DOI: https://doi.org/10.54393/pjhs.v5i07.1804

PAKISTAN JOURNAL OF HEALTH SCIENCES
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 7 (July 2024)

Original Article

Validity of prothrombin-induced Vitamin K antagonist versus Alpha-Fetoprotein (Tumor Markers) in Diagnosis of Hepatocellular Carcinoma, Using Computed Tomography scan as Gold Standard

Amer Latif[1], Riffat Saeed[2*], Tariq Ali Banghash[1], Muhammad Khawar Shahzad[1], Hassam Ahmed[1], Muhammad Asif Naveed[1] and Usama Amer[3]

[1]Department of Hepatobiliary Unit, Shaikh Zayed Hospital, Lahore, Pakistan
[2]Department of Anesthesiology, Shaikh Zayed Hospital, Lahore, Pakistan
[3]Department of Anesthesiology, Army Medical College Combined Military Hospitals, Lahore, Pakistan

ARTICLE INFO

Keywords:
Alpha Fetoproteins, Hepatocellular Carcinoma, Tumor Markers

How to Cite:
Latif, A., Saeed, R., Banghash, T. A., Shahzad, M. K., Ahmed, H., Naveed, M. A., & Amer, U. (2024). Validity of Prothrombin-induced Vitamin K antagonist versus Alpha-Fetoprotein (Tumor Markers) in Diagnosis of Hepatocellular Carcinoma, Using Computed Tomography scan as Gold Standard: Prothrombin-induced Vitamin K antagonist versus Alpha-Fetoprotein in Diagnosis. Pakistan Journal of Health Sciences, 5(07). https://doi.org/10.54393/pjhs.v5i07.1804

***Corresponding Author:**
Riffat Saeed
Department of Anesthesiology, Shaikh Zayed Hospital, Lahore, Pakistan
riffatsaeeddr@gmail.com

Received Date: 31st May, 2024
Acceptance Date: 28th July, 2024
Published Date: 31st July, 2024

ABSTRACT

Biomarkers like alpha-fetoprotein and prothrombin-induced Vitamin K deficiency/ antagonist are used in the early diagnosis and staging of hepatocellular carcinoma and are useful for better outcomes in the treatment and overall survival of the patient. **Objective:** To compare the diagnostic accuracy of alpha-fetoprotein and prothrombin-induced Vitamin K antagonist in the diagnosis of hepatocellular carcinoma using a computed tomography scan as a gold standard. **Methods:** A cross-sectional study was conducted in the Liver Transplant Unit of Shaikh Zayed Postgraduate Medical Complex, Lahore from July 2023 to January 2024. A total of 94 patients older than 12 years old with cirrhosis and CT scan suggestive of hepatocellular carcinoma were selected. Blood was collected to test for AFP and PIVKA-II. The samples were sent to the labs after labeling them properly and the results were collected and entered in the data sheet. Patients were advised to have a multiphase contrast-enhanced CT scan. Patients were followed up in the clinic after 7 days. **Results:** The diagnostic accuracy of AFP was 78% with a 74.7% sensitivity, 100% specificity, 100% positive predictive value, and 41.67% negative predictive value. The diagnostic accuracy of PIKVA-II was found to be 87.76% with 89% sensitivity, 80% specificity, 96.1% PPV, and 57.14% NPV. **Conclusions:** On comparing the tumor markers AFP with PIVKA-II against the gold standard multiphase CT scan it was found that PIVKA-II has better diagnostic accuracy than AFP.

INTRODUCTION

Liver cancer especially hepatocellular carcinoma is one of the most frequently occurring cancers in males and females [1]. Hepatocellular carcinoma (HCC) is common in cirrhotic patients in Asia and is the leading cause of death in Pakistan. HCC management has improved since last decade but prognostic outcomes are still not satisfactory. 75% of cases of HCC in Asia are due to a high incidence hepatitis B and C [2]. Timely detection of HCC is significant to ensure better treatment and eventually better outcomes. HCC is associated with cirrhotic liver disease regardless of the etiology in the majority of the patients but HCC also occurs in non-cirrhotic only in 10 percent of total HCC Cases [3]. Biomarkers are used in the early detection and staging of HCC and are useful for better outcomes in the treatment and overall survival of the patient. The most commonly used biomarker is AFP (Alpha-Fetoprotein) which is compared with PIVKA-II (prothrombin-induced Vitamin K deficiency/ antagonist). The diagnostic accuracy of AFP is unsatisfactory. The sensitivity ranges from 39-65 % and specificity for detection of HCC ranges from 76 -94

DOI: https://doi.org/10.54393/pjhs.v5i07.1804

%, which is not ideal [4]. PIVKA-II is tumor marker for hepatocellular carcinoma, it corresponds to HCC oncogenesis and disease progression. PIVKA-II is also utilized in discriminating neoplastic from regenerative nodules in cirrhotic patients. PIVKA-II has a higher diagnostic accuracy than AFP and shows enhanced results in combination of AFP for early detection of HCC [5, 6]. High levels of PIVKA-II have been seen in patients at risk of developing HCC within the first two years of cirrhosis [7]. PIVKA-II can also be used in combination with AFP and it is seen to increase the sensitivity and specificity of both biomarkers for HCC detection at a very early stage. The other modality used in the diagnosis of HCC is a contrast-enhanced multiphase CT scan. Recent guidelines recommend a CT scan as the first-line tool for the screening, diagnosis, staging, and surveillance of HCC [8]. The typical enhancement pattern which shows contrast uptake on the arterial phase and washout on the venous phase confirms the diagnosis of HCC. If this specific pattern is not seen on a CT scan, then the other modality used is Dynamic MRI scan. According to a recent meta-analysis, the sensitivity of contrast-enhanced multiphase CT scan ranges between 63-76% and the specificity ranges from 87-98 % [9]. On CT scan the diagnostic cutoff is 1cm in most of the guidelines. Due to the lack of evidence in the literature regarding early diagnosis of HCC in Pakistani patients with cirrhosis, it was mandatory to find a tumor marker that could give us better diagnostic and prognostic yield in these patients. Cancer treatment worldwide is very expensive, especially in Pakistan where people cannot bear the expenses of cancer treatment, by using the proposed tumor markers and imaging modalities which are sensitive to picking up the HCC at an early stage, we can significantly reduce the morbidity and mortality in our patients and they can avail better treatment options for an overall better survival in hepatocellular carcinoma.

This study was conducted to compare the diagnostic accuracy of alpha fetoprotein and prothrombin-induced Vitamin K antagonist in the diagnosis of hepatocellular carcinoma using a computed tomography scan as a gold standard.

METHODS

A cross-sectional study was conducted in the Liver Transplant Unit of Shaikh Zayed Postgraduate Medical Complex, Lahore from July 2023 to January 2024. A total of 94 patients older than 12 years old with cirrhosis and CT scans suggestive of hepatocellular carcinoma were selected by convenient sampling. The sample size was calculated by Epi Info software by keeping 0.69 expected sensitivity, 0.88 expected specificity, 0.89 expected prevalence, 0.10 desired precision and 95% confidence interval [10]. Patients with bi-lobar HCC with Childs Class C cirrhosis, any other malignancy except HCC, metastatic liver disease due to other malignancy, liver disease with known Vitamin K deficiency, and patients on warfarin or Vitamin K antagonist were excluded. All patients provided their informed consent for their data being used for research. The ethical board of the hospital approved the study Ref No. SZMC/TERC/371/23. Blood was collected for testing for AFP and PIVKA-II. The samples were sent to the labs after labeling them properly and the results were collected and entered in the datasheet. Patients were advised to have a multiphase contrast-enhanced CT scan. Patients were followed up in the clinic after 7 days and the proformas were filled. Data were entered and analyzed using SPSS version 24.0. Quantitative variables were presented in the form of mean ± SD whereas, qualitative data were presented in the form of frequency and percentages. Sensitivity, Specificity, positive predictive value, negative predictive value, and the diagnostic accuracy of PIVKA-II and AFP were calculated by taking contrast-enhanced multiphase CT as a gold standard. A 2x2 table was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy.

RESULTS

The demographic data collected in the current study shows the age groups mainly affected were ranging from late 40 to 70s (N = 87). On gender analysis the males were seventy (71.4%) out of 98 and the females were 28 (28.6%) out of 98. 86 (87.8%) patients had Hep-C infection and eight (8.2%) patients were Hep-B positive. Forty-two (42.9%) patients had international normalized ratio <1.3 and 56 (57.1%) patients had INR > 1.3. Ten (10.2%) participants had ascites. Thirty-eight (38.8%) patients had raised bilirubin. Thirty (30.6%) patients had low albumin. Seven (7.1%) patients had episodes of encephalopathy during their illness. The majority of patients in our study group had a short duration of illness and were not treated appropriately in their local health setting. A major subset of patients participating in our study group were from Child Pugh class A (77.5%)(Table 1).

Table 1: Patient's Baseline Characteristics

Variables	N (%)
Age	
15-30 Years	4 (4.1%)
31-45 Years	7 (7.1%)
46-60 Years	52 (53.1%)
61-75 Years	35 (35.7%)
Gender	
Male	70 (71.4%)
Female	28 (28.6%)
Viral Hepatitis	
HBV	8 (8.2%)
HCV	86 (87.8%)
Miscellaneous	1 (1%)

DOI: https://doi.org/10.54393/pjhs.v5i07.1804

B, C Negative	1 (1%)
B, C Positive	2 (2%)
INR	
<1.3	42 (42.9%)
>1.3	56 (57.1%)
Ascites	10 (10.2%)
Bilirubin	
Normal	60 (61.2%)
High	38 (38.8%)
Albumin	
Normal	68 (69.4%)
Abnormal	30 (30.6%)
Encephalopathy	7 (7.1%)
Previous Treatment	8 (8.2%)
Duration of Symptoms	
Less than 6 Months	68 (69.4%)
More 6 Months	25 (25.5%)
More than 1 Year	5 (5.1%)
Child-Pugh Score	
A	76 (77.5%)
B	18 (18.4%)
C	4 (4.1%)

Twenty-six (26.5%) patients were diabetic, 32 (32.7%) patients had a treatment history of hypertension, 8 (8.2%) patients had a history of ischemic heart disease, 11 (11.2%) patients had a previous history of tuberculosis, 16 (16.3%) patients had a previous history of asthma. Sixty-three (64.3%) patients had pain, 47 (48%) patients had a fever, 64 (65.3%) patients had some degree of loss of appetite, 74 (75.5%) patients developed generalized weakness, and 13 (13.3%) patients had a previous history of gastrointestinal (GI) bleed (Table 2).

Table 2: Co-Morbidities and Clinical Manifestations

Variables	N (%)
Comorbidities	
Diabetes	26 (26.5%)
Hypertension	32 (32.7%)
Ischemic Heart Disease	8 (8.2%)
Tuberculosis	11 (11.2%)
Asthma	16 (16.3%)
Clinical Manifestations	
Pain	63 (64.3%)
Fever	47 (48%)
Loss of Appetite	64 (65.3%)
Weakness	74 (75.5%)
GI Bleed	13 (13.3%)

Regarding the tumor, 36 (36.7%) patients had tumor sizes between 4-6 cm, 89 (90.8%) patients had single lesions, and 83 (84.7%) tumors were malignant (Table 3).

Table 3: Tumor Size, frequency and Type of Tumor Assessment

Variables	N (%)
Tumor Size	
1-3cm	25 (25.5%)
4-6cm	36 (36.7%)
7-10cm	24 (24.5%)
11-15cm	11 (11.2%)
More than 15cm	2 (2%)
Tumor Frequency	
Single Lesion	89 (90.8%)
Multifocal Lesion	9 (9.2%)
Tumor Type	
Benign	15 (15.3%)
Malignant	83 (84.7%)

The diagnostic accuracy of AFP was 78% with a sensitivity of 74.7%, specificity of 100%, positive predictive value of 100%, and a negative predictive value of 41.67%. The diagnostic accuracy of PIKVA-II was found to be 87.76% with a sensitivity of 89%, specificity of 80%, PPV of 96.1%, and NPV of 57.14% (Table 4).

Table 4: Validity of Alpha-Fetoprotein Test and PIVKA-II Taking CT Scan as the Gold Standard for Detection of HCC

Biomarkers	Gold Standard N (%)	
	Present	Absent
AFP		
Positive	62 (100%)	0
Negative	21 (58.3%)	15 (41.7%)
PIVKA-II		
Positive	74 (96.1%)	3 (3.9%)
Negative	9 (42.9%)	12 (57.1%)

AFP:.....PIVKA-II
Sensitivity: 74.7%.....Sensitivity: 89%
Specificity: 100%.....Specificity: 80%
PPV: 100%.....PPV: 96.1%
NPV: 41.67%.....NPV: 57.14%
Accuracy: 78%.....Accuracy: 87.76%

Regarding the presence of tumors on computer tomography, 83 (85%) cases had visible lesions on CT scan and 15% had no detectable lesions (Figure 1).

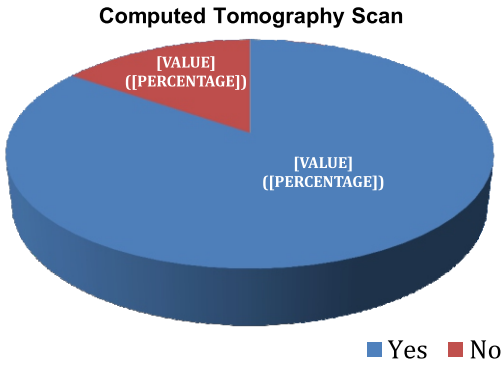

Figure 1: Presence of Tumor on Computer Tomography

DOI: https://doi.org/10.54393/pjhs.v5i07.1804

Seventy-seven (79%) patients had raised PIVKA-II and twenty-one (21%) had normal PIVKA-II levels indicating high sensitivity of this marker in diagnosis of HCC (Figure 2).

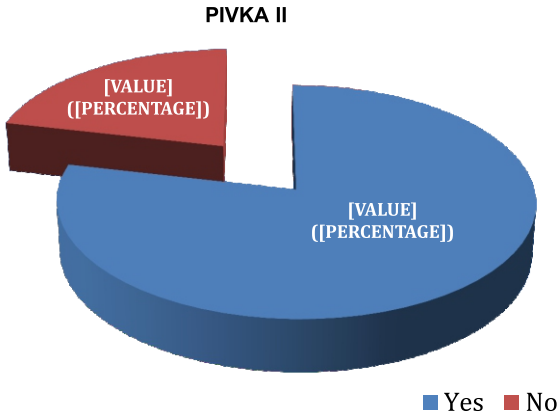

Figure 2: PIVKA-II is Highly Sensitive in the Diagnosis of HCC

DISCUSSION

Presently AFP is considered as the tumor marker that is used in the detection of HCC. However, it has been seen that in some patients even with very large tumor size the AFP remains normal so the diagnostic accuracy remains questionable [11]. Our study is aimed at identifying and validating the effective non-invasive tumor marker for HCC. We used a multiphase CT scan for confirmation of the diagnosis although the biopsy is taken as the gold standard in literature. It has been reported that due to the issue of tumor seedlings and the patient with cirrhosis patients having deranged coagulation, there was a lot of evidence favoring the usage of radiological investigation like multiphase CT scan for the diagnosis of HCC [12, 13]. In our study CT scan showed the presence of tumors in 83 (85%) patients and these parameters were comparable with the international values [14, 15]. In our study, PIVKA-II was seen as a promising biomarker for diagnosis of HCC with a sensitivity of 89%, specificity of 80%, PPV of 96.1%, NPV of 57.14% and diagnostic accuracy of 87.76% as compared to AFP with a diagnostic accuracy of 78%, sensitivity of 74.7%, specificity of 100%, positive predictive value of 100% and a negative predictive value of 41.67% and the same pattern is noticeable in the previous studies [16-18]. On comparison of the demographics, it was seen that males were predominantly more involved than females, this gender distribution was also reported by previous studies [19, 20]. Age distribution in our study showed a majority of patients in the age group of 40 to 70 years and older. A higher incidence of HCC in elder patients is also supported by the literature [21, 22]. 77.5% of the population had a Child Class A score, previous studies in HCC patients were also conducted in considerably healthier patients [23, 24]. In terms of the diagnosis, it was seen that sensitivity/ specificity/ PPV/ NPV along with the diagnostic accuracy of AFP was comparable with the previous studies which were 78% and 75.6% respectively [16-18]. For PIVKA-II the sensitivity/ specificity/ PPV/ NPV was also comparable along with the diagnostic accuracy which was 87.76% vs 86.1%. This was no statistical difference. There were some limitations of the present study. It is recommended that the sample size of the study be large, more studies should be conducted with the involvement of multiple centers and large sample size in order to find more biomarkers with better diagnostic accuracy to detect HCC at an early stage and provide relief to patient sufferings by providing them better curative treatment options.

CONCLUSIONS

On comparing the tumor markers AFP with PIVKA-II against the gold standard multiphase CT scan it was found that PIVKA-II has better diagnostic accuracy than AFP.

Authors Contribution

Conceptualization: AL
Methodology: AL, TAB, MKS, HA, UA
Formal analysis: RS
Writing, review and editing: AL, RS, TAB, MKS, HA, MAN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Petrick JL and McGlynn KA. The changing epidemiology of primary liver cancer. Current Epidemiology Reports. 2019 Jun; 6: 104-11. doi: 10.1007/s40471-019-00188-3.

[2] Zhang CH, Cheng Y, Zhang S, Fan J, Gao Q. Changing epidemiology of hepatocellular carcinoma in Asia. Liver International. 2022 Aug; 42(9): 2029-41. doi: 10.1111/liv.15251.

[3] Desai A, Sandhu S, Lai JP, Sandhu DS. Hepatocellular carcinoma in non-cirrhotic liver: A comprehensive review. World Journal of Hepatology. 2019 Jan; 11(1): 1. doi: 10.4254/wjh.v11.i1.1.

[4] Zhang J, Chen G, Zhang P, Zhang J, Li X, Gan DN *et al.* The threshold of alpha-fetoprotein (AFP) for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis. PLOS One. 2020 Feb; 15(2): e0228857. doi: 10.1371/journal.pone.0228857.

[5] Tian S, Chen Y, Zhang Y, Xu X. Clinical value of serum AFP and PIVKA-II for diagnosis, treatment and prognosis of hepatocellular carcinoma. Journal of Clinical Laboratory Analysis. 2023 Jan; 37(1): e24823.

DOI: https://doi.org/10.54393/pjhs.v5i07.1804

doi: 10.1002/jcla.24823.

[6] Xu F, Zhang L, He W, Song D, Ji X, Shao J. The diagnostic value of serum PIVKA-II alone or in combination with AFP in Chinese hepatocellular carcinoma patients. Disease Markers. 2021 Feb; 2021(1): 8868370. doi: 10.1155/2021/8868370.

[7] Loglio A, Iavarone M, Facchetti F, Di Paolo D, Perbellini R, Lunghi G *et al.* The combination of PIVKA-II and AFP improves the detection accuracy for HCC in HBV caucasian cirrhotics on long-term oral therapy. Liver International. 2020 Aug; 40(8): 1987-96. doi: 10.1111/liv.14475.

[8] Chartampilas E, Rafailidis V, Georgopoulou V, Kalarakis G, Hatzidakis A, Prassopoulos P. Current imaging diagnosis of hepatocellular carcinoma. Cancers. 2022 Aug; 14(16): 3997. doi: 10.3390/cancers14163997.

[9] Wang G, Zhu S, Li X. Comparison of values of CT and MRI imaging in the diagnosis of hepatocellular carcinoma and analysis of prognostic factors. Oncology letters. 2019 Jan; 17(1): 1184-8. doi: 10.3892/ol.2018.9690.

[10] Bolarinwa, O. A. (2020). Sample size estimation for health and social science researchers: The principles and considerations for different study designs. Nigerian Postgraduate Medical Journal, 27(2), 67-75. DOI: 10.4103/npmj.npmj_19_20

[11] Hanif H, Ali MJ, Susheela AT, Khan IW, Luna-Cuadros MA, Khan MM *et al.* Update on the applications and limitations of alpha-fetoprotein for hepatocellular carcinoma. World Journal of Gastroenterology. 2022 Jan; 28(2): 216. doi: 10.3748/wjg.v28.i2.216.

[12] Semaan S, Vietti Violi N, Lewis S, Chatterji M, Song C, Besa C *et al.* Hepatocellular carcinoma detection in liver cirrhosis: diagnostic performance of contrast-enhanced CT vs. MRI with extracellular contrast vs. gadoxetic acid. European Radiology. 2020 Feb; 30: 1020-30. doi: 10.1007/s00330-019-06458-4.

[13] Park JH, Park MS, Lee SJ, Jeong WK, Lee JY, Park MJ *et al.* Contrast-enhanced US with perfluorobutane for hepatocellular carcinoma surveillance: a multicenter diagnostic trial (SCAN). Radiology. 2019 Sep; 292(3): 638-46. doi: 10.1148/radiol.2019190183.

[14] Shin J, Lee S, Bae H, Chung YE, Choi JY, Huh YM *et al.* Contrast-enhanced ultrasound liver imaging reporting and data system for diagnosing hepatocellular carcinoma: a meta-analysis. Liver International. 2020 Oct; 40(10): 2345-52. doi: 10.1111/liv.14617.

[15] Pace C, Nardone V, Roma S, Chegai F, Toti L, Manzia TM *et al.* Evaluation of Contrast-Enhanced Intraoperative Ultrasound in the Detection and Management of Liver Lesions in Patients with Hepatocellular Carcinoma. Journal of Oncology. 2019 Aug; 2019(1): 6089340. doi: 10.1155/2019/6089340.

[16] Tayob N, Kanwal F, Alsarraj A, Hernaez R, El-Serag HB. The performance of AFP, AFP-3, DCP as biomarkers for detection of hepatocellular carcinoma (HCC): a phase 3 biomarker study in the United States. Clinical Gastroenterology and Hepatology. 2023 Feb; 21(2): 415-23. doi: 10.1016/j.cgh.2022.01.047.

[17] Liu Z, Pu Y, Bao Y, He S. Investigation of potential molecular biomarkers for diagnosis and prognosis of AFP-negative HCC. International Journal of General Medicine. 2021 Aug; 4369-80. doi: 10.2147/IJGM.S323868.

[18] Suttichaimongkol T, Mitpracha M, Tangvoraphonkchai K, Sadee P, Sawanyawisuth K, Sukeepaisarnjaroen W. PIVKA-II or AFP has better diagnostic properties for hepatocellular carcinoma diagnosis in high-risk patients. Journal of Circulating Biomarkers. 2023 Jan; 12: 12-16. doi: 10.33393/jcb.2023.2453.

[19] Lai MW, Chu YD, Lin CL, Chien RN, Yeh TS, Pan TL *et al.* Is there a sex difference in postoperative prognosis of hepatocellular carcinoma?. BioMed Central Cancer. 2019 Dec; 19: 1-3. doi: 10.1186/s12885-019-5453-3.

[20] Tan DJ, Setiawan VW, Ng CH, Lim WH, Muthiah MD, Tan EX *et al.* Global burden of liver cancer in males and females: changing etiological basis and the growing contribution of NASH. Hepatology. 2023 Apr; 77(4): 1150-63. doi: 10.1002/hep.32758.

[21] Cho E, Cho HA, Jun CH, Kim HJ, Cho SB, Choi SK. A review of hepatocellular carcinoma in elderly patients focused on management and outcomes. In Vivo. 2019 Sep; 33(5): 1411-20. doi: 10.21873/invivo.11618.

[22] Chu KK and Chok KS. Is the treatment outcome of hepatocellular carcinoma inferior in elderly patients?. World Journal of Gastroenterology. 2019 Jul; 25(27): 3563. doi: 10.3748/wjg.v25.i27.3563.

[23] Fu CC, Chen YJ, Su CW, Wei CY, Chu CJ, Lee PC *et al.* The outcomes and prognostic factors of patients with hepatocellular carcinoma and Child-Turcotte-Pugh class B. Journal of the Chinese Medical Association. 2023 Oct; 86(10): 876-84. doi: 10.1097/JCMA.0000000000000975.

[24] Gu J, Liang BY, Zhang EL, Huang ZY. Prognostic Nomograms Based on the Cirrhotic Severity Scoring for Preoperative Prediction of Long-Term Outcomes in Patients with HBV-Related Hepatocellular Carcinoma and Child-Pugh Grade A Liver Function. Journal of Oncology. 2022 May; 2022(1): 7031674. doi: 10.1155/2022/7031674.