two-sided $p < 0.05$ was considered significant unless otherwise specified; adjusted p or FDR values were reported for external database analyses. Figures were generated with the ggplot2, ggpubr, survival, survminer, and pROC packages.

RESULTS

LDHB Is Upregulated in TCGA-LUAD and TCGA-LUSC

LDHB expression was significantly higher in tumor than normal tissue in both subtypes. In LUAD, median log2 (TPM + 1) was 3.84 in tumors versus 3.26 in normal tissue (n = 540 vs 59; Wilcoxon $p = 6.997 \times 10^{-8}$). In LUSC, median values were 3.58 versus 2.92 (n = 511 vs 51; $p = 1.687 \times 10^{-6}$). LDHB upregulation is thus a shared transcriptomic alteration in both subtypes (Figure 2).

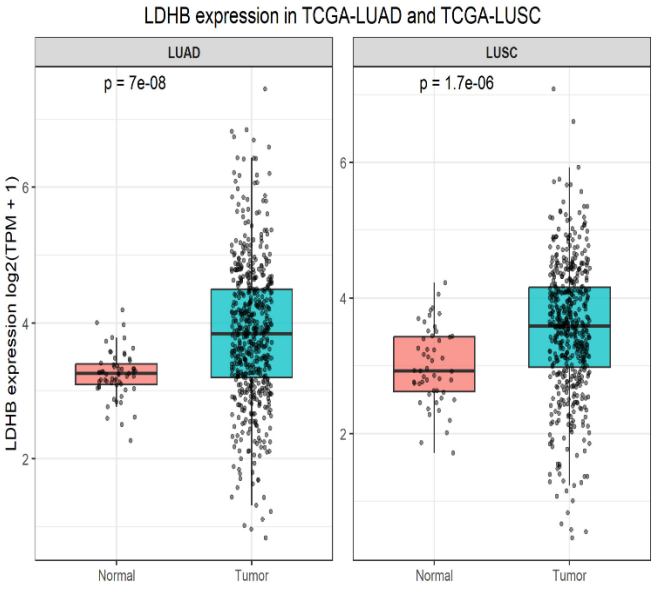

Figure 2. LDHB transcriptomic upregulation in TCGA-LUAD and TCGA-LUSC. Boxplots compare LDHB expression (log2[TPM + 1]) between normal and tumor tissue in each subtype. Boxes show the median and interquartile range; whiskers extend to 1.5 times the interquartile range; points represent individual samples. P values are from the Wilcoxon rank-sum test (LUAD, n = 540 tumor vs 59 normal, $p = 6.997 \times 10^{-8}$; LUSC, n = 511 tumor vs 51 normal, $p = 1.687 \times 10^{-6}$); values displayed in the panels are rounded.

Paired Analysis Confirms Upregulation

Matched tumor-normal pairs reproduced this pattern. In 58 LUAD pairs, median LDHB rose from 3.251 to 3.692 (median difference 0.483 log2 units; paired Wilcoxon $p = 2.021 \times 10^{-4}$). In 51 LUSC pairs, it rose from 2.923 to 3.586 (median difference 0.570; $p = 3.498 \times 10^{-5}$), supporting LDHB upregulation as a recurrent tumor-associated event independent of inter-individual variability (Figure 3).

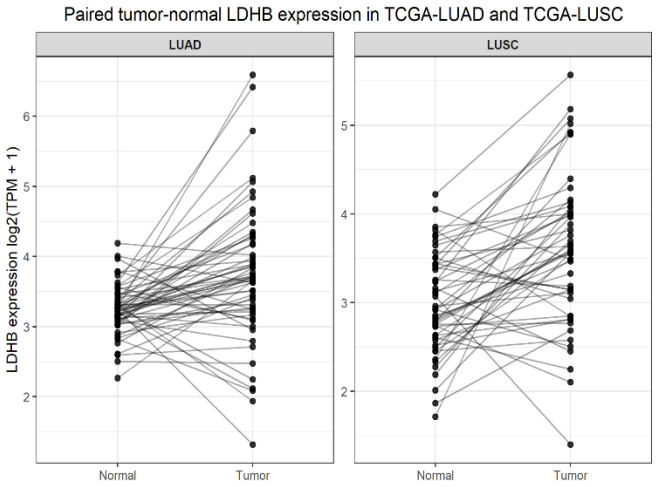

Figure 3. Paired tumor-normal LDHB expression in TCGA-LUAD and TCGA-LUSC. Lines connect matched tumor and normal samples from the same patient (LUAD, 58 pairs; LUSC, 51 pairs). Expression is shown as log2 (TPM + 1). Comparisons used the Wilcoxon signed-rank test (LUAD, $p = 2.021 \times 10^{-4}$; LUSC, $p = 3.498 \times 10^{-5}$).

Moderate Tumor-Normal Discrimination

ROC analysis showed moderate discrimination, with AUC 0.714 (95% CI 0.670-0.757) in LUAD and 0.703 (95% CI 0.645-0.761) in LUSC. LDHB therefore captures a measurable tumor-associated shift but does not reach standalone diagnostic performance (Figure 4).

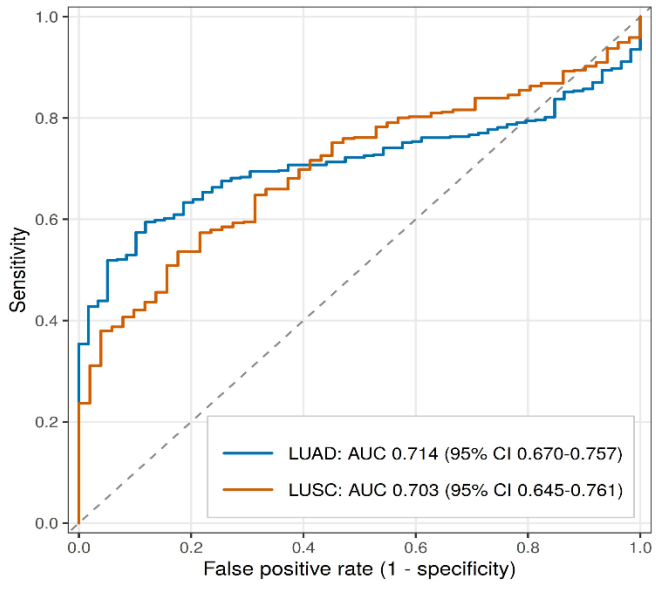

Figure 4. ROC analysis of LDHB for discriminating tumor from normal tissue. AUC values are 0.714 (95% CI 0.670-0.757) for LUAD and 0.703 (95% CI 0.645-0.761) for LUSC. The diagonal indicates random performance.

External Transcriptomic Validation

GEPIA and ENCORI/starBase reproduced the direction and significance of LDHB upregulation in both subtypes. In GEPIA, LDHB was higher in tumors for LUAD ($p = 1.66 \times 10^{-21}$) and LUSC ($p = 1.32 \times 10^{-23}$). ENCORI/starBase confirmed increased expression in LUAD (fold-change 2.03, $p = 1.9 \times 10^{-5}$, FDR $= 7.7 \times 10^{-5}$) and LUSC (fold-change 1.94, $p = 1.3 \times 10^{-5}$, FDR $= 4.1 \times 10^{-5}$).

Subtype-Specific Survival Association

LDHB showed a subtype-specific link to OS. In TCGA-LUAD (443 patients; 221 low, 222 high), high LDHB was associated with worse OS (log-rank p = 0.0276; univariate HR 1.387, 95% CI 1.035-1.859, p = 0.0284) (Figure 5).

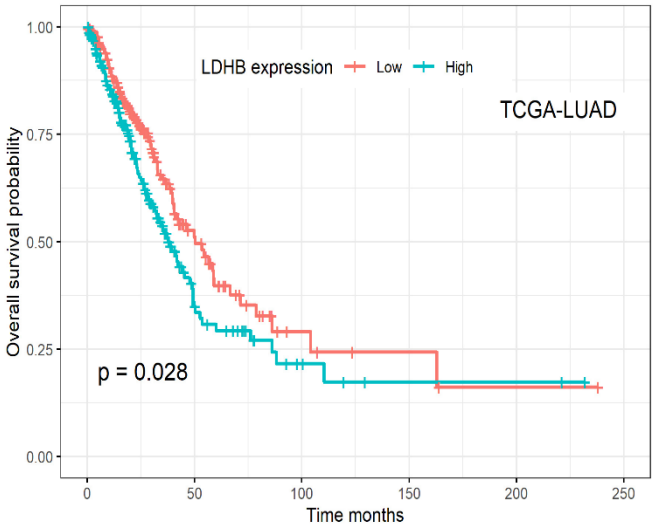

Figure 5. Kaplan-Meier overall survival in TCGA-LUAD stratified by LDHB expression. Patients were dichotomized at the cohort-specific median (low, n = 221; high, n = 222). Groups were compared by the log-rank test (p = 0.0276).

In TCGA-LUSC (470 patients; 235 low, 235 high), no association was seen (log-rank p = 0.6882; HR 0.946, 95% CI 0.722-1.240, p = 0.6883) (Figure 6).

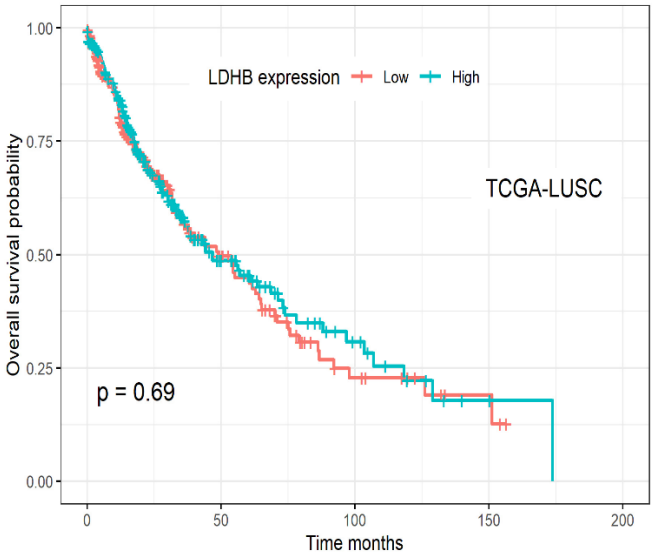

Figure 6. Kaplan-Meier overall survival in TCGA-LUSC stratified by LDHB expression. Patients were dichotomized at the cohort-specific median (low, n = 235; high, n = 235). Groups were compared by the log-rank test (p = 0.6882).

Adjusted and Continuous Models

After adjustment for age and pathological stage, high LDHB remained associated with poorer OS in LUAD (HR 1.476, 95% CI 1.024-2.127, p = 0.0368) but not in LUSC (HR 0.963, 95% CI 0.692-1.342, p = 0.8255) (Figure 7). Modeled continuously, LDHB was associated with OS in LUAD on univariate analysis (HR 1.182, 95% CI 1.021-1.368, p = 0.0256) but lost significance after adjustment (HR 1.133, 95% CI 0.945-1.359, p = 0.1767); LUSC showed no association in either model. Schoenfeld testing showed no major violations in the continuous models.

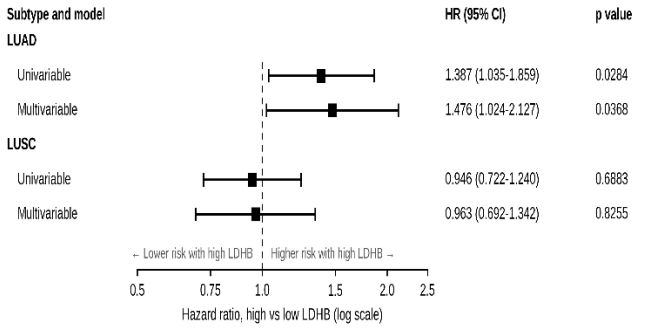

Figure 7. Cox regression analysis of LDHB expression and overall survival in TCGA-LUAD and TCGA-LUSC. The forest plot shows HRs for high versus low LDHB expression, with low expression as the reference group; patients were dichotomized at the cohort-specific median. HRs, 95% CIs, and Cox regression p-values are displayed for univariable and multivariable models. Multivariable models were adjusted for age at diagnosis and pathological stage. In LUAD, the univariable HR was 1.387 (95% CI 1.035-1.859; p = 0.0284) and the adjusted HR was 1.476 (95% CI 1.024-2.127; p = 0.0368). In LUSC, the corresponding HRs were 0.946 (95% CI 0.722-1.240; p = 0.6883) and 0.963 (95% CI 0.692-1.342; p = 0.8255). The horizontal axis is on a logarithmic scale, and the dashed vertical line indicates HR = 1.

External Validation

External validation in Lung Cancer Explorer (LCE) reproduced both the expression and survival patterns. LDHB upregulation was confirmed by a significant standardized mean difference in LUAD (0.577, 95% CI 0.123-1.031, adjusted p = 0.0230) and LUSC (0.457, 95% CI 0.098-0.816, adjusted p = 0.0227) (Figure 8A). For overall survival, LCE reproduced the subtype-specific pattern: higher LDHB was associated with worse OS in LUAD (HR 1.087, z = 2.575, p = 0.0100, adjusted p = 0.0432) but not in LUSC (HR 1.061, z = 1.430, p = 0.1527, adjusted p = 0.7484), with a small LUAD effect size consistent with a modest prognostic contribution (Figure 8B). Cohort-level outputs were heterogeneous: high LDHB was significantly unfavorable in Rousseaux_2013 (HR 1.441, p = 0.010) and Botling_2013 (HR 1.480, p = 0.019), showed a non-significant unfavorable trend in Okayama_2012 (HR 1.628, p = 0.187), and was non-significant in the opposite direction in Der_2014 (HR 0.889, p = 0.607). The unfavorable association was therefore reproducible in some but not all independent cohorts (Figure 8C).

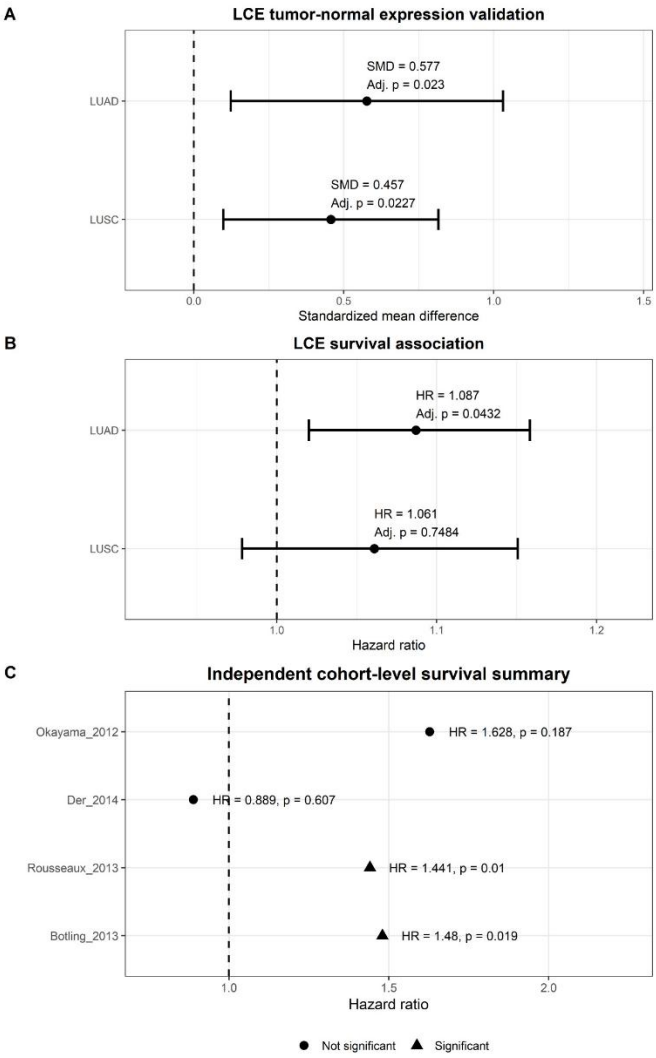

Figure 8. External validation in Lung Cancer Explorer (LCE). (A) Tumor-normal expression differences in LUAD and LUSC, expressed as standardized mean differences (SMDs) with 95% CIs. (B) Overall survival associations for LDHB expression modeled as a continuous variable, expressed as HRs with 95% CIs. Adjusted p values are reported in panels A and B. (C) Independent cohort-level survival associations; filled triangles indicate statistically significant associations (p < 0.05) and filled circles indicate non-significant associations. Values displayed in the panels are rounded; exact values are given in the Results.

Exploratory GEO2R Analyses

In GSE19804, two LDHB probes showed positive tumor-versus-normal log fold-change without reaching significance after correction. In GSE19188, probe 201030_x_at showed a borderline non-significant increase. These directionally consistent but non-significant results were retained as supplementary support only.

Supportive Protein and Pathology Evidence

Protein-level assessment using UALCAN-CPTAC showed a significant LDHB total protein difference in LUAD, whereas no significant difference was observed in LUSC. HPA immunohistochemistry data further indicated protein-level evidence for LDHB with predominantly cytoplasmic staining, and the transcriptome-based HPA prognostic annotation classified LDHB as unfavorable in LUAD. These

findings were considered supportive and were not used as primary evidence.

LDHB was consistently upregulated at the transcriptomic level in both subtypes across TCGA, paired analysis, GEPIA, ENCORI/starBase, and LCE. Survival and protein analyses, however, revealed a subtype-dependent pattern, with significant prognostic relevance and protein-level support in LUAD but not in LUSC.

DISCUSSION

This integrated analysis shows a dual pattern: LDHB is commonly upregulated at the transcriptomic level in both major NSCLC subtypes, whereas its prognostic and protein-level relevance is more evident in LUAD. The transcriptomic finding was consistent across TCGA, paired analysis, and three external resources, and the paired design reduces inter-individual variability, supporting LDHB upregulation as a tumor-associated event rather than a cohort artifact.

The contribution here is not the discovery that LDHB carries prognostic weight in LUAD, which prior protein-level work and HPA annotation already indicated (11,12). It is the multi-omic demonstration that transcriptomic upregulation is shared between LUAD and LUSC while prognostic and proteomic support diverge, refining LDHB from a generic NSCLC marker toward a subtype-specific one.

ROC analysis indicated moderate tumor-normal discrimination in both subtypes. Because LDHB is, by design, differentially expressed in the same cohorts, this reflects in-sample effect size rather than validated diagnostic accuracy. LDHB is better viewed as one component of a broader metabolic dysregulation profile than as a standalone diagnostic marker.

The prognostic results require careful interpretation. In LUAD, the categorical median-split model remained significant after adjustment for age and stage, yet the continuous model lost significance after the same adjustment. This discordance is compatible with a threshold-dependent or non-linear effect, but it also raises the possibility that the categorical signal is partly driven by dichotomization. The continuous adjusted estimate is the more conservative one, and the LUAD prognostic effect should therefore be presented as modest and in need of confirmation rather than as a robust independent predictor. Consistent with this, the external LCE LUAD hazard ratio, although significant, was small. Late-time convergence of the LUAD survival curves further indicates that the proportional hazards assumption should be interpreted cautiously for the dichotomized model.

By contrast, LUSC showed transcriptomic upregulation without a survival association in either TCGA or LCE, and without a protein-level difference in CPTAC. The convergence of these independent layers strengthens the conclusion that expression change alone does not imply prognostic relevance in LUSC. This subtype divergence is consistent with histology-dependent LDHB associations previously reported at the protein level (11).

A biologically plausible basis for the LUAD-predominant effect involves metabolic plasticity and oncogene-linked redox dependency. Convergent functional work indicates that LDHB protects tumor cells from oxidative death: it noncanonically promotes ferroptosis defense in KRAS-driven lung cancer by supporting glutathione metabolism (24), maintains the mitochondrial glutathione catabolism required for invasion and metastasis (9), and limits mitochondria-associated ferroptosis by modulating the ubiquinone-to-ubiquinol ratio in parallel with GPX4 and DHODH (25). Across these studies LDHB silencing is consistently anti-tumor, which is mechanistically concordant with the unfavorable direction of high LDHB observed here in LUAD. Because KRAS-mutant, redox-adapted tumor states are common in molecularly heterogeneous LUAD but uncommon in LUSC, this redox-protective function offers a coherent, though unproven, explanation for the subtype divergence. A complementary and more speculative possibility is epigenetic: lactate accumulation drives histone and protein lactylation, an emerging modification linked to LUAD prognosis and immune phenotype (26), and whether LDHB-associated lactate handling intersects this axis in a subtype-specific manner remains untested. Driver mutation status was not available as a covariate, and because KRAS jointly shapes LDHB biology and LUAD outcome, the observed LUAD association may be partly confounded by driver context.

Supportive proteomic data are consistent with the subtype distinction. A significant LDHB protein difference in LUAD but not in LUSC suggests that mRNA upregulation is more likely to translate into protein-level change in adenocarcinoma. The absence of a protein difference in LUSC despite mRNA upregulation may reflect post-transcriptional regulation, protein turnover, stromal composition, or platform differences, consistent with the distinct proteogenomic landscape of LUSC (27). HPA findings support LDHB as a biologically relevant but low-specificity protein, indicating that it should not be read as a lung cancer-specific biomarker but rather as context-dependent, emerging most clearly when expression, survival, subtype, and protein evidence are considered together (12).

Several limitations apply. The study is retrospective and based on public datasets, precluding causal inference, and these datasets differ in processing, normalization, and clinical annotation. Survival models were limited to age and stage; treatment, recurrence, driver mutation, and comorbidity data were not uniformly available. External validation was partly heterogeneous, with one independent cohort showing an opposite, non-significant effect, and much of the supporting mechanistic literature derives from a limited number of groups and cell-line models; therefore, independent functional validation in subtype-defined cohorts is still required. No multiplicity control was applied across the full set of platform analyses, so individual external p-values should be read as supportive rather than confirmatory. Finally, no functional experiments were performed, so it remains open whether LDHB contributes

directly to LUAD progression or reflects broader metabolic reprogramming.

CONCLUSION

LDHB is significantly upregulated at the transcriptomic level in both LUAD and LUSC, supporting its role as a shared marker of metabolic dysregulation in major NSCLC subtypes. Its prognostic and protein-level relevance, however, is more pronounced in LUAD, indicating subtype-specific clinical significance. LDHB may therefore represent a candidate metabolic prognostic marker in LUAD rather than a universal NSCLC biomarker, although its survival effect in LUAD is modest and requires confirmation. Prospective and functional studies, including driver-stratified analyses and combination with other metabolic, hypoxic, or immune markers, are warranted.

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Conflict of interest: The authors declare no conflicts of interest.

Ethical approval: This article does not require ethics committee approval as it does not involve human or animal studies.

Informed consent: Not applicable.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author.

Author contributions: Concept, Design, Control Data Collection and/or Processing, Analysis and/or Interpretation, Literature, Review, Article Writing, Critical Review: E.N.Y.T.

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