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Abstract

Background: Hepatocellular carcinoma (HCC) is a significant health problem, and the associated mortality rate is increasing.

Aim: We aimed to determine the clinical characteristics and prognosis for HCC in member countries of the OncoBridge Study Group.

Methods: We recruited 630 patients diagnosed with HCC between 2013 and 2019 from 4 countries (Türkiye, Russia, Georgia, and Greece). Univariate and multivariate analyses were conducted to investigate clinical and laboratory prognostic factors. Receiver operating characteristic (ROC) analysis was used to determine the prognostic value of the neutrophil to lymphocyte ratio (NLR) and alpha-fetoprotein (AFP) value.

Results: The 3 most common etiological factors were hepatitis B infection (39.7%), hepatitis C virus infection (17.0%) and non-alcoholic fatty liver disease (9.0%). Median overall survival for the whole group was 25 [95% confidence interval (CI): 15.7–34.2] months. Cut-off values for AFP and NLR were accepted as 200 ng/mL and 3.45, respectively. The area under the ROC curve values for AFP, NLR and NLR+AFP were 0.625 (95% CI: 0.547–0.704), 0.589 (95% CI: 0.512–0.667) and 0.657 (95% CI: 0.583–0.731). From the multivariate analysis, advanced tumour size, lymph node involvement and metastasis (TNM) stage, presence of cirrhosis, high AFP, and high NLR values were associated with poor survival.

Conclusion: AFP, NLR, advanced TNM, and presence of cirrhosis may predict prognosis in patients with HCC. Studies involving more countries are needed to corroborate these findings.

Keywords: hepatocellular carcinoma, prognosis, neutrophil to lymphocyte ratio, Türkiye, Russia, Georgia, Greece

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Introduction

According to the surveillance, epidemiology, and end results database, rates for new liver cancer cases increased by an average of 2.1% annually in the past decade (1). Mortality rates increased by an average of 2.4% between 2007 and 2016. The incidence of hepatocellular carcinoma (HCC) varies among ethnic groups and even among regions in the same country (1,2). Although it is more common in Asian and African countries, the incidence is thought to have increased in developed countries because of the increased access to more effective diagnostic screening and immigration to these countries from high risk regions (2).

Risk factors for HCC are well defined compared with some other cancers. Viral hepatitis, chronic alcoholism, non-alcoholic fatty liver disease (NAFLD) are among the main factors. Although the frequency of risk factors varies from region to region, on the whole, chronic viral hepatitis is the most common cause (1).

The Child–Turcotte–Pugh classification is the oldest assessment tool for evaluating HCC prognosis, but many other prognostic factors have been studied recently because of the limitations of this commonly used scoring system, which is based on liver function tests (3,4). The other prognostic factors include tumour histology, serum alpha-fetoprotein (AFP) level, hepatitis B and C, antiviral therapy, diabetes mellitus and inflammation markers (5–10).

In the bone marrow, the production and release of neutrophils increase in response to inflammation (11,12). The chemokines playing a significant role in cancer-related inflammation induce neutrophil release from the bone marrow with the accumulation of neutrophils in peripheral tissue (13). The effects of inflammation increases the neutrophil count in the peripheral blood while the lymphocyte count decreases. Consequently, these changes increase the neutrophil to lymphocyte ratio (NLR). Considering that increased NLR may be a marker for cancer-related inflammation, it may also be associated with prognosis. Research has shown that high NLR may be associated with poor prognosis in various types of cancer (14).

As part of the OncoBridge Working Group, our aim in this study was to clarify the etiological and prognostic factors of HCC and to provide basic data for health practitioners and healthcare professionals.

Methods

OncoBridge Study Group

The OncoBridge Project started in 2014 with the participation of 8 countries (Azerbaijan, Armenia, Egypt, Greece, Israel, Morocco, Saudi Arabia and Türkiye) with the aim of increasing scientific and educational collaboration on various platforms, including international congresses, cooperative study groups, fellow exchanges, etc. The participants agreed to organize scientific meetings annually in Türkiye. The initiative is open to all other neighbouring countries interested in the aims of the platform and willing to participate. Eventually, representatives of several other countries, including Bulgaria, Georgia, Kazakhstan, Lebanon and Romania, joined the various activities of OncoBridge.

Study design and patient cohort

This was a retrospective study conducted by the OncoBridge Study Group in which the etiological and prognostic factors of HCC were studied. Patients who were diagnosed with HCC between 2013 and 2019 in 9 centres in 4 countries (Georgia, Greece, Russia and Türkiye) were studied. Patients aged 18 years or older were eligible for enrolment if they had been histologically or radiologically diagnosed according to the European Association for the Study of the Liver consensus recommendations on HCC (15) or had any stage of tumour size lymph node involvement metastasis (TNM). After applying the eligibility criteria, 630 patients were eligible for the final analysis.

Data collection

An Excel spreadsheet template was used for data collection. Each centre entered their data into that template and the main database was developed. This was then converted and entered into SPSS statistical software. Each patient was represented by her/his initials and given a unique identification number representing their country, centre, researcher and case number systematically. Coding tables were kept separate from the data table from a third party within each centre in order to maintain patient anonymity.

Coding rules

On the coding table for patient identification, the code for the patient started from 1 and ended with the number of the last participant at each centre (e.g. 1, 2, 3, ... 205). The subsequent parts of the codes were the initial of the participating country, the initials of the participating centre and the initials of the researcher and initials of the participant. Each researcher recorded the national ID and hospital ID of the patients on their own computer. These data were not shared in the dataset.

Demographic and clinical variables included age at diagnosis, sex, geographical region (rural or urban), liver cirrhosis, viral hepatitis, smoking, alcohol intake, NAFLD and other cirrhosis-related factors, Child–Pugh score, treatment for hepatitis B virus/hepatitis C virus (HBV/HCV), diabetes and its treatment, statin and aspirin use, blood type, height and weight, sorafenib treatment, TNM staging, local ablative therapy and surgical treatment. Neutrophil and lymphocyte counts and serum AFP levels were also recorded.

Ethical approval

The study protocol conformed with the ethical guidelines of the 2008 Declaration of Helsinki and was approved by Manisa Celal Bayar University (No. 20478486).

Statistical analysis

All statistical analyses were done using SPSS, version 22. All statistical assessments were 2-sided. Statistical significance was set at P = 0.05. Overall survival was calculated from the diagnosis of the patient up to either the date of death from any cause or the date of the last follow-up. Differences in cumulative survival were determined using the Kaplan–Meier method and a log-rank test. Univariate and multivariate analyses for survival difference were carried out using the Cox proportional hazards model, and were expressed as hazard ratio and 95% confidence interval (CI). The area under the receiver operating characteristic (ROC) curve for AFP and NLR to determine the prognosis of HCC patients were calculated using SPSS along with the optimal cut-off value, sensitivity, specificity, positive predictive value, and negative predictive value.

Binary logistic regression is a statistical analysis that determines how much (if any) variance is explained on a dichotomous dependent variable by a set of independent variables. We used binary logistic regression analysis to determine the combined use of AFP and NLR parameters and consequently to determine the prognosis for HCC.

Results

Patients

The characteristics of the patient cohort are presented in Table 1 . The largest group, 453 patients (71.9%), were from Türkiye, 111 (17.6%) were from Russia, 55 (8.7%) from Georgia and 11 (1.7%) from Greece. Hepatocellular carcinoma was more common among male patients. Mean age at the time of diagnosis was 60.0 (SD 12.8) years. The 3 most common etiological factors were HBV infection (39.7%), HCV infection (17.8%) and NAFLD (9.0%).

Prognostic efficacy of neutrophil to lymphocyte ratio and alpha-fetoprotein in hepatocellular carcinoma patients

We used the ROC analysis method to evaluate the prognostic ability at the time of diagnosis, NLR, AFP and the combination (NLR+AFP) in HCC patients. The results are presented in Table 2 and Figure 1. According to the ROC analysis, the cut-off value for NLR was 3.45. The cut-off value for AFP was accepted as 200 ng/mL (16). Both AFP and NLR had high specificity (but lower sensitivity) for prognosis; AFP gave a larger area under the ROC curve (0.625, 0.547–0.704; P = 0.003) than NLR (0.589; 0.512–0.667; P = 0.036). Further evaluation of the combination of NLR+AFP had the highest area under the ROC curve (0.657; 0.583–0.731; P Figure 2). In the low AFP group (AFP Figure 3). They were grouped as follows to show the relationship between AFP and NLR use and survival: AFP and NLR both higher (combined high group), AFP and NLR both low (combined low group), only patients with high NLR (high NLR group). None of the patients had high AFP only (i.e. without high NLR). The median survival time of HCC patients in the combined high, combined low and high NLR groups were 8.0 (95% CI: 5.232–10.768) months, 15.0 (95% CI: 9.332–20.668) months and 11.0 (95% CI: 8.136–13.864) months, respectively (Figure 4).

Sorafenib treatment outcomes

Sorafenib was used in the treatment of 228 patients in 2007–2019. It was administered until disease progression, unacceptable toxicity or withdrawal of consent. The treatment resulted in 5 (2.2%) complete responses, 31 (13.7%) partial responses, 116 (50.4%) with stable disease, and 76 (33.6%) with progressive disease. Median progression-free survival was 5 months (95% CI: 1.5–27) and median overall survival was 9 months (95% CI: 7.2–10.7).

Univariate analysis

Median overall survival for all patients after diagnosis was 25 months (95% CI: 15.7–34.2) (Figure 5). The 3-year median overall survival rate among TNM stage I–IV patients was 77%, 62%, 34% and 29%, respectively (Log Rank; P Table 3). The univariate analysis showed that male sex, urban residence, advanced TNM stage, smoking, chronic HBV infection, chronic HCV infection, cirrhosis, diabetes mellitus, metformin use, insulin use, high AFP, high NLR and combined (NLR+AFP) high group were all associated with a high mortality risk while HBV treatment, HCV treatment, statin use, local ablative treatment and surgical treatment were associated with low mortality risk. Age, Child–Pugh

grade, alcohol intake, sulfonylurea use, body mass index, aspirin use, chemotherapy treatment, sorafenib treatment and ABO blood type were not associated with overall survival in this analysis.

Multivariate analysis

The variables found to be associated with prognosis in the univariate analysis were evaluated using the Cox proportional hazard multivariate model (Table 3). The model demonstrated that high NLR was an independent prognostic factor for overall survival (P = 0.048). The other independent prognostic factors for poor overall survival included high AFP value (P = 0.040), high combined score (P = 0.009), cirrhosis (P = 0.035) and advanced TNM stage (P = 0.015).

Discussion

The distribution of HCC for age, sex and etiology varies by region. Overall, worldwide, the proportion of men with HCC is greater than for women, with a male:female ratio ranging from 2:1 to 4:1. Liver cancer is more common among men in Middle Eastern countries (17,18). The median age at diagnosis tends to peak in the 55–64 years age group, although it may vary by region (1). These age-specific differences are due to differences in the age at time of infection with hepatitis virus in this region. In rural areas, where there is high pollution from insecticides, HCC is more common but other environmental factors may also be contributors (19). In our study, the median age at diagnosis for HCC was 55 years and the male to female ratio was 3.6:1 (males 78.4%, females 21.4%). Unlike in some other research, our HCC patient population had more urban than rural residents, possibly due to the fact that the centres participating in the study were located in big cities.

Chronic HBV infection is responsible for 50–80% of HCC cases worldwide (20). However, the ratio is 75–90% in areas where HBV is endemic, such as Türkiye. Like HBV infection, the contribution of HCV infection to HCC varies worldwide. In Europe and the United States of America, HCV is the main risk factor for HCC. However, HCV infection is the second most common infection in Asia. According to research from 12 countries in the WHO Eastern Mediterranean Region and the Middle East, HCC cases in the Islamic Republic of Iran, Lebanon, Türkiye and Yemen were mainly attributable to HBV, while in Pakistan, Saudi Arabia and the North African countries, cases were predominantly related to HCV (21).

Infection with HBV or HCV and excessive alcohol intake have been identified in 56.0%, 23.2% and 15.9% of Turkish HCC patients (22–24). Recent research suggests that NAFLD causes the development of HCC, especially in Western European countries and the United States of America (25). In our study, infection with HBV and HCV were the most important reasons for the development of HCC. Since vaccination against HBV is becoming more common, this may lead

to more instances where HCV is the cause of HCC over time. Unfortunately, there is currently no vaccine for HCV. Therefore, measures such as better blood screening techniques and other harm reduction programmes will further reduce the risk of HCC. We found that NAFLD was the third most common cause of HCC; the high NAFLD rate may be related to the high rates of diabetes and obesity in our study group.

The TNM stage has been shown to be associated with poor prognosis among patients with HCC (26), however, it is the liver function that determines the prognosis of patients with underlying cirrhosis. The prognosis for HCC depends not only on tumour stage but also on liver failure due to cirrhosis. The Okuda and CLIP systems may be more useful than TNM stage to assess prognosis (27). However, irrespective of cirrhosis in our patients, TNM stage was statistically significantly associated with mortality (TNM stage III–IV vs I–II: hazard ratio:3.489, P = 0.015).

The accumulating evidence indicates that outcomes for patients with HCC are significantly correlated with the level of tumour-associated inflammation (28,29). While these inflammatory changes lead to tumour growth, normal distribution in haematological parameters is disrupted (lymphopenia, granulocytosis, etc.). It is known that pro-inflammatory factors (IL–1, TNF-α, vascular endothelial growth factor, tissue factor and cancer procoagulant) are secreted by cancer cells (30,31) and cause changes in blood cell count. These changes in hematologic parameters among cancer patients have been studied as prognostic factors among HCC patients (32,33). The NLR can elucidate the complex prognostic information of these 2 conditions (granulocytosis and lymphopenia), and can be a very strong predictor of clinical outcome. Higher levels of NLR are an indication of poor survival for patients with HCC and NLR can be considered a biomarker in making clinical decisions about HCC treatment (14). There have been more studies on AFP than on NLR to determine the prognosis of HCC; high AFP values are associated with poorly differentiated tumour and have been reported to be an independent predictor of survival (34) but there is no generally accepted AFP cut-off value associated with prognosis. Our findings confirmed the prognostic importance of AFP and NLR values. Until now, NLR and AFP have not been evaluated together for diagnosis or prognosis (35). In our study, the prognostic values of AFP and NLR as well as their combinations were evaluated and compared and our data showed that AFP remained a good prognostic marker, and that NLR was also a prognostic marker and was comparable to AFP. Further evaluation of the biomarker combination showed that the combination of AFP and NLR had the highest prognostic accuracy. The area under the ROC curve for this combination was 0.657, with sensitivity 88.3% and specificity 29.8%, indicating prognostic accuracy comparable to AFP and NLR alone. The combination of AFP and NLR is a useful prognostic marker for HCC. We observed that the combined use of these markers was better at predicting survival than their use individually. However, it should be noted that sensitivity for these markers is low.

In the Cox regression analysis, sorafenib did not reduce the risk of death. This may be because sorafenib can be used after local ablative and chemotherapy treatments in some of the countries in our study. However, the median overall survival and median progression-free survival value with sorafenib was compatible with the findings of previous research (36–38). In a study by Manghisi et al., median survival following diagnosis ranged from approximately 6 to 20 months in patients with HCC (39). It is obvious that, with targeting therapies and immunotherapies, survival from time of diagnosis will be extended, therefore, the results from long-term survival should be included . Similar to previous findings (40), the median survival among our HCC patients followed up between 2013 and 2019 was 25 months. According to the multivariate analysis, we identified advanced TNM stage and the presence of cirrhosis as independent prognostic factors, and again this agreed with the findings of previous research (41).

In conclusion, the risk factors significantly associated with mortality among patients with HCC were advanced TNM stage, cirrhosis and high AFP and NLR levels. Combined use of NLR and AFP was a better prognostic indicator than either of these factors taken separately. Overall survival calculated from the time of diagnosis, and after sorafenib use, among our patients was consistent with previous reports (38,40).

Although there were some limitations to this study, it was an important attempt at reflecting the HCC data of the 4 participating countries. The major limitation was the retrospective nature of the study. Another limitation was that we could not access some data for the patients. Lastly, the sample size from each country in our study was not proportionate with the population size; convenience sampling was used to determine the sample size used. There were no other criteria for the sampling method except that the centre be available and willing to participate.

Our findings need to be validated by further studies with the participation of more OncoBridge member countries.

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Competing interests: None declared.

Étude multicentrique et multinationale des caractéristiques cliniques et du pronostic du carcinome hépatocellulaire

Résumé

Contexte : Le carcinome hépatocellulaire (CHC) représente un problème de santé majeur, et le taux de mortalité qui lui est associé est en augmentation.

Objectifs : Nous avons cherché à déterminer les caractéristiques cliniques et le pronostic du CHC dans les pays membres du groupe d'étude OncoBridge.

Méthodes : Nous avons recruté 630 patients diagnostiqués avec un CHC entre 2013 et 2019 dans quatre pays (Géorgie, Grèce, Russie et Türkiye). Des analyses univariées et multivariées ont été menées pour étudier les facteurs pronostiques cliniques et biologiques. L'analyse de la courbe ROC (caractéristique du fonctionnement du récepteur) a été utilisée pour déterminer la valeur pronostique du rapport neutrophiles/lymphocytes (NLR) et du taux d'alpha-fœtoprotéine (AFP).

Résultats : Les trois facteurs étiologiques les plus courants étaient l'infection par le virus de l'hépatite B (39,7 %), l'infection par le virus de l'hépatite C (17,0 %) et la stéatose hépatique non alcoolique (9,0 %). La survie médiane globale pour l'ensemble du groupe était de 25 mois [intervalle de confiance (IC) à 95 % : 15,7-34,2]. Les valeurs seuils pour l'AFP et le NLR ont été acceptées respectivement à 200 ng/mL et 3,45. L'aire sous les valeurs de la courbe ROC pour l'AFP, le NLR et le NLR+AFP était de 0,625 (IC à 95 % : 0,547-0,704), 0,589 (IC à 95 %: 0,512-0,667) et 0,657 (IC à 95 % : 0,583-0,731). L'analyse multivariée a montré que la taille avancée de la tumeur, l'atteinte ganglionnaire lymphatique et le stade métastatique (classification TNM), la présence d'une cirrhose, ainsi que des valeurs d'AFP et de NLR élevées étaient associés à une faible survie.

Conclusion : L'AFP, le NLR, un stade TNM avancé et la présence d'une cirrhose peuvent permettre de prédire le pronostic chez les patients atteints de CHC. Des études incluant un plus grand nombre de pays sont nécessaires pour corroborer ces résultats.

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