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THE RELATIONSHIP BETWEEN DURATION OF DIALYSIS AND HISTORY OF BLOOD TRANSFUSION WITH HEPATITIS C SEROPREVALENCE IN HEMODIALYSIS PATIENTS: A CROSS-SECTIONAL STUDY AT GADJAH MADA UNIVERSITY ACADEMIC HOSPITAL

HUBUNGAN DURASI DIALISIS DAN RIWAYAT TRANSFUSI DARAH DENGAN SEROPREVALENSI HEPATITIS C PADA PASIEN HEMODIALISIS: STUDI CROSS-SECTIONAL DI RUMAH SAKIT AKADEMIK UNIVERSITAS GADJAH MADA

Original Research Article
Penelitian

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A B S T R A C T

Background: *Hepatitis C Virus (HCV) is an RNA virus that causes hepatitis C disease. Hemodialysis patients are a group at high risk of becoming infected with the HCV. Based on prior research, the duration of hemodialysis has been identified as an independent risk factor for HCV. Risk factors for HCV transmission in hemodialysis patients can also include blood transfusions.* ***Purpose:*** *This research aimed to determine the relationship between the duration of dialysis and the history of blood transfusion with HCV seroprevalence in hemodialysis patients at Gadjah Mada University Academic Hospital.* ***Method:*** *This research utilized a cross-sectional research design. The research data were based on secondary data from the medical records of hemodialysis patients at Gadjah Mada University Academic Hospital.* ***Result:*** *The results were analyzed descriptively and statistically using the Chi-square test with significance (α = 0.05). Data obtained from this research showed that the HCV seroprevalence of hemodialysis patients at Gadjah Mada University Academic Hospital is 20.5%. The test results revealed a relationship between duration of dialysis with HCV seroprevalence in hemodialysis patients is a p-value = 0.021 (p-value < α), and a relationship between history of blood transfusion with HCV seroprevalence in hemodialysis patients is a p-value = 0.024 (p-value < α).* ***Conclusion:*** *The results of the Chi-square test showed a relationship between duration of dialysis and history of blood transfusion with HCV seroprevalence in hemodialysis patients at Gadjah Mada University Academic Hospital.*

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A B S T R A K

Latar belakang: Virus Hepatitis C (HCV) merupakan virus RNA dan menyebabkan penyakit hepatitis C. Pasien hemodialisis adalah kelompok yang mempunyai risiko tinggi terinfeksi HCV. Berdasarkan penelitian sebelumnya, durasi dialisis merupakan faktor risiko HCV. Faktor risiko penularan HCV pada hemodialisis juga melalui transfusi darah. **Tujuan:** Tujuan penelitian ini untuk mengetahui hubungan durasi dialisis dan riwayat transfusi darah dengan seroprevalensi HCV pada pasien hemodialisis di Rumah Sakit Akademik Universitas Gadjah Mada. **Metode:** Penelitian ini menggunakan desain penelitian cross-sectional. Data penelitian berdasarkan data sekunder rekam medis pasien hemodialisis di Rumah Sakit Akademik Universitas Gadjah Mada. Hasil dianalisis secara deskriptif dan statistik menggunakan uji Chi-square dengan derajat kemaknaan (α = 0,05). **Hasil:** Data yang diperoleh pada penelitian ini yaitu seroprevalensi HCV pada pasien hemodialisis di Rumah Sakit Akademik Universitas Gadjah Mada sebesar 20,5%. Hasil uji statistik hubungan durasi dialisis dengan seroprevalensi HCV pada pasien hemodialisis p-value = 0,021 (p-value < α), hubungan riwayat transfusi darah dengan seroprevalensi HCV pada pasien hemodialisis p-value = 0,024 (p-value < α). **Kesimpulan:** Kesimpulan dari penelitian ini didapatkan seroprevalensi HCV pada pasien hemodialisis sebesar 20,5 %. Hasil uji Chi-square menunjukkan adanya hubungan antara durasi dialisis dan riwayat transfusi darah dengan seroprevalensi HCV pada pasien hemodialisis di Rumah Sakit Akademik Universitas Gadjah Mada.

Kata kunci:
Transfusi darah, Virus hepatitis C, Hemodialisis

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INTRODUCTION

Hepatitis C Virus (HCV) is an RNA virus that causes hepatitis C disease. HCV that enters the body will trigger antibodies to HCV. HCV antibodies (anti-HCV) can be measured through a serological examination (Deniz and Akhan, 2023). HCV initially causes no symptoms and later develops into a chronic form, causing liver cirrhosis and liver cancer. An acute infection can result in severe liver damage and in rare cases, even lead to death (Niepmann and Gerresheim, 2020). Hemodialysis patients are a group at high risk of being infected with HCV. Hemodialysis is an invasive procedure that carries a risk of infection. Dialysis procedures, blood contamination on device surfaces, and the presence of a large number of patients undergoing dialysis in shared spaces are the causes of these risk factors. Hemodialysis patients infected with HCV can become carriers and have the potential to spread the virus in the hemodialysis environment. HCV infection within dialysis units suggests a nosocomial infection with various risk factors related to the dialysis procedure. The duration of hemodialysis was found to be an independent risk factor for HCV (Dharmesti *et al*., 2022). The incidence of hepatitis C in hemodialysis patients is much higher than in healthy subjects (Morishita *et al*., 2019).

According to the Global Hepatitis Report, people have chronic HCV infection an estimated 58 million with about 1.5 million new infections occurring per year (WHO, 2023). The prevalence of HCV in Indonesia is based on study data from the National Basic Health Research in 2014, which shows the prevalence of anti-HCV positive by 0.8 - 1% in Indonesia (Ministry of Health, 2019). HCV infection is asymptomatic in its earliest stages, but up to 30% of cases progress to cirrhosis within 10 to 30 years. The probability rate of complications of liver cirrhosis to hepatocellular carcinoma associated with HCV infection is about 1 to 4% every year (Bohorquez *et al*., 2023). The World Health Organization (WHO) estimated that 1 in 3 people in the world have been infected by either Hepatitis V Virus (HBV) or HCV, and 1.3 million people died as a result of this disease in 2015. It has been reported that approximately 185 million of those people are infected with HCV (Jefferies *et al*., 2018). Chronic HCV infection is a global health burden with an estimated prevalence varying between 0.6% – 10% (Modin *et al*., 2019). On the seroprevalence for HCV in blood donors at UTD PMI Semarang Java Middle in 2019, the percentage of HCV reactive blood was 0.2%, namely 183 bags out of 83.074 bags (Adhyatma *et al*., 2020). According to a study by Novayanti and Loesnihari (2019), the prevalence of patients with positive anti-HCV undergoing hemodialysis was 120 patients (93.7%) out of 128 patients.

Nosocomial transmission in hemodialysis patients infected with HCV can be caused by poor hygiene of dialysis equipment. The risk factor for transmission of hepatitis infection through hemodialysis is estimated at around 10% per year. Blood transfusions can also be a risk factor for HCV transmission in hemodialysis patients, who serve as a significant medium in the transmission of HCV infection. Most cases of hepatitis infection occur after blood transfusions. About 1 per 100.000 or 0.001% of units of blood used for transfusion are at risk of HCV contamination. The average prevalence rate of HCV infection in patients who receive packed red cell or plasma transfusions is around 19% (Alhawaris, 2019). Transmission of HCV also occurs through contact with the blood or body fluids of an infected person (Mustika and Simatupang, 2020).

Research on the relationship between risk factors for duration of dialysis and history of blood transfusion with HCV seroprevalence in hemodialysis patients at the Gadjah Mada University Academic Hospital (RSA UGM) has never been conducted. Patients with an anti-HCV reactive at the RSA UGM are not isolated and do not use special machines. Hemodialysis patients with reactive anti-HCV can use a re-dialyzer. The sterilization room for repeat dialyzer used in hemodialysis patients with reactive anti-HCV and non-reactive anti-HCV is a single room, with a separate washing area. The incidence of chronic kidney failure patients undergoing hemodialysis with hepatitis C seropositivity is an indicator of the quality of the hemodialysis unit at the RSA UGM. This research aimed to determine the seroprevalence of HCV antibodies in hemodialysis patients at the RSA UGM. The purpose of this research was also to determine the relationship between risk factors for the duration of dialysis and the history of blood transfusion with seroprevalence for HCV in hemodialysis patients at the RSA UGM.

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MATERIAL AND METHOD

The data collected were analyzed through univariate and bivariate analyses. The statistical test used for this research was chi-square with a 95% confidence level. This research has been registered and obtained a research ethics permit from the Health Research Ethics Commission, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University – Dr Sardjito General Hospital with registration number Ref. No.: KE/FK/0707/EC/2020 and date of approval June 30, 2020.

The type of research used was a cross-sectional study based on secondary data from medical records of hemodialysis patients at the hemodialysis installation and the integrated clinical laboratory installation at the RSA UGM. The inclusion criteria in this research were patients undergoing hemodialysis, aged ≥18 years old, and having complete medical record data at the RSA UGM hemodialysis installation. Exclusion criteria from this research were patients with infections of Human Immunodeficiency Virus (HIV), tuberculosis infection (tuberculosis), hepatitis B virus infection, and patients with incomplete medical record data.

Data collection was carried out in July 2020 in kidney failure patients undergoing hemodialysis in February 2020. The sample size for this research was an affordable population that met the patient selection criteria. Research was conducted on 83 hemodialysis patients undergoing dialysis in February 2020. The formula for Isaac and Michael's sample numbers was used to determine the minimum number of samples used in this research. The sampling technique was purposive sampling.

Data were collected through the Electronic Health Record (EHR) system at the UGM. The data collected included results of anti-HCV laboratory tests from hemodialysis patients, duration of dialysis, and history of blood transfusion. The first data taken were the results of laboratory tests for anti-HCV in hemodialysis patients. In this research, anti-HCV data were obtained by examining the Enzyme-Linked Fluorescent Assay (ELFA) method. The reagent used is Vidas Anti-HCV from bioMérieux SA which is produced in Marcy l'Étoile France. The result is considered positive (reactive) if the anti-HCV concentration through the ELFA method has a cut-off value of >1.0. Anti-HCV results are considered negative (non-reactive) if the anti-HCV concentration has a cut-off value <1.0. The duration of the patient's dialysis was then split into three criteria: (1) Hemodialysis patients for 0 to 12 months, (2) 12 to 24 months, and (3) More than 24 months. The third data taken were the history of blood transfusions of patients undergoing hemodialysis. The history of blood transfusion was then divided into two criteria, namely ever and never blood transfusion.

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RESULT

The research was conducted based on the secondary data from the medical records of hemodialysis patients taken in July 2020. The research was conducted on 83 hemodialysis patients that underwent dialysis in February 2020. The results of anti-HCV in hemodialysis patients are shown in Table 1, there were 17 patients with reactive HCV has a cut-off value >1.0, and 66 patients with non-reactive HCV has a cut-off value <1.0.

The seroprevalence of anti-HCV data in hemodialysis patients based on time dialysis shown in Table 2, There were 17 patients (27.9%) who were reactive to anti-HCV out of 61 patients undergoing hemodialysis >24 months. There were non-reactive anti-HCV in patients undergoing hemodialysis in the groups of 0 - 12 months and 12 - 24 months.

The seroprevalence of anti-HCV in hemodialysis patients based on gender is shown in Table 3, there were 7 male patients with reactive HCV and 10 women patients with reactive HCV. The seroprevalence of anti-HCV in hemodialysis patients based on the history of blood transfusion is shown in Table 4, there were 3 patients (60%) who were reactive to anti-HCV and never received a blood transfusion, while 14 patients (17.9%) ever had a blood transfusion.

The results of the Chi-square test of the relationship between duration of dialysis and seroprevalence of anti-HCV in hemodialysis patients at RSA UGM showed a significant level of p-value = 0.021, indicating the relationship between the duration of dialysis and seroprevalence of anti-HCV in hemodialysis patients at the RSA UGM. Reactive anti-HCV was present in 17 patients undergoing dialysis for more than 24 months. The results of the Chi-square test for the relationship between the history of blood transfusion and HCV seroprevalence in hemodialysis patients at the RSA UGM obtained a significant level of 0.024, so the results show that there is a relationship between the history of blood transfusion and HCV seroprevalence in hemodialysis patients at the RSA UGM. Reactive anti-HCV results were found in 14 hemodialysis patients who had a history of blood transfusions.

Table 1. Seroprevalence of anti-HCV in hemodialysis patients at the RSA UGM

Sample	Cut-off value	N	Prevalence (%)
Reactive anti-HCV	>1.0	17	20.5
Non-reactive anti-HCV	<1.0	66	79.5

Table 2. Seroprevalence of anti-HCV in hemodialysis patients based on time dialysis

Dialysis duration	N	Anti-HCV		
		Non-reactive (-)	Reactive (+)	Prevalence
		N	N	%
0 - 12 months	11	11	0	0
12 - 24 months	11	11	0	0
>24 months	61	44	17	27.9
p-value		0.021*		

* p-value < 0.05

Table 3. Seroprevalence of anti-HCV in hemodialysis patients based on gender

Gender	N	Results of reactive anti HCV (+)	Prevalence (%)
Man	43	7	8.4
Woman	40	10	12.1
Total	83	17	20.5

Table 4. Seroprevalence of anti-HCV in hemodialysis patients based on a history of blood transfusion

History of blood transfusion	N	Anti-HCV		Prevalence (%)
		Non-reactive (-)	Reactive (+)	
Never received blood transfusion	5	2	3	60
Ever had a blood transfusion	78	64	14	17.9
p-value		0.024*		

* p-value < 0.05

DISCUSSION

Hepatitis C Virus (HCV) is an RNA virus that attacks the liver and causes systemic infection. HCV infection is still common in developing countries, including Indonesia. HCV infection causes individuals to develop chronic hepatitis, hepatic cirrhosis, and hepatocellular carcinoma, making it a global health concern (Yerizel, 2018). The prevalence of chronic HCV worldwide is between 5% - 60% (Caragea *et al.*, 2018). Research conducted by Kerollos *et al.* (2020) shows that repeated blood transfusion, the handling by medical staff of equipment and blood products, and the insertion of temporary dialysis catheters were significant risk factors for HCV seroconversion. HCV transmission occurs primarily through exposure to blood contaminated with viruses, with most incidents in drug users injectable about > 80%, in patients with a history of transfusion and hemodialysis about 70% (Purwanita and Natsir, 2021).

The prevalence of patients with reactive anti-HCV undergoing hemodialysis in the study was 20.5%. Our results align with research conducted by Dharmesti *et al.* (2022) in Denpasar, Bali, Indonesia, that found that the total HCV seroconversion in dialysis patients was 94 out of 338 patients (27.8%). The research further showed that vascular access, dialyzer reuse, and type of HD unit consistently showed a significant association with HCV infection. Patients with reactive anti-HCV at the RSA UGM are not isolated and do not use special machines. Patients with reactive anti-HCV can use the dialyzer again, but the washing area is separated. Hemodialysis patients with reactive anti-HCV laboratory results are not re-checked every six months, but hemodialysis patients with non-reactive anti-HCV are routinely re-checked every six months. Data on anti-HCV results in hemodialysis patients were recorded in the hemodialysis unit. Universal precautions and precautions for routine infection control have also been carried out well in the RSA UGM hemodialysis unit. Dialyzer was sterilized by using Renalin ™ 100 Cold Sterilant. The composition of Renalin consists of 20% hydrogen peroxide, 4% peracetic acid, and 76% inert ingredients. Contamination directly or indirectly through the dialyzer can occur. Another factor that hemodialysis patients experience is changes in the immune system, which cause the immune system to decrease, making it easier for infections to occur. Additionally, HCV infection, which may have occurred before hemodialysis, cannot be ruled out.

This research found that 27.9% of the patients undergoing hemodialysis for >24 months were reactive for anti-HCV. The duration of dialysis is a risk factor for the transmission of HCV infection. Long dialysis can describe the presence of nosocomial transmission. The transmission can occur through dialyzer reprocessing or failure of infection control. Patients may be in the window period at the time of the first examination. The major limitations of anti-HCV testing are its inability to differentiate between acute, past, and persistent infection and its poor sensitivity in the early treatment window during the first 4-6 weeks of infection (Kannan *et al.*, 2021).

The seroprevalence of reactive anti-HCV in patients with a history of blood transfusion was 17.9%, and the seroprevalence in patients who never received blood transfusion was 60%. Providing blood transfusions is a major risk factor for the transmission of HCV. The results of the anti-HCV examination can yield false negative results, particularly during the window period. Anti-HCV antibodies may only be detected 30 - 60 days after infection; hence, a confirmation test for HCV RNA was needed (Jatikusuma, 2018).

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Blood product screening for HCV is a very effective way of preventing transmission of HCV infection. The risk factors for HCV from previous studies among hemodialysis patients are blood transfusion, multiple visits to different hemodialysis, and frequency of hemodialysis. Research conducted by Chizoba and Chiboguwo (2018) showed there was a significant association between the duration of dialysis and HCV infection. Patients with a longer duration of dialysis of >1 year had the highest prevalence of HCV at a rate of 36.4%; furthermore, those who had blood transfusions (5 times) showed the highest prevalence of HCV infection. Reactive anti-HCV results were more frequently discovered in patients undergoing dialysis for more than 24 months. The patient's dialysis time was calculated from the time the patient first underwent hemodialysis at the RSA UGM until February 2020.

In Indonesia, treatment is usually not given to hemodialysis patients with HCV infection, and data on the progression to liver cirrhosis is not documented (Lidya *et al.*, 2019). The Indonesian Nephrology Association (PERNEFRI) in 2006 issued recommendations for controlling nosocomial transmission of HCV infection in hemodialysis units. A study conducted by Lidya *et al*. (2019) in the three hospitals at the hemodialysis unit of Cipto Mangunkusumo Hospital, Persahabatan Hospital, and Fatmawati Hospital in Jakarta, Indonesia, the process of using the dialyzer is currently carried out using a separate machine. A multicenter study showed HCV seroconversion was reduced from 1.41% to 0% per year by adopting stricter universal treatment measures. Good universal prevention can prevent nosocomial transmission of HCV in hemodialysis units (Lidya *et al.*, 2019).

In this research, a significant association was discovered between blood transfusion and HCV seroprevalence in hemodialysis patients at the RSA UGM. Here, it was found that the prevalence of reactive anti-HCV was higher in patients who had a history of blood transfusions compared to patients who did not have a history of transfusions. Blood transfusions are an important factor in the transmission of HCV infection. Kerollos *et al*. (2020) found a highly statistically significant difference between HCV seroconverted and HCV seronegative patients regarding the history of previous blood transfusion. Frequent blood transfusions over a long period of time can increase the risk of being infected with HCV.

The prevalence of HCV was 0.7% worldwide, with approximately 56.8 million HCV infections (Tang *et al.*, 2023). The prevalence of HCV in donor blood in Central Blood Transfusion in Lampung was 0.30% (Aditya *et al.*, 2022). The prevalence of HCV in the blood donors at the Blood Transfusion Unit in Bantul, Indonesia, in 2019 - 2020 was 0.15%. The prevalence in 2019 was 0.14%, and in 2020 it was 0.16% (Martias *et al.*, 2022). Anti-HCV screening test on blood donors or blood products and organ donors is very important to prevent transmission of HCV. Many cases of HCV infection occurred after blood transfusions. Approximately 1 per 100.000 or 0.001% of units of blood used for transfusion are at risk of being contaminated with the HCV (Alhawaris, 2019).

HCV is transmitted through blood transfusion, and screening blood donors can lower the risk of transfusion-transmitted HCV. Window periods, rare subtypes, viral variants, and immune silence are the main causes of safety hazards in blood transfusion, which can result in false negative test results (Zhou *et al.*, 2023). Product screening blood only with anti-HCV examination can result in the transmission of HCV infection from blood transfusions. The seroconversion period from the incident infection to the detection of anti-HCV was 4 – 6 months, and the false positive rate was up to 70% in blood donors from low-endemic areas. Recommended HCV examination includes Enzyme Immunoassay (EIA) or Nucleic Acid (NAT). Examination of HCV RNA by RT PCR is the most sensitive and specific method for detecting HCV (Jiang *et al.*, 2021). The use of erythropoietin to reduce blood transfusions can also lower the prevalence of HCV infection. This method can reduce the risk of transmission of HCV infection (Lydia *et al.*,2019).

This research's limitation was that hemodialysis patients with reactive anti-HCV at the RSA UGM were not re-checked every six months. Data collection was done through the EHR so that blood transfusion or dialysis data received by the patient that are not included in the system are not recorded in this research. Data on the history of blood transfusions and duration of dialysis from patients who performed before undergoing hemodialysis at the RSA UGM were not recorded in this research. Data on the number of patients that have received blood transfusions and those that have never received blood transfusions are uneven due to the number of dialysis patients undergoing blood transfusions based on dialysis patients experiencing blood deficiency according to laboratory results. The clinical condition of hemodialysis patients and the results of complete blood tests determine the decision for blood transfusion by the doctor in charge of the hemodialysis patient. The use of the Chi-Square test is also a limitation of this research because it only provides information about whether or not there is a relationship between the two variables, while the size of the relationship between the two variables and the direction of the relationship are not revealed by this test.

The study can be continued by including other risk factors for HCV seroprevalence. HCV testing in hemodialysis patients with reactive anti-HCV can be confirmed using HCV RNA testing and re-examination every six months. This research can be used as a basis for a policy on handling reactive HCV in hemodialysis patients at the RSA UGM.

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CONCLUSION

There is a relationship between the duration of dialysis and a history of blood transfusion with the seroprevalence of HCV in hemodialysis patients at the RSA UGM.

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