The Role of Genedrive in *Point of Care* Method For Hepatitis C Elimination in Hemodialysis Center

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ABSTRACT

Background: *Point of care is laboratory testing conducted close to the site of the patient. Point of care assessment is essential to detect and treat the hepatitis C virus in a single visit. The potential use of Genedrive extends to remote areas and key populations Therefore, there is a need for a simple, and cost-effective examination of methods, such as Genedrive. Genedrive is a rapid and low-cost diagnostic tool for the identification and treatment selection of infectious diseases. The World Health Organization targets to eliminate hepatitis by 2030, which decreases infections by 90%, and decreases deaths by 65%. Point of care could play a significant role in contributing to the elimination of hepatitis C. Chronic kidney disease (CKD) patients on hemodialysis are among the population at risk of hepatitis C due to nosocomial transmission. This study aimed to assess the role of Genedrive in measuring hepatitis C in chronic hepatitis C patients with chronic kidney disease on hemodialysis.* ***Methods:*** *This study used a cross-sectional design. There were 64 CKD on Hd patients in Cipto Mangunkusumo Hospital tested by Genedrive. ROC analysis was conducted to assess significant hepatitis C among chronic kidney disease on hemodialysis.* ***Results:*** *The calculated detection limit of Genedrive was $3.1x10^3$ IU/mL. Genedrive HCV assay showed 90.6% sensitivity, 96.8% specificity, 92% negative predictive value, and 97% positive predictive value to detect HCV, 10.36 positive likelihood ratio, and 0.09 negative likelihood ratio.* ***Conclusion:*** *Genedrive could be a simple and reliable point of care method to detect hepatitis C with chronic kidney disease on hemodialysis.*

Keywords: *Hepatitis C, chronic kidney disease, hemodialysis, genedrive, point of care.*

INTRODUCTION

Globally, 58 million people are living with Hepatitis C virus infection.[1] Based on a systematic review and meta-analysis study, it was estimated that the prevalence of hepatitis C was 1.8% (95% CI: 1.4%-2.3%) [2] In Indonesia, the prevalence of anti-HCV positive is 1.01% or around 2.5 million people.[3] Chronic kidney disease (CKD) is also a significant global health issue, affecting over 800 million individuals with a prevalence of 10%.[4] In Indonesia, the prevalence of CKD is 0.38% or approximately

713.783 people.[5] Moreover, up to 11% of patients with stage 3 CKD may progress to end-stage kidney disease due to untreated kidney fibrosis.[6]

Hemodialysis, as one of the vital clinical practices for end-stage renal diseases, is a frequent site for HCV infection in patients undergoing hemodialysis therapy, primarily due to nosocomial transmission. According to research conducted by Widhani (2017) at Cipto Mangunkusumo Hospital, the prevalence of hepatitis C in CKD on hemodialysis patients was 38%.[7] CKD on HD patients with hepatitis C have a higher risk of experiencing a more rapid decrease in kidney function. A meta-analysis study found that hepatitis C on hemodialysis had a relative risk of death of 1.35% (95%CI: 1.25- 1.47)[7]. Therefore, routine screening for hepatitis C is necessary for hemodialysis patients to prevent the transmission of Hepatitis C. It aligns with the WHO's 2030 target to eliminate hepatitis, which aims to reduce hepatitis incidence by 90% and mortality by 65%.[8]

According to the Guidelines from the Centers for Disease Control and Prevention (CDC), screening for HCV is crucial in patients with high-risk infections, particularly in those undergoing hemodialysis. Hepatitis C testing is generally based on enzyme immunoassays, a serological test to detect the presence of HCV antibodies. Anti-HCV will have positive long life, even if the HCV RNA was no detected. Hence, the patient needs a confirmation test.[9] Confirmation of HCV RNA in a patient is important for establishing the treatment.[11] The current gold standard for HCV RNA detection is Nucleic Acid Amplification Test (NAT) such as RT PCR (Genexpert). However, this method requires relatively high costs, sophisticated laboratory equipment, and trained laboratory technicians.[10]

Utilization point of care HCV assays that can detect active infection and provide a diagnosis in a single visit, thereby optimizing the care continuum.[12,13] Point of care is laboratory testing conducted close to the site of the patient. POC needs to be further decentralized, thereby increasing diagnostic and treatment options for Hepatitis C patients One of the points of care that can detect hepatitis C is Genedrive. Genedrive is a rapid and low-cost diagnostic tool for the identification and treatment selection of infectious diseases. Based on the study, Genedrive has good sensitivity and specificity results for the qualitative detection of HCV RNA (98.6%vs 100%).[14] However, there have been no validation studies of the Genedrive HCV Kit in special populations, such as chronic kidney disease on hemodialysis patients, who are at high risk for hepatitis C transmission. Thus, in this study, we aim to assess the role of Genedrive to detect hepatitis C in chronic hepatitis C patients with chronic kidney disease on hemodialysis, which has never been done before, both in the world and Indonesia.

METHODS

Design Study

This study used a *cross-sectional* design. ROC analysis was conducted to identify the optimal cut-off values to assess significant hepatitis C among chronic kidney disease on hemodialysis.

Patients

A total of 64 chronic kidney disease patients on hemodialysis were selected from Cipto Mangunkusumo National General Hospital in Jakarta, Indonesia. Inclusion criteria include chronic kidney disease with hemodialysis. Exclusion criteria include: (i) being diagnosed with hepatitis B, HIV, or HCC, (ii), having ascites. Baseline data such as age, sex, and HCV antibody were analyzed. The study was approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia (ethical clearance certificateNo.317/UN2.F1/ETIK/PPM.00.02/2021), and informed consent was obtained from each participant.

Genedrive HCV RNA

The Genedrive HCV Kit is a qualitative test for hepatitis C. This examination required 30 µL of blood plasma or serum, which was then diluted with 60 µL of water. The diluted sample was placed into the channel, with 15 µL for each of the three channels. The HCV RNA test will take approximately 60 minutes. The results will be presented in qualitative forms, including positive, negative, indeterminate, and invalid.

GeneXpert (Cepheid) HCV RNA Viral Load at the Reference Laboratory

GeneXpert HCV RNA is a quantitative test for Hepatitis C test that utilizes the real-time PCR method. This kit is routinely used in the CMH laboratory and serves as the gold standard for diagnosing Hepatitis C. The process of running HCV viral load GeneXpert is using 9ml of whole blood. Results were interpreted quantitatively in units of IU/mL within 105 minutes. The GeneXpert threshold for non-detection is 1 log 10 IU/mL, while a detection result yields a value above 8 logs 1- IU/mL. In the case of invalid results, the test is repeated until valid results are obtained.

Statistical Analysis

The collected data was analyzed using SPSS 23. Baseline characteristic data, such as age, sex, and hepatitis status, were described as a proportion if the data is categorical and in the form of mean or median if the data is numerical. Diagnostic tests were carried out by determining sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LRs +), and negative likelihood ratio (LRs -). Receiver Operating Characteristic (ROC) analysis was conducted to identify the optimal cutoff values to assess significant hepatitis C among chronic kidney disease on hemodialysis.

RESULTS

Baseline Characteristic of Study Participants

According to the data presented in **Table 1**, the study consisted mainly of male participants, representing 51.65% of the total sample. The mean age of the participants was (**Table 1**). 49.42 ± 15.37 years and the highest percentage of samples testing positive for anti-HCV was 67.2%.

Based on **Table 2**, of 64 samples, the twenty nine samples were detected both in Genedrive and GeneXpert. Amongst 30 positive samples in Genedrive, 1 samples were detected as negative by GeneXpert. and the results of the probability test between Genedrive and GeneXpert showed a *p-value* <0.001, indicating a significant correlation. It means that the higher the virus load, the higher it is detected on Genedrive, while the lower the virus load, the lower the load detected on Genedrive.

Cut-off Values of Genedrive for Detection of Significant HCV RNA among Chronic Kidney Patients Hemodialysis

ROC analysis was performed to evaluate the diagnostic performance of Genedrive in detecting significant HCV RNA in CKD patients who were on hemodialysis. The results revealed an AUC of 0.966 (95% CI: 0.872-1.000) for Genedrive (**Figure 1**). The determined cut-off value for HCV RNA detection was $3.1x10^3$ COI, with a sensitivity of 90.6%, specificity of 96.8%, negative predictive value (NPV) of 92%, and positive predictive value (PPV) of 97%. The diagnostic positive and negative likelihood ratios of the Genedrive assay to detect HCV RNA were 10.36 and 0.09, respectively (**Table 3**).

DISCUSSION

WHO has identified five different HCV viral load assays for confirmation purposes. These include three laboratory-based assays, specifically Abbott Real time HCV PCR, Alinity m HCV RT-PCR, and Abbott Architect HCV Ag, as well as two point-of-care assays, namely Xpert HCV viral load and Genedrive HCV.[15] To our knowledge, this is the first study to detect

Tabel 1. Baseline Characteristic of Study Participants.

Characteristics	Patient Number
Patients	n= 64
Sex, n (%)	
- Male	33 (51.6)
- Female	31 (48.4)
Age (mean ± SD)	49.42 ± 15.37
HCV antibody, n (%)	
- Reactive	43 (67.2)
- Non-reactive	21 (32.8)

Table 2. Qualitative results of viral load in Genedrive and GeneXpert.

Gene-drive	GeneXpert Viral load - n (%)			p-Value
	Virus detected	Virus not detected	Total	
Virus detected	29 (96.7%)	1 (3.3%)	30 (100%)	<0.001
Virus not detected	3 (8.8 %)	31 (91.2%)	34 (100%)	

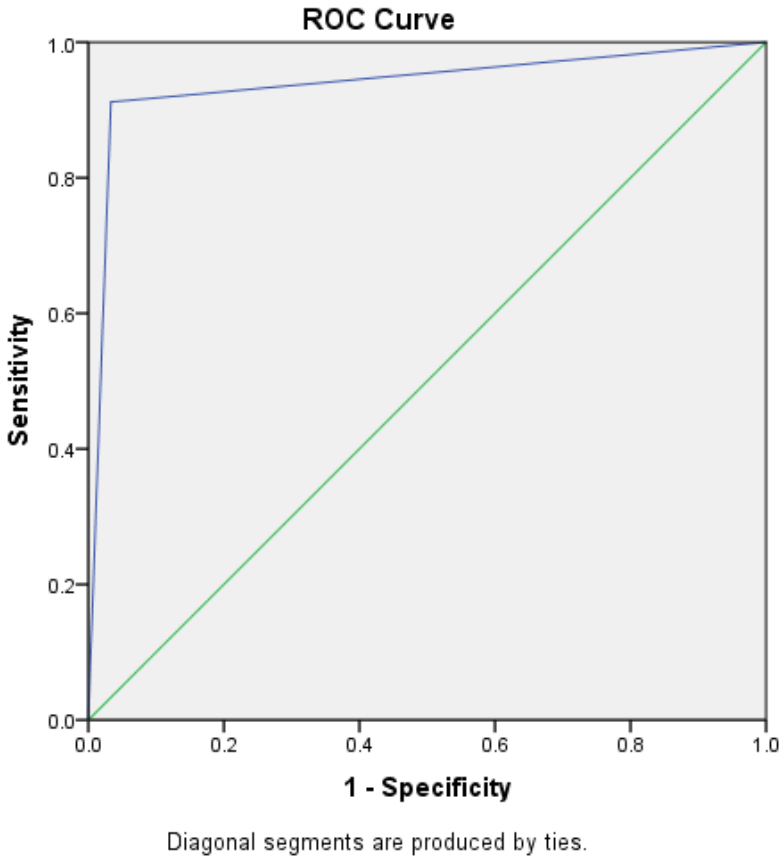

Figure 1. ROC Graphs of HCV RNA for Evaluating Significant Genedrive

Table 3. Cutt- Off Genedrive for Evaluating Significant HCV RNA in Chronic Kidney Diasease Patients on Hemodialysis.

	Cutoff	AUC	Sen	Spe	NPV	PPV	LR +	LR -
HCV RNA	3.1 x 10^3	0.966 (0.872-1.000)	0.906	0.968	0.92	0.97	10.36	0.09

Hepatitis C in CKD patients on hemodialysis diagnostic performance of qualitative Genedrive assay.

This study demonstrated excellent diagnostic accuracy in detecting HCV RNA in CKD patients on hemodialysis, as evidenced by the ROC analysis result (AUC: 0.966). The Genedrive assay exhibited high sensitivity and specificity of 90.6% and 96.8%, respectively. The results of a study conducted by Lamoury (2021) demonstrated that the Genedrive assay detected HCV RNA in chronic hepatitis C infection population had a specificity of 99.5% (95% CI:97.4-100).[16] The WHO has acknowledged the high sensitivity and specificity values above 95% and 98%, respectively. Therefore, the WHO has validated the Genedrive HCV RNA test as a qualitative method for detecting Hepatitis C.[17,18]

The cut-off level limit of detection in this study was 3.1 x 10^3 IU/mL. The detection limit of Genedrive in this study aligns with the limit set by the WHO, which is 3000 IU/mL.[19] Other studies have reported a lower detection limit of Genedrive, specifically 2362 IU/mL using 30µL of plasma, which is lower than the limit for GeneXpert (10 IU/mL or 1 mL plasma).[20] In this study, there was one false positive result of Genedrive, and there were three false-negative results using Genedrive. Another study reported there was one false positive results, and eight false-negative results of Genedrive.[16] Thus, this study found significantly fewer false negatives in comparison to previous research on Genedrive.

The results of this study, obtained from frozen samples, demonstrated excellent diagnostic accuracy in detecting significance, as indicated

by the positive likelihood ratio of 10.60 and negative likelihood ratio of 0.09. Meanwhile, the research conducted by Llibre (2017) utilizing frozen samples yielded the negative likelihood ratio was of 0.014. These findings imply that the outcomes of this study carry greater significance when compared to a previous study.[14]

The benefits of Genedrive include its portability, which allows it to be used in various settings including remote communities and special populations. Genedrive simplifies specimen collection, eliminating the need for a centrifuge or complex laboratory equipment. This enables immediate diagnosis and treatment for patients with Hepatitis C.[14,21] This portable testing method can be deployed in rural and remote areas. It is particularly suitable for countries with limited resources.[22]

Decentralization testing through *point of care* has the potential to facilitate the improvement of diagnostic tests for Hepatitis C, enabling faster treatment outcomes.[23] Currently, many countries have difficulties detecting hepatitis C elimination programs in identified patients.[24] Australia has found a way to eliminate hepatitis C through point-of-care treatment provided by the "Kombi Clinic," a mobile clinic that operates using a car. The Kombi Clinic aims to offer free HCV checks and reach communities that are closer and more easily accessible. Therefore, this strategy is easier to implement and can lead to the eradication of Hepatitis C.[25] Research in other countries in Norway showed that hepatitis C elimination with the GeneXpert HCV can be done with a "mobile clinic" because it is considered effective and feasible to reach the People Who Inject Drug.[26]

Genedrive has several limitations. Firstly, there is a risk of haemolysis, this occurrence can be attributed to various factors such as inconsistent sample storage temperatures, delays in processing hepatitis C samples from the time of collection, and variations in operators handling the samples.[14] Therefore, conducting a Genedrive examination requires experienced operators to ensure reliable and valid results while minimizing the rate of invalidity. According to a study conducted by Lamoury (2021), the rate of invalidity for Genedrive was 1.6%, which is lower than the WHO recommended rate of 3.1%.[16]

Nevertheless, to the best of our knowledge, this is the first study to evaluate the the diagnostic performance of Genedrive for detection of hepatitis C in hemodialysis patient in the world and Indonesian population. The result of this study may serve as foundation for further research and the development of policies aimed at detecting and eliminating hepatitis C, especially within special populations.

CONCLUSION

Genedrive examination demonstrates excellent sensitivity, specificity, negative predictive value, positive predictive values, positive likelihood ratio, and negative likelihood ratio. Thus, Genedrive could be a simple and reliable diagnostic tool to detect in chronic hepatitis C patients with CKD on HD.

DATA AVAILABILITY

The dataset generated and/or analyzed during the current study is available from the corresponding author upon reasonable request.

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