The Relationship Between Platelet-to-Lymphocyte Ratio (PLR) and HCV RNA Levels in HCV-HIV Coinfected Patients Before and After Receiving Direct-Acting Antiviral (DAA) Therapy at Dr. Mohammad Hoesin Hospital Palembang

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Abstract

The background described in the introduction section highlights the importance of studying the correlation between the platelet-to-lymphocyte ratio (PLR) and HCV RNA levels in these patients. This research follows an analytical correlational observational design with a cross-sectional approach. The study was conducted at the Internal Medicine Polyclinic of Dr. Mohammad Hoesin Hospital, Palembang. It involved 38 subjects who met the inclusion and exclusion criteria. The primary objective was to determine the correlation between PLR and HCV RNA levels in HIV-HCV coinfected patients receiving DAA therapy. The research findings concluded that there was a decrease in PLR and HCV RNA Viral Load levels in HIV-HCV coinfected patients after receiving DAA therapy compared to before receiving DAA therapy. The Platelet-to-Lymphocyte Ratio (PLR) was directly proportional to the quantitative HCV RNA Viral Load levels in HIV-HCV coinfected patients with a strong correlation value both before and after DAA therapy.

Keywords: *Platelet-to-lymphocyte (PLR), HCV RNA Levels, HCV Patients, HIV co-infection, DAA Therapy.*

A. INTRODUCTION

Hepatitis C is one of the diseases that affects the liver cells and tissues. This disease is caused by the hepatitis virus, which can trigger infections and inflammation in the liver (Setiati et al., 2014). Hepatitis C is characterized by infection with the Hepatitis C Virus (HCV), a single-stranded RNA virus that primarily targets the human liver. It is an inflammatory liver disease resulting from HCV infection, which is transmitted through blood exposure. Approximately 70-80% of those infected with the hepatitis virus may remain asymptomatic. Individuals with hepatitis infection, whether acute or chronic, can experience similar symptoms, including fatigue, abdominal pain, jaundice, and loss of appetite (Jameson et al., 2018; Christopher et al., 2014).

Hepatitis C infection can be detected or diagnosed using specific antibody tests, such as the ELISA test. The presence of hepatitis C antibodies indicates that the individual has been infected with HCV, although it cannot determine whether the infection is acute, chronic, or resolved (Jameson et al., 2018; Christopher et al., 2014). Data shows that more than 354 million people worldwide are living with chronic

hepatitis, with over 8,000 new hepatitis B and C infections occurring daily, leading to over a million deaths annually due to advanced liver disease and liver cancer (WHO, 2021).

Over 2.6 million people are estimated to have hepatitis C coinfected with the human immunodeficiency virus (HIV). End-stage liver disease has become the leading cause of death in this patient group. Effective treatment with Direct-Acting Antivirals (DAA), with or without ribavirin, not only reduces overall AIDS-related deaths in this population but also slows down the progression of liver disease. However, the increasing incidence of liver-related complications can only be halted by successfully eliminating HCV in this patient population (Manns et al., 2017).

More than HIV-positive patients who acquire the infection through injection drug use experience hepatitis C coinfection. Only 4-8% of HIV-positive gay men also experience HCV coinfection because hepatitis C is not easily transmitted through sexual contact. Patients with HIV infection and HCV are more likely to transmit HIV than HCV through heterosexual contact. The presence of HIV can increase the risk of acquiring HCV, as seen in several studies. Two to 10% of HIV/HCV-coinfected women transmit HCV to their newborns.

Complete blood count and differential leukocyte count, later known as the diff count, are the most common tests performed in clinical laboratories and can be measured using automated hematology analyzers, which are cost-effective, quick, and accurate. The results of these laboratory tests, as hematological values, have been widely used in assessing individual health status, and various blood and non-blood disorders can be evaluated using these tests (Moosazadeh et al., 2019; van der Meijden et al., 2019).

Laboratory test results have limited clinical significance unless explained by providing comparisons between health status and disease. Hematological values are influenced by factors such as age, gender, race, nutrition, environment, altitude, timing, and measurement methods. Some studies have indicated that blood-based indicators like the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) can serve as potential prognostic indicators for various diseases, including infections, cancer, and injuries (Moosazadeh et al., 2019; van der Meijden et al., 2019).

Several studies have linked PLR to hepatitis C. Research notes that chronic infectious diseases, including various types of hepatitis viruses, are characterized by persistent chronic inflammation. Studies also confirm that PLR and NLR are associated with the development and prognosis of hepatitis virus-associated liver carcinoma (Lee et al., 2018). Based on the description above, the researcher aims to investigate the role of PLR values in measuring HCV RNA levels in HIV-HCV coinfected patients before and after receiving DAA therapy.

There is limited research publication regarding the comparison of PLR with HCV RNA levels in HIV-HCV coinfected patients before and after receiving DAA therapy. Therefore, the researcher is interested in examining and understanding the comparison of PLR in measuring HCV RNA levels in HIV-HCV coinfected patients

before and after receiving DAA therapy at Dr. Mohammad Hoesin General Hospital in Palembang. The objective of this study is to determine the relationship between PLR and HCV RNA levels in HIV-HCV coinfected patients before and after receiving DAA therapy at Dr. Mohammad Hoesin Hospital, Palembang.

B. METHOD

This research is an analytical correlational observational study with a cross-sectional design. The study will be conducted at the Internal Medicine Polyclinic of Dr. Mohammad Hoesin General Hospital (RSUP) in Palembang, with an estimated timeframe from August 2022 until the sample size is reached. The study population consists of all HIV-HCV coinfected patients receiving DAA therapy. The accessible population includes HIV-HCV coinfected patients at Dr. Mohammad Hoesin Hospital (RSMH) in Palembang who received DAA therapy from January 2023 to June 2023. The subjects for the study will be selected using selective proportional sampling, with the number of subjects chosen proportionally. The sample size for this study is 38 individuals.

Data collection will involve primary and secondary data sources, including medical records, patient history, physical examinations, and laboratory test results. PLR and HCV RNA level measurements will be conducted at the clinical laboratory of RSMH Palembang. The collected research data will undergo a process of coding, editing, and eventually will be analyzed using computer software (SPSS version 26.0 for Windows). The study subjects consist of a single group measured at two time points: before and after receiving DAA therapy. Univariate analysis will be presented in the form of graphs and tables, with categorical data presented as counts and percentages, while numeric data will be presented as means (standard deviation) or medians (range).

Bivariate analysis will be used to test the hypotheses in this study. The analysis employed will be the paired T-test or paired T-Test. The use of the Paired Sample T-Test assumes that the data are normally distributed and that the data are on a numeric scale (ratio or interval). If the data are not normally distributed, the researcher will use an alternative test, which is the Wilcoxon test. In comparative hypothesis testing, a p-value < 0.05 indicates a significant difference between the tested variables.

C. RESULTS AND DISCUSSION

This study was conducted at RSUP Dr. Mohammad Hoesin in Palembang from August 2022 to June 2023. The research population consisted of HIV-HCV coinfected patients receiving DAA therapy as outpatient treatment at RSUP Dr. Mohammad Hoesin (RSMH) in Palembang. The total number of successfully obtained samples was 38 subjects who met the inclusion and exclusion criteria. The objective of this study was to determine the correlation between platelet-to-lymphocyte ratio (PLR) and HCV-RNA levels in HIV-HCV coinfected patients receiving DAA therapy at RSMH Palembang.

A Shapiro-Wilk test for normality was conducted to assess the distribution of numerical characteristics of the research subjects, while categorical data were presented as frequencies and percentages. Data that followed a normal distribution (if $p > 0.05$) were presented as mean ± standard deviation (SD), while data that did not follow a normal distribution were presented as median (minimum-maximum). Data were presented in the form of narrative descriptions, frequency distributions, tables, graphs, and curves.

The characteristics of the research subjects included gender, education, occupation, risk factors, Viral Load, PLR, and hepatic cirrhosis status, which were displayed in Tables 1 and 2 for categorical data and Table 3 for numerical data. In this study, the median age of the research subjects was 44 years, with the youngest subject being 25 years old and the oldest subject being 59 years old. The majority of the subjects were male, with 30 subjects (78.9%).

Based on education, the research subjects were grouped as follows: 2 subjects (5.3%) had elementary school education, 2 subjects (5.3%) had junior high school education, 27 subjects (71%) had senior high school education, 3 subjects (7.9%) had a diploma, and 4 subjects (10.5%) had a bachelor's degree. Regarding occupation, the research subjects were categorized as follows: 1 (2.6%) were unemployed, 4 (10.5%) were housewives (IRT), 17 (44.7%) were entrepreneurs, 5 (13.2%) were civil servants (PNS), and 11 (29%) had other occupations.

Table 1. General Characteristics of Research Subjects (Categories)

Characteristics	N	%
Gender		
Male	30	78.9
Female	8	21.1
Education		
Primary School	2	5.3
Junior High School	2	5.3
Senior High School	27	71.0
Diploma	3	7.9
Bachelor	4	10.5
Occupation		
Not Working	1	2.6
Housewives	4	10.5
Self-Employed	17	44.7
Civil Servant	5	13.2
Others	11	29.0

The risk factors found in this study include blood transfusion in 2 subjects (5.3%) and IDU (Injecting Drug Use) in 15 individuals (39.5%). The distribution of Viral Load in this study is divided into < 400,000 found in 19 subjects (50%) and > 400,000 in 19 subjects (50%). The status of hepatic cirrhosis in the research subjects was found to be as follows: 21 subjects (55.3%) had no hepatic cirrhosis, 8 subjects

(21%) had compensated hepatic cirrhosis, and 9 subjects (23.7%) had decompensated hepatic cirrhosis.

Table 2. Specific Characteristics of Research Subjects (Categories)

Characteristics	N	%
Viral Load		
<400.000	19	50
>400.000	19	50
Treatment Status		
Sustained Virological Response (SVR)	31	81
Non-SVR	7	19
Risk Factors		
Blood Transfusion	2	5.3
Same-sex Relationship	17	39.5
Cirrhosis Status		
No Cirrhosis	21	55.3
Cirrhosis Compensation	8	21.0
Cirrhosis Decompensation	9	23.7

In this study, it was found that the median Viral Load value before therapy was 43.1x104 with the lowest value being 10 and the highest being 60.4x106 and the average PLR value before therapy was 159.01 with the lowest value being 14.08 and the highest value being 999.36. Meanwhile, the median Viral Load value after therapy was 0 with the lowest value being 0 and the highest being 48.8x103 and the median PLR value was 76.15 with the lowest value being 24.82 and the highest value being 1272.36.

Table 3 Characteristics of Research Subjects (Numerical)

Characteristics	Median	Min – Max	p*
Viral Load HCV RNA Pretherapy	$43.1x10^4$	$10 – 60.04x10^6$	< 0.001*
Viral Load HCV RNA Postherapy	0	$0 - 48.8x10^3$	
PLR Pretherapy	159.01	14.08 - 999.36	0.005
PLR Postherapy	76.15	24.82 – 1272.36	

Explanation: Tested using Shapiro-Wilk, p > 0.05 = normally distributed, *Wilcoxon test, before and after DAA therapy, p < 0.05 significant.

The correlation between the PLR and quantitative HCV RNA levels before receiving DAA therapy in HIV-HCV coinfected patients in this study was analyzed using the Spearman correlation test due to the non-normal distribution of PLR and quantitative HCV RNA data. The analysis results revealed a significant correlation with a p-value of < 0.001 and an r-value of 0.706, indicating a strong correlation. This suggests that as the PLR value increases, the HCV RNA level also increases before DAA therapy in HIV-HCV coinfected patients.

The correlation between the PLR and quantitative HCV RNA levels after 12 weeks of DAA therapy in HIV-HCV coinfected patients in this study was analyzed using the Spearman correlation test due to the non-normal distribution of PLR and quantitative HCV RNA data. The analysis results showed a positive correlation with

a p-value of < 0.001 and an r-value of 0.675, which indicates a strong and significant correlation. This implies that as the PLR value increases, the HCV RNA Viral Load decreases after 12 weeks of DAA therapy in HIV-HCV coinfected patients.

In this study, HIV-HCV co-infection cases undergoing outpatient treatment at Dr. Mohammad Hoesin Hospital in Palembang were more commonly found in males, with 30 individuals (78.9%), while females accounted for 8 individuals (21.1%). This distribution differs slightly from the data published by the World Health Organization (WHO), which reported that the prevalence of Hepatitis C cases worldwide showed a higher percentage in males at 51% and females at 49%[10]. However, epidemiological studies, such as the one conducted by Akhtar et al. in 2022 in Malaysia, align more closely with the findings of this current research, with prevalence rates of approximately 76.4% for males and 23.6% for females with HIV-HCV co-infection (Akhtar et al., 2022). Similar data were also obtained from epidemiological surveys based on records from the Ministry of Health of the Republic of Indonesia (Kemenkes RI), indicating that 17% of Hepatitis C cases were found in females and 83% in males (Muljono, 2017).

Men are more susceptible to having more severe degrees of Hepatitis C compared to women. This is related to the involvement of the protein E2 receptor activity binding to receptor sites on the surface of hepatocyte cells. Protein E2 is more commonly found in males, and its expression is hypothesized to be regulated by estrogen hormones. Increased expression of the E2 protein in hepatosis is associated with an increased risk of HCV infection in males. The higher prevalence of male chronic hepatitis C patients is due to the fact that males have greater risk factors for infection. One of the risk factors is those who use injectable drugs (injecting drug users or IDUs). IDUs have a higher risk of HCV infection compared to other risk factors because the sharing of injectable drugs more frequently facilitates transmission, especially through parenteral exposure to body fluids containing blood. This can also be attributed to the fact that the virus can easily transmit through blood-to-blood contact (Abdel-Gawad et al., 2023).

In this study, the median age of the research subjects was 44 years, with the youngest subject being 25 years old and the oldest subject being 69 years old. This finding aligns with existing research. Saputri et al. reported that the highest age group affected was in the 60-69 years range, indicating that older age is associated with an increased risk of infection and worse outcomes[9]. In the elderly, there is a multisystem dysregulation that leads to a decrease in physiological reserves, which may be related to increased susceptibility to infectious diseases, often attributed to immune system decline. In advanced age, the aging process leads to a decline in various organ systems' structure and function, including the immune system's function and reduced production of immune cells, a phenomenon known as immunosenescence.

The educational levels of the research subjects were predominantly high school graduates (SMA) with 27 subjects (71%), followed by bachelor's degree holders with 4 subjects (10.5%). This was followed by those with a diploma (D3) degree, which accounted for 3 subjects (7.9%), and elementary school (SD) and junior high school

(SMP) graduates, each with 2 subjects (5.3%). In the study conducted by Saputri et al., education and skills played a role in understanding the impact of HIV and Hepatitis C infections, which had implications for the spread and survival rates of patients (Mustika et al., 2020). Therefore, the spread of these diseases is also highly dependent on individual and social behaviors. Behavioral changes play a significant role in this context and are influenced by education and skills.

In this study, the majority of research subjects had occupations in the entrepreneurial sector (44.7%). The distribution of Body Mass Index (BMI) data in this study followed a normal distribution, and the mean BMI of the research subjects was 20.98 ± 6.04 kg/m2. Research by Saputri et al. concluded that there is a correlation between BMI and the outcome of Hepatitis C, as evidenced by patients with overweight and obesity having longer-lasting and more severe Hepatitis C symptoms compared to others (Mustika et al., 2020). This may be related to individuals with excess body weight having excess fat reserves in adipose tissue, which can stimulate the release of inflammatory mediators. This continuous inflammation can disrupt the immune response (Migdad et al., 2022). In this study, the majority of patients had a normal BMI based on the criteria set by the Ministry of Health of the Republic of Indonesia in 2017.

This study demonstrates a significant difference in HCV RNA levels in HIV-HCV coinfected patients before and after receiving treatment ($p = 0.000$). It is observed that the average HCV RNA levels in HIV-HCV coinfected patients before treatment are higher than after treatment. Research conducted by Loomba et al. explains that high HCV RNA levels in hepatitis C patients before treatment indicate a virological response, indicating that the hepatitis C virus has infected the patient. Conversely, low HCV RNA levels after treatment suggest recovery and viral clearance (Loomba et al., 2011).

In this study, there is a significant difference in PLR values in HIV-HCV coinfected patients before and after receiving treatment ($p = 0.046$). The average PLR value before treatment is higher than after treatment. The results of the study by Hanberg et al. suggest that a higher PLR is an independent predictor of poor treatment response in HIV-HCV coinfected patients (Hanberg et al., 2019). In the study by Yaprak et al., it is explained that a high PLR is a marker of increased inflammatory response and is associated with increased mortality in HCV patients undergoing hemodialysis (Yaprak et al., 2016).

The correlation between PLR levels and quantitative HCV RNA levels in this study was analyzed using Spearman's correlation test. The analysis revealed a positive correlation between PLR levels and quantitative HCV RNA levels with a significance level of $p < 0.000$ and $r = 0.709$, indicating a strong correlation. Based on this analysis, it can be concluded that as PLR levels increase, quantitative HCV RNA levels also increase, and vice versa. This finding is consistent with a study conducted by Saputri et al. (2020), which found a significant relationship between PLR values and HCV RNA levels in chronic Hepatitis C patients with compensated liver cirrhosis before receiving therapy. Meng et al. also reported in their 2016 study that an increase

in PLR can indicate a good virological response in HCV patients (Meng et al., 2016). In the study by Hayashi et al. (2017), which investigated the relationship between postoperative changes in PLR values in adult living donor liver transplantation (AA-LDLT), it was found that a higher increase in PLR can be used as a predictor of worsening prognosis due to inflammatory changes in AA-LDLT recipients. Shmagel's research (2016) on HIV-HCV coinfected patients showed that hepatocellular injury is associated with systemic inflammatory response measured by several parameters, including PLR, and it also showed a correlation with CD4 lymphocyte count.

The correlation between PLR levels and quantitative HCV RNA levels after 12 weeks of DAA therapy in this study was also analyzed using Spearman's correlation test. The analysis revealed a positive correlation between PLR levels and quantitative HCV RNA levels with a significance level of $p < 0.005$ and $r = 0.603$, indicating a moderate correlation. This suggests that as PLR levels increase, quantitative HCV RNA levels also tend to increase, and conversely, after 12 weeks of DAA therapy, PLR levels decrease in line with the decrease in quantitative HCV RNA levels. This finding aligns with Saputri et al.'s (2020) study, which found a significant relationship between PLR values and HCV RNA levels in chronic Hepatitis C patients with compensated liver cirrhosis after receiving 12 weeks of DAA therapy. He et al.'s (2016) study in 2016 revealed that PLR values were significantly lower in patients with liver cirrhosis compared to chronic Hepatitis C patients without liver cirrhosis and patients without hepatitis C virus infection. Meng et al.'s research (2016) indicated that a high PLR value in chronic Hepatitis C patients indicates a good virological response in patients with liver cirrhosis.

D. CONCLUSION

There is a decrease in PLR and quantitative HCV RNA levels in HIV-HCV coinfected patients after receiving DAA therapy compared to before the DAA therapy. The Platelet-to-Lymphocyte Ratio (PLR) is directly related to the quantitative HCV RNA levels in HIV-HCV coinfected patients, with a strong correlation before and after DAA therapy. Future research is expected to compare several inflammatory markers involved in HIV-HCV coinfected patients to the clinical outcomes of patients using a prospective study design.

REFERENCES

1. Abdel-Gawad, M., Nour, M., El-Raey, F., Nagdy, H., Almansoury, Y., & El-Kassas, M. (2023). Gender differences in prevalence of hepatitis C virus infection in Egypt: a systematic review and meta-analysis. *Scientific Reports*, *13*(1), 2499.
2. Akhtar, A., Fatima, S., Saeed, H., Soo, C. T., & Khan, A. H. (2022). HIV-HCV coinfection: prevalence and treatment outcomes in Malaysia. *Intervirology*, *65*(2), 87-93.
3. Christopher, L., Stedman, M., & Catherine, A. M. (2014). *The Textbook of Hepatology: From Basic Science to Clinical Practice*. Elsevier Health Sciences.

4. Hanberg, J. S., Freiberg, M. S., Goetz, M. B., Rodriguez-Barradas, M. C., Gibert, C., Oursler, K. A., ... & VACS Project Team. (2019, October). Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as prognostic inflammatory biomarkers in human immunodeficiency virus (HIV), hepatitis C virus (HCV), and HIV/HCV coinfection. In *Open forum infectious diseases* (Vol. 6, No. 10, p. ofz347). US: Oxford University Press.
5. He, Q., He, Q., Qin, X., Li, S., Li, T., Xie, L., ... & Wei, Z. (2016). The relationship between inflammatory marker levels and hepatitis C virus severity. *Gastroenterology research and practice*, *2016*.
6. Jameson, J. L., Kasper, D. L., Fauci, A. S., Hauser, S. L., Longo, D. L., & Loscalzo, J. (Eds.). (2018). *Harrison's principles of internal medicine*. McGraw-hill education.
7. Lee, J. S., Kim, N. Y., Na, S. H., Youn, Y. H., & Shin, C. S. (2018). Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine*, *97*(26).
8. Lewis, K. C., Barker, L. K., Jiles, R., & Gupta, N. (2023). Estimated prevalence and awareness of hepatitis C virus infection among US adults—National Health and Nutrition Examination Survey, January 2017–March 2020. *Clinical Infectious Diseases*, ciad411.
9. Loomba, R., Rivera, M. M., McBurney, R., Park, Y., Haynes-Williams, V., Rehermann, B., ... & Heller, T. (2011). The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. *Alimentary pharmacology & therapeutics*, *33*(5), 559-565.
10. Manns, M. P., Buti, M., Gane, E. D., Pawlotsky, J. M., Razavi, H., Terrault, N., & Younossi, Z. (2017). Hepatitis C virus infection. *Nature reviews Disease primers*, *3*(1), 1-19.
11. Meng, X., Wei, G., Chang, Q., Peng, R., Shi, G., Zheng, P., ... & Ming, L. (2016). The platelet-to-lymphocyte ratio, superior to the neutrophil-to-lymphocyte ratio, correlates with hepatitis C virus infection. *International Journal of Infectious Diseases*, *45*, 72-77.
12. Migdal, A. L., Jagannathan, R., Qayed, E., Cusi, K., McCoy, R. G., Pasquel, F. J., & Miller, L. S. (2022). Association of obesity, diabetes, and alcohol use with liver fibrosis among US adults with hepatitis C virus infection. *JAMA Network Open*, *5*(3), e2142282-e2142282.
13. Moosazadeh, M., Maleki, I., Alizadeh-Navaei, R., Kheradmand, M., Hedayatizadeh-Omran, A., Shamshirian, A., & Barzegar, A. (2019). Normal values of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio among Iranian population: Results of Tabari cohort. *Caspian journal of internal medicine*, *10*(3), 320.
14. Muljono, D. H. (2017). Epidemiology of hepatitis B and C in Republic of Indonesia. *Euroasian journal of hepato-gastroenterology*, *7*(1), 55.
15. Mustika, S., Anita, K. W., & Saputri, N. E. W. (2020). Hubungan Antara Rasio Neutrofil-Limfosit (RNL) dan Rasio Platelet-Limfosit (RPL) dengan Kadar RNA VHC pada Pasien Hepatitis C Kronik. *Majalah Kesehatan*, *7*(3), 159-166.

16. Shmagel, K. V., Saidakova, E. V., Shmagel, N. G., Korolevskaya, L. B., Chereshnev, V. A., Robinson, J., ... & Lederman, M. M. (2016). Systemic inflammation and liver damage in HIV/hepatitis C virus coinfection. *HIV medicine*, *17*(8), 581-589.
17. Setiati, S., Alwi, I., Sudoyo, A. W., Simadibrata, K., Setiyohadi, B., & Syam, A. F. (2016). *Buku Ajar Ilmu Penyakit Dalam*. Interna Publishing.
18. van der Meijden, P. E., & Heemskerk, J. W. (2019). Platelet biology and functions: new concepts and clinical perspectives. *Nature Reviews Cardiology*, *16*(3), 166-179.
19. World Health Organization's (WHO). (2021). *Hepatitis can't wait - WHO commemorates World Hepatitis Day 2021*. World Health Organiozation. Retrieved from: https://www.who.int/news/item/28-07-2021-hepatitis-can-t-wait---who-commemorates-world-hepatitis-day-2021
20. Yaprak, M., Turan, M. N., Dayanan, R., Akın, S., Değirmen, E., Yıldırım, M., & Turgut, F. (2016). Platelet-to-lymphocyte ratio predicts mortality better than neutrophil-to-lymphocyte ratio in hemodialysis patients. *International Urology and Nephrology*, *48*, 1343-1348.