

Organ-specific tumor dynamics predict survival of patients with metastatic colorectal cancer

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Objectives

Several tumor growth inhibition (TGI) models have been developed to evaluate the longitudinal trajectories of tumor size and their associated metrics (e.g., tumor growth rate, KG)[1]. KG is a strong predictor of long-term efficacy outcomes such as overall survival (OS), which can serve as an exploratory endpoint in early proof-of-concept or phase II studies and support the design of phase III trials[2]. The TGI models are usually developed based on the time-course data of the sum of the longest diameter (SLD)[2]. However, heterogeneity in tumor dynamics across organs is typically seen in many cancer types (**Figure 1**)[3]. We aim to compare the prognostic value of organ-specific dynamics (KG, early tumor response) with SLD dynamics in patients with metastatic colorectal cancer (mCRC).

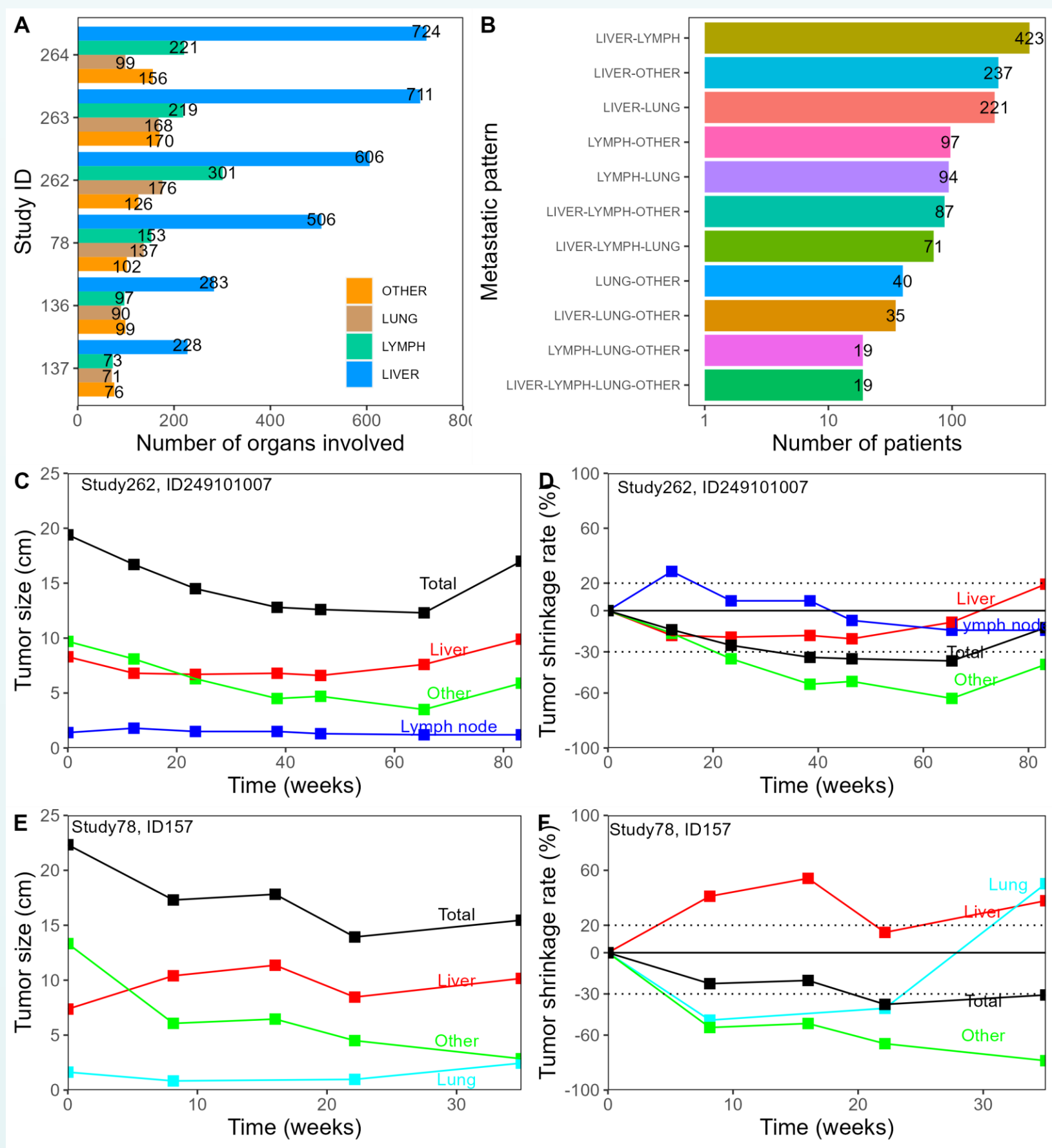


Figure 1. Number of metastatic organ involved in each studies (A). Metastatic patterns distribution for patients with more than one organ involved (B). Tumor growth rates/tumor response are different across organs within a patient (C-F).

KG. The early tumor response from baseline to the first measurement after treatment (≈ 8 weeks) was also evaluated. Patients with a tumor size reduction of over 30% were defined as responders. The relationship between organ-specific dynamics, SLD dynamics, and survival outcomes (overall survival, OS; progression-free survival, PFS) was quantified using Kaplan-Meier analysis and Cox regression.

Results

This study included 3905 patients from 6 phase III mCRC trials. The liver emerged as the most frequent metastatic site (3058/3905, 78.3%), with variable KGs across different organs in individual patients. For patients with multiple metastatic organs (n=1343), the liver and lung have a higher KG (0.024 and 0.0201 [week⁻¹], respectively) than the lymph node (0.0126 [week⁻¹]) and other (0.0117 [week⁻¹]). Notably, the dynamics for different organs did not equally contribute to predicting survival outcomes. In liver metastasis cases, liver KG proved to be a superior prognostic biomarker for OS and surpasses the predictive performance of SLD (**Figure 2**). In addition, the univariate Cox regression showed that liver KG presented higher HR (LIVER KG 2.244 vs. SLD KG 2.109), indicating a greater risk of poor survival. Similar results were observed for PFS. What's more, early liver dynamics also outperform early SLD dynamics in predicting survival. Cox regression analysis confirmed the independence of liver KG and early liver response as variables in survival prediction. In addition, liver KG was identified as the most significant covariate in both multivariate analyses of OS and PFS (**Figure 3**).

Methods

All datasets are accessible in Project Data Sphere, an open-access platform. The lesions were classified into four metastatic sites based on the organ information: liver, lymph nodes, lung, and other (e.g., bone, skin)[4]. The tumor growth inhibition models developed based on organ-level SLD and SLD were used to estimate the organ-specific KGs and SLD

Conclusions

In mCRC patients with liver metastasis, liver dynamics is the primary prognostic indicator for both PFS and OS. In future drug development for mCRC, greater emphasis should be directed towards understanding the dynamics of liver metastasis development.

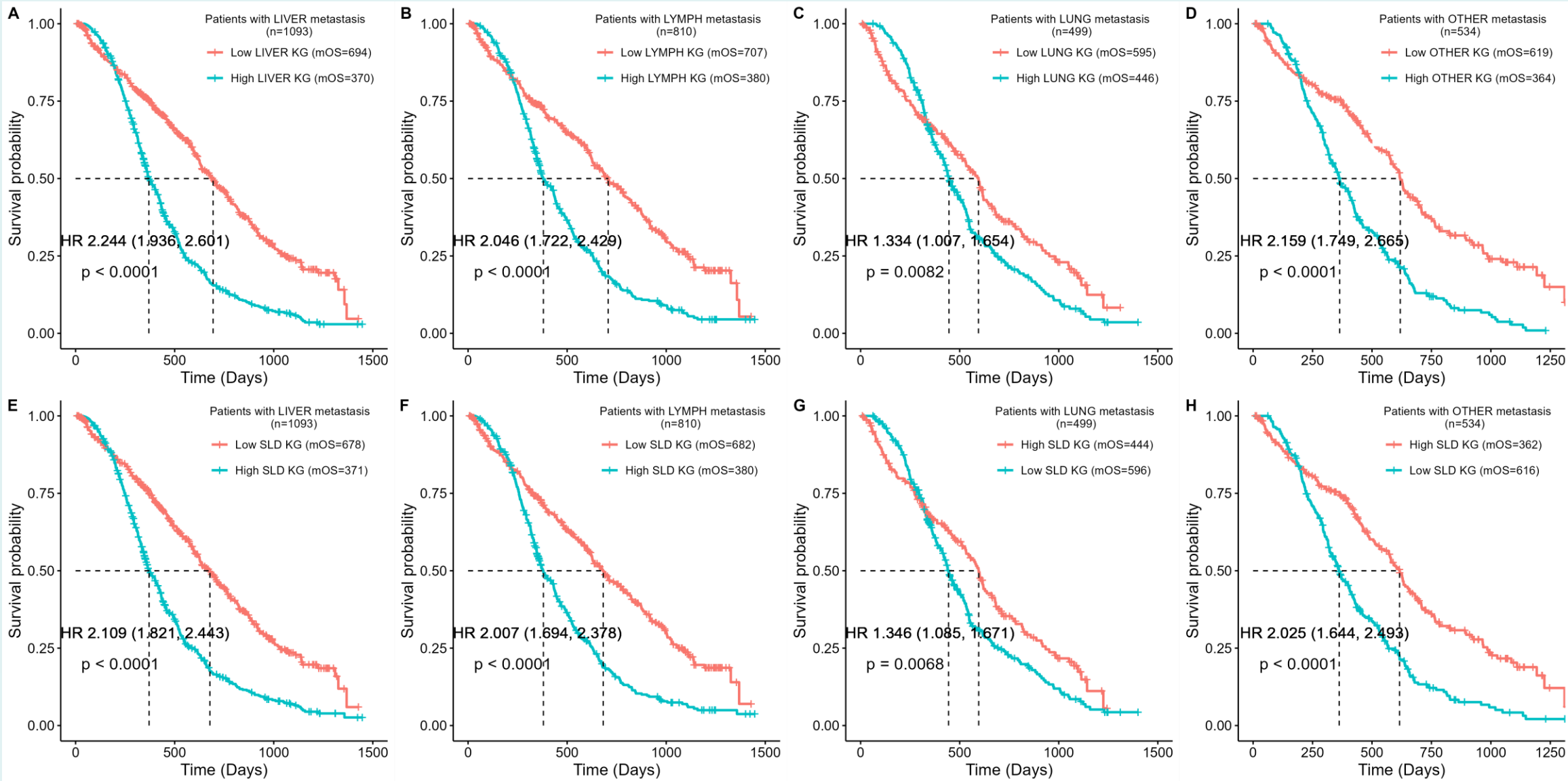


Figure 2. Kaplan-meier curves show the predictive performance of organ-specific KGs (A-D) and SLD KG (E-H).

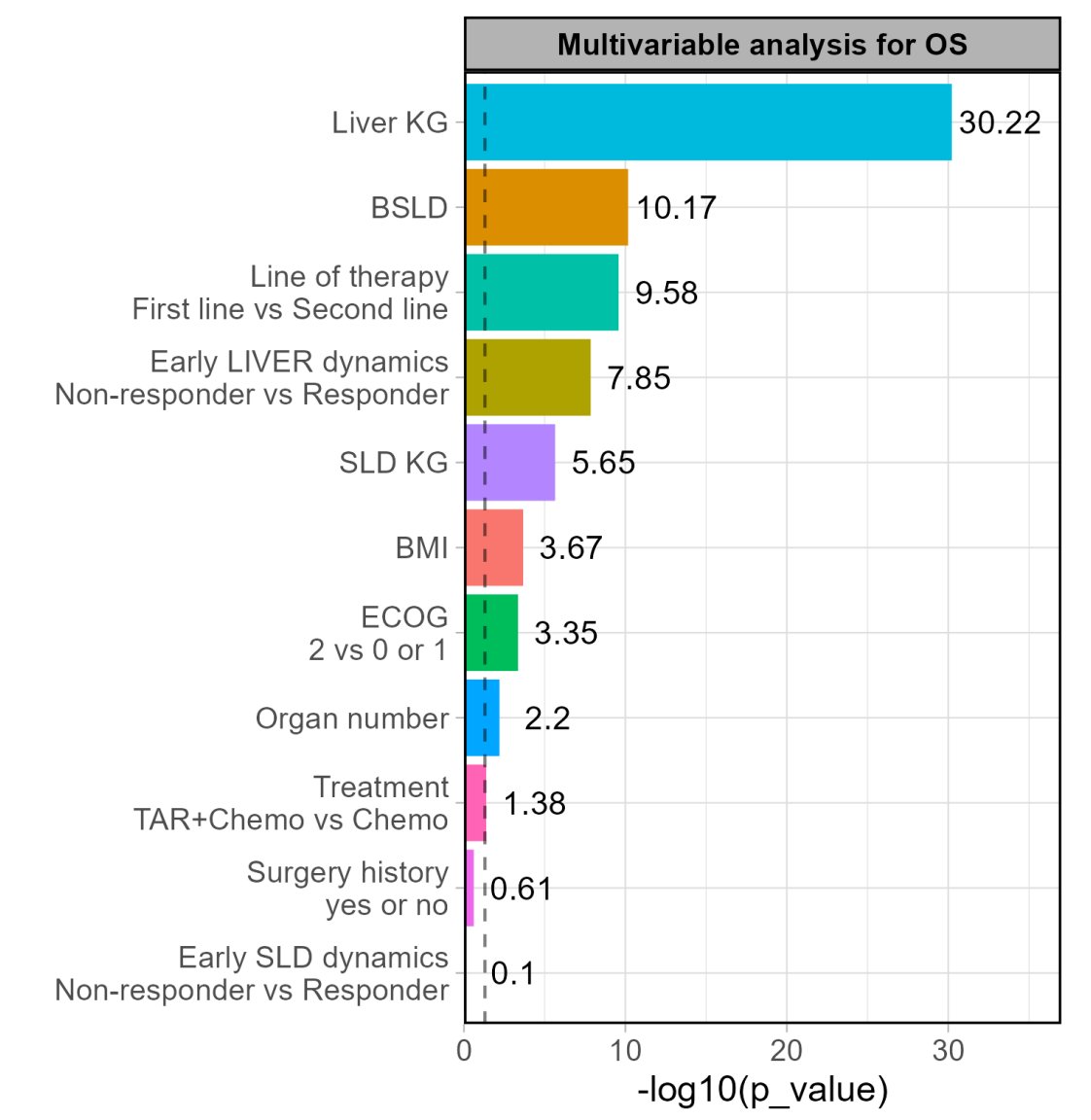


Figure 3. The multivariate Cox regression analysis results assess the association between liver KG, early liver dynamics, and survival outcomes.

Reference

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