Original Article



# Age-adjusted Charlson Comorbidity Index predicts survival in intrahepatic cholangiocarcinoma patients after curative resection

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**Background:** Comorbidity among cancer patients is prevalent and influential to prognosis after operation. Limited data are available on comorbidity evaluations in patients with intrahepatic cholangiocarcinoma (ICC). This study aimed to assess the comorbidity distribution in ICC patients and to adapt the Charlson Comorbidity Index (CCI) or the age-adjusted CCI (ACCI) for survival prediction.

**Methods:** The study cohort included 268 ICC patients treated with curative surgery from January 2000 to December 2007 at the Department of Liver Surgery, Zhongshan Hospital. The association between the comorbidity index and overall survival (OS) or disease-free survival (DFS). was analyzed by the Kaplan-Meier method. Multivariable analysis was established to select the determinant parameters.

**Results:** Major comorbid conditions of ICC patients included liver disease, hypertension, diabetes and ulcer. The median follow-up time was 25.5 months in the whole data set. Among the entire cohort, the 1-, 3- and 5-year OS rates were 55.3%, 26.0% and 15.6%, respectively. In multivariate analysis, the ACCI correlated with OS, and higher scores were associated with poorer prognosis (hazard ratio =1.134, 95% confidence interval: 1.015–1.267 and P value =0.026). CCI was not an independent predictive factor for OS or DFS.

**Conclusions:** In contrast to CCI, ACCI was a more promising model to accurately predict OS in ICC patients who underwent liver resection. Further research should be focused on the impact of comorbidity therapies.

**Keywords:** Intrahepatic cholangiocarcinoma (ICC); comorbidity; age-adjusted Charlson Comorbidity Index (ACCI); survival

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## Introduction

Intrahepatic cholangiocarcinoma (ICC), arising from the epithelial cells of the secondary bile duct and its branch in the liver, is the second most common primary liver malignancy in humans and accounts for up to 15% of primary liver cancer cases, next to hepatocellular carcinoma (HCC) (1-3). Over the past few decades, there has been a rapid uptrend of the incidence of ICC worldwide (4,5). Due to its high mortality and the swift progression of the tumor, therapies for ICC remain deficient (6). Surgical resection

is still the mainstay for treatment and provides curative opportunity (3,5). In 2011, our institution proposed an outcome study based on a massive cohort of ICC patients who underwent resection. Specifically, the median survival was only 17.6 months (7). Such poor survival may be contributed by multiple factors.

ICC comprises different morphological features and molecular subsets. Determinant factors, including C-reactive protein (CRP), immune infiltrating condition and pathological characteristics, such as multiple lesions, tumor budding and vascular invasion, have been proven to be highly associated with outcomes after resection (8-11).

Comorbidities are chronic conditions that impact patients' life quality, especially in long-term postoperative recovery. The management of comorbidities in cancer treatment is crucial to physicians. Recent studies have demonstrated the strong influence of comorbidities on survival after surgery in different kinds of solid neoplasms, including vulvar cancer, colorectal cancer and breast cancer (12-14). The Charlson Comorbidity Index (CCI), first proposed in 1984 by reviewing hospital charts, managed to account for the influence of a patients' comorbidity condition in longitudinal studies (15). Since age has been subsequently determined to be correlated with prognosis, Charlson *et al.* modified the scoring system with the addition of patients' age in 1994. The age-adjusted CCI (ACCI) incorporates the age as a correction variable of the final score by adding 1 point for every decade over 40 years old (16). Both CCI and ACCI have been widely validated in surgical and nonsurgical settings (17-19). Better understanding of comorbidity can promote the recognition of prognostic implications to malignancies. Nevertheless, the role of comorbidities in ICC has not yet been evaluated. Moreover, whether CCI or ACCI shows predictive performance in ICC patients needs further verification.

In the present study, we sought to assess the diversity and incidence of comorbidities in ICC patients through detailed history. We performed a cohort study to evaluate the prognostic capacities of comorbidities, and CCI and ACCI were calculated and stratified to predict the survival of patients after curative resections.

## Methods

### *Data set*

A total of 283 ICC patients who underwent liver resection between January 2000 and December 2007 at the Department of Liver Surgery, Zhongshan Hospital, Fudan University, were prospectively collected. The inclusion criteria were as follows: no preoperative anticancer therapy; without other malignancies; and diagnosed with ICC histopathologically. Patients diagnosed as HCC or combined hepatocellular-cholangiocarcinoma or hilar or extrahepatic cholangiocarcinoma, those with hepatic encephalopathy at the time of surgery, those with perioperative mortality and those with deficient follow-up information or surgery records were excluded from our study cohort. Ultimately, our data set selected 268 specimens. The study was approved by the institutional review board of Zhongshan Hospital and complied with the standards of the Declaration of Helsinki and current ethical guidelines.

### *Diagnosis and follow-up*

Detailed history, complete physical examination and accessory tests were used for preoperative diagnosis. Blood was drawn from the patients for determination of the levels of platelets, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibody, serum albumin (ALB), total bilirubin (TB), alanine aminotransferase (ALT), aspartate transaminase (AST), γ-glutamyl transferase (GGT), α-fetoprotein (AFP), carbohydrate 19-9 (CA19-9), and carcinoembryonic antigen (CEA). Imagining examinations included abdominal ultrasound, contrast-enhanced computed tomography (CT), magnetic resonance imaging, and positron emission tomography (PET), if needed. Confirmative diagnosis relied on pathological results of the resected tissue, assessed by authoritative experts.

The study was censored on April 2012. A standardized follow-up protocol was adopted for all patients. Patients had follow-up visits with blood tests for liver function and tumor markers every 3 months. Radiological examinations included computed tomography or abdominal magnetic resonance imaging scans every 6 months for the first 2 years. The end-points of the study were overall survival (OS) and disease-free survival (DFS). OS was defined as the interval between the date of surgery and the date of patient death or the last follow-up. DFS was defined as the time from the date of resection to the date of recurrence, metastasis, or last follow-up.

### *Comorbidities and ACCI*

Patients' comorbidities based on detailed history were assessed rigorously on the basis of the disease definition (15).

 

**Table 1** Different weights assigned for specific conditions in the age adjusted Charlson Comorbidity Index and patients' distribution

| Scores | Conditions | N=268, n (%) |
|---|---|---|
| Assigned weights for disease | | |
| 1 | Myocardial infarction | 0 (0.0) |
| | Congestive heart failure | 1 (0.4) |
| | Peripheral vascular disease | 0 (0.0) |
| | Dementia | 2 (0.7) |
| | Cerebrovascular disease | 3 (1.1) |
| | Chronic pulmonary disease | 4 (1.5) |
| | Ulcer disease | 12 (4.5) |
| | Diabetes | 13 (4.9) |
| | Hypertension | 36 (13.4) |
| | Mild liver disease | 83 (31.0) |
| 2 | Moderate or severe renal disease | 0 (0.0) |
| | Hemiplegia | 1 (0.4) |
| | Malignant lymphoma | 2 (0.7) |
| | Any tumor | 10 (3.7) |
| 3 | Moderate or severe liver disease | 41 (15.3) |
| 6 | Metastatic solid tumor | 0 (0.0) |
| | Acquired immune deficiency syndrome | 0 (0.0) |
| Assigned weights for age | | |
| 1 | For each decade over age 40 years (up to 4 points) | |

CCI incorporated different medical conditions, with each weighted from 1 to 6 points. Patients' age was sorted and counted according to ACCI. Both the CCI and ACCI scores were then calculated by the appropriate formula (*Table 1*).

### *Statistical methods*

Demographic, clinical and tumor characteristics are described as summary statistics and are presented as percentages for categorical variables and medians (ranges) for continuous variables. We evaluated categorical variables using the Pearson Chi-square test. The Mann-Whitney U test was employed to compare continuous variables. The Kaplan-Meier method and log-rank test were used to estimate OS and DFS. Univariable and multivariable analysis were established based on a logistic regression model.

Statistical inferences were two-sided, and a P value <0.05 was considered statistically significant. All the statistical tests were performed using SPSS 22.0 (SPSS, Chicago, IL)

### *Selection of most predictive comorbidities in ACCI*

Data were analyzed using the Statistical Analysis System (SAS, Version 9.4). The models were limited to the 6 most predictive comorbidities in ICC patients after adjusting for age. Partial R-square values were calculated to appraise the independent proportion of explained variance within ACCI scores by each comorbidity included in the model. The 6 most predictive comorbidities accounted for the variance of ACCI scores.

## Results

### *Comorbidity distributions in the data set*

The distributions of different comorbidities are summarized

 

in *Table 1*. Among 268 ICC patients, 83 were diagnosed with mild liver disease, which was the most common comorbidity (31%). In the group of 1-point comorbidities, hypertension, diabetes and ulcer disease ranked next to mild liver disease, with ratios of 13.4%, 4.9% and 4.5%, respectively. Among the comorbidities that scored 2 points, solid tumor history was found in 10 patients (3.7%). Meanwhile, 2 patients (0.7%) displayed cooccurrence of both malignant lymphoma and ICC. One patient (0.4%) had hemiplegia. Among the comorbidities that accounted for more than 2 points, moderate and severe liver diseases were declared in only 41 patients (15.3%).

### *Clinicopathological characteristics of patients*

The demographic and clinicopathological data are shown in *Table 2*. The proportions of males and females were 60.4% and 39.6%, respectively. The median age of the data set was 55 years (range, 27–89 years). Among 268 patients, 85 patients were positive for HBsAg (31.7%). The median max-diameter of the tumor was 6.0 cm (range, 1.0–18.0). Most patients (n=150) had stage I ICC. The population ratios for stage II, III, and IVa were 16.8%, 3.0%, and 24.3%, respectively. Most nodules of ICC patients did not have complete capsules (87.1%). The median score of ACCI was 3 (range, 0–6). The distributions of ACCI were low (≤2), medium [3] and high (≥4) groups in 36.6%, 22.8%, and 40.7% of patients, respectively. Similar results for CCI are shown in *Table 2*.

The median follow-up time was 25.5 months (range, 1 to 134) in the whole data set. Among the entire cohort, 88.1% of the patients (236/268) developed a recurrence, and 81.0% of the patients (217/268) died during follow-up. The 1-, 3- and 5-year OS rates were 55.3%, 26.0% and 15.6%, respectively; the 1-, 3- and 5-year DFS rates were 43.5%, 18.7% and 10.8%, respectively.

### *CCI and survival*

To investigate the capacities of the CCI and ACCI to predict prognosis, the 5-year OS and DFS rates according to the comorbidity index were estimated using Kaplan-Meier curves. In *Figure 1*, we evaluated the relationship between comorbidity index and OS with both continuous and categorical variables. When using continuous variables (*Figure 1B*), patients with higher ACCI scores showed increasing risk of worse OS (P=0.038). The median survival times in ACCI =0, 1, 2, 3 and 5 stratification were 50.9, 25.9, 16.0, 14.5 and 9.0 months, respectively. In contrast, there was no significant difference between CCI scores and OS times (P=0.973). From the prospective of categorical variables, three stages of ACCI also revealed efficacious prognostic performance, with 3-year OS rates =34.9%, 26.2%, 15.1% and 5-year OS rates =22.7%, 15.0%, 9.3% in the low, moderate and high groups (P=0.019).

In *Figure 2*, we assessed DFS according to CCI or ACCI. No statistical significance was found in CCI or ACCI when considering continuous variables (P=0.841 and 0.078, respectively). Unlike CCI stratification, ACCI stratification displayed a strong influence on the DFS (P=0.030).

### *Predictive factors for OS and DFS*

Utilizing a Cox proportional hazard model, we performed a multivariable analysis to define the predictive determinants (*Table 3*). For OS, CEA [hazard ratio (HR): 1.804, 95% CI: 1.133–2.874, P=0.013], CA19-9 (HR: 1.838, 95% CI: 1.219–2.771, P=0.004), max-diameter (HR: 1.078, 95% CI: 1.004–1.158, P=0.040), tumor differentiation (P=0.007), ACCI (HR: 1.134, 95% CI: 1.015–1.267, P=0.026) and ACCI classification (P=0.040) were determined to be independent prognostic factors. For DFS, the prognostic determinants were AFP (HR: 1.840, 95% CI: 1.042–3.249, P=0.035), max diameter (HR: 1.088, 95% CI: 1.019–1.163, P=0.012), micro vascular invasion (MVI) (HR: 7.374, 95% CI: 1.812–30.005, P=0.005), CEA (HR: 1.809, 95% CI: 1.161–2.819, P=0.009) and vascular invasion (VI) (HR: 0.632, 95% CI: 0.424–0.941, P=0.024). The multivariable analysis on DFS is shown in the *Table S1*.

### *The 6 most predictive comorbidities in ACCI*

*Table 4* revealed the results of the multivariate linear regression analysis and explained the variance ($R^2$) of ACCI scores by the 6 most predictive comorbidities (explaining approximately 56.56%). The candidates were as follows: moderate or severe liver disease, ulcer, tumor, diabetes, mild liver disease and lymphoma. The calculation process is shown in the *Figure S1*.

## Discussion

Despite the development in surgical techniques, management after curative resection is a priority in cancer therapy, in which long-term comorbidity contributes greatly to survival. In our present study, we originally investigated

 

**Table 2** Demographic, clinical, and tumor characteristics of patients with intrahepatic cholangiocarcinoma

| Patient demographics | Variables | N (%) |
|---|---|---|
| Gender | Female | 106 (39.6) |
| | Male | 162 (60.4) |
| Age (y) | Median (R) | 55 (27, 89) |
| HBsAg | – | 183 (68.3) |
| | + | 85 (31.7) |
| Anti-HCV | – | 257 (97.0) |
| | + | 8 (3.0) |
| TB (mg/dL) | <17 | 192 (71.6) |
| | ≥17 | 76 (28.4) |
| AST (U/L) | Median (R) | 28 (10, 246) |
| ALB (g/dL) | Median (R) | 44 (26, 57) |
| ALT (U/L) | <35 | 161 (60.3) |
| | ≥35 | 106 (39.7) |
| PT (s) | <13 | 244 (91.0) |
| | ≥13 | 24 (9.0) |
| AFP (ng/mL) | <20 | 227 (88.3) |
| | ≥20 | 30 (11.7) |
| CEA (μg/mL) | <5 | 191 (77.0) |
| | ≥5 | 57 (23.0) |
| CA19-9 (U/mL) | <37 | 88 (36.1) |
| | ≥37 | 156 (63.9) |
| CCI Score | Median (R) | 1 (0, 6) |
| | 0 | 103 (38.4) |
| | 1 | 87 (32.5) |
| | ≥2 | 78 (29.1) |
| ACCI Score | Median (R) | 3 (0, 6) |
| | ≤2 | 98 (36.6) |
| | 3 | 61 (22.8) |
| | ≥4 | 109 (40.7) |
| Max-diameter(cm) | Median (R) | 6.0 (1.0, 18.0) |
| Tumor number | Median (R) | 1 (1, 20) |
| Lymphoid metastasis | None | 206 (76.9) |
| | Yes | 62 (23.1) |
| Tumor capsule | None & partial | 229 (87.1) |
| | Complete | 34 (12.9) |
| Differentiation | I | 2 (1.0) |
| | I–II, II | 118 (59.0) |
| | II–III, III | 79 (39.5) |
| | III–IV, IV | 1 (0.5) |
| TNM | I | 150 (56.0) |
| | II | 45 (16.8) |
| | III | 8 (3.0) |
| | IVa | 65 (24.3) |
| MVI | None | 234 (87.3) |
| | Yes | 34 (12.7) |
| VI | None | 234 (87.3) |
| | Yes | 34 (12.7) |

Values are presented as No. (%) or median (minimum, maximum). Median (R), median (range); HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TB, total bilirubin; PT, prothrombin time; AST, aspartate transaminase; ALB, albumin; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate 19-9; ALT, alanine aminotransferase; CCI, Charlson Comorbidities Index; ACCI, age-adjusted Charlson Comorbidities Index; TNM, tumor node metastasis stage; VI, vascular invasion; MVI, micro vascular invasion.

the distribution of comorbidities in ICC patients treated with surgery and assessed the prognostic performance of ACCI. From *Table 1*, we clearly found that liver disease was the most common comorbidity, regardless of severity. In the CCI, the definition of liver disease mainly depended on cirrhosis, portal hypertension and a history of variceal bleeding (15). Therefore, the pathophysiological changes of the primary tumor could elucidate the high incidence of liver disease (20,21). Hypertension, diabetes and ulcer occupied the 2$^{nd}$–4$^{th}$ major proportions, which was broadly consistent with recent epidemiological studies (22). In particular, gastrointestinal ulcer occurred more frequently in ICC patients than in other solid tumors. This phenomenon was mainly attributed to the derivative effects of portal hypertension and coagulation disorder (23).

CCI was initially developed to evaluate one-year

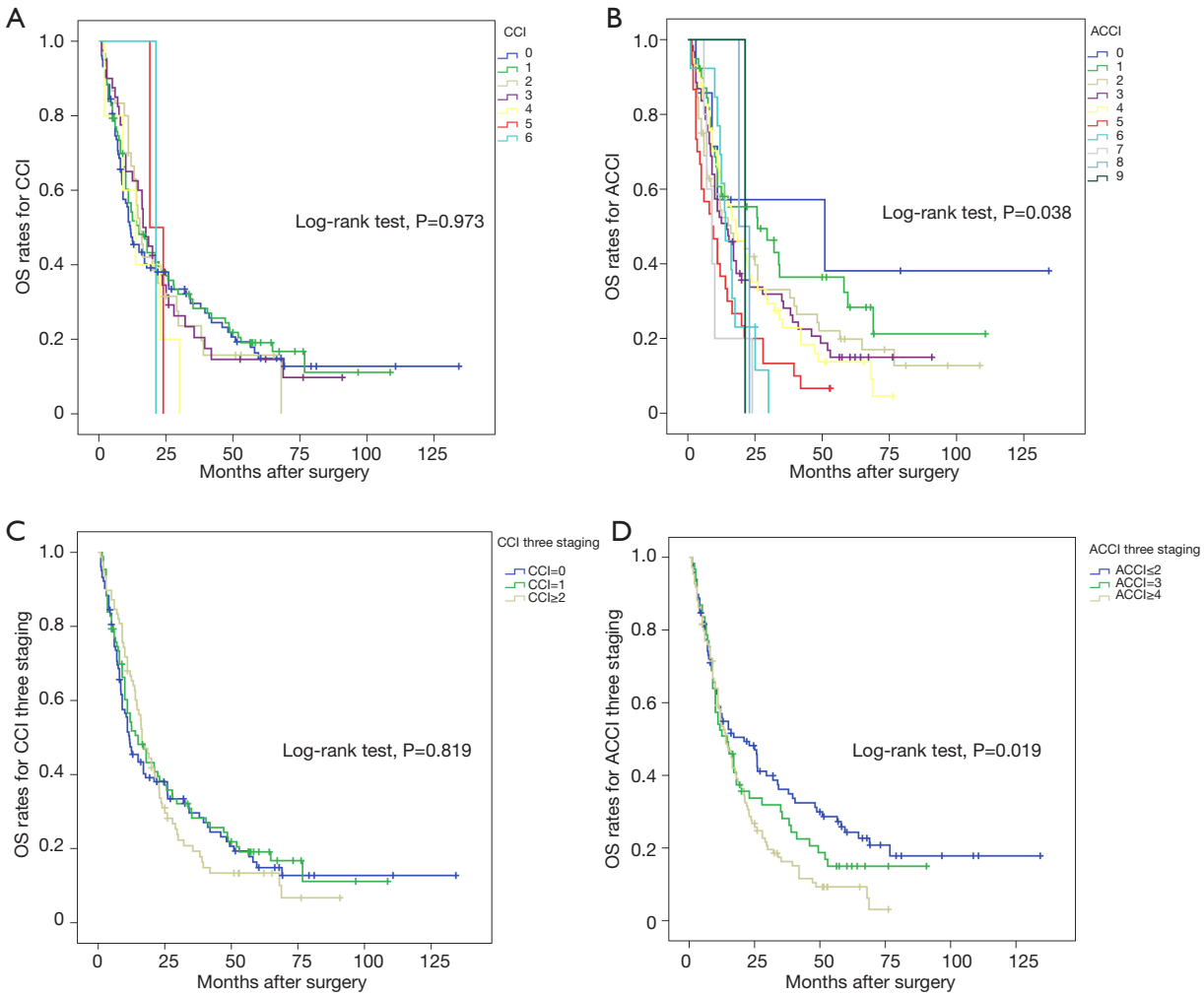


**Figure 1** Kaplan-Meier curve estimates of overall survival according to (A) CCI, (B) ACCI, (C) CCI three staging and (D) ACCI three staging. Survival probability is plotted on the Y-axis against postoperative time on the X-axis. Different color stands for different index scores. ACCI, age-adjusted Charlson Comorbidity Index; CCI, Charlson Comorbidity Index.

mortality rates in medical care. However, along with the improvements of surgical techniques and postoperative management, the indication of CCI or ACCI expanded to appraise patients' long-term survival after surgery (18,24,25). In our study, for the first time, CCI and ACCI were utilized to determine the influence of comorbidity in ICC. It turned out that ACCI performed well in predicting outcomes after ICC resection. The 5-year OS rates in the ACCI low, moderate and high groups were 22.7%, 15.0% and 9.3%, with P values =0.019 (*Figure 1D*). Interestingly, the Kaplan-Meier curve for continuous variables depicted a meticulous survival comparison (*Figure 1B*). In the ACCI =7, 8, 9 groups, OS rates decreased to 0% after one year of recovery. The low populations in these classifications, which deteriorated the diversity, may be the explanation for these results. However, the other stratifications had similar prognostic trends, in which survival time declined incrementally with higher ACCI scores. All these results highlighted the decisive role of comorbidity management for ICC patients. Timely and considerate treatments for preoperative comorbidities may bring about decent survival after resection.

Growing evidence has suggested that age carries a considerable weight in predicting the prognosis of patients with different cancers (26-28). Researchers obtained corresponding results in ICC patients. There was a

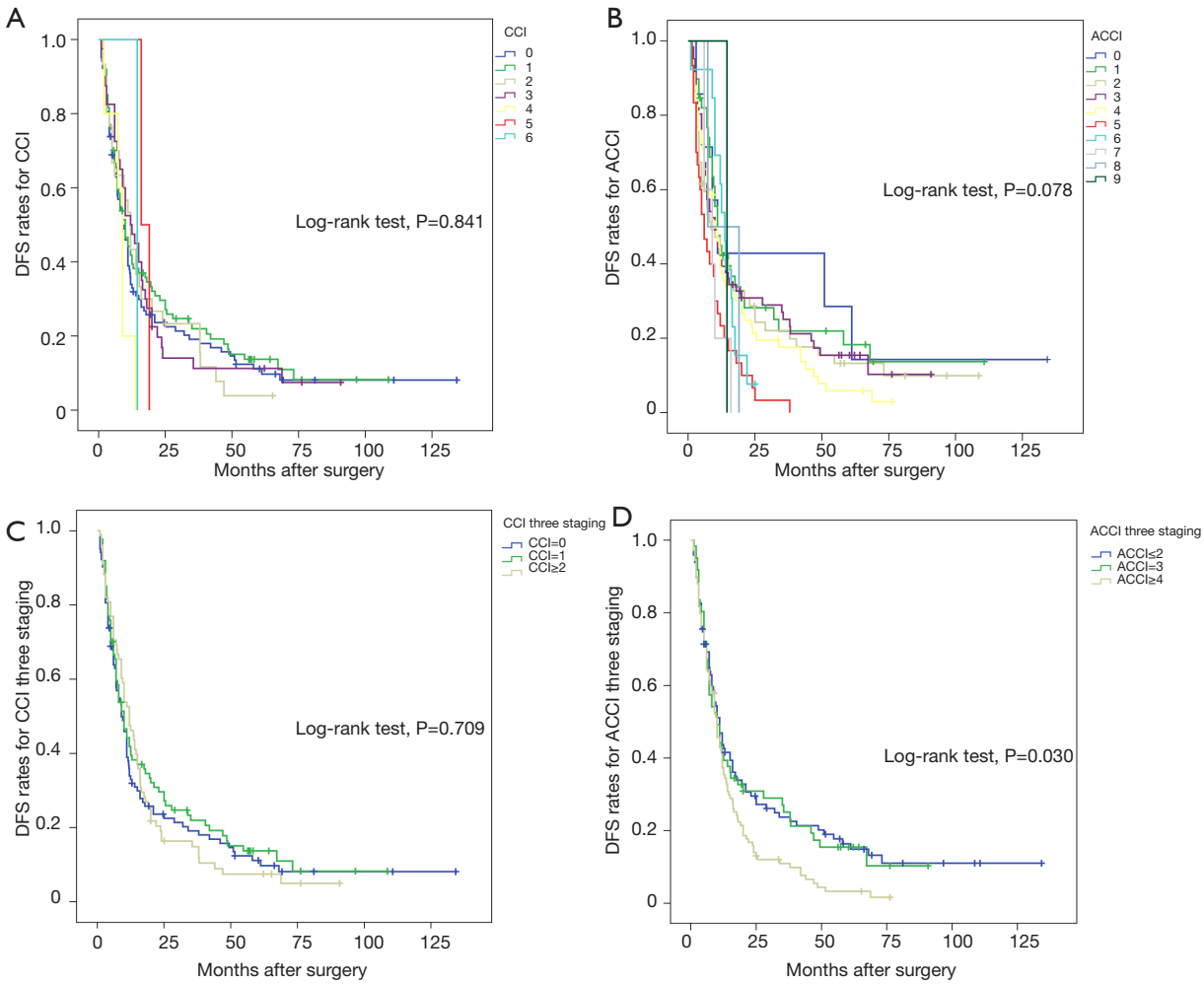


**Figure 2** Kaplan-Meier curve estimates of disease-free survival according to (A) CCI, (B) ACCI, (C) CCI three staging and (D) ACCI three staging. Survival probability is plotted on the Y-axis against postoperative time on the X-axis. Different color stands for different index scores. ACCI, age-adjusted Charlson Comorbidity Index; CCI, Charlson Comorbidity Index.

prominent survival difference between the high ACCI score group and the low group. One positive finding was that patients without any comorbidities and who were under 40 years old had a 3-year OS of 57.1% and a 5-year OS of 38.1% (*Figure 1D*). The data visually underlined the potentially strong link between younger patients and better prognosis. Careful treatment of elderly individuals, more comprehensive screening and rapid surgical decision would be of great advantage in improving outcomes. In contrast to ACCI, CCI failed to show statistical significance in both OS and DFS (*Figures 1C,2C*). To some extent, adjusting age to CCI was a relatively profound method to evaluate the role of comorbidities.

In view of ACCI's outstanding performance in the survival curve, we selected ACCI rather than CCI as one of the candidates in the multivariable analysis. As a result, CEA, CA19-9, max-diameter, tumor differentiation, ACCI and ACCI classification were indicative of poorer OS (*Table 3*). Consistently, preoperative CA19-9 and tumor size were also identified as independent predictive parameters in our previous study (10). Of note, a recent study from He *et al.* demonstrated that supplementing CEA to CA19-9 had a better effect for survival prediction (29). For DFS, the prognostic determinants were AFP, CEA, Max diameter, MVI and VI. Vascular invasion, known as the potential evidence of tumor cell metastasis, has recently been proven to be related to ICC recurrence (30). Based on the manifestation of serum markers, tumor morphology and

**Table 3** Cox proportional hazards regression model showing the multivariate analysis of variables with OS and DFS according to ACCI

| Variable | OS | | | DFS | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Sex (female/male) | 1.122 | 0.724–1.740 | 0.606 | 1.281 | 0.848–1.935 | 0.239 |
| HBsAg (yes/no) | 0.651 | 0.426–0.994 | 0.047 | 0.691 | 0.469–1.017 | 0.061 |
| Anti-HCV (yes/no) | 0.388 | 0.090–1.675 | 0.205 | 0.354 | 0.083–1.507 | 0.160 |
| AFP (≥20/<20, ng/mL) | 1.710 | 0.932–3.139 | 0.083 | 1.840 | 1.042–3.249 | 0.035 |
| CEA (≥5/<5, ng/mL) | 1.804 | 1.133–2.874 | 0.013 | 1.809 | 1.161–2.819 | 0.009 |
| CA19-9 (≥37/<37, U/mL) | 1.838 | 1.219–2.771 | 0.004 | 1.155 | 0.791–1.686 | 0.456 |
| ALT (≥35/<35, U/L) | 0.932 | 0.558–1.556 | 0.786 | 0.732 | 0.450–1.191 | 0.209 |
| AST, U/L | 1.004 | 0.998–1.010 | 0.202 | 1.004 | 0.998–1.010 | 0.190 |
| PT (≥13/<13, s) | 0.635 | 0.304–1.327 | 0.227 | 0.630 | 0.320–1.243 | 0.183 |
| TB (≥17/<17, μmol/L) | 1.456 | 0.924–2.295 | 0.106 | 1.365 | 0.889–2.096 | 0.155 |
| Lymphoid metastasis (yes/no) | 1.536 | 0.983–2.400 | 0.059 | 1.439 | 0.942–2.199 | 0.093 |
| Tumor numbers | 0.984 | 0.892–1.086 | 0.751 | 0.973 | 0.874–1.084 | 0.620 |
| Max diameter, cm | 1.078 | 1.004–1.158 | 0.040 | 1.088 | 1.019–1.163 | 0.012 |
| VI | 1.038 | 0.692–1.556 | 0.857 | 0.632 | 0.424–0.941 | 0.024 |
| MVI | 1.107 | 0.269–4.548 | 0.888 | 7.374 | 1.812–30.005 | 0.005 |
| Capsule | 0.731 | 0.400–1.338 | 0.310 | 0.617 | 0.344–1.105 | 0.104 |
| Tumor differentiation | | | 0.007 | | | 0.063 |
| I *vs.* I–II, II | 1.816 | 0.119–27.656 | 0.668 | 0.691 | 0.047–10.081 | 0.787 |
| I–II, II *vs.* II–III, III | 1.195 | 0.140–10.213 | 0.871 | 0.423 | 0.050–3.547 | 0.427 |
| II–III, III *vs.* III–IV, IV | 2.308 | 0.261–20.386 | 0.452 | 0.669 | 0.078–5.753 | 0.715 |
| ACCI | 1.134 | 1.015–1.267 | 0.026 | 1.069 | 0.964–1.186 | 0.205 |
| ACCI 3 staging | | | 0.040 | | | 0.253 |
| ≤2 *vs.* 3 | 0.706 | 0.462–1.078 | 0.107 | 0.793 | 0.535–1.175 | 0.247 |
| 3 *vs.* ≥4 | 1.254 | 1.077–1.398 | 0.045 | 0.679 | 0.417–1.105 | 0.119 |

OS, overall survival; DFS, disease free survival; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TB, total bilirubin; PT, prothrombin time; AST, aspartate transaminase; ALB, albumin; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate 19-9; ALT, alanine aminotransferase; CCI, Charlson Comorbidities Index; ACCI, age-adjusted Charlson Comorbidities Index; TNM, tumor node metastasis stage; VI, vascular invasion; MVI, micro vascular invasion.

ACCI, we achieved further recognition of ICC from the clinical and hematological prospective.

The SAS analysis results revealed that moderate or severe liver disease played the most decisive role among all the comorbidities. This was possibly caused by the potential relationship between primary malignancy and its pathophysiological changes in the liver. The subsequent candidates included serious diseases, such as solid tumor or lymphoma, and widely known conditions, such as ulcer or diabetes. Further studies should explore more specific comorbidity therapies, such as drug intake, or habit changes and patients' compliance to the treatments.

Although our study covered a large sample of an ICC cohort, it had limitations. First, it was a retrospective study, which inevitably brought about selection bias. Second, our data were derived from a single center; further validation

 

**Table 4** Explained variance (R2) of ACCI by the 6 most predictive factors

| Order | Comorbidity | Partial $R^2$ | $R^2$ | C(p) | F | Pr > F |
|---|---|---|---|---|---|---|
| 1 | Moderate and severe liver disease | 0.2294 | 0.3941 | 104.474 | 98.82 | <0.001 |
| 2 | Ulcer | 0.0559 | 0.4499 | 73.4218 | 26.41 | <0.001 |
| 3 | Tumor | 0.0473 | 0.4973 | 47.4101 | 24.39 | <0.001 |
| 4 | Diabetes | 0.0288 | 0.5260 | 32.3989 | 15.65 | <0.001 |
| 5 | Mild liver disease | 0.0287 | 0.5548 | 17.4072 | 16.58 | <0.001 |
| 6 | lymphoma | 0.0108 | 0.5656 | 12.9937 | 6.39 | 0.0121 |

All models are adjusted for age. ACCI, age-adjusted Charlson Comorbidities Index.

with additional data sets is needed. Third, the diversity of multiple comorbidities was insufficient. Fourth, further studies should be proposed to pursue the association between specific comorbidities and treatment benefits.

## Conclusions

Compared with the CCI, the ACCI is a more promising model to accurately predict OS in ICC patients treated with curative resection. The results in our study highlight the importance of comorbidities in ICC patients, including liver disease, hypertension, diabetes and ulcer. Future research should focus on the impact of comorbidity therapy.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.23). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the institutional review board of Zhongshan Hospital (No. Y2017-279) and complied with the standards of the declaration of Helsinki and current ethical guidelines.



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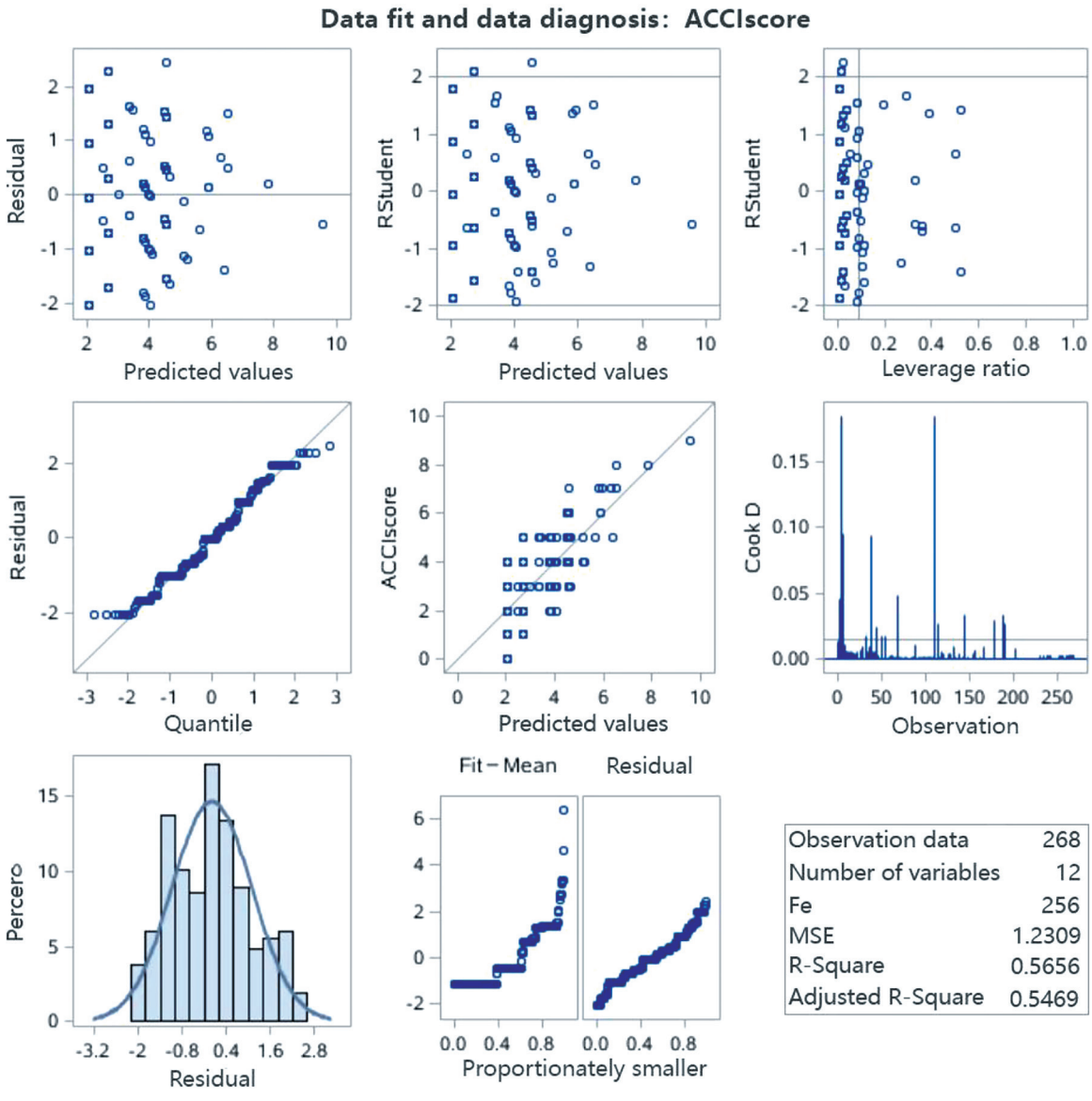
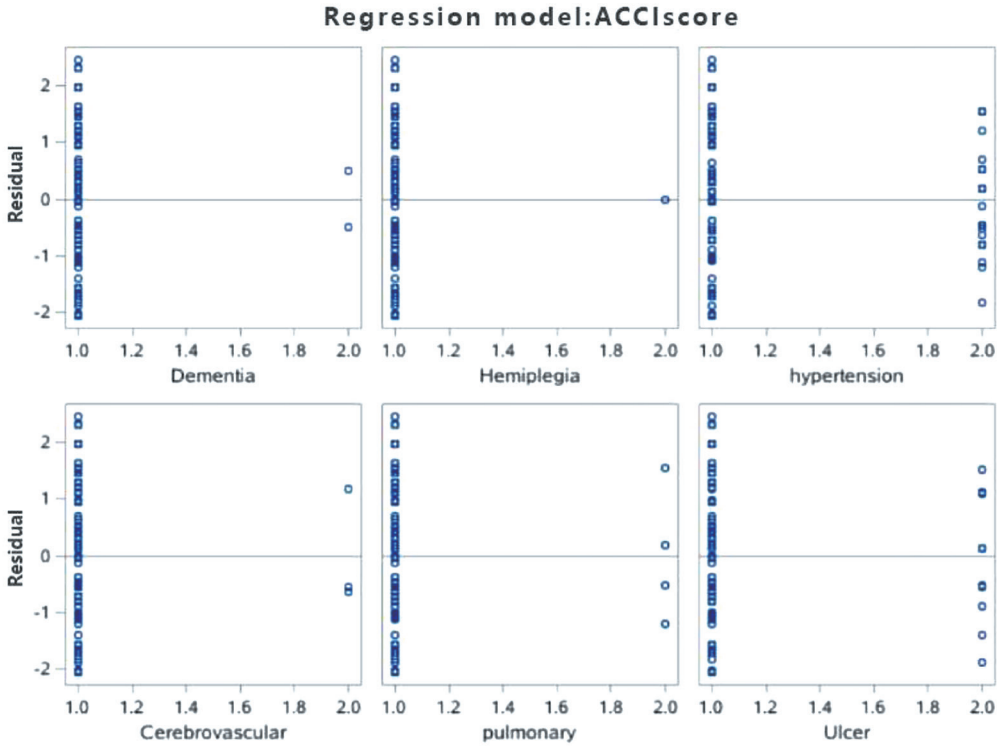
## Supplementary

**Table S1** Cox proportional hazards regression model showing the multivariate analysis of variables with OS and DFS according to CCI

| Variable | OS | | | DFS | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Sex (female/male) | 1.173 | 0.751–1.832 | 0.482 | 1.353 | 0.889–2.059 | 0.158 |
| Age, years | 1.030 | 1.011–1.050 | 0.002 | 1.028 | 1.010–1.046 | 0.003 |
| HBsAg (yes/no) | 0.927 | 0.554–1.549 | 0.771 | 1.009 | 0.631–1.614 | 0.971 |
| Anti-HCV (yes/no) | 0.350 | 0.081–1.517 | 0.160 | 0.306 | 0.072–1.303 | 0.109 |
| AFP (≥20/<20, ng/mL) | 1.674 | 0.913–3.072 | 0.096 | 1.793 | 1.015–3.166 | 0.044 |
| CEA (≥5/<5, ng/mL) | 1.710 | 1.071–2.731 | 0.025 | 1.709 | 1.093–2.672 | 0.019 |
| CA19-9 (≥37/<37, U/mL) | 1.820 | 1.202–2.757 | 0.005 | 1.150 | 0.782–1.690 | 0.477 |
| ALT (≥35/<35, U/L) | 0.940 | 0.561–1.574 | 0.815 | 0.744 | 0.455–1.215 | 0.237 |
| AST, U/L | 1.006 | 0.999–1.012 | 0.082 | 1.006 | 1.000–1.012 | 0.050 |
| PT (≥13/<13, s) | 0.711 | 0.338–1.495 | 0.369 | 0.690 | 0.350–1.363 | 0.285 |
| TB (≥17/<17, μmol/L) | 1.420 | 0.895–2.253 | 0.137 | 1.334 | 0.866–2.057 | 0.191 |
| Lymphoid metastasis (yes/no) | 1.612 | 1.031–2.520 | 0.036 | 1.487 | 0.973–2.274 | 0.067 |
| Tumor numbers | 0.980 | 0.890–1.080 | 0.686 | 0.971 | 0.874–1.079 | 0.589 |
| Max diameter, cm | 1.092 | 1.015–1.175 | 0.018 | 1.106 | 1.033–1.185 | 0.004 |
| VI | 0.980 | 0.645–1.488 | 0.924 | 0.592 | 0.395–0.889 | 0.011 |
| MVI | 1.233 | 0.289–5.258 | 0.777 | 8.608 | 2.081–35.612 | 0.003 |
| Capsule | 0.709 | 0.384–1.306 | 0.270 | 0.589 | 0.326–1.063 | 0.079 |
| Tumor differentiation | | | 0.015 | | | 0.109 |
| I *vs.* I–II, II | 0.996 | 0.062–15.894 | 0.997 | 0.361 | 0.024–5.517 | 0.464 |
| I–II, II *vs.* II–III, III | 1.038 | 0.121–8.920 | 0.973 | 0.367 | 0.043–3.097 | 0.357 |
| II–III, III *vs.* III–IV, IV | 1.909 | 0.215–16.956 | 0.562 | 0.553 | 0.064–4.784 | 0.590 |
| CCI | 0.972 | 0.820–1.153 | 0.747 | 0.901 | 0.764–1.063 | 0.217 |
| CCI 3 staging | | | 0.980 | | | 0.503 |
| ≤2 *vs.* 3 | 1.002 | 0.594–1.692 | 0.993 | 1.304 | 0.788–2.159 | 0.302 |
| 3 *vs.* ≥4 | 0.956 | 0.572–1.599 | 0.864 | 1.006 | 0.620–1.630 | 0.982 |

OS, overall survival; DFS, disease free survival; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TB, total bilirubin; PT, prothrombin time; AST, aspartate transaminase; ALB, albumin; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate 19-9; ALT, alanine aminotransferase; CCI, Charlson Comorbidities Index; TNM, tumor node metastasis stage; VI, vascular invasion; MVI, micro vascular invasion.



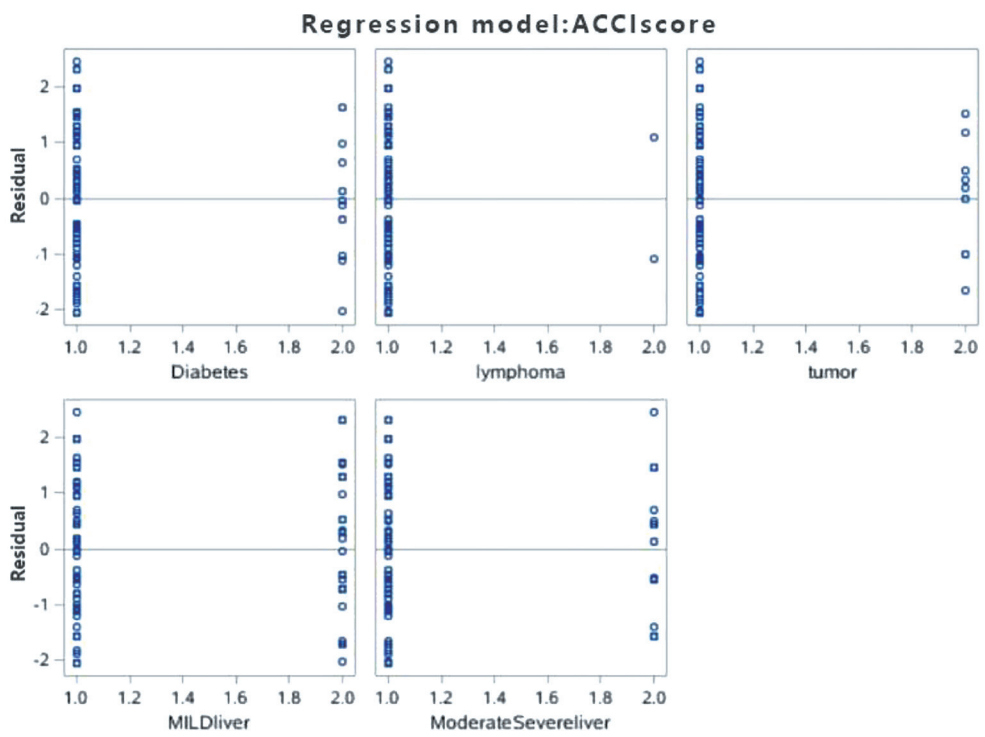




**Figure S1** The calculation process for the multivariate liner regression analysis. The data results satisfy the condition of multiple linear regression: the homogeneity of independent normal variance. The 6 most predictive comorbidities explain approximately 56.56% of the variance (R2) of ACCI scores.