Dynamically prognosticating patients with hepatocellular carcinoma through survival paths mapping based on time-series data

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Patients with hepatocellular carcinoma (HCC) always require routine surveillance and repeated treatment, which leads to accumulation of huge amount of clinical data. A predictive model utilizes the time-series data to facilitate dynamic prognosis prediction and treatment planning is warranted. Here we introduced an analytical approach, which converts the time-series data into a cascading survival map, in which each survival path bifurcates at fixed time interval depending on selected prognostic features by the Cox-based feature selection. We apply this approach in an intermediate-scale database of patients with BCLC stage B HCC and get a survival map consisting of 13 different survival paths, which is demonstrated to have superior or equal value than conventional staging systems in dynamic prognosis prediction from 3 to 12 months after initial diagnosis in derivation, internal testing, and multicentric testing cohorts. This methodology/model could facilitate dynamic prognosis prediction and treatment planning for patients with HCC in the future.
**Table 1 Baseline characteristics of derivation, validation, and testing cohort at initial diagnosis**

| Variable              | Derivation cohort no. (%) | Internal testing cohort no. (%) | P value | Multicenter testing cohort no. (%) | P value |
|-----------------------|---------------------------|--------------------------------|---------|-----------------------------------|---------|
| **Age (years)**       |                           |                                 |         |                                   |         |
| ≤50                   | 370 (37.8)                | 249 (39.7)                      | 0.441   | 199 (48.1)                        | <0.001  |
| >50                   | 609 (62.2)                | 378 (60.3)                      |         | 215 (51.9)                        |         |
| **Gender**            |                           |                                 |         |                                   |         |
| Male                  | 889 (90.8)                | 554 (88.4)                      | 0.113   | 361 (87.2)                        | 0.043   |
| Female                | 90 (9.2)                  | 73 (11.6)                       |         | 53 (12.8)                         |         |
| **HBV infection**     |                           |                                 |         |                                   |         |
| No                    | 33 (3.4)                  | 32 (5.1)                        | 0.086   | 15 (3.6)                          | 0.813   |
| Yes                   | 946 (96.6)                | 595 (94.9)                      |         | 399 (96.4)                        |         |
| **AFP (IU/ml)**       |                           |                                 |         |                                   |         |
| <25                   | 318 (32.5)                | 214 (34.1)                      | 0.493   | 146 (35.3)                        | 0.314   |
| ≥25                   | 661 (67.5)                | 413 (65.9)                      |         | 268 (64.7)                        |         |
| **Child-Pugh class** |                           |                                 |         |                                   |         |
| A                     | 841 (85.9)                | 536 (85.5)                      | 0.815   | 360 (87.0)                        | 0.602   |
| B                     | 138 (14.1)                | 91 (14.5)                       |         | 54 (13.0)                         |         |
| **Tumor size (cm)**   |                           |                                 |         |                                   |         |
| Mean ± SD             | 7.20 ± 3.57               | 7.07 ± 3.48                     | 0.727   | 7.12 ± 3.51                       | 0.939   |
| ≤5                    | 732 (33.6)                | 216 (34.4)                      |         | 140 (33.8)                        |         |
| >5                    | 650 (66.4)                | 411 (65.6)                      |         | 274 (66.2)                        |         |
| **Number of lesions** |                           |                                 |         |                                   |         |
| ≤3                    | 391 (39.9)                | 238 (38.0)                      | 0.428   | 166 (40.1)                        | 0.956   |
| >3                    | 588 (60.1)                | 389 (62.0)                      |         | 248 (59.9)                        |         |

*All values are presented as numbers of patients followed by percentages in the parentheses. P values were calculated by comparing categorical variables between testing cohorts and derivation cohort with chi-square test.*
cases with effective data, respectively; the significance value α was set at 0.006. After completing all the processing cycle of the derivation cohort, the data from time slice 1 – 9 were divided into 2, 4, 7, 10, 12, 10, and 7 subclasses, respectively; subclasses with <6 cases were excluded from the mapping to reduce the risk of model overfitting. By connecting the class with its derivative classes, a total of 13 survival paths were constructed, which were illustrated in different colors (Fig. 1).

In this model of survival path, every bifurcation point is called a node, and each node integrates the information of previous nodes to facilitate prognosis prediction.

**Prognostic value of survival path in derivation cohort.** In the derivation cohort, the prognostic power between the survival path system, BCLC staging system, AJCC staging system, and ART score system was compared at all nine time slices (Table 2). The survival path system had superior or non-inferior c-index in predicting OS than BCLC staging system, AJCC staging system, and ART score system from time slice No.3 to time slice No.5. At time slice No.2, the AJCC staging system had superior c-index than survival path system, while no significant difference in c-index between the survival path system and BCLC staging system was found. It was interesting to note that the survival differences between stage B and stage C in BCLC staging system, as well as the differences between stage IIIa, stage IIIb, and stage IVb in AJCC staging system, diminished to insignificance starting at time slice No.5; by contrast, the survival path system presented superior performance in dynamically discrimination the OS of HCC patients (Fig. 2).

**Validation of the survival path system in testing cohorts.** Generally, the survival curves in the internal testing cohort and multicenter testing cohort fit well with the curves in the derivation cohort (Fig. 3). In the internal testing cohort, the survival path system showed superior and non-inferior prognostic value than the BCLC staging system and AJCC staging system from time slice No.3 to time slice No.5. The advantages of the survival path system diminished starting at time slice No.6. The results in the multicenter testing cohort confirmed the advantages of the survival path system over other two staging systems from time slice No.3 to time slice No.5 (Table 3). The significance of each path bifurcation was also evaluated in the testing cohorts (Table 4). A P value < 0.05 could be achieved in all the bifurcation with enough (≥6) cases in each of the following comparator nodes, which demonstrated the stability of the survival path system we built.

**Long-term survival based on the survival paths system.** Of the 13 paths constructed, 3 paths lead to long-term survival (>60 months), including No.1, No.2, and No.8. The No.1 and No.2 paths reached long-term survival when no viable lesions was achieved. However, disease progression could occur at any time.
slice in a small proportion of patients even they are on the paths of long-term survival. For the No. 8 path, due to the limitation of our sample size, the key factors related to long-term survival fail to be identified.

**Treatment and the path transfer.** Of all the nodes in the survival path system, five nodes went down from bifurcated nodes in the previous time slice and bifurcated in the following time slice. These nodes had unfavorable prognosis and the survival path system might provide guidance. Surgery and ablative therapies are considered aggressive management and therefore we described the proportion of patients receiving surgery/ablation in these nodes (Table 5). The surgery/ablation rates in S(p=4), S(p=5), S(p=6) and S(p=7) were 23.3%, 24.5%, 31.4%, 25.2%, and 13.2%, respectively; candidates who received surgery/ablation had rates of 83.3%, 84.6%, 81.3%, 71.2% and 56.7%, going to the upper node in the next time slice, respectively. We define a node meets both following conditions: (1) median OS time of its upper bifurcated node had 10 months higher than that of the lower bifurcated node; (2) more than 80% patients receiving surgery/ablation went to the upper bifurcated node, as a chance node; then the S(p=3), S(p=4) and S(p=5) are candidate nodes.

**Incurable disease based on the survival paths system.** Of all the paths in this map, two paths (No.10 and No.13) only have one valid node after bifurcation. We define a node without following valid node after bifurcation and had a median OS time less than 5 months as an incurable node, then S(p=10, ts=4) is the incurable node.

**Discussion**

In this work, we developed an analytical model to dynamically trace the prognosis of cancer patients with BCLC stage B HCC. Time slice was employed for data conversion and Cox-based feature selection for constructing the cascade structure of survival path. The survival path model showed superior or non-inferior prognostic value than the conventional BCLC and AJCC staging system from time slice No.3 to time slice No.5, which were confirmed in internal and multicenter testing cohorts. These results suggest that this tool is valuable in dynamic prognosis prediction and treatment planning for patients with intermediate-stage HCC during the time frame of 3–12 months after diagnosis.

Currently, studies on developing re-staging systems for malignant tumors were always hindered by the lack of effective methods in utilizing with time-series data, and by the fact that different treatments could lead to different re-staging strategies, which restrict the generalization of established models. In HCC, the BCLC staging system is most widely used for staging and re-staging during clinical practice. This classification uses variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms, and has been validated as the best staging system for treatment guidance. However, the provided information of BCLC staging system was not enough to support dynamic prognosis prediction and real-time treatment planning, as reflected by our results that the survival differences between Stage B and Stage C subgroups gradually decreased over time. Hence we proposed to create a more precise system. The survival path we built for intermediate-stage HCC integrated the time-series information of variables utilized in BCLC classifications, variables on image change after treatment, and variables on important serum markers; although only one selected feature was utilized for node subdivision at each time slice, the model constructed showed superior or non-inferior prognostic value than the BCLC staging system at all time slices in the derivation cohort, indicating that this methodology had great potential.

In the testing cohorts, we observed that the c-index of survival path system decreased at time slice No.6 and the advantages of the survival path system compared to BCLC and AJCC staging systems diminished starting at time slice No.6. Moreover, the c-index of BCLC staging system was significantly higher than the survival path system in the internal testing cohort at time slice No.6. These phenomena may be caused by the fact that no more path bifurcations were made since time slice No.6 due to the

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**Table 2 Comparison of c-index between the survival path system, BCLC staging system, AJCC staging system, and ART score at each time slice in the derivation cohort**

| Time slice | Number of cases (modeling/all) | Survival path system | BCLC staging system | AJCC staging system | ART class |
|------------|-------------------------------|----------------------|---------------------|---------------------|-----------|
|            | Number of nodes | c-index (95% CI)     | Number of classes | c-index (95% CI)     | Number of classes | c-index (95% CI)     | Number of classes | c-index (95% CI)     |
| No.1       | 979/979                      | 2                    | 0.624              | (0.623–0.625)       | 1                      | 0.602              | (0.601–0.603)       | 1                      |
| No.2       | 822/822                      | 4                    | 0.695              | (0.693–0.697)       | 5                      | 0.702              | (0.702–0.704)       | 2                      |
| No.3       | 506/513                      | 7                    | 0.733              | (0.730–0.736)       | 4                      | 0.725              | (0.722–0.728)       | 2                      |
| No.4       | 374/390                      | 10                   | 0.760              | (0.756–0.764)       | 4                      | 0.724              | (0.720–0.727)       | 2                      |
| No.5       | 307/336                      | 12                   | 0.768              | (0.763–0.773)       | 4                      | 0.731              | (0.726–0.730)       | 2                      |
| No.6       | 245/294                      | 12                   | 0.771              | (0.764–0.778)       | 5                      | 0.749              | (0.742–0.756)       | 2                      |
| No.7       | 199/246                      | 10                   | 0.792              | (0.783–0.801)       | 4                      | 0.764              | (0.755–0.773)       | 2                      |
| No.8       | 167/221                      | 10                   | 0.811              | (0.799–0.823)       | 4                      | 0.773              | (0.762–0.784)       | 2                      |
| No.9       | 128/202                      | 7                    | 0.830              | (0.816–0.844)       | 4                      | 0.769              | (0.752–0.786)       | 2                      |

*Nodes of survival path system with less than six cases were excluded from the computing of c-index. Therefore, the number of cases in modeling is less than the number of all cases with effective data.*

*The c-index of the interested system was lower than survival path system, with P < 0.006.*

*The c-index of the interested system was higher than the survival path system, with P < 0.006.*
The survival path model we established can also guide treatment planning for intermediate-stage HCC. In the management of patients on the paths going up, we need to closely pay attention to the key variables that could transfer the patient to unfavorable clinical behavior of cancer. The third aspect is to develop methods in dealing with irregular time series. Converting the time-series data further improve this model/methodology. The first aspect is to use learning algorithms to explore the best cutoff for individual variable and optimizing the process of feature selection, including random forest, k-nearest neighbor, and neural networks, bootstrap validation could be utilized alongside to ensure quality control and reduce the risk of overfitting. The second aspect is to develop algorithms for node fusion, which may enhance our utilization of the database and give us an insight into the biological behavior of cancer. The third aspect is to develop methods in dealing with irregular time series. Converting the time-series data into time slices of 3 months will result in some missing data, therefore, a learning algorithm that dynamically design the interval of time slice in specific node based on the characteristics of data is needed to maximally utilize the data.

In conclusion, the survival path model constructed in this study offers a superior method for dynamic prognostication for HCC patients during the time frame of 3–12 months after diagnosis, compared with the current BCLC staging system. The methodology utilized in this study also pioneers as an effective tool in processing the clinical big data of cancer patients in the future.
Methods
Patients and variables of interest. Between January 2007 and May 2012, 5005 consecutive patients with newly diagnosed HCC at Sun Yat-sen University Cancer Center (SYSUCC) were retrospectively reviewed to develop the derivation cohort. Between June 2012 and December 2015, an independent consecutive series of 3843 HCC patients treated at SYSUCC were reviewed to develop the internal testing cohort. Besides, between January 2010 and December 2016, 843 patients from Fifth Affiliated Hospital of Sun Yat-sen University, 415 patients from the Third Affiliated Hospital of Sun Yat-sen University, and 437 patients from the Second Hospital of Guangzhou Medical University were reviewed to develop the multicenter testing cohort. The inclusion criteria were as follows: (1) clinically diagnosed with BCLC stage B HCC; (2) complete data of any of the following at initial diagnosis: computed tomography (CT) or magnetic resonance imaging (MRI) of the abdominal region, radiography or CT of the chest, routine bloodwork test, biochemical routine test, serum AFP level, and coagulation indices; and (3) without history of other malignancies. A total of 979, 627, and 414 patients were included in the derivation cohort, internal testing cohort, and multicenter testing cohort, respectively.

The Department of Clinical Research of Sun Yat-sen University Cancer Center approved the study protocol (2017-FXY-129). The Hospital Ethics Committee of the four medical centers approved this study, which waived the need for written informed consent based on the retrospective nature of the study.

Most patients (1852/2020, 91.7%) in the above-mentioned medical centers received TACE as their first-line treatment; 135 (6.7%) patients received surgical resection as initial treatment and 33 (1.6%) patients refused to receive treatment. The subsequent therapies after TACE, which constituted of ablative therapies, surgical resection, targeted therapies, or palliative chemotherapy, were adopted based on the decision of the multidisciplinary teams, including hepatologists, radiologists, and interventional radiologists. Patients were followed up monthly during the period of initial treatment, subsequently at every 2–3 months for the first 2 years if complete remission was achieved. The frequency gradually decreased to every 3–6 months after 2 years’ remission.

Time-series data on serum tumor markers, biochemical and hematological indices, medical imaging, and associated changes (CT and/or MRI) of each patient were collected. Based on past literatures on staging systems and laboratory tests, a total of nine variables were designed, covering imaging results, laboratory tests, and performance status; all the variables were dichotomized (Table 6).

Transformation of datasets for analysis. To analyze the data, the time-series data were grouped into data at standard time slices. For every patient, the zero
Table 3 Comparison of c-index between the survival path system, BLC C staging system, and AJCC staging system in the internal testing cohort and multicenter testing cohort

| Time slice (modeling/ all) | Number of nodes | Survival path system c-Index (95% CI) | BLC C staging system c-Index (95% CI) | AJCC staging system c-Index (95% CI) |
|---------------------------|----------------|---------------------------------------|---------------------------------------|---------------------------------------|
|                           | Number of classes |                                               |                                       |                                       |
| Internal testing cohort   | No.1 627/627     | 2 0.634 (0.632-0.636)                   | 1 0.634                               | 6 0.634 (0.632-0.636)                 |
|                           | No.2 562/562     | 4 0.659 (0.692-0.698)                   | 5 0.724a (0.721-0.727)                | 6 0.732b (0.730-0.736)                |
|                           | No.3 367/367     | 8 0.747 (0.722-0.752)                   | 4 0.792b (0.725-0.733)                | 6 0.737b (0.732-0.742)                |
|                           | No.4 271/277     | 10 0.774 (0.766-0.782)                  | 4 0.759b (0.743-0.759)                | 6 0.737b (0.729-0.745)                |
|                           | No.5 210/222     | 11 0.764 (0.755-0.773)                  | 4 0.760a (0.749-0.771)                | 6 0.728b (0.712-0.739)                |
|                           | No.6 171/181     | 11 0.756 (0.743-0.769)                  | 5 0.785a (0.755-0.775)                | 6 0.746 (0.732-0.760)                 |
|                           | No.7 125/148     | 8 0.820 (0.803-0.837)                   | 4 0.817 (0.801-0.833)                 | 6 0.824 (0.808-0.840)                 |
| Multicenter testing cohort| No.1 414/414     | 2 0.631 (0.628-0.634)                   | 1 —                                   | 3 0.602a (0.599-0.605)                |
|                           | No.2 359/359     | 4 0.689 (0.685-0.693)                   | 4 0.698a (0.694-0.702)                | 6 0.715a (0.711-0.719)                |
|                           | No.3 233/234     | 7 0.725 (0.718-0.732)                   | 4 0.715a (0.709-0.721)                | 6 0.720 (0.714-0.726)                 |
|                           | No.4 181/189     | 8 0.790 (0.781-0.799)                   | 4 0.752b (0.742-0.762)                | 6 0.759b (0.749-0.769)                |
|                           | No.5 131/149     | 7 0.778 (0.765-0.791)                   | 4 0.757b (0.745-0.769)                | 6 0.754b (0.743-0.765)                |
|                           | No.6 113/128     | 7 0.769 (0.750-0.788)                   | 4 0.714b (0.695-0.733)                | 6 0.734 (0.716-0.752)                 |

*The c-index of the interested system was higher than the survival path system, with P < 0.006

Table 4 Hazard ratio and significance of upper node versus lower node at each path bifurcation in the derivation, internal testing, and multicenter testing cohorts

| Bifurcation node | Derivation cohort HR (95% CI) | P value | Internal testing cohort HR (95% CI) | P value | Multicenter testing cohort HR (95% CI) | P value |
|------------------|--------------------------------|---------|-------------------------------------|---------|---------------------------------------|---------|
| S[0; ts = 1]     | 2.33 (1.97-2.75)               | <0.0001 | 2.58 (2.00-3.32)                    | <0.001 | 2.34 (1.80-3.05)                      | <0.001  |
| S[p = 1, ts = 1] | 3.70 (2.78-4.93)               | <0.0001 | 3.69 (2.40-5.69)                    | <0.001 | 2.79 (0.17-4.53)                      | <0.001  |
| S[p = 1, ts = 2] | 3.50 (2.26-5.43)               | <0.0001 | 2.52 (1.29-4.91)                    | 0.007  | 5.95 (2.98-11.91)                     | <0.001  |
| S[p = 1, ts = 3] | 5.25 (2.97-9.31)               | <0.0001 | 4.02 (1.57-10.31)                   | 0.004  | 12.27 (4.53-33.26)                    | <0.001  |
| S[p = 1, ts = 4] | 5.08 (2.24-11.52)              | <0.0001 | 6.35 (1.51-26.75)                   | 0.012  | —                                    | —       |
| S[p = 2, ts = 1] | 2.73 (2.04-3.66)               | <0.0001 | 3.31 (2.06-5.32)                    | <0.001 | 2.47 (1.64-3.73)                      | <0.001  |
| S[p = 3, ts = 3] | 6.45 (3.29-12.62)              | <0.0001 | 7.16 (2.00-25.60)                   | 0.002  | 6.12 (2.69-13.94)                     | <0.001  |
| S[p = 4, ts = 2] | 5.61 (2.05-15.34)              | <0.0001 | —                                   | 0.052a | —                                    | —       |
| S[p = 5, ts = 3] | 4.26 (2.35-7.72)               | <0.0001 | 3.83 (1.84-7.98)                    | <0.001 | 3.48 (1.33-9.11)                      | 0.011   |
| S[p = 5, ts = 4] | 10.35 (3.17-33.82)             | <0.0001 | —                                   | —      | —                                    | —       |
| S[p = 6, ts = 4] | 6.89 (1.47-32.14)              | 0.005   | —                                   | —      | —                                    | —       |
| S[p = 7, ts = 4] | 4.45 (1.67-11.85)              | 0.003   | 3.67 (1.03-8.71)                    | 0.048  | —                                    | —       |

*p = path; ts = time slice
*No deaths were recorded in one node and Kaplan-Meier Method with log rank test was utilized
*Sample size in one node of the two comparators was <6

Table 5 The correlation between surgery/ablation and path transfer in KEY nodes

| Nodes, n | With surgery/ablation | Without surgery/ablation | P value |
|----------|-----------------------|--------------------------|---------|
|          | Go up (n, %)          | Go down (n, %)           | Died/NS (n, %) | Go up (n, %) | Go down (n, %) | Died/NS (n, %) | P value |
| S[p = 3, ts = 2] | 20 (83.3)             | 2 (8.3)                  | 2 (8.3)       | 37 (46.8)    | 2 (2.5)       | 40 (50.6)      | <0.001  |
| S[p = 5, ts = 3] | 11 (84.6)             | 1 (7.7)                  | 1 (7.7)       | 20 (50.0)    | 2 (12.5)      | 15 (37.5)      | 0.072a  |
| S[p = 8, ts = 4] | 13 (81.3)             | 2 (12.5)                 | 1 (6.3)       | 16 (45.7)    | 12 (34.3)     | 7 (20.0)       | 0.070a  |
| S[p = 2, ts = 1] | 79 (71.2)             | 24 (21.6)                | 8 (7.2)       | 50 (15.2)    | 203 (61.5)    | 77 (23.3)      | <0.001  |
| S[p = 4, ts = 2] | 17 (56.7)             | 7 (23.3)                 | 6 (20.0)      | 28 (14.2)    | 38 (19.3)     | 131 (66.5)     | <0.001  |

*p = path; ts = time slice, NS: no surveillance
*Fisher’s exact test
point was set at the time of diagnosis of HCC. An interval of 3 months was utilized and the time ranges (in months) of −1~0, 0.5~3, 3.1~6, 6.1~9, 9.1~12, 12.1~15, 15.1~18, 18.1~21, and 21.1~24 were transformed into 9 consecutive time slices. For variables measured more than once in each time slice, the newest values were selected to be associated with the time slice. The time slice with complete data of the nine variables was defined as slice with complete data. If the data in one time slice were incomplete or unavailable, but the follow-up suggested the patient was still alive, the data in this slice and subsequent slices were regarded as point with no surveillance. If the patient died or lost follow-up, the data in the following time slice were regarded as nonexistent (Fig. 4a).

The primary outcome was OS. For data in the first slice, OS was defined as time from diagnosis to death by any causes. For subsequent time slices, OS was defined as time from image examination of that time slice to death by any causes.

Feature selection and construction of survival path. Step 1: We start with using the data at first time slice of the derivation cohort, which is denoted $S_{(all; ts = 1)}$ (Fig. 4b). Univariate analysis with Kaplan–Meier (KM) method was utilized to identify candidate variables ($X_1, X_2, \ldots, X_p$). In constructing the survival path, each feature selection process at a specific time slice was considered as an independent experiment. To control the false discovery rate, suppose we have $m$ time slices, the preselected significance level for feature selection in each path was calculated by the formula below:

$$\alpha \leq \frac{m}{m}$$

Step 2: Judgment: The sample size required for the Cox proportional hazard regression model with multiple covariates was calculated\(^{25}\). If the sample size is larger than the calculated one, the data would proceed to feature selection. Less than calculated sample size will stop any future feature selection process and the group will remain the current classification.

Step 3: Feature selection: All the significant variables detected using the KM method were put into the Cox proportional hazard regression model, which

| Categories and variables | Methods of dichotomization |
|--------------------------|---------------------------|
| Laboratory tests         |                           |
| Serum AFP level (IU/ml)  | <200 vs. ≥200; <400 vs. ≥400 |
| Child-Pugh class         | Class B/C vs. class A; class C vs. class A/B |
| Imaging examination      |                           |
| Diameter of main lesion (mm) | ≤50 vs. >50; ≤70 vs. >70; ≤100 vs. >100 |
| Number and size of hepatic lesions | ≤3 lesions/2~3 lesions, D ≤30 mm vs. >3 lesions/2~3 lesions, D >30 mm; <4 lesions vs. ≥4 lesions |
| Vascular invasion        | With vs. without          |
| Distant metastasis       | With vs. without          |
| Vascular invasion/NL/N1/M1| With vs. without          |
| Change of lesions        | With viable lesion vs. without viable lesion |
| Performance status       | 0-2 vs. >2                |

### Table 6 Variables and methods of dichotomization for construction of the survival paths

| Categories and variables | Methods of dichotomization |
|--------------------------|---------------------------|
| Laboratory tests         |                           |
| Serum AFP level (IU/ml)  | <200 vs. ≥200; <400 vs. ≥400 |
| Child-Pugh class         | Class B/C vs. class A; class C vs. class A/B |
| Imaging examination      |                           |
| Diameter of main lesion (mm) | ≤50 vs. >50; ≤70 vs. >70; ≤100 vs. >100 |
| Number and size of hepatic lesions | ≤3 lesions/2~3 lesions, D ≤30 mm vs. >3 lesions/2~3 lesions, D >30 mm; <4 lesions vs. ≥4 lesions |
| Vascular invasion        | With vs. without          |
| Distant metastasis       | With vs. without          |
| Vascular invasion/NL/N1/M1| With vs. without          |
| Change of lesions        | With viable lesion vs. without viable lesion |
| Performance status       | 0-2 vs. >2                |
assumes the hazard as follows,

\[ h(t) = h_0(t) \exp \left( \sum_{j=1}^{p} \beta_j X_j \right) \]  

(2)

where \((X_1, X_2, \ldots, X_p)\) is a vector of \(p\) predictor variables, and \(\beta_1, \beta_2, \ldots, \beta_p\) are the corresponding regression coefficients, which are the weights given to each variable by the model. The original model included all the candidate variables and was presented as follows:

\[ Y = \beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p + \epsilon \]  

(3)

The backward elimination (BE) procedure was carried out, with the following \(p\) tests, \(H_0: \beta_j = 0, j = 1, 2, \ldots, p\), the lowest partial \(F\)-value \(F_1\) corresponding to \(H_0 : \beta_0 = 0\) is compared with the preselected significance values \(F_0\). If \(F_1 < F_0\), then \(F_1\) can be deleted and the new original model is:

\[ Y = \beta_0 + \beta_1 X_1 + \ldots + \beta_{p-1} X_{p-1} + \epsilon \]  

(4)

Then, a stepwise BE procedure was continued, until all \(F_i > F_0\) and the model is what we choose. The importance of each variable in the fixed Cox model can be obtained as follows:

\[ I_\beta = -2 \log \left( \frac{f_{0}(X_\beta)}{f_{0}(X)} \right) \]  

(5)

where \(I_\beta\) refers to the likelihood of the fixed model and \(f_{0}(X)\) refers to the likelihood of model after elimination of the variable \(X\). The variable eliminated from the model with the maximal change of \(-2\log\) likelihood was selected.

Step 4: Based on the selected dichotomized variable \(X_h\), the cohort \(S_{all = n-1}\) can be divided into two subgroups \(S_{- \beta = n/2}\) and \(S_{\beta = n/2}\). The data of the two subgroups at the next time slice, i.e., the \(S_{- \beta = n/2}\) and \(S_{\beta = n/2}\) will repeat steps 1–3, respectively (Fig. 4B). If there is no variable selected, the cohort stays the current classification and the data in the next time slice will repeat step 1–3.

Step 5: Graphic representation: The survival path was constructed and visualized using two-dimensional graph, with the time slices on \(x\)-axis and median OS time on \(y\)-axis.

**Statistical analysis.** Pearson \(r^2\) test was used to compare categorical variables between groups. To compare the efficacy in dynamic prognosis prediction between the survival path method and conventional staging systems, the measurement of \(c\)-index in each time slice was computed and compared using \(Z\) test method. All analyses were performed using SPSS version 20.0 (IBM Corporation, USA) and R version 3.3.2 (The R Foundation for Statistical Computing, 2016).

**Data availability.** All the relevant raw data that support the findings of this study have been deposited in the Dryad Digital Repository (https://datadryad.org/) datasets (doi:10.5061/dryad.pd44k8r). In addition, the authenticity of this data has also been validated by uploading the critical raw data onto the Research Data public platform (www.researchdata.org.cn), with the approval RDD number as RDDA2018000603.

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**Author contributions**

L.S. and W.L. designed and implemented methodology of survival path. L.S., Q.Z., P.G., J.H., C.L., B.C., Q.C., and T.H. participated in collecting the clinical data for modeling. L.S., Q.Z., J.H., T.P., L.Y., Q.C., and T.H. participated in collecting the clinical data for validation. N.W. and P.W. managed and advised on the project. L.S., Q.Z., P.G., and N.W. wrote the paper.
Additional information

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