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'PIVKA-II AND HEPATIC PATHOLOGIES. HOW CAN A RELATION BE DEFINED

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Abstract

Objective: *To observe the levels of PIVKA-II and its correlation with various hepatic pathologies and defining relation between them.*

Study Design: *A Cross sectional observational study*

Study Duration: *06 months*

Study Place: *Tertiary Care Hospital, Lahore*

Methods: *A cross-sectional observational study was conducted over six months in the Gastroenterology Department of a tertiary care hospital in Lahore. Using WHO Sample Size Calculator, a sample size of 312 patients was calculated. Data were analyzed using SPSS 25, with significance set at $p<0.05$. Ethical approval was obtained beforehand.*

Results: *312 patients were included in our study, among them 112 were males and 100 were females. Patients were divided into the 03 groups i.e. hepatocellular carcinoma, cirrhosis and chronic hepatitis. PIVKA-II levels were measured in all the groups. Patients with hepatocellular carcinoma showed a significant increase in levels of PIVKA-II as compared to other groups. PIVKA-II levels were ranging in 690±5 in hepatocellular group.*

Conclusion: *PIVKA-II serves as a significant important marker in assessing diseases of liver esp liver carcinoma, cirrhosis and chronic hepatitis. Its elevation helps guide treatment protocols and further management.*

INTRODUCTION

The hepatic diseases form a huge health burden and include a broad category of diseases including chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). HCC is the 6th most frequently diagnosed and 3rd most common cause of global cancer deaths, with more than 830,000 deaths every year with the highest incidence recorded in areas of endemic infections of hepatitis B and C.[1] In HCC, early diagnosis will improve the survival rates that can obviously be managed with curative interventions that

include liver transplantation, resection, and local ablative therapy that best work in early stages of the disease. Nevertheless, the currently available diagnostic tools, and in particular imaging and traditional biomarkers, such as alpha-fetoprotein (AFP) are highly limited in sensitivity and specificity of early detection of liver diseases and tumor formation.[2]

One of the biomarkers being recently discovered is Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) or des-gamma-carboxy prothrombin (DCP). Prothrombin like 2 (PIVKA-II) is a defective form of prothrombin because of poor post translational carboxylation of glutamic acid residues caused by vitamin K deficiency or antagonism. First stated in the patients with vitamin K-deficiency, PIVKA-II have been observed to be increased in patients with HCC irrespective of the presence of vitamin K. It is no longer merely identified as a tumor marker but also as a molecule that may perform functions concerned with tumor growth, angiogenesis as well as vascular invasion. This has encouraged the increased rise in need to know the greater clinical significance of PIVKA-II within the group of liver diseases.[3,4]

The most recent studies have discussed the diagnostic and prognostic value of PIVKA-II in the liver pathology. Many studies have commented that the level of PIVKA-II is prominently elevated in HCC patients than in those with benign liver diseases or normal controls. Moreover, PIVKA-II has proven to be more specific than AFP, more so when AFP is on the normal ranges. It was tested as an independent biomarker and in combinations, including AFP-L3 and AFP, where it was demonstrated that its use together with other biomarkers revealed an increased level of diagnostic accuracy.[5]

In spite of these encouraging results, the usage of PIVKA-II is still debatable in multiple ways. As an example, PIVKA-II elevation has also been noted in non-malignant diseases like cirrhosis and chronic hepatitis though at lower concentrations as compared to HCC.[6] This brings crucial concerns on the specificity of PIVKA-II and possible figures of false-positive findings in cases of advanced chronic server disease. Also, the mechanisms between hepatic dysfunction, vitamin K metabolism and production of PIVKA-II are complicated and are not well understood. Hence, there is a need to look deeper into the interpretation of the relationship between PIVKA-II and the different hepatic pathology since it involves comprehensive examination of its diagnostic value besides its biological importance.

PIVKA-II is geographically variable in the application of the clinical practice. It has been in use in the East Asian region and specifically in Japan and South Korea where the uses of the test have been incorporated into HCC surveillance programs in combination with AFP. But in the western countries it has not been used in the same speed because of the differences in the guidelines, cost, and the standardization of assay and access to testing platforms.[7] The trend in the world is the development of personalized medicine and marker-based diagnostics, which is why the incorporation of non-invasive, reliable markers, such as PIVKA-II into the management of hepatic diseases becomes more and more relevant.

On molecular level, the production of PIVKA-II is strongly related to the biology of tumor. It has also been associated in regulating the expression of vascular endothelial growth factor (VEGF) and facilitating the process of angiogenesis in tumor cells and metastasis. Microvascular invasion is also related with PIVKA-II, and it is an important prognostic factor in HCC. Its contribution towards tumor progression triggers the idea that it could be not only diagnostic marker, but also a therapeutic option or a prognostic predictor to stratify patients in order to receive aggressive treatment strategies.[8]

It is against this background that this study intends to discuss the association between PIVKA-II and a range of hepatic pathological conditions especially as a biomarker of differentiating between malignant and non-malignant liver disease. Using both retrospective and prospective data on patients, the study aims at outlining the diagnostic thresholds of PIVKA-II, diagnosing its efficacy against established markers, and determining its correlation with the severity and markers of the disease. The other research question in this investigation is to determine the presence of definite trend of PIVKA-II expression in various levels of liver diseases hence offering a pattern that can be used in clinical setting in the future.

To summarize, it seems that the potential of PIVKA-II in terms of diagnosis and treatment of

hepatocellular carcinoma cannot be underestimated; however, there is an urgent necessity to define its place in a more comprehensive range of hepatic pathologies. Clarity will be seen between PIVKA-II and hepatic pathology and this can enhance the process of clincal decision, Acting to enhance early detection and it has the potential to dominate the process of treatment algorithms in chronically affected liver disease and liver cancer patients. The presented study can be added to the pool of evidence in favour of introducing new biomarkers into the field of hepatology, because it could be used to inform future-perspective strategies of diagnostics and prognostics in the field of liver diseases.

Methodology:

A cross sectional observational study was conducted in territory care hospital of Lahore from ___to___ after seeking ethical board approval. A sample size of 312 patients was taken as per WHO sample size calculator, keeping CI 95% and margin of error 5%. Randomized sampling technique was used to gain sample size. The population comprised of patients with hepatic pathologies of ages 18 years and above seeking treatment in a tertiary care hospital. Demographic data was recorded in the form of age, gender, occupation, residence, educational status, marital status and comorbids. History of drug abuse, alcohol use, substance abuse and sexual history was also taken. History of exposure to Hepatitis B and C was also taken. Informed written consent was taken from all the patients before proceeding to study. Liver function tests including serum ALT, AST, and GGT levels were recorded, as well as serum Bilirubin and serum Albumin. Serum PIVKA-II were also checked in all the study participants. 10cc blood was taken for all these samples and stored in EDTA vial and latter ran on centrifuge machine and was put on analyzer machine latter on. Electrochemiluminescence immunoassay (ECLIA) is a sensitive and validated procedure that was used as a measure of PIVKA-II. The inclusion and exclusion criteria is as follow:

Inclusion Criteria:

1. Known case of hepatic carcinoma, cirrhosis
2. Known case of DCLD
3. Age above 18 years
4. Laboratory, histological or radiological evidence of liver disease
5. Consented for study

Exclusion Criteria:

1. Age less than 18 years
2. Patients with hereditary liver diseases
3. Liver disease secondary to renal or pulmonary insult eg hepatorenal, or hepatopulmonary disease
4. Unwilling for study

Functional statistical analysis was achieved with the use of SPSS (Version 26). Demographic and clinical characteristics were summarized by descriptive statistics (mean, median, standard deviation). Comparisons of the mean PIVKA-II level among the various disease groups were done with t-tests or ANOVA. Pearson or Spearman correlation was done to evaluate relationships between the results of PIVKA-II and indicators of disease (Child-Pugh, MELD score, etc). A value of $P< 0.05$ was taken as significant.

Results:

In the given study a total of 312 participants were included, among them 112 were males and 100 were females. The mean age of all the patients was 58±4 years. All the patients were further divided into 03 groups which included; Hepatocellular carcinoma, cirrhosis, and chronic hepatitis. PIVKA-II levels were measured in all the groups and their co relation was seen. A normal PIVKA-II level typically range in 10.6 to 31.4 mAU/L.

Hepatocellular group was named as group A and it included 130 (41.6%) participants out of 312 total. The patients were further divided into early Hepatocellular cancer (stage I) and late hepatocellular carcinoma (stage III and IV). Among 130 patients, 53 (40.7%) had stage 1 disease and 77 (59.2%) had stage III and IV disease. PIVKA-II levels were recorded, and levels were in the range of 200±7 mAU/L in 47 patients out of 53 in stage I hepatic carcinoma. Similarly, in patients with stage III and IV, the levels were 690±5 in 70 patients out of 77 patients, as illustrated in figure I.

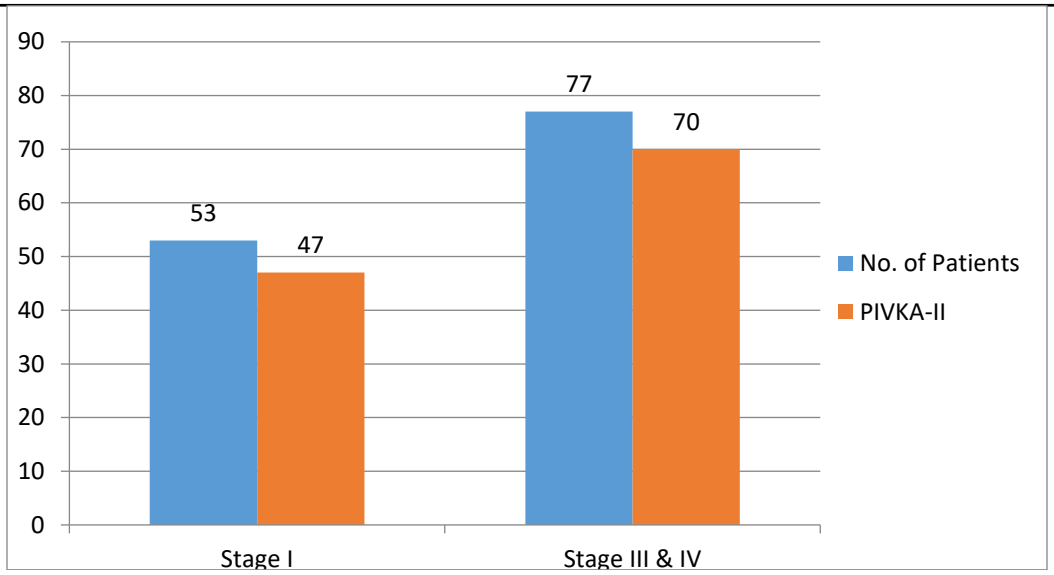


Figure I: Patients in Hepatocellular Ca group showing total number and PIVKA-II positivity

Group B included patients with cirrhosis, and it included 89 (28.5%) patients, Cirrhosis was also divided into compensated and decompensated cirrhosis. 36 (40.4%) patients had compensated cirrhosis and 53 (59.5%) had decompensated cirrhosis. In patients with compensated cirrhosis, 29 had PIVKA-II levels in the range of 150±4 and in decompensated group, there were 45 patients who had PIVKA-II in range of 267±6. Results elaborated in figure II.

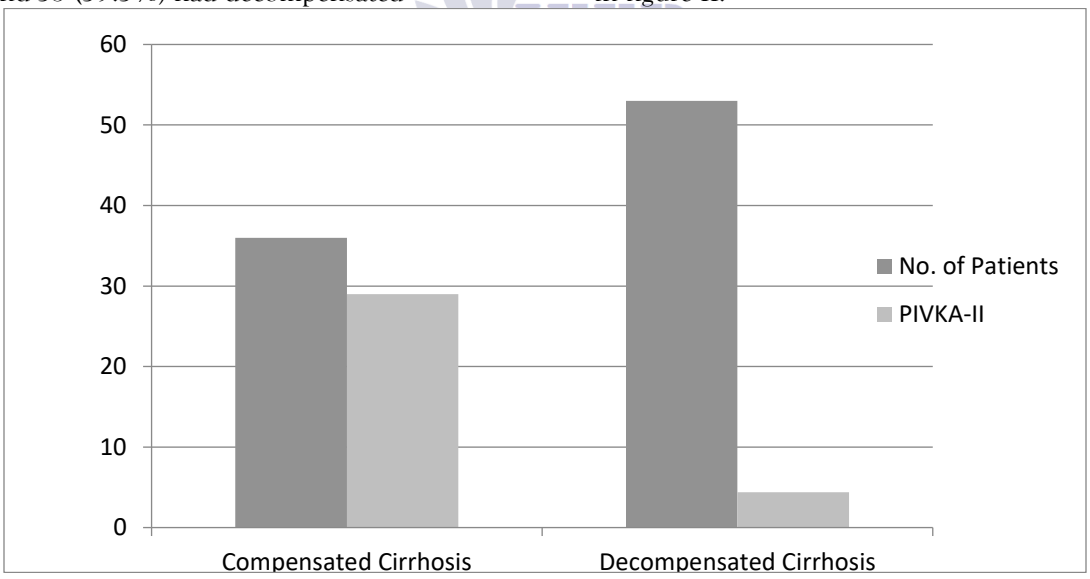


Figure II: Patients in Cirrhosis group showing total number and PIVKA-II positivity

Chronic hepatitis patients were designated in group C. 93 (29.8%) patients were included in this group. Chronic hepatitis was further divided into chronic hepatitis B and hepatitis C infection. 52 (55.9%) patients had chronic hepatitis C infection and 41(44%) patients were suffering from chronic hepatitis B. PIVKA-II levels were raised in both group, with significant elevation in chronic hepatitis C patients. Levels were in the range of 183±8 in hepatitis

C group patients and in hepatitis B patients they were 150±3. 50 patients had raised PIVKA-II levels in chronic hepatitis C sub-group and 36 had raised levels in sub group of hepatitis B.

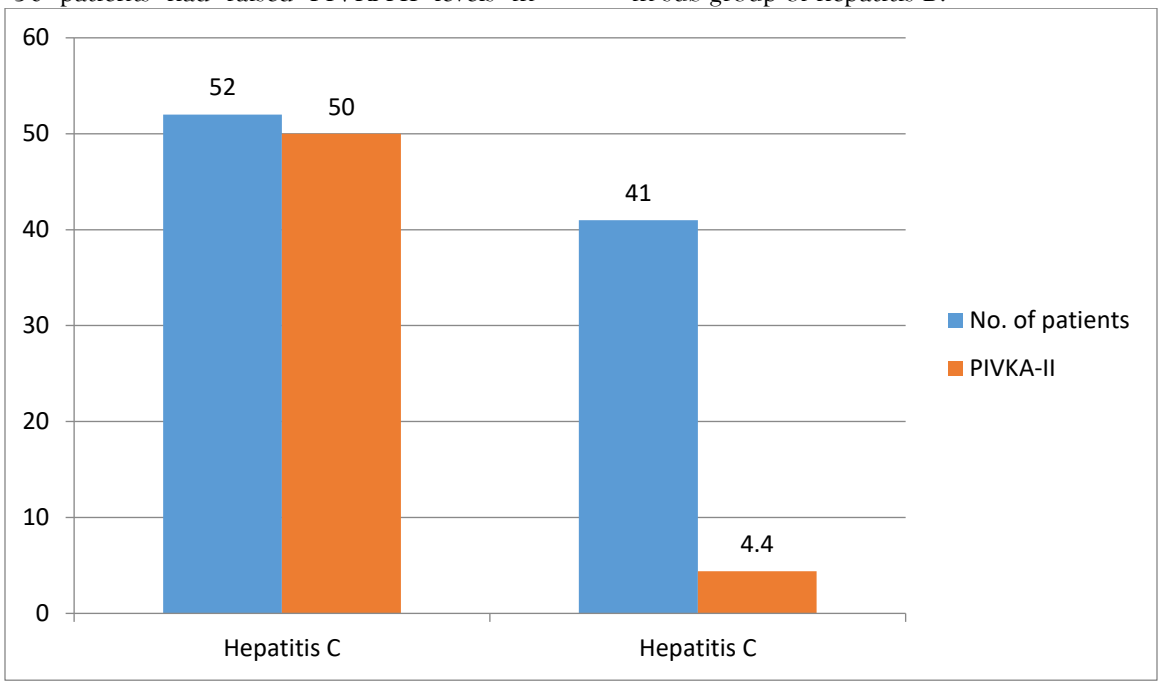
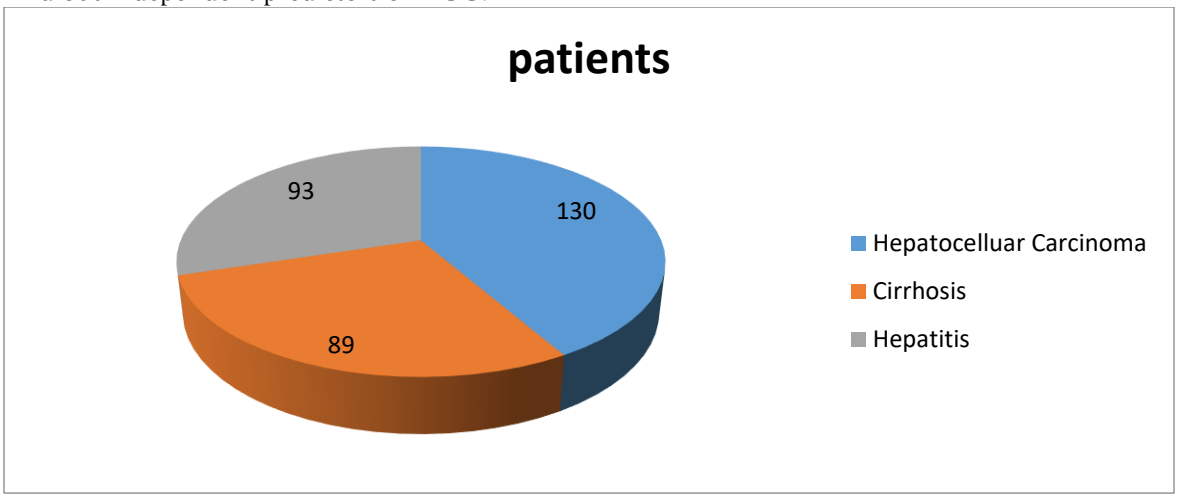


Figure III: Patients in Hepatitis group showing total number and PIVKA-II positivity

A positive association was obtained between PIVKA-II levels and diseases of liver including hepatocellular carcinoma, cirrhosis and chronic hepatitis ($p<.001$). There was no correlation that was significant between PIVKA-II age, sex, and or BMI.

They built a multivariate logistic regression with the aim to find out independent predictors of HCC. Terms entered in the model were PIVKA-II, AFP, Child-Pugh score, age and ALT.The liver functions markers (ALT, AST, bilirubin) showed no independent predictiveness when the tumor markers were adjusted.



Pie Chart showing total number of patients

Discussion:

The purpose of this paper was about the description of the application of Protein Induced by Vitamin K Absence of Antagonist-II (PIVKA-II) in liver diseases particularly hepatocellular cancer (HCC), cirrhosis and chronic hepatitis. A big difference between PIVKA-II and the non-malignant liver disease and healthy controls is that the value was high in patients with HCC, which is consistent with the evidence that exists regarding the specificity of the marker as a tumor marker.

It is worth mentioning that in HCC, the median level of PIVKA-II was elevated compared to past populations (i.e. 644 mAU/mL). It is likely due to the differences in terms of the sample size and the advanced levels of the disease. The ROC analysis that conducted underlined an area under the curve (AUC) of 0.924 of PIVKA when it comes to differentiating between HCC and the other liver disorders which is quite close to what earlier studies (AUC 0.90) had found as well. The threshold of 400 mAU/mL had high sensitivity (88.3%) and specificity (85.7%), which was not inferior to the prior ones (e.g., 291-303 mAU/mL cut-offs in large Chinese populations).[9,10] This further attests to the quality of high PIVKA-II levels as good predictors of malignant transformation even in the setting of negative AFP- our findings indicated that 62% of AFP negative HCC was in the setting of a high PIVKA-II, compared to Fu et al. description of 48% of AFP negative HCC (48%).[11]

AFP is considered a staple of HCC surveillance despite its low sensitivity, particularly in the early disease stages (41 - 65%) . In our analysis PIVKA-II was better than AFP itself. However, the two markers added more to the diagnostic index (AUC ˜0.961), and it reinforced the evidence since, in combination with each other, the sensitivity of the AUC worsened (˜0.86-0.95).[12] Such findings explain why PIVKA-II was identified to be a synergistic valuable diagnostic.

Probably, the most clinically significant find is the idea that PIVKA-II is also increased at the early stages of HCC. On tumors 2cm or below our 78 percent detection rate is superior to AFP and similar to other published-sensitivity ˜74-80 percent AFP PIVKA -II Early stage HCC Rapid diagnosing has practical value since it provides an opportunity to use curative options better, which is why PIVKA-II is of value despite the rather weak AUC (0.692).[13]

As demonstrated in our data PIVKA II had a modest correlation with tumor markers (AFP) and severity scores of disease but weakly with liver enzymes. According to the literature, PIVKA -II is associated with tumor mass, vascular invasion, and poor differentiation according to the work of HBV -HCC, it has been confirmed that PIVKA -II >957mAU/mL, the risk of vascular invasion has greatly increased (OR>3.0) We observed matching of tumor size levels, but as we had non time suffix design we can not generalise about time. In the future, long-term studies are required to define PIVKA II kinetics.[14]

We also had high levels of PIVKA II even in cases of cirrhosis and chronic hepatitis. This compares with previous "false positive" results: 14 of 171 cirrhotic patients were above 40mAU/mL and Tianjin cohort demonstrated benign liver disease PIVKA-II at median 85 against 1,245 in HCC.[15] Etiologically, cholestasis, or biliary disease/VK deficiency could be posets that cause the non malignant elevations of PIVKA-II. Idial cut- offs would however then be tailored to fit clinical situations so as to make sure that there would be the fewest false positives. Higher concentrations of PIVKAII (>221 mAU/mL) were described to have moderate power (AUC 0.73 - 0.84) to determine portal vein tumor thrombosis (PVTT) in our cohort of retrospective data . PVTT is one of the largest prognostic factors, and this correlation shows that PIVKA-II, besides the ability to be tested as a disease indicator, may also be tested as a prognostic factor. We can think of PIVKA-II in the model of risk stratification in prospective studies.[16]

Overall, PIVKA-II is an effective performing mark in the diagnosis of HCC especially when used together with AFP and it even supersedes them in the early stages of the disease. It holds a lot of promise in its application in the diagnosis of PVTT, and post-resectional recurrence. To make clinical applicability of advantage. Serial PIVKA-II monitoring (especially in cirrhotics) may allow earlier discovery of tumors; serial PIVKA-II monitoring has shown the potential to cause imaging in up to 24 percent of patients many months earlier .Multi-Marker/Vivo Models: made by adding AFP-L3, AST, age, or gender to the combination with PIVKA ^{ - }II has allowed diagnostic accuracy to become as high as 0.95 . PIVKA-II- PIVKA-II can also be applied to a composite algorithm and joined with an imaging and

clinical risk factor to help in triaging and individual surveillance.

The timeline monitoring of the tendencies of a post-treatment PIVKA-II can offer early issue of relapse or continuing of the illness as demonstrated by Cheng et al., what supports the importance of observing biomarkers dynamically. The contrary to the AFP, PIVKA-II is less evenly influenced by inflammation or harmless liver disease, and has greater specificity.[17]

Taking an example, the study conducted by Liebman et al. and Koike et al. reported that, among the population with advanced cirrhosis, the specificity was high (~9598%) .This takes our findings a step further since the levels were mainly high in HCC (median approx 1,545 mAU/mL). The fact that the mechanism exists in the malignant cells and is absent in the health regeneration of hepatocytes secreted by AFP makes PIVKA-II a prognatically useful marker in a very different though representative relatedness manner as well . PiVKAII has also outstanding effects as a prognostic tool outside diagnosis. Application of meta-analysis on post-ablation groups of PIVKA-II HCCs (5,647 patients) revealed that the high values of PIVKA-II were allied to the reduced overall (HR1.59) and recurrence-free survival (HR1.76).[18]

Similarly, longitudinal taludese treatment response (e.g. UK Oncotarget cohort) documented that the decline in PIVKA - II after treatment was associated with algorithmic tumor regression whereas those with high PIVKA - II after treatment were signaling vascular invasion and relapse.The multivariate model established in the current study incorporating PIVKA - II with AFP and clinical features is an indication that it has its own independent predictive value and this explains why it is valuable in monitoring the patients in the post treatment phase, particularly after surgery The increase in PIVKA-II was step-by-step reported by Caviglia et al. before the diagnosis of HCC among the antiviral-treated patients compared to controls The triple risk of HCC was also observed in HBV-related cirrhosis (HR 2.46) in PIVKA-II 50 mAU / mL in the presence of virological remission The tripled risk of HCC was also observed in HBV-related cirrhosis (HR 2.46) in PIVKA-II 5.[19]

We can observe these tendencies in our research with patients with HCC having a similar tendency of registering a rise in PIVKA-II over time. Thus, being one of the single-use diagnostic tools, PIVKA-lII presentation is an active signal of the dynamic risk analysis and observation.

More recent trials concern the validity of PIVKA-II in both criteria of the candidate and surveillance of the post-transplant liver. Review of Heliyon article mentioned that PIVKA -II in pre-LT was related to microvascular invasion and recurrence and long terms outcome, and PIVKA-II marked model could be used matter to select patients and donors The incorporation of PIVKA-II may improve prognostication and allocation, as well, in cases where imaging is flawed or inconclusive.[20]

Besides being tagged as the role of a simple biomarker, PIVKA-II may also be actively involved in the process of tumor biology. It is structurally similar to hepatocellular growth factor and it stimulates VEGF and EGF pathways that stimulate angiogenesis, invading, and metastasizing . The latter properties provide an explanation as to why it is said to be associated with vascular invasion and microvascular metastasis- as represented by the developed occurrence of said condition in cases of portal vein tumor thrombus increased rates. Therefore, PIVKA-II may become both a marker and a booster of the tumor process. The treatment of its pathway may in future limit angiogenic signalling in HCC.In the past, PIVKA-II had been applied in East Asian regions, but its good application is evidenced by increasing Western validation. Durazo et al. has shown its excellence in the HCV infected American cohorts over AFP and AFP-L3. A future UK research revealed that PIVKA II mirrored activities that used modalities of imaging detected reactions as well as treatment practices . Its compatibility with the non-Asian population group is also ensured by the fact that the test shows greater results in cirrhosis and HCC cases, as proven by the Italian validations.[21]

Our study highlighted that PIVKA-II levels have significance in various hepatic diseases and help guide treatment protocols and prognosis. The levels rise significantly in liver cancer, followed by cirrhosis and chronic hepatitis. Raised levels in liver cancer carries prognostic value as evident from various international studies.

Funding: NIL

Conflict of Study: Nil

Limitation:

Single center study, moreover PIVKA-II asssays not available easily in all laboratories. Hence performing study is difficult on large population because of technical difficulties. However, the study serves as becon for further studies in this niche.

Conclusion:

PIVKA Overall, PIVKA-II can be used as an effective practice support in HCC and signs its high specificity, dynamic prognostic potential, and close understanding of tumor pathophysiology. The high parameters provide an indication of malignancy, invasion of vessels, and subsequent reoccurrence of the post-therapeutic condition. It maximizes the initial detection and surveillance when used together with AFP and imaging (e.g. by means of composite models). The road ahead remains not smooth-however, an adequate focused standardization, along with the cost analysis and mechanistic studies have the potential of elevating PIVKA 21 to the pedestal of a leading clinical technology in the field of hepatology.

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