The prognostic value of stromal tumor-infiltrating lymphocytes in intrahepatic cholangiocarcinoma: a population-based study

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ABSTRACT

Objective: We assess the predictive value impacted by tumor-infiltrating lymphocytes (TILs) for overall survival (OS) and progression-free survival (PFS) in patients with intrahepatic cholangiocarcinoma (ICC) undergoing complete resection.

Methods: Sixty-eight patients with resectable ICC were included in this study. We studied stromal TIL density and scored it by staining sections from surgically resected ICC patients with hematoxylin and eosin (HE). The clinical data and prognosis of patients with ICC were obtained by searching clinical and follow-up records.

Results: A stromal TIL negative status was a predictor of poor OS ($HR = 0.41, 95\% CI 0.20–0.83, p = .01$) and poor PFS ($HR = 0.47, 95\% CI 0.23–0.97, p = .04$) independently. Low stromal TIL density was associated with high levels of CA125 ($p = .03$) and CA19-9 ($p < .01$). The high level of CA19-9 ($p = .05$), high differentiation ($p = .02$), a large diameter ($p = .05$), a positive bile duct/vascular cancer embolus ($p = .03$) and positive satellite nodules ($p = .02$) were tendencies to develop tumors for patients with a negative status of stromal TIL.

Conclusion: Our data prompt for the prediction of the PFS and OS of patients with ICC after complete resection, stromal TILs play an important role.

Introduction

Intrahepatic cholangiocarcinoma (ICC) refers to an adenocarcinoma that occurs in the secondary bile duct and its branch epithelium. ICC that is identified as the second common hepatic malignancy is reported to account for 10%–15% of primary liver malignancies [1,2]. The incidence and mortality rate of ICC have continued to increase globally in recent years [3]. Surgical resection is the most effective way to treat early-stage ICC [4]. Nevertheless, due to the high recurrence rate, the prognosis of ICC after curative resection is still very poor [5]. Therefore, other prognostic factors must be identified to predict progression-free survival (PFS) and overall survival (OS) in patients with ICC after complete resection, which may be valuable in developing treatment strategies and selecting appropriate treatment options for individual patients.

Recent researches has suggested that the predictive value of tumor-infiltrating immune cells play a distinct role for many solid tumors [6–10]. A research assessing tumor-infiltrating lymphocytes (TILs) in pancreatic ductal adenocarcinoma (PDAC) showed that the existent of CD4 and CD8 TILs served as an outstanding index of prognosis after surgical operation [11,12]. Another study found that the expected outcomes of liver metastasis and the OS after complete resection of PDAC can be obtained by evaluating stromal TILs [13]. However, the study of stromal TILs in ICC has rarely reported.

Recently, the International TILs Working Group performed a standardized hematoxylin and eosin (HE) staining section analysis of stromal TILs in breast carcinoma taken for the primary target arguments [10]. This conclusion was also confirmed in a study of PDAC [13]. However, the prognosis of ICC patients with complete resection generally tends to be much worse. It has been found that the tumor microenvironment has an inherent immunosuppressive effect and many mechanisms to evade immune surveillance [14–16]. The density of TILs in breast cancer tissues may differ significantly from that in ICC tissues. Tougher criteria may be more appropriate for ICC. Therefore, the stromal TILs and clinical arguments were analyzed to predict PFS and OS after complete resection in patients with ICC. We conducted this study to assess the predictive value of TILs and clinical arguments for PFS and OS in ICC patients after complete resection.

Methods

Ethics statement

This research was authorized by the Clinical Ethics Committee of Henan Provincial People’s Hospital. We did not obtain written consent from the participants on account of the retrospective study that this study was. We performed all
methods according to relevant guidelines or stipulation. Furthermore, we analyzed all participants’ data anonymously.

**Study population and design**

All patients in this study were registered at Henan Provincial People’s Hospital between January 2010 and December 2016. This study included patients with ICC who suffered complete resection as well as were the postoperative specimens was proved by pathology. Participants whose preoperative examination revealed that the tumor invaded surrounding organs or distant metastases were excluded. In addition, the cut edge of patients with ICC must have been confirmed to be negative by a postoperative pathological examination. Finally, only 68 patients with complete follow-up data were included in this study. TIL assessment was performed on tumor specimens from 83 patients with ICC. Fifteen ICC patients’ TILs could not be assessed because their argument HE-stained sections were unavailable. All 68 ICC patient specimens were pathologically evaluated to determine tumor differentiation, lymph node metastasis and surgical margins. We determined the pathological staging of ICC in line with the 8th edition of the American Joint Committee on Cancer (AJCC) staging system [17].

**Determination of postoperative recurrence or metastasis**

In the course of the postoperative follow-up, routine laboratory tests, incorporating tumor markers, computed tomography (CT) scans, magnetic resonance examinations (MRI), ultrasonography, and positron emission tomography (PET-CT), were performed. If new nodus were found in all organs by the CT scan, magnetic resonance examination, ultrasonography, or PET-CT and there was no clear evidence of other cancer metastasis or recurrence elsewhere, we considered these patients to be relapsed or metastatic.

**Stromal TIL assessment**

Stroma TILs were evaluated in each patient by collecting HE-stained sections from surgically resected specimens through the pathology department. The region of stromal TILs assessed was in the boundaries of the aggressive tumor internal. Immune infiltration adjacent to normal tissue or intraductal growth types was not included. TILs in the region of tumor with squeezing artifacts, necrosis or regressive transparency were shut out likewise. Stromal TILs were considered all stromal monocytes that did not come into direct contact with cancer cells. We report different levels of stromal TILs as none, low, medium or high (scores 0, 1, 2 and 3, respectively). Figure 1(A–D) shows representative images of different levels of stromal TILs. Lymphocytes are mostly small lymphocytes, 5–8 mm in diameter, with round nuclei, shallow concaves unilateral, compact chromatin, and a small cytoplasm. Through dendritic cells (DCs) (10–20 mm) and other monocytes (14–20 mm), we find that lymphocytes are various and are easily distinguishable, especially for experienced pathologists. Patients with ICC were classified as TIL negative (none to low) and TIL positive (medium to high) according to the pathological score. The various areas were estimated and the average of the peak standard in patients with heterogeneous stromal cell density in a single tumor section was reported. Two experienced pathologists were unaware

![Figure 1](image-url)
of the clinical results and independently assessed the stromal TILs. The final score was obtained after the two pathologists had consistently assessed the score. If the percentage of stromal TILs varied, we selected the higher grade to represent the final grade.

**Statistical analysis**

We analyzed the corresponding variables by the Mann–Whitney U test, the χ² test, Kaplan–Meier curve analysis, the log-rank test, multivariate Cox regression and other methods. On the Basis of the univariate analysis, multivariate logistic regression analysis was used to determine the independent variables from variables with p <.05. SPSS 22.0 statistical software (SPSS, IL, USA) was used to analysis all data. A value of p <.05 was considered statistically significant.

**Results**

**Patient characteristics**

A total of 68 patients who had primary ICC and underwent complete resection were enrolled, including 38 males and 30 females, aged 35–80 years, with an average age of 60.28 years. All participants’ diagnoses were confirmed clinically and pathologically. Our follow-up data showed that 45 patients died when follow-up terminated. There were 38 patients with clear causes of death, including 24 relapses or metastases. According to the scoring method shown in Figure 1, we calculated the information of all patients. Table 1 shows the clinical characteristics; meanwhile Table 2 shows the clinical data of the classification. Totally, 32 patients were positive for TILs, and the remaining 36 patients were negative for TILs.

**Comparison of OS-related clinical variables after hepatectomy**

The univariate analysis showed stromal TILs, adjuvant therapy, the CA125 level, and the CA19-9 level had statistical significance (all p <.05; Table 3). All of them had important predictive value for poor OS. There was connection between TIL density, adjuvant therapy and OS as well (Figures 2 and 3).

**Comparison of PFS-related clinical variables after hepatectomy**

In the univariate analysis, the CA19-9 level, adjuvant therapy, and stromal TILs (both p <.05) had important prognostic value for PFS following hepatectomy (Table 3). The multivariate analysis assessed the above variables and showed a stromal TIL negative status (HR = 0.47, 95% CI 0.23–0.97, p = .04) was an important autocephalous predictor for PFS (Table 3). The PFS curve also demonstrated stromal TILs (Figure 4) and adjuvant therapy (Figure 5) possessed important predictive capacity.

**Clinical parameters for a TIL negative and TIL positive status in patients with ICC**

As shown in Table 1, the difference of CA125 and CA19-9 between TIL negative and TIL positive was statistically significant (all p <.05). Table 2 shows the statistical analyses of clinical data in regard to stromal TILs. The PFS curve also demonstrated stromal TILs (Figure 4) and adjuvant therapy (Figure 5) possessed important predictive capacity.

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**Table 1.** Comparison of quantitative factors between TIL-negative group and TIL-positive group.

| Parameters            | TIL-negative | TIL-positive | p     |
|-----------------------|--------------|--------------|-------|
| Age (years)           | Mean 61.56   | Standard deviation 6.42 | Mean 58.25 | Standard deviation 10.91 | < 0.05 |
| AFP (U/mL)            | 69.32        | 331.92       | 37.73  | 69.51                | .59   |
| CA125 (U/mL)          | 221.18       | 214.00       | 72.37  | 100.91               | .03   |
| CA19-9 (U/mL)         | 3097.67      | 9942.69      | 184.79 | 252.32               | .00   |
| Platelets (×10⁹/mL)   | 231.14       | 67.70        | 193.19 | 117.90               | .39   |
| Lymphocytes (×10⁹/mL) | 1.53         | 0.54         | 1.55   | 0.60                 | .89   |
| Neutrophils (×10⁹/mL) | 4.87         | 2.12         | 6.33   | 3.71                 | .32   |
| Monocytes (×10⁹/mL)   | 0.41         | 0.23         | 0.39   | 0.18                 | .58   |
| Diameter (cm)         | 6.22         | 2.76         | 5.70   | 3.51                 | .49   |

TILs: tumor-infiltrating lymphocytes.
significant ($p = .03$, $p < .01$). There were no significant differences between the two groups in terms of clinical quantitative parameters such as age, AFP, platelets, lymphocytes, neutrophils, monocytes and diameter.

The categorical variables in both two groups were compared and the results pointed out that based on the stromal TIL density, CA19-9 level ($p = .05$), differentiation ($p = .02$), tumor diameter ($p = .02$), bile duct/vascular cancer embolus ($p = .05$) and satellite nodules ($p = .02$) had significant differences (Table 2). There were no significant differences in sex, age, the CA125 level, tumor location, lymph node (LN) metastasis, AJCC stage or nerve invasion between the two groups (Table 2).

### Discussion

We conducted the current study by evaluating pathological sections to substantiate that stromal TILs had important prognostic capacity in patients with ICC whose primary lesions were completely resected. The results showed that negative stromal TILs were a poor prognostic index for the OS in patients with ICC ($p = .01$), the results which was the same with related reports about other tumors, including breast cancer, lung cancer and colorectal cancer [6–10]. Such results show that lymphocytes may perform a crucial part in restricting tumor development. The data also showed the negative status of TIL which 52.94% (36/68) of patients with ICC undergoing complete resection had suggests that many patients with ICC did not have a good prognosis. These factors may result in a poor prognosis in patients with ICC. The poorly vascularization of tumor tissue and limitation of lymphocyte infiltration may lead to a poor prognosis in patients with ICC.

Moreover, recurrence or metastasis was the major reason (66.17%) leading to death in patients with ICC whose primary lesions were completely resected. Hence, it is important for us to screen out an efficient predictive factor associating with PFS undergoing complete resection. The results revealed low levels of stromal TILs were associated with PFS.

### Table 3. Statistical analyses of clinical data in regard to PFS and OS after complete resection.

| Parameters                  | N  | Univariate analysis $p$ | Multivariate analysis $p$ | N  | Univariate analysis $p$ | Multivariate analysis $p$ |
|-----------------------------|----|-------------------------|---------------------------|----|-------------------------|---------------------------|
| Sex                         |    |                         |                           |    |                         |                           |
| Male                        | 38 | .74                     |                           |    | .51                     |                           |
| Female                      | 30 |                         |                           |    |                         |                           |
| Age (years)                 |    |                         |                           |    |                         |                           |
| <65                         | 45 | .45                     |                           |    | .63                     |                           |
| ≥65                         | 23 |                         |                           |    |                         |                           |
| CA125 (U/mL)                |    |                         |                           |    |                         |                           |
| <35                         | 26 | .52                     |                           |    | .04                     | 1.97(1.02–3.81)           | .045                     |
| ≥35                         | 42 |                         |                           |    | .28                     | 2.31(1.03–5.16)           | .042                     |
| CA19-9 (U/mL)               |    |                         |                           |    |                         |                           |
| <39                         | 23 | .02                     | 1.54(0.70–3.40)           | .28 | <.01                    | 2.31(1.03–5.16)           | .042                     |
| ≥39                         | 45 |                         |                           |    |                         |                           |
| Differentiation             |    |                         |                           |    |                         |                           |
| Poor                        | 22 | .72                     |                           |    | .78                     |                           |
| Well to moderate            | 46 |                         |                           |    |                         |                           |
| Diameter (cm)               |    |                         |                           |    |                         |                           |
| <5.5                        | 34 | .51                     |                           |    | .86                     |                           |
| ≥5.5                        | 34 |                         |                           |    | .12                     |                           |
| LN metastasis               |    |                         |                           |    |                         |                           |
| Negative                    | 56 | .67                     |                           |    | .12                     |                           |
| Positive                    | 12 |                         |                           |    |                         |                           |
| AJCC stage                  |    |                         |                           |    |                         |                           |
| IIIb                        | 43 | .89                     |                           |    | .27                     |                           |
| ≥IIIb                       | 25 |                         |                           |    | .59                     |                           |
| Nerve invasion              |    |                         |                           |    |                         |                           |
| Negative                    | 56 | .69                     |                           |    | .29                     |                           |
| Positive                    | 12 |                         |                           |    | .45                     |                           |
| Bile duct/vascular cancer embolus | | |                           |    |                         |                           |
| Negative                    | 42 | .90                     |                           |    | .45                     |                           |
| Positive                    | 26 |                         |                           |    | .45                     |                           |
| Satellite nodules           |    |                         |                           |    |                         |                           |
| Negative                    | 48 | .63                     |                           |    | .45                     |                           |
| Positive                    | 20 |                         |                           |    | .45                     |                           |
| adjuvant therapy            |    |                         |                           |    |                         |                           |
| No                          | 42 | <.01                    | 0.60(0.26–1.35)           | .22 | <.01                    | 0.98(0.44–2.17)           | .96                      |
| Yes                         | 26 |                         |                           |    |                         |                           |
| Stromal TILs                |    |                         |                           |    |                         |                           |
| Negative                    | 36 | <.01                    | 0.47(0.23–0.97)           | .04 | <.01                    | 0.41(0.20–0.83)           | .01                      |
| Positive                    | 32 |                         |                           |    |                         |                           |

PFS: progression-free survival; OS: overall survival; TILs: tumor-infiltrating lymphocytes; LN: lymph node; HR: hazard ratio; CI: confidence interval.

**Figure 2.** Graph of overall survival based on tumor-infiltrating lymphocyte groups.
The density of stromal TIL uncovers immunocompetence of the tumor microenvironment (TME). The defect of an efficient immune environment will facilitate recurrence or metastasis. Studies have revealed cancer cells can form a suppressive TME, that gets through a series of mechanisms to inhibit TIL infiltration, finally benefits for immune escape [18]. Ogiya’s research demonstrated that immune escape performed an important part in the process of tumor by comparing the stromal TILs of patients with primary and metastatic breast cancer [19]. Based on the above results, the stromal TILs were closely related to metastasis, OS and recurrence in patients with ICC undergoing complete resection. Therefore, the further comparison between two groups indicates that a low level of stromal TILs is related to a high level of CA19-9, a large tumor diameter, high differentiation, a positive bile duct/vascular cancer embolus and positive satellite nodules. This phenomenon can be explained by the detect of TME. Uncommitted tumor progression often promotes high levels of serum tumor markers, increases tumor burden as well as tumor differentiation, and promotes bile duct/vascular cancer embolus and satellite nodules. Adjuvant therapy, including chemotherapy or radiotherapy, is the key measure to reduce the recurrence rate and prolong the survival time of many postoperative patients. In this study, failure to receive adjuvant therapy is the risk factor for poor PFS and OS, but it is not the independent risk factor. We think that Adjuvant therapy may indirectly affect the survival time of patients by changing other related factors. When multivariate analysis is used to adjust the influence of some factors, this indirect influence relationship disappears. In addition, the small sample size will also lead to the bias of the results.

Studies have shown that the 1-, 3- and 5-year survival rates of patients are related to tumor stage, LN metastasis, vascular invasion and tumor number at the time of surgery [20,21]. Vascular invasion and lymph node metastasis indicate a higher possibility of postoperative recurrence, while a tumor size larger than 5 cm, tumor number, vascular invasion and peripheral nerve invasion suggest early recurrence [20–22]. Our study did not reach the above conclusions. In this study, we find the OS and PFS has no relation with AJCC staging, etc. We think the reasons are as follows: First, the sample size included studies was relatively small, which might influence the validity of our analysis to some extent.
Second, AJCC 8th still has some disputes on T-staging. Spolverato et al. [23] found that the risk of death in patients with stage T3 is lower than that in patients with stage T1b and T2 according to AJCC 8th. Kang et al. [24] reported that the overall survival rates of stage T2 and T3 patients were similar by using TNM staging of AJCC 8th. Therefore, more in-depth research is necessary to improve the staging of prognosis. Finally, individual differences, cut-off values or grouping analysis criteria will also lead to different final results. Although our data are not completely consistent with the above reports, the overall trend of relevant data is consistent. Moreover, our data also indicate that other clinical factors, like CA19–9 (p = .042) and CA125 (p = .045) levels, which are clinically widely used serum markers as prognostic indicators, are also independent predictors of poor OS in ICC patients they.

Conclusions

Our study demonstrated that the stromal TIL status was an important indicator of OS and PFS in patients with ICC. Lymphocytes may be a potential treatment for ICC. Nevertheless, the inhibitory effect of lymphocytes on tumor tissues at the cellular and molecular levels was not examined, meanwhile, the impact of certain lymphocytes detected from ICC was assessed by existing articles. Further researches are needed to study the inhibitory effect of lymphocytes on tumor tissues at the cellular and molecular levels and to elucidate the specific mechanism by which certain lymphocytes affect ICC cells. Overall, for prediction of PFS and OS, stromal TILs can be used as an inexpensive, convenient and effective prognostic indicator in patients with ICC after complete resection.

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Author contributions

QZ and DK are the co-first authors. QZ and YH designed the study. QZ, HY, YZ and ZH collected the data. QZ and DK were involved in data cleaning, mortality follow-up, and verification. HY and TL analyzed the data. QZ drafted the manuscript. QZ and YH contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. QZ and YH are the study guarantors. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This research was authorized by the Institutional Review Board of Henan Provincial People’s Hospital (2015) Ethics Review No. (27). The study was conducted consistent with the declaration of the 1964 Declaration of Helsinki, as well as its principles of subsequent amendments.

Disclosure statement

The authors declare that they have no competing interests.

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Data availability statement

For materials and data requests, please get in touch with the corresponding author.

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