PIVKA-II Combined with Alpha-Fetoprotein for the Diagnostic Value of Hepatic Tumors in Children: A Multicenter, Prospective Observational Study

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Research

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Abstract

Background:

We aimed to investigate whether the protein induced by the vitamin K antagonist-II (PIVKA-II) combined with alpha-fetoprotein (AFP) can improve the diagnostic and differential diagnostic accuracy of childhood hepatic tumors.

Methods:

A multicenter prospective observational study was performed at nine regional institutions around China from October 1, 2018 to September 30, 2020, and a total of 257 eligible patients were enrolled. Children with confirmed hepatic masses were placed in the test group (Group T, n=144) and divided into the hepatoblastoma group (Group T_{HB}, n=98) and the hemangioendothelioma group (Group T_{HE}, n=46), and children with extrahepatic abdominal masses were placed in the control group (Group C, n=113). Peripheral blood was collected from each patient prior to surgery or chemotherapy. Receiver operating characteristic (ROC) curves and area under the curve (AUROC) were used to evaluate the diagnostic and differential diagnostic efficiency.

Results:

The mean levels of PIVKA-II and AFP were both significantly higher in Group T than in Group C ($P=0.001$, $P=0.001$) and in Group T_{HB} than in Group T_{HE} ($P=0.018$, $P=0.013$). For the diagnosis performance, PIVKA-II had a sensitivity of 86.7% and a specificity of 81.3% at a cutoff of 32.6 mAU/ml vs. 84.1% and 81.8% for AFP at a cutoff of 120 ng/ml (AUROC 0.867 vs. 0.857, respectively). The combination of PIVKA-II and AFP had higher sensitivity (88.5%), specificity (84.7%) and AUROC (0.891) than PIVKA-II or AFP alone. The differential diagnostic value of PIVKA-II and AFP in differentiating hepatoblastoma from hemangioendothelioma was further assessed. PIVKA-II had a sensitivity of 71.7% and a specificity of 88.7% at a cutoff of 47.1 mAU/ml, and there was 63.0% and 78.6% of AFP at a cutoff of 560 ng/ml (AUROC 0.876 vs. 0.743, respectively). The combined markers also showed a higher sensitivity (72.7%), a higher specificity (91.8%) and a higher AUROC (0.895) than PIVKA-II or AFP alone.

Conclusions:

The serum level of PIVKA-II was significantly higher in children with hepatic tumors, especially those with malignant tumors. PIVKA-II had superior sensitivity and specificity in the diagnosis of childhood hepatic tumors. The combination of PIVKA-II and AFP further increased the diagnostic performance.

Trial registration: Clinical Trials, NCT03645655. Registered 20 August 2018, <https://www.clinicaltrials.gov/ct2/show/NCT03645655>

Background

Although hepatic tumors rarely occur during childhood, they are associated with significantly higher morbidity and mortality in affected patients. Hepatoblastoma (HB) is the most common malignant hepatic tumor in children under the age of 3 years (1), and comprise approximately 5% of the total neoplasms of various types occurring in young children(2). The clinical features of HB are nonspecific but include the presence of an upper abdominal mass, loss of appetite, weight loss, anemia, jaundice, and ascites, all of which can seriously endanger the lives and health of children.

Hemangioendothelioma (HE) is the most common hepatic vascular tumor in infants less than 6 months of age, with a prevalence of 1% (3). Most patients with HE present with an asymptomatic abdominal mass and hepatomegaly, but these tumors may be associated with high-output cardiac failure due to the presence of arteriovenous shunts within the tumor.

Monitoring and early diagnosis play a vital role in the treatment of childhood hepatic tumors. In some clinical practices, ultrasound and contrast-enhanced computed tomography (CECT) are used as the primary modalities for the evaluation of palpable abdominal masses and the screening of hepatic masses (4, 5).

Although alpha-fetoprotein (AFP) has been recognized as a biomarker of hepatic tumors (6), it is not always elevated in all hepatic tumor cases. Elevated AFP levels alone are not sufficient for the diagnosis of hepatic tumors due to the physiological elevation seen in normal infants during the first 2 months and because of their association with other primary tumors (7).

The protein induced by the vitamin K antagonist-II (PIVKA-II) is also known as des-γ-carboxyprothrombin (DCP) or carboxy prothrombin and is an abnormal form of prothrombin induced by the absence of vitamin K or antagonist-II(8). Motohara, K reported PIVKA-II levels were highly elevated in all three hepatoblastoma patients in 1987; plasma PIVKA-II might be useful as a new marker of hepatoblastoma (9).

Elevation of PIVKA-II, due to an excess production by tumor cells, has been shown to be associated with hepatocellular carcinoma (HCC) (8, 10, 11). Many studies have demonstrated the clinical value of PIVKA-II for HCC surveillance, and PIVKA-II has been recommended by the guidelines of the Japan Society of Hepatology (JSH) (12).

Theoretically, AFP and PIVKA-II are independently produced by tumors and are not correlated with one another. The diagnostic accuracy was better when using a combination of the biomarkers, AFP and PIVKA-II, compared to each marker alone for detecting HCC and early HCC in cirrhotic patients (13–15). Measurement of both PIVKA-II and AFP levels may yield useful information on the treatment response and prognosis in HCC patients (16, 17).

Given their application in HCC, we intend to investigate whether PIVKA-II combined with AFP can also improve the diagnostic and differential diagnostic accuracy of childhood hepatic tumors.

Methods

Study design

This is a multicenter prospective observational study sponsored by the Shanghai Children's Medical Center and joined by nine regional institutions around China, including the Children's Hospital of Fudan University, the Children's Hospital of Chongqing Medical University, the Children's Hospital of Nanjing Medical University, the Qilu Children's Hospital of Shandong University, the Children's Hospital Affiliated to Zhengzhou University, the Anhui Provincial Children's Hospital, the Sun Yat-Sen Memorial Hospital, the Sun Yat-Sen University and the First Affiliated Hospital of Anhui Medical University. The study was conducted in accordance with the Declaration of Helsinki, and all participating centers obtained the relevant Institute Review Board ethics committee approval before patient enrollment. The study was registered in <http://register.clinicaltrials.gov> as NCT03645655.

Eligible population

Children (age ≤ 144 months) first diagnosed with an abdominal mass in the pediatric general surgery inpatient department from October 1, 2018 to September 30, 2020 were consecutively enrolled in this study. The clinical diagnoses and differential diagnoses were based on contrast-enhanced computed tomography (CECT), histopathology, or both according to the International Childhood Liver Tumors Strategy Group (SIOPEL) protocols (18). A cavitation ultrasonic surgical aspirator (Soering GmbH) was used for tumor biopsies and resections, which was safe and reliable. Children confirmed to have a hepatic mass were placed in the testing group (Group T) and were further divided into the hepatoblastoma group (Group T_{HB}) and the hemangioendothelioma group (Group T_{HE}); the other children confirmed to have an extrahepatic abdominal mass were placed in the control group (Group C). Informed consent was obtained from each child's legal guardian. Children with extra-abdominal tumors, ongoing vitamin K or warfarin treatment or lacking informed consent were excluded from this study.

Laboratory measurements

Peripheral blood was collected from each patient prior to any treatment (surgery and/or chemotherapy). Blood samples were centrifuged, and serum was aliquoted and stored at -80°C. All serum samples were tested in a single center to decrease the possibility of bias. Serum levels of AFP and PIVKA-II were determined by a chemiluminescence enzyme immunoassay (CLEIA) (ARCHITECH 2000, Abbott Laboratory, US) using an enzyme-linked immunosorbent assay kit (Abbott Laboratory, US) per the manufacturer's instructions. All samples were analyzed in duplicate.

Sample size calculation

A sample size calculation was performed using PASS 15.0 (Power Analysis and Sample Size software, NCSS, Kaysville, UT, US) using the log-rank test. The planned sample size was determined after assuming the use of a 2-sided log-rank test with a type I error rate of 0.05 and a statistical power of 90%. A dropout

rate of up to 20% was factored into the computations. Ninety-three patients in each group were asked to participate in this study.

Statistical analysis

Student's *t* test (or Wilcoxon test) was used to compare the continuous variables, and the chi-square test (or Fisher's exact test) was used for the categorical variables. The average tumor marker levels were compared between Group T and Group C and between Group T_{HB} and Group T_{HE}. Receiver operating characteristic curves (ROCs) and area under the ROC curve (AUROC) were used to assess the diagnostic and differential diagnostic efficiencies of PIVKA-II, AFP and the combination of the two tumor markers. A two-sided *P* value less than 0.05 was considered statistically significant. All statistical analyses were carried out with SPSS version 20.0 (SPSS Inc., an IBM Company, Chicago, IL, US).

Results

Patient characteristics

A total of 257 eligible patients were enrolled in this study from October 1, 2018, to September 30, 2020. Table 1 shows the demographics of the participants. A total of 144 patients (mean age 24.4 ± 28.5 months) were confirmed to have hepatic masses (Group T), 98 patients (mean age 28.4 ± 31.6 months) were diagnosed with hepatoblastoma (Group T_{HB}), 46 patients (mean age 16.0 ± 18.2 months) were diagnosed with hemangioendothelioma (Group T_{HE}), and the other 113 patients (mean age 35.8 ± 28.9 months) were confirmed to have extrahepatic abdominal masses (Group C). There were no significant differences in age ($P = 0.156$), sex ($P = 0.159$), aspartate amino transferase (AST, $P = 0.262$), alanine amino transferase (ALT, $P = 0.442$), gamma-glutamyl transpeptidase (GGT, $P = 0.924$), total protein (TP, $P = 0.604$), albumin (ALB, $P = 0.083$) or total bilirubin (TBIL, $P = 0.897$) between Group T and Group C. Patients in Group T_{HE} were younger than Group T_{HB} ($P = 0.014$); except for AST ($P = 0.035$), there were no significant differences in sex ($P = 0.075$), ALT ($P = 0.218$), GGT ($P = 0.779$), TP ($P = 0.564$), ALB ($P = 0.378$), or TBIL ($P = 0.092$) between Group T_{HB} and Group T_{HE}.

Table 1
Baseline characteristics of patients

	Group T	Group C	<i>P</i>	Group T _{HB}	Group T _{HE}	<i>P</i>
Sample size	144	113		98	46	
Age (Month)	24.4 ± 28.5	35.8 ± 28.9	0.156	28.4 ± 31.6	16.0 ± 18.2	0.014
Gender			0.159			0.075
Male n(%)	79 (54.9)	52 (46.0)		53 (54.1)	26 (56.5)	
Female n(%)	65 (45.1)	61 (54.0)		45 (45.9)	20 (43.5)	
AST (UI/l)	52.944 ± 30.352	50.575 ± 35.833	0.262	56.591 ± 31.500	45.174 ± 26.421	0.035
ALT (UI/l)	31.458 ± 18.987	30.832 ± 32.638	0.442	32.800 ± 21.471	28.609 ± 11.816	0.218
GGT (UI/l)	31.479 ± 25.966	25.319 ± 45.375	0.924	31.898 ± 21.287	30.587 ± 34.126	0.779
TP (g/l)	63.217 ± 7.428	69.133 ± 8.352	0.604	63.462 ± 6.522	62.694 ± 9.123	0.564
ALB (g/l)	41.522 ± 5.553	42.412 ± 6.390	0.083	41.241 ± 4.783	42.120 ± 6.941	0.378
TBIL (μmol/l)	17.172 ± 14.139	15.988 ± 22.637	0.897	18.534 ± 14.287	14.272 ± 13.516	0.092
Group T: hepatic mass group, Group C: extrahepatic abdominal mass group, Group T _{HB} : hepatoblastoma group, Group T _{HE} : hemangioendothelioma group. AST: aspartate amino transferase, ALT: alanine amino transferase, GGT: gamma-glutamyl transpeptidase, TP: total protein, ALB: albumin, TBIL: total bilirubin.						

Serum Levels Of Pivka-ii And Afp

Serum PIVKA-II and AFP levels were compared between the patients in the hepatic mass group and the patients in the control group and between the patients in the hepatoblastoma group and the patients in the hemangioendothelioma group. The mean level of PIVKA-II in Group T was 717.687 ± 3026.936 mAU/mL, which was significantly higher than that of Group C (29.954 ± 24.924 mAU/mL, $P = 0.001$) (Fig. 1A). The mean level of AFP in Group T was significantly higher than that in Group C (6982.617 ± 17833.972 ng/mL vs 226.368 ± 772.413 ng/mL, $P = 0.001$) (Fig. 1B).

A similar trend was found in serum PIVKA-II and AFP levels between Group T_{HB} and Group T_{HE}. Serum levels of PIVKA-II and AFP were both significantly higher in Group T_{HB} than Group T_{HE} (PIVKA-II: 1025.091 ± 3634.021 mAU/mL vs 62.467 ± 68.900 mAU/mL, $P = 0.018$; AFP: 9504.202 ± 21023.325 ng/mL vs 1610.545 ± 3825.377 ng/mL, $P = 0.013$) (Fig. 1C, 1D).

Diagnostic values of PIVKA-II and AFP in childhood hepatic tumor patients

To evaluate the diagnostic value of PIVKA-II and AFP in childhood hepatic tumor patients, ROC curves were plotted to identify the cutoff values that would best differentiate hepatic tumor patients from controls. The area under the ROC curve (AUROC) of PIVKA-II was 0.867 (95% CI 0.822–0.911, $P < 0.001$), and the AUROC of AFP was 0.857 (95% CI 0.808–0.906, $P < 0.001$). The optimal cutoff value of PIVKA-II was 32.6 mAU/ml, the sensitivity was 86.7%, and the specificity was 81.3%. The optimal cutoff value of AFP was 120 ng/ml, the sensitivity was 84.1%, and the specificity was 81.9%. Serum levels of PIVKA-II and AFP were then combined to obtain a new marker for childhood hepatic tumor diagnosis. ROC analysis showed that PIVKA-II + AFP further increased the diagnostic efficiency. The AUROC was 0.891 (95% CI 0.850–0.933), higher than that of PIVKA-II or AFP alone. The combined sensitivity and specificity were 88.5% and 84.7%, respectively (Fig. 2A).

Differential diagnostic values of PIVKA-II and AFP in hepatoblastoma patients

To further assess the diagnostic value of PIVKA-II and AFP levels in differentiating hepatoblastoma patients from hemangioendothelioma patients, another ROC curve was constructed. The AUROC of PIVKA-II was 0.876 (95% CI 0.818–0.934, $P < 0.001$), and the AUROC of AFP was 0.743 (95% CI 0.651–0.835, $P < 0.001$). The optimal cutoff value of PIVKA-II was 47.1 mAU/ml, sensitivity was 71.7% and specificity was 88.7%. The optimal cutoff value of AFP was 560 ng/ml, sensitivity was 63.0% and specificity was 78.6%. ROC analysis showed that PIVKA-II + AFP further increased the differential diagnostic efficiency. The AUROC was 0.895 (95% CI 0.841–0.948), which was higher than that of PIVKA-II or AFP alone. The combined sensitivity and specificity were 72.7% and 91.8% (Fig. 2B).

Discussion

Regular monitoring and an early diagnosis of childhood tumors can improve the clinical course and treatment response, which ultimately improves long-term outcomes (19). The blood tumor markers that are described in this study can be considered good indicators and can provide an acceptable diagnostic accuracy and are convenient and cost-effective.

The results of this study showed that hepatic tumor patients had significantly higher serum levels of PIVKA-II and AFP than extrahepatic abdominal tumor patients.

Prothrombin glutamate carboxylation in the liver gives rise to normal prothrombin, which contains 10-carboxylic glutamate residues. The process depends on the presence of vitamin K. In pathological states

when vitamin K is too low or in the presence of a vitamin K-dependent antagonist of carboxylase, the insufficient carboxylation of glutamic acid results in the production of PIVKA-II(20).

Motohara K. et al. reported that vitamin K treatment in two hepatoblastoma patients resulted in only a moderate reduction in PIVKA-II levels. An immunohistochemical study of liver tissue showed the presence of PIVKA-II in hepatoblastoma cells (9). Maha F. et al. reported similar outcomes; after vitamin K administration, PIVKA-II levels decreased in both the chronic hepatitis group ($P = 0.022$) and the cirrhosis group ($P = 0.024$) but not in the HCC group ($P = 0.187$) (21). These findings suggested that the elevation of PIVKA-II in patients with liver tumors was not due to deficiency in the nutrient vitamin K but due to the overproduction of PIVKA-II in tumor cells.

The subgroup analysis showed that PIVKA-II and AFP levels in patients with malignant hepatoblastoma were higher than those in patients with the benign tumor, hemangioendothelioma, in our study.

Imamura et al. reported that serum PIVKA-II levels were significantly elevated in patients with more aggressive tumor characteristics (22). Recently, many studies have demonstrated that elevated serum PIVKA-II is related to larger tumor size, more frequent vascular invasion, more intrahepatic metastasis, and recurrence after treatment(23).

A couple of previous studies reported that the optimal cutoff value of serum PIVKA-II for HCC diagnosis was estimated to range from 30 to 42 mAU/ml(24). The ROC curve analysis showed that the optimal cutoff value of PIVKA-II for the diagnosis of childhood hepatic tumors was 32.6 mAU/ml and that for differentiating hepatoblastoma from hemangioendothelioma was 47.1 mAU/ml. The cutoff values of serum PIVKA-II for the diagnosis of hepatic tumors in children and adults were similar and were not affected by age.

In previous studies, the sensitivity of PIVKA-II in the diagnosis of HCC was 51.0%-77%, the specificity was 67.8%-91.2%, and the AUROC was 0.701–0.854, all of which were higher than the sensitivity, specificity, and the AUROC of AFP (17, 25, 26). In our study, the sensitivity, specificity and AUROC of PIVKA-II in the diagnosis of childhood hepatic tumors and in the differentiation of hepatoblastoma from benign hepatic tumors were all higher than AFP. PIVKA-II is a good marker with good sensitivity and specificity in the diagnosis of hepatic tumors in both children and adults.

Serum PIVKAII and AFP are produced through different mechanisms. AFP secretion in HCC results from a reexpression of a fetal antigen in the tumor, and PIVKA-II results from an independently acquired posttranslational defect in protein processing(27). Therefore, the two markers are independent from each other in the diagnosis of hepatic tumors(28). A few studies reported that PIVKA-II combined with AFP had great advantages as a biomarker for HCC screening(29, 30). The maximum AUROC was 0.846, which was higher than that of PIVKA-II or AFP alone(31). We further evaluated the diagnostic performance of the combination of the two markers. The results showed that the combination of PIVKA-II and AFP further increase the efficiency for the diagnosis of childhood hepatic tumors (AUROC = 0.891) and for the

differentiation of hepatoblastoma from benign hepatic tumors (AUROC = 0.895). Our study was broadly consistent with these findings.

Conclusion

This study demonstrated that the serum level of PIVKA-II was significantly higher in childhood patients with hepatic tumors, especially in those with malignant tumors. As a biomarker, PIVKA-II had superior sensitivity and specificity in the diagnosis of hepatic tumors, and its cutoff value was not affected by age. The combination of PIVKA-II with AFP further increased the diagnostic performance. Therefore, serum PIVKA-II combined with AFP levels may be considered a screening marker for the clinical diagnosis of childhood hepatic tumors.

Abbreviations

PIVKA-II

protein induced by vitamin K antagonist-II; AFP:α-fetoprotein; ROC:receiver operating characteristics; AUROC:area under the curve; HB:hepatoblastoma; HE:hemangioendothelioma; CECT:contrast-enhanced computed tomography; DCP:des-γ-carboxyprothrombin; HCC:hepatocellular carcinoma; JSH:Japan Society of Hepatology; SIOPEL:International Childhood Liver Tumors Strategy Group; CLEIA:chemiluminescence enzyme immunoassay.

Declarations

Ethics approval and consent to participate.

This study was approved by the Institutional Review Board of the Shanghai Children's Medical Center affiliated with the Shanghai Jiao Tong University of Medicine (SCMCIRB-K2017027). All patients' parents/guardians provided written informed consent.

Consent for publication

Not applicable.

Competing interests

None declared.

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Authors' Contributions H.G., M.X., S.G. conceived of and designed the study. R.D., S.W., Y.F., Y.W., X.Z., X.L., Y.L. and W.L. made substantial contributions to study design. H.G., C.X., R.D., S.W., Y.F., Y.W., X.Z., X.L., Y.L. and W.L. were responsible for collecting data. J.W., J.M. Y.Z. and Q.P. were responsible for laboratory measurement. S.L. and L.X. provided statistical support. H.G. and C.X. drafted the manuscript. All authors were involved in critically reviewing the manuscript, and all gave final approval of the version to be published.

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Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

References

1. Brown J, Perilongo G, Shafford E, Keeling J, Pritchard J, Brock P, et al. Pretreatment prognostic factors for children with hepatoblastoma– results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. *European journal of cancer*. 2000;36(11):1418–25.
2. Isaacs H. Jr. Fetal and neonatal hepatic tumors. *Journal of pediatric surgery*. 2007;42(11):1797–803.
3. Lazarevic V, Gaia N, Girard M, Leo S, Cherkaoui A, Renzi G, et al. When Bacterial Culture Fails, Metagenomics Can Help: A Case of Chronic Hepatic Brucelloma Assessed by Next-Generation Sequencing. *Frontiers in microbiology*. 2018;9:1566.
4. Baheti AD, Luana Stanescu A, Li N, Chapman T. Contrast-enhanced CT features of hepatoblastoma: Can we predict histopathology? *Clinical imaging*. 2017;44:33–7.
5. Li J, Wang J, Duan Y, Wang H, Dong C, Xu W. Comparison between infantile hepatic hemangioendothelioma and hepatoblastoma in pediatric patients: clinical manifestations and contrast-enhanced computed tomography features. *Minerva pediatrica*. 2018;70(5):497–8.
6. Finegold MJ, Lopez-Terrada DH, Bowen J, Washington MK, Qualman SJ. College of American P. Protocol for the examination of specimens from pediatric patients with hepatoblastoma. *Arch Pathol Lab Med*. 2007;131(4):520–9.
7. Musick SR, Babiker HM. Cancer, Hepatoblastoma. *StatPearls*. Treasure Island (FL)2019.

8. Liebman HA, Furie BC, Tong MJ, Blanchard RA, Lo KJ, Lee SD, et al. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. *N Engl J Med*. 1984;310(22):1427–31.
9. Motohara K, Endo F, Matsuda I, Iwamasa T. Acarboxy prothrombin (PIVKA-II) as a marker of hepatoblastoma in infants. *J Pediatr Gastroenterol Nutr*. 1987;6(1):42–5.
10. Fujiyama S, Morishita T, Hashiguchi O, Sato T. Plasma abnormal prothrombin (des-gamma-carboxy prothrombin) as a marker of hepatocellular carcinoma. *Cancer*. 1988;61(8):1621–8.
11. Zinkin NT, Grall F, Bhaskar K, Otu HH, Spentzos D, Kalmowitz B, et al. Serum proteomics and biomarkers in hepatocellular carcinoma and chronic liver disease. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2008;14(2):470–7.
12. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Digestive diseases*. 2011;29(3):339–64.
13. Lim TS, Kim DY, Han KH, Kim HS, Shin SH, Jung KS, et al. Combined use of AFP, PIVKA-II, and AFP-L3 as tumor markers enhances diagnostic accuracy for hepatocellular carcinoma in cirrhotic patients. *Scand J Gastroenterol*. 2016;51(3):344–53.
14. Park H, Kim SU, Park JY, Kim DY, Ahn SH, Chon CY, et al. Clinical usefulness of double biomarkers AFP and PIVKA-II for subdividing prognostic groups in locally advanced hepatocellular carcinoma. *Liver international: official journal of the International Association for the Study of the Liver*. 2014;34(2):313–21.
15. Katzenstein HM, Langham MR, Malogolowkin MH, Krailo MD, Towbin AJ, McCarville MB, et al. Minimal adjuvant chemotherapy for children with hepatoblastoma resected at diagnosis (AHEP0731): a Children's Oncology Group, multicentre, phase 3 trial. *The Lancet Oncology*. 2019;20(5):719–27.
16. Gentile I, Buonomo AR, Scotto R, Zappulo E, Carriero C, Piccirillo M, et al. Diagnostic Accuracy of PIVKA-II, Alpha-Fetoprotein and a Combination of both in Diagnosis of Hepatocellular Carcinoma in Patients Affected by Chronic HCV Infection. *In vivo*. 2017;31(4):695–700.
17. Pote N, Cauchy F, Albuquerque M, Voitot H, Belghiti J, Castera L, et al. Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascular invasion. *Journal of hepatology*. 2015;62(4):848–54.
18. Busweiler LA, Wijnen MH, Wilde JC, Sieders E, Terwisscha van Scheltinga SE, van Heurn LW, et al. Surgical treatment of childhood hepatoblastoma in the Netherlands (1990–2013). *Pediatr Surg Int*. 2017;33(1):23–31.
19. Zhang SK, Sun XB. Achievements and challenges for childhood cancer in China. *Annals of translational medicine*. 2015;3(22):366.
20. Liebman HA. Isolation and characterization of a hepatoma-associated abnormal (des-gamma-carboxy)prothrombin. *Cancer research*. 1989;49(23):6493–7.

21. Saja MF, Abdo AA, Sanai FM, Shaikh SA, Gader AG. The coagulopathy of liver disease: does vitamin K help? Blood coagulation & fibrinolysis: an international journal in haemostasis and thrombosis. 2013;24(1):10–7.
22. Imamura H, Matsuyama Y, Miyagawa Y, Ishida K, Shimada R, Miyagawa S, et al. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. Br J Surg. 1999;86(8):1032–8.
23. Park H, Park JY. Clinical significance of AFP and PIVKA-II responses for monitoring treatment outcomes and predicting prognosis in patients with hepatocellular carcinoma. BioMed research international. 2013;2013:310427.
24. Wang BL, Tan QW, Gao XH, Wu J, Guo W. Elevated PIVKA-II is associated with early recurrence and poor prognosis in BCLC 0-A hepatocellular carcinomas. Asian Pacific journal of cancer prevention: APJCP. 2014;15(16):6673–8.
25. Jang ES, Jeong SH, Kim JW, Choi YS, Leissner P, Brechot C. Diagnostic Performance of Alpha-Fetoprotein, Protein Induced by Vitamin K Absence, Osteopontin, Dickkopf-1 and Its Combinations for Hepatocellular Carcinoma. PloS one. 2016;11(3):e0151069.
26. Li C, Zhang Z, Zhang P, Liu J. Diagnostic accuracy of des-gamma-carboxy prothrombin versus alpha-fetoprotein for hepatocellular carcinoma: A systematic review. Hepatology research: the official journal of the Japan Society of Hepatology. 2014;44(10):E11–25.
27. Weitz IC, Liebman HA. Des-gamma-carboxy (abnormal) prothrombin and hepatocellular carcinoma: a critical review. Hepatology. 1993;18(4):990–7.
28. Lefrere JJ, Armengaud D, Leclercq M, Guillaumont M, Gozin D, Alagille D. Des-gamma-carboxyprothrombin and hepatoblastoma. J Clin Pathol. 1988;41(3):356.
29. Viggiani V, Palombi S, Gennarini G, D'Ettorre G, De Vito C, Angeloni A, et al. Protein induced by vitamin K absence or antagonist-II (PIVKA-II) specifically increased in Italian hepatocellular carcinoma patients. Scand J Gastroenterol. 2016;51(10):1257–62.
30. Ertle JM, Heider D, Wichert M, Keller B, Kueper R, Hilgard P, et al. A combination of alpha-fetoprotein and des-gamma-carboxy prothrombin is superior in detection of hepatocellular carcinoma. Digestion. 2013;87(2):121–31.
31. Yu R, Ding S, Tan W, Tan S, Tan Z, Xiang S, et al. Performance of Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) for Hepatocellular Carcinoma Screening in Chinese Population. Hepatitis monthly. 2015;15(7):e28806.

Figures

Figure 1

Serum levels of PIVKA-II and AFP. (A, B) Serum PIVKA-II and AFP levels in Group T and Group C patients; (C, D) Serum PIVKA-II and AFP levels in Group THB and Group THE patients. PIVKA-II: protein induced by vitamin K absence-II, AFP: alpha-fetoprotein. Group T: hepatic mass group, Group C: extrahepatic abdominal mass group, Group THB: hepatoblastoma group, Group THE: hemangioendothelioma group.

Figure 2

Diagnostic values of PIVKA-II and AFP in childhood hepatic tumor patients. A The AUROCs of PIVKA-II, AFP and PIVKA-II + AFP for the diagnosis of hepatic tumors were 0.867, 0.857 and 0.891, respectively. B The AUROCs of PIVKA-II, AFP and PIVKA-II + AFP to differentiate hepatoblastoma from hemangioendothelioma patients were 0.876, 0.743 and 0.895, respectively. PIVKA-II: protein induced by vitamin K absence-II, AFP: alpha-fetoprotein.