SUPPLEMENTAL INFORMATION FOR

Necroptosis-driving genes RIPK1, RIPK3 and MLKL-p are associated with intratumoral CD3+ and CD8+ T cell density and predict prognosis in hepatocellular carcinoma

Lorenzo Nicolè¹,²*, Tiziana Sanavia³,*, Rocco Cappelless⁴, Valeria Maffeis⁵, Jun Akiba⁶, Akihiko Kawahara⁶, Yoshiki Naito⁶, Claudia Maria Radu⁷, Paolo Simioni⁷, Davide Serafin⁸, Giuliana Cortese⁸, Maria Guido¹,⁵, Giacomo Zanus⁹,¹⁰, Hirohisa Yano¹¹ and Ambrogio Fassina¹§

¹ Department of Medicine (DIMED), University of Padova, Padova, Italy
² Department of Pathology, Angelo Hospital, Aulss 3 Serenissima, Mestre, Italy
³ Department of Medical Sciences, University of Torino, Torino, Italy
⁴ Department of Pathology, Padova University Hospital, Padova, Italy
⁵ Department of Pathology, Azienda ULSS2 Marca Trevigiana, Treviso, Italy
⁶ Department of Diagnostic Pathology, Kurume University Hospital, Kurume, Japan
⁷ Department of Medicine, General Internal Medicine and Thrombotic and Hemorrhagic Diseases Unit, University of Padova, Padova, Italy
⁸ Department of Statistical Sciences, University of Padova, Padova, Italy
⁹ Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy
¹⁰ II Surgery Unit, Regional Hospital Treviso, Treviso, Italy
¹¹ Department of Pathology, Kurume University School of Medicine, Kurume, Japan

* These authors contributed equally

§ Correspondence author; Email: ambrogio.fassina@unipd.it

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**Consensus Score of Immune Infiltration from RNA-seq data**

From the filtered 280 LIHC-TCGA patients, TCGAbiolinks R package was used to collect the gene expression (RNA-seq) data from The Cancer Genome Atlas (TCGA), quantified using RSEM [1]. Genes showing a normalized number of read counts less than or equal to 10 in at least 95% of the samples in the dataset were filtered out.

TCGA has allowed for the large-scale interrogation of immune activity in multiple tumor types. Expression data have been utilized to measure the cytolytic activity in the tumor microenvironment (TME) and, more recently, to quantify the infiltration levels of individual immune cell subsets from gene expression data [2]. Various computational approaches based on deconvolution approaches have been developed for estimating the relative abundance of different cell types in the TME using bulk tumor RNA-seq data. In particular, deconvolution algorithms consider gene expression profiles of a heterogeneous sample as the *convolution* of the gene expression levels of the different cells and estimate the unknown cell fractions leveraging on a signature matrix describing the cell-type-specific expression profiles [3]. However, cell-type estimation in the TME using bulk tumor RNA-seq data is a challenging task as certain stromal and immune cell populations are lowly abundant cell populations and it is further convoluted since the expression of particular genes is rarely unique to any particular cell type. Thus, there is not a straightforward solution for accurate TME cell estimation and various different gene signatures, computational approaches and statistical frameworks were suggested as the optimal solution. Here, we considered the three most known and used deconvolution algorithms for inferring estimates of the immune infiltration (i.e. CIBERSORT [4], TIMER2.0 [5] and xCell [6]) and built a consensus score based on the ranking of their estimates, which were directly downloaded from TIMER2.0 web portal (http://timer.comp-genomics.org/). The portal provides the estimates also of CIBERSORT and xCell extracted through the R package immunodeconv [6,7]. Specifically, the consensus score was generated considering the average of the ranking positions obtained by each algorithm for the CD8\(^+\) T-cell infiltration, assigning the same ranking position to ties (Supplemental Table 1). Since we are interested in using the
estimates to rank the HCC samples from TCGA in order to define groups of samples at low and high CD8+ infiltration, in Figure S1 we report the correlogram with pairwise Spearman correlation between the deconvolution methods and between each method and our consensus score.

**Image Analysis**

Reactions for CD3+ and CD8+ Antibodies on two consecutive whole-slide sections were digitized with Aperio CS2 scanner (Leica Microsystem, Wetzlar, Germany) at the maximum magnification of 200x. Density of CD3+ and CD8+ cells were automatically quantified in tumoral and non-tumoral tissues, using a custom-made algorithm created with Visiopharm software, version 4.5.6.5 (Visiopharm, Hoersholm, Denmark). Briefly, consecutive slides of each case were uploaded in Visiopharm environment and automatically aligned with Tissue Align tool (Visiopharm, Hoersholm, Denmark), in order to produce a precise stacking of the two tissue sections that allowed CD3+ and CD8+ cells quantification within the same tissue area. After the alignment, a pathologist (LN) selected the region of interest (ROI), including the whole tumoral component. Within the ROI, CD3+ and CD8+ cells were automatically quantified and the number of positive cells per mm² was estimated (density of infiltrating cells).

**Immunofluorescence microscopy**

FFPE sections were dewaxed in xylene, rehydrated through serial alcohols and heat-treated for antigen retrieval. Subsequently, after washing with phosphate buffered saline (PBS, pH 7.4), the sections were permeabilized with 0.5% Triton X-100 in PBS for 15 min. and treated with 50 mM NH₄Cl for 15 min. at room temperature. Samples were then labelled by a sequential double stain to analyse the simultaneous expression of the following copy of antigens: RIPK3-RIPK1 and MLKL-RIPK1. Firstly, the samples were stained with a 1:50-diluted mouse anti-human RIP3 antibody, and 1:100-diluted mouse anti-human MLKL antibody incubated for 1h at 37°C. Secondly, after washing with PBS, the sections were labelled with 1:100-diluted rabbit anti-human RIPK1 antibody incubated at 37°C for 1h. Finally, the samples were stained with the secondary
antibodies 1:200-diluted anti-mouse IgG fluorescein isothiocyanate conjugated (FITC) and 1:200-diluted anti-rabbit IgG Alexa Fluor® 594 conjugated, incubated at 37°C for 1h.

Secondary antibodies were also used in the absence of primary antibodies in order to assess nonspecific bindings. The primary and secondary antibodies were diluted in PBS containing 0.5% bovine serum albumin (Sigma Aldrich).

Nuclei were labelled with 1.5 μg/ml Hoechst 33258 (Sigma Aldrich) for 20 min. at room temperature in the dark and slides were mounted with Mowiol antifade medium (Sigma Aldrich).

Samples were examined by Leica DMI6000CS fluorescence microscope (Leica Microsystems, Wetzlar, Germany). Sections were analysed with differential interference contrast (DIC) and fluorescence objectives. Images were analysed at 40x/0.60 dry objective or a 63x/1.4 oil immersion lens. Images were acquired using a DFC365FX camera and processed using the Leica Application Suite (LAS-AF) 3.1.1 software (Leica Microsystems, Wetzlar, Germany).

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**Supplementary Figures**

**Figure S1.** Correlogram plot of the three deconvolution methods considered in the study and the consensus score based on the average rank from the three deconvolution approaches. Absolute values of Spearman correlations are displayed since the consensus score considers the ranking of the samples from high to low infiltrations, therefore a low average rank corresponds to high CD8\(^+\) T-cell infiltration.

**Figure S2** Barplots displaying the percentage of concordance of each pathologist with respect to the final expression score used in this study. For each receptor (i.e. RIPK1, RIPK3 and MLKL), asterisks report the significance of the highest p-value from Fisher's Exact Test comparing the scores assigned by each pathologist of each level of expression (i.e. 0,1,2,3): *<0.05, **<0.01, ***<0.001.
Figure S3: Boxplots comparing mRNA expression levels of the three receptors of the necrosome (RIPK1, RIPK3, and MLKL) between Caucasian and Asian patients of TCGA-LIHC dataset. Reported Benjamini-Hochberg adjusted p-values from Wilcoxon Rank Sum test.
**Figure S4** Associations between the expression of each receptor of the necrosome (RIPK1, RIPK3 and MLKL) and the intra-/extra-tumoral infiltration of CD3+ and CD8+, evaluated in both Japanese and Italian cohorts, separately. A: Boxplots showing the density levels of immune infiltration according to the IHC scores assigned to each receptor; Benjamini-Hochberg adjusted p-values for pairwise comparisons performed through Wilcoxon’s rank sum test are reported for significant comparisons. B: Results from Wilcoxon’s rank sum test evaluating the distribution of IHC scores, dichotomizing the density levels of immune infiltration according to their median value. Adjusted p-values: *<0.05, **<0.01, ***<0.001.
**Figure S5** Kaplan-Meier curves for both overall and disease-free survival, comparing the Japanese and the Italian cohort.

| Cohort     | Number at risk | Overall Survival | Disease-free Survival |
|------------|----------------|------------------|-----------------------|
| Japan (J)  |                |                  |                       |
|            | 86             | 82               | 78                    |
|            | 82             | 71               | 62                    |
|            | 62             | 57               | 49                    |
|            | 51             | 57               | 49                    |
|            | 34             | 30               | 28                    |
| Italy (I)  |                |                  |                       |
|            | 80             | 62               | 52                    |
|            | 62             | 45               | 30                    |
|            | 41             | 36               | 19                    |
|            | 36             | 19               | 10                    |
|            | 19             | 10               | 6                     |

**Time in months**

**Figure S6** Kaplan-Meier curves for both overall and disease-free survival, evaluating NCS using the joint dataset of patients from Japanese and Italian cohorts.

| NCS        | Number at risk | Overall Survival | Disease-free Survival |
|------------|----------------|------------------|-----------------------|
| Low (L)    |                |                  |                       |
|            | 42             | 30               | 21                    |
|            | 86             | 81               | 73                    |
|            | 60             | 30               | 30                    |
| Intermediate (I) |            |                  |                       |
|            | 15             | 13               | 8                     |
|            | 59             | 48               | 27                    |
|            | 30             | 30               | 18                    |
| High (H)   |                |                  |                       |
|            | 12             | 11               | 9                     |
|            | 76             | 55               | 39                    |
|            | 39             | 38               | 36                    |
|            | 39             | 28               | 23                    |
|            | 21             | 14               | 6                     |

**Time in months**
**Figure S7** Kaplan-Meier curve for overall survival, evaluating intra-tumoral CD8⁺ on both the two cohorts (Italian and Japanese) separately and the joint dataset.

| CD8⁺ | Low (L) | Intermediate (I) | High (H) |
|------|---------|------------------|----------|
| Italy | ![Graph](image1) |
| Japan | ![Graph](image2) |
| Italy + Japan | ![Graph](image3) |

Time in months

**Figure S8** Kaplan-Meier curves for both overall and disease-free survival, comparing Caucasian vs. other ethnicities (represented at 89% by Asian) in the cohort of patients retrieved from the TCGA-LIHC study.

| Ethnicity | CAUCASIAN (C) | OTHER, 89% ASIAN (O) |
|-----------|---------------|----------------------|
| Number at risk | ![Graph](image4) | ![Graph](image5) |

Time in months
Figure S9 Kaplan-Meier curves for overall survival, evaluating the prognostic value of NCSrna and the inferred CD8\(^+\) T-cell infiltration in the cohort of patients retrieved from the TCGA-LIHC study.

Supplemental Tables

Table S1 Panel of clones and primary antibodies used for this study.

| Antigen | Clone   | Source          | Vendor          | Dilution | Positive control       |
|---------|---------|-----------------|-----------------|----------|------------------------|
| RIPK1   | NBP1-77077 | rabbit polyclonal | Novus Biologicals | 1:150 | Human tonsilla         |
| RIPK3   | 780115  | mouse monoclonal | R&D System      | 1:300 | Human tonsilla         |
| MLKL-p  | 954702  | mouse monoclonal | R&D System      | 1:300 | Penile squamous cell carcinoma |
| CD3     | LN10    | mouse monoclonal | Leica Biosystems | 1:100 | Human tonsilla         |
| CD8     | C8/144B | mouse monoclonal | Agilent Technologies | 1:100 | Human tonsilla         |
Table S2 Demographic and pathological data of the 70+70 TCGA-LIHC patients at low and high immune infiltration. The two groups of patients were selected according to the ranking based on the deconvolution methods used to estimate the CD8⁺ immune infiltration, considering first and last quartiles to define patients at low and high infiltration, respectively. P-values correspond to Kolmogorov-Smirnov and Chi-square tests for numerical and nominal data, respectively. Abbreviations: AJCC: American Joint Committee on Cancer.

| Patient/Tumor Characteristics | Low CD8+ Infiltration (n=70) | High CD8+ Infiltration (n=70) | P-value |
|------------------------------|------------------------------|-------------------------------|---------|
| Age (years)                  |                              |                               |         |
| Mean (SD)                    | 58 (13)                      | 60 (12)                       | 0.39    |
| valid (missing)              | 70 (0)                       | 69 (1)                        |         |
| Sex, % (n)                   |                              |                               |         |
| Female                       | 40% (28)                     | 34% (24)                      | 0.6     |
| Male                         | 60% (42)                     | 66% (46)                      |         |
| Ethnicity, % (n)             |                              |                               |         |
| Caucasian                    | 47% (33)                     | 44% (31)                      | 1       |
| Other (89% Asian)            | 53% (37)                     | 51% (36)                      |         |
| missing                      | 0% (0)                       | 4.3% (3)                      |         |
| CHILD-PUGH, % (n)            |                              |                               |         |
| A                            | 63% (44)                     | 63% (44)                      | 0.52    |
| B                            | 10% (7)                      | 7.1% (5)                      |         |
| C                            | -                            | 1.4% (1)                      |         |
| missing                      | 27% (19)                     | 29% (20)                      |         |
| STAGE (AJCC), % (n)          |                              |                               |         |
| Stage I – II                 | 70% (49)                     | 80% (56)                      | 0.35    |
| Stage III – IV               | 24% (17)                     | 17% (12)                      |         |
| missing                      | 5.7% (4)                     | 2.9% (2)                      |         |
| Grade, % (n)                 |                              |                               |         |
| G1 – G2                      | 64% (45)                     | 57% (40)                      | 0.49    |
| G3 – G4                      | 36% (25)                     | 43% (30)                      |         |
| Vascular Invasion, % (n)     |                              |                               |         |
| Macro                        | 4.3% (3)                     | 4.3% (3)                      | 0.79    |
| Micro                        | 24% (17)                     | 20% (14)                      |         |
| None                         | 56% (39)                     | 61% (43)                      |         |
| missing                      | 16% (11)                     | 14% (10)                      |         |
Table S3  Paths resulted statistically significant (p-value<5% from likelihood ratio test and p-values <0.05 in the Wald tests of all the estimated coefficients for each selected gene) from the multivariate logistic regression models applied to the Necroptosis pathway.

| Statistically significant paths                                      | Likelihood ratio test (p-value) |
|---------------------------------------------------------------------|---------------------------------|
| IFNGR1 → JAK3 → STAT2                                                | 9.785E-06                       |
| JAK3 → STAT2                                                        | 1.669E-05                       |
| JAK3 → STAT5A → IRF9                                                | 3.109E-05                       |
| JAK3 → STAT5A                                                       | 5.3E-05                         |
| JAK3 → STAT1 → RIPK1                                                | 5.619E-05                       |
| CHMP4A → MLKL → NLRP3 → CASP1 → IL1B                               | 3.434E-04                       |
| MLKL → NLRP3 → CASP1 → IL1B                                         | 0.001                           |
| TNFAIP3 → RIPK3 → MLKL → CHMP4C                                     | 0.001                           |
| STAT4 → RIPK1 → RIPK3 → MLKL → CHMP1A                               | 0.001                           |
| NLRP3 → CASP1 → ILB1                                                | 0.001                           |
| STAT1 → RIPK1 → RIPK3 → CYBB                                        | 0.002                           |
| RIPK3 → MLKL → CHMP4C                                               | 0.003                           |
| TNFAIP3 → RIPK3 → MLKL → CHMP1B                                     | 0.005                           |
| TNFAIP3 → RIPK3 → MLKL → CHMP1A                                     | 0.006                           |
| HSP90AB1 → RIPK3 → CYBB                                             | 0.012                           |
| IRF9 → STAT1 → EIF2AK2                                              | 0.031                           |
| RIPK3 → MLKL → CHMP1A                                               | 0.033                           |
| RIPK3 → CYBB                                                        | 0.043                           |
| RIPK3 → MLKL → RNF103-CHMP3                                         | 0.047                           |
Table S4 Distribution of the immunohistochemical scores for RIPK1, RIPK3 and MLKL across the Italian and Japanese cohorts. P-values correspond to Chi-square tests.

| Group      | Japan (n=86) | Italy (n=82) | p-value |
|------------|--------------|--------------|---------|
| RIPK1, % (n) |              |              |         |
| 0          | 0% (0)       | 16% (13)     | 0.0017  |
| 1          | 36% (31)     | 32% (26)     |         |
| 2          | 47% (40)     | 35% (29)     |         |
| 3          | 17% (15)     | 17% (14)     |         |
| RIPK3, % (n) |              |              |         |
| 0          | 3.5% (3)     | 9.8% (8)     | 0.15    |
| 1          | 24% (21)     | 13% (11)     |         |
| 2          | 27% (23)     | 29% (24)     |         |
| 3          | 45% (39)     | 48% (39)     |         |
| MLKL, % (n) |              |              |         |
| 0          | 35% (30)     | 29% (24)     | 0.25    |
| 1          | 30% (26)     | 45% (37)     |         |
| 2          | 28% (24)     | 21% (17)     |         |
| 3          | 7% (6)       | 4.9% (4)     |         |
| NCS, % (n) |              |              |         |
| low        | 23% (20)     | 27% (22)     | 0.27    |
| intermediate| 49% (42)     | 54% (44)     |         |
| high       | 28% (24)     | 20% (16)     |         |

Table S5 Cox Regression models of NCS for both overall and disease-free survival in the whole dataset, stratifying for Italian and Japanese cohorts. The models were evaluated in terms of: 1) p-value from log-rank test (p-value) assessing the fit performance of the whole model including both NCS and confounder cohorts; 2) p-value from assessing the statistical significance of the specific coefficient estimated for NCS in the model, used to derive the corresponding hazard ratio with the related confidence intervals (CI 95%). The confounders reported in the last column are those selected for the final model after the step-down selection procedure described in the Materials and Methods section. Abbreviations: CHILD: Child-Pugh Staging System; BCLC: Barcelona Clinic Liver Cancer Staging System.

| Survival | Log-rank test | Likelihood ratio test | Hazard Ratio | CI 95% | Confounders |
|----------|---------------|-----------------------|--------------|--------|-------------|
| OS       | 1.12e-07      | 4.28e-06              | 0.434        | (0.304,0.62) | CHILD, Multinodularity |
| DFS      | 0.00244       | 0.0418                | 0.745        | (0.561,0.989) | BCLC |
Table S6 Cox Regression models of RIPK1, RIPK3 and MLKL for both overall and disease-free survival in the Italian and Japanese cohorts separately and in the joint dataset, stratifying for the two cohorts. The models were evaluated in terms of: 1) p-value from log-rank test (p-value) assessing the fit performance of the whole model including both NCS and confounder cohorts; 2) p-value from assessing the statistical significance of the specific coefficient estimated for NCS in the model, used to derive the corresponding hazard ratio with the related confidence intervals (CI 95%). The confounders reported in the last column are those selected for the final model after the step-down selection procedure described in the Materials and Methods section. Cox models reporting significance for both log-rank and likelihood ratio tests are highlighted in red. Abbreviations: AlphaFP: Alpha-fetoprotein tumor marker; CHILD: Child-Pugh Staging System; BCLC: Barcelona Clinic Liver Cancer Staging System.

| Receptor | Cohort | Survival | Log-rank test | Likelihood ratio test | Hazard Ratio | CI 95%          | Confounders              |
|----------|--------|----------|---------------|-----------------------|--------------|-----------------|--------------------------|
| RIPK1    | Italy  | OS       | 4.69e-07      | 2.96e-05              | 0.454        | (0.314,0.658)   | AlphaFP, CHILD, Stage    |
| RIPK1    | Japan  | OS       | 0.0312        | 0.0786                | 0.615        | (0.358,1.06)    | Age                      |
| RIPK1    | Stratified | OS   | 2.58e-06      | 3.85e-05              | 0.539        | (0.402,0.724)   | CHILD, Stage             |
| RIPK1    | Italy  | DFS      | 0.0154        | 0.0164                | 0.66         | (0.47,0.927)    |                          |
| RIPK1    | Japan  | DFS      | 0.0219        | 0.361                 | 0.845        | (0.588,1.21)    | BCLC                     |
| RIPK1    | Stratified | DFS | 0.00075      | 0.0144                | 0.737        | (0.577,0.941)   | BCLC                     |
| RIPK3    | Italy  | OS       | 3.83e-06      | 0.000578              | 0.578        | (0.423,0.797)   | CHILD, Multinodularity   |
| RIPK3    | Japan  | OS       | 0.0346        | 0.0375                | 0.672        | (0.462,0.977)   |                          |
| RIPK3    | Stratified | OS   | 2.45e-06      | 7.77e-05              | 0.614        | (0.482,0.782)   | CHILD, Multinodularity   |
| RIPK3    | Italy  | DFS      | 0.035         | 0.437                 | 0.867        | (0.604,1.24)    | Multinodularity          |
| RIPK3    | Japan  | DFS      | 0.0282        | 0.52                  | 0.908        | (0.678,1.22)    | BCLC                     |
| RIPK3    | Stratified | DFS | 0.0127       | 0.404                 | 0.909        | (0.727,1.14)    | BCLC                     |
| MLKL     | Italy  | OS       | 1.22e-05      | 0.00399               | 0.551        | (0.367,0.827)   | AlphaFP, CHILD, Multinodularity |
| MLKL     | Japan  | OS       | 0.0509        | 0.163                 | 0.762        | (0.52,1.12)     | Age                      |
| MLKL     | Stratified | OS   | 5.84e-05      | 0.00532               | 0.673        | (0.509,0.889)   | AlphaFP, CHILD, Multinodularity |
| MLKL     | Italy  | DFS      | 0.0468        | 0.964                 | 1.01         | (0.718,1.41)    | Multinodularity          |
| MLKL     | Japan  | DFS      | 0.0251        | 0.411                 | 0.886        | (0.663,1.18)    | BCLC                     |
| MLKL     | Stratified | DFS | 0.0167       | 0.712                 | 0.959        | (0.769,1.2)     | BCLC                     |
Table S7 Cox Regression models of intra-extra-tumoral infiltration of CD3\(^+\) and CD8\(^+\) for both overall and disease-free survival in the Italian and Japanese cohorts separately and in the joint dataset, stratifying for the two cohorts. The models were evaluated in terms of: 1) p-value from log-rank test (p-value) assessing the fit performance of the whole model including both NCS and confounder cohorts; 2) p-value from assessing the statistical significance of the specific coefficient estimated for NCS in the model, used to derive the corresponding hazard ratio with the related confidence intervals (CI 95%). The confounders reported in the last column are those selected for the final model after the step-down selection procedure described in the Materials and Methods section. Cox models reporting significance for both log-rank and likelihood ratio tests are highlighted in red. Abbreviations: AlphaFP: Alpha-fetoprotein tumor marker; CHILD: Child-Pugh Staging System; BCLC: Barcelona Clinic Liver Cancer Staging System.

| Infiltration         | Cohort     | Survival | Log-rank test | Likelihood ratio test | Hazard Ratio | CI 95%       | Confounders                      |
|----------------------|------------|----------|---------------|-----------------------|--------------|--------------|---------------------------------|
| CD8\(^+\) Intra-tumoral | Italy      | OS       | 5.95e-05      | 0.0243                | 0.625        | (0.415, 0.941) | AlphaFP, CHILD, Multinodularity |
| CD8\(^+\) Intra-tumoral | Japan      | OS       | 0.0205        | 0.0517                | 0.654        | (0.427, 1)    | Age                             |
| CD8\(^+\) Intra-tumoral | Stratified | OS       | 3.87e-05      | 0.00316               | 0.642        | (0.478, 0.862) | AlphaFP, CHILD, Multinodularity |
| CD8\(^+\) Intra-tumoral | Italy      | DFS      | 0.0455        | 0.808                 | 1.05         | (0.713, 1.54) | Multinodularity                 |
| CD8\(^+\) Intra-tumoral | Japan      | DFS      | 0.0177        | 0.25                  | 0.835        | (0.614, 1.14) | BCLC                            |
| CD8\(^+\) Intra-tumoral | Stratified | DFS      | 0.0136        | 0.463                 | 0.914        | (0.718, 1.16) | BCLC                            |
| CD3\(^+\) Intra-tumoral | Italy      | OS       | 0.00309       | 0.745                 | 1.07         | (0.725, 1.57) | CHILD                           |
| CD3\(^+\) Intra-tumoral | Japan      | OS       | 0.033         | 0.0883                | 0.691        | (0.452, 1.06) | Age                             |
| CD3\(^+\) Intra-tumoral | Stratified | OS       | 0.00104       | 0.205                 | 0.83         | (0.622, 1.11) | AlphaFP, CHILD, Multinodularity |
| CD3\(^+\) Intra-tumoral | Italy      | DFS      | 0.037         | 0.493                 | 1.14         | (0.781, 1.67) | Multinodularity                 |
| CD3\(^+\) Intra-tumoral | Japan      | DFS      | 0.0214        | 0.33                  | 0.858        | (0.63, 1.17)  | BCLC                            |
| CD3\(^+\) Intra-tumoral | Stratified | DFS      | 0.0171        | 0.772                 | 0.965        | (0.759, 1.23) | BCLC                            |
Table S8 Cox Regression models of NCSrna, RIPK1, RIPK3, MLKL and CD8⁺ T-cell infiltration for overall survival in TCGA-LIHC cohort. The models were evaluated in terms of: 1) p-value from log-rank test (p-value) assessing the fit performance of the whole model including both NCS and confounder cohorts; 2) p-value from assessing the statistical significance of the specific coefficient estimated for NCS in the model, used to derive the corresponding hazard ratio with the related confidence intervals (CI 95%). For all the models, no confounders were found statistically significant. Cox models reporting significance for both log-rank and likelihood ratio tests are highlighted in red.

| Target | Survival | Log-rank test | Likelihood ratio test | Hazard Ratio | CI 95%       |
|--------|----------|---------------|-----------------------|--------------|--------------|
| NCSrna | OS       | 0.0287        | 0.0292                | 0.67         | (0.468,0.96) |
| RIPK1  | OS       | 0.386         | 0.387                 | 0.899        | (0.708,1.14) |
| RIPK3  | OS       | 0.00495       | 0.00518               | 0.699        | (0.544,0.899) |
| MLKL   | OS       | 0.858         | 0.858                 | 1.02         | (0.798,1.31) |
| CD8⁺   | OS       | 0.0246        | 0.0254                | 0.716        | (0.535,0.96) |