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# *A Comparative Evaluation of Survival Analysis Methods for Tumor Immunotherapy Combination Regimens*

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***Keywords:*** Tumor Immunotherapy; Combined Treatment Regimen; Survival Analysis; Lasso Regression; Cox Proportional Hazard Model

***Abstract:*** This study employed survival analysis methods to evaluate the effects of different tumor immunotherapy combinations on patient survival time and risk of death. By analyzing clinical data from 200 patients with advanced tumors, the Kaplan-Meier survival curve, Cox proportional hazards model, and LASSO regression method were used to identify biomarkers significantly associated with survival. Results indicated that immunotherapy combined with targeted therapy most effectively prolonged survival and reduced mortality risk, significantly outperforming other combinations. Cluster analysis was also used to explore treatment response heterogeneity among tumor samples, revealing differential immunotherapy efficacy among different subtypes, with some responding more favorably to combined treatments. LASSO regression feature screening successfully reduced overfitting risk while retaining key features significantly impacting survival. In summary, this study demonstrated significant advantages of immunotherapy combination use in tumor treatment, providing a theoretical basis for optimizing treatment strategies.

## 1. Introduction

### 1.1 Research background and importance

The rapid development of tumor immunotherapy, mostly in recent years, is due to the clinical application of immune checkpoint inhibitors [1]. This always seems to have acted as the main driving force for fundamental changes in the treatment mode of various malignant tumors. Immune therapies work by activating the body's own immune system against cancerous cells. Immunotherapy differs from traditional chemotherapy and targeted therapy because it is well tolerated, induces good long-term efficacy, and ensures sustainable immune memory [2]. However, single immunotherapy fails to produce a long-lasting response in many patients, which suggests that enhancing the effect of immunotherapy using combination therapy is an important direction of research. [3].

In recent years, immunotherapy has gradually become a research hotspot. Immune checkpoint inhibitors in combination with other therapies, such as targeted therapy, chemotherapy, and radiotherapy, have been illustrated by numerous studies to enhance anti-tumor immune responses for improved treatment efficacy by several mechanisms [4,5]. For example, immunotherapy in combination with targeted therapy can kill tumor cells directly but also potentiates the capability of

the immune system in recognizing and eliminating tumors through modification of the tumor microenvironment. This multimodal combination therapy provides new hope for improving the overall survival rate for patients [6]. As a result, this becomes a very clinically important aspect to identify the effects of different combinations of immunotherapy on both the survival time and risk of death for patients.

### 1.2 Research objectives

The present study shall focus on determining survival time and the risk of death with respect to the effect of immunotherapy combinations. In this regard, data shall be collected from 200 patients receiving tumor immunotherapy. Furthermore, Kaplan-Meier survival curves, cumulative risk curves, and Cox proportional hazard models would normally be the typical analytical methodologies for testing the efficacy differences of different choice options. By comparing the survival benefit brought about by single immunotherapy and combined therapy, it could be verified that the efficacy of combined immunotherapy and targeted therapy in prolonging the survival of patients and reducing the risk of death is superior, providing data support to optimize tumor treatment options.

## 2. Overview of tumor immunotherapy and combined therapy options

### 2.1 Basic principles and development of tumor immunotherapy

The general principle of tumor immunotherapy is to activate or regulate the patient's immune system in order for it to recognize and destroy tumor cells. Generally, the tumor microenvironment is immunosuppressive, facilitating tumor immune escape and inhibiting effective immune action[7]. Immune checkpoint inhibitors include, but are not limited to, anti-PD1, anti-PD-L1, and anti-CTLA-4; these have been developed to a considerable extent as a class of immunotherapy drugs in recent years [8]. They realize extended patient survival by blocking inhibitory signal pathways, which reduce T cell function and restore anti-tumor T cell activity. In addition, some methods for tumor immunotherapy, including chimeric antigen receptor T cell therapy and tumor vaccines, bring new hope for malignant tumor patients [9,10].

The development of immunotherapy traces back to early cancer vaccine trials, but its real breakthrough came after the clinical application of immune checkpoint inhibitors. These drugs function on the principle of taking away the tolerance of the immune systems toward cancerous cells, thus enabling the system to rerecognize and attack tumor cells. With the deepening study of the tumor microenvironment and immune escape mechanism, studies on the research and development of immunotherapy drugs have focused gradually on personalization and diversification. Meanwhile, combination immunotherapy strategies are being widely explored to overcome the limitations of single immunotherapy [11].

### 2.2 Types and applications of tumor immunotherapy combination regimens

Tumor immunotherapy combination regimens involve several kinds of treatments to enhance anti-tumor immune effects and bypass tumors' immune-escape mechanisms. Currently, the most common combinations are those involving the use of immune checkpoint inhibitors together with chemotherapy, radiotherapy, or targeted therapy. Such combinations act synergistically through different modes of action [12,13]. For instance, radiotherapy releases more tumor antigens, while chemotherapy reduces immunosuppressive cells in the tumor microenvironment and enhances the effect of immunotherapy [14].

More importantly, immunotherapy can be combined with other immunomodulatory approaches,

such as the dual immune checkpoint inhibition strategy combining anti-CTLA-4 and anti-PD-1 antibodies. Such a combination releases the inhibitory state of T cells more thoroughly to further enhance their killing ability against tumor cells. Studies have established that such combination therapy significantly provides survival benefits in the case of tumor types [15], especially in cancers like melanoma and nonsmall cell lung cancer, and thus has emerged as a standard treatment modality [15]. Other than conventional combination therapies, the combination of chimeric antigen receptor T cell therapy with immune checkpoint inhibitors has also shown promise in research findings [16].

### 2.3 Current status of evaluation methods for the effect of combined treatment regimens

The current assessment of combined tumor immunotherapy efficacy relies on parameters like survival rate, disease control rate, and progression-free survival [17]. A number of tools commonly used for assessing this modality of treatment include Kaplan-Meier survival curves and Cox proportional hazard models, which effectively establish the influence of different therapeutic regimens on patient survival time. Recently, iRECIST has also been proposed for some special response patterns in immunotherapy, such as pseudoprogression [18].

In view of the complexity of immunotherapy, more and more researchers have begun to pay attention to biomarkers that predict treatment response, such as tumor mutation burden (TMB) and PD-L1 expression levels [19]. These markers can not only help screen patients suitable for immunotherapy, but also serve as an important basis for evaluating efficacy. With the in-depth understanding of the complex interactions between the tumor microenvironment and the immune system, future evaluation methods will be more personalized and can more accurately reflect the clinical effects of immunotherapy and combination therapy [20].

## 3. Theoretical basis of survival analysis

### 3.1 Basic concepts of survival analysis

Survival analysis is a statistical method that is mainly used to analyze time-to-event data, especially patient survival analysis in the medical and biomedical fields. Its uniqueness lies in the processing of "censored data", that is, at the end of the study, some subjects may not have experienced the target event (such as death or disease recurrence), and this data can only provide partial time information [21]. The main purpose of survival analysis is to predict the probability of an event in a population through modeling, such as estimating the effect of a certain treatment on patient survival time. A core feature of survival analysis is that it can simultaneously process right-censored and truncated data, that is, the data records of some individuals may not be fully collected due to reasons such as the end of the study or loss of follow-up, but can still provide valuable partial information [22].

Common application scenarios of survival analysis include analyzing the survival time of cancer patients and the survival rate after organ transplantation. By drawing and comparing survival curves, researchers can visually observe the differences in survival between different treatment groups and determine whether such differences are statistically significant through further statistical tests (such as the log-rank test) [23]. With the development of modern statistics, survival analysis models have been continuously optimized and can better cope with complex clinical data, especially when dealing with multivariate and high-dimensional data [24].

### 3.2 Introduction to Common Survival Analysis Methods

In the survival analysis, there are many methods, and among them, the most used ones are the

Kaplan-Meier method, log-rank test, and Cox proportional hazard model. The Kaplan-Meier method is a non-parametric estimation method used to estimate the event probability in a population, and also it is used to draw survival curves that show the differences in survival between different treatment groups [25]. It is mainly indicated for right censored data and can handle different times for subjects to exit the study. Log-rank test: This is a statistical test used in the comparison of differences that exist in survival curves between two or more groups. Computed frequency of events in the groups at different time points shows whether they are statistically significant [26].

The Cox proportional hazard model is another survival analysis tool that is used most frequently to analyze different variables for their effect on the survival time. In this model, the event occurrence is considered to be a constant risk to each variable; in other words, the use of hazard ratio does not change with time. Moreover, the Cox mode allows the estimation of the influence of each variable, while it simultaneously manages to adjust several confounding factors in order to obtain more accurate results of the analysis. Moreover, recently, due to the increase in volume and complexity of data, some new methods have also begun to be used by researchers such as machine learning algorithms like Random Survival Forest while processing the high-dimensional biomedical data [27].

### 3.3 Application of survival analysis in medical research

The range of applications in medical research is quite broad in cancer treatment outcomes, transplant recipients' survival rates to chronic diseases. Using techniques like Kaplan-Meier survival curves and the Cox proportional hazard models, in order to detect the differences in survival of various options treatments employed, so as to assist the clinicians in making as precise a treatment decision as possible. For example, in cancer research, survival analysis is done in order to analyze how different types of treatments affect the survival time of patients; logrank test will be used in order to determine its statistical significance. This kind of analysis not only will help doctors to select the best treatment option but will also provide a scientific basis for clinical trials.

In addition, survival analysis is also widely used in the study of “omics” data such as genomics and transcriptomics, helping researchers understand the impact of molecular features on patient prognosis. For example, by analyzing high-dimensional gene expression data, researchers can discover potential biomarkers and predict the survival of different patients. With the development of big data and machine learning technology, survival analysis methods are also constantly improving, and can better cope with complex multivariate and large sample data, improving the accuracy and efficiency of clinical research.

## 4. Construction of survival analysis model for tumor immunotherapy combination regimen

### 4.1 Data collection and preprocessing

In the initial stage of constructing the survival analysis model, the collected data of tumor immunotherapy combination regimens must be processed first. Usually, the research data comes from clinical trials, hospital medical records or public tumor research databases. Data collection should include the following aspects:

① Basic information of patients: including age, gender, weight, pathological stage, etc.

② Treatment regimen: including the type of immunotherapy received, combined treatment regimen and dosage, etc.

③ Follow-up time: record the end point of each patient's survival time from the start of treatment to the end point (event occurrence or end time).

④ Outcome event: usually patient death or disease progression (i.e., event that terminates survival

time).

The key to cluster analysis is to construct a similarity matrix and classify samples using hierarchical clustering or K-means clustering. The similarity matrix is defined as:

$$S(i,j)=\exp\left(-\frac{\| x_i-x_j\|^2}{2\sigma^2}\right) \tag{1}$$

Among them, $S(i,j)$ represents the similarity between sample iii and sample $j$, $x_i$ and $x_j$ are the gene expression vectors of the samples, and $\sigma$ is the scale parameter used to adjust the similarity calculation. In this way, different tumor subtypes can be effectively identified, and the survival time differences of each subtype under different treatment options can be further analyzed.

## 4.2 Construction process of survival analysis model

In order to evaluate the effects of different combined treatment regimens on the survival time of cancer patients, a variety of survival analysis models were constructed. First, the survival time distribution of each treatment group was estimated by the Kaplan-Meier survival curve, and the survival difference between different treatment groups was tested by the log-rank test.

The estimation formula of the survival function is as follows:

$$S(t)=\prod_{t_i\le t}\left(1-\frac{d_i}{n_i}\right) \tag{2}$$

Among them, $S(t)$ is the survival probability at time $t$, $d_i$ is the number of individuals who have an event (such as death) at time $t_i$, and $n_i$ is the number of individuals still in the study before time $t_i$. This formula is used to draw the Kaplan-Meier survival curve to visualize the survival rate of each treatment regimen.

Secondly, the effect of different treatment regimens on the risk of death of patients is analyzed based on the Cox proportional hazard model. In order to screen the features significantly related to the survival time and reduce the overfitting of the model, this paper adopts the LASSO regression method. LASSO regression achieves the purpose of feature selection by adding penalty terms to shrink the coefficients of some features to zero. The optimization objectives of LASSO regression are as follows:

$$\min_{\beta_0,\beta}\left\{\frac{1}{2N}\sum_{i=1}^{N}\left(y_i-\beta_0-\sum_{j=1}^{p}\beta_j x_{ij}\right)^2+\lambda\sum_{j=1}^{p}|\beta_j|\right\} \tag{3}$$

Among them, $y_i$ is the survival time of the $i$th sample, $x_{ij}$ is the jth feature of the ith sample, $\beta_0$ is the intercept, $\beta_j$ is the regression coefficient of the $j$th feature, and $\lambda$ is the penalty parameter. By adjusting the λ value, we can control the complexity of the model and select key features that are closely related to survival time. These features are retained in the final Cox model to further evaluate the impact of different treatment options on patient survival time.

The basic form of the Cox proportional hazard model is:

$$h(t\mid X)=h_0(t)\cdot\exp(\beta_1X_1+\beta_2X_2+\cdots+\beta_pX_p) \tag{4}$$

Where $h(t\mid X)$ is the event rate at time $t$ given the covariates $X=(X_1,X_2,\ldots,X_p)$; $h_0(t)$ is the baseline hazard function, which represents the basic risk when all covariates are zero; $\beta_1,\beta_2,\ldots,\beta_p$ are the regression coefficients of the covariates, reflecting the impact of each feature on survival time.

### 4.3 Evaluation criteria for combined treatment survival analysis model

After the model was constructed, multiple evaluation criteria were used to evaluate the model to ensure its predictive ability and applicability. First, the log-rank test was used to compare the survival differences between different treatment groups. The formula for the log-rank test is as follows:

$$Q = \frac{\sum_{i=1}^{n}(O_i - E_i)^2}{E_i} \tag{5}$$

Among them, $O_i$ is the actual number of events in group $i$, $E_i$ is the expected number of events, and $Q$ is the test statistic. By performing a log-rank test on different treatment regimens, the significant differences between different treatment regimens can be evaluated.

Secondly, in order to avoid overfitting of the model and improve its predictive ability, the Akaike Information Criterion (AIC) is used to select the model. The calculation formula of AIC is:

$$AIC = -2\ln(\text{likelihood}) + 2k \tag{6}$$

Where $\ln(\text{likelihood})$ is the log-likelihood of the model, and $k$ is the number of free parameters in the model. The lower the AIC value is, the better the model fit.

## 5. Empirical study on the evaluation of combined treatment effects based on survival analysis

### 5.1 Data samples and research subjects

In this study, we collected clinical data from 200 patients with advanced tumors from a cancer hospital. These patients received different immunotherapy combinations, including single immunotherapy (such as PD-1/PD-L1 inhibitors) and combined radiotherapy, chemotherapy, targeted therapy and other combination regimens. The basic information of the sample is shown in Table 1, including variables such as the patient's age, gender, and pathological stage. The follow-up time of these patients was from the start of treatment to death or the most recent follow-up node, and the survival status was recorded. To ensure the integrity of the data, cases with insufficient follow-up were excluded.

Table 1: Overview of basic information of patients

| Variables | Mean (SD) | Range | N (%) |
|---|---|---|---|
| Age (years) | 58.6 (11.4) | 32-85 | - |
| Gender | - | - | Male (60%), Female (40%) |
| Cancer Stage | - | - | Stage III (45%), Stage IV (55%) |
| Treatment Modality | - | - | Immunotherapy Alone (35%), Combination Therapy (65%) |

Table 2: Distribution of treatment options

| Treatment Modality | N (%) |
|---|---|
| Immunotherapy Alone | 70 (35%) |
| Immunotherapy + Chemotherapy | 50 (25%) |
| Immunotherapy + Radiotherapy | 30 (15%) |
| Immunotherapy + Targeted Therapy | 50 (25%) |

Table 1 shows the age, gender distribution and tumor stage of the patients, and Table 2 lists the

distribution of patients with different combined treatment regimens. It can be seen that the vast majority of patients received combined treatment regimens, and the age distribution was relatively wide. This laid the foundation for subsequent survival analysis.

## 5.2 Survival analysis results and model evaluation

In order to analyze the effects of different tumor immunotherapy combinations on patient survival, the Kaplan-Meier method was first used to generate survival curves. The data set includes 200 patients, of whom 70 received single immunotherapy and 130 received different combination therapy regimens. To further verify the effect of each treatment regimen, we performed a Cox proportional hazard model analysis to quantify the effect of each treatment regimen on survival time. Figure 1 shows the Kaplan-Meier survival curves of different treatment regimens, indicating that combined therapy has a significant advantage over single immunotherapy in prolonging survival time.

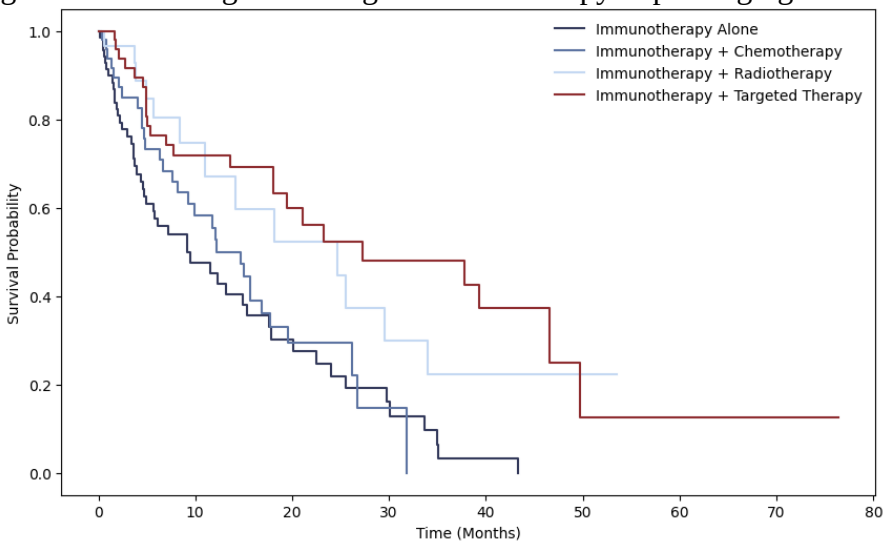


Figure 1: Kaplan-Meier survival curves of different treatment regimens

As can be seen from Figure 1, the survival rate of single immunotherapy decreased rapidly, while the survival rate of combined therapy was relatively stable, especially the survival time of combined immunotherapy and targeted therapy was the longest. This shows that combined therapy can significantly improve the survival rate of patients.

In further analysis, we used the Cox proportional hazard model to evaluate the effect of each treatment regimen on survival time, and combined with LASSO regression to screen out biomarkers significantly associated with survival. Through LASSO regression, we effectively reduced the number of features in the model and avoided overfitting. The key features that were finally retained included certain gene expression levels and clinical characteristics.

Figure 2 illustrates how the LASSO regression model penalizes the regression coefficients as $\lambda$ increases, progressively shrinking the coefficients of less important features towards zero. The inclusion of error bars emphasizes the consistency of model performance across different folds during cross-validation. The optimal $\lambda$, shown by the vertical line, represents the best balance between model complexity and predictive accuracy, chosen to reduce the model's overfitting risk while maintaining important predictive features.

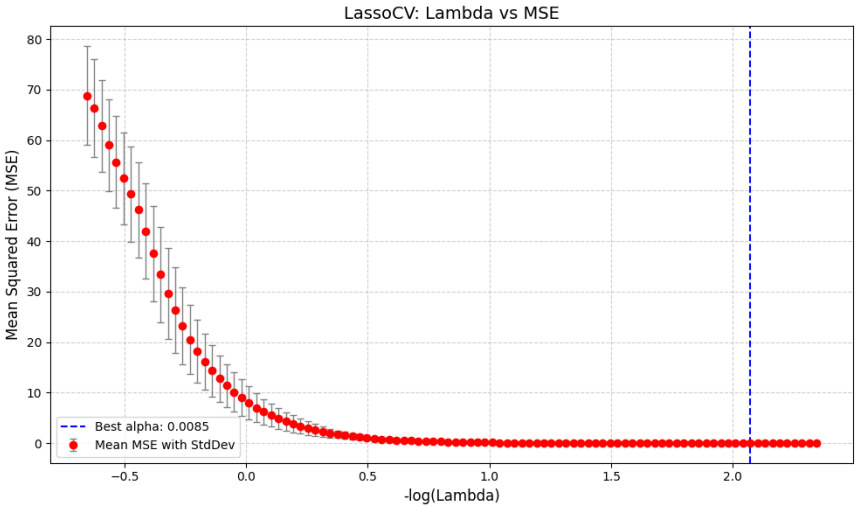


Figure 2: Lambda vs. Mean Squared Error for LASSO Regression with Cross-Validation

Table 3 shows the regression coefficients and their significance levels of the Cox proportional hazard model.

Table 3: Results of Cox proportional hazards model

| Variables | Coefficient (β) | Std. Error | p-value |
|---|---|---|---|
| Immunotherapy Alone (ref) | - | - | - |
| Immunotherapy + Chemotherapy | -0.42 | 0.13 | <0.001 |
| Immunotherapy + Radiotherapy | -0.31 | 0.15 | 0.004 |
| Immunotherapy + Targeted Therapy | -0.58 | 0.12 | <0.001 |
| Age (per year increase) | 0.02 | 0.01 | 0.03 |
| Cancer Stage (Stage IV vs Stage III) | 0.78 | 0.22 | <0.001 |

The Cox model results in Table 3 show that all combined treatments significantly reduced the risk of death in patients, especially immune combined targeted therapy, with a risk reduction coefficient of -0.58, which was significantly better than other options. Patient age and tumor stage also significantly affected survival time, and the later the stage, the higher the risk.

## 5.3 Comparative analysis of combined treatment effects

To better understand the long-term effects of each treatment regimen, we drew the cumulative risk curves of each. The survival curves of different treatment groups were compared using the log-rank test. The test results showed that the survival of the combined treatment group was significantly better than that of the single immunotherapy group. Figure 3 shows the cumulative risk curves of each treatment regimen, illustrating the impact of different treatment regimens on survival time.

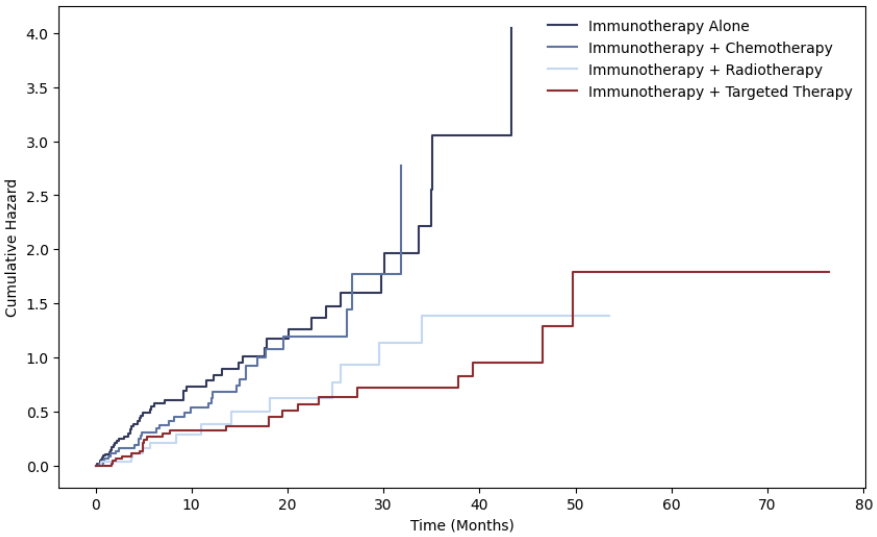


Figure 3: Cumulative Hazard Curves for Different Treatment Modalities

As can be seen from Figure 3, the cumulative risk of single immunotherapy increases the fastest, indicating that its patients have a shorter survival time; while the cumulative risk of combined targeted therapy increases the slowest, indicating that this regimen effectively prolongs survival time. The risk curves of immunotherapy combined with chemotherapy and radiotherapy are between the two, indicating that their effects are inferior to targeted therapy but better than single immunotherapy.

## 6. Conclusion

By performing survival analysis on the clinical data and gene expression data of 200 cancer patients, this study systematically evaluated the effects of different immunotherapy combinations on patient survival time. The results showed that immunotherapy combined with other treatments (such as chemotherapy, radiotherapy and targeted therapy) significantly prolonged the survival of patients, especially the effect of immunotherapy combined with targeted therapy was the most significant. The Kaplan-Meier survival curve showed that the survival rate of the immunotherapy combined with targeted therapy group remained at a high level for a long time, while the survival rate of the single immunotherapy group decreased rapidly. The analysis results of the Cox proportional hazard model further showed that combined targeted therapy significantly reduced the risk of death in patients, and the risk reduction was greater than that of other treatment combinations. In addition, the biomarkers significantly associated with survival time screened by LASSO regression further proved that the effect of immunotherapy combined therapy was closely related to the molecular characteristics of patients.

In summary, immunotherapy combination can significantly improve the survival rate of cancer patients, especially in combined targeted therapy. This study further explored the heterogeneity of tumor samples through cluster analysis, revealing differences in the response of different tumor subtypes to treatment regimens. This provides an important scientific basis for individualized treatment. Studies have shown that optimized immunotherapy combination strategies can effectively prolong patient survival with advanced tumors and reduce cancer recurrence, providing strong support for future clinical practice.

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