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Original article

PIVKA-II – AN INDEPENDENT INDICATOR OF ACUTE AND ACUTE-ON-CHRONIC LIVER FAILURE

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Abstract

Introduction: PIVKA-II is an abnormal coagulation factor induced by vitamin K absence or use of vitamin K antagonists, and is useful in the diagnosis of hepatocellular carcinoma (HCC). PIVKA-II may also correlate with liver failure, with one study demonstrating an association with hepatitis E infection.

Materials and methods: A total of 406 subjects with chronic viral hepatitis, steatofibrosis, cirrhosis and hepatocellular carcinoma were evaluated for PIVKA-II, AFP, BCLC (only HCC patients), Child-Pugh-Tourcotte score, and MELD-Na score.

Results: A statistically significant positive correlation was found between PIVKA-II and MELD-Na and CPT scores.

Conclusion: PIVKA-II may be an independent indicator of acute and acute-on-chronic liver failure.

Keywords: PIVKA-II, hepatocellular carcinoma, liver failure, screening.

Introduction

In patients without previously diagnosed liver cirrhosis, liver failure is acute fulminant or sub-fulminant, while in the setting of underlying chronic liver disease it occurs in the form of acute-on-chronic failure, or decompensation, with or without multiorgan insufficiency. Manifestations commonly associated with liver failure are encephalopathy, jaundice, edema, ascites, coagulopathy, and bleeding diathesis. Disordered biosynthetic function is a cardinal feature of liver failure[1,2]. Parameters usually evaluated depicting the liver's synthetic function are serum albumin, prothrombin time, and INR. Other analyses that are now seldom used for this indication are concentrations of lipoproteins, ceruloplasmin, ferritin, and alpha-1 anti-trypsin[3]. Scores such as MELD-Na, Child-Pugh-Tourcotte, and CLIF-ACLF are used in patients with liver cirrhosis and consist of numerous clinical features and laboratory values. Aside from providing a measure of liver function at a given time, they also have a prognostic and predictive value on the future course and outcome of the disease. In the case of MELD-

Na, the score is used to determine the order of patients on liver waiting transplant lists in many healthcare systems worldwide[1,2].

PIVKA-II (Prothrombin induced by vitamin K absence or antagonist-II) is also known as des-gamma-carboxy prothrombin (DCP). Deactivation of vitamin K dependent carboxylase (in the absence of vitamin K or the presence of vitamin K antagonists) results in irregular methylation of N-terminal glutamate residues on coagulation factors, leading to creation of an abnormal and non-functional coagulation factor known as PIVKA-II[3]. The aim of this study was to demonstrate the association between PIVKA-II and liver failure, by showing its correlation with a rising CPT class and MELD-Na score.

Material and methods

PIVKA-II testing was introduced at the University Clinic for Gastroenterohepatology for the first time in 2021, while 2023 marked the beginning of a study titled "Measures for early detection and diagnosis of hepatocellular carcinoma – one of the initiatives for realization of the European Beat Cancer plan", which significantly increased the frequency of testing for PIVKA-II. In this study patients with chronic viral hepatitis, steatofibrosis, cirrhosis and hepatocellular carcinoma were followed at regular 6-month intervals during the course of 3 years after screening. For the purpose of cross-sectional analysis of a sample of 406 examinees (2021-2024, and patients from the first months of 2025), the PIVKA-II values at diagnosis of HCC, or from the last available visit in patients without an HCC diagnosis, were used. Age, gender, stage of fibrosis, and etiology of liver disease were established for each patient. Additionally, examinees in the study sample had an AFP measurement, CPT and MELD-Na scores calculated corresponding to the same visit as the PIVKA-II result in use. Data was organized and analyzed.

Results

Ninety-four of 406 patients had CPT class B, while 83 had class C. Of the remaining 229, many of whom patients with steatofibrosis, without an established diagnosis of cirrhosis, 198 patients had class A, while only 31 patients did not have all necessary parameters for

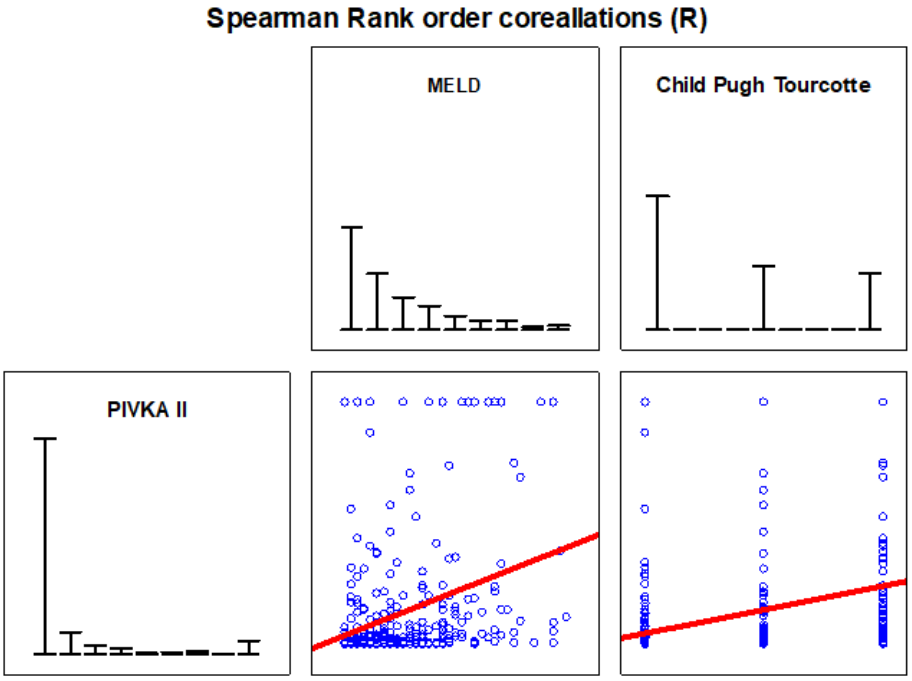

Fig. 1. Correlation between PIVKA-II and MELD Na/Child Pugh Tourcotte class

calculating the scores. Hepatocellular carcinoma was diagnosed in 61 of 406 patients with the following BCLC class at the time of diagnosis: Class A - 11 patients, Class B - 8 patients, Class C - 18 patients, and Class D - 24 patients. In the HCC group, the CPT score distribution was fairly even: Class A - 40%, Class B - 33%, and Class C - 27%.

Statistical analysis demonstrated a significantly positive moderate correlation ($R_{(374)}$=0.492; p=0.00001) between levels of PIVKA-II and MELD-Na – the level of PIVKA-II was significantly elevated with the value of MELD-Na. Also, between the level of PIVKA-II and Child-Pugh-Tourcotte (A→C) there was a significant linear moderate correlation ($R_{(374)}$=0.576; p=0.00001) – the level of PIVKA-II was significantly elevated with Child Pugh Tourcotte classes (A→C) (Figure 1).

Discussion

In a retrospective study from 2015 by Kang K *et al.* 76 patients with chronic liver disease, elevated PIVKA-II levels (>125mAU/ml), and without a diagnosis of hepatocellular carcinoma were studied. A comparison was made with a control group of the same number of study subjects matched for gender, age distribution and diagnosis of cirrhosis. Statistically significant differences were found between the two groups for several parameters which were more prevalent in the first group, and these were antibiotic use, alcohol etiology, elevated transaminases and GGT. Furthermore, a significant association was found between group 1, a higher Child-Pugh-Tourcotte class, and the separate constituent elements of the CPT score when compared to group 2 in univariate analysis; however, this was not reproduced and confirmed with multivariate analysis[4].

In a 2022 study by Chen Y *et al*., PIVKA-II was evaluated in 84 patients with hepatitis E viral infection. Elevation in the PIVKA-II value (>32 mAU/ml) was found in 50/84 study subjects. A higher elevation (>125 mAU/ml) was associated with lower values of albumin and a longer hospital stay, in comparison with moderate elevations (32-125 mAU/ml). After resolution of the infection, PIVKA-II values decreased and subsequently normalized. These findings suggest a correlation between PIVKA-II values and liver failure in patients with hepatitis E viral infection[5]. Honda T *et al*. in 2023 studied PIVKA-II values in 441 patients with liver disease, and without a diagnosis of hepatocellular carcinoma. In women, an association was found between PIVKA-II and CPT class B and C, elevated P1NP (type 1 procollagen N-propeptide), a low titer of ucOC (undercarboxylated osteocalcin), and an association between IgA and PT-INR. In men, an association was found between alcohol etiology, low levels of vitamin D, and an association with fibrosis-4, IgG, total bilirubin, PT-INR, and SARC-F. Elevated values of PIVKA-II were also associated with abnormal bone physiology in women, muscle weakness in men, and severe liver disease in both genders[6].

As inferred in the aforementioned publications, the statistically significant correlation in our study between PIVKA-II values and the two most commonly used scores for measuring liver function (MELD-Na and CPT) denotes that PIVKA-II may serve as an independent indicator of acute and acute-on-chronic liver failure. The applicability of this finding may play a role in determining which patients require more aggressive treatment and possibly triage for admission to intensive care. However, for this purpose additional studies will be necessary to demonstrate and determine a cut-off value, as the typical cut-off values used for screening and diagnosing HCC (ranging 50-180 mAU/ml)[7] are not suitable. Analysis investigating whether elevated PIVKA-II values are associated with death caused by cirrhosis-related complications would further aid in understanding the utility of this tumor marker. In interpreting the results, it is important to emphasize that the distribution of CPT classes is fairly even in the HCC group. In the hypothetical circumstance that CPT class C had been the predominant class in HCC patients, it could have been argued that HCC acted as a confounder between PIVKA-II and CPT. Finally, the results demonstrate that the applicability of PIVKA-II in diagnosing HCC in patients with decompensated liver cirrhosis is limited, particularly in the absence of liver nodules detected on ultrasound.

Conclusion

PIVKA-II elevation is associated with an increase in MELD-Na and Child-Pugh-Tourcotte class. Therefore, PIVKA-II may be an independent predictor of acute and acute-on-chronic liver failure.

Conflict of interest statement. None declared.

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