

# Incidence trend and prognosis of intrahepatic cholangiocarcinoma: a study based on the SEER database

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## Research Article

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# Abstract

**Background:** Intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC) have different cellular origins; therefore, ICC is significantly different from HCC in terms of aetiology, mechanism, tumour biological behaviour, treatment methods, and prognosis. The objective of this study was to investigate the current incidence trend and prognosis of intrahepatic cholangiocarcinoma (ICC) and deepen the understanding of ICC.

**Methods** A large sample of ICC and hepatocellular carcinoma (HCC) patient data was obtained from the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute (NCI), USA. The incidence trend, prognosis, and the effect of surgery and lymph node dissection on the prognosis of ICC patients were analysed.

**Results** In recent years, the incidence of ICC has increased. The prognosis of ICC patients is significantly worse than that of HCC patients. Surgery can benefit all stages of ICC, and lymph node dissection is beneficial for the prognosis of patients with positive lymph nodes (N1).

**Conclusion** In recent years, the incidence of ICC has been increasing, and its prognosis remains poor, which is a cause for concern.

## 1 Introduction

Intrahepatic cholangiocarcinoma (ICC) refers to cholangiocarcinoma that occurs above the secondary bile duct of the liver; it accounts for approximately 10% of primary liver cancer cases<sup>1</sup>. It is the second most common primary liver cancer after hepatocellular carcinoma (HCC). ICC and HCC have different cellular origins; therefore, ICC is significantly different from HCC in terms of aetiology, mechanism, tumour biological behaviour, treatment methods, and prognosis. Recent studies have suggested that ICC may also be directly caused by transdifferentiation of hepatocytes<sup>2</sup>. In fact, ICC has a high degree of malignancy and a poor prognosis<sup>3</sup>. The overall 5-year survival rate of ICC is less than 5%, and the postoperative 5-year survival rate is approximately 20%, even for patients who undergo surgery<sup>4</sup>. Recent studies have shown that the incidence of ICC is increasing<sup>5,6</sup>. Although the worldwide incidence of ICC is much lower than that of HCC, it is important to note that this increase is rapid<sup>7</sup>, and it is expected to continue to do so for decades to come. At present, the overall understanding of ICC is insufficient, and there is a lack of studies with large sample sizes. First, we know little about the epidemiology of ICC compared to HCC<sup>7</sup>. Secondly, our understanding of the therapeutic efficacy of ICC patients is also inadequate. Given the increasing incidence of ICC, a disease with a very poor prognosis, difficult to treat and fatal, we are increasingly recognizing ICC as a unique cancer. In this study, a large sample of ICC and HCC patient data was obtained from the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute (NCI), USA. Current trends in the incidence and prognosis of ICC compared with HCC are presented in the form of data to improve the understanding of ICC.

## 2 Patients And Methods

### 2.1 Data sources

The data used in this study comprised two parts: ICC patient data from between 1973 and 2014 collected in the SEER database and ICC patient data from between 2010 and 2014 in the SEER database (The American Joint Committee on Cancer (AJCC) 7th edition staging was used<sup>8</sup>). The first part of the data (from 1973 to 2014) was used to calculate and analyse trends in the ICC incidence and prognosis. The second part of data (2010 to 2014) was used for the analysis of the prognostic differences between ICC and HCC and the impact of surgery and lymph node dissection on the prognosis of ICC.

### 2.2 Method

#### 2.2.1 Joinpoint regression analysis

The joinpoint regression model is also called a piecewise regression, broken-line regression, or multiphase regression. Its basic principle is to divide a long-term trend line into several segments, each of which presents continuous linearity. The commonly used linear model can only describe or predict one trend, and the time series model also has many limitations. The joinpoint regression model does not have strict requirements regarding the presence of a trend in the data sequence itself. In recent years, it has been increasingly used by researchers to determine the trends of changes in tumours, tuberculosis, acquired immunodeficiency syndrome (AIDS), and smoking. The annual percent change (APC) was used to evaluate the temporal trend of the incidence of ICC.

#### 2.2.2 Kaplan–Meier prognostic analysis

The endpoint of follow-up was cancer-specific death, and the prognostic indicator was cancer-specific survival (CSS). The Kaplan–Meier method was used to calculate the CSS, and the log-rank method was used to compare the differences in CSS between groups. The difference was statistically significant when  $P < 0.05$ .

#### 2.2.3 Competitive risk prognostic model

Clinical survival data often have multiple outcomes, and there is often a competitive relationship among these outcomes. In the past, the Kaplan–Meier method was often used in tumour prognosis studies, and the influence of other prognostic outcomes (competitive events) was ignored when studying the impact of a certain factor on a certain outcome. Therefore, in this study, the competitive risk model was used. The competitive risk model is applicable to the survival data of multiple outcomes. Concerns with outcome A and a lack of concern with outcome B are not independent of each other and are in competition when the occurrence of A causes B not to occur. In this study, we used a competitive risk model to evaluate the effect of surgery on the prognosis of ICC patients. One outcome was death from a tumour, and the other outcome was death from non-tumour factors.

## **3 Results**

### **3.1 Comparison of general information for ICC and HCC patients between 1973 and 2014**

A total of 8160 ICC and 8170 HCC patients were identified in the SEER database from between 1973 and 2014. Table 1 shows the clinical characteristics of the patients.

Table 1  
Trends in the Baseline Demographic and Pathological Characteristics of the Study Population  
(1973–2014)

Variable	ICC (8160)	HCC (8170)
No. of patients (n)	12629	89816
Median age (years)	67.93	63.89
Sex, n (%)		
Female	6243(49.4)	21808(24.3)
Male	6386(50.6)	68008(75.7)
Race, n (%)		
White	10058(79.6)	60080(66.9)
Black	956(7.6)	11546(12.9)
Other*Asian/Pacific Islander, American Indian/Alaskan Native	1580(12.5)	17827(19.8)
Unknown	35(0.3)	363(0.4)
SEER historic stage, n (%)		
Localized	3197(25.3)	38702(43.2)
Regional	3029(24.0)	23957(26.7)
Distant	3841(30.4)	14537(16.2)
Unstaged	2562(20.3)	12620(14.1)
Grade, n (%)		
Well differentiated	555(4.4)	10396(11.6)
Moderately differentiated	1957(15.5)	12325(13.7)
Poorly differentiated	1818(14.4)	7077(7.9)
Undifferentiated	81(0.6)	789(0.9)
Unknown	8218(65.1)	59229(65.9)
*Asian/Pacific Islander, American Indian/Alaskan Native		

## 3.2 Analysis of incidence trend

From 1973 to 2011, the incidence of HCC showed an overall increasing trend that accelerated from 1984 to 2011. The APC was 4.82 from 1984 to 2011, while it was 1.88 from 1973 to 1984. However, the incidence of HCC decreased between 2011 and 2014, with an annual decrease of approximately 1.33% (Fig. 1A). In contrast, although the incidence of ICC decreased by 13.4% per year from 1999 to 2002, it

increased rapidly at an annual rate of 7.31% from 2002 to 2014 (Fig. 1A).). Therefore, the incidence of ICC has increased significantly in recent years.

### **3.3 Analysis of prognostic trends**

The data for ICC patients between 1973 and 2014 were grouped chronologically into five decades: the 1970s, 1980s, 1990s, 2000s, and 2010s. The study data showed that the survival time of ICC patients has gradually increased, and the median survival time increased from 3 months in 1970s to 14 months in 2010s. This indicates that the treatment efficacy for ICC patients has significantly improved with the development of medical technology. However, the median survival time of ICC patients in the 2010s was still only 14 months, indicating a very urgent need to prolong the survival of ICC patients.

### **3.4 General data of ICC and HCC patients between 2010 and 2014 (AJCC 7th edition staging).**

The second part of the study data included data for 8408 HCC patients and 1081 ICC patients from between 2010 and 2014. The general clinicopathological data of the patients are shown in Table 2.

Table 2  
Trends in the Baseline Demographic and Pathological  
Characteristics of the Study Population (2010–2014)

<b>Variable</b>	<b>HCC (8170)</b>	<b>ICC (8160)</b>
No. of patients (n)	8408	1081
Median age (years)	64	65
Sex, n (%)		
Female	2003 (23.8)	535 (49.5)
Male	6405 (76.2)	546 (50.5)
Race, n (%)		
White	5732 (68.2)	843 (78.0)
Black	1147(13.6)	83(7.7)
Other*	1529(18.2)	155(14.3)
T stage		
T0	2(0.0)	3(0.3)
T1	4237(50.4)	385(35.6)
T2	1952(23.2)	835(41.9)
T3	1930(23.0)	149(13.8)
T4	287(3.4)	91(8.4)
N stage		
N0	7893(93.9)	768(71.0)
N1	515(6.1)	313(29.0)
M stage		
M0	7647(90.9)	805(74.5)
M1	761(9.1)	276(25.5)
Tumour size, cm	5.98	6.65
Grade, n (%)		
Well differentiated	2669(31.7)	117(10.8)
Moderately differentiated	4008(47.7)	528(48.8)

\* Asian/Pacific Islander, American Indian/Alaskan Native

Variable	HCC (8170)	ICC (8160)
Poorly differentiated	1621(19.3)	427(39.5)
Undifferentiated	110(1.3)	9(0.8)
Surgery		
No	4372(52.0)	548(50.7)
Yes	4036(48.0)	533(49.3)
* Asian/Pacific Islander, American Indian/Alaskan Native		

### 3.5 The difference in prognosis between ICC and HCC patients between 2010 and 2014

Between 2010 and 2014, there was a significant difference in the prognosis of ICC patients and HCC patients. The survival time of ICC patients was shorter than that of HCC patients (14 vs. 19 months,  $p \leq 0.01$ ), indicating that the prognosis of ICC patients was worse.

### 3.6 The effect of surgery on the prognosis of ICC

A competitive risk prognostic model was used to analyse the effect of surgery on the prognosis of ICC patients. Surgery benefited ICC patients in both the early and advanced stages (A, all ICC ( $p \leq 0.01$ ,  $p_2 = 0.117$ ); B, ICC stage  $\square$  and  $\square$  ( $p_1 \leq 0.01$ ,  $p_2 = 0.025$ ); C, ICC stage  $\square$  and  $\square$  ( $p_1 \leq 0.01$ ,  $p_2 = 0.092$ )).

### 3.7 The effect of lymph node dissection on the prognosis of ICC patients with positive lymph nodes (N1)

For patients with positive lymph nodes (N1), the need for lymph node dissection remains controversial. The study showed that the median survival time was 14 months in the lymph node dissection group compared to 5 months in the non-lymph node dissection group, and there was a difference in prognosis between the two groups ( $p \leq 0.01$ ).

## 4 Discussion

ICC arises from intrahepatic bile duct cells and must be differentiated from HCC in clinical practice. A considerable amount of clinical and basic research has focused on HCC. However, the research on ICC generally inadequate, and the studies that have been conducted have small sample sizes<sup>9</sup>. The present study revealed some epidemiological, clinical pathological and prognostic characteristics of ICC from multiple aspects, indicating that ICC warrants sufficient attention. In this study, in the 102445 patients enrolled in between 1973 and 2014, the ratio of HCC to ICC was approximately 7.11:1, and the overall number of HCC cases was still significantly higher than the number of ICC cases. The proportions of male and female ICC patients were similar (50.6:49.4), while males accounted for a large proportion (75.7%) of the HCC patients. At the time of detection, more HCC patients (43.2%) were in the localized

stage, while 30.4% of the ICC patients were already in the distant metastasis stage, and ICC was more poorly differentiated than HCC. In terms of the incidence trend, the incidence of HCC decreased by approximately 1.33% per year from 2011 to 2014, but the incidence of ICC increased rapidly, with an annual growth rate of 7.31% from 2002 to 2014. Some scholars believe that the current increase in ICC incidence may be due to the advantage of modern diagnostic methods to identify earlier lesions and biliary malignancies that were not previously diagnosed<sup>10</sup>. Of course, the increased incidence of ICC may be related to the increase in some newly recognized risk factors, such as viral hepatitis and nonviral chronic liver disease<sup>11,12</sup>. In addition, although the survival of the ICC patients increased over time, their median survival was still only 14 months. Currently, there is a lack of effective treatment for ICC to prolong patient outcomes<sup>13</sup>.

In addition to differences in pathogenesis, tissue origin, and clinical pathology, HCC and ICC also have significant differences in prognosis. Our study showed that the survival time of ICC patients was worse than that of HCC patients (median survival time of 14 vs. 19 months,  $p \leq 0.01$ ), which may be related to the high degree of malignancy in ICC. However, there is still a lack of clinical and basic research on ICC, which is worthy of further in-depth study. Compared with HCC, most cases of ICC are at an advanced stage when the cancer is discovered, the postoperative recurrence rate is high, and the overall treatment efficacy is poor<sup>14</sup>. Previous studies reported that the postoperative 5-year survival rate of ICC was approximately 20%, and the recurrence rate was approximately 50%<sup>7</sup>. Our results indicate that active surgery is still necessary. The competitive risk prognostic model used in this study showed that surgery could prolong the survival of ICC patients at different stages. Especially for stage III and IV patients, conservative treatment was considered suitable in the past. Currently, R0 resection surgery is the only effective treatment for ICC<sup>15</sup>. Unfortunately, studies have shown that only about 20–40% of ICC patients can be surgically removed<sup>16</sup>. Whether patients with intermediate and advanced ICC need aggressive surgical resection needs further discussion. Currently, intrahepatic metastasis is considered the most common type of ICC metastasis, followed by lymph node metastasis. Lymph node metastasis is widely regarded as a poor prognostic factor in ICC patients<sup>15</sup>. However, the need for active lymph node dissection in ICC is still controversial<sup>17</sup>. The controversy has focused on whether routine lymph node dissection should be performed and the extent of lymph node dissection<sup>15,18</sup>. Many scholars believe that lymph node dissection can benefit ICC patients and prolong their survival<sup>19,20</sup>. It is believed that routine lymphadenectomy can reduce local recurrence and prolong the prognosis of patients<sup>4,21,22</sup>. However, Uenishi et al.<sup>23</sup> believe that routine lymph node dissection cannot improve the overall survival rate of ICC patients and has a high incidence of surgical complications. Kim et al. also hold this viewpoint<sup>24</sup>. Previous studies have shown that lymph node metastasis is an independent poor prognostic factor for ICC patients.<sup>25</sup> The data considered in the present study showed that for patients with lymph node metastasis, active lymph node dissection was also beneficial. The median survival times of patients who underwent lymph node dissection and those who did not were 14 months and 5 months, respectively, and the difference was significant ( $p \leq 0.01$ ). This view is consistent with Bridgewater et al., who believe that intraoperative regional lymph node dissection can reduce the postoperative local recurrence rate and the

biliary obstruction caused by lymph node invasion. In our experience, lymphadenectomy should be performed regardless of whether locally positive lymph nodes are found on preoperative examination or during surgery.

## Conclusions

In recent years, the incidence of ICC has increased yearly. As a highly malignant tumour, ICC has a significantly worse prognosis than HCC. Although medical treatment has greatly improved in recent years, and the prognosis for ICC is improving, the absolute survival time is still very short. We need to understand the epidemiological and pathophysiological characteristics of ICC and explore more effective treatment methods. Therefore, as hepatobiliary and pancreatic specialists, we should pay more attention to ICC and conduct reliable clinical studies with large sample sizes to improve the efficacy of treatment for ICC patients and prolong their survival.

## Abbreviations

ICC

Intrahepatic cholangiocarcinoma

HCC

Hepatocellular carcinoma

SEER

Surveillance, Epidemiology, and End Results database

AJCC

The American Joint Committee on Cancer

APC

Annual percent change

CSS

Cancer-specific survival.

## Declarations

### Acknowledgements

We would like to thank the NCI for open access to their SEER database.

### Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Authors' contributions

Contributions: (I) BW designed the study; (✉) JY and ZZ collected the data; (✉) XC and JY performed the statistical analysis; (✉) BW drafted the manuscript; (✉) XW revised and proofread the manuscript; (✉) All authors read and approved the final manuscript.

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## Ethics approval and consent to participate

Not applicable. This study was deemed exempt from review by the institutional ethics committee of The Second Affiliated Hospital of Jiaxing University. Because our data were from the SEER database, which is open to the public. All procedures performed in studies involving human participants were in accordance with the Helsinki declaration or comparable ethical standards.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests

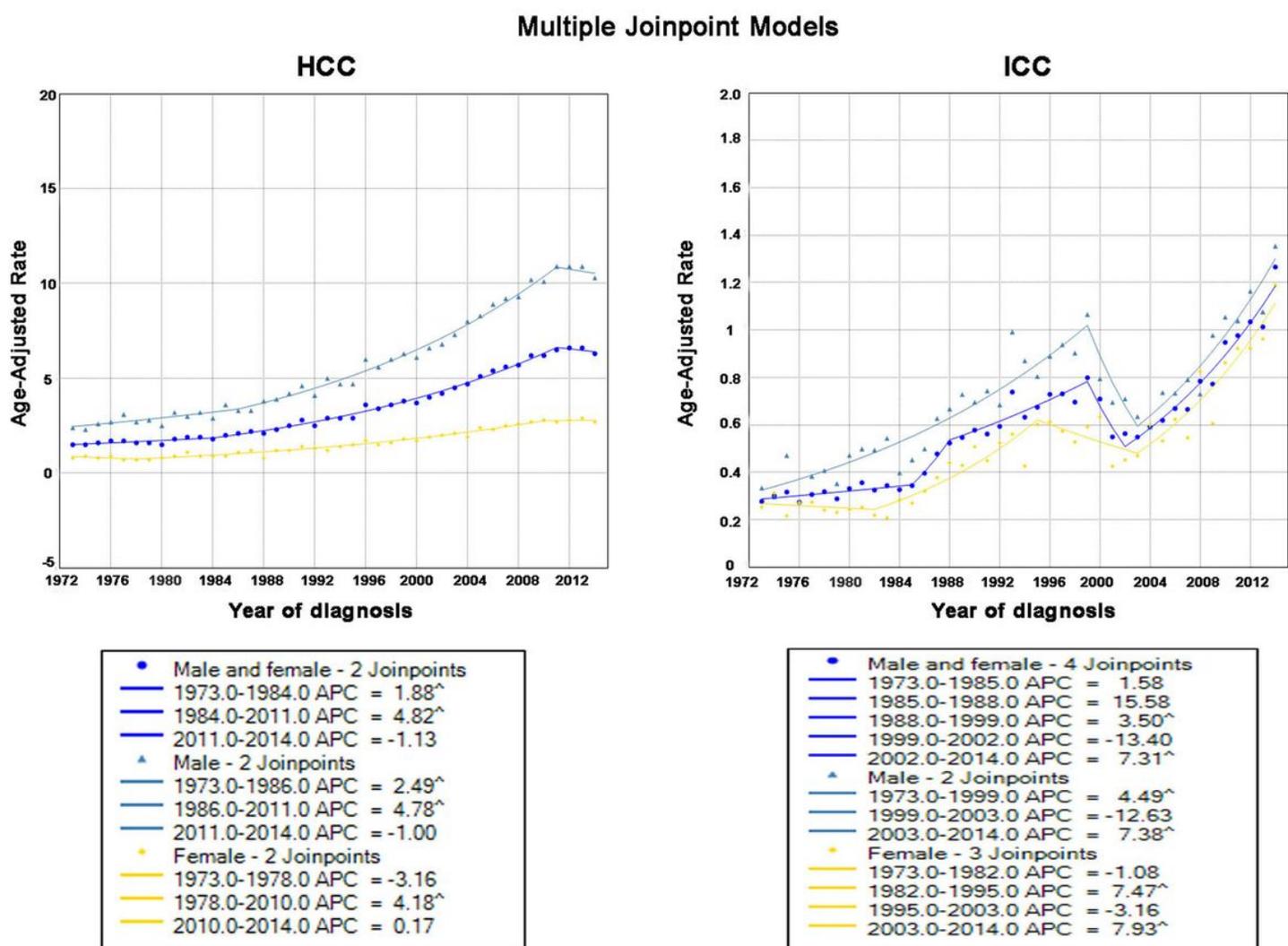
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## Figures



**Figure 1**

A: The overall trend of HCC incidence from 1973 to 2014; B: The overall trend of ICC incidence from 1973 to 2014.

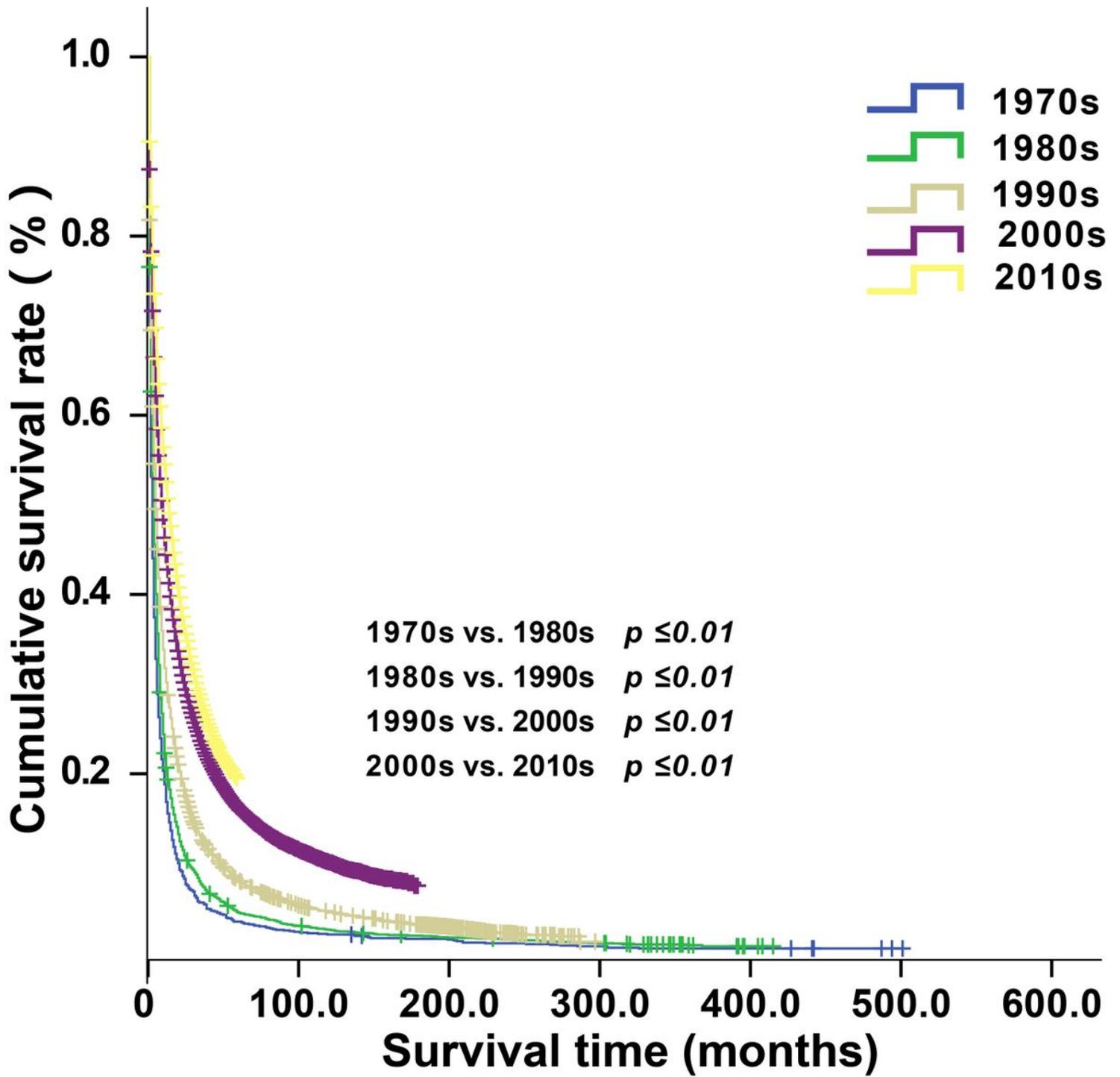


Figure 2

Comparison of the prognosis of ICC patients between the 1970s and 2010s

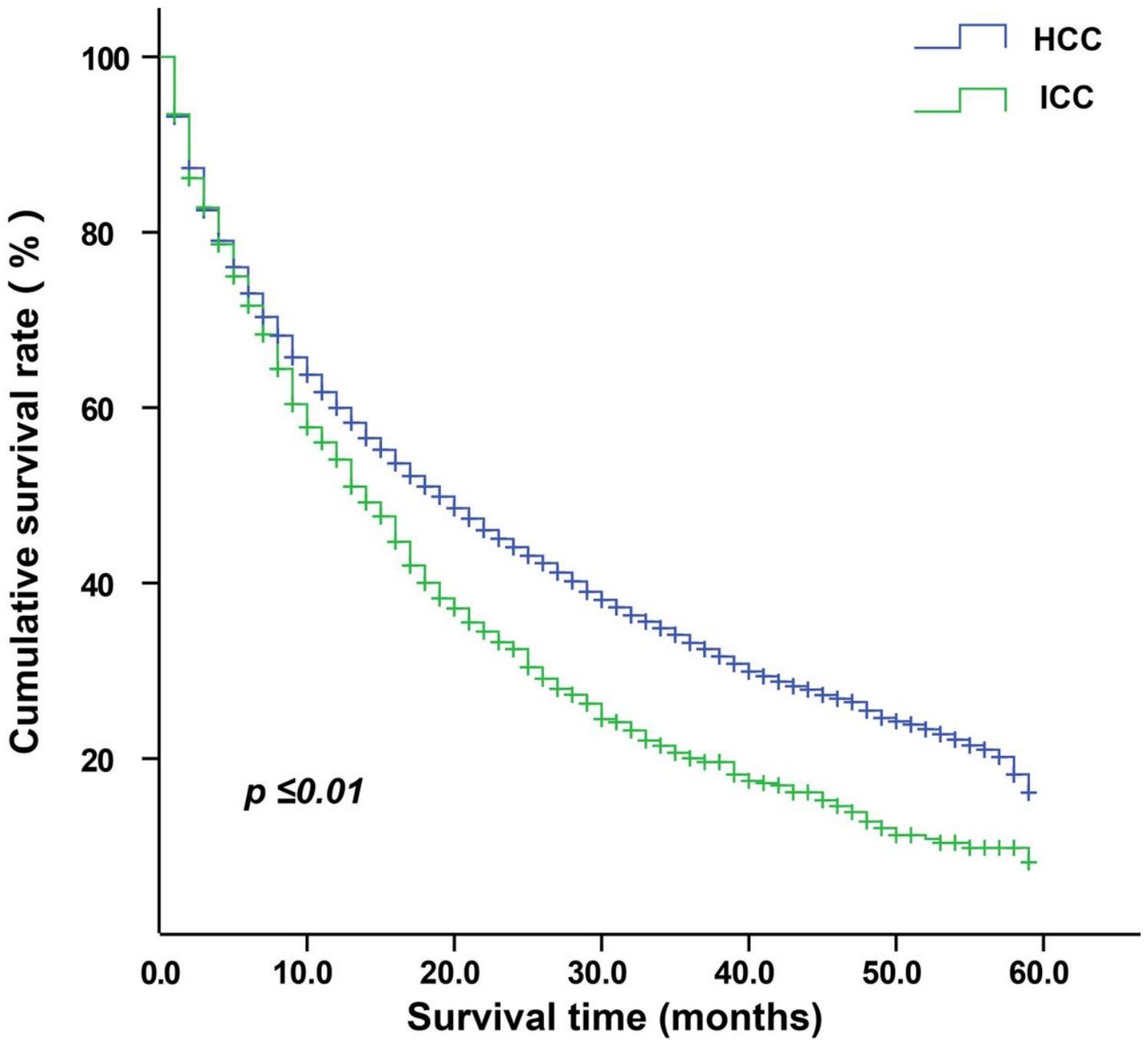
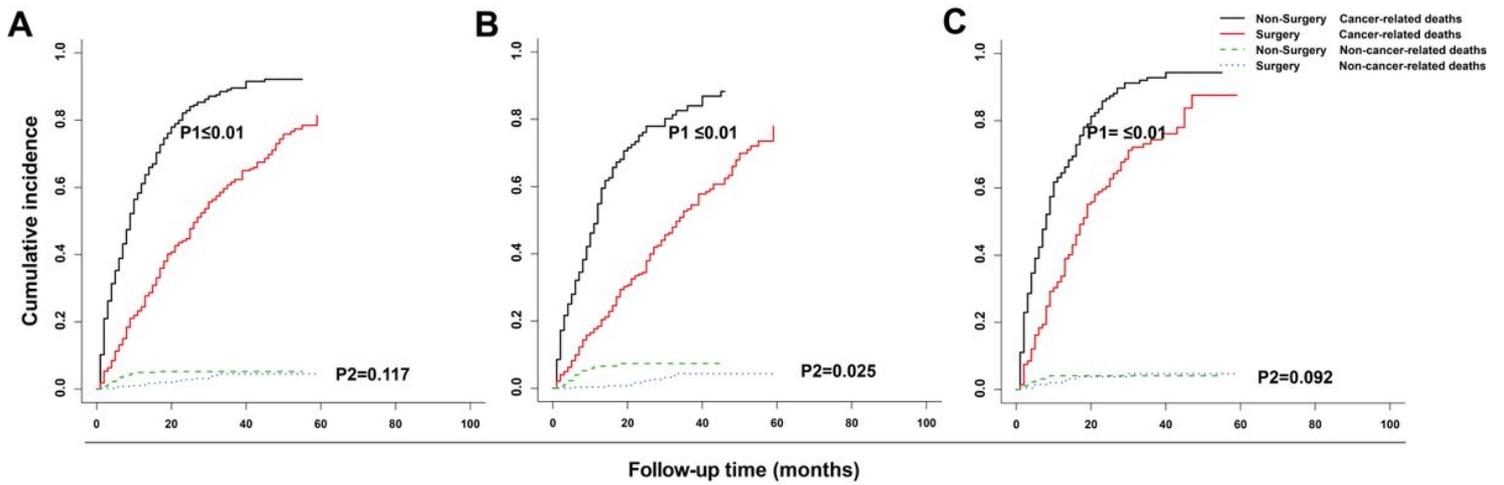


Figure 3

Differences in overall survival rates between ICC and HCC patients between 2010 and 2014 (ICC vs. HCC, 14 vs. 19 months,  $p \le 0.01$ )



**Figure 4**

The competitive risk model showed that surgery could improve the prognosis of ICC patients. A: All ICC ( $p_1 \leq 0.01$ ,  $p_2 = 0.117$ ); B: ICC stages I and II ( $p_1 \leq 0.01$ ,  $p_2 = 0.025$ ); C: ICC stages III and IV ( $p_1 \leq 0.01$ ,  $p_2 = 0.092$ ).

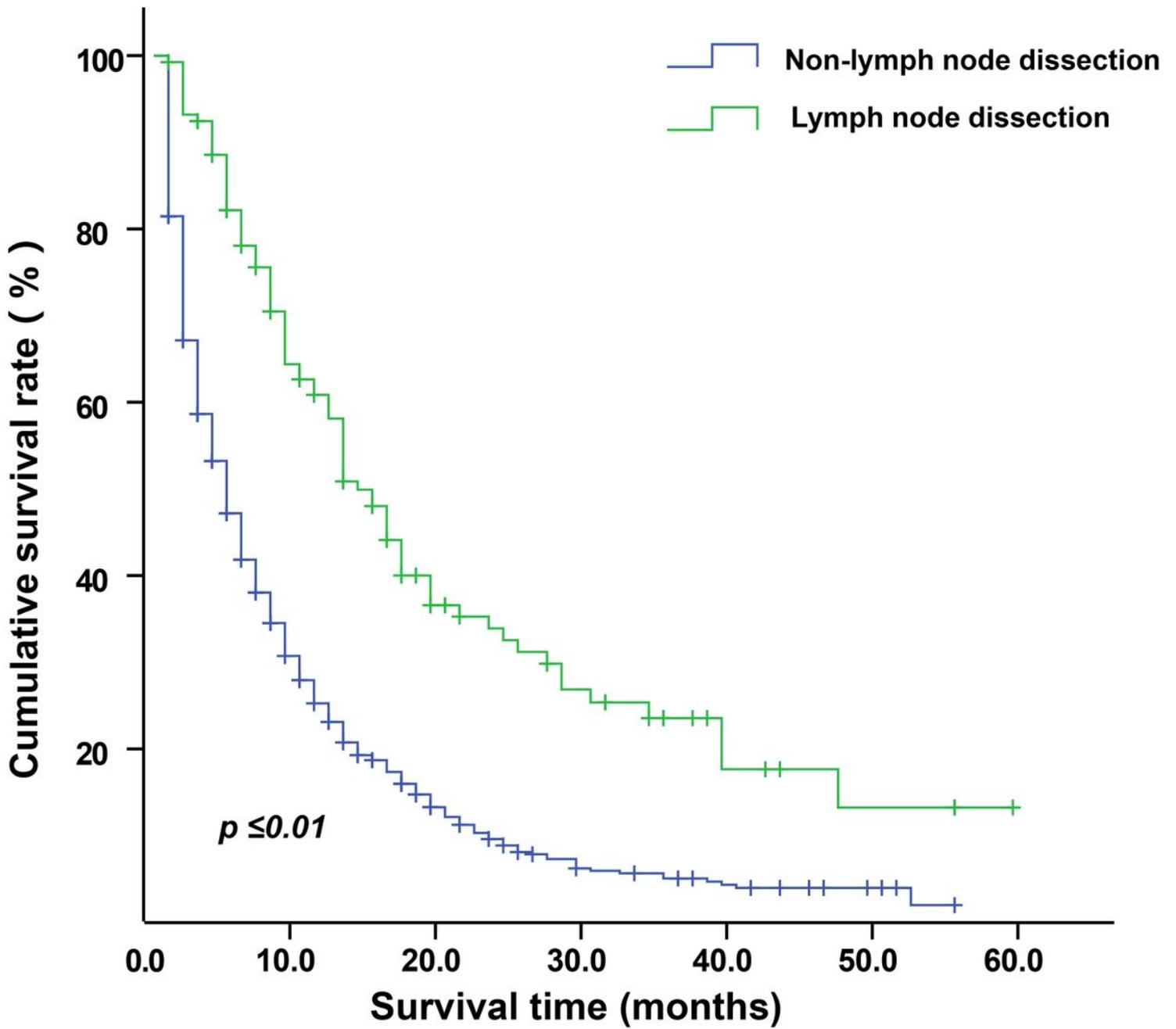


Figure 5

The effect of lymph node dissection on the prognosis of ICC patients with lymph node metastasis. The prognosis of the lymph node dissection group was significantly better than that of the non-lymph node dissection group (14 months vs. 5 months,  $p \leq 0.01$ )