RESEARCH ARTICLE

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Efficacy of P2/MS and AFP in Early Prediction of Hepatocellular Carcinoma Recurrence

ABSTRACT

Objective: P2/MS is a simple, inexpensive and non-invasive test for the evaluation of hepatic fibrosis in cirrhosis. Elevated alpha-fetoprotein levels in hepatocellular carcinoma is related with recurrence. We aimed to examine the efficacy of P2/MS and alpha-fetoproteinin early prediction of hepatocellular carcinoma recurrence and to determine a cut-off value for P2/MS and alpha-fetoprotein.

Methods: Sixty nine patients with hepatocellular carcinoma were retrospectively scanned for recurrence existence. The recurrence of hepatocellular carcinoma was diagnosed radiologically, via 3-phase tomography and magnetic resonance investigation. The formula of P2/MS was platelet count $(10^9/L)^2$/[monocyte count (%)x neutrophil count(%)].

Results: Forty two patients had hepatocellular carcinoma recurrence. For the recurrence prediction, the cut-off value of P2/MS was ≤59.9 with 100% specificity and 95.24% sensitivity. The cut-off value of alpha-fetoprotein was found >57.5 with 83.3% sensitivity and 92.6% specificity.

Conclusions: With these findings, P2/MS and alpha-fetoprotein seems as reliable markers for the prediction of hepatocellular carcinoma recurrence. We suggest that they can be used as non-invasive tools for the early estimation of hepatocellular carcinoma recurrence.

Keywords: P2/MS, AFP, Hepatocellular Carcinoma, Recurrence.

P2/MS ve AFP'nin Hepatoselüler Kanser Nüksünü Öngördürmedeki Yeri

ÖZET

Amaç: P2/MS sirozdaki karaciğer fibrozunu değerlendirmek kullanılan basit, pahalı olmayan, non-invaziv bir testtir. Hepatoselüler karsinomda artmış alfa-fetoprotein düzeyleri ise rekürrens ile ilişkilidir. Bu çalışmada hepatoselüler karsinom nüksünün erken öngörümünde P2/MS ve alfa-fetoprotein etkinliğini değerlendirmeyi ve bir cut-off değeri araştırmayı amaçladık.

Gereç ve Yöntem: Hepatoselüler karsinoması olan 69 hasta retrospektif olarak rekürrens varlığı açısından tarandı. Hastalardaki rekürrens varlığı radyolojik olarak trifazik bilgisayarlı tomografi ve magnetik rezonans inceleme ile değerlendirildi. P2/MS formülü olarak trombosit sayısı $(10^9/L)^2$/[monosit yüzdesi (%) x nötrofil yüzdesi (%)].

Bulgular: Toplam 42 hastada hepatoselüler karsinom rekürrensi belirlendi. Rekürrens öngörümü açısından P2/MS cut-off değeri ≤59.9 alındığında %100 spesifite ve %95.24 sensiviteye sahip olduğu bulundu. Alfa-fetoprotein için cut-off değeri >57.5 alındığındaysa sensivitesi %83.3 ve spesifitesi %92.6 saptandı.

Sonuç: Bu bulgular ışığında P2/MS ve alfa-fetoproteinin hepatoselüler karsinom rekürrensini öngördürmede güvenilir belirteçler gibi değerlendirilebilmektedir. Bu iki non-invaziv yöntemin hepatoselüler rekürrensinin erken tahmininde kullanılması gerektiğini önermekteyiz.

Anahtar Kelimeler: P2/MS, AFP, Hepatoselüler Karsinoma, Rekürrens.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy (1). HCC is the fourth leading cause of cancer deaths in the world (2). It is mostly seen in men (male/female ratio 2.4:1) and generally occurs in the elderly ages (1). But in high incidence areas, male/female ratio can increase up to 5.7:1 and the disease can affect people in their thirties (3, 4). HCC still has a poor prognosis. Mean survival is usually between 6 and 20 months (5). HCC incidence has been increased in the last 20 years (6). The most important risk factors for HCC are HBV, HCV and cirrhosis, regardless of etiology (1).

Cirrhosis is the most common and the highest risk for HCC and 80-90% of HCC develops on cirrhosis (7). Also, HCC may occur without cirrhosis in the patients with perinatal or early childhood HBV infections (8). Cirrhosis develops on increased hepatic fibrosis and is the leading etiologic factor of HCC (8). It is possible that hepatic fibrosis is an early carcinogenesis step for HCC (9). Also severe hepatic fibrosis is related with short survival rates (10). Therefore, evaluation of hepatic fibrosis in HCC is quite important.

Although liver biopsy is gold standard for hepatic fibrosis, there are multiple disadvantages such as high complication risk due to invasive intervention, limited chance of repeatability, the risk of gaining insufficient tissue and observer-dependent evaluation (11). Radiologic and biochemical non-invasive methods have been investigated for hepatic fibrosis detection and determining HCC prognosis (12-17). But these methods generally have low sensitivity and specificity ratios and some of them are expensive. Therefore liver biopsy is still gold-standard despite of its disadvantages (18). Recently, P2/MS was developed which predicts hepatic fibrosis in a simple and accurate manner (19). It is an inexpensive and simple method based on complete blood count (19). There are studies showing that P2/MS is useful in predicting esophageal variceal bleeding and hepatic decompensation, as well as hepatic fibrosis (20, 21).

It is well known that, in the HCC patients undergoing liver transplantation, AFP is a biomarker of HCC recurrence and elevated AFP is related with poor prognosis (22). But, a certain AFP level to estimate HCC recurrence has not been stated. So, we aimed to examine the efficacy of P2/MS and AFP and to determine cut-off values of P2/MS and AFP in the early prediction of HCC recurrence.

MATERIAL AND METHODS

Patients: The medical records of the adult patients, who diagnosed with HCC between 2013 and 2018 in a tertiary hospital in the western Turkey, were retrospectively scanned. The inclusion criteria were having complete blood count (CBC), magnetic resonance investigation (MRI) and computer tomography (CT) of the liver, being treated at least one of those treatment options: surgical resection, local treatment or liver transplantation. HCC recurrence was diagnosed by recognizing specific vascular pattern with 3-phase CT and MRI. P2/MS scores of the patients were calculated with the values of CBC before the recurrence diagnosis. The formula of P2/MS was as written: P2/MS=platelet count $(10^9/L)^2$/monocyte count (%) x segmented neutrophil count (%) (Lee et al., 2009). AFP levels and demographic features of the patients were also recorded.

Statistical Analysis: IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, ABD) was used for the analyses. The classification performances of AFP and P2/MS for HCC recurrence was evaluated with Receiver Operating Characteristic (ROC) curve analysis by Medcalc program. Area Under the Receiver Operating Characteristic Curve (AUROC), cut-off values, sensitivity and specificity measurements were also calculated. $p<0,05$ was used as the cut-off for significance.

RESULTS

Totally, 69 patients were included in the study. Among 69 patients, 80% of the patients had HBV associated HCC and 20% of them had HCV associated HCC. The mean age was found 52.2±9.1 and 74.2% of the patients were male. HCC recurrence was detected in 42 patients. For HCC recurrence prediction, AUROC value of P2/MS was found 0.987 (95% Confidence Interval (CI); 0.924-1.000; $p<0.0001$), and AUROC value of AFP was 0.913 (95% CI; 0.820-0.967; $p<0.0001$).

Cut-off value for P2/MS score was found ≤59.9. With this score, specificity was 100% (95% CI; 0.872-1.000) and sensitivity was 95.24% (95% CI; 0.838-0.994) for predicting HCC recurrence.

Cut-off value for AFP level was >57.5. With this AFP level, specificity was 92.6% (95% CI; 0.75-0.991) and sensitivity was 83.3% (95% CI; 0.686-0.93) for predicting HCC recurrence (Figure 1).

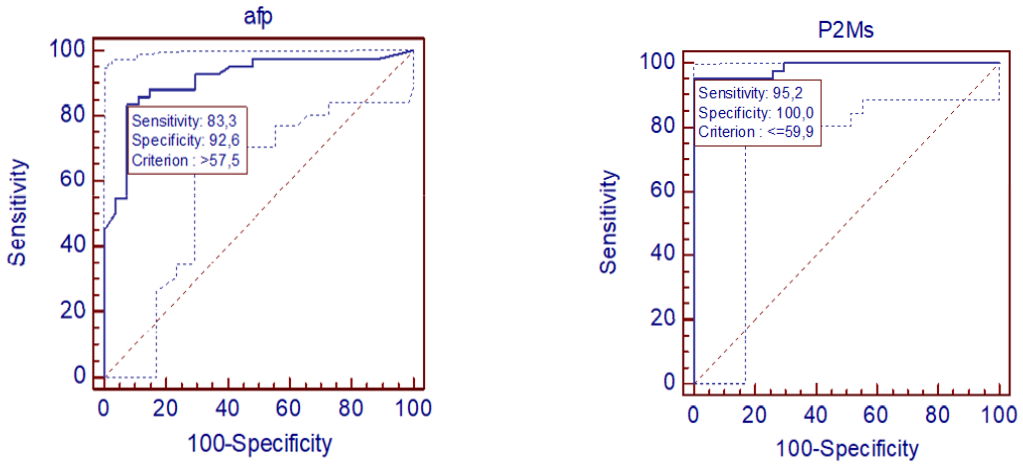

Figure 1. ROC curves of AFP and P2/MS.

DISCUSSION

One of the aims of this study was to examine the efficacy of P2/MS and AFP for the estimation of HCC recurrence. AUROC values showed that P2/MS and AFP are both useful for the prediction of HCC recurrence. It is not a surprise that AUROC value of AFP was found statistically significant for the prediction of HCC recurrence. Because, AFP is a biomarker of HCC recurrence in the patients undergoing liver transplantation. But the study population included the patients treated with local treatment and surgical resection beside liver transplantation. So, the relationship between AFP and HCC recurrence in HCC patients, who did not undergo liver transplantation, should be checked with further studies.

The other aim of the study to determine a cut-off value of P2/MS and AFP for the prediction of HCC recurrence. We found that P2/MS score ≤ 59.9 is helpful to show HCC recurrence with high specificity and sensitivity ratios. We also found that AFP>57.5 is associated with HCC recurrence, but with lower specificity and sensitivity ratios than P2/MS. So, we strongly suggest to calculate P2/MS scores of the HCC follow-up patients and to investigate the patients with a score ≤59.9 for HCC recurrence. We also suggest to carefully examine the patients with AFP>57.5.

There was not any similar study in the literature and we couldn't compare the results. Furthermore, there are several limitations of the study. This is a single-center and a retrospective study. The sample size is low. Also, we did not make any comparison between P2/MS and other non-invasive methods or liver biopsy results. On the other hand, P2/MS could be the simplest and cost-effective way to predict HCC recurrence.

HCC mostly develops on cirrhosis and hepatic fibrosis and hepatic fibrosis seems like a step of carcinogenesis (23). The success of P2/MS in the HCC recurrence prediction may be related with its success to predict hepatic fibrosis. Therefore, other methods that shows hepatic fibrosis might be chosen for the prediction of HCC recurrence. Liver biopsy is gold-standard, but high risk of complication and cost are its disadvantages (11). The radiological tools to measure liver elasticity have also high costs and it's observer-dependent (12). There are multiple blood sample tests based on AST and ALT levels for the prediction of hepatic fibrosis, such as FIB-4, APRI and AAR (14-16). But AST and ALT levels are an unstable in chronic viral hepatitis infections and liver masses like HCC. Unstable liver transaminase levels restrict the use of the methods based on AST and ALT (24). Therefore, P2/MS seems a more appropriate choose for the prediction of HCC recurrence.

CONCLUSION

With these findings, we suggest that P2/MS may be an effective tool to predict HCC recurrence. AFP>57.5 should be alarmed us for HCC recurrence. But further prospective studies with larger sample sizes are needed.

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