

RNA expression-based hypoxia score as a prognostic and predictive biomarker in hepatocellular carcinoma (HCC)

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Background

- Hepatocellular carcinoma (HCC) has rising incidence and mortality rates.
- Tumor hypoxia is important in HCC pathogenesis but has not been effectively translated into practice.
- We studied whether an RNA expression-based hypoxia score (HS) can serve as a prognostic and predictive biomarker in HCC.

Methods

- Solid tumors across a range of tissues (N=91516) were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome), including 1382 HCC tumors.
- Mutation prevalence (-Mt) was calculated for pathogenic SNVs/indels.
- PD-L1 expression (SP142; +: ≥2+, ≥5%) tested by IHC.
- HS based on RNA expression of 15 genes and normalized across a range of solid tumors was implemented as previously described (Bhandari et al, 2019). Tumors were defined as HS high (-H), medium (-M) and low (-L) by a combination of hierarchical clustering and empirically setting thresholds.
- A transcriptomic signature associated with immunotherapy response (T-cell inflamed score) was applied.
- Fisher's Exact/ χ^2 tests were applied as appropriate with p-values adjusted for multiple comparisons ($p < 0.05$).
- Real-world overall survival (OS) data was obtained from insurance claims, and log-rank estimates were calculated for molecularly defined subpopulations.

Results

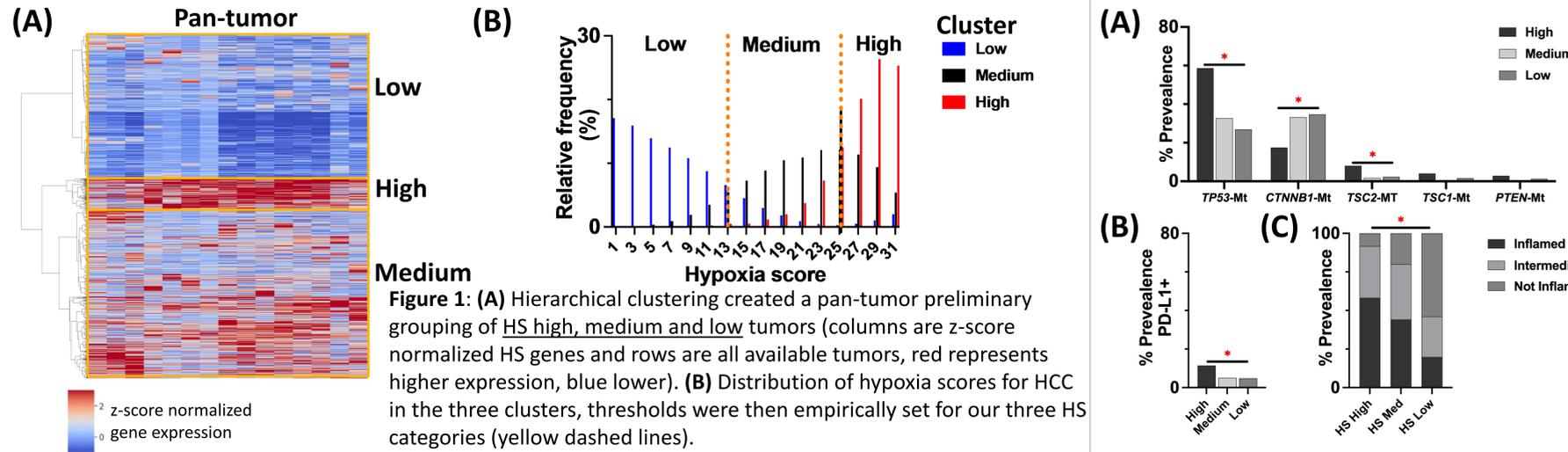


Table 1: Demographic data for HCC tumors

HCC	HS High	HS Med	HS Low	q-value
Count (N)	285	194	903	
Median Age [range]	67 [13 - >89]	67 [19 - 89]	67 [13 - >89]	0.865
% Male	76.1% (217/285)	73.2% (142/194)	77.5% (700/903)	0.530

Figure 3:

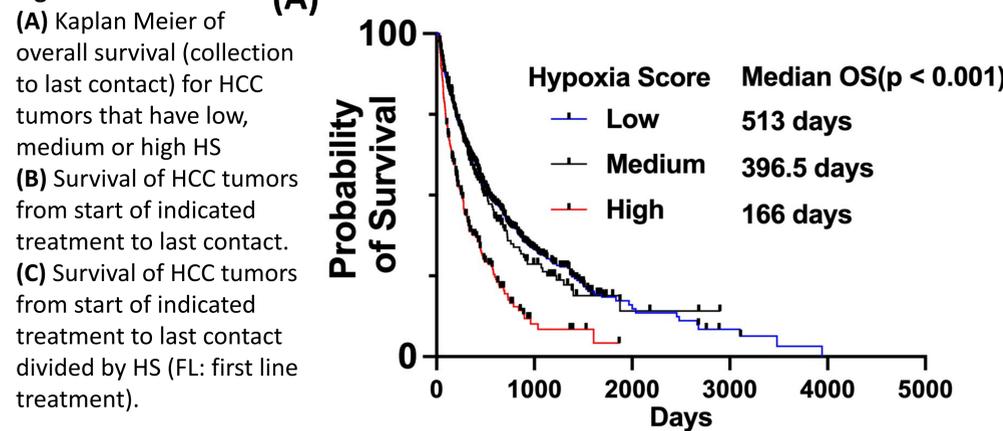


Figure 2: (A) landscape of genomic alteration in HCC (all statistically significant alterations are shown in addition to TSC1 and PTEN-Mt) (B) Prevalence of PD-L1 positivity (C) Prevalence of T cell-inflamed tumors.

Study Highlights

- In HCC, RNA expression-based HS high is associated with a higher prevalence of *TP53*-Mt and a lower rate of *CTNNB1*-Mt
- High HS is also associated with a more inflamed immune microenvironment.
- HS high tumors had worse OS.
- There was no significant difference in survival when segmenting HS-high, medium and low tumors by the first-line treatments that they received.

Conclusions

- HS is a potential prognostic biomarker in HCC that merits validation in orthogonal data sets and prospective studies.

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