Molecular expression of glycosaminoglycans modifies the plasticity of biphasic mesothelioma in favor of tumor progression

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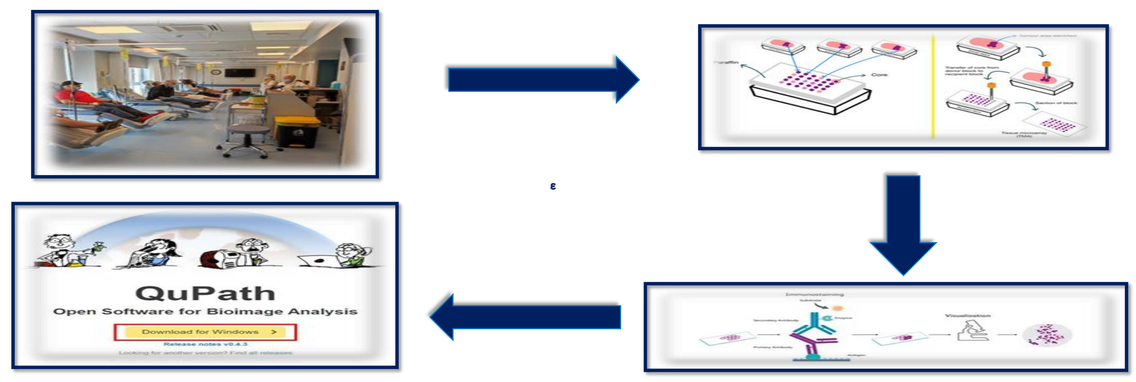
Introduction

Malignant pleural mesothelioma (MPM) is a rare and highly aggressive malignancy with a steadily increasing incidence worldwide. It does not follow the classical molecular model of cancer progression and lacks typical genetic alterations, while exhibiting profound molecular and histological heterogeneity. This heterogeneity is a major factor underlying therapeutic failure and poor clinical outcomes. Histologically, MPM is classified into epithelioid, sarcomatoid, and biphasic subtypes, with biphasic MPM representing an especially heterogeneous and aggressive phenotype composed of both epithelioid and sarcomatoid elements. Tumor lineage plasticity, enabling phenotypic transitions between these histotypes, promotes tumor progression, invasiveness, and resistance to therapy. Increasing evidence suggests that MPM tumors exist along a continuous phenotypic spectrum rather than as rigid histological categories. The extracellular matrix (ECM) of the pleura plays a fundamental role in regulating tumor behavior and mechanics. In particular, glycosaminoglycans (GAGs) and proteoglycans (PGs) are key ECM components involved in cell–matrix interactions, tissue remodeling, and inflammatory responses. Alterations in their expression may critically influence MPM plasticity and disease progression.

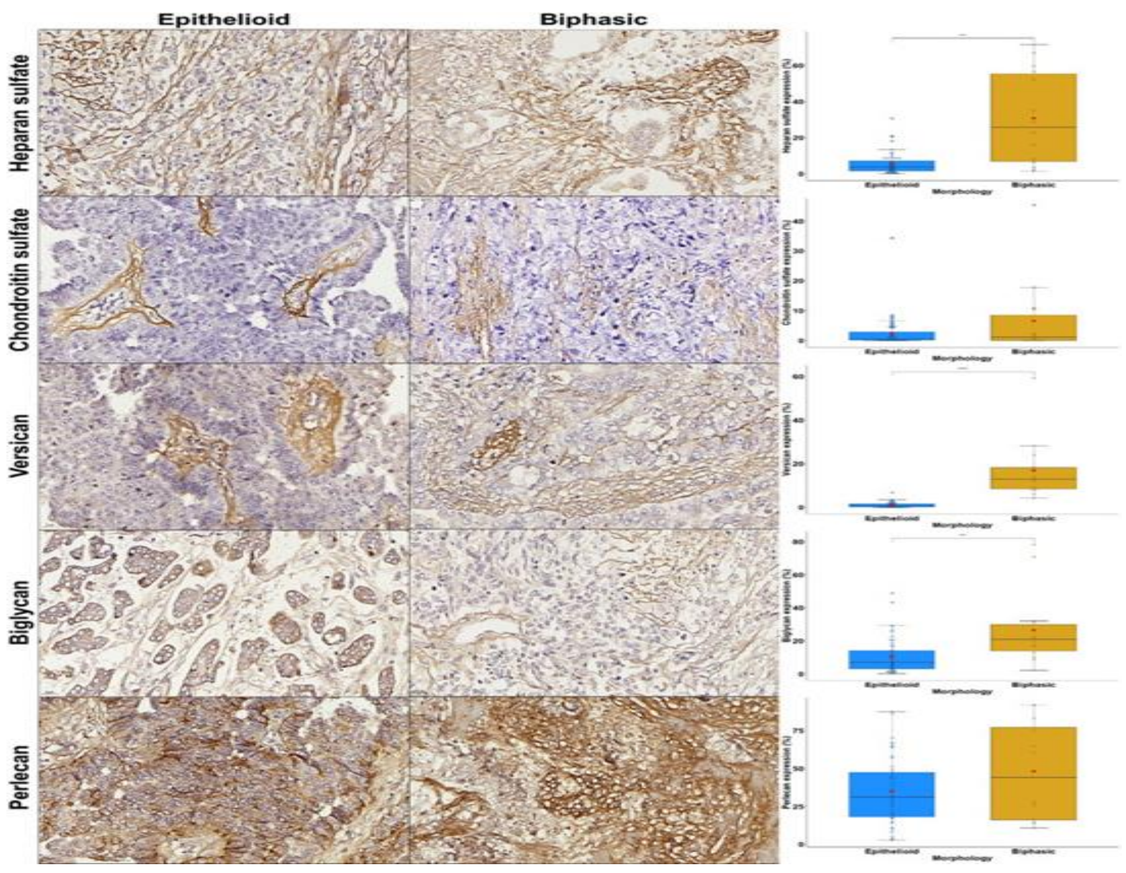
Aim

The aim of this study was to investigate the role of extracellular matrix glycosaminoglycans (GAGs) and proteoglycans (PGs) in the plasticity of biphasic malignant pleural mesothelioma. Specifically, we sought to evaluate the expression of heparan sulfate, chondroitin sulfate, versican, biglycan, and perlecan and to correlate their distribution with tumor phenotype, disease progression, therapeutic resistance, and patient prognosis

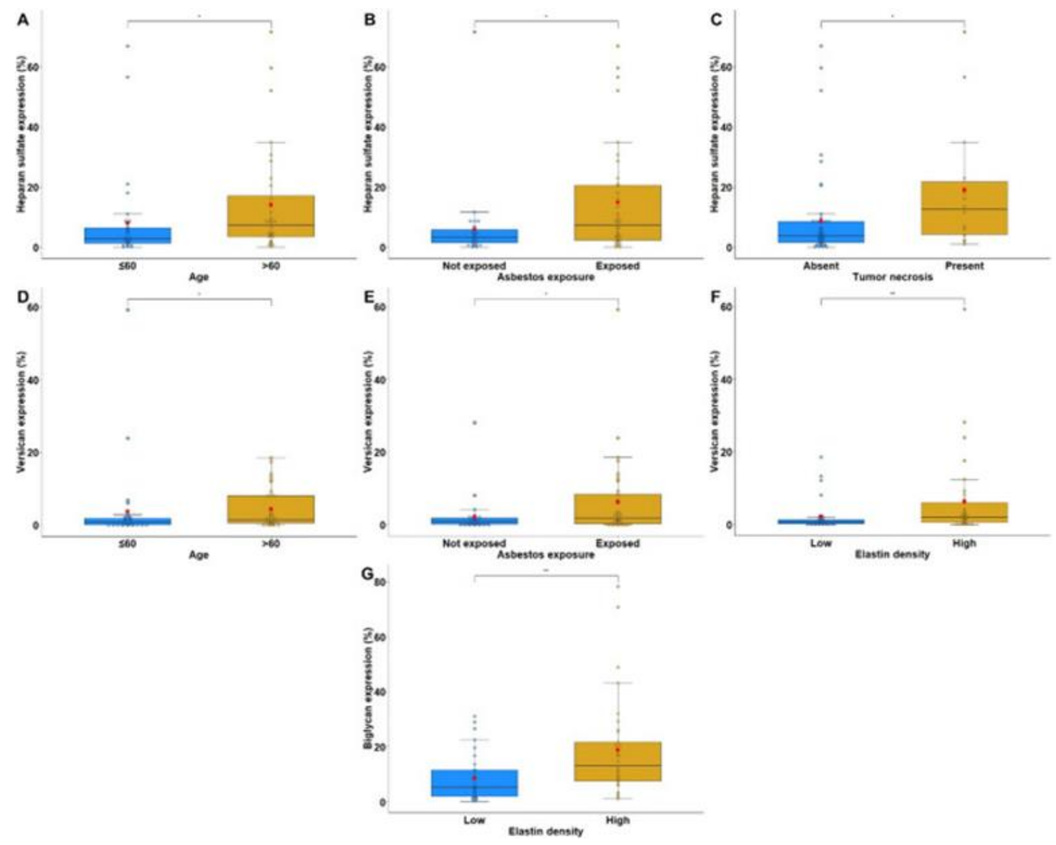
Experimental workflow



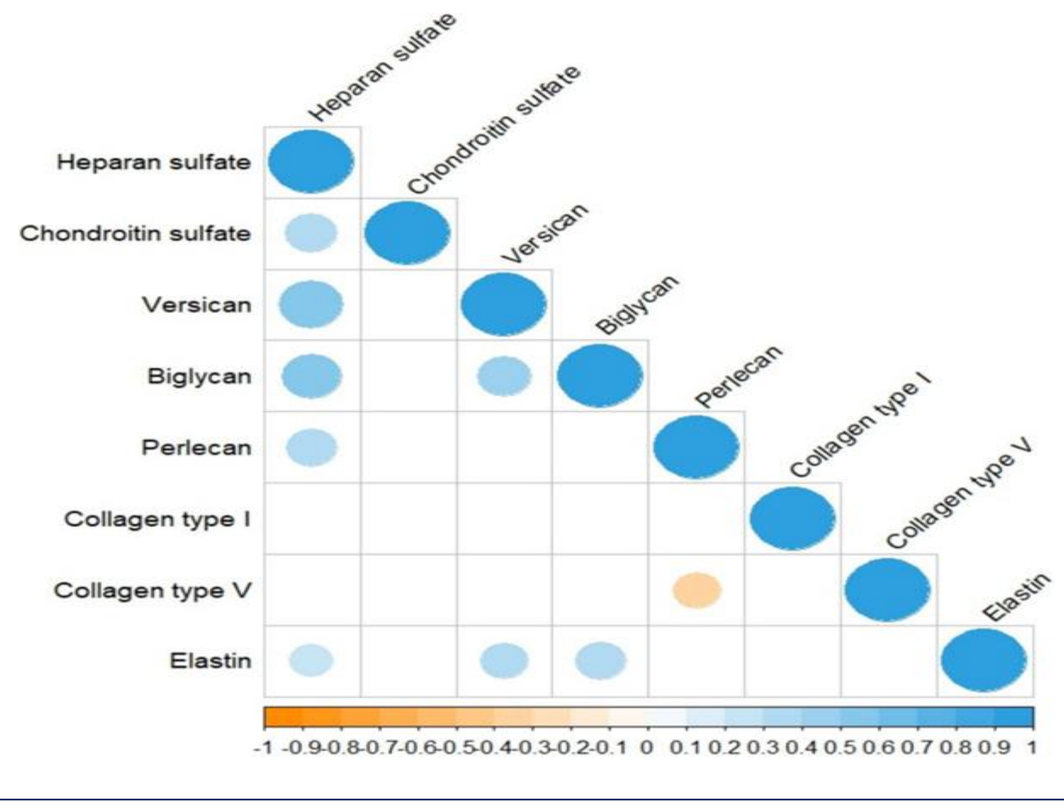
Histological analysis



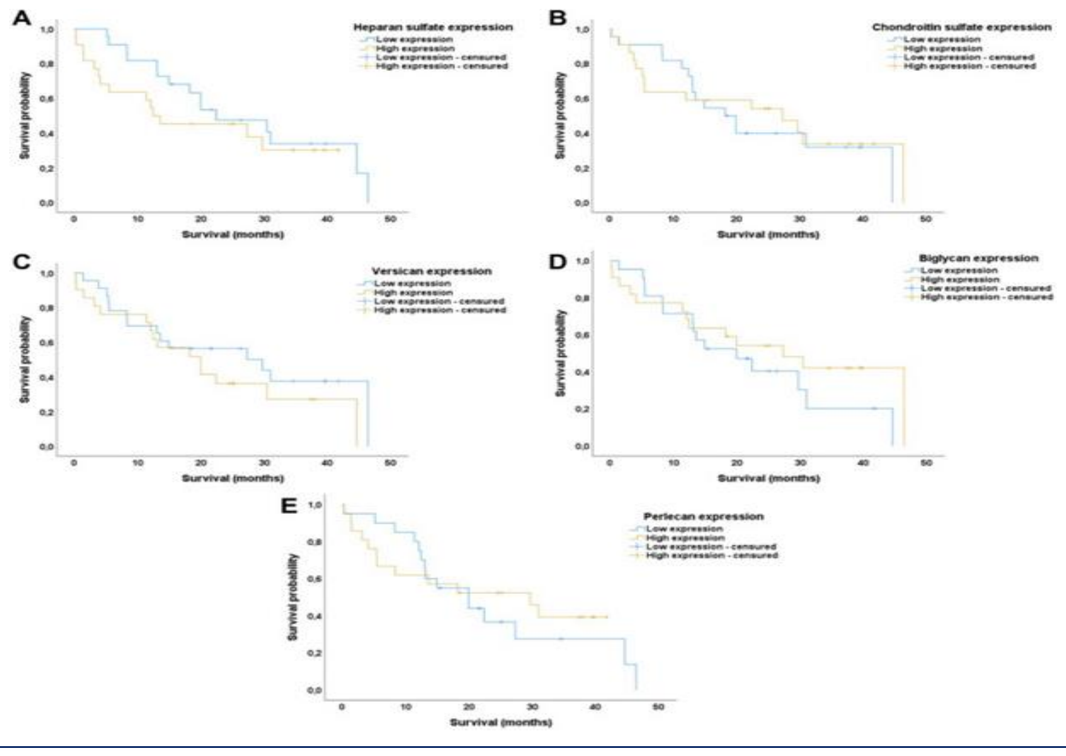
Expression of GAGs and PGs



Association between ECM markers



Kaplan–Meier survival analysis



Conclusion

- Increased expression of HS, versican, and biglycan characterizes sarcomatoid and biphasic morphological patterns.
- Higher expression levels of HS and biglycan were observed in the biphasic subtype compared with epithelioid tumors.
- Elevated HS expression correlated with increased tumor aggressiveness, whereas high biglycan expression suggested a regulatory and protective role.
- A negative correlation between perlecan and collagen V was linked to enhanced tumor infiltration, particularly in biphasic tumors.
- Positive correlations among versican, biglycan, and elastin were associated with tumor progression and increased plasticity.
- Kaplan–Meier survival analysis showed no statistically significant association between individual ECM markers and overall survival, indicating limited prognostic value when considered as single biomarkers.
- GAG molecular expression modulates B-MPM plasticity and promotes tumor progression.