Alpha-fetoprotein level to total tumor volume as a predictor of hepatocellular carcinoma recurrence after resection. A retrospective cohort study

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ABSTRACT

Background: Total tumor volume (TTV) and serum alpha fetoprotein (AFP) level are important risk factors linked with the high possibility of hepatocellular carcinoma (HCC) recurrence. The aim of the study was to evaluate the role of AFP/TTV ratio, as a prognostic marker, in the prediction of HCC recurrence after resection.

Methods: Patients who underwent liver resection for HCC between 2010 and 2018 were retrospectively analyzed. Patients were divided into 2 groups; a group with AFP/TTV \( \leq \) 2 and another group with AFP/TTV > 2. Risk factors for HCC recurrence were recorded.

Results: A total of 286 HCC patients underwent liver resection (184 patients with AFP/TTV \( \leq \) 2, and 102 patients with AFP/TTV > 2). There was a significant difference between the 2 groups in the preoperative total bilirubin level, serum AFP level, mean tumor diameter, TTV, operative blood loss, microvascular invasion and hospital stay (all \( P \) values < 0.05). The 1-, 3-, and 5-year tumor recurrence rates were 24.1%, 43%, and 57.6% respectively. The independent risk factors for tumor recurrence were AFP/TTV > 2 (HR = 1.62, 95% CI = 1.29–1.98, \( P \) = 0.042), Macrovascular invasion (HR = 2.03, 95% CI = 2.17–2.38, \( P \) = 0.021, and microvascular invasion (HR = 1.36, 95% CI = 1.08–1.77, \( P \) = 0.019).

Conclusion: AFP/TTV ratio is a feasible prognostic marker for prediction of HCC recurrence after resection so, it can help in providing an intensive postoperative surveillance program to high risk patients for early detection and management of any recurrence.

1. Introduction

Surgical resection for hepatocellular carcinoma (HCC) is considered the most appropriate and curative treatment among the several therapeutic approaches in clinically resectable tumors. However, new lesions can develop as a metachronous HCC recurrence or intrahepatic recurrence of the primary resected tumor [1–3].

Recurrence of HCC is an important factor that may adversely affect patients’ survival after liver resection with a devastating outcome. Different factors have been shown to have a significant risk for early or late HCC recurrence including the high preoperative level of alpha fetoprotein (AFP), multiple tumors, large tumor size, macrovascular or microvascular invasion, and type of liver resection. Early identification of these patients with a high risk of tumor recurrence can help in providing an intensive surveillance program that may improve their survival [4–6].

AFP level is commonly used to estimate the severity of tumor burden and as a prognostic measure for the response to different treatments. Some staging systems for HCC showed that using AFP in the scoring system can provide more prognostic benefit in the prediction of the outcome. Total tumor volume (TTV) is another prognostic marker for tumor burden that can accurately predict the outcome by incorporation of the size and number of tumor nodules into one formula [7–10]. The objective of this study was to evaluate the prognostic value of AFP per TTV in the prediction of HCC recurrence after resection.

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1.1. Patients and methods

We retrospectively identified cirrhotic patients who had a liver resection for HCC in the period between January 2010 and January 2018 at the National Liver Institute, Menoufia University, Egypt. The preoperative, operative and postoperative data were collected and analyzed from the prospective database and the patients’ files after the Institutional Review Board (IRB) approval. The study goes with the standards of the Declaration of Helsinki and ethical guidelines and registered in the clinical trial no CTR2000030403. The work was reported in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria [11].

Patients included in the study had HCC on top of a cirrhotic liver with Child-Pugh score A. Patients with Child B, C score or with any other tumor than HCC were excluded from our study. Patients who had the first 6 months mortality after liver resection were also excluded from the study, for accurate follow up of the recurrence rate. The diagnosis of HCC was done by contrast-enhanced computed tomography (CT) scan or magnetic resonance image (MRI) and confirmed after resection by the histopathological study.

Measurement of the tumor volume was done by the volumetric study in the CT scan or the MRI when available or calculated by using this formula: \(4/3 \times 3.14 \times (\text{maximum tumor radius in cm})^3\) [9,10,12], TTV of 65.5 cm³ is nearly equal to a tumor with a diameter of 5 cm. Preoperative peak serum AFP level was measured and AFP to TTV ratio was calculated. Patients were divided into 2 groups; a group with AFP/TTV ≤2 and another group with AFP/TTV > 2, as the median and mean of AFP/TTV were nearly equal to 2 and further classification of AFP/TTV ≤10 and > 10 was done for early detection of HCC recurrence as reported in different series [13,14].

Follow up of the patients for detection of HCC recurrence was done from the date of surgery up to February 2020 with a median period of follow up 49 months. Follow up was done by AFP and abdominal ultrasound every 3-6 months and contrast-enhanced CT scan or MRI were done in the first year then yearly. HCC recurrence in the first year was considered as early recurrence, and after 1 year was a late recurrence [15]. Risk factors for HCC recurrence and the feasibility of AFP/TTV ratio in prediction of early and late HCC recurrence was investigated. Early postoperative complications were recorded and classified from 0-V according to the Clavien Dindo grades of postoperative complications [16].

The management of recurrent HCC either surgical, interventional or palliative was reported.

1.2. Statistical analysis

Statistical analysis was done using SPSS 23 (IBM SPSS Inc., Chicago, IL). Chi-square or Fisher's exact test was used for comparison of the categorical variables. While in continuous variables, the Mann-Whitney U test or Kruskal-Wallis test was used for comparison. Recurrence-free survival was calculated by the Kaplan-Meier method, and Log-rank test was applied to compare the difference in survival rates. Logistic regression analysis was appraised in multivariate analysis for risk factors for HCC recurrence. Statistically significant values were considered when the P value was less than 0.05.

2. Results

A total of 286 HCC patients who received liver resection were included and analyzed in this study. The mean age of overall patients was 59.2 years, and 79.4% of them were male patients. The most common cause of liver cirrhosis was the hepatitis C virus (HCV) (90.2%).

One hundred and two patients had AFP/TTV ≤2, and 184 patients had AFP/TTV > 2. Table 1, shows the difference between the 2 groups. In the univariate analysis, there was a significant difference between the 2 groups of patients in the preoperative total bilirubin level

### Table 1

| Variable                                | AFP/TTV ≤2 (n = 184) | AFP/TTV > 2 (n = 102) | P-value |
|-----------------------------------------|----------------------|-----------------------|---------|
| Age                                     |                      |                       | 0.69    |
| Mean ± SD                               | 57.8 ± 4.5           | 60.2 ± 5.3            |         |
| Range                                   | 47–73                | 45–71                 |         |
| Gender                                  |                      |                       | 0.86    |
| Male                                    | 148 (80.4%)          | 79 (77.5%)            |         |
| Female                                  | 36 (19.6%)           | 23 (22.5%)            |         |
| Etiology of liver disease               |                      |                       | 0.91    |
| HCV                                     | 168 (91.3%)          | 90 (88.3%)            |         |
| HBV                                     | 8 (4.3%)             | 5 (4.9%)              |         |
| HCV&HBV                                 | 3 (1.6%)             | 3 (2.9%)              |         |
| Other                                   | 5 (2.7%)             | 4 (3.9%)              |         |
| Total bilirubin (mg/dL)                 |                      |                       | 0.04    |
| Mean ± SD                               | 0.9 ± 0.48           | 1.1 ± 0.52            |         |
| Range                                   | 0.46–1.9             | 0.55–2.4              |         |
| Albumin (g/dL)                          | 3.7 ± 0.4            | 3.5 ± 0.6             | 0.75    |
| Range                                   | 2.8–4.6              | 2.8–4.3               |         |
| INR                                     |                      |                       | 0.32    |
| Mean ± SD                               | 1.1 ± 0.3            | 1.2 ± 0.31            |         |
| Range                                   | 0.9–1.6              | 0.9–1.5               |         |
| ALT                                     |                      |                       | 0.09    |
| Mean ± SD                               | 51 ± 45              | 58 ± 76               |         |
| Range                                   | 29–110               | 13–137                |         |
| MELD                                    |                      |                       | 0.22    |
| Mean ± SD                               | 9 ± 3.1              | 9 ± 4.2               |         |
| Range                                   | 5–16                 | 6–15                  |         |
| ≤10                                     | 125 (67.9%)          | 74 (72.5%)            | 0.27    |
| > 10                                    | 59 (32.1%)           | 28 (27.5%)            |         |
| AFP (µ/ml)                              |                      |                       | 0.001   |
| Mean ± SD                               | 49 ± 196             | 142 ± 2036            |         |
| Range                                   | 2.7–634              | 3–2058                |         |
| Tumor number                            |                      |                       | 0.22    |
| 1                                       | 159 (81.5%)          | 89 (90.6%)            |         |
| 2–3                                     | 25 (18.5%)           | 13 (9.4%)             |         |
| Tumor site                              |                      |                       | 0.35    |
| Right lobe                              | 116 (63%)            | 61 (59.8%)            |         |
| Left Lobe                               | 53 (28.8%)           | 30 (29.8%)            |         |
| Bilobar                                 | 15 (8.2%)            | 11 (10.8%)            |         |
| Tumor diameter (cm)                     |                      |                       | 0.01    |
| Mean ± SD                               | 5.4 ± 3.6            | 3.5 ± 3.1             |         |
| Range                                   | 3–12                 | 2.5–7                 |         |
| TTV (cm³)                               |                      |                       | 0.001   |
| Mean ± SD                               | 74 ± 320             | 52 ± 45               |         |
| Range                                   | 15–1200              | 10–270                |         |
| Macrvascular invasion                   |                      |                       | 0.82    |
| Absent                                  | 176 (95.7%)          | 98 (96.1%)            |         |
| Present                                 | 8 (4.3%)             | 4 (3.9%)              |         |
| Type of operation                       |                      |                       | 0.43    |
| Laparoscopic                            | 11 (6%)              | 15 (14.7%)            |         |
| Open                                    | 173 (94%)            | 87 (85.3%)            |         |
| Type of resection                       |                      |                       | 0.30    |
| Anatomical                              | 57 (31%)             | 25 (24.5%)            |         |
| Non anatomical                          | 127 (69%)            | 77 (75.5%)            |         |
| Operative blood loss (ml)               |                      |                       | 0.03    |
| Mean ± SD                               | 355 ± 310            | 478 ± 290             |         |
| Range                                   | 50–2500              | 100–3000              |         |
| Intraoperative blood transfusion        |                      |                       | 0.18    |
| Mean ± SD                               | 2 ± 1                | 2 ± 3                 |         |
| Range                                   | 0–12                 | 0–8                   |         |
| Operative time (min)                    |                      |                       | 0.08    |
| Mean ± SD                               | 230 ± 55             | 220 ± 65              |         |
| Range                                   | 178–430              | 160–220               |         |
| Tumor differentiation                   |                      |                       | 0.56    |
| well                                    | 38 (20.7%)           | 17 (16.7%)            |         |
| moderate or poor                        | 146 (79.3%)          | 85 (83.3%)            |         |
| Microvascular invasion                  |                      |                       | 0.05    |
| Yes                                     | 39 (21.2%)           | 36 (35.3%)            |         |
| No                                      | 145 (78.8%)          | 66 (64.7%)            |         |
| Hospital stay (days)                    |                      |                       | 0.04    |
| Mean ± SD                               | 8 ± 6                | 6 ± 9                 |         |
| Range                                   | 3–22                 | 4–31                  |         |

(continued on next page)
(P = 0.04), serum AFP level (P = 0.001), mean tumor diameter (P = 0.01), TTV (P = 0.001), operative blood loss (P = 0.04), microvascular invasion (P = 0.05), and hospital stay (P = 0.04).

The 1, 3, and 5-year overall recurrence-free survival rates were 75.9%, 57%, and 42.4% respectively. The 1, 3, and 5-year recurrence-free survival in patients with AFP/TTV ≤ 2 was 79.3%, 65.8%, and 48.1% respectively. While, it was 69.6%, 41.1%, and 32.1% in patients with AFP/TTV > 2, Log-rank: (P = 0.01) with a significant difference in recurrence-free survival between both groups (Fig. 1).

During the follow up the 1-, 3-, and 5-year tumor recurrence rates were 69 patients (24.1%), 121 patients (43%), and 150 patients (57.6%) respectively.

Table 2 shows the risk factors for early and late HCC recurrence. In univariate analysis the risk factors for 3y HCC recurrence were pre-operative total serum bilirubin > 1.5 mg/dl (P = 0.04), preoperative model of end stage liver disease (MELD) score > 10 (P = 0.03), AFP > 400 ng/ml (P = 0.04), TTV > 65.5 cm³ (P = 0.03), AFP/TTV > 2 (P = 0.01), macrovascular invasion (P = 0.001), pathological tumor grades III&IV (P = 0.02), and microvascular invasion (P = 0.001). AFP/TTV > 10 was risk factor for early and late HCC recurrence (P = 0.001).

In the multivariate analysis, independent risk factors for tumor recurrence (Table 3) were AFP/TTV > 2 (HR = 1.62, 95% CI = 1.29–1.98, P = 0.042), Macrovascular invasion (HR = 2.03, 95% CI = 1.62–2.54, P = 0.01).

SD (standard deviation), AFP (alpha fetoprotein), TTV (total tumor volume), ALT (alanine aminotransferase), INR (international normalized ratio), MELD (model of end stage liver disease).

![Survival Functions](image)

**Fig.1.** Kaplan-Meier curve for recurrence free survival in patients with AFP/TTV ≤ 2 and AFP/TTV > 2.

**Table 2**

| Variable                                  | All patients | 1y Recurrence | 3y recurrence | P       |
|-------------------------------------------|--------------|---------------|---------------|---------|
| Age (years)                               | (n = 286)    | (n = 69)      | (n = 121)     |         |
| ≥ 60                                      | 124          | 38 (30.6%)    | 56 (45.2%)    | 0.37    |
| < 60                                      | 162          | 31 (19.1%)    | 65 (40.1%)    |         |
| Gender                                    |              |               |               | 0.09    |
| Male                                      | 227          | 50 (22%)      | 91 (40.1%)    |         |
| Female                                    | 59           | 19 (32.2%)    | 30 (50.8%)    |         |
| Total bilirubin (mg/dl)                   |              |               |               | 0.04    |
| ≤ 1.5                                     | 204          | 41 (20.1%)    | 77 (37.7%)    |         |
| > 1.5                                     | 82           | 28 (34.1%)    | 44 (53.7%)    |         |
| MELD score                                |              |               |               | 0.03    |
| ≤ 10                                      | 199          | 39 (19.7%)    | 74 (37.2%)    |         |
| > 10                                      | 87           | 30 (34.4%)    | 47 (54%)      |         |
| AFP (ng/ml)                               |              |               |               | 0.44    |
| ≤ 100                                     | 172          | 38 (22.1%)    | 70 (40.7%)    |         |
| > 100                                     | 114          | 31 (27.2%)    | 51 (44.7%)    |         |
| AFP (ng/ml)                               |              |               |               | 0.04    |
| ≤ 400                                     | 217          | 45 (20.7%)    | 83 (38.2%)    |         |
| > 400                                     | 69           | 24 (34.8%)    | 38 (55.1%)    |         |
| Tumor number single                       |              |               |               | 0.09    |
| Multiple                                   | 248          | 57 (23%)      | 101 (40.7%)   |         |
| Tumor size (cm)                           |              |               |               | 0.08    |
| ≤ 5                                       | 177          | 35 (19.8%)    | 66 (37.3%)    |         |
| > 5 cm                                    | 109          | 34 (31.2%)    | 55 (50.5%)    |         |
| TTV (cm³)                                 |              |               |               | 0.03    |
| ≤ 65.5                                    | 163          | 30 (18.4%)    | 56 (34.4%)    |         |
| > 65.5                                    | 123          | 39 (31.7%)    | 65 (52.8%)    |         |
| AFP/TTV                                   |              |               |               | 0.01    |
| ≤ 2                                       | 184          | 38 (20.7%)    | 60 (32.6%)    |         |
| > 2                                       | 102          | 31 (30.4%)    | 61 (59.8%)    |         |
| Macrovascular invasion                    |              |               |               | 0.001   |
| Absent                                    | 274          | 62 (22.6%)    | 112 (40.9%)   |         |
| Present                                   | 12           | 7 (58.3%)     | 9 (75%)       |         |
| Type of operation                         |              |               |               | 0.27    |
| Laparoscopic                              | 26           | 5 (19.2%)     | 9 (34.6%)     |         |
| Open                                      | 260          | 64 (24.6%)    | 112 (43.1%)   |         |
| Type of resection                         |              |               |               | 0.06    |
| Anatomical                                | 82           | 18 (22%)      | 27 (32.9%)    |         |
| Non anatomical                            | 204          | 51 (25%)      | 94 (46.1%)    |         |
| Extent of hepatectomy                     |              |               |               | 0.62    |
| Wedge or 1 segment                        | 165          | 41 (24.8%)    | 75 (45.5%)    |         |
| ≥ 2 segments                              | 121          | 28 (23.1%)    | 46 (38%)      |         |
| Operative time (min)                      |              |               |               | 0.24    |
| ≤ 300                                     | 194          | 43 (22.2%)    | 77 (39.7%)    |         |
| > 300                                     | 92           | 26 (28.3%)    | 44 (47.8%)    |         |
| Operative blood loss                      |              |               |               | 0.15    |
| ≤ 1000                                    | 173          | 39 (22.5%)    | 66 (38.2%)    |         |
| > 1000                                    | 113          | 30 (26.5%)    | 55 (48.7%)    | 0.12    |
| Blood transfusion                         |              |               |               |         |
| Yes                                       | 199          | 52 (26.1%)    | 90 (45.2%)    |         |
| No                                        | 87           | 17 (19.5%)    | 31 (35.6%)    |         |
| Resection margin (cm)                     |              |               |               | 0.09    |
| ≤ 1                                       | 110          | 29 (26.4%)    | 54 (49.1%)    |         |
| > 1                                       | 176          | 40 (22.7%)    | 67 (38.1%)    |         |
| Tumor Grading                             |              |               |               | 0.02    |
| I,II                                      | 119          | 22 (18.5%)    | 35 (29.4%)    |         |
| III,IV                                    | 167          | 47 (28.1%)    | 86 (51.5%)    |         |
| Microvascular invasion                    |              |               |               | 0.001   |
| Yes                                       | 75           | 31 (41.3%)    | 48 (64%)      |         |
| No                                        | 211          | 38 (18%)      | 73 (34.6%)    |         |

SD (standard deviation), HCC (hepatocellular carcinoma), AFP (alpha fetoprotein), MELD (model of end stage liver disease), TTV (total tumor volume).
By knowing these patients with the possibility of a high risk of HCC recurrence, we can try to provide some preventive measures like interventional radiology or new adjuvant chemotherapy instead of surgical resection but this still needs further studies [13,14].

Whether this correlation between AFP and TTV is applicable to be adjusted for patients with previous treatment by loco-regional therapy like chemoembolization or radioembolization rather than resection also has not been studied yet, and need further study and analysis.

The limitations of this study were that it is a retrospective single-center study so liable for statistical bias, the commonest cause of liver cirrhosis and HCC in our study was HCV, which may differ than predominant causes of liver disease and HCC in the other Eastern or Western countries so the tumor biology and secretion of AFP may be affected.

Conclusions: In multivariate analysis, a newly proposed marker of AFP/TTV ratio was an independent risk factor for HCC recurrence than using AFP or TTV alone. It is a feasible surrogate that can be used in selecting the high-risk patients of tumor recurrence that may need intensive postoperative surveillance for early detection and possible treatment or we can consider providing appropriate preventive measures like loco-regional therapy or new-adjuvant chemotherapy for those high-risk patients but further studies are still needed to clarify. This study confirms the previous results of East Asian studies.

Statement of ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission and pre-operative to use their prospective data base and files for research work. The study protocol was approved by the National Liver Institute committee and review board.

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Author contribution

Hazem Zakaria, Anwar Mohamed, Hazem Omar, Nahla Gaballa, actively participated in the preparation, study design, collection of the data and editing of the manuscript. Statistical analysis was done by Hazem Zakaria.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

No conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2020.04.014.

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