



Clinical features and molecular landscape of cuproptosis signature-related molecular subtype in gastric cancer

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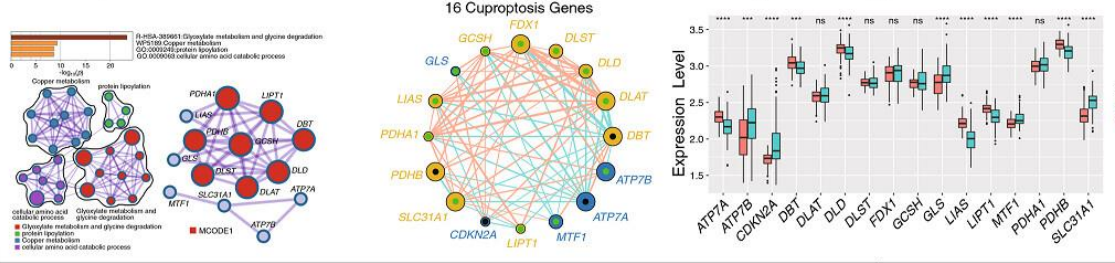


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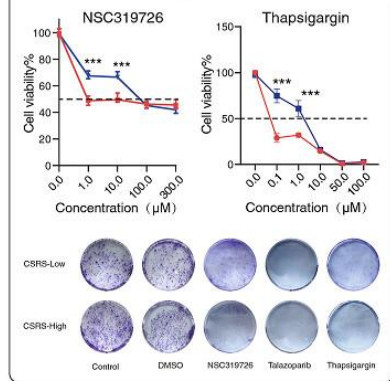
Graphical Abstract

Comprehensive characteristics of cuproptosis-related genes in gastric cancer

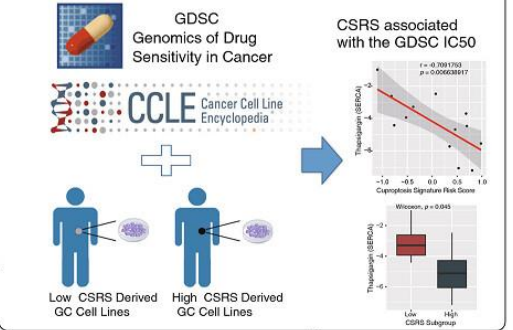


Clinical Features and Molecular Landscape of Cuproptosis Signature Related Molecular Subtype in Gastric Cancer

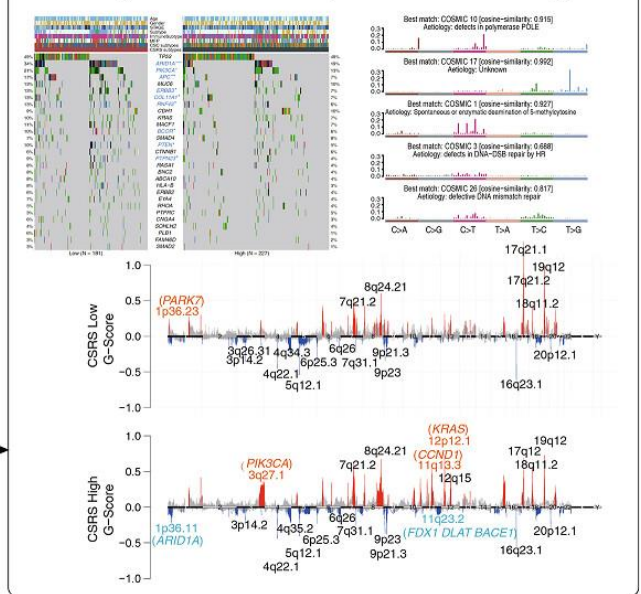
Verifying the differences through Western blot experiments and drug sensitivity experiments



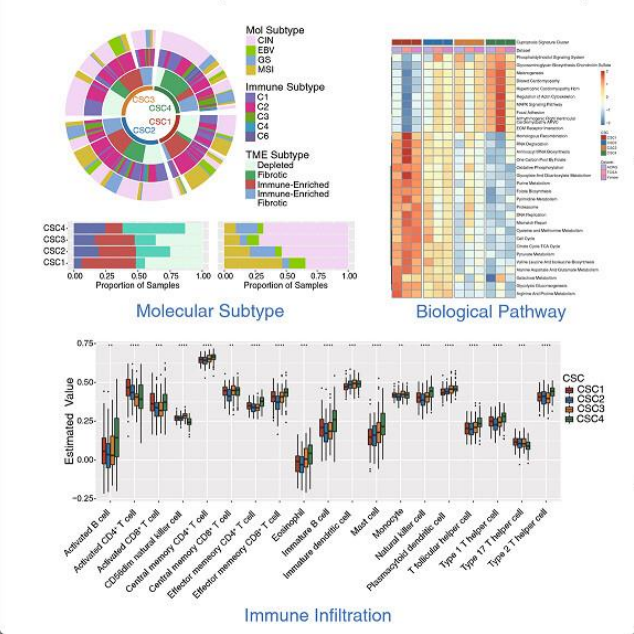
Correlation and effectiveness between CSRS score and antineoplastic drugs



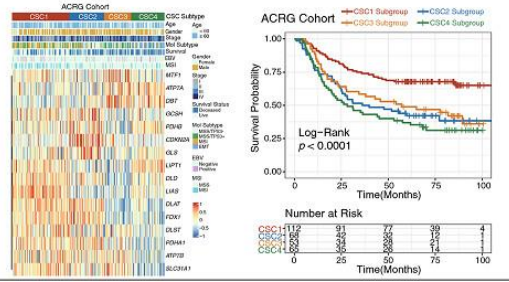
Tumor genomic landscapes in CSRS subtypes



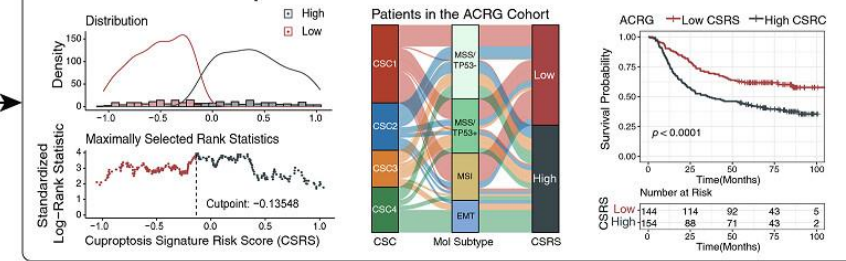
The cuproptosis signature clusters characterized by distinct molecular landscapes



Identification of cuproptosis signature clusters and its clinical features



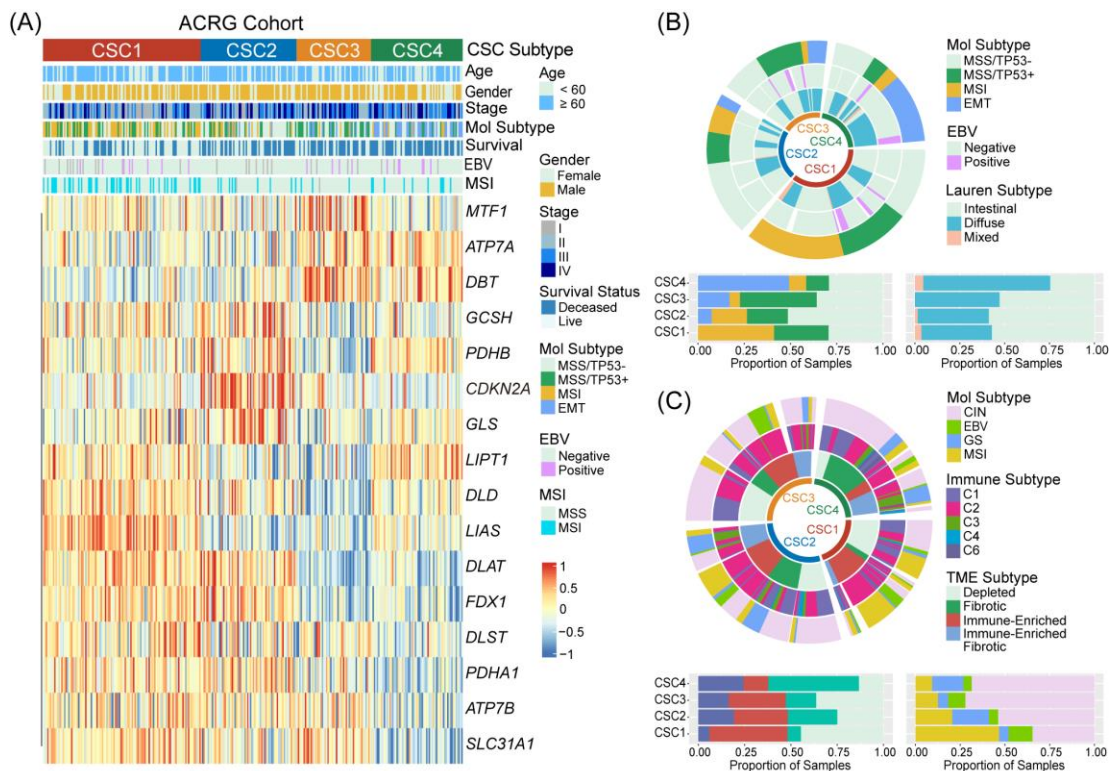
Construction of the cuproptosis signature risk score and exploration of its clinical relevance



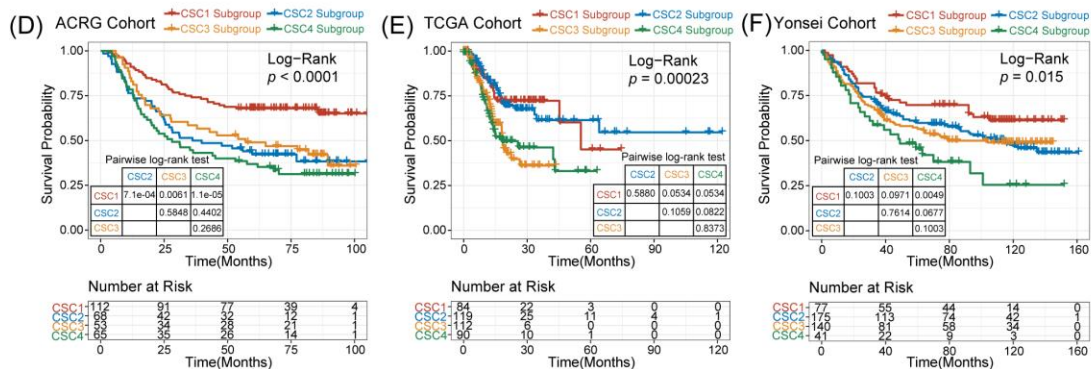


RESULTS

Cuproptosis signature patterns characterized by specific clinical features and molecular subtypes



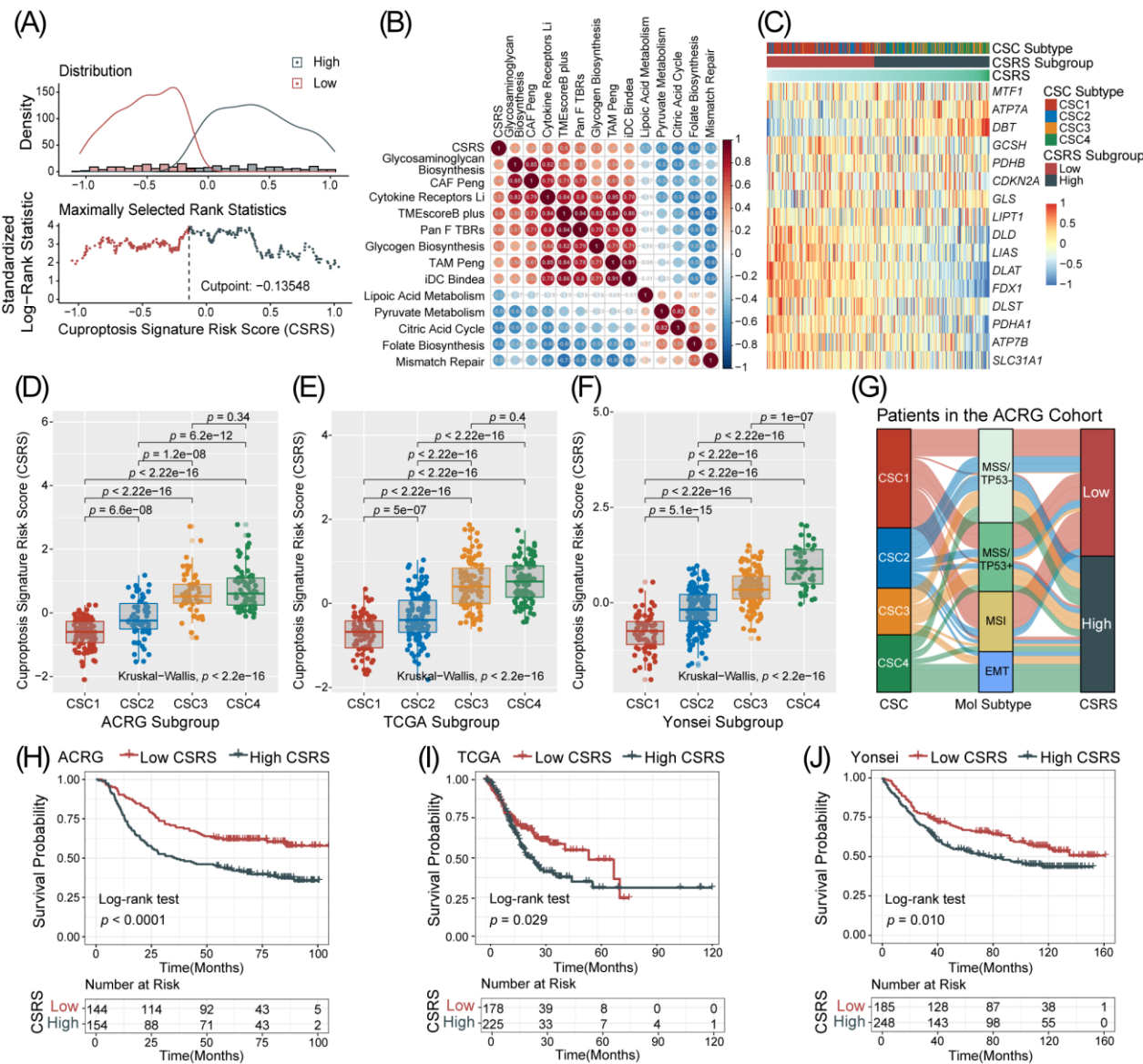
- Four cuproptosis signature clusters (CSC)
- Microsatellite instability (MSI)-positive tumors converged within the CSC1 subtype, culminating in the amalgamation of a hypermutated phenotype, MSI, and an immune-enriched subtype
- CSC4 subtype exhibited a strong correlation with advanced tumor staging, the mesenchymal phenotype, the diffuse histological subtype, and a fibrotic tumor microenvironment (TME) subtype





RESULTS

Construction of cuproptosis signature risk score and exploration of its clinical relevance

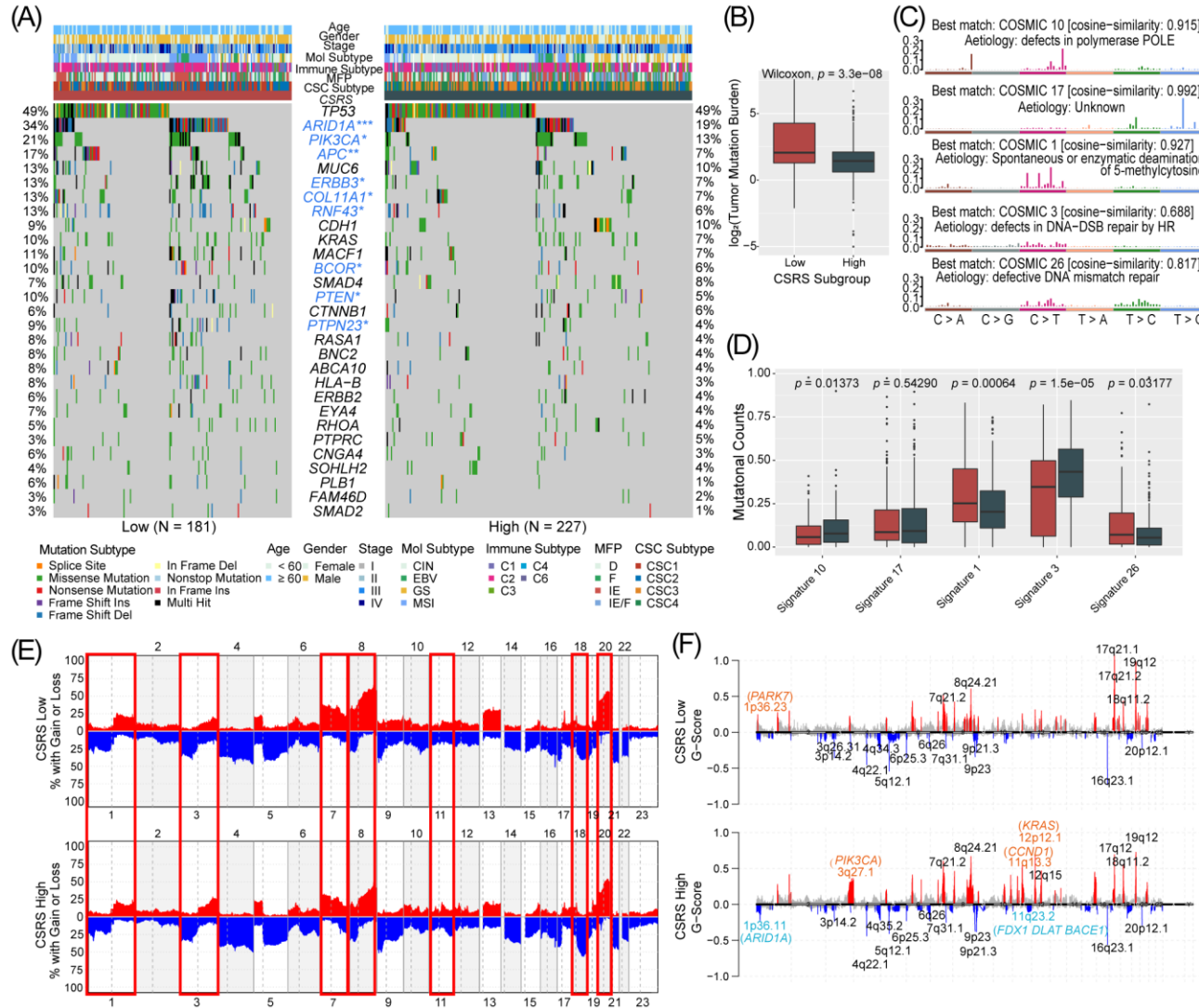


- Specifically, the cuproptosis signature risk score was markedly negatively correlated with lipoic acid, pyruvate metabolism, and the citric acid cycle. Conversely, it showed a positive correlation with signatures related to cancer fibroblasts, tumor-associated macrophages, glycogen and glycosaminoglycan biosynthesis, as well as cytokine receptors.
- DBT, MTF1, and ATP7A were significantly elevated in the CSRS-High subtype; ATP7B, SLC31A1, GCSH, LIAS, DLAT, FDX1, DLD, and PDHA1 were obviously increased in the CSRS-Low subtype in the 3 databases
- CSRS-High patients exhibit significantly worse prognosis



RESULTS

Tumor genomic landscapes in Cuproptosis signature mutation gastric cancer

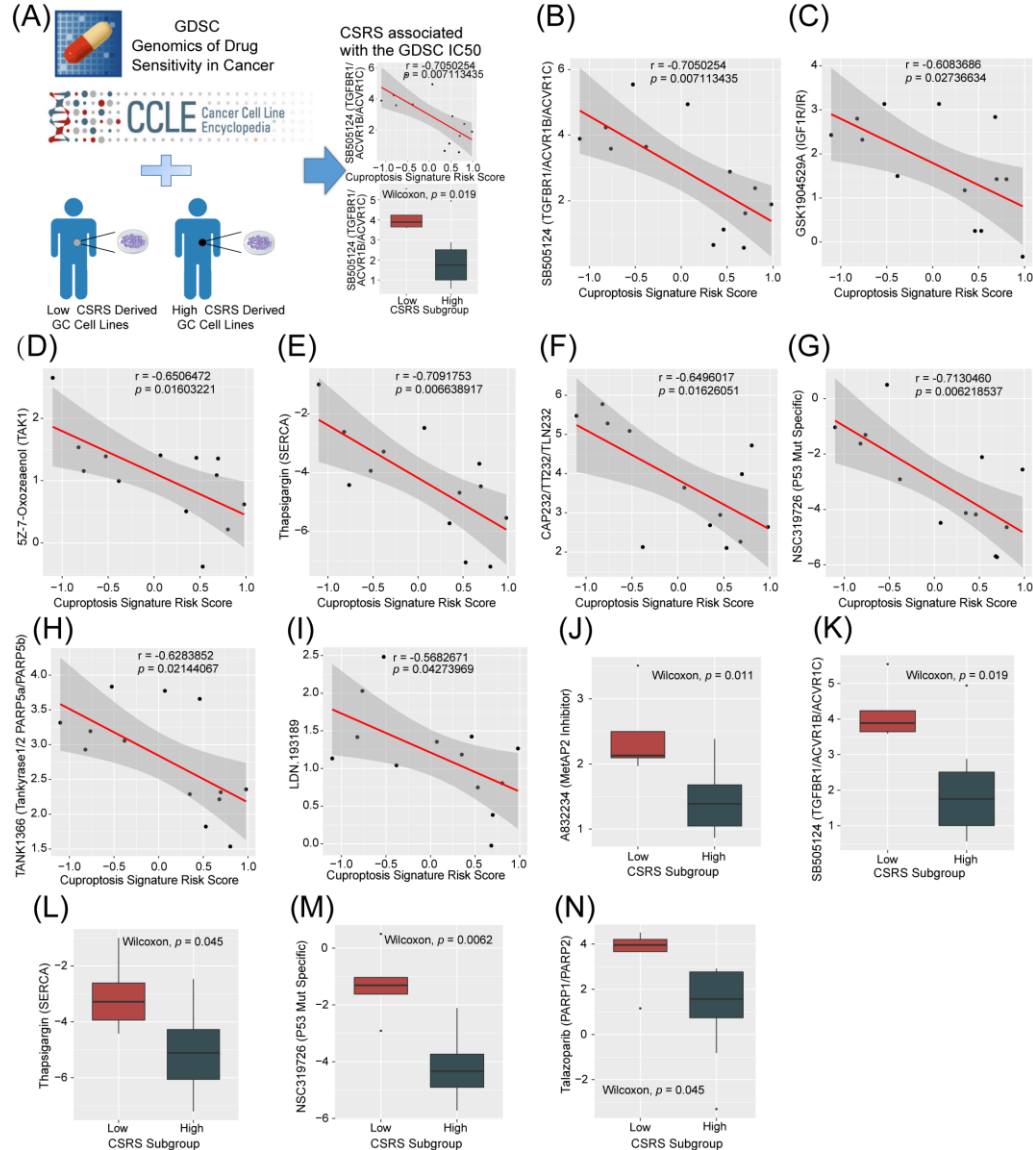


- *ARID1A*, *PIK3CA*, *APC*, *ERBB3*, *COL11A1*, *RNF43*, *BCOR*, *PTEN*, and *PTPN23* had higher mutation rates in the CSRS-Low subtype
- CSRS-Low in patients were significantly associated with higher tumor mutational load
- and cytobands in *1p36.11* (*ARID1A*) and *11q23.2* (*FDX1*, *DLAT*, *BACE1*) in cuproptosis signature risk high score subtype contained the frequently deleted regions



RESULTS

Analysis of correlation and effectiveness between CSRS score and antineoplastic drugs

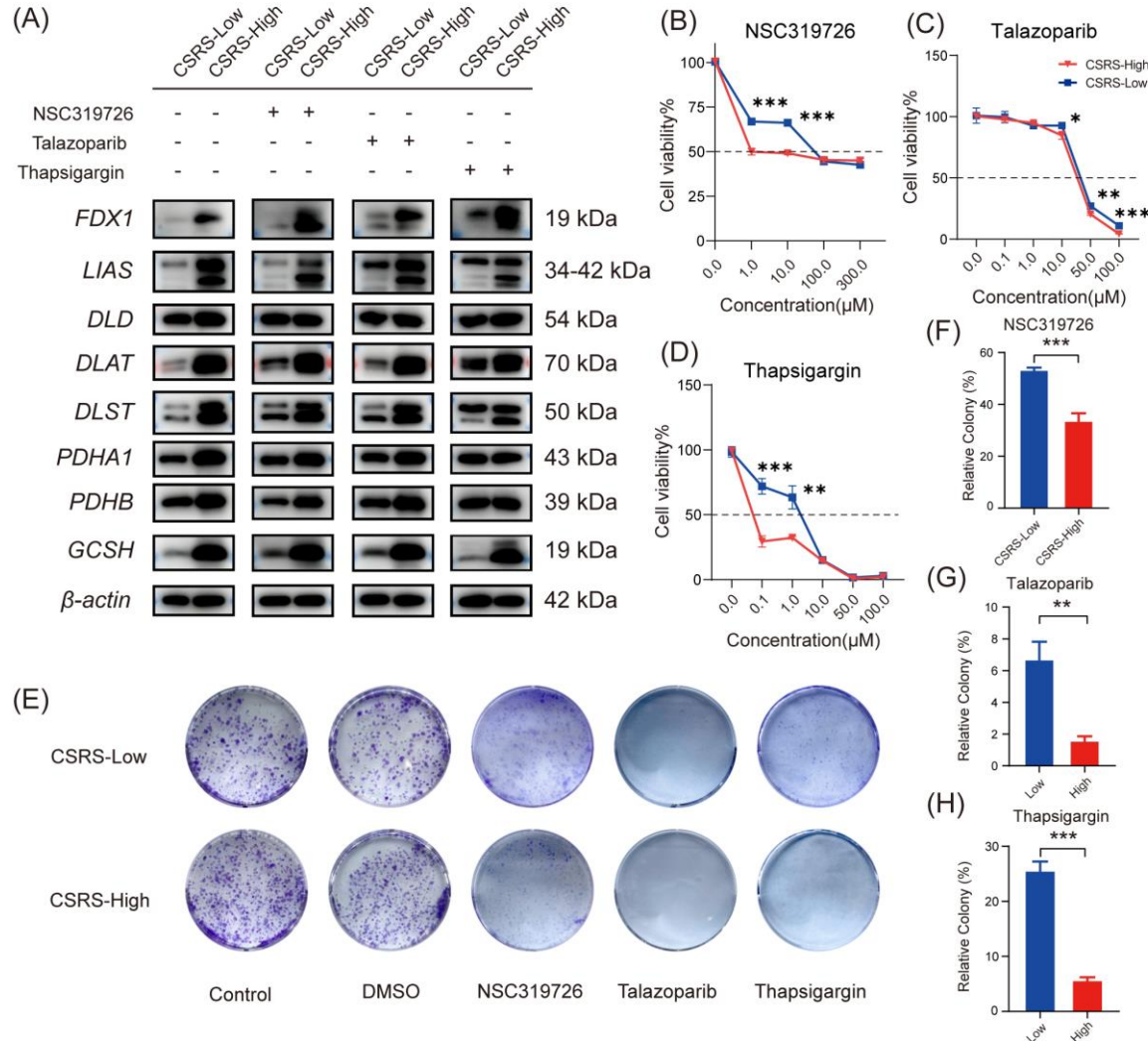


- We further jointly analyzed the Cancer Cell Line Encyclopedia (CCLE) and Genomics of Drug Sensitivity in Cancer (GDSC1) databases to determine the association between CSRS score and antineoplastic drug sensitivity of gastric cancer cell lines
- Screening out potential small molecule drugs for the treatment of CSRC High gastric cancer patients, such as SB505124, Talazoparib, Thapsigargin, and NSC319726



RESULTS

Verifying the differences between CSRS-Low (AGS) and CSRS-High (HGC-27) subtypes through Western blot experiments and drug sensitivity experiments



- Western blot analysis revealed: In the CSRS-High subtype of gastric cancer cells, the expression of proteins related to cuproptosis progression was significantly increased, while the CSRS-Low subtype was opposite.
- drug sensitivity experiments: NSC319726, talazoparib, and thapsigargin have relatively high IC50s in the CSRS-Low subtype of gastric cancer cells

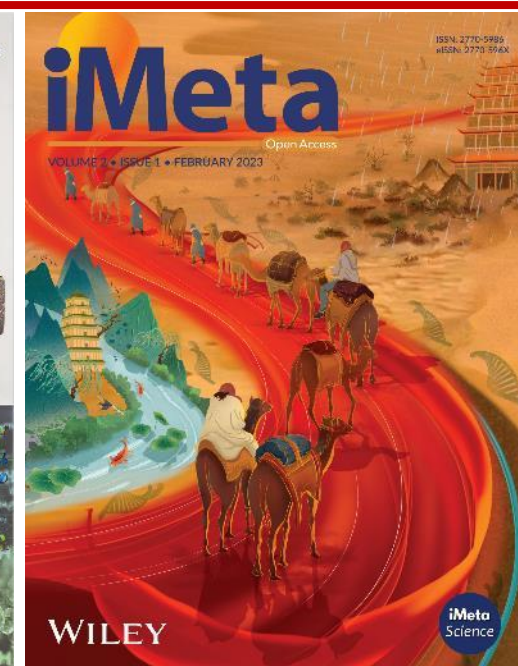


Summary

- ❑ Four distinct cuproptosis signature-based clusters are associated with different clinical outcomes and biological pathways and are highly consistent with distinct tumor immune contextures, respectively.
- ❑ Based on the cuproptosis signature risk score, GC patients with a higher CSRS score were characterized by decreased survival time and correlated with tumor adhesion state and lower tumor mutation loads.
- ❑ *DBT*, *MTF1*, or *ATP7A* were significantly elevated in the CSRS-High subtype, while *ATP7B*, *SLC31A1*, *GCSH*, *LIAS*, *DLAT*, *FDX1*, *DLD*, and *PDHA1* were increased in the CSRS-Low subtype.
- ❑ Drug sensitivity analyses revealed potential therapeutic compounds for GC with high CSRS scores.

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