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MATTERS ARISING

Comment on: Low expression of HSP27 and HSP70 predicts poor prognosis in laryngeal squamous cell carcinoma

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Abstract

Borowczak et al. recently explored the prognostic role of heat shock proteins HSP27 and HSP70 in laryngeal squamous cell carcinoma (LSCC). Their study demonstrated that lower expression levels of these proteins were linked to significantly reduced overall survival, suggesting potential utility as prognostic biomarkers in this patient population. This work adds important evidence to the limited pool of molecular predictors available for LSCC. However, paradoxical findings, such as the survival advantage observed with higher HSP expression despite their well-known cytoprotective roles, raise questions regarding underlying mechanisms. Factors such as subcellular localization, treatment intensity, and environmental exposures like alcohol consumption may influence these associations. Consequently, further translational research is needed to validate the prognostic significance of HSP27 and HSP70 and to clarify their clinical applicability in LSCC management.

Keywords Laryngeal squamous cell carcinoma · Heat shock proteins · HSP27 · HSP70 · Prognostic biomarkers · Subcellular localization · Alcohol consumption

Dear Editor,

We congratulate Borowczak et al. on their recent article, which examines the prognostic value of HSP27 and HSP70 in survival outcomes for patients with laryngeal squamous cell carcinoma (LSCC) (Borowczak et al. 2025). Study results revealed that low expression of HSP27 and HSP70 predicts poor overall survival in this population. This study makes a valuable contribution to ongoing efforts seeking dedicated prognostic biomarkers for LSCC, where such indicators remain limited. However, several aspects warrant further discussion to clarify the clinical utility and translational relevance of these biomarkers.

First, the authors observed that HSP27 was significantly overexpressed in tumor tissues relative to adjacent controls, with expression correlating to higher tumor stage and nodal metastasis. Paradoxically, low HSP27 expression emerged as an independent predictor of shorter survival in this study and in The Cancer Genome Atlas Program cohort. This finding contrasts with the protein's well-documented anti-apoptotic and pro-survival role in oncogenesis, where overexpression typically correlates with therapy resistance and worse prognosis (Lee et al. 2007; Albakova et al. 2020). One possible explanation, as the authors suggest, is that HSP27 overexpression in advanced tumors may coincide with more intensive multimodal treatment, indirectly linking higher expression to improved survival. Another explanation relates to subcellular localization. Kaigorodova et al. reported that nuclear and cytoplasmic HSP27 carry distinct prognostic implications in LSCC,

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with nuclear HSP27 regulating transcription and DNA repair, and cytoplasmic HSP27 primarily mediating apoptosis inhibition (Kaigorodova et al. 2016). Ignoring this spatial heterogeneity may obscure clinically relevant associations and contribute to conflicting prognostic results. Future studies should employ spatial proteomics or multiplex immunohistochemistry to achieve high-resolution mapping of protein expression within distinct cellular compartments. Such approaches will clarify compartment-specific functions of HSP27 and other heat shock proteins, refining their prognostic utility in LSCC.

Second, although ethanol is a classical stressor that typically induces HSP expression acutely, the authors observed that chronic alcohol consumption was associated with lower intratumoral HSP27 levels. Experimental evidence suggests that prolonged ethanol exposure may inhibit HSP transcription, likely via sustained oxidative stress, acetaldehyde-induced protein adduct formation, and epigenetic modifications of stress-responsive genes (Nakahara et al. 2006). These findings indicate that chronic alcohol disrupts cellular defense pathways, promoting carcinogenesis while diminishing the prognostic relevance of stress proteins. Importantly, this highlights the importance of considering lifestyle and environmental exposures when interpreting HSP expression as a biomarker. Supporting this notion, alcohol consumption can modify the prognostic value of established biomarkers. For example, body mass index predicted survival only among alcohol users with esophageal squamous cell carcinoma, not in abstainers (Chen et al. 2022). Even low-to-moderate alcohol intake introduces inter-individual variability in molecular biomarkers, complicating efforts to establish consistent correlations (Constantini et al. 2023). Consequently, prospective studies integrating epidemiological factors with molecular profiling are essential to elucidate these complex interactions and improve the reliability of HSP-based prognostication.

Third, the prognostic relevance of HSP70 remains a contentious issue. While the authors reported no difference in tissue expression between tumor and normal mucosa, higher expression correlated with tumor grade, and low expression predicted worse survival. This contrasts with studies in gastrointestinal and genitourinary cancers, where HSP70 overexpression typically indicates poor prognosis due to its role in apoptosis inhibition, oncogenic signaling stabilization, and immune evasion (Albakova et al. 2020; Gao et al. 2021). These discrepancies may reflect context-specific biological factors in LSCC, likely stemming from unique tumor-host interactions within the aerodigestive tract. Furthermore, relying solely on transcriptomic data may not fully capture the post-transcriptional regulation of HSP70, including phosphorylation and acetylation that affect protein stability and function. Integrating proteomic and post-translational datasets will be crucial to refine the prognostic interpretation of HSP70 in this setting.

From a therapeutic perspective, the dual role of HSP27 and HSP70 as cytoprotective proteins and potential biomarkers presents both challenges and opportunities. Preclinical studies demonstrate that silencing HSP27 enhances radiosensitivity and restores cisplatin responsiveness (Aloy et al. 2008), while HSP70 inhibition promotes apoptosis and modulates DNA repair pathways (Dimas et al. 2018). Nevertheless, the paradoxical association of higher HSP expression with improved prognosis in LSCC, combined with modulation by lifestyle factors such as alcohol, suggests that direct clinical translation is premature. Longitudinal assessment of HSP expression before and after therapy is recommended to distinguish intrinsic tumor biology from treatment-induced or environmentally influenced changes.

In conclusion, Borowczak et al. provide compelling evidence that HSP27 and HSP70 may serve as prognostic biomarkers in LSCC. However, observed paradoxes highlight the complexity of HSP biology in cancer. Mechanistic studies addressing subcellular localization, treatment-induced modulation, and post-translational regulation are necessary to elucidate their clinical role fully.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no conflict of interest.

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