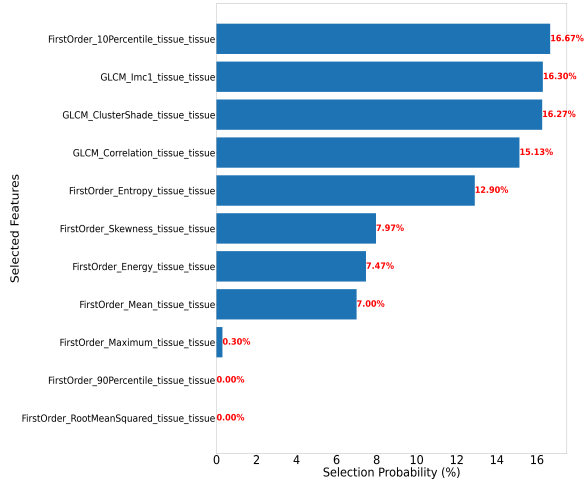
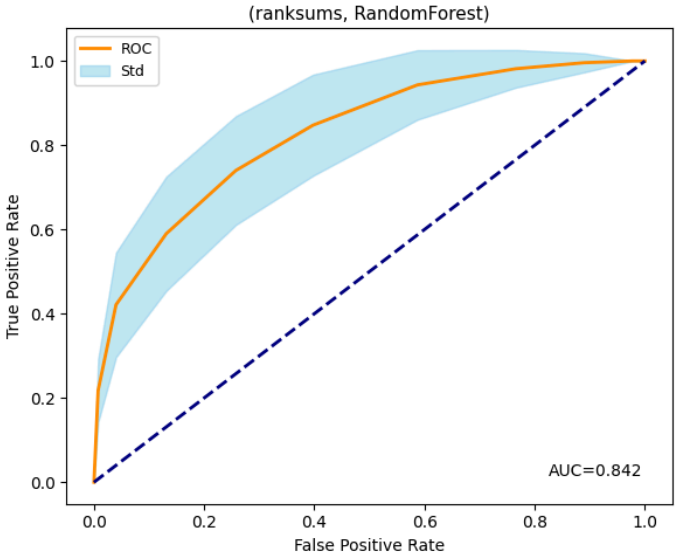
Pathological Analysis Report

1. Cross-Validation AUC

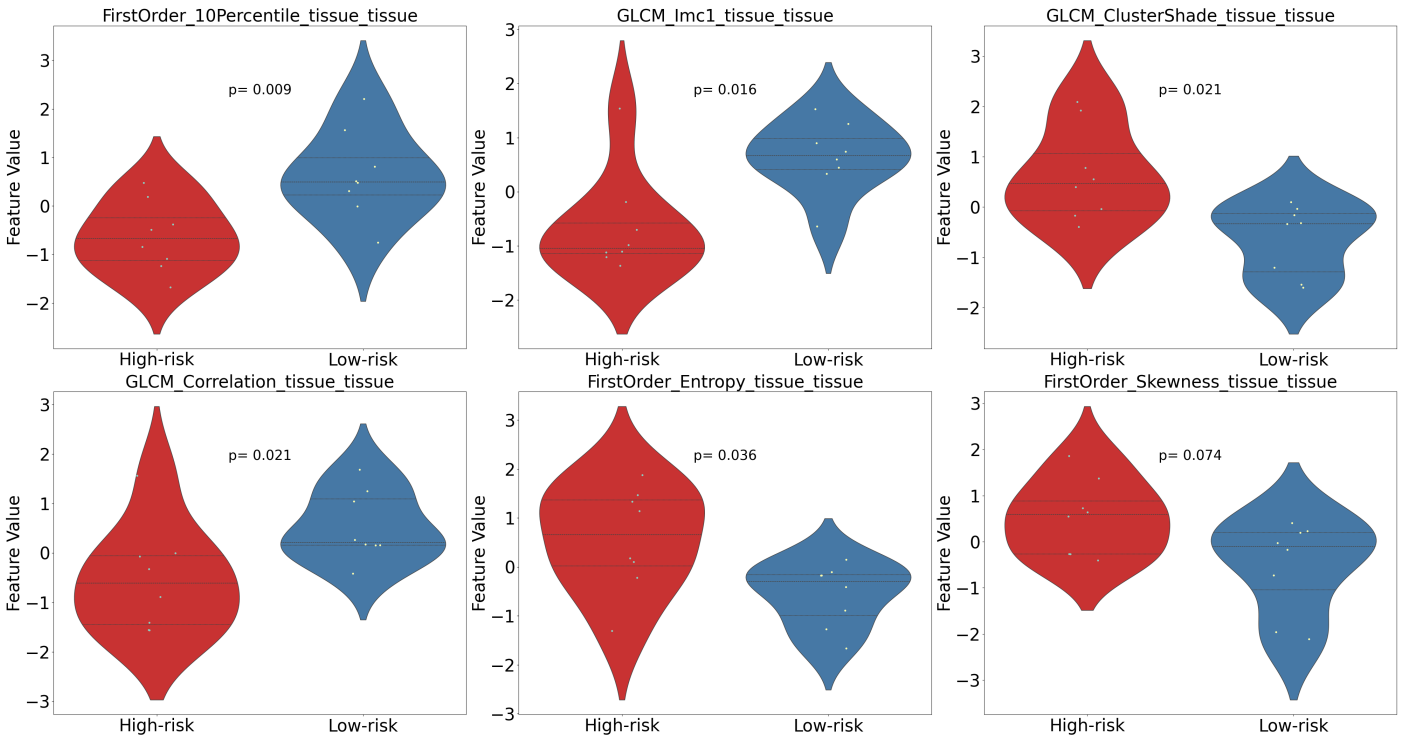
	LDA	RandomForest	LinearSVC
ranksums	0.6839/0.09614	0.8415/0.05456	0.6897/0.09435
mutualInfo	0.6495/0.1056	0.8207/0.06531	0.6958/0.1062

2. Feature Selection And ROC Curve

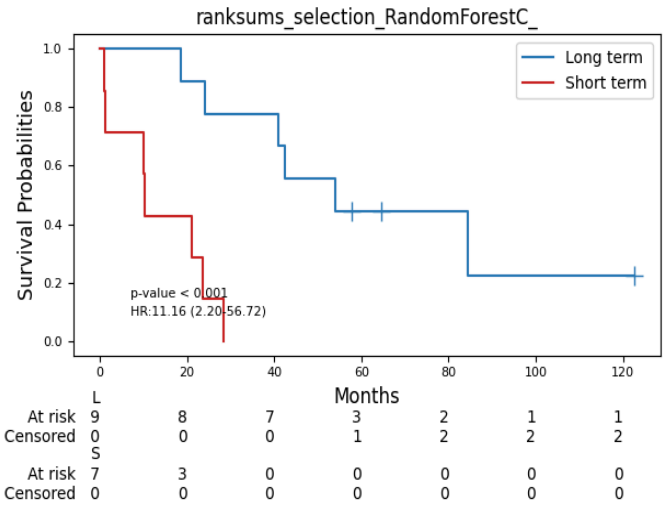


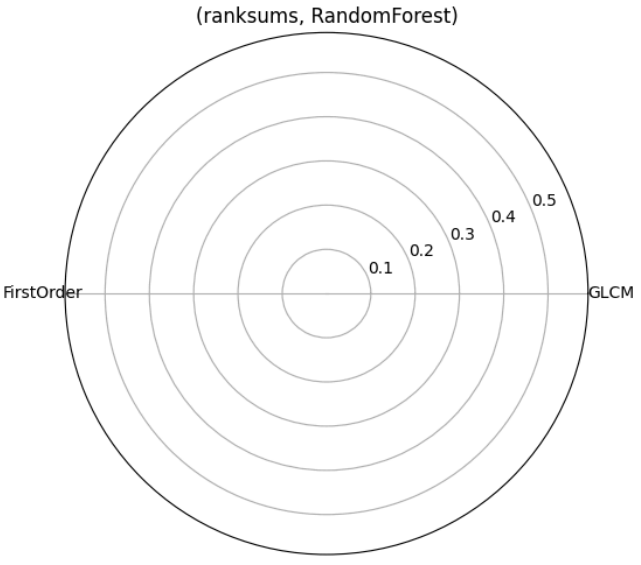


3. Top Feature Violin Plot

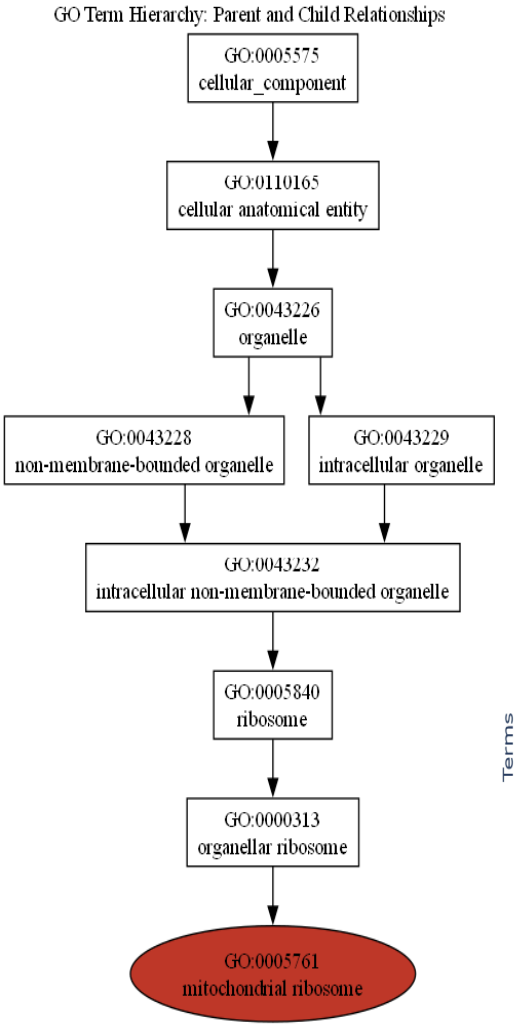


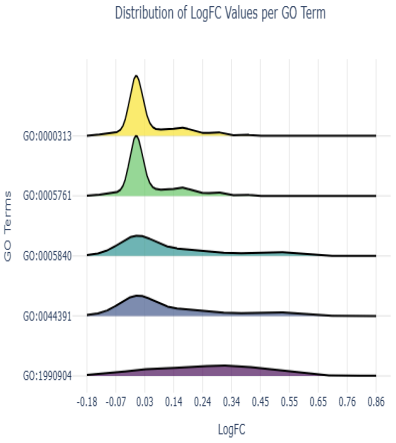
4. Kaplan-Meier-Curve And Radar-Chart

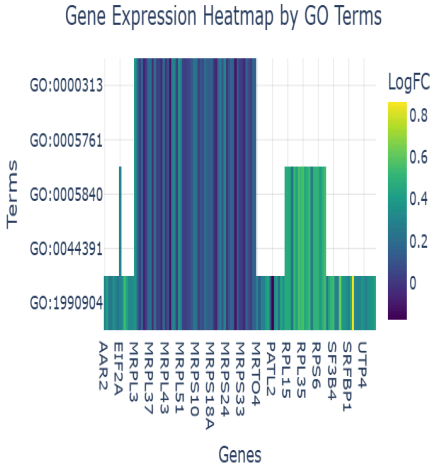


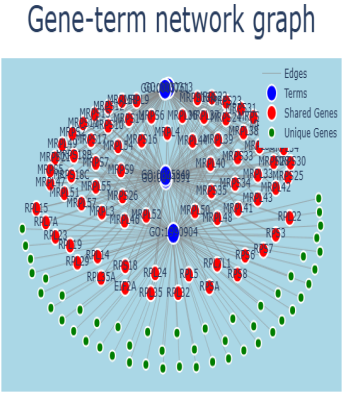


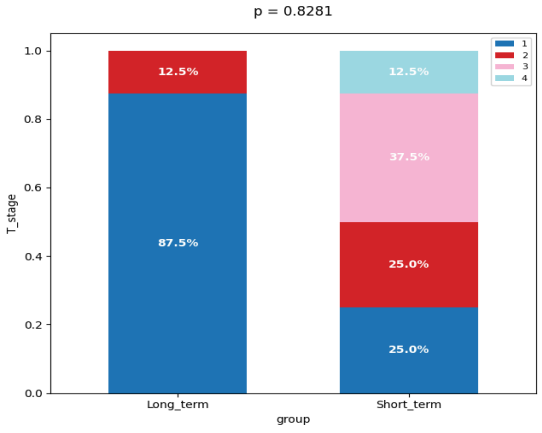
5. Gene Analysis

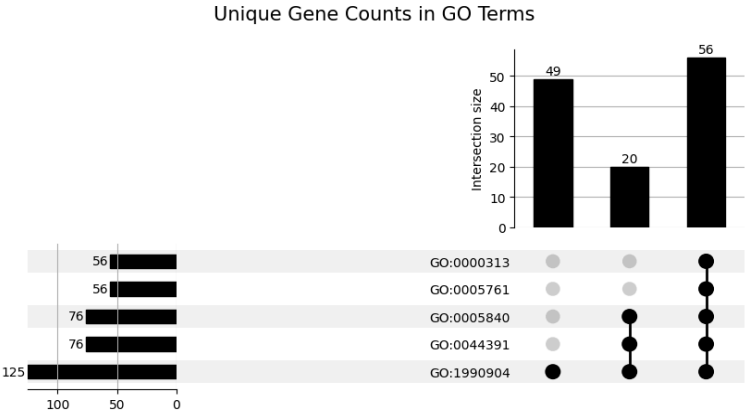


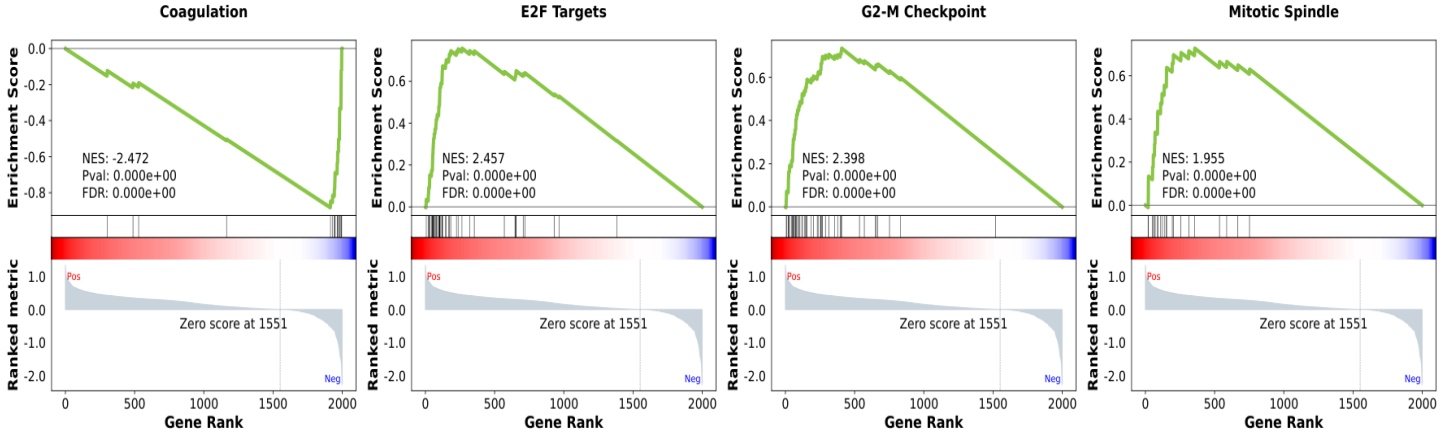












6. LLM Analysis

Comprehensive Analysis Report: Biological Pathways and Clinical Correlations

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1. Coagulation Pathway

The *Coagulation* pathway is significantly downregulated, as indicated by a negative enrichment score (ES = -0.882) and a strong normalized enrichment score (NES = -2.472). The pathway shows highly significant statistical support with a nominal *p*-value and FDR *q*-value both equal to 0.0, suggesting robust downregulation in the dataset.

Downregulation of this pathway implies reduced expression of key coagulation-related genes such as *APOA1*, *SERPINC1*, *F12*, *VWF*, and *PROZ*. In the context of cancer or other chronic diseases, impaired coagulation signaling may reflect systemic dysregulation of plasma protease inhibitors and hemostasis, potentially linked to disease progression. This downregulation is associated with high-risk patient profiles, indicating that patients exhibiting lower activity in coagulation pathways may have more aggressive disease states or compromised physiological responses.

Clinically, when correlating with T_stage distribution, no direct association was found, as the chi-square test revealed no significant difference between long-term and short-term groups ($p = 0.8281$). However, given that short-term (presumably higher-risk) patients show broader T_stage spread (including stages 3–4), while long-term survivors are concentrated in early stages (T1: 87.5%), the observed coagulation downregulation may be part of a molecular signature preceding advanced tumor staging rather than being stage-dependent.

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2. E2F Targets Pathway

The *E2F Targets* pathway is markedly upregulated (ES = 0.758, NES = 2.457, $p = 0.0$, FDR = 0.0), placing it among the most significantly enriched gene sets. This pathway includes critical regulators of cell cycle progression from G1 to S phase, including *E2F3*, *MYBL2*, *CDK1*, *CDC20*, *MCM* family members, and DNA replication enzymes like *MCM6* and *TOP2A*.

Upregulation of E2F targets indicates active cell proliferation and DNA synthesis, which are hallmarks of rapidly dividing tumor cells. Therefore, elevated activity in this pathway strongly correlates with high-risk patients who likely exhibit faster tumor growth and poorer prognosis. These findings align with known oncogenic mechanisms where RB-E2F axis deregulation drives uncontrolled cell division.

In terms of clinical characteristics, although T_stage does not differ significantly between groups, the presence of proliferative signatures like E2F activation suggests an underlying biological aggressiveness even if anatomical staging remains variable. Thus, despite overlapping T_stages, molecular stratification reveals functional divergence—short-term outcome patients may harbor tumors with intrinsically higher replicative potential.

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3. G2-M Checkpoint Pathway

This pathway is also significantly upregulated (ES = 0.734, NES = 2.398, $p = 0.0$, FDR = 0.0), reflecting enhanced expression of genes involved in mitotic entry and chromosome segregation. Key lead genes include *CDC20*, *CDK1*, *AURKA*, *BUB1*, *TTK*, *KIF* family kinesins, and chromosomal maintenance proteins such as *CENPA* and *SMC2*.

Activation of the G2-M checkpoint typically ensures genomic fidelity before mitosis; however, its constitutive upregulation in cancer often reflects aberrant cell cycle control and dependency on mitotic machinery for survival. Consequently, upregulation here points toward high-risk status, where tumor cells rely heavily on precise but dysregulated mitotic regulation to sustain rapid proliferation.

Similar to E2F targets, this signature is not directly mirrored in T_stage distributions due to lack of statistical significance ($p = 0.8281$). Nevertheless, the pronounced enrichment underscores a phenotype of mitotic addiction—a feature commonly seen in advanced or therapy-resistant cancers. Even within similar T_stages, patients with elevated G2-M activity may face worse outcomes due to increased chromosomal instability and resistance to apoptosis.

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4. Mitotic Spindle Pathway

The *Mitotic Spindle* pathway shows clear upregulation (ES = 0.727, NES = 1.955, $p = 0.0$, FDR = 0.0), implicating overexpression of genes essential for spindle assembly, microtubule dynamics, and kinetochore attachment. Notable genes include *TPX2*, *AURKA*, *KIF2C*, *KIF11*, *MAPRE1*, *ECT2*, and *RACGAP1*—all crucial for bipolar spindle formation and accurate chromosome segregation.

Overactivity in this pathway supports continuous and error-prone cell division, again marking a high-risk molecular profile. Aberrant spindle function can lead to aneuploidy and tumor heterogeneity, contributing to therapeutic resistance and metastatic potential. Hence, upregulation is indicative of biologically aggressive tumors.

Despite the absence of statistically significant differences in T_stage between long- and short-term groups, the persistent upregulation across multiple mitosis-related pathways (E2F, G2-M, Mitotic Spindle) highlights a coherent oncogenic program independent of conventional staging. This suggests that molecular phenotyping adds value beyond anatomical classification by identifying high-risk individuals earlier and more accurately.

Summary and Interpretation

Four top-ranked pathways reveal a consistent biological theme: **downregulation of physiological homeostasis mechanisms (e.g., coagulation)** and **concurrent upregulation of cell cycle and mitotic processes**. Specifically:

- Downregulation of *Coagulation* is linked to high-risk status, possibly reflecting systemic metabolic or vascular dysfunction.
- Upregulation of *E2F Targets*, *G2-M Checkpoint*, and *Mitotic Spindle* pathways collectively indicate hyperproliferative, genomically unstable tumors characteristic of aggressive disease.

Although clinical T_stage did not significantly differ between long- and short-term survivor groups ($p = 0.8281$), molecular pathway analysis uncovers profound functional distinctions. Long-term survivors predominantly present at early T_stages (T1: 87.5%) with minimal representation in advanced stages, whereas short-term patients are distributed across T2–T4, indicating greater disease burden.

Importantly, the lack of statistical significance in T_stage distribution suggests limited power or small sample size; nonetheless, the strong and reproducible enrichment of proliferation pathways provides compelling evidence for intrinsic biological risk stratification. These results advocate integrating transcriptomic pathway profiling with clinical staging to improve prognostic accuracy and guide personalized treatment strategies.