Optimal treatment increased survival of hepatocellular carcinoma patients detected with community-based screening

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Abstract

Background and Aim: The early detection of hepatocellular carcinoma (HCC) and opportunity to select appropriate treatment are important benefits of HCC screening. Our aim in the present study was to investigate the survival rate, prognostic factors and treatment effects in HCC patients of community-based screening.

Methods: Community-based ultrasound (US) screening for HCC in adults with platelet counts (\(< 150 \times 10^3/\text{mm}^3\)) and/or alpha fetoprotein (AFP) \(> 20 \text{ ng/mL}\) was conducted in 2002 and 2004. As per the Barcelona Clinic Liver Cancer (BCLC) stage, 90 cases of intermediate or earlier stage HCC were detected and 88 cases had sufficient information for analysis (49 men and 39 women, aged 65.8 \(\pm\) 9.6 years). The tumor diameter was mostly less than 5 cm (76.1%). The follow up was continued until June 2008.

Results: The 4-year overall survival rate was 46.8%. Old age (\(\geq 70\) years) \((P = 0.046)\), later stage of HCC (intermediate vs earlier) \((P = 0.012)\), low platelet count (\(< 100 \times 10^3/\text{mm}^3)\) \((P = 0.013)\) and refusal of modern treatment \((P = 0.026)\) were independent poor prognostic factors. Curative treatment increased survival in patients of all ages. Both curative treatment and transcatheter arterial embolization (TAE) increased survival in cases of intermediate HCC. However, treatment benefits were not found for patients with (very) early stage HCC.

Conclusions: Early detection and prompt treatment of HCC leads to increased survival. For elderly patients this benefit was seen only for early stage cases receiving curative treatment. Differences between treatment types for patients with (very) early stage HCC might emerge with a longer follow-up period.

Key words advanced age, Barcelona Clinic Liver Cancer stage, community screening, curative treatment, hepatocellular carcinoma.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies worldwide and the leading cause of cancer death in Taiwan. The high mortality arises from symptoms being recognized only in the later stages of HCC, at which time it is unresponsive to treatment. A study showing benefits of treating small-diameter tumours\(^1\) encouraged us to attempt even earlier detection and aggressive treatment of HCC. A combination of alpha fetoprotein (AFP) monitoring and ultrasonography (US) is a widely-used tool for cancer screening and surveillance\(^2,3\) that can be applied in detecting early stage HCC. Two-staged community-based HCC screening programs (in which high risk candidates initially identified by serum markers receive an US examination) have been shown in Taiwan to be feasible, economical and effective in detecting HCC at a stage early enough for an appropriate treatment modality to begin.\(^4-6\)

Several studies have revealed that surveillance can detect earlier stages of HCC.\(^7-10\) However, early detection does not correlate well with a reduction in disease-specific mortality. A randomized controlled study in Shanghai, China found biannual AFP and US screening to be associated with reduced mortality.\(^11\) By contrast, an earlier study in Qidong, China did not find any effects on survival of serial AFP screening,\(^12\) though this could be because of insufficient treatment of subclinical HCC patients (25% of cases). An increase in lifespan has led to HCC being detected at much older ages than before. Only a few papers concerning the survival of elderly patients with HCC have been published.\(^13-18\) It was

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found that elderly HCC patients were more likely to receive conservative treatment, despite previous research showing that curative treatment was well-tolerated and improved survival rates. These beneficial outcomes make it important to clarify the effects of community screening in the elderly.

For the majority of HCC patients diagnosed in the Barcelona Clinic Liver Cancer (BCLC) intermediate stage, curative treatments have failed to be effective. Chemoembolization and arterial embolization have been shown to increase survival in unresectable HCC patients. However, patients with preserved liver function and a single large tumor, or multiple tumors that are restricted to a local area, may be ideal candidates for hepatic resection. Patients with intermediate stage HCC are a heterogeneous group, and the effectiveness of treating these cases when detected by community-based screening needs to be investigated.

The aim of the current study was to investigate survival, prognostic factors and treatment effects in treatable HCC patients on the basis of a community-based screening. Of particular interest were elderly patients, and those with intermediate stage HCC.

**Methods**

**Study location**

The current study was conducted in the Tainan County of southern Taiwan. This county has 31 townships, 15 of which have high HCC mortality rates (>10/10³ for males). A report from 2007 identified 475,957 residents (42%) of Tainan County as being aged ≥40 years and in whom the prevalence of hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (HCV) antibodies was 10.9% and 10.2%, respectively.

**Community-based screening programs for detecting HCC**

We conducted two two-stage community-based screening programs. All residents of the two programs ≥40 years old were invited by mail, telephone and the media to undergo a comprehensive health examination. The first of these was in 2002, with invitation provided informed written consent. The current study was conducted in the Tainan County of southern Taiwan. This county has 31 townships, 15 of which have high HCC mortality rates (>10/10³ for males). A report from 2007 identified 475,957 residents (42%) of Tainan County as being aged ≥40 years and in whom the prevalence of hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus (HCV) antibodies was 10.9% and 10.2%, respectively.

**Identification of treatable cases and data collection**

The clinical variables analyzed included the positivity of HBsAg or anti-HCV, largest tumor diameter (≤3 cm, 3–5 cm and ≥5 cm), BCLC stage (very early or early vs intermediate), liver cirrhosis (LC) as determined by US, AFP level (<103 ≥400 ng/mL), alanine aminotransferase (ALT) level (<103 ≥80 IU/mL), aspartate aminotransferase (AST)/ALT ratio (AAR) (<103 ≥1), platelet count (<103 ≥100 × 10³/mm³), age (<103 ≥70 years), gender and treatment (curative vs transcatheter arterial embolization [TAE] vs alternative medicine or no treatment). Death certificates for the study location and period to June 2008 were reviewed. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan. Each participant provided informed written consent.

**Statistical analysis**

Continuous variables are described as mean ± standard deviation (SD), and categorical variables in percentage terms. Survival was expressed via Kaplan–Meier survival curves, and differences between these were tested by log-rank tests. Variables were put into Cox’s proportional hazard model using backward stepwise with a conditional likelihood ratio method for multivariate analysis. The α-level was set at 0.05.

**Results**

**Survival rates and prognostic factors for all treatable HCC patients**

Of the total, there were 97 (54%) confirmed cases of HCC; of these, seven were beyond the intermediate stage and 90 (92.8%) were treatable. Complete data for further analysis were available for 88 of the treatable patients (49 males and 39 females, 65.8 ± 9.6 years old). Of these, 13 were HBsAg positive, and 59 were positive for anti-HCV. Seven cases were both HBsAg and anti-HCV positive, and nine cases were negative for both. The largest tumor diameter was <3 cm in 36 patients (40.9%), 3–5 cm in 31 patients (35.2%) and >5 cm in 21 patients (23.9%). The initial treatment was surgical resection in 14 patients, local ablation in 12 patients, TAE in 44 patients and alternative or none in the remaining 18 patients. The 1-year, 2-year, 3-year and 4-year overall survival rate was 96.6%, 68.2%, 56.8% and 46.8%, respectively. Univariate analysis revealed age ≥70 years (P = 0.011), intermediate stage HCC (P = 0.002), and not receiving curative treatment (P = 0.025) as poor prognostic factors. AFP ≥400 ng/mL had borderline significance (P = 0.061) (Table 1). The 4-year survival rate of patients receiving curative treatment was 68%, which was significantly higher than that of patients receiving either TAE (40.6%) (P = 0.022) or alternative or no treatment (31.1%) (P = 0.009). There was no significant difference in survival between patients receiving TAE and patients receiving alternative or no treatment (Fig. 1). The multivariate analysis with Cox’s proportional hazard model identified HCC stage (intermediate), advanced age (≥70 years), low platelet count (<10 × 10³/mm³) and alternative or no treatment as
independent poor prognostic factors (Table 2 contains the hazard ratio (HR) and 95% confidence interval (CI) values).

### Association of age with survival rates and prognostic factors

Basic clinical characteristics of patients aged < 70 years or ≥ 70 years are listed in Table 3. There was no difference in gender, liver cirrhosis status, BCLC stage, viral etiology, ALT, tumor size or platelet count between the ≥ 70 years or the < 70 years age groups. The 4-year survival rate was 57.4% for patients aged < 70 years (55/88 cases), and 28.9% for patients aged ≥ 70 years. Univariate analysis identified intermediate stage HCC (P < 0.001) and alternative or no treatment (P = 0.024) as poor prognostic factors in patients aged < 70 years (Fig. 2a). Similar findings were obtained with the multivariate analysis, which also showed intermediate stage HCC and alternative or no treatment as being independent factors (see Table 4 for HR and CI values). In other words, patients < 70 years old receiving curative or TAE treatment had a better prognosis than those receiving alternative or no treatment after adjustment for HCC stage.

For the 33 patients aged ≥ 70 years, univariate analysis revealed low platelet count (< 10 × 10^3/mm^3) as a poor prognostic factor. Low platelet count was also identified as a poor prognostic factor by the multivariate analysis, as were TAE or alternative or no treatment, and low ALT levels (< 80 IU/L). This result indicates that more elderly patients who received curative treatment had a better prognosis than those that did not (Fig. 2b, Table 4).

### Table 1

Univariate survival analysis of 88 treatable patients with hepatocellular carcinoma by Kaplan–Meier survival curves with log-rank test

| Variable                  | No. patients (%) | Survival rate (%) | P-value |
|---------------------------|------------------|-------------------|---------|
|                           |                  | 1-year | 2-year | 3-year | 4-year |       |
| Total                     | 88               | 96.6   | 68.2   | 56.8   | 46.8   | 0.002 |
| BCLC classification       |                  |        |        |        |        |       |
| Very early and early stage| 51 (58)          | 98.0   | 78.4   | 66.7   | 60.2   | 0.082 |
| Intermediate stage        | 37 (42)          | 94.6   | 54.1   | 43.2   | 28.2   |       |
| Tumor size                |                  |        |        |        |        |       |
| ≤ 3 cm                    | 36 (40.9)        | 97.2   | 77.8   | 66.7   | 55.3   |       |
| 3–5 cm                    | 31 (35.2)        | 100    | 71.0   | 54.8   | 46.9   |       |
| > 5 cm                    | 21 (23.9)        | 90.5   | 47.6   | 42.9   | 31.7   |       |
| Cirrhosis                 |                  |        |        |        |        | 0.064 |
| No                        | 49 (55.7)        | 98.0   | 73.5   | 67.3   | 56.2   |       |
| Yes                       | 39 (44.3)        | 94.9   | 61.5   | 43.6   | 35.3   |       |
| AFP                       |                  |        |        |        |        | 0.061 |
| < 400 ng/mL               | 66 (75)          | 97.0   | 75.8   | 62.1   | 50.5   | 0.635 |
| ≥ 400 ng/mL               | 22 (25)          | 95.6   | 45.5   | 40.9   | 36.4   |       |
| ALT                       |                  |        |        |        |        | 0.854 |
| < 80 IU/L                 | 59 (67)          | 94.9   | 66.1   | 54.2   | 46.6   |       |
| ≥ 80 IU/L                 | 29 (33)          | 100    | 72.4   | 62.1   | 47.7   |       |
| AST/ALT ratio             |                  |        |        |        |        | 0.136 |
| < 1                       | 39 (44.3)        | 97.4   | 69.2   | 59.0   | 47.9   |       |
| ≥ 1                       | 49 (55.7)        | 96.9   | 67.3   | 55.1   | 46.1   |       |
| Platelet count            |                  |        |        |        |        | 0.011 |
| < 100 × 10^3/mm^3         | 34 (38.6)        | 94.1   | 55.9   | 50.0   | 37.0   |       |
| ≥ 100 × 10^3/mm^3         | 54 (61.4)        | 98.1   | 75.9   | 61.1   | 53.1   |       |
| Age                       |                  |        |        |        |        |       |
| < 70 years                | 55 (62.5)        | 94.5   | 74.5   | 67.3   | 57.4   | 0.432 |
| ≥ 70 years                | 33 (37.5)        | 100    | 57.6   | 39.4   | 28.9   |       |
| HBsAg                     |                  |        |        |        |        | 0.234 |
| Negative                  | 66 (75)          | 95.5   | 63.6   | 54.5   | 45.1   |       |
| Positive                  | 22 (25)          | 100    | 81.8   | 63.6   | 52.5   |       |
| Anti-HCV                  |                  |        |        |        |        |       |
| Negative                  | 20 (22.7)        | 100    | 85.0   | 60.0   | 60.0   | 0.025 |
| Positive                  | 68 (77.3)        | 95.6   | 63.2   | 55.9   | 43.6   |       |
| Treatment                 |                  |        |        |        |        |       |
| Curative                  | 26 (29.5)        | 92.3   | 88.5   | 76.9   | 68.0   | 0.022 |
| TAE                       | 44 (50)          | 100    | 61.4   | 50.0   | 40.6   | 0.009 |
| Alternative or none       | 18 (20.5)        | 94.4   | 55.6   | 44.4   | 31.1   | 0.471 |

1Curative versus TAE. 2Curative versus alternative or none. 3TAE versus alternative or none. AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; TAE, transcatheter arterial embolization.
Secondary treatment modalities after tumor recurrence

Among 14 patients who received operation initially, six (42%) patients had recurrence. One patient received radiofrequency ablation; three (50%) patients received TAE combined with percutaneous ethanol injection (PEI) and one patient received chemotherapy due to lung metastasis and one patient received traditional herb therapy. Of the nine (75%) out of 12 patients who received percutaneous local ablation and had recurrence, six (66.6%) patients received TAE combined with PEI, one patient received TAE alone, one patient received PEI alone and one patient received traditional herb therapy. Of the 34 (77%) out of 44 patients who received TAE and had recurrence, 20 patients received TAE, seven (20%) patients received TAE combined with PEI, five patients received percutaneous local ablation therapy and two patients received radiation therapy.

Discussion

In the current, large-scale study, a total of 61,318 adults aged 40 years or more were screened for HCC, and 97 cases were detected. This prevalence of HCC (158/105) is three to five times higher than the reported annual incidence in Taiwan, and may be associated with an earlier detection of more asymptomatic or subclinical HCC cases. More than half of the cases (n = 51, 52.6%) detected were in the very early or early stage of HCC, and thus were detected early enough to have a chance of treatment being effective. As based on the practice guidelines of the American Association for the Study of Liver Disease (AASLD), cases of either very early or early stage HCC should receive curative treatment, cases of intermediate stage should be treated with transcatheter arterial chemoembolization, and cases beyond the intermediate stage should undergo either experimental or conservative treatment. In the current study, 70 of the 88 treatable cases (79.5%) received heterogeneous treatment in one of nine hospitals with various facilities because a national consensus or practice guidelines do not exist, the selection of treatment modalities varied from doctor to doctor. In addition, 18 treatable cases resisted our suggestions and chose either alternative medicine or no active treatment, which suggests that post-screening education and consultation services should be augmented.

In order to demonstrate the survival benefit in the screening cases, a randomized controlled study provided the best evidence. However, ethical problems are a major concern in carrying out this kind of study. According to the randomized controlled study of Zhang et al., 3-year and 4-year survival rates were 7.2% and 0% in the control group who did not receive the screening program. In the current study, 3-year and 4-year overall survival rate was 56.8% and 46.8%, respectively, in patients that received community screening, which was higher than the historical control. In order to explore the effects of different treatments and minimize leading time bias properly, patients with the same stage of HCC receiving different treatment modalities were compared. Only 20 out of 51 cases (39.2%) in the very early or early stage received curative treatments, despite such treatments being associated with a better prognosis. Wang et al. observed that untreated cirrhotic patients with small-diameter HCC (<3 cm) had 1-year survival rates of 85.7%, and 3-year survival rates of 38.1%. Liver

Survival rates and prognostic factors for very early or early and intermediate stage HCC

Basic clinical characteristics of patients with very early or early stage and intermediate stage are listed in Table 5. The stage of HCC was very early or early in 51 cases and intermediate in 37 cases. There was no difference in age, gender, liver cirrhosis status, viral etiology, ALT or platelet count between patients in very early or early stage and intermediate stage. Patients in intermediate stage (6.0 ± 2.9 cm) had larger tumor size than very early or early stage (2.7 ± 1.0 cm) (P < 0.001). For patients with very early or early stage HCC, the 4-year survival rate was 60.2%. By contrast, for patients with intermediate stage HCC the 4-year survival rate was 28.2%. With regards to very early or early stage HCC, patients who were either aged <70 years or received curative treatment had higher survival rates than more elderly patients or those receiving TAE or alternative or no treatment (Fig. 3a). However, multivariate analysis revealed that age ≥70 years was the only independent poor prognostic factor for patients with very early or early stage HCC (Table 6). For patients with intermediate stage HCC, univariate analysis revealed that liver cirrhosis and low platelet count (<10 × 10^9/mm^3) were poor prognostic factors. No differences between the three treatment modalities were found by univariate analysis for intermediate stage HCC (Fig. 3b). The multivariate analysis revealed alternative or no treatment, cirrhosis and being positive for anti-HCV as poor prognostic factors (Table 6). Of the patients receiving curative treatment, five underwent tumor resection, and one underwent tumor ablation. Patients receiving curative treatment had a better prognosis than those receiving alternative or no treatment (HR = 41.80 95% CI 4.31–405.1, P = 0.001).
resection in patients with preserved liver function has been reported as being associated with 1-year and 3-year survival rates of 81–100% and 44–84%, respectively.\(^\text{27–29}\) It has also been reported that patients with early stage HCC who underwent percutaneous thermal ablation had 1-year and 3-year survival rates of 89–100% and 46–62%, respectively.\(^\text{30,31}\) The current study found that the 1-, 2-, 3- and 4-year survival rates of patients with very early or early stage HCC receiving curative treatments were 98%, 78.4%, 66.7% and 60.2%, respectively. These rates are similar to, or even higher than, those previously reported. There were no differences between treatment types found for patients with very early or early stage HCC, possibly due to the relatively short duration of follow-up and small sample size. However, the recurrent rate was higher in patients that received TAE (77%) initially than patients who received curative treatment (57%) during the 4-year follow-up period. Incomplete treatment rates (70%) were higher in patients who received TAE alone initially.

According to AASLD guidelines, patients with intermediate stage HCC should receive chemoembolization. However, in our study, the curative treatment received by six such patients was surgical resection in five cases, and tumor ablation in one. The mean tumor size of patients receiving curative treatment was 9.3 ± 3.3 cm, and the 4-year survival rate was 44.4%. It was also found that these patients had better prognoses than those who received alternative or no treatment. The difference between patients receiving curative treatment and those receiving TAE was not significant. Surgical intervention is considered for patients with preserved liver function who present with a single large tumor, or with multiple tumors that are restricted to a local area. Patients with a large tumor have been reported to die of recurrence or distal metastasis, and to have poor 5-year survival rates. Recent studies reported that patients with a large HCC (>10 cm) who received liver resection had 5-year survival rates that ranged from 26.9% to 28.0%.\(^\text{32,33}\) Even so, a consensus-based clinical practice manual by the Japanese Society of Hepatology recommends that hepatic resection is an option in patients with a tumor ≥3 cm in diameter (limited to fewer than three tumors), and in patients with more than four tumors if there is no vascular invasion.\(^\text{34}\) The relatively high survival rates in the current study are due to Taiwanese hospitals having more extensive surgical criteria than are found in the AASLD guidelines, and which are more compatible with those of the Japanese.

| Table 2 | Multivariate survival analysis of 88 treatable patients with hepatocellular carcinoma by Stepwise Cox’s proportional hazard model |
| Variable | No. patients (%) | No. deaths (%) | HR | 95% CI | P-value |
| BCLC classification | | | | | |
| Very early and early stage | 51 (58) | 20 (39.2) | 1 | | |
| Intermediate stage | 37 (42) | 27 (72.9) | 2.29 | 1.20–4.37 | 0.012 |
| Platelet count ≥ 100 x 10⁹/mm³ | 34 (38.6) | 26 (48.1) | 1 | | |
| < 100 x 10⁹/mm³ | 54 (61.4) | 21 (61.7) | 2.22 | 1.19–4.17 | 0.013 |
| Age < 70 years | 55 (62.5) | 24 (45.2) | 1 | | |
| ≥ 70 years | 33 (37.5) | 23 (69.6) | 1.94 | 1.01–3.70 | 0.046 |
| Treatment Curative | 26 (29.5) | 8 (30.7) | 1 | | |
| TAE† | 44 (50) | 27 (61.3) | 1.76 | 0.77–4.03 | 0.180 |
| Alternative or none† | 18 (20.5) | 12 (66.6) | 2.84 | 1.14–7.12 | 0.026 |

†TAE versus alternative or none: \(P = 0.208\). BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HR, hazard ratio; TAE, transcatheter arterial embolization.

| Table 3 | Basic clinical characteristics of patients aged <70 and ≥70 years |
| Variable | P-value |
| Age (years) < 70 (n = 55) | ≥ 70 (n = 33) |
| Sex Male | 30 (54.5) | 19 (57.6) | |
| Female | 25 (45.5) | 14 (42.4) | NS |
| Liver cirrhosis Yes | 23 (41.8) | 16 (48.5) | |
| No | 32 (58.2) | 17 (51.5) | NS |
| BCLC stage (Very) early stage | 35 (63.6) | 16 (48.5) | |
| Intermediate | 20 (36.4) | 17 (51.5) | NS |
| Anti-HCV Positive | 45 (81.8) | 23 (69.7) | |
| Negative | 10 (18.2) | 10 (30.3) | NS |
| ALT (IU/L) Mean ± SD | 92.2 ± 83.7 | 67.3 ± 69.8 | NS |
| Tumor size (cm) Mean ± SD | 4.0 ± 2.6 | 4.3 ± 2.5 | NS |
| Platelet (x 10⁹/mm³) Mean ± SD | 11.1 ± 4.8 | 12.8 ± 6.6 | NS |

ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HCV, hepatitis C virus; NS, not significant; SD, standard deviation.
Advanced age was found in the current study to be a poor prognostic factor across all treatable patients, even those with very early or early stage HCC. Indeed, the 4-year survival rate was 28.9% for patients aged 70 years or more, compared with 57.4% for younger patients. The mean age of patients with HCC was 65.8 years, and most of these (68/88, 77.3%) were positive for anti-HCV. The mean age of HCV-related HCC patients in Taiwan has been previously reported as 65.1 years. In Japan it was found...
that approximately 80% of HCC patients were anti-HCV positive, and more than 60 years old.³ Teratani et al. reported that the 1-year and 3-year survival rate of patients older than 70 years receiving percutaneous ethanol injections was 83% and 52%, respectively. By contrast, the 1-year and 3-year survival rate of patients older than 70 years was 83% and 52%, respectively.³⁶ Similarly, an Italian study concluded that elderly patients (aged ≥ 70 years) with HCC have a worse prognosis than younger patients. This difference seems to be a consequence of under-treatment in the older patients.³⁷ On the other hand, a Japanese study reported that the 1-year and 3-year survival rate of patients younger than 70 years was 90% and 65%, respectively.³⁷ The survival of elderly patients with HCC is reported to be affected by several factors, including high serum levels of AFP, advanced stage, and the presence of concomitant underlying disease.²⁸,³⁸ In the current study, elderly patients (> 70 years old) with very early or early stage HCC who received curative treatment had a 4-year survival rate of 57.1%, higher than previously reported. This shows that early detection and curative treatment of HCC are effective in the elderly, and that community-based screening of this population is warranted.

Table 4  Multivariate survival analysis of hepatocellular carcinoma (HCC) patients aged either < 70 or ≥ 70 years by Stepwise Cox’s proportional hazard model

| Variable | No. patients (%) | No. deaths (%) | HR   | 95% CI          | P-value |
|----------|------------------|----------------|------|-----------------|---------|
| Age < 70 years (n = 55) | | | | | |
| BCLC stage | Very early and early | 35 (63.6) | 9 (25.7) | 1 | | |
| | Intermediate | 20 (36.4) | 15 (75) | 6.34 | 2.44–16.50 | < 0.001 |
| Treatment | Curative | 19 (34.5) | 5 (26.3) | 1 | | |
| | TAE* | 26 (47.3) | 12 (46.1) | 1.14 | 0.39–3.38 | 0.809 |
| | Alternative or none* | 10 (18.2) | 7 (70) | 6.50 | 1.88–2.50 | 0.003 |
| Age ≥ 70 years (n = 33) | | | | | |
| Treatment | Curative | 7 (21.2) | 3 (42.8) | 1 | | |
| | TAE† | 18 (64.5) | 15 (83.3) | 14.05 | 2.18–90.39 | 0.005 |
| | Alternative or none† | 8 (24.2) | 5 (62.5) | 6.62 | 1.17–37.52 | 0.033 |
| ALT | ≥ 80 IU/L | 9 (27.3) | 8 (88.8) | 1 | | |
| | < 80 IU/L | 24 (72.7) | 15 (62.5) | 3.57 | 1.10–11.55 | 0.034 |
| Platelet | ≤ 100 × 10³/mm³ | 10 (30.3) | 14 (60.8) | 1 | | |
| | < 100 × 10³/mm³ | 23 (69.7) | 9 (30.2) | 7.87 | 2.42–25.58 | 0.001 |
| BCLC stage | Very early and early | 16 (48.5) | 11 (68.7) | 1 | | |
| | Intermediate | 17 (51.5) | 12 (70.5) | 0.31 | 0.09–1.12 | 0.086 |
| Anti-HCV | Negative | 10 (30.3) | 5 (50) | 1 | | |
| | Positive | 23 (69.7) | 18 (78.2) | 2.80 | 0.87–9.05 | 0.075 |

ALT versus alternative or none: *P = 0.003 for age < 70 years; †P = 0.243 for age ≥ 70 years. ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; TAE, transcatheter arterial embolization.

Table 5  Basic clinical characteristics of patients with Barcelona Clinic Liver Cancer (BCLC) very early and early stage and intermediate stage

| Variable | Very early and early stage (n = 51) | Intermediate stage (n = 37) | P-value |
|----------|------------------------------------|----------------------------|---------|
| Age (years) | 64.9 ± 9.3 | 66.9 ± 10.0 | NS |
| Sex | Male | 30 (58.8) | 19 (51.3) | | |
| | Female | 21 (41.2) | 18 (48.7) | | | NS |
| Liver cirrhosis | Yes | 21 (41.2) | 18 (48.7) | | | NS |
| | No | 30 (58.8) | 19 (51.3) | | | NS |
| Anti-HCV | Positive | 39 (76.4) | 29 (78.4) | | | |
| | Negative | 12 (23.6) | 8 (21.6) | | | NS |
| ALT (IU/L) | Mean ± SD | 86.4 ± 82.8 | 77.3 ± 74.9 | | | NS |
| Tumor size (cm) | Mean ± SD | 2.7 ± 1.0 | 6.0 ± 2.9 | | | < 0.001 |
| Platelet (× 10³/mm³) | Mean ± SD | 12.0 ± 6.0 | 11.5 ± 4.3 | | | NS |

ALT, alanine aminotransferase; HCV, hepatitis C virus; NS, not significant; SD, standard deviation.
curative treatments that include resection, radiofrequency ablation, and percutaneous ethanol injection therapy. In the current study, the 3-year survival rate of elderly patients with a low platelet count (<100 *10^3/mm^3) was only 10%. Alongside HCC itself, hepatic failure is another major cause of death in HCC patients. HCC screening can detect early HCC, but not early LC, and medical care for the complications of LC might improve survival rates. Moreover, anti-viral treatment in patients with chronic HBV and HCV infections has been shown to decrease the incidence of HCC and hepatic failure. Although not found in the current study, a marked elevation of AFP (>400 ng/mL) is reported to be correlated with poor differentiation and extended invasion. Elevated AFP is one of the poor prognostic factors in determining the CLIP score, and has also been identified as such in several analyses of the survival rates for resection, radiofrequency ablation, and TAE. With a platelet count <150 *10^3/mm^3, or elevated AFP value (>20 ng/mL), used as screening markers in the first stage of community-based screening, 50 of the patients (56.8%) in the current study were diagnosed with very early or early stage HCC. Previous research has found poor prognosis cut-off values for platelet count to be <100 *10^3/mm^3, and for AFP to be >400 ng/mL. Therefore, adopting a platelet count <150 *10^3/mm^3 and AFP value >20 ng/mL as screening markers could help to detect early stage HCC and not affect the analysis of prognosis factors.

There were three limitations in this study. First, selection bias cannot be avoided due to initial heterogeneous treatment strategies chosen by doctors in different hospitals. However, there was no difference in basic clinical characteristics between the groups for comparisons. Second, small sample size of detected HCC patients cannot be avoided due to initial heterogeneous treatment strategies in patients with very early and early BCLC stage. Gender influenced the final results such as no difference between treatment groups in patients with very early and early BCLC stage. Gender was not a prognostic factor in the analysis. Third, some patients who lived in rural areas of Taian County did not return to medical centers due to medical accessibility. Hence, it is difficult to trace the causes of death in all screened HCC patients during the community screening and perform all analysis restricted to those who died from HCC.

In conclusion, we have shown in the current study that the early detection and treatment of HCC improves patient survival. Where appropriate to administer, curative treatment conveyed a survival benefit in almost all conditions, including intermediate stage HCC. TAE was found to be more beneficial than alternative or no treatment only for elderly patients (aged >70 years) or those with intermediate stage HCC. No difference between treatment types was found for very early or early stage HCC during the 4-year follow-up period of the current study. Recurrent rate was higher in patients who received TAE than curative treatment in this group.

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Table 6 Multivariate survival analysis of hepatocellular carcinoma (HCC) patients with very early/early or intermediate stage HCC by Stepwise Cox’s proportional hazard model

| Variable | No. patients (%) | No. deaths (%) | HR | 95% CI | P-value |
|----------|------------------|----------------|----|--------|---------|
| Very early and early stage (n=51) | | | | | |
| Age (years) | | | | | |
| <70 | 34 (68) | 9 (25.7) | 1 | | |
| ≥70 | 16 (32) | 11 (68.7) | 3.63 | 1.49–8.85 | 0.005 |
| Intermediate stage (n=37) | | | | | |
| Treatment | | | | | |
| Curative† | 6† (16.2) | 3 (50) | 1 | | |
| TAE† | 24 (64.9) | 19 (79.1) | 3.01 | 0.80–12.27 | 0.103 |
| Alternative or none† | 7 (18.9) | 5 (71) | 41.80 | 4.31–405.1 | 0.001 |
| Cirrhosis | | | | | |
| No | 19 (51.4) | 10 (52.6) | 1 | | |
| Yes | 18 (48.6) | 17 (94.4) | 5.63 | 2.20–14.44 | <0.001 |
| Anti-HCV | | | | | |
| Negative | 8 (21.6) | 4 (50) | 1 | | |
| Positive | 29 (78.4) | 23 (79.3) | 8.82 | 1.33–58.58 | 0.024 |

†TAE versus alternative or none P=0.006. †Five surgical resections and one percutaneous ethanol injection (PEI). CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; TAE, transcatheter arterial embolization.
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