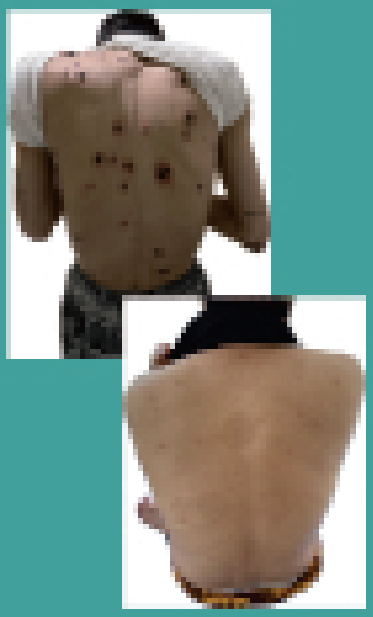
ISSN 0125-9326

Volume 56, Number 1, January 2024

Acta Medica Indonesiana

# The Indonesian Journal of Internal Medicine

A Publication of The Indonesian Society of Internal Medicine



IJIM

# Antimicrobial Resistance Issue: A Matter of Practice and Capacity to Conduct an Audit

*Erni Juwita Nelwan**

Division of Tropical Medicine and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Corresponding Author:***
*Prof. Erni Juwita Nelwan, MD., PhD. Division of Tropical Medicine and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: erni.juwita@ui.ac.id.*

The World Health Organization released the practical toolkit for antimicrobial stewardship in health-care facilities in low- and middle-income countries in 2019 due to increasing rates of antimicrobial resistance (AMR) causing the diminishing of treatment options and that the available antibiotics seem to no longer work. The introduction of this toolkit indicates the need to be more down-to-earth in combating the problems of antimicrobial resistance.

This situation happened because we have taken antibiotics for granted for too long with less awareness, which results in the potential loss of its use and benefits. On the other hand, even though medicine is available, a major issue on the limited access to antibiotics are still reported in many parts of the world.[1]

Limato R, et al.[2] in 2022 reported in 'The Lancet', based on the real-world situation on the practice of antibiotics use and its potential intervention, it appears that context-specific intervention strategies are needed for the Indonesian setting. There are approximately 9000 current reports related to the context of AMR. The evidence for the need of prudent antibiotics use is clear, yet unfortunately the prescribing of antibiotics by physicians might not much improved for the past years. A study by Ginting et al.[3], evaluated the diagnosis and strategy for antibiotics prescription in 2021 among severely ill patients with sepsis, showed that the practice of obtaining evidence for the pathogen as the cause of infection (e.g blood cultures or any cultures) needed to be encouraged for Indonesian physicians. As it was shown in the paper, nearly 50% (n=525) of patients received antibiotics with unknown reasons.

The need of doing an audit is clear. Nelwan et al.[4] in 2022 presented a study on the mechanism of implementing an audit by conducting an audit at the national referral hospital, Cipto Mangunkusumo Hospital; by comparing 'traditional' hospital clinical rounds using the Gyssens flowchart with reference to the Point Prevalence Survey (PPS). This report is relevant to the fact that, the clinical round might not be suitable due to the limited number of human resources including experts specializing in the field of Tropical infection and and the availability of microbiology specialists. There is also a high number of patients with low number of opportunities to sit and discuss cases, and lack of regular audits to search for the root cause of a problem to provide grounds for improvement.

The problem of antimicrobial resistance extended to the community; the population that is difficult to evaluate. In a hospital setting, patients are expected to be monitored which allows data to be gained easily. One way to learn about this is by measuring the quantitative report of the Defined Daily Dose (DDD) as reported by Apriyanti et al.[5] in Bengkulu, Indonesia. This group classified the prescribing of antibiotics in accordance to the WHO classification release in 2019 that describes the Access, Watch and Reserve (AWARE) criteria, which is also

adopted by The Ministry of Health Republic of Indonesia. Moreover, the commitment to combat resistance is also demonstrated by the Indonesian government through the establishment of the National Committee of Antibiotics mentioned in Permenkes no. 8 (2015) that is adopted in each hospital and the upscaling of the issues of Antimicrobial Resistance to become one of the national priorities and program.[6]

In this issue, Fadrian, et al.[7] conducted a study to measure the quality of antibiotics use at the western part of Indonesia. In 2021, research was conducted at the Dr. M. Djamil Hospital, Padang in which, during the COVID-19 pandemic, the inappropriate antibiotics use in this hospital was reported high using Gyssens flowchart.

Every year between 18 to 24 November, we are celebrating the World AMR Awareness Week, with a strong hope to reduce the number of deaths which is at an estimate of 1.27 million people in 2019 who have been presumed to have died as a result to drug resistance.

The hope must be followed by a strong commitment and understanding of the risk of overprescribing antibiotics, and if we ignore this, there will be a chance of a 9 times increase in mortality rates which translates to up to an estimate of 10 million deaths per year after 2050.[8]

## REFERENCES


1. Antimicrobials stewardship programmes in health-care facilities in low- and middle-income countries [Internet]. Available from: https://iris.who.int/bitstream/handle/10665/329404/9789241515481-eng.pdf
2. Limato R, Lazarus G, Dernison P, et al. Optimizing antibiotic use in Indonesia: A systematic review and evidence synthesis to inform opportunities for intervention. The Lancet Regional Health - Southeast Asia [Internet]. 2022;2. Available from: https://www.thelancet.com/journals/lansea/article/PIIS2772-3682(22)00013-0/fulltext
3. Ginting F, Sugianli AK, Barimbing M, et al. Appropriateness of diagnosis and antibiotic use in sepsis patients admitted to a tertiary hospital in Indonesia. Postgraduate Medicine [Internet]. 2021;133(6):674–9. Available from: https://scholar.unair.ac.id/en/publications/appropriateness-of-diagnosis-and-antibiotic-use-in-sepsis-patient
4. Nelwan EJ, Guterres H, Pasaribu AI, Shakinah S, Limato R, Widodo D. The comparison of point prevalence survey (PPS) and Gyssens flowchart approach on antimicrobial use surveillance in Indonesian National Referral Hospital. Acta Med Indones - Indones J Intern Med [Internet]. 2022;53(4):505. Available from: https://www.actamedindones.org/index.php/ijim/article/view/1779
5. Apriyanti YF, Saepudin, Siti Maisharah S. Gadzi. Five years outpatients antibiotics consumption at public tertiary hospital in Bengkulu according to access, watch and reserve classification. Jurnal Farmasi dan Ilmu Kefarmasian Indonesia [Internet]. 2023;10(3):360–8. Available from: https://e-journal.unair.ac.id/JFIKI/article/download/50344/27453/270342
6. Permenkes no. 8 tahun 2015 Tentang Program Pengendalian resistensi antimikroba di Rumah Sakit [Internet]. [cited 2024 Jul 9]. Available from: https://peraturan.go.id/id/permenkes-no-8-tahun-2015
7. Fadrian, Aliska G, Utami WN. The relationship between appropriateness of antibiotic use based on the Gyssens algorithm and mortality: A retrospective cohort study in Indonesian tertiary hospital. Acta Med Indones - Indones J Intern Med. 2024;56(2):137-44.
8. World Antimicrobial Awareness Week 2024 [Internet]. www.who.int. Available from: https://www.who.int/campaigns/world-amr-awareness-week/2024.

# Diagnostic Accuracy of Serum Procalcitonin to Diagnose Sepsis in Advanced Solid Tumor Patients with Fever

*Erni Juwita Nelwan[1,2], Reza Nugraha Yulisar[3], Randy Adiwinata[4], Ikhwan Rinaldi[5], Cleopas Martin Rumende[6], Robert Sinto[1]**

[1]Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[3]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Department of Internal Medicine, Faculty of Medicine Sam Ratulangi University, Manado, Indonesia.
[5]Division of Hematology-Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[6]Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Corresponding Author:***
*Robert Sinto, MD. Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 71, Jakarta 10430, Indonesia. Email: robert.sinto@ndm.ox.ac.uk.*

## ABSTRACT

***Background:*** *Diagnosis of infection in advanced solid tumor patients can be challenging since signs and symptoms might be overlapping due to paraneoplastic condition. Delay diagnosis of existing infection can lead to more severe conditions and increased mortality. Procalcitonin (PCT) has been used to support the diagnosis of bacterial infection and sepsis. Unfortunately, PCT also increases in malignancy even without an infection. We investigated the diagnostic accuracy of PCT in advanced solid tumor patients with fever to diagnose sepsis.* ***Methods:*** *A cross-sectional study was conducted in solid advanced tumor patients with fever patients who were admitted to Cipto Mangunkusumo Hospitals, Indonesia between June 2016 and April 2018. Sepsis was defined using 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference criteria. The diagnostic accuracy of PCT was determined using the receiver operating characteristic (ROC) curve.* ***Results:*** *A total of 194 subjects were enrolled in this study. 60.3% were female with a mean age of 49.47±12.87 years old. 143 patients (73.7%) with advanced solid tumors. Among this latter group, 39 patients (27%) were sepsis. The ROC curve showed that the levels of PCT for sepsis in advanced solid tumor patients with fever were in the area under the curve (AUC) 0.853 (95%CI 0.785 – 0.921). The Cut-off of PCT in advanced solid tumor patients with fever to classify as sepsis was 2.87 ng/mL, with a sensitivity of 79.5%, and a specificity of 79.8%.* ***Conclusion:*** *PCT has good diagnosis accuracy in advanced solid tumor patients with fever to classify as sepsis, however a higher cut-off compared to non-cancerous patients should be used.*

***Keywords:*** *Procalcitonin, Solid tumor, Advance Stage Cancer, Sepsis, Cut-off.*

## INTRODUCTION

Cancer patients have a higher risk of acquiring infection, which may be caused by impaired immunity due to cancer treatment-related adverse events, underlying immune dysregulation, and associated comorbidities. Infections in cancer patients may lead to serious outcomes.[1] Study showed cancer patients with fatal infections had almost three times higher mortality rates compared to general populations.[2] Another study showed infection may be the cause of death in 60% of cancer patients.[3] Sepsis, which is a life-threatening condition due to organ dysfunction caused by a dysregulated host response to infection, was more commonly found among cancer patients.[4] Lower survival rate was found in cancer patients group with sepsis compared to non-cancer patients, therefore early diagnosis and aggressive treatment are important in managing this high-risk group.[5]

Diagnosing infection in patients with cancer was challenging. Fever, which is commonly caused by infections, may also occur in cancer patients and is not related to infectious causes.[6] Several noninfectious causes of fever in cancer patients may be caused due to chemotherapy-induced mucositis, neoplastic fever, drug-induced fever, and others.[7] Inappropriate use of antibiotics in cancer patients with fever may lead to antimicrobial resistance.[8] Therefore, several biomarkers were evaluated to differentiate between infectious and noninfectious causes of fever in cancer patients. Leukocytosis, which is usually an indicator of underlying inflammation or infection, was reportedly found in 4.0-25.6% of patients with solid tumors.[9] Procalcitonin (PCT) has been commonly used as a specific marker for bacterial infection and sepsis, however, studies showed that PCT level may be influenced by solid tumor presence. Therefore, some authors proposed a higher cut-off serum PCT level for diagnosing sepsis in cancer patients. The stage of cancer also proposed may influence the PCT cut-off level. Many variations of cut-off levels were reported between studies, establishing a challenge for PCT level interpretation, especially in advanced-stage tumor patients.[10,11] We aimed to find out the cut-off point of PCT for diagnosing sepsis in advanced solid tumor patients with fever in the Indonesian population.

## METHODS

### Study Design

A cross-sectional study was conducted on solid tumor patients with fever who were admitted to Cipto Mangunkusumo Hospitals, Jakarta, Indonesia between June 2016 and April 2018. Subjects were chosen consecutively from surgical and non-surgical wards, emergency departments, and outpatients.

### Study Participants

Study participants were adult solid tumor patients who had a complete staging confirmed by histological, imaging examinations, and had acute fever during inclusion (temperature > 38.3$^{o}$C). Patients with any conditions that can influence serum PCT were excluded (medullary thyroid carcinoma, neuroendocrine lung cancers, previous antibiotics therapy within the last 72 hours, shock, recent surgical, multiple trauma, resuscitation, dialysis, cirrhosis, or received any colony-stimulating factors). Informed consent forms were completed by each subject before enrolling in this study. All subjects underwent history taking, physical examinations, chest x-rays, and laboratory examinations (complete blood count, blood glucose, blood urea nitrogen, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urine analysis, serum PCT, blood and site-specific culture). Patients with any conditions that can influence serum PCT were excluded. Tests of liver ultrasound and hepatitis markers were done in patients with increased ALT, AST, or any suspicion of cirrhosis. Sepsis was defined according to 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (documented infections and either of the general parameters: fever >38.3$^{o}$C, hypothermia <36$^{o}$C, heart rate >90 bpm, tachypnea > 30 bpm, altered mental status, significant edema or positive fluid balance (>20 ml/kg over 24 hours), hyperglycemia plasma glucose >140 in the absence of diabetes, and bacteremia).[12]

Tumor staging was reviewed by a certified oncologist according to the American Joint Committee on Cancer (AJCC) criteria. All subjects were already examined and confirmed histopathologically by an experienced pathologist

from the Department of Pathology Cipto Mangunkusumo Hospital. The types of tumors were grouped into head and neck, colorectal, musculoskeletal, breast, lung, genitourinary, gynecology, and pancreaticobiliary. Tumor staging was grouped into early and advanced stages (locally advanced and metastasis).

### Laboratory Examinations

Blood was taken by a certified nurse and processed according to the hospital's standard protocol. PCT levels were measured in the Department of Clinical Pathology Cipto Mangunkusumo Hospital laboratorium using the BRAHMS PCT KRYPTOR® tool, which was calibrated as specified by the manufacturer's protocol. This tool has a lower limit of quantification of 0.02 ng/mL. BACTEC bottles were used for blood culture media. Standard media transport was used for site-specific culture (urine, feces, sputum, etc). All examinations were run through the appropriate machines which were calibrated and generated automatically. We considered that the investigators of the laboratory were blinded, as the laboratory staff were not included in the investigation team and did not know about the subjects.

### Statistical Analysis

Analysis was done using the Statistical Package for the Social Sciences (SPSS), v.22 (IBM-corp. Armonk, NY) software. Mann-Whitney test was used to compare WBC and PCT values between groups. The *p-value* <0.05 was considered statistically significant. The cut-off point of PCT level for sepsis in metastatic solid tumor subjects with fever was done by AUC analysis from the ROC curve.

### Ethical Consideration and Approval

This study was performed under the Declaration of Helsinki, the World Health Organization, and the ICH guideline for good clinical practice. The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia (235/UN2. F1/ETIK/2016). All study respondents were given study information, the study purpose, and the confidentiality of the result. All patients provided written informed consent to participate before study inclusion.

## RESULTS

194 subjects participated in this study, mean age of 49 years old and predominantly female. Gynecology cancer was the most common type, followed by head and neck, colorectal, breast, genitourinary, and pancreaticobiliary cancer. Subjects were divided into early and advanced stages. We also divided subjects into sepsis and non-sepsis groups. There were 143 patients included in the advanced stage according to AJCC criteria. A total of 39 advanced solid tumor patients were diagnosed with sepsis, mostly caused by pneumonia. Bacteremia was found in 16 patients, among them we found 4 patients with only blood showed positive culture. Subject characteristics are shown in **Table 1** and advanced solid tumor patients with sepsis are shown in **Table 2**.

**Table 1.** Baseline characteristics of the subjects.

| Characteristics | N=194 |
|---|---|
| Age, years, mean±SD | 49.47±12.873 |
| Sex, n (%) | |
| Male | 77 (39.7) |
| Tumor group, n (%) | |
| Gynecology | 49 (25.3) |
| Head and neck | 47 (24.2) |
| Colorectal | 21 (10.8) |
| Breast | 18 (9.3) |
| Genitourinary | 17 (8.8) |
| Pancreatobilliary | 17 (8.8) |
| Lung | 14 (7.2) |
| Musculoskeletal | 9 (4.6) |
| Stage | |
| Early | 51 (26.3) |
| Advanced | 143 (73.7) |
| Sepsis, n(%) | 49 (25.3) |
| Procalcitonin, ng/mL, median (min - max) | 1.325 (0.04 – 923.10) |

**Table 2.** Characteristics of solid tumor patients with sepsis.

| Characteristics | N= 49 |
|---|---|
| Stage | |
| Early | 10 (20.4) |
| Advanced | 39 (79.6) |
| Infection site, n (%) | |
| Pneumonia | 30 (61.2) |
| Urinary Tract | 11 (22.4) |
| Skin and soft tissue | 4 (8.1) |
| Intra-abdominal | 4 (8.1) |
| Blood | 16 (32.6) |
| Procalcitonin, ng/mL, median (min-max) | 9.04 (0.24 – 923.10) |

In the advanced stage solid tumor group (n=143), PCT level was significantly higher among patients with sepsis (n=39) compared to non-sepsis patients (9.03 (IQR 57.45) vs. 0.685 (IQR 1.83) ; p<0.05). PCT concentration was higher among advanced-stage solid tumor patients with sepsis compared to early-stage solid tumor sepsis patients (p<0.05). Meanwhile, WBC levels were not different in all groups. (**Table 3**)

We found PCT has good diagnosis accuracy for sepsis diagnosis in advanced solid tumor patients with fever (AUC 0.853 [95%CI 0.785–0.921]). The cut-off for diagnosing sepsis in advanced solid tumor patients with fever was 2.87 ng/mL, with a sensitivity of 79.5% and specificity of 79.8% (**Figure 1**).

## DISCUSSION

Female patients had a higher proportion in this study. This finding may be explained due to WHO GLOBOCAN report in 2020, that the most common cancer in Indonesia was breast (16.6%) and cervix uteri cancer (9.2%).[13] Most of our patients had advanced-stage solid tumors. This finding may be related to a lack of detection, screening programs, and patient awareness and knowledge.[14]

In this study, we found a higher level of PCT was observed in advanced-stage solid tumor patients with sepsis compared to early-stage solid tumor patients with sepsis. Elevated PCT levels may be attributed to numerous factors in cancer patients, including the presence of metastasis or neuroendocrine function of malignant tissue.

**Table 3. Serum PCT and WBC in advanced vs. early solid tumor group with sepsis.**

| Variable | Advanced | Early |
|---|---|---|
| | Sepsis (N=39) | Sepsis (N=10) |
| PCT, ng/ml, median (min-max) | 23.14 (0.96 – 923.10) | 9.03 (0.24 – 252.7) |
| WBC, median (min-max) | 17,660 (1.440 – 72.470) | 21,940 (4.770 – 26.970) |

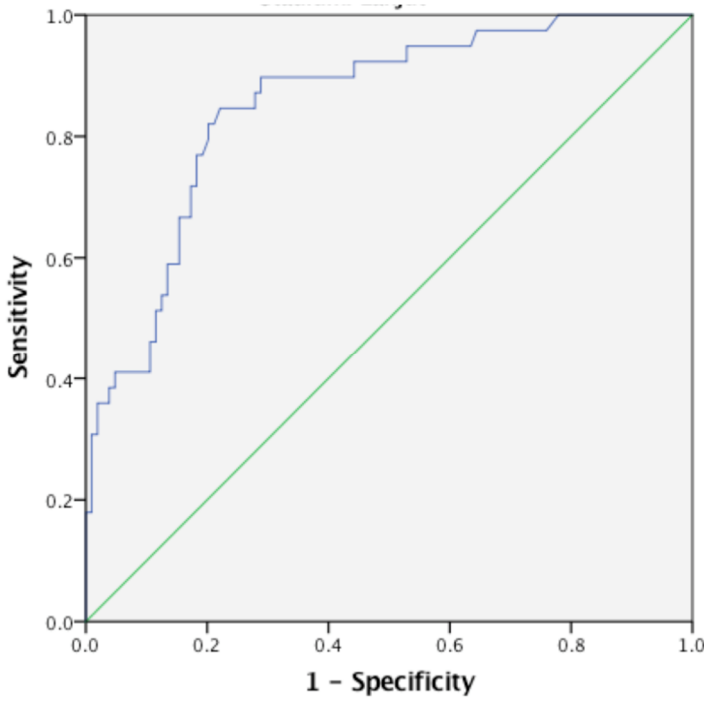



**Figure 1.** Procalcitonin ROC curve for sepsis in advanced solid tumor patients with fever.

This can be seen in the study by Matzaraki et al that found that PCT level was correlated with different tumor stages. They found higher PCT levels in healthy solid tumor patients with generalized metastatic disease compared to the healthy control group or solid tumor without metastases group.[11] Chaftari et al also found higher PCT levels in stage IV cancer patients compared to stage I-III cancer non-febrile patients (0.190 vs. 0.127 ng/ml, p<0.0001). However, they also stated that febrile cancer patients with sepsis had higher PCT levels compared to non-infectious febrile cancer patients (0.49 vs. 0.31 ng/ml, p:0.003), implying the usefulness of PCT in predicting sepsis in cancer patients.[15] Procalcitonin secretion was induced through two mechanisms. The first pathway was due to direct stimulation by lipopolysaccharides (LPS) or other toxins that produced by pathogens. The second pathway was by indirect stimulation of inflammatory cytokines such as IL-6, and TNF-α.[16] Solid tumors may produce inflammatory cytokines which may affect the tumor microenvironment and produce a chronic inflammatory state.[17] Michalaki et al found that significantly higher levels of IL-6 and TNF-α in metastatic disease compared to localized disease (9.3 ±7.8 vs. 1.3 ±0.8 pg/ml; p<0.001 and 6.3±3.6 vs. 1.1.±0.5 pg/ml; p<0.001).[18] This finding may explain why higher median level of PCT in patients with advanced-stage solid tumors although without infection.

Interpretation of PCT level to determine sepsis may be difficult, due to higher level PCT baseline level in tumor patients. Therefore, the usual cut-off level of PCT in the general population may not apply to cancer patients, especially those in an advanced stage. Advanced-stage cancer may decrease the specificity of PCT in determining infection. The reported cut-off level of PCT in cancer patients varied between studies.[19] Our study found that a cut-off point of 2.87 ng/mL had an overall good performance in detecting sepsis among febrile advanced-stage tumor patients. Azis et al previously reported PCT cut-off for determining sepsis in metastatic cancer patients was 1.14 ng/ml (sensitivity 86% and specificity 88%). They also found higher PCT levels in metastasis cancer patients with sepsis compared to non-metastasis cancer patients without sepsis (3.48 vs.2.92 ng/ml). The different cut-off levels may be explained due to Azis et al only included patients with metastasis, while our study included all advanced-stage cancer patients.[10] Vincenzi et al showed a PCT cut-off of 1.52 ng/mL had a sensitivity of 61.6%, and specificity 70.1% to detect bacteremia in advanced stage solid tumor patients with fever patient. However, the proposed cut-off by Vincenzi et al was determined based on hemoculture positive or negative, they did not evaluate whether the patient's condition which already in a septic condition or not.[20] Similarly, Blouin et al found that a cut-off value of 1.7 ng/mL (sensitivity 61% and specificity 74%) was able to detect bacteremia in cancer patients. However, this study did not account for the possibility of receiving treatment before drawing PCT samples from the patients.[21] Vassallo et al found that a PCT cut-off of 0.52 ng/ml (sensitivity 75% and specificity 55%) was a sensitive marker to differentiate between infection and tumor-associated fever in solid tumor patients. However, the determined cut-off did not differentiate between sepsis condition or localized infection.[19] Ding et al reported a lower cut-off value for PCT, namely 0.105 ng/mL (sensitivity 79.7% and specificity 80.4%). Unfortunately, the cut-off of this study also did not differentiate between sepsis and localized infection.[22]

The strength of our study was our study method which had tight inclusion criteria to minimize bias of PCT level. We did not use retrospective data which was mainly utilized in other studies; therefore, we can accurately determine the sepsis condition and relationship with the PCT level at admission. However, our study had also several limitations. First, we did not use the SEPSIS-3 criteria for diagnosing sepsis in our study, due to the timing of the SEPSIS-3 criteria guidance released and the starting date of our study.[23] Second, we did not determine the type of bacteria that caused sepsis in our studies. Gram-negative bacteremia is generally thought to produce more LPS than gram-positive and, therefore may variably affect

the PCT level. We propose a prospective study to determine the accuracy of our cut-off PCT level using real-world data.

## CONCLUSION

PCT has good diagnosis accuracy for sepsis diagnosis in advanced solid tumor patients with fever. The cut-off for diagnosing sepsis in advanced solid tumor patients with fever was 2.87 ng/mL, with sensitivity and specificity of 79.5% and 79.8%, respectively.

## LIST OF ABBREVIATIONS

AJCC American Joint Committee on Cancer
ALT Alanine Aminotransferase
AST Aspartate Aminotransferase
AUC Area Under Curve
PCT Procalcitonin
ROC Receiver Operating Characteristics

## ACKNOWLEDGMENTS

We thank the Division of Tropical and Infectious Disease Department of Internal Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital for accommodating and encouraging this research.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## FUNDING

This study was funded by the Cipto Mangunkusumo Hospital Research Grant.

## REFERENCES

1. Zembower TR. Epidemiology of infections in cancer patients. Cancer Treat Res. 2014;161:43-89.
2. Zheng Y, Chen Y, Yu K, et al. Fatal infections among cancer patients: A population-based study in the United States. Infect Dis Ther. 2021;10(2):871-95.
3. Elfaituri MK, Morsy S, Tawfik GM, et al. Incidence of infection-related mortality in cancer patients: trend and survival analysis. J Clin Oncol. 2019;37:15(suppl):e23095
4. Taccone FS, Artigas AA, Sprung CL, et al. Characteristics and outcomes of cancer patients in European ICUs. Crit Care. 2009;13(1):R15.
5. Xiang MJ, Chen GL. Impact of cancer on mortality rates in patients with sepsis: A meta-analysis and meta-regression of current studies. World J Clin Cases. 2022;10(21):7386-96.
6. Pasikhova Y, Ludlow S, Baluch A. Fever in patients with cancer. Cancer Control. 2017;24(2):193-7.
7. Joudeh N, Sawafta E, Abu Taha A, et al. Epidemiology and source of infection in cancer patients with febrile neutropenia: an experience from a developing country. BMC Infect Dis. 2023;23(1):106.
8. Nanayakkara AK, Boucher HW, Fowler VG Jr, et al. Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward. CA Cancer J Clin. 2021;71(6):488-504.
9. Qiu MZ, Xu RH, Ruan DY, et al. Incidence of anemia, leukocytosis, and thrombocytosis in patients with solid tumors in China. Tumour Biol. 2010;31(6):633-41.
10. Aziz SA, Nelwan EJ, Sukrisman L, et al. Higher cut-off serum procalcitonin level for sepsis diagnosis in metastatic solid tumor patients. BMC Res Notes. 2018;11(1):84.
11. Matzaraki V, Alexandraki KI, Venetsanou K, et al. Evaluation of serum procalcitonin and interleukin-6 levels as markers of liver metastasis. Clin Biochem. 2007;40(5-6):336-42.
12. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med. 2003;31(4):1250-1256.
13. World Health Organization. 360 Indonesia Fact Sheets GLOBOCAN 2020. 2020. https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf. Accessed 20 February 2023.
14. Agodirin O, Olatoke S, Rahman G, et al. Determinants of late detection and advanced-stage diagnosis of breast cancer in Nigeria. PLoS One. 2021;16(11):e0256847.
15. Chaftari AM, Hachem R, Reitzel R, et al. Role of procalcitonin and interleukin-6 in predicting cancer, and its progression independent of infection. PLoS One. 2015;10(7):e0130999.
16. Vijayan AL, Vanimaya, Ravindran S, et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care. 2017;5:51.
17. Lan T, Chen L, Wei X. Inflammatory cytokines in cancer: Comprehensive understanding and clinical progress in gene therapy. Cells. 2021;10(1):100.
18. Michalaki V, Syrigos K, Charles P, et al. Serum levels of IL-6 and TNF-alpha correlate with clinicopathological features and patient survival in patients with prostate cancer. Br J Cancer. 2004;90(12):2312-6.
19. Vassallo M, Michelangeli C, Fabre R, et al. Procalcitonin and C-reactive protein/procalcitonin ratio as markers of infection in patients with solid tumors. Front Med (Lausanne). 2021;8:627967.
20. Vincenzi B, Fioroni I, Pantano F, et al. Procalcitonin as a diagnostic marker of infection in solid tumor patients with fever. Sci Rep. 2016;6:28090.
21. Blouin AG, Hsu M, Fleisher M, Ramanathan LV, Pastores SM. Utility of procalcitonin as a predictor

of bloodstream infections and supportive modality requirements in critically ill cancer patients. Clin Chim Acta. 2020;510:181-5.
22. Ding S, Ma J, Song X, et al. Diagnostic accuracy of procalcitonin, neutrophil-to-lymphocyte ratio, and c-reactive protein in detection of bacterial infections and prediction of outcome in nonneutropenic febrile patients with lung malignancy. J Oncol. 2020;2020:2192378.
23. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-10.

# Multidrug-Resistant Bacteria Colonization in Patients Admitted to Dr. Cipto Mangunkusumo Hospital Jakarta, Indonesia

*Selvi Nafisa Shahab[1], Anis Karuniawati[1]*, Omar Mukhtar Syarif[2], Yulia Rosa Saharman[1], Robert Sinto[3], Pratiwi Pujilestari Sudarmono[1]*

[1]Department of Clinical Microbiology, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[3]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Corresponding Author:***
*Anis Karuniawati, MD., PhD. Department of Clinical Microbiology, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital. Jl. Salemba no. 6, Jakarta 10430, Indonesia. Email: anis.karuniawatimk@ui.ac.id*

## ABSTRACT

***Background:*** *Antibiotic resistance is the main problem in infectious disease management. Multidrug-resistant (MDR) bacteria could be carried by admitted patients and become a source of spread in the hospital, causing infections in other patients or the patients themselves. However, the screening of MDR bacteria has not been a standard in developing countries. This study aimed to get the prevalence of MDR bacteria colonization in patients on admission to Dr. Cipto Mangunkusumo Hospital.* ***Methods:*** *Selective liquid media with added antibiotics were used for culturing the MDR bacteria. While admitted to the hospital, subjects were sampled and interviewed to fill out a questionnaire. The screening specimens used for this study were throat, navel, rectal, nasal, and armpit swabs. During hospitalization, hospital-acquired infections (HAIs) were recorded.* ***Results:*** *Of 100 patients included in the study, the prevalence of MDR bacteria colonization on admission was 63% (n=63) with the prevalence of CR-GNB, ESBL-PE, and MRSA were 11%, 54%, and 11%, respectively. Two-thirds of the patients with HAIs (n=8/12) were colonized with MDR bacteria. Factors associated with MDR bacteria colonization were the recent use of invasive medical devices and comorbidity, while a factor associated with CR-GNB colonization was the recent use of antibiotics.* ***Conclusion****: The prevalence of MDR bacteria colonization in patients on admission to Dr. Cipto Mangunkusumo Hospital in 2022 was 63% (n=63), of which 12.68% (n=8) experienced HAIs during hospitalization. MDR bacteria colonization was associated with the recent use of invasive medical devices and comorbidity. History of antibiotic use was associated with CR-GNB colonization.*

***Keywords****: multi-drug resistance bacteria, colonization, healthcare-associated infections.*

## INTRODUCTION

Antibiotic resistance is a major problem in the management of bacterial infections since it can lead to therapeutic failure, prolonged hospitalization, and increased treatment costs leading to an increased socioeconomic burden.[1] Resistant bacteria can be carried by newly admitted patients and become a source of the spread in the hospital, causing infections in other patients or for themselves.[2,3] Monitoring antibiotic-resistant bacteria is one of the first steps in reducing mortality and morbidity due

to these pathogenic infections.[4]

As the Indonesian national referral hospital, Dr. Cipto Mangunkusumo Hospital (CMH) has a high prevalence of resistant bacteria, especially in those with long-stay and intensive care.[5,6] The prevalence of carbapenem-resistant Gram-negative bacilli (CR-GNB) among patients admitted to the ICU of CMH reached 34.35%.[5] Among the Enterobacterales found in CMH, more than half (58.4%) of them produced extended spectrum beta-lactamase (ESBL) which can cause bacteria to become resistant to various antibiotics.[7-10] Based on blood culture results, the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) in RSCM in 2020 was 9.2%, the highest among multidrug-resistant (MDR) Gram-positive bacteria.[11]

It was difficult to determine whether the high prevalence of MDR bacteria was acquired during hospitalization or already present at the time of admission. Several studies have been conducted and described the benefits of monitoring MDR bacteria in hospitalized patients.[12-15] However, detection by culture using standard media has low sensitivity. The addition of antibiotics in the culture media is known to improve culture sensitivity for the detection of MRSA and ESBL-producing Enterobacterales (ESBL-PE).[16-18] Therefore, we used antibiotics as selective agents to the culture media to optimize the detection.

In this study, we conducted screening to determine the prevalence of MDR bacterial colonization in patients admitted to CMH, associated factors, and outcome at discharge. The MDR bacteria tested were critical priority pathogens defined by WHO, such as carbapenem-resistant *Acinetobacter baumannii,* carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacterales, and ESBL-PE. In addition, MRSA, which is a bacterium that is often reported as a major cause of healthcare-associated infections (HAIs) with high morbidity and mortality, was tested as well.[19,20]

## METHODS

We conducted a cohort study to determine the prevalence of MDR bacterial colonization in hospitalized patients at admission, its risk factors and incidence of HAIs. Screening specimens were collected and validated questionnaires were filled by interview in the first 24 hours from the admission. Bacterial culture for identification and antibiotic susceptibility testing was conducted at the Clinical Microbiology Laboratory of the Faculty of Medicine, Universitas Indonesia. Patient recruitment was held from March 1, 2022, to May 31, 2022.

The inclusion criteria were being over 18 years old, having been admitted to RSCM for at least 24 hours, and agreeing to participate in the study. Subjects were excluded if a complete set of specimens was not possible to collect or if they were not competent enough to answer the questions in the questionnaire and were not accompanied by a competent guardian. Comorbidities were assessed by the Charlson comorbidity index (CCI) and high comorbidity was defined as a CCI of 3 or more.[21,22]

The study subjects were interviewed by the research team using a questionnaire instrument to determine demographic characteristics and factors associated with the occurrence of MDR bacterial colonization in patients. There were five types of screening specimens used in the study, namely throat swab, navel swab, rectal swab, nasal swab, and axillary swab. Specimens were collected using sterile cotton swabs inserted into Tryptic Soy Broth (TSB) medium as soon as the specimens were obtained. Swab specimens were transported at 2-7°C to the laboratory for further processing.

In the laboratory, the TSB medium is then supplemented with antibiotics based on the target MDR bacteria (**Figure 1**). Then, incubation was carried out at 35°C for 24 hours before subculturing to a selective agar plate medium. The growing bacterial colonies were identified using VITEK2 (bioMerieux). If *A. baumannii*, *P. aeruginosa*, or Enterobacterales were identified, a carbapenem susceptibility test was performed using the Kirby-Bauer method with Mueller Hinton agar plates. The growth of Enterobacterales on MacConkey agar plates was also followed by a double disc synergy test (DDST) using ceftazidime 30 mcg, cefepime 30 mcg, and cefotaxime 30 mcgwith amoxicillin-clavulanate (clavulanate 10 mcg) on Mueller Hinton agar plates according to

EUCAST guidelines to determine the ESBL production.[23] When *S. aureus* identified, a cefoxitin susceptibility test was performed to determine the methicillin-resistant strains.

Data processing and analysis were performed using the SPSS version 20 program for the

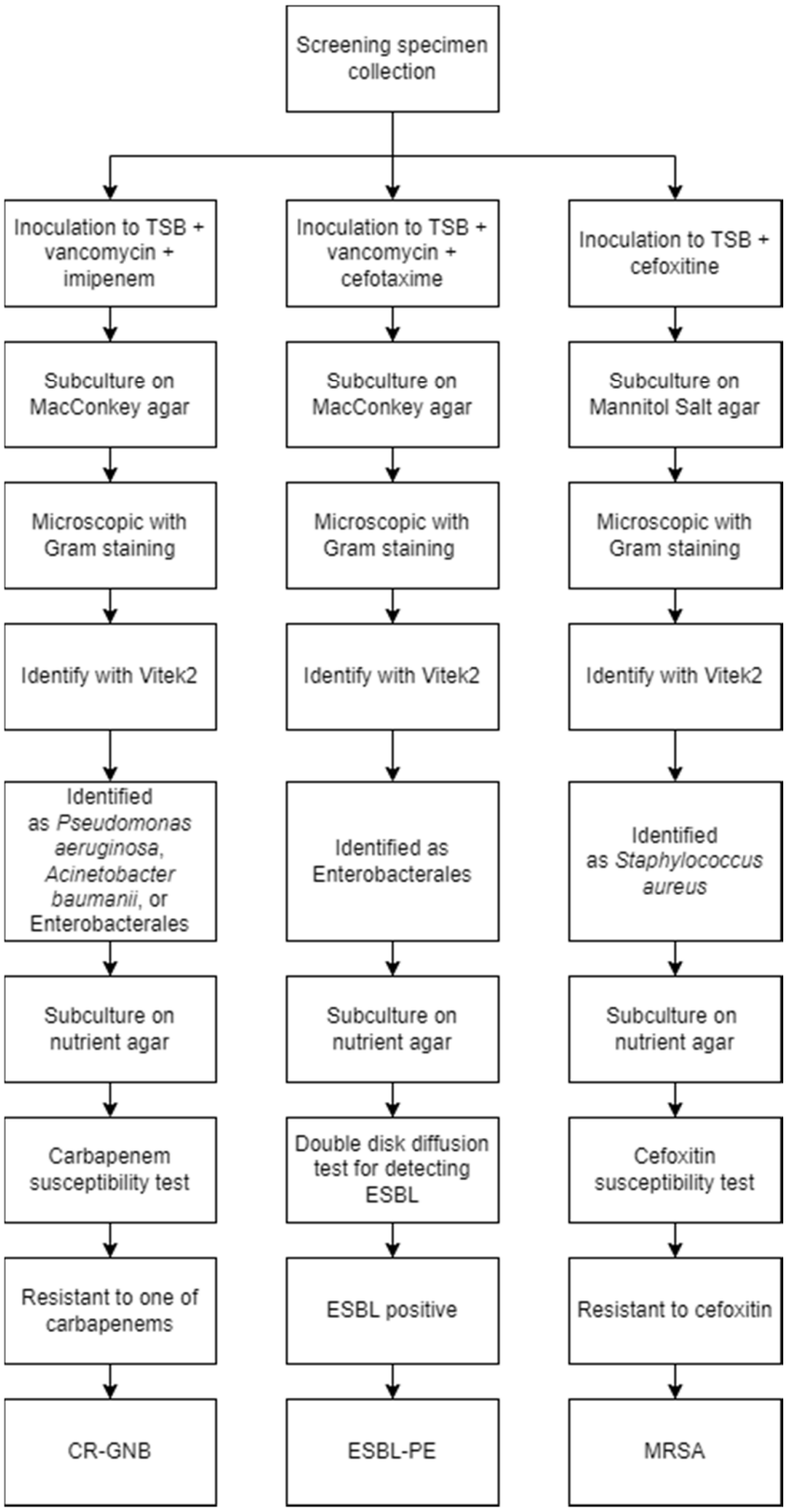



**Figure 1.** Laboratory test for detecting multidrug-resistant bacteria

Windows system. From the data obtained, analysis was carried out to determine the factors associated with MDR bacterial colonization in patients. The analysis began with bivariate analysis, then continued with multivariate for factors with a p-value of less than 0.25.[24] Bivariate analysis was also performed to determine the association of MDR bacterial colonization with the occurrence of HAIs in patients. Factors were considered associated if the p-value was less than 0.05. The research proposal has received ethical approval from the Ethics Committee of FKUI-RSCM with number KET-1235/UN2.F1/ETIK/PPM.00.02/2021 dated December 27, 2021.

## RESULTS

A total of 100 patients who met the inclusion and exclusion criteria were selected (**Figure 1**). The median length of stay was 5 (3-9.5) days with 49% of the patients staying for 1-5 days. The demographic characteristics of the subjects can be seen in **Table 1**. There were 15 patients with the infection on admission, however, the infections did not occur in the area of specimen collection for screening purposes . Therefore, any

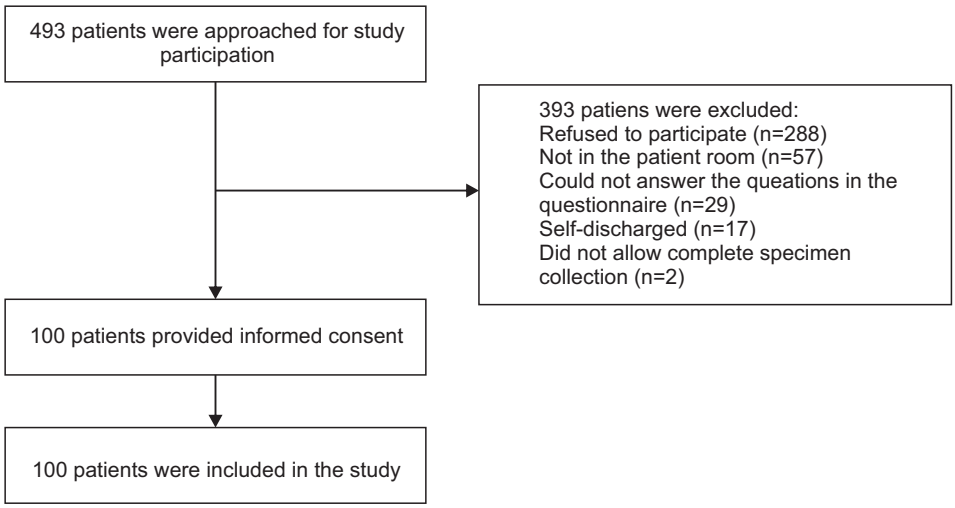



**Figure 1.** Patients recruitment.

**Table 1.** Demographic characteristics of subjects.

| Parameter | N =100 | Bacterial Colonization of MDR[a] Positive N = 63 | Negative N = 37 |
|---|---|---|---|
| Sex, n (%) | | | |
| Male | 63 | 42 (66.7) | 21 (56.8) |
| Female | 37 | 21 (33.3) | 16 (43.2) |
| Age (year), median (IQR) | 51.0 (18-81) | 52.0 (18-81) | 50.0 (19-77) |
| Diagnosis on admission, n (%) | | | |
| Tumors and malignancies | 39 | 24 (38.1) | 15 (40.5) |
| Trauma | 13 | 8 (12.7) | 5 (13.5) |
| Kidney disease | 12 | 11 (17.5) | 1 (2.7) |
| Cardiovascular disease | 4 | 1 (1.6) | 3 (8.1) |
| Autoimmune diseases | 3 | 1 (1.6) | 2 (5.4) |
| Other diagnosis[b] | 23 | 18 (28.6) | 11 (29.7) |
| Infection on admission[c], n (%) | | | |
| Yes | 15 | 7 (11.1) | 8 (21.6) |
| No | 85 | 56 (88.9) | 29 (78.4) |
| BMI[e], mean (SD) | 21.6 (4.8) | 21.9 (5.1) | 21.1 (4.1) |

[a]Colonization of multidrug-resistance bacteria, including carbapenem-resistant Gram-negative bacilli, extended-spectrum beta-lactamase-producing Enterobacterales, and methicillin-resistant *Staphylococcus aureus*
[b]Other diagnosis: Liver abscess, stroke, acute cholangitis, gastric ulcers, anemia, diabetes melitus, digital abscess, Internal hemorroid, arthiritis, hydropneumothorax, condyloma acuminata, systemic sclerosis, choledocolithiasis, achalasia, palatum fistula, hernia, multiple gangrene, urethral stenosis, hirschsprung, anal stenosis
[c]infection at admission did not occur around specimen collection for screening purpose [d]BMI = body mass index

positive results from those screening specimens were marked as colonization. The infections were acute cholangitis (n=3), musculoskeletal infection (n=3), community-acquired pneumonia (n=2), urinary tract infection (n=2), and others (n=5).

### MDR Bacterial Colonization

The prevalence of MDR bacterial colonization in patients admitted to RSCM in 2022 was 63%. Of the 100 patients examined, 54 patients were ESBL-PE colonized, 11 patients were CR-GNB colonized, and 11 patients were MRSA colonized (**Table 2**).

### Risk Factors for MDR Bacterial Colonization

The most commonly 3-month prior antibiotics used were cephalosporins (18 of 37 subjects), such as cefixime (10 subjects), ceftriaxone (4 subjects), and cefoperazone (4 subjects). The number of subjects who had high comorbidity was 50 subjects, of which 72% were colonized with MDR bacteria. The median total score of living behavior was 24 (IQR 14-28), therefore the subjects were characterized as having healthy living behavior if the score were ≥24.

Based on the multivariate analysis, history of invasive medical device use (OR 3.48, 95%CI 1.23-9.79) and high comorbidity (OR 2.41, 95%CI 1.02-5.72) were associated with MDR

**Table 2.** List of CR-GNB and ESBL-PE found on the basis of specimen type.

| Swab of throat - TSB-VI (N=2/100) | Navel swab - TSB-VI (N=2/100) | Rectal swab– TSB-VI (N=8/100) | Rectal swab – TSB-VC (N=54/100) | Nasal swab – TSB-Cx (N=10/100) | Axillary swab – TSB-Cx (N=10/100) |
|---|---|---|---|---|---|
| *K. pneumoniae* CR (N=1)<br>*P. aeruginosa* CR (N=1) | *A. baumannii* CR (N=1)<br>*P. aeruginosa* CR (N=1) | *K. pneumoniae* CR (N=3)*<br>*E. coli* CR (N=3)*<br>*P. aeruginosa* CR (N=2)<br>*A. baumannii* CR (N=2) | *E. coli* ESBL (N=48)<br>*K. pneumoniae* ESBL (N=5)<br>*Salmonella typhi* ESBL (N=1) | MRSA (N=10) | MRSA (N=10) |

*2 the patient has co-colonization *K. pneumoniae* CR dan *E. coli* CR on a rectal swab
TSB-VI = Trypticase soy broth with vancomycin and imipenem
TSB-VC = Trypticase soy broth with vancomycin and cefotaxime
TSB-Cx = Trypticase soy broth with cefoxitine
CR-GNB = carbapenem-resistant Gram negative bacilli
ESBL-PE = extended-spectrum beta lactamase-producing Enterobacterales
MRSA= methicillin resistant *Staphylococcus aureus*

**Table 3.** Bivariate analysis of risk factors for MDR bacterial colonization.

| Parameter | MDR bacterial colonization - n (%) | | Value of p | OR (IK 95%) |
|---|---|---|---|---|
| | Yes | No | | |
| History of antibiotic consumption | | | 0.57 | 0.79 |
| Yes | 22 (34.9) | 15 (40.5) | | (0.34-1.82) |
| No | 41 (65.1) | 33 (59.5) | | |
| Inpatient history | | | 0.81 | 1.11 |
| Yes | 39 (61.9) | 22 (59.5) | | (0.48-2.54) |
| No | 24 (3.1) | 15 (40.5) | | |
| History of invasive medical equipment use | | | 0.02 | 3.18 (1.16-8.74) |
| Yes | 24 (38.1) | 6 (16.2) | | |
| No | 39 (61.9) | 31 (83.4) | | |
| CCI | | | 0.06 | 2.19 |
| High | 36 (57.1) | 14 (37.8) | | (0.95-5.03) |
| Low | 27 (42.9) | 23 (62.2) | | |
| Lifestyle | | | 0.50 | 1.32 |
| Unhealthy | 35 (55.6) | 18 (48.6) | | (0.58-2.98) |
| Healthy | 28 (44.4) | 19 (51.4) | | |

CCI = Charlson comorbidity index
MDR = multi-drugs resistant

bacterial colonization. History of antibiotic use in the last 3 months increased the risk to 5.48 (95%CI 1.31-22.87) times for CR-GNB colonization. No risk factor was associated with ESBL-PE and MRSA colonization.

During hospitalization, 12 patients got HAIs, of which 4 were diagnosed with hospital acquired pneumonia (HAP), 3 with catheter-associated urinary tract infection (CAUTI), 2 with bloodstream infection (BSI), 2 with surgical site infection (SSI), and 1 with hospital acquired gastrointestinal infection. A total of 12.68% (N=8/63) patients with MDR bacterial colonization experienced HAIs during hospitalization with a relative risk of 1.18 (95%CI 0.38-3.63, p=0.52) compared to patients without MDR bacterial colonization.

## DISCUSSION

The prevalence of MDR bacterial colonization in patients admitted to RSCM in 2022 was very high (64.3%) and dominated by ESBL-producing *E. coli*. The prevalence of CR-GNB colonization was found to be lower (11%) than previous studies on the prevalence of carbapenem-resistant *A. baumannii*.[25] ESBL-PE colonization occurred in more than half of the patients admitted to RSCM (54%).[10] The high prevalence can be a source of spread of MDR bacteria in the hospital environment and can cause HAIs if the implementation of IPC, especially contact precaution in hospitals is not carried out optimally, in vulnerable populations. MRSA colonization at the beginning of treatment was found to be 11%, higher than the previous study (0.8%).[26] This may be influenced by the use of antibiotics for culture medium supplementation that can increase MRSA culture positivity. Several reports show the benefits of using throat swabs in detecting MRSA.[27] In this study, MRSA screening was only performed on anterior nasal swabs and axillary swabs, while throat swabs were used for Gram-negative screening.

The prevalence of MDR bacterial colonization was higher in patients with a history of antibiotic use in the past 3 months although it was not statistically significant. In this study, the history of antibiotic use was only associated with CR-GNB colonization. Previous studies related to carbapenem resistance have also shown an association between antibiotic use and colonization of carbapenem-resistant bacteria.[28] History of hospitalization in the past year was not associated with MDR bacterial colonization, unlike previous reports.[29,30] This suggests that the resistant bacteria in these patients were acquired from the community. A history of using invasive medical equipment increases the risk of MDR bacterial colonization by almost 3.5 times, so MDR bacterial screening should be done in this group of patients. In this study, patients with high comorbidity had a 2.4 times higher risk of MDR bacterial colonization.

The prevalence of HAIs in patients in this study was high (12%), in line with the results of the study by Goh et al.[31] who reported the prevalence of HAIs in Southeast Asia ranged from 8.4-30.4%, with risk factors for HAIs being the most common. Given the high prevalence of HAIs that occur, it is important to implement IPC in hospitals. IPC problems that are often encountered in Indonesia include communication problems with management, limited antimicrobial sensitivity testing, and not enough IPC nurses available.[32]

The limitation of this study was that the data regarding the history of antibiotic consumption within three months was obtained from interview only relying on the subjects' memories and knowledge. Therefore, there is a possibility of recall bias in collecting this data. Although MDR bacterial colonization in this study was not statistically proven to be associated with the occurrence of HAIs, patients who are colonized at admission have the potential to experience HAIs during treatment. Efforts that must be made in preventing the spread of MDR bacteria from the body of colonized patients to the surrounding environment are the application of contact precautions and isolation or cohorting. The commitment of hospital leaders is needed by making policies for handling patients who enter the hospital, especially those with risk factors.

## CONCLUSION

The prevalence of MDR bacterial colonization (consisting of CR-GNB, ESBL-PE, and MRSA

in patients during inpatient admissions at RSCM in 2022 was 63%, of which 12.68% experienced HAIs during hospitalization. Risk factors for MDR bacterial colonization in patients were history of invasive medical device use and high comorbidities. History of antibiotic use was associated to CR-GNB colonization. Screening of MDR bacterial colonization in patients with risk factor is needed to prevent its spread.

## ACKNOWLEDGMENTS

This study was funded by Dr. Cipto Mangunkusumo Hospital.

## REFERENCES

1. Abat C, Fournier PE, Jimeno MT, Rolain JM, Raoult D. Extremely and pandrug-resistant bacteria extra-deaths: myth or reality? Eur J Clin Microbiol Infect Dis. 2018;37(9):1687-97.
2. Lin MY, Ray MJ, Rezny S, Runningdeer E, Weinstein RA, Trick WE. Predicting Carbapenem-resistant Enterobacteriaceae carriage at the time of admission using a statewide hospital discharge database. Open Forum Infect Dis. 2019;6(12):ofz483.
3. Manyahi J, Majigo M, Kibwana U, Kamori D, Lyamuya EF. Colonization of extended-spectrum β-lactamase producing Enterobacterales and meticillin-resistant S. aureus in the intensive care unit at a tertiary hospital in Tanzania: Implications for Infection control and prevention. Infect Prev Pract. 2022;4(2):100212.
4. Tacconelli E, Cataldo MA, Dancer SJ, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014;20 Suppl 1:1-55.
5. Karuniawati A, Saharman YR, Lestari DC. Detection of carbapenemase encoding genes in Enterobacteriace, Pseudomonas aeruginosa, and Acinetobacter baumanii isolated from patients at Intensive Care Unit Cipto Mangunkusumo Hospital in 2011. Acta Med Indones. 2013;45(2):101-6.
6. Saharman YR, Pelegrin AC, Karuniawati A, et al. Epidemiology and characterisation of carbapenem-non-susceptible Pseudomonas aeruginosa in a large intensive care unit in Jakarta, Indonesia. Int J Antimicrob Agents. 2019;54(5):655-60.
7. Adler A, Katz DE, Marchaim D. The continuing plague of extended-spectrum β-lactamase producing Enterbacterales infections: An update. Infect Dis Clin North Am. 2020;34(4):677-708.
8. Ouchar Mahamat O, Tidjani A, Lounnas M, et al. Fecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae in hospital and community settings in Chad. Antimicrob Resist Infect Control. 2019;8:169.
9. Kawamura K, Nagano N, Suzuki M, Wachino JI, Kimura K, Arakawa Y. ESBL-producing Escherichia coli and its rapid rise among healthy people. Food Saf (Tokyo). 2017;5(4):122-50.
10. Saharman YR, Lestari DC. Phenotype characterization of Beta-lactamase producing enterobacteriaceae in the intensive care unit (ICU) of Cipto Mangunkusumo Hospital in 2011. Acta Med Indones. 2013;45(1):11-6.
11. Sinto R, Lie KC, Setiati S, et al. Blood culture utilization and epidemiology of antimicrobial-resistant bloodstream infections before and during the COVID-19 pandemic in the Indonesian national referral hospital. Antimicrob Resist Infect Control. 2022;11(1):73.
12. Karampatakis T, Tsergouli K, Iosifidis E, et al. Effects of an active surveillance program and enhanced infection control measures on Carbapenem-resistant Gram-negative bacterial carriage and infections in pediatric intensive care. Microb Drug Resist. 2019;25(9):1347-56.
13. Karampatakis T, Tsergouli K, Iosifidis E, et al. Impact of active surveillance and infection control measures on carbapenem-resistant Gram-negative bacterial colonization and infections in intensive care. J Hosp Infect. 2018;99(4):396-404.
14. Freeman R, Moore LS, Charlett A, Donaldson H, Holmes AH. Exploring the epidemiology of carbapenem-resistant Gram-negative bacteria in west London and the utility of routinely collected hospital microbiology data. J Antimicrob Chemother. 2015;70(4):1212-8.
15. Snyder GM, D'Agata EM. Diagnostic accuracy of surveillance cultures to detect gastrointestinal colonization with multidrug-resistant gram-negative bacteria. Am J Infect Control. 2012;40(5):474-6.
16. Murk JL, Heddema ER, Hess DL, Bogaards JA, Vandenbroucke-Grauls CM, Debets-Ossenkopp YJ. Enrichment broth improved detection of extended-spectrum-beta-lactamase-producing bacteria in throat and rectal surveillance cultures of samples from patients in intensive care units. J Clin Microbiol. 2009;47(6):1885-7.
17. Kluytmans-van den Bergh MF, Verhulst C, Willemsen LE, Verkade E, Bonten MJ, Kluytmans JA. Rectal Carriage of Extended-Spectrum-Beta-Lactamase-Producing Enterobacteriaceae in Hospitalized Patients: Selective Preenrichment Increases Yield of Screening. J Clin Microbiol. 2015;53(8):2709-12.
18. Safdar N, Narans L, Gordon B, Maki DG. Comparison of culture screening methods for detection of nasal carriage of methicillin-resistant Staphylococcus aureus: a prospective study comparing 32 methods. J Clin Microbiol. 2003;41(7):3163-6.
19. Kim M-N. Multidrug-resistant organisms and healthcare-associated infections. Hanyang Medical Reviews. 2011;31(3):141-52.
20. Alhunaif SA, Almansour S, Almutairi R, et al.

Methicillin-resistant Staphylococcus aureus Bacteremia: Epidemiology, clinical characteristics, risk factors, and outcomes in a tertiary care center in Riyadh, Saudi Arabia. Cureus. 2021;13(5):e14934.
21. Khan HA, Baig FK, Mehboob R. Nosocomial infections: Epidemiology, prevention, control and surveillance. Asian Pacific Journal of Tropical Biomedicine. 2017;7(5):478-82.
22. Bhargava A, Hayakawa K, Silverman E, et al. Risk factors for colonization due to carbapenem-resistant Enterobacteriaceae among patients exposed to long-term acute care and acute care facilities. Infect Control Hosp Epidemiol. 2014;35(4):398-405.
23. Drieux L, Brossier F, Sougakoff W, Jarlier V. Phenotypic detection of extended-spectrum β-lactamase production in Enterobacteriaceae: review and bench guide. Clinical Microbiology and Infection. 2008;14:90-103.
24. Dahlan MS. Statistik untuk kedokteran dan kesehatan. 5 ed. Jakarta: Penerbit Salemba Medika; 2011.
25. Saharman YR, Karuniawati A, Sedono R, et al. Endemic carbapenem-nonsusceptible Acinetobacter baumannii-calcoaceticus complex in intensive care units of the national referral hospital in Jakarta, Indonesia. Antimicrob Resist Infect Control. 2018;7:5.
26. Nelwan EJ, Sinto R, Subekti D, et al. Screening of methicillin-resistant Staphylococcus aureus nasal colonization among elective surgery patients in referral hospital in Indonesia. BMC Res Notes. 2018;11(1):56.
27. Kuntaman K, Hadi U, Setiawan F, Koendori EB, Rusli M, Santosaningsih D, et al. Prevalence of Methicillin resistant Staphylococcus aureus from nose and throat of patients on admission to medical wards of dr. Soetomo Hospital, Surabaya, Indonesia. Southeast Asian J Trop Med Public Health. 2016;47(1):66-70.
28. Palacios-Baena ZR, Giannella M, Manissero D, et al. Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review. Clin Microbiol Infect. 2021;27(2):228-35.
29. Msanga DR, Silago V, Massoza T, et al. High fecal carriage of multidrug resistant bacteria in the community among children in Northwestern Tanzania. Pathogens. 2022;11(3).
30. Viau R, Frank KM, Jacobs MR, et al. Intestinal carriage of Carbapenemase-producing organisms: Current status of Surveillance methods. Clin Microbiol Rev. 2016;29(1):1-27.
31. Goh LPW, Marbawi H, Goh SM, Bin Abdul Asis AK, Gansau JA. The prevalence of hospital-acquired infections in Southeast Asia (1990-2022). J Infect Dev Ctries. 2023;17(2):139-46.
32. Supriadi IR, Haanappel CP, Saptawati L, et al. Infection prevention and control in Indonesian hospitals: identification of strengths, gaps, and challenges. Antimicrob Resist Infect Control. 2023;12(1):6.

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

***Andri Sanityoso Sulaiman[1]*, Nuri Dyah Indrasari[2], Ni Made Hustrini[3], Desti Rachmani[1]***

[1]Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Department of Clinical Pathology, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Corresponding Authors:***
*Andri Sanityoso Sulaiman, MD. Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia.*
*Email: andri_sani@yahoo.com; hepato.ui@gmail.com.*

## 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%) | |

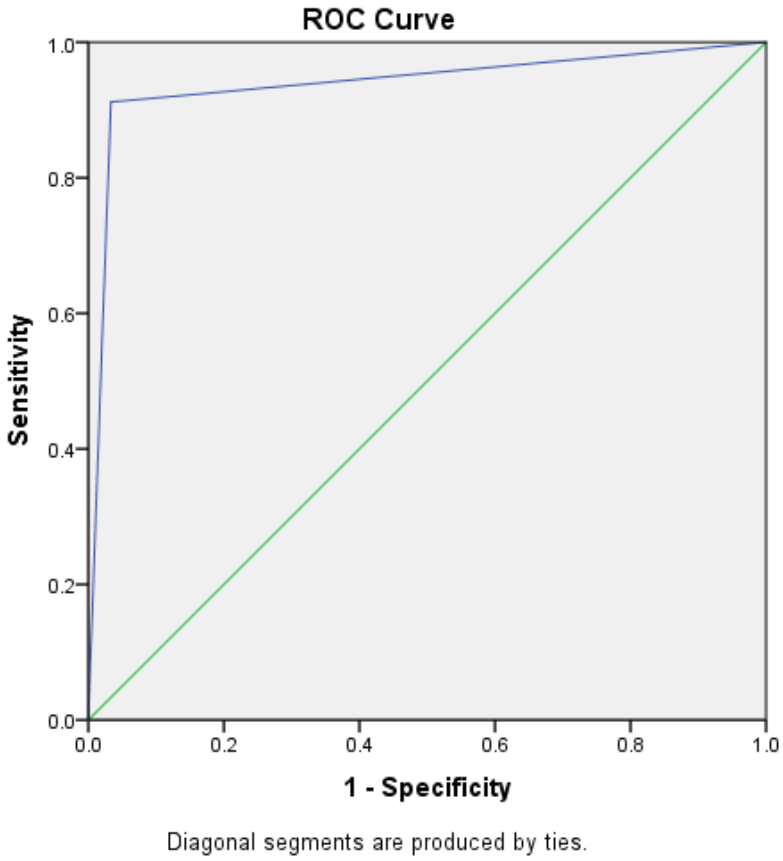



**Figure 1.** ROC Graphs of HCV RNA for Evaluating Significant Genedrive

**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.

## ACKNOWLEDGMENTS

The author would like to thank all staffs from Hemodialysis Unit at Cipto Mangunkusumo Hospital who supported this study. Moreover, the author would also extend their gratitude to Ms. Anugrah Dwi Handayu, dr. Cyhntia Hani, dr. Maria Teressa (Hepatobiliary Division, Faculty of Medicine Universitas Indonesia) for their excellent technical assistance on sample collection and processing.

## REFERENCES

1. World Health Organization. Hepatitis C. (2021).
2. Salari N. The global prevalence of hepatitis C in a general population: A systematic review and meta-analysis. Travel Med Infect Dis. 2022;46:102255.
3. Kemenkes RI. Hasil Riskesdas 2013. (2013).
4. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl. 2022;12:7–11.
5. Kemenkes RI. Laporan Nasional_RKD2018_FINAL.pdf. Riskesdas. 2018;182–3.
6. Hill NR. Global prevalence of chronic kidney disease – A systematic review and meta-analysis. PLoS One. 2016;103–16. doi:10.4103/0019-5359.122734.

7. Widhani A, Lydia A, Gani RA, Setiati S. Serokonversi Hepatitis C pada pasien hemodialisis di RS Cipto Mangunkusumo. *J Penyakit Dalam Indones.* 2017;**2**:15.
8. WHO. WHO releases first-ever global guidance for country validation of viral hepatitis B and C elimination. (2021).
9. Parry JV, Easterbrook P, Sands AR. One or two serological assay testing strategy for diagnosis of HBV and HCV infection? The use of predictive modelling. BMC Infect Dis. 2017;17.
10. Firdaus R. Current molecular methods for the detection of hepatitis C virus in high risk group population: A systematic review. World J Virol. 2015;4:25.
11. Easterbrook PJ, Roberts T, Sands A, Peeling R. Diagnosis of viral hepatitis. Curr Opin HIV AIDS. 2017;12:302–14.
12. Lüllau A. Linkage to care of HbsAg-positive and anti-HCV-positive patients after a systematic screening approach in the German primary care setting. Eur J Gastroenterol Hepatol. 2018;30:280–3.
13. Citarella A. Screening, linkage to care and treatment of hepatitis c infection in primary care setting in the south of Italy. Life. 2020;10:1–9.
14. Llibre A. Development and clinical validation of the Genedrive point-of-care test for qualitative detection of Hepatitis C virus. Gut. 2018;67:2017–24.
15. Morgan JR. Determining the lower limit of detection required for HCV viral load assay for test of cure following direct-acting antiviral-based treatment regimens: Evidence from a global data set. J Viral Hepat. 2022;29:474–86.
16. Lamoury FMJ. Diagnostic performance and usability of the genedrive® hcv id kit in two decentralized settings in cameroon and georgia. Diagnostics. 2021; 11:1–10.
17. FIND. High-priority target product profile for hepatitis C diagnosis in decentralized settings: Report of a consensus meeting. 2015.
18. Reipold IE. Optimising diagnosis of viraemic hepatitis C infection: The development of a target product profile. BMC Infect. Dis. 2017;17.
19. The World Health Organisation. Guidelines on hepatitis B and C testing. Guidelines on hepatitis B and C testing. Vol. 66 (2017).
20. Lamoury FMJ. Evaluation of the Xpert HCV viral load fingerstick point of care assay. (2018) doi:10.1093/infdis/jiy114/4925218.
21. Chevaliez S, Pawlotsky JM. New virological tools for screening, diagnosis and monitoring of hepatitis B and C in resource-limited settings. J Hepatol. 2018;69: 916–26.
22. Lamoury FMJ. Evaluation of the Xpert HCV viral load finger-stick point-of-care assay. J Infect Dis. 2018;217: 1889–96.
23. Mohamed Z. Time matters: Point of care screening and streamlined linkage to care dramatically improves Hepatitis C treatment uptake in prisoners in England. Int J Drug Policy. 2020;75:102608.
24. Hutin Y, Luhmann N, Easterbrook P. Evaluating the impact of Georgia's Hepatitis C elimination plan: lessons learned for the global initiative. Lancet Glob Heal. 2020;8:e163–e164.
25. Cheng YL. We are IntechOpen, the world's leading publisher of open access books built by scientists, for scientists TOP 1%. Intech. 2016;11:13.
26. Midgard H. Peer support in small towns: A decentralized mobile Hepatitis C virus clinic for people who inject drugs. Liver Int. 2022;42:1268–77.

# The Severity, Quality of Life, and Correlated Factors of Chronic Kidney Disease-associated Pruritus between Hemodialysis and Kidney Transplant Patients: A Cross-sectional Study

***Melody Febriana Andardewi[1], Lili Legiawati[1], Danang Tri Wahyudi[2], Maruhum Bonar Hasiholan Marbun[3*], Larisa Paramitha Wibawa[1]***

[1]Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.
[2]Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia - Dharmais Cancer Hospital, Jakarta, Indonesia.
[3]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Corresponding Author:***
*Maruhum Bonar Hasiholan Marbun, MD., PhD. Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: mbhmarbun@gmail.com.*

## ABSTRACT

***Background:*** *Chronic kidney disease-associated pruritus (CKD-aP) mainly occurs in hemodialysis (HD) patients and could persist in kidney transplant (KT) recipients. This study aims to compare the severity, correlation of various biochemical factors, and quality of life (QoL) concerning pruritus in CKD.* ***Methods:*** *A cross-sectional study was conducted on HD and KT recipients with chronic pruritus, where the 5-Dimensional (5-D) Itch Scale and Dermatology Life Quality Index (DLQI) were used to evaluate pruritus severity and QoL.* ***Results:*** *Among the 60 subjects, 76.7% of HD patients had moderate-to-severe pruritus, whereas in the KT group, 83.3% experienced mild pruritus ($p < 0.001$). The median DLQI score was 5 (3–6) and 3 (2–4), respectively ($p < 0.001$). There was a correlation between hs-CRP and the 5-D itch score in the HD group ($r = 0.443$; $p < 0.05$), whereas e-GFR was correlated with the 5-D itch score in the KT group ($r = -0.424$; $p < 0.05$).* ***Conclusion:*** *Moderate-to-severe pruritus was more common in HD patients. While pruritus in KT recipients had a mild effect on QoL, pruritus in the HD group had a mild-moderate impact on QoL. There was a correlation between hs-CRP and e-GFR and the severity of pruritus in HD and KT recipients, respectively.*

***Keywords:*** *chronic kidney disease, hemodialysis, kidney transplant, pruritus, quality of life.*

## INTRODUCTION

Pruritus is an unpleasant sensation that prompts the urge to scratch and could be induced by chronic kidney disease (CKD).[1,2] Approximately 69% of clinicians were not proactively searching for the possibility of CKD-associated pruritus (CKD-aP).[3,4] Where the prevalence of pruritus in patients who underwent hemodialysis (HD) varies between 26% in Germany and 48% in England,[4] studies in Indonesia reported that 46.2%–75.8% of HD patients experienced pruritus,[5-7] which may be persistent in kidney transplant (KT) recipients. The incidence of pruritus in KT recipients was

12%–32%.[8-10]

In general, CKD-aP occurs over large areas of the skin, usually symmetrical and generalized in 25–50% of cases.[3] Additionally, xerosis mostly occurs in conjunction and exacerbates the symptoms.[4-6] Complications of pruritus include erosion, excoriation, ulceration, prurigo nodularis, lichen simplex chronicus, and secondary infection,[11] and additionally, pruritus in HD and KT recipients may contribute to a lower quality of life (QoL).[8]

Studies have reported various factors related to CKD-aP but with varying results.[12] While hypotheses regarding the pathogenesis of CKD-aP include inflammation, which may cause an imbalance of calcium and phosphate, and decreased kidney function leading to severe symptoms of pruritus,[13,14] xerosis, increased histamine, uremic toxins, endogenous opioid imbalance, neuropathy, and hyperparathyroidism further contribute to the pathogenesis of CKD-aP.[15,16] The objective of this study was to compare the severity of pruritus, and QoL, and to assess various biochemical factors between CKD-aP patients who underwent HD and KT.

## METHODS

### Study Design

Non-interventional cross-sectional study was carried out in the Department of Dermatology and Venereology and the Hemodialysis Unit at Dr. Cipto Mangunkusumo National Hospital Jakarta, Indonesia, from September 2022 to April 2023.

### Sample Size and Study Population

Based on the correlation sample size formula, the minimum sample size required was 30 subjects for each group, with a 95% level of confidence and 80% power. The target population included all patients with CKD stage V and pruritus, who underwent HD and KT recipients. The study population consisted of CKD patients with pruritus who underwent HD and KT recipients registered in the Hemodialysis Unit, Dermatology and Venereology Clinic, or Internal Medicine Clinic, Dr. Cipto Mangunkusumo National Hospital Jakarta, Indonesia.

### Patient Recruitment Criteria

Subjects were recruited consecutively based on inclusion and exclusion criteria. Inclusion criteria were as follows: CKD patients receiving HD twice a week, KT recipients ≥3 months post-surgery, chronic pruritus (≥6 weeks), and age ≥ 18 years. The exclusion criteria were: patients with systemic diseases such as hepatobiliary, thyroid, psychiatric, or neurological disease; patients with primary skin diseases (e.g., autoimmune dermatosis, skin infection, genodermatosis, dermatosis in pregnancy); and malignancy.

### Patients Assessment

Patient data were collected from medical records, interviews, and physical examinations. Sociodemographic and clinical characteristics data included age, gender, duration of CKD (< 3 years or ≥3 years), dialysis vintage (≤1 year or > 1 year), etiology of CKD (hypertension, diabetes mellitus, glomerulonephritis, cystic/congenital disease, or unknown), comorbidities (hypertension, diabetes mellitus, or other), body mass index (BMI), cutaneous findings (xerosis, scratch lesion, and discoloration), and laboratory parameters (hs-CRP, calcium, phosphate, e-GFR, urea, and creatinine). A skin examination was conducted by a dermatologist. Body mass index was calculated using the formula BMI = weight (kg)/height ($m^2$).

### Assessment of Pruritus and Quality of Life

Pruritus was assessed using the 5-D Itch Scale questionnaire, a multidimensional tool covering five domains (duration, degree, direction, disability, and distribution). Patients with scores <5 points were defined as having no itch; a score of 6–10 points indicated mild pruritus, 11–20 points moderate pruritus, and 21–25 points indicated severe pruritus.[17] In this study, pruritus severity was categorized into mild pruritus (6–10) and moderate-to-severe pruritus (11–25) groups.

The Dermatology Life Quality Index (DLQI), which has proven to be a dependable and valid assessment tool for measuring QoL across various skin conditions, was used

to assess the quality of life.[18] The DLQI, comprising ten questions categorized into six groups: symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment, is interpreted as having no effect at all on the patient's life (0–1), small effect (2–5), moderate effect (6–10), very large effect (11–20), and extremely large effect on the patient's life (21–30).[19]

### Laboratory Test

The laboratory parameters assessed were as follows: high-sensitivity C-reactive protein (hs-CRP), calcium, phosphate, urea, creatinine, and estimated glomerular filtration rate (e-GFR). According to the standard laboratory assessment guideline, blood samples (5 ml) were drawn from the vein using sterile equipment by trained laboratory personnel to assess hs-CRP, urea, calcium, and phosphate. Blood samples were then placed in labeled vacuum tubes. Before analysis, blood was allowed to clot at room temperature for 10 minutes, then centrifuged at 3000 – 10.000 rpm for 15 minutes to separate the serum. The serum was separated and analyzed on the same day. The e-GFR and creatinine within the last three months from the assessment day were also collected from the patient's medical record.

### Ethical Consideration

Ethical clearance was obtained from the Research Ethics Committee Faculty of Medicine Universitas Indonesia (clearance number: KET-725/UN2.F1/ETIK/ PPM.00.02/2022). Informed consent was requested from all participants.

### Statistical Analysis

Statistical analysis was performed using IBM® SPSS software (version 27; SPSS Inc., Chicago, IL, USA). Qualitative variables were presented as percentages and quantitative variables were expressed as mean ± standard deviation or as median (interquartile range) for data with an abnormal distribution. The normality of data distribution was assessed using the Shapiro-Wilk test. Results were considered statistically significant at $p < 0.05$. Correlations between laboratory variables and the 5-D itch scores for each group were analyzed using Spearman's rho test. Differences in the proportion of pruritus severity across groups were examined using the Chi-square test, while differences in the mean of Dermatology Life Quality Index (DLQI) scores between groups were assessed using the nonparametric Mann–Whitney U-test.

## RESULTS

Sixty-four subjects met the inclusion criteria, while, after further assessment, four patients were excluded because of thyroid disease and pruritus related to dermatological disorders (psoriasis vulgaris, irritant contact dermatitis, or fungal skin disease). This led to a total of 60 subjects being included in our study (**Figure 1**).

### Sociodemographic and Clinical Characteristics

The sociodemographic and clinical characteristics are presented in **Tables 1** and **2**. Skin manifestations are documented in **Figure 2.**

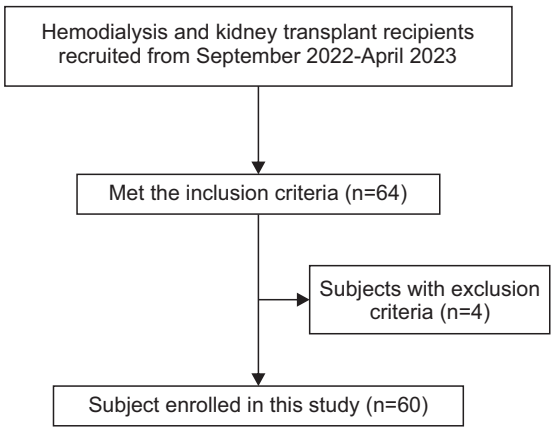



**Figure 1.** Flow chart of patient recruitment.

**Table 1.** Sociodemographic characteristics of subjects in hemodialysis and kidney transplant groups (n = 60)

| Variables | Hemodialysis (n = 30) | Kidney Transplant (n = 30) |
|---|---|---|
| Age (years)* | 46.63 ± 16.33 | 38.0 ± 10.66 |
| Gender (n, %) | | |
| Male | 17 (56.7) | 18 (60) |
| Female | 13 (43.3) | 12 (40) |

*Data shown in means (standard deviation), n: number of subjects

**Table 2.** Clinical characteristics of subjects in hemodialysis and kidney transplant groups (n = 60)

| Variables | Hemodialysis (n = 30) | Kidney Transplant (n = 30) |
|---|---|---|
| Duration of CKD (n, %) | | |
| <3 years | 10 (33.3) | 10 (33.3) |
| ≥3 years | 20 (66.7) | 20 (66.7) |
| Dialysis vintage (n, %) | | |
| ≤1 year | 5 (16.7) | 7 (23.3) |
| >1 years | 25 (83.3) | 23 (76.7) |
| Etiology of CKD (n, %) | | |
| Hypertension | 22 (73.3) | 18 (60) |
| Diabetes mellitus | 5 (16.7) | 1 (3.3) |
| Glomerulonephritis | 1 (3.3) | 5 (16.7) |
| Cystic or congenital | 0 (0) | 2 (6.7) |
| Unknown | 2 (6.7) | 4 (13.3) |
| Comorbidities (n, %) | | |
| Hypertension | 27 (90) | 23 (76.7) |
| Diabetes mellitus | 8 (26.7) | 4 (13.3) |
| Other | 7 (23.3) | 2 (6.7) |
| Body mass index (kg/m$^2$)* | 22.92 ± 4.34 | 23,50 ± 4.64 |
| Cutaneous findings (n, %) | | |
| Xerosis | 24 (80) | 5 (16,7) |
| Secondary scratch lesion | 15 (50) | 3 (10) |
| Discoloration | 9 (30) | 3 (10) |
| Laboratory parameters | | |
| hs-CRP (mg/L)** | 3.07 (0.93–7.60) | 1.07 (0.38–2.40) |
| Calcium (mg/dl)* | 8.51 ± 0.64 | 9.25 ± 0.54 |
| Phosphate (mg/dl)* | 5.17 ± 1.75 | 2.69 ± 0.47 |
| e-GFR (ml/min/1.73 m$^2$)* | 4.94 ± 2.07 | 67.07 ± 21.60 |
| Urea (mg/dl)* | 154.73 ± 48.69 | 41.33 ± 17.59 |
| Creatinine (mg/dl)* | 11.62 ± 4.65 | 1.32 ± 0.41 |

*Data shown in means (standard deviation), **Data shown in median (interquartile range)
CKD: chronic kidney disease, e-GFR: estimated glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, n: number of subjects

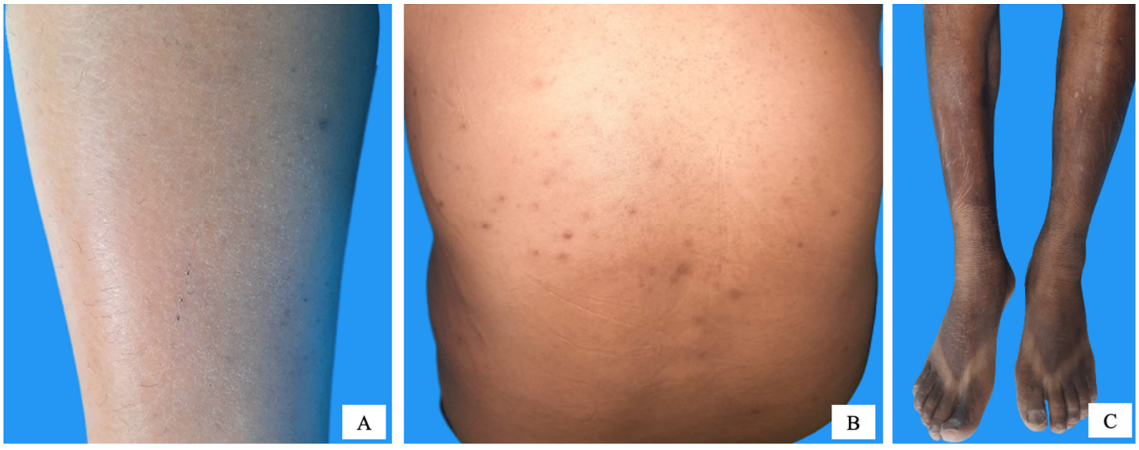



**Figure 2.** Clinical appearance of skin lesions in subjects (A) Xerosis cutis and excoriation on the leg. (B) Prurigo nodularis and postinflammatory hyperpigmentation on the lower back. (C) Hyperpigmentation on the lower legs

### Pruritus Severity

Moderate-to-severe pruritus, with HD patients being 4.6 times more likely to experience it than KT recipients (RR = 4.6, 95% CI = 2.02–10.49), was significantly higher in HD group than in the KT recipients group ($p < 0.001$) **(Table 3)**. HD patients are 4.6 times more likely to experience moderate-to-severe pruritus than KT recipients (RR = 4.6, 95% CI = 2.02–10.49).

**Table 3.** The severity of pruritus between hemodialysis and kidney transplant group (n = 60)

| Group | Pruritus | | RR (95% CI) | p-value |
|---|---|---|---|---|
| | Moderate-severe | Mild | | |
| Hemodialysis | 23 (76.7%) | 7 (23.3%) | 4.6 (2.02–10.5) | <0.001[a] |
| Kidney transplant | 5 (16.7%) | 25 (83.3%) | | |

[a]Chi-Square test, significant if p < 0.05, 95% CI: confidence interval 95%, RR: relative risk

### Quality of Life

The median DLQI score in the HD group was 5 (3–6) points, whereas in the KT group was 3 (2–4) points (p < 0.001). The DLQI score in the HD group was slightly higher than in the KT group.

### Correlation of Biochemical Parameters

High-sensitivity CRP positively correlated with the 5-D itch score in the HD group (r = 0.443, p = 0.014). In the KT group, e-GFR showed a negative correlation (r = −0.424, p = 0.02) (**Table 4**).

## DISCUSSION

In the present study, moderate-to-severe pruritus was more common in HD compared to the KT group. Hemodialysis patients are 4.6 times more likely to experience moderate-to-severe pruritus than KT recipients, with the majority in the KT recipients group experiencing mild pruritus. Based on a study in Turkey, pruritus was also more common in HD patients and less in KT recipients.[20] A study in Germany reported that pruritus in KT recipients is mild, with an average Visual Analog Scale (VAS) of 3.2 points.[9] Persistent pruritus in KT could be caused by persistent pruritic stimuli or sensitization of pruritus signaling pathways, with kidney transplantation eliminating the need for dialysis and reducing factors that trigger pruritus.[8] In addition, xerosis, systemic disease, or various biochemical factors could potentially trigger pruritus in KT recipients. While a study in Poland reported no difference in the prevalence and intensity of pruritus between various immunosuppressants used in KT recipients,[10] immunosuppressants for KT recipients could influence the incidence and severity of pruritus, with examples of these recipients being calcineurin inhibitors, cyclosporine, or tacrolimus.

Based on DLQI, there was a mild-to-moderate impact on the QoL in the HD group, while in the KT group pruritus had a mild effect on QoL (p < 0.001). A study in Pakistan reported a DLQI score of 9.8 ± 1.7 points in HD patients (moderately affected QoL). The study only included male subjects.[19] A study in South Korea reported higher means of DLQI score in HD patients with pruritus (10.4 ± 6.46 points).[21] No other studies have assessed QoL using DLQI in the KT population.

A positive correlation was found between hs-CRP and the 5-D itch scale in the HD group (r = 0.443; p = 0.014). This result is similar to that of a study in China and Cairo.[13,14] A study in China reported a significant relationship between hs-CRP and the severity of pruritus based on the 5-D itch scale. The hs-CRP of HD

**Table 4.** Correlation analysis of hs-CRP, calcium, phosphate, and e-GFR with 5-D itch score in hemodialysis and kidney transplant recipients (n = 60).

| Variables | Hemodialysis (n = 30) | | Kidney Transplant (n = 30) | |
|---|---|---|---|---|
| | R | p-value | R | p-value |
| hs-CRP (mg/L) | 0.443 | 0.014 | 0.132 | 0.486 |
| Calcium (mg/dl) | −0.016 | 0.932 | −0.001 | 0.994 |
| Phosphate (mg/dl) | 0.232 | 0.218 | 0.114 | 0.550 |
| e-GFR (ml/min/1,73 m$^2$) | 0.186 | 0.325 | −0.424 | 0.020 |

Spearman's rho test, significant if p < 0.05, R: correlation coefficient.
e-GFR: estimated glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, n: number of subjects.

patients with moderate-to-severe pruritus was significantly higher.[13] A study in Cairo reported a significant increase in hs-CRP in the HD group with pruritus compared to those without pruritus. High-sensitivity CRP positively correlated with the severity of pruritus both by measurement using the VAS ($r = 0.34$; $p < 0.001$) and the Pruritus Scoring System ($r = 0.33$; $p < 0.001$), indicates that on average KT recipients have a well-controlled inflammatory status, in the KT group there was a positive correlation between hs-CRP and the 5-D itch scale but it was statistically insignificant ($r = 0.132$; $p = 0.486$).[14] The role of inflammation in the KT group was less dominant in the severity of pruritus, with the means of hs-CRP levels in the KT group being lower compared to the HD group.

Microinflammation plays a role in the pathogenesis of pruritus. In CKD, there is an increase in pro-inflammatory cytokines, especially interleukin (IL)-6 and tumor necrosis factor-α (TNF-α).[22] C-reactive protein, which is produced by liver cells in response to stimulation by IL-6 under inflammatory conditions, is closely related to IL-6.[23] Where it is seen that high CRP levels can reflect high IL-6 levels,[23] Hemodialysis patients have higher IL-6 than healthy patients up to 15-fold, especially those with pruritus,[24] with interleukin-6 playing a pivotal role in the differentiation of T helper (Th)-2 and Th-17 cells. Th-2 cell predominance causes an increase in cytokine, which is crucial in the pathogenesis of pruritus. These cytokines include IL-31, IL-4, IL-13, and IL-2. IL-31 cytokines can induce pruritus directly by binding to IL-31Rα and Oncostatin M receptor (OSMR β) on sensory neurons. Other cytokines (IL-4, IL-13, and IL-2) indirectly act as neuronal enhancers by activating other pruritus pathways.[25]

The results in the KT group showed a moderately negative correlation between e-GFR and the 5-D itch scale ($r = -0.424$; $p = 0.02$). Decreased kidney function results in inadequate excretion of toxic substances and metabolic waste products, leading to an accumulation and imbalance of biochemical factors that increase the severity of pruritus.[26] In nondialysis CKD patients, a decrease in e-GFR of 5 ml/minute/1.73 $m^2$ was associated with significantly worsening pruritus ($p < 0.01$).[27] A study in Turkey reported that e-GFR was associated with pruritus in both HD and KT recipients ($p = 0.024$).[20] However, in the present study, there was no significant correlation between e-GFR, which is thought not to correlate with the severity of pruritus because in HD pruritus is more influenced by the adequacy of dialysis and the levels of various uremic toxin substances in the body as well as the severity of pruritus in this group. A study in Taiwan reported that low dialysis adequacy (Kt/V) and the usage of a low-flux dialyzer were significantly associated with severe pruritus. Reducing the severity of pruritus in hemodialysis patients, optimizing dialysis with a target $Kt/V \geq 1.5$, and using a high-flux dialyzer could increase the clearance of pruritogen molecules.[28] The results in the KT group also showed differences from studies in Italian and Polish populations, with these results reporting that there was no association between e-GFR and pruritus severity. [8,10]

Increased phosphate and calcium in the blood could trigger the formation of calcium-phosphate products deposited in the basal layer of the epidermis and other tissues. As a result, activation of local nerve fibers occurs and triggers pruritus, and, although we did not find a significant correlation between calcium and phosphate with pruritus, high calcium and phosphate were associated with the severity of pruritus.[29] This result was similar to the study in China. No significant relationship was found between calcium and phosphate and the severity of pruritus in HD patients ($p = 0.485$ and 0.227, respectively).[13] A study in Italy also reported no significant difference between calcium and phosphate, which are influenced by nutritional intake, supplementation, and malnutrition, in HD patients and KT with pruritus.[8] In this study, we found that calcium and phosphate did not correlate with the severity of pruritus because most subjects in both groups displayed well-controlled calcium and phosphate levels. **Table 5** summarizes the key findings from diverse studies.

Our study has several limitations as well. Data were collected over a period using a cross-sectional design; therefore we could

not determine the causal relationship between factors associated with pruritus in CKD. Immunosuppressant therapy to prevent organ rejection may affect the severity of pruritus in KT recipients; however, we did not analyze other factors that could influence the severity of pruritus, for example, other uremic toxins and oxidative stress.

**Table 5.** Summary of Key Findings from Different Studies

| Author (Year) | Type of Study | Participants | Key Findings |
|---|---|---|---|
| Schricker S, et al (2020)[9] | Cohort | - 132 KT patients<br>- Male and female | - Mean pruritus VAS = 3.2<br>- A moderate correlation between the intensity of pruritus and transplant function (r = 0.3; p = 0.018) |
| Krajewski PK, et al (2020)[10] | Cohort | - 197 KT patients<br>- Male and female | - 21.3% KT recipients had pruritus<br>- The majority reported symptoms relieved after successful transplantation, the rest had residual itch.<br>- WI-NRS itch was 5.98 ± 2.17 points<br>- No significant correlation between hs-CRP, calcium, phosphate, and e-GFR levels with the severity of pruritus |
| Satti MZ, et al (2019)[19] | Cross-sectional | - 173 HD patients<br>- Male only | - Prevalence of pruritus was 49.1%<br>- Mean DLQI score 9.8 ± 1.7 points |
| Guvercin B, et al (2019)[20] | Cohort | - HD group (n = 30), PD group (n = 26), KT group (n = 30), CKD stage I-V group (n = 29), control (n = 30)<br>- Male and female | - Pruritus inversely correlated with GFR, Hb, and albumin levels (p < 0.005)<br>- No differences in serum IL-31 and UGCG levels among study groups<br>- Pruritus was highest in the dialysis group and less frequent in the KT group. |
| Noh SH, et al (2018)[21] | Cross-sectional | - 83 HD patients<br>- Male and female | - Mean pruritus VAS score 6.17 ± 2.62<br>- Mean DLQI score 10.40 ± 6.46 (moderate to extreme large effect of QoL) found in 78.3% of subjects<br>- Higher calcium levels were associated with pruritus |
| Zhao JH, et al (2021)[13] | Cross-sectional | - 148 HD patients<br>- Male and female | - Incidence rate of pruritus 40.54%<br>- Patients with pruritus had higher levels of iPTH, Hb, BUN, nPCR, and hs-CRP<br>- A higher level of hs-CRP was associated with more severe pruritus (OR = 9.440; 95% CI = 3.547–25.124; p < 0.01) |
| Sarhan II, et al (2020)[14] | Case-control | - 100 HD patients<br>- Male and female | - Mean VAS 2.41 ± 2.99 points<br>- Significant increase level of hs-CRP (p < 0.001), phosphate (p < 0.05), and bilirubin (p < 0.05), in a pruritic group compared to non-pruritic group<br>- Significant correlation between hs-CRP with intensity and severity of pruritus using VAS (r = 0.339 and 0.325, respectively) |
| Panuccio V, et al (2017)[8] | Cohort | - KT group (n = 133), HD group (n = 29), control group (n = 62)<br>- Male and female | - The prevalence of pruritus was 62% in HD patients and 32% in KT patients<br>- No association was found between pruritus score and GFR |

BUN: blood urea nitrogen, CKD: chronic kidney disease, GFR: glomerular filtration rate, Hb: hemoglobin, HD: hemodialysis, Hs-CRP: high-sensitivity C-reactive protein, IL-31: interleukin-31, iPTH: parathyroid hormone, KT: kidney transplant, nPCR: normalized protein catabolic rate, PD: peritoneal dialysis, UGCG: uridine diphosphate glucose ceramide glucosyltransferase, VAS: visual analog scale, WI-NRS: worst-itch numerical rating scale

## CONCLUSION

Hemodialysis patients are more prone to moderate-to-severe pruritus, whereas pruritus in KT recipients is mostly mild. In HD patients, itch had a mild-to-moderate influence on QoL, whereas in KT recipients, pruritus had a minor impact. There was a positive correlation between hs-CRP and pruritus in HD patients, and a negative correlation between e-GFR and pruritus in KT recipients.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## ACKNOWLEDGMENTS

The authors would like to express their gratitude to Siti Rizny Fitriana Saldy, Apt., M.Sc. for the assistance with the statistical analysis in this research. We would like to thank all participants, nurses, and laboratory staff at the Dermatology and Venereology Clinic and Hemodialysis Center at Dr. Cipto Mangunkusumo National Hospital.

## FUNDING

This study was supported by Universitas Indonesia (Hibah Publikasi Terindeks Internasional (PUTI) Pascasarjana 2022). Grant number: NKB-180/UN2.RST/HKP.05.00/2022.

## REFERENCES

1. Ständer S. Classification of itch. Curr Probl Dermatol. 2016;50:1-4.
2. Weisshaar E, Szepietowski JC, Dalgard FJ, et al. European S2k guideline on chronic pruritus. Acta Derm Venereol. 2019;99(5):469-506.
3. Molina P, Ojeda R, Blanco A, et al. Etiopathogenesis of chronic kidney disease-associated pruritus: Putting the pieces of the puzzle together. Nefrologia. 2023;43(1):48-62.
4. Rayner HC, Larkina M, Wang M, et al. International comparisons of prevalence, awareness, and treatment of pruritus in people on hemodialysis. Clin J Am Soc Nephrol. 2017;12(12):2000-7.
5. Regina R, Kurniawan M, Surya SP, et al. Hubungan fungsi ginjal, kalsium, dan fosfor dengan xerosis dan pruritus pada pasien yang menjalani hemodialisis. MDVI. 2020;47(4):174-77.
6. Manurung THP, Indriatmi W, Tambunan M. Management of pruritus and xerosis in hemodialysis patients in Indonesia. In: Proceedings of 24th World Congress of Dermatology. Milan, Italy. 2019. p. 1-2.
7. Harlim A. Factors associated with pruritus uremic in chronic kidney failure patients. J Pak Assoc Dermatol. 2020;30(1):86-97.
8. Panuccio V, Tripepi R, Bellantoni M, et al. Pruritus and quality of life in renal transplant patients. Clin Transplant. 2017;31(3):1-7.
9. Schricker S, Weisshaar E, Kupfer J, et al. Prevalence of pruritus in a single cohort of long-term kidney transplant recipients. Acta Derm Venereol. 2020;100(4):1-2.
10. Krajewski PK, Olczyk P, Krajewska M, et al. Clinical characteristics of itch in renal transplant recipients. Front Med. 2020;7:1-8.
11. Szepietowski JC, Balaskas E, Taube KM, et al. Quality of life in patients with uraemic xerosis and pruritus. Acta Derm Venereol. 2011;91(3):313-7.
12. Makar M, Smyth B, Brennan F. Chronic kidney disease-associated pruritus: A review. Kidney Blood Press Res. 2021;46(6):659-69.
13. Zhao JH, Zhu QS, Li YW, et al. Determinants of the intensity of uremic pruritus in patients receiving maintenance hemodialysis: A cross-sectional study. PLoS One. 2021;16(1):1-14.
14. Sarhan II, Abdel-Halim M, Kamel NM, et al. Association of high sensitive C reactive protein and dialysis adequacy with uremic pruritus in hemodialysis patients. Alexandria J Med. 2020;56(1):111-17.
15. Shirazian S, Aina O, Park Y, et al. Chronic kidney disease-associated pruritus: Impact on quality of life and current management challenges. Int J Nephrol Renovasc Dis. 2017;10:11-26.
16. Schricker S, Kimmel M. Unravelling the pathophysiology of chronic kidney disease-associated pruritus. Clin Kidney J. 2021;14 Suppl 3:i23-i31.
17. Wulandari MP, Dachlan AS, Yusharyahya SN. Validity and reliability of 5-D itch scale in the Indonesian language on adult and geriatric patients at Dr. Cipto Mangunkusumo Hospital. Adv Sci Lett. 2018;24(9):6994-8.
18. Szabo A, Brodszky V, Rencz F. A comparative study on the measurement properties of dermatology life quality index (DLQI), DLQI-relevant and Skindex-16. Br J Dermatol. 2022;186(3):485-95.
19. Satti MZ, Arshad D, Javed H, et al. Uremic pruritus: Prevalence and impact on quality of life and depressive symptoms in hemodialysis patients. Cureus. 2019;11(7):1-10.
20. Guvercin B, Kaynar K, Arica DA, et al. The relationship between dermatological findings and serum interleukin 31 and serum uridine diphosphate glucose ceramide glucosyltransferase levels among patients with chronic kidney disease. Hippokratia. 2019;23(2):75-80.
21. Noh SH, Park K, Kim EJ. The incidence of pruritus and biochemical marker associated with pruritus in hemodialysis patients. Ann Dermatol. 2018;30(4):473-5.
22. Espi M, Koppe L, Fouque D, et al. Chronic kidney disease-associated immune dysfunctions: Impact of

protein-bound uremic retention solutes on immune cells. Toxins (Basel). 2020;12(5):1-16.
23. Seo HS. The role and clinical significance of high-sensitivity c-reactive protein in cardiovascular disease. Korean Circ J. 2012;42(3):151-3.
24. Keshari S, Sipayung AD, Hsieh CC, et al. IL-6/p-BTK/p-ERK signaling mediates calcium phosphate-induced pruritus. FASEB J. 2019;33(11):12036-46.
25. Cevikbas F, Lerner EA. Physiology and pathophysiology of itch. Physiol Rev. 2020;100(3):945-82.
26. Agarwal P, Garg V, Karagaiah P, et al. Chronic kidney disease-associated pruritus. Toxins. 2021;13(8):1-15.
27. Wulczyn KE, Zhao SH, Rhee EP, et al. Trajectories of uremic symptom severity and kidney function in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2022;17(4):496-506.
28. Ko MJ, Peng YS, Wu HY. Uremic pruritus: Pathophysiology, clinical presentation, and treatments. Kidney Res Clin Pract. 2022;42(1):39-52.
29. Xie Q, Hu N, Chen Y. Chronic kidney disease-associated pruritus significantly impacts on quality of life of patients on hemodialysis and is associated with increased levels of serum calcium and phosphorus. Postgrad Med J. 2022;98(1161):1-7.

# Genotypic Analysis of Transmitted and Acquired HIV Drug Resistance in People Living with HIV/AIDS in Surabaya, Indonesia, from 2018 to 2019

***Brian Eka Rachman[1,2,#], Ni Luh Ayu Megasari[3,4,#], Siti Q. Khairunisa[4,5], Tomohiro Kotaki[6], M. Vitanata Arfijanto[7], Usman Hadi[7], Nasronudin[2,7], Masanori Kameoka[4,8,9*]***

[1]Internal Medicine Subspecialist Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Universitas Airlangga Hospital, Universitas Airlangga, Surabaya, Indonesia.
[3]Postgraduate School, Universitas Airlangga, Surabaya, Indonesia.
[4]Indonesian-Japan Collaborative Research Center for Emerging and Re-Emerging Infectious Diseases, Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia.
[5]Student of Doctoral Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[6]Department of Virology, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan.
[7] Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[8]Center for Infectious Diseases, Kobe University Graduate School of Medicine, Kobe, Japan.
[9]Division of Global Infectious Diseases, Department of Public Health, Kobe University Graduate School of Health Sciences, Kobe, Japan.
#Authors with equal contribution.

***Corresponding Author:***
*Masanori Kameoka, PhD. Department of Public Health, Kobe University Graduate School of Health Sciences, 7-10-2 Tomogaoka, Suma-ku, Kobe, Hyogo 654-0142, Japan. E-mail: mkameoka@port.kobe-u.ac.jp.*

## ABSTRACT

***Background:*** *Despite the availability of various effective antiretroviral (ARV) drugs, human immunodeficiency virus (HIV) infection has come with HIV drug resistance (HIVDR), which compromises its effectiveness in reducing HIV-related morbidity, mortality, and transmission. The emergence of transmitted (TDR) and acquired HIVDR (ADR) among antiretroviral therapy (ART)-naïve and experienced individuals have been reported in several Indonesian regions. Therefore, continuous HIVDR surveillance is needed in Indonesia, especially in Surabaya, which is identified as having the highest prevalence of HIV infection in East Java; thus, this study aimed to identify the emergence of TDR and ADR among people living with HIV/acquired immune deficiency syndrome (AIDS) (PLWHA).* ***Methods:*** *Fifty-eight PLWHA infected with HIV type 1 (HIV-1), comprising 21 and 37 ART-naïve and experienced individuals were enrolled in this study, respectively. Blood samples collected from study participants were subjected to genotypic analysis, mainly towards the pol gene encoding protease (PR gene) and reverse transcriptase (RT gene) of HIV-1.* ***Results:*** *Seventeen PR and 21 RT genes were successfully amplified and sequenced from 29 samples. HIV-1 subtyping revealed CRF01_AE as the most dominant subtype (24/29; 82.76%), followed by subtype B (3/29; 10.34%). Uncommon subtypes, including subtype D and a recombinant containing subtypes B and G genomic fragments, were also identified. TDR for PR inhibitors was not detected; however, TDR and ADR for RT inhibitors were identified in 11.11% and 41.67% of samples, respectively. Two amino acid insertions at position 69 of the RT gene (69ins), a previously never-reported mutation in Indonesia, were identified in this study.* ***Conclusion:*** *Both TDR and ADR have emerged among PLWHA residing in Surabaya,*

*East Java, Indonesia. Uncommon drug-resistance mutations and subtypes were identified in this study. These situations might hamper ART efficacy and treatment success. Continuous surveillance of HIVDR is necessary to monitor both TDR and ADR in Indonesia.*

***Keywords:*** *HIV-1, Surabaya, antiretroviral therapy (ART), transmitted HIV drug resistance (TDR), acquired HIV drug resistance (ADR).*

## INTRODUCTION

The human immunodeficiency virus (HIV) infection remains a major public health problem, claiming approximately 650,000 lives in 2021. Despite the existing efforts to reduce its transmission, more than one million new HIV infections have been reported annually since its peak in 1996. About 38.4 million people in the world were living with HIV/-acquired immune deficiency syndrome (AIDS) (PLWHA), including 15% of those who did not know their HIV status.[1]

The World Health Organization (WHO) recommends all individuals infected with HIV receive antiretroviral therapy (ART), which typically includes three medications from two antiretroviral (ARV) drug classes. Currently, the Food and Drug Administration (FDA) of the United States of America has approved nine classes of HIV medication, including nucleoside reverse transcriptase inhibitors (nRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), attachment inhibitors, CCR5 antagonists, fusion inhibitor, post-attachment inhibitors, and pharmacokinetic enhancers.[2] Before September 2022, the Indonesian Ministry of Health recommended two drugs from the nRTI class and one drug from the NNRTI class as the first-line ART regimen; thus, PLWHA in Indonesia relied heavily on nRTI and NNRTI-based regimens. Two NRTIs plus one boosted-PI, and one boosted-PI, one INSTI, and one-to-two nRTI were recommended as second and third-line regimens, respectively.[3]

ART was not only effective in achieving viral suppression and CD4 cell count recovery but also in improving physical, and psychological, levels of independence, environment, and spiritual quality of life.[4–6] However, despite the availability of various effective ARV drugs, the management of HIV infection now faces the emergence of HIV drug resistance (HIVDR), which compromises effectiveness in reducing HIV-related morbidity, mortality, and transmission. HIVDR towards NNRTIs can affect more than 10% of ART-naive adult individuals and is found up to three times more often among ART-experienced individuals.[7,8]

Genotypic studies in Indonesia have identified several major transmitted HIVDR (TDR) among ART-naive and acquired HIVDR (ADR) among ART-experienced PLWHA residing in several Indonesian regions.[9–15] Two studies published in 2015 reported the prevalence of TDR and ADR was 4.3% and 37.7% in Surabaya, respectively.[16,17] These situations suggest the necessity of continuous HIVDR surveillance in Indonesia, especially in Surabaya, with the highest prevalence of HIV type 1 (HIV-1) infection in East Java. In 2019, the prevalence of HIV-1 infection in East Java was the fourth highest among Indonesian provinces.[18] This study aimed to identify the emergence of TDR and ADR among PLWHA in 2018-2019 through genotypic analysis.

## METHODS

This study was approved by the Institutional Ethics Committees of Universitas Airlangga (Approval No.: 25-995/UN3.14/PPd/2013) and Kobe University Graduate School of Medicine (Approval No.: 784). The inclusion criteria of research participants were those: 1) at 18 years and older; 2) already diagnosed with HIV-1 infection by an authorized healthcare provider; and 3) giving written informed consent to enroll in the study.

Sample collection was performed at a Teaching Hospital in Surabaya from late 2018 to early 2019. Five milliliters of ethylenediaminetetraacetic acid (EDTA)-

anticoagulated peripheral blood samples were collected from each participant. Cellular DNA was extracted from whole blood using the QIAamp DNA blood mini kit (QIAGEN, Hilden, Germany), followed by PCR amplification and sequencing analysis of viral *pol* gene encoding reverse transcriptase (RT gene) and protease (PR gene), as described in Khairunisa et al.[9] New sequence data and corresponding viral gene fragments of reference HIV-1 strains retrieved from the HIV sequence database (www.hiv.lanl.gov/) were compiled and aligned using MEGA7 software.[19]

A phylogenetic tree analysis performed HIV-1 subtyping, jumping profile Hidden Markov Model (jpHMM)-HIV tools (http://jphmm.gobics.de/submission_hiv), and recombinant identification program (RIP) (www.hiv.lanl.gov/). Neighbor-joining (NJ) trees with the Kimura two-parameter model were constructed using MEGA7 software,[19] with bootstrap values (1,000 replicates) for relevant nodes reported on a representative tree. Identification of drug resistance mutations (DRMs) in successfully sequenced PR and RT genes was based on the International Antiviral Society-United States (IAS-USA) guidelines.[20] Transmitted and acquired HIVDR were then defined as the presence of at least one major DRM in sequences obtained from ART-naïve and experienced individuals, respectively. The level of resistance towards ARV was determined based on the HIVDR database of Stanford University (https://hivdb.stanford.edu/hivdb/by-patterns/). The nucleotide sequences of viral gene fragments have been deposited in the GenBank database under accession numbers OR547957-OR547994.

## RESULTS

### Participants Characteristics

Fifty-eight PLWHA, comprising of 21 ART-naïve and 37 ART-experienced individuals, were enrolled in this study. Overall, the predominant age group was 18-30 years old (20/58; 34.48%). Most participants were male (43/58; 74.14%) and acquired HIV-1 infection through a heterosexual transmission route (44/58; 68.97%). Among ART-experienced individuals, 91.89% (34/37) received first-line ART regimen, comprising of lamivudine (3TC) + zidovudine (AZT) + nevirapine (NVP) (21/37; 56.76%), 3TC + AZT + efavirenz (EFV) (1/37; 2.7%), 3TC + TDF + NVP (1/37; 2.7%), and 3TC + tenofovir (TDF) + EFV (11/37; 29.73%). Three individuals (3/37; 8.11%) received a second-line ART regimen containing 3TC + TDF + ritonavir-boosted lopinavir (LPV/r). Thirty-seven (63.79%) participants were Javanese, while the rest were Chinese and of other ethnicities. The characteristics of the participants are shown in **Table 1**.

**Table 1. Demographic Characteristics of Study Participants.**

| | ART-naïve (n) | % | ART-experienced (n) | % | Total (n) | % |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| 18-30 | 11 | 32.35 | 9 | 24.32 | 20 | 34.48 |
| 31-40 | 5 | 14.71 | 10 | 27.03 | 15 | 25.86 |
| 41-50 | 4 | 11.76 | 12 | 32.43 | 16 | 27.59 |
| 51-60 | | | 3 | 8.11 | 3 | 5.17 |
| >60 | 1 | 2.94 | 3 | 8.11 | 4 | 6.90 |
| **Sex** | | | | | | |
| Male | 17 | 80.95 | 26 | 70.27 | 43 | 74.14 |
| Female | 4 | 19.05 | 11 | 29.73 | 15 | 25.86 |
| **Transmission** | | | | | | |
| Heterosexual | 18 | 85.71 | 22 | 59.46 | 40 | 68.97 |
| Homosexual | 3 | 14.29 | 7 | 18.92 | 10 | 17.24 |
| IDU | | | 8 | 21.62 | 8 | 13.79 |
| **ART Regimen** | | | | | | |
| 3TC (L) + TDF + LPV/r | N/A | - | 3 | 8.11 | | |
| 3TC+AZT+NVP | N/A | - | 21 | 56.76 | | |
| 3TC-TDF+EFV | N/A | - | 11 | 29.73 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3TC+TDF+NVP | N/A | - | 1 | 2.70 | | |
| 3TC+AZT+EFV | N/A | - | 1 | 2.70 | | |
| **Ethnicity** | | | | | | |
| Javanese | 18 | 85.71 | 19 | 51.35 | 37 | 63.79 |
| Chinese | 2 | 9.52 | 13 | 35.14 | 15 | 25.86 |
| Other | 1 | 4.76 | 5 | 13.51 | 6 | 10.34 |

3TC – lamivudine; AZT – zidovudine; TDF – tenofovir; NVP – nevirapine; EFV – efavirenz; LPV/r – ritonavir-boosted lopinavir

### HIV-1 Subtype

Sequencing data of 17 PR genes [297 base pairs (bp); nt 2253–2549 by HXB2 numbering, and 21 N-terminus of RT genes (741 bp; nt 2571–3311) were successfully sequenced from cellular DNA extracted from 29 PLWHA. NJ trees for the PR and RT genes are shown in **Figure 1**. Viral subtyping by RIP, jpHMM-HIV, and phylogenetic trees showed consistent results (data not shown). Twenty-four samples (24/29; 82.76%) were classified as CRF01_AE, three samples (3/29; 10.34%) were subtype B, one sample (1/29; 3.45%) was subtype D, and one sample (1/29; 3.45) was a recombinant virus containing subtypes B and G genomic fragments (B/G recombinant).

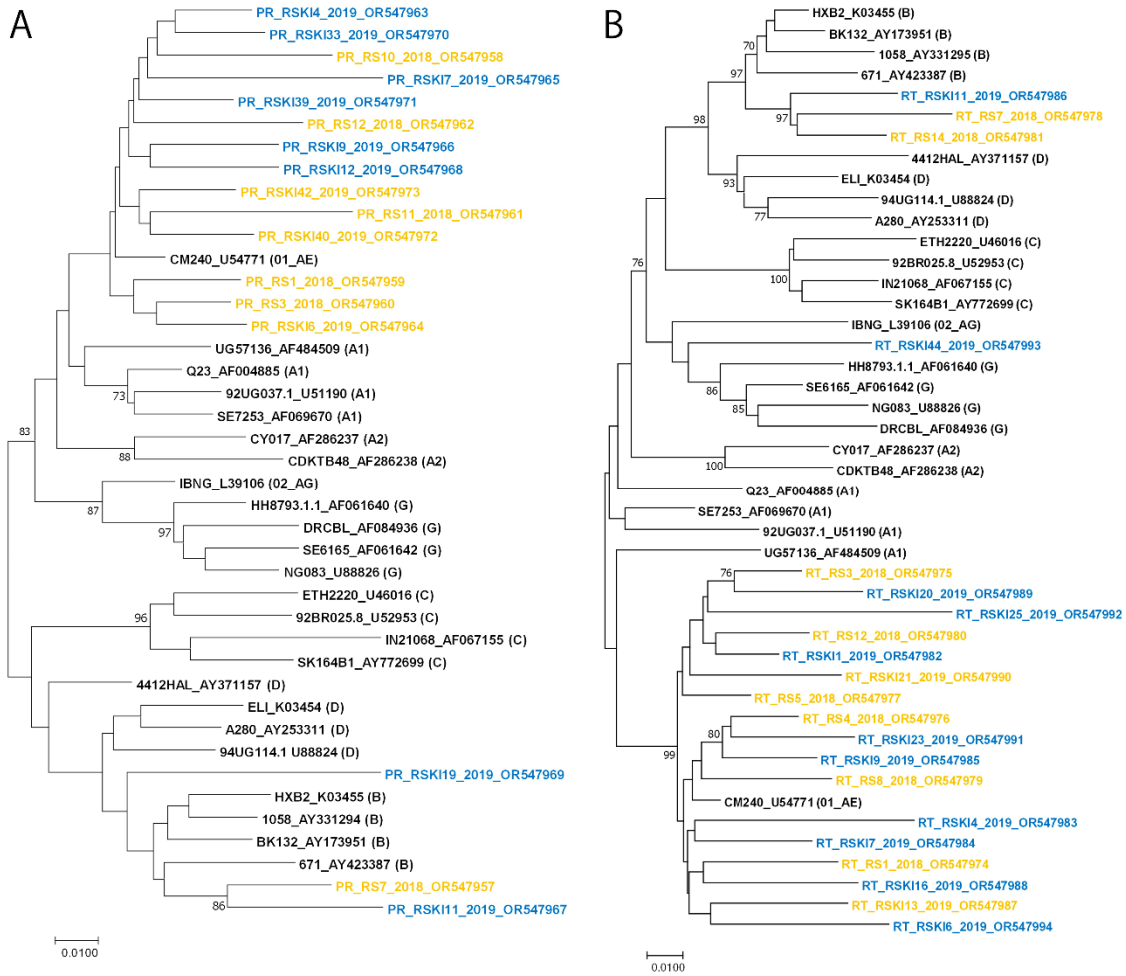



**Figure. 1.** Phylogenetic tree analysis of HIV-1 PR and RT gene sequences collected from ART-naïve and experienced individuals residing in Surabaya, East Java, Indonesia. Blue and orange colors denote samples from ART-naïve and experienced individuals, respectively.

Phylogenetic trees were constructed for the HIV-1 PR (A) and RT (B) genes newly sequenced in the present study. The corresponding viral genes of reference HIV-1 strains representing subtypes A1, A2, B, C, D, and G, as well as CRF01_AE (01_AE) and CRF02_AG (02_AG) were included in the analyses (shown in black color). Sequence IDs are presented as a sample ID or the ID of the reference HIV-1 strain, a GenBank accession number, and the subtype or CRF of the reference strain (shown in parentheses) in that order. Bootstrap values were shown if they were >70.

### Detection of TDR

Eight PR and 9 RT genes were successfully sequenced from 14 ART-naïve individuals. TDR related to the PR genes was not observed; however, several minor mutations were identified, including L10I/V [amino acid substitution from leucine (L) to isoleucine (I) or valine (V) at position 10 in the PR gene] (2/8; 25%), K20R (3/8; 37.5%), M36I (6/8; 75%), I62V (2/8; 25%), H69K (6/8; 75%), A71T (1/8; 12.5%), V77I (3/8; 37.5%), and L89M (6/8; 75%). One sample (1/9; 11.11%) possessed TDR, the G190A mutation, in the RT genes (as presented in **Table 2**).

### Detection of ADR

Nine PR and 12 RT genes were successfully sequenced from 14 ART-experienced individuals. Similar to those of ART-naïve individuals, there was also no ADR in the PR genes of ART-experienced individuals. Several minor mutations in the PR genes were identified, including L10I/F (5/9; 55.55%), K20R (2/9; 22.22%), L33F (1/9; 11.11%), M36I (8/9; 88.89%), H69K (8/9; 88.89%), V77I (1/9; 11.11%), and L89M (7/9; 77.78%). Five samples (5/12; 41.67%) possessed ADR in the RT genes. The most common major RT genes mutation observed was M184V/I (4/12; 19.05%), followed by M41L (3/12; 14.29%), T215Y/F (3/12; 14.29%), K101P/E (2/12; 9.52%), K103N/S (2/12; 9.52%), Y181C (2/12; 9.52%), and G190A (2/12; 9.52%). Other mutations, including A62V, D67N, 69ins (S-A) [2-amino acid (serine and alanine) insertion in the following position 69 in the RT gene], K70R, V108I, L210W, and H221Y, were each observed in one sample (1/12; 4.76%). Individual samples with major DRMs in RT genes and levels of resistance toward ARV are shown in **Table 2**.

**Table 2. HIV-1 Drug Resistance Mutations of Individual Samples**

| Sample Code | ART status | Subtype | nRTI-related mutations | NNRTI-related mutations | Levels of ARV resistance |
|---|---|---|---|---|---|
| RS1_2018 | Experienced | CRF01_AE | | K103N, G190A | High-level resistance to EFV and NVP, low-level resistance to RVP, and potential low-level resistance to ETV. |
| RS7_2018 | Experienced | B | M41L, M184V, L210W, T215Y | V108I, Y181C, H221Y | High-level resistance to ABC, AZT, FTC, 3TC, NVP, and RPV. Intermediate resistance to TDF, DOR, EFV, and ETV. |
| RSKI6_2019 | Experienced | CRF01_AE | M41L, A62V, 69INS, M184V, T215Y | K101E, Y181C, G190A | High-level resistance to AZT, FTC, 3TC, NVP, EFV, ETV, and RPV. Intermediate resistance to ABC, and DOR, and low-level resistance to TDF. |
| RSKI13_2019 | Experienced | CRF01_AE | M41L, D67N, K70R, M184V, T215F | K101P, K103S | High-level resistance to ABC, AZT, FTC, 3TC, EFV, ETV, NVP, and RPV. Intermediate resistance to TDF, and potential low-level resistance to DOR |
| RSKI21_2019 | Experienced | CRF01_AE | M184I | | High-level resistance to FTC and 3TC, and low-level resistance to ABC. |
| RSKI25_2019 | Naïve | CRF01_AE | | G190A | High-level resistance to NVP, intermediate resistance to EFV, low-level resistance to RPV, and potential low-level resistance to ETV. |

ABC – Abacavir, FTC – Emtricitabine, 3TC – Lamivudine, TDF – Tenofovir, AZT – Zidovudine, ddI – Didanosine, d4T – Stavudine, DOR – Doravirine, EFV – Efavirenz, ETV – Etravirine, NVP – Nevirapine, RPV – Rilpivirine

## DISCUSSION

We herein report the circulating HIV-1 subtype and prevalence of HIVDR among HIV-1-infected, ART-naïve, and experienced individuals in Surabaya, East Java, Indonesia. Among 28 successfully sequenced samples, the most common HIV-1 subtype identified was the CRF01_AE (24/29; 82.76%). This finding is consistent with those previously reported in Surabaya,[17,21], and with the reports in several other Indonesian regions, including Bali, Jakarta, Pontianak, and Makassar.[9–14] Subtype B was identified in three samples (3/29; 10.34%) Along with CRF02_AG, subtype B was the second most-identified HIV-1 subtype in Indonesia.[9,10,12] Other subtypes, including subtype D and the B/G recombinant identified in this study, have not previously emerged in Indonesia. Subtype D was mostly found in East and Central Africa,[22] while B/G recombinant was previously reported in Mexico, Spain, and Portugal.[23,24] However, it is necessary to carry out further analysis in a future study, using other gene fragments or carrying out nearly full-length genomic sequencing to determine whether unique HIV-1 subtypes and recombinants were circulating in Indonesia. The HIV-1 gene fragments analyzed in the present study were considered insufficient to identify actual recombinant forms.

Compared to HIV genotypic studies conducted in Surabaya in 2015,[16,17] TDR and ADR in the present study showed a higher prevalence of 11.11% (1/9) and 41.67% (5/12), respectively. Previously, prevalence rates of 4.3% and 37.7% for TDR and ADR were reported in Surabaya, respectively.[16,17]

Several major DRMs in the RT genes were identified in ART-experienced individuals, including M41L, D67N, K101P/E, K103N/S, V108I, Y181C, M184V/I, L210W, T215Y/F, and H221Y. These mutations were associated with drug resistance to AZT, stavudine (d4T), abacavir (ABC), EFV, etravirine (ETR), NVP, and rilpivirine (RPV). A mutation, A62V is related to 151 complex that affects all nRTIs currently approved by the FDA, excluding TDF. In addition, mutations, K70R, L210W, and T215Y/F are also related to Thymidine Analogue-Associated Mutations or TAMs, which affect all approved nRTIs other than emtricitabine (FTC) and 3TC.[20] Amino acid insertion at amino acid position 69, along with A62V, K70R, and L210W, T215Y/F are related to the 69-insertion complex that affects all nRTIs currently approved by the FDA. Interestingly, the 69ins mutation described in this study has not been reported in previous genotypic studies carried out in Indonesia. A mutation, G190A was identified in both ART-naïve and -experienced individuals. This mutation affects EFV and NVP,[20] two NNRTIs that were mainly used in first-line ART regimens.[3]

This current study revealed no evidence of circulating PI-related TDR and ADR in Surabaya. This may have been due to the limited usage of PIs. Among ART-experienced individuals enrolled in this study, only 8.11% received a second-line ART regimen containing PI drug class. The Indonesian Ministry of Health reported that 123,895 PLWHA (97%) received first-line ART regimens and 3,718 individuals (3%) received second-line ART regimens in 2019.[18]

Despite no major DRMs being detected in the PR genes, minor mutations, including L10I/F/V, K20R, L33F, M36I, I62V, H69K, A71T, V77I, and L89M, were identified in both ART naïve and experienced PLWHA enrolled in this study. These mutations might potentially affect viral susceptibility to ritonavir-boosted atazanavir (ATV/r), ritonavir-boosted lopinavir (LPV/r), ritonavir-boosted tipranavir (TPV/r), ritonavir-boosted fosamprenavir (FPV/r), ritonavir-boosted indinavir (IDV/r), nelfinavir (NFV), and ritonavir-boosted saquinavir (SQV/r).[20] Previous studies confirmed the presence of similar PI-related minor DRMs among PLWHA in other Indonesian regions, including Bali, Jakarta, Pontianak, and Makassar.[9–14] The presence of these minor mutations, especially those affecting the efficacy of LVP/r, might need to be considered when a second-line regimen is being recommended for PLWHA in Indonesia.[3]

The results of the present study should raise awareness of TDR and ADR present in PLWHA residing in Surabaya, East Java, Indonesia. According to the WHO, the prevalence of HIVDR in a geographical area is categorized

into three groups: low level (<5%), moderate level (5–15%), and high level (>15%).[25] Based on these categories, the prevalence of TDR and ADR in Surabaya in 2018-2019 was considered to be moderate and high, respectively. However, current results may have overestimated the prevalence due to the limitation in the study design. The number of samples collected was limited; therefore, continuous monitoring of TDR and ADR with a larger sample size is necessary.

## CONCLUSION

Both TDR and ADR emerged in PLWHA residing in Surabaya, East Java, Indonesia. A drug resistance mutation that was previously not reported, 69ins, along with uncommon HIV-1 subtypes (subtype D and B/G recombinant), have been identified in this study. These situations warrant serious consideration due to the hampering impact of drug resistance on ART efficacy and treatment success. Continuous surveillance of HIVDR, especially with a larger sample size, is necessary to monitor TDR and ADR in Indonesia. Besides, it is necessary to strengthen the national policy regarding the appropriate choice of ART.

## ACKNOWLEDGMENTS

This study was supported by the Japan Initiative for the Global Research Network on Infectious Diseases (J-GRID) from the Ministry of Education, Culture, Sport, Science and Technology of Japan, the Japan Agency for Medical Research and Development (AMED), and the Institute of Tropical Disease as the Center of Excellence (COE) program by The Indonesian Ministry of Education, Culture, Research, and Technology. This article was proofread by Sastra Lingua, Sumenep, Indonesia.

## COMPETING INTEREST

The authors declared no competing interest.

## REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). Fact Sheet 2022. UNAIDS: Geneva; 2022.
2. Tyler R. Kemnic, Peter G. Gulick. HIV antiretroviral therapy. StatPearls Publishing: Treasure Island (FL); 2023.
3. Indonesian Ministry of Health. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/ MENKES/90/2019 tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana HIV. 2019.
4. Megasari NLA, Wijaksana IKE. Factors affecting HIV viral load of antiretroviral therapyexperienced and naïve individuals residing in Bali, Indonesia. Mal J Med Health Sci 2023;19(Supp 3):111–5.
5. the AFRICOS Study Group, Bahemana E, Esber A, et al. Impact of age on CD4 recovery and viral suppression over time among adults living with HIV who initiated antiretroviral therapy in the African Cohort Study. AIDS Res Ther 2020;17(1):66; doi: 10.1186/s12981-020-00323-x.
6. Pimentel GS, Ceccato M das GB, Costa J de O, et al. Qualidade de vida em indivíduos iniciando a terapia antirretroviral: um estudo de coorte. Rev saúde pública 2020;54:146; doi: 10.11606/s1518-8787.2020054001920.
7. World Health Organization. HIV drug resistance report 2021. World Health Organization: Geneva; 2021.
8. Pratama MohHR, Arfijanto MV, Lusida MLI. CD4 association with mortality in HIV patients with dyspnea in Dr Seotomo general academic Hospital Surabaya. CIMRJ 2023;4(1):20–22; doi: 10.20473/ cimrj.v4i1.42609.
9. Khairunisa SQ, Megasari NLA, Ueda S, et al. 2018–2019 Update on the molecular epidemiology of HIV-1 in Indonesia. AIDS Research and Human Retroviruses 2020;36(11):957–963; doi: 10.1089/aid.2020.0151.
10. Khairunisa SQ, Megasari NLA, Indriati DW, et al. Identification of HIV-1 subtypes and drug resistance mutations among HIV-1-infected individuals residing in Pontianak, Indonesia. Germs 2020;10(3):174–83. doi: 10.18683/germs.2020.1203.
11. Khairunisa SQ, Megasari NLA, Rahayu RP, et al. Detection of human immunodeficiency virus type 1 transmitted drug resistance among treatment-Naive individuals residing in Jakarta, Indonesia. Infectious Disease Reports 2020;12(11):8740; doi: 10.4081/ idr.2020.8740.
12. Khairunisa SQ, Megasari NLA, Ueda S, et al. Subtype distribution and drug resistance patterns among HIV-1 strains prevalent in Makassar, Indonesia. AIDS Research and Human Retroviruses 2023;39(3):124–29; doi: 10.1089/aid.2022.0139.
13. Megasari NLA, Oktafiani D, Ana EF, et al. Genotypic characterization of human immunodeficiency virus type 1 isolated from antiretroviral treatment-experienced individuals in Buleleng regency, Bali, Indonesia. AIDS Research and Human Retroviruses 2019;35(8):769–74; doi: 10.1089/aid.2019.0058.
14. Megasari NLA, Oktafiani D, Fitriana E, et al. The emergence of HIV-1 transmitted drug resistance mutations among antiretroviral therapy-naive

individuals in Buleleng, Bali, Indonesia. Acta Med Indones. 2019;51(3):197–204.
15. Widiyanti M, Fitriana E, Natalia EI, et al. Identification of antiretroviral mutation in protease and reverse trancriptase inhibitor in human immunodeficiency virus-1 of HIV/AIDS patients in Mimika regency, Papua. FMI 2017;53(1):56; doi: 10.20473/fmi.v53i1.5491.
16. Khairunisa SQ, Kotaki T, Witaningrum AM, et al. Appearance of drug resistance-associated mutations in human immunodeficiency virus type 1 protease and reverse transcriptase derived from drug-treated Indonesian patients. AIDS Research and Human Retroviruses. 2015;31(2):255–9; doi: 10.1089/aid.2014.0221.
17. Kotaki T, Khairunisa SQ, Witaningrum AM, et al. HIV-1 transmitted drug resistance mutations among antiretroviral therapy-naïve individuals in Surabaya, Indonesia. AIDS Res Ther 2015;12(1):5; doi: 10.1186/s12981-015-0046-y.
18. Indonesian Ministry of Health. Laporan situasi perkembangan HIV AIDS dan PIMS di Indonesia Januari-Desember 2019. Jakarta; 2019.
19. Kumar S, Stecher G, Tamura K. MEGA7: Molecular evolutionary genetics analysis version 7.0 for bigger datasets. Molecular biology and evolution 2016;33(7):1870–4; doi: 10.1093/molbev/msw054.
20. Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2022 update of the drug resistance mutations in HIV-1. Top Antivir Med. 2022;30(4):559–74.
21. Kotaki T, Khairunisa SQ, Sukartiningrum SD, et al. High prevalence of HIV-1 CRF01_AE viruses among female commercial sex workers residing in Surabaya, Indonesia. PLoS One. 2013;8(12):e82645; doi: 10.1371/journal.pone.0082645.
22. Hemelaar J, Elangovan R, Yun J, et al. Global and regional epidemiology of HIV-1 recombinants in 1990–2015: a systematic review and global survey. The Lancet HIV 2020;7(11):e772–e781; doi: 10.1016/S2352-3018(20)30252-6.
23. Fernández-García A, Delgado E, Cuevas MT, et al. Identification of an HIV-1 BG Intersubtype Recombinant Form (CRF73_BG), Partially Related to CRF14_BG, Which Is Circulating in Portugal and Spain. In: Tee KK,. ed. PLoS ONE. 2016;11(2):e0148549; doi: 10.1371/journal.pone.0148549.
24. Vázquez-Valls E, Escoto-Delgadillo M, López-Márquez FC, et al. Molecular epidemiology of HIV type 1 in Mexico: Emergence of BG and BF intersubtype recombinants. AIDS Research and Human Retroviruses. 2010;26(7):777–81; doi: 10.1089/aid.2009.0195.
25. Bennett DE, Myatt M, Bertagnolio S, et al. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. Antivir Ther 2008;13 Suppl 2:25–36.

# The Relationship Between Appropriateness of Antibiotic Use Based on the Gyssens Algorithm and Mortality: A Retrospective Cohort Study in Indonesian Tertiary Hospital

*Fadrian[1,2,3]*, Gestina Aliska[3,4,5], Widy Nur Utami[3]*

[1] Division of Tropical and Infectious Disease, Department of Internal Medicine, Dr. M. Djamil Central General Hospital, Padang, Indonesia.
[2]Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Andalas, Padang, Indonesia.
[3]Antimicrobial Resistance Stewardship Committee, Dr. M. Djamil Central General Hospital, Padang, Indonesia.
[4]Department of Clinical Pharmacology, Dr. M. Djamil Central General Hospital, Padang, Indonesia.
[5]Department of Clinical Pharmacology and Therapeutics, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

***Corresponding Author:***
*Fadrian, MD. Division of Tropical and Infectious Disease, Department of Internal Medicine, Dr. M. Djamil Central General Hospital. Jl. Perintis Kemerdekaan, Padang, Indonesia. Email: fadrian@med.unand.ac.id.*

## ABSTRACT

***Background:*** *Some studies have reported that antibiotic use as therapy and prophylaxis in hospitals is inappropriate in approximately 9% to 64% of cases. The Gyssens algorithm is used for qualitative evaluation by assessing the appropriate antibiotic use. This study aimed to determine and evaluate the quality of antibiotic use in inpatients at Dr. M. Djamil Central General Hospital using the Gyssens algorithm.* ***Methods:*** *This was a retrospective cohort study at Dr. M. Djamil Central General Hospital from January to December 2021. We collected data from the medical records of inpatients who received antibiotics using a random sampling technique, and the number of patients from each department was calculated through a preliminary survey.* ***Results:*** *There were three hundred and sixty samples from the population that met the inclusion criteria, adults (59.4%), patients treated for >14 days (38.9%), patients discharged with improvement (66.9%), and patients diagnosed with pneumonia (49.5%). Most antibiotics were appropriate (56.5%), with ceftriaxone being the most commonly used antibiotic (199 cases). Appropriate antibiotic use (Gyssens 0) is mostly found in the Internal Medicine Department Meanwhile, antibiotic use without indications (Gyssens V) is mostly found in the Surgery Department. A significant correlation was found betweenthe appropriateness of antibiotic administration and patient outcomes after discharge from the hospital ($p<0.05$). There was an increase in the risk of death in inappropriate antibiotic use (Gyssens I-IV) and antibiotic use without indications (Gyssens V) by 1.96 and 4.05 times, respectively.* ***Conclusion:*** *There are many cases of inappropriate antibiotic use in Dr. M. Djamil Central General Hospital; therefore, education regarding appropriate antibiotic use is necessary.*

***Keywords:*** *antibiotic use, Gyssens algorithm.*

## INTRODUCTION

In several studies, antibiotic use as a therapy and prophylaxis in hospitals showed an inappropriate indication in approximately 9% to 65% of cases.[1,2] A study by Luciana et al., in Indonesia reported that 44% to 97% of patients in hospitals were prescribed antibiotics unnecessarily.[3] Inappropriate use of antimicrobials can increase morbidity, mortality, health care costs, the emergence or selection of resistant microorganisms, and *Clostridium difficile* infection rates. In addition, it can cause antimicrobial drug toxicity and can increase drug interactions, catheter-related infections associated with intravenous antimicrobial administration, and other nosocomial infections that prolong hospitalization.[4]

Appropriate antibiotic use was evaluated qualitatively using the Gyssens algorithm. This algorithm can be used to evaluate the accuracy of antibiotic use selected as initial or empirical therapy in cases of infection. Evaluation of antibiotic use is conducted not only to identify the amount and quality of antibiotic use in the hospital but also to serve as a fundamental step in establishing surveillance of antibiotic use in a systematic and standardized manner as an indicator of the quality of hospital services.[5] A study by Hadi et al., divided the appropriateness of antibiotic use into 3 groups, including appropriate antibiotic use (Gyssens 0), inappropriate antibiotic use (Gyssens I-IV), and antibiotic use without indications (Gyssens V).[6] This study aims to identify and assess the quality and the outcome due to the appropriateness of antibiotic use in patients at Dr. M. Djamil Central General Hospital using the Gyssens algorithm.

## METHODS

This was a retrospective cohort study with data collection from the medical records of all patients who were treated with antibiotics at Dr. M. Djamil Central General Hospital from January to December 2021. Patients who received antibiotics for empirical and definitive indications were included in the study. Patients were selected using a random sampling technique in each department. In the sampling selection, a random sampling technique was used in each department and then the number of patients from each department was calculated through a preliminary survey. The preliminary survey was conducted in two phases. The first phase was conducted at the antimicrobial stewardship committee of Dr. M. Djamil Central General Padang. In the first phase, it was found that there were 11 appropriate uses of antibiotics from 30 patients, thus obtaining a total minimal sample size of 356 patients. After that, the second phase of the preliminary survey recorded the usage of antibiotics from all departments of Dr. M. Djamil Central General Padang in one week. The calculation of the proportion of patients in each department was carried out with a preliminary survey for one week, the results per department were as follows: pediatric (34 patients), surgery (102), cardiovascular care unit (14), the ICU (37), internal medicine (91), cardiology (18), ophthalmology (2), OB-GYN (9), pulmonology (24), intensive observation room (2), neurology (16), and ENT (11). Demographic data (age, gender, body weight, number of medical records, and dates of admission and discharge), diagnosis, admission and discharge conditions, laboratory test results, chest X-rays, and antibiotic treatments were collected. An evaluation was conducted using the Gyssens algorithm by classifying each antibiotic administration into six categories, category VI (inappropriate use because the medical record was incomplete for evaluation), category V (inappropriate use because it was not as indicated), category IVa (inappropriate use because there were more effective antibiotics), category IVb (inappropriate use because there were safer antibiotics), category IVc (inappropriate use because there were cheaper antibiotics), category IVd (inappropriate use because there were other antibiotics with a narrower or more specific spectrum), category IIIa (inappropriate use because of very long administration), category IIIb (inappropriate use because of very short administration), category IIa (inappropriate use of administration dose), category IIb (inappropriate use of administration interval), category IIc (inappropriate use of administration procedure), category I (inappropriate administration time), and category 0 (appropriate antibiotic use or not included in categories I-VI).[7,8] Patients who were in Gyssens category VI were excluded

from this study. The appropriateness of antibiotic use in this study will be divided into 3 groups, including appropriate antibiotic use (Gyssens 0), inappropriate antibiotic use (Gyssens I-IV), and antibiotic use without indications (Gyssens V). Data on the characteristics of the patients and the quality profile of antibiotic use were presented as descriptive statistics. Patient outcome was a dichotomous variable, documented as either recovery or dead state. An analysis of the relationship between the appropriateness of antibiotic use and the patient's outcome was carried out by using the chi-square method. The collected quantitative data were processed and analyzed by computerization.

## RESULTS

According to the inclusion and exclusion criteria based on the proportion in each department, the number of patients in this study was 360. Out of a total of 360 patients, there were 608 antibiotics used.

**Table 1** presents the characteristics of the subjects. The majority of the patients in this study were male (59.2%), adults (59.4%), patients who had a length of stay >14 days (38.9%), and patients who had an improved or recovered outcome (66,9%) after antibiotic administration. Out of a total of 360 patients, there were 278 infectious diseases and 100 without diagnosis of infections in the medical record. Pneumonia

**Table 1.** Characteristics of the subjects.

| Characteristics | Distribution (n = 360) | Frequency (%) |
|---|---|---|
| **Gender** | | |
| Male | 213 | 59.2 |
| Female | 147 | 40.8 |
| Age Category | | |
| Children | 51 | 14.2 |
| Adult | 214 | 59.4 |
| Elderly | 95 | 26.4 |
| Department/Room | | |
| Pediatric | 34 | 9.4 |
| Surgery | 102 | 28.3 |
| CVCU[1] | 14 | 3.9 |
| ICU[2] | 37 | 10.3 |
| Internal Medicine | 91 | 25.3 |
| Cardiology | 18 | 5.0 |
| Ophthalmology | 2 | 0.6 |
| OB-GYN[3] | 9 | 2.5 |
| Pulmonology | 24 | 6.7 |
| Intensive Observation Room | 2 | 0.6 |
| Neurology | 16 | 4.4 |
| ENT[4] | 11 | 3.1 |
| Length of Stay | | |
| 0-7 days | 102 | 28.3 |
| 7-14 days | 118 | 32.8 |
| >14 days | 140 | 38.9 |
| Outcome | | |
| Recovery | 241 | 66.9 |
| Dead | 119 | 33.1 |
| Infectious Disease (n=378) | | |
| Pneumonia | 188 | 49.7 |
| Skin and soft tissue infection | 23 | 6.1 |
| Urinary tract infection | 16 | 4.2 |
| Intra-abdominal infection | 15 | 4.0 |
| CNS[5] infection | 12 | 3.2 |
| Other infections | 24 | 6.3 |
| No diagnosis of infections in medical record | 100 | 26.5 |

[1]CVCU, cardiovascular care unit; [2]ICU, intensive care unit; [3]OB-GYN, obstetrics and gynecology; [4]ENT, ear, nose throat; [5]CNS, central nervous system

was the most common infectious disease (49.5%) observed in this study. There were 100 patients without a diagnosis of infection who received antibiotics from medical records. This is generally found in postoperative patients who receive antibiotics without infection.

**Figure 1** shows that antibiotic use at Dr. M. Djamil General Hospital was appropriate (Gyssens 0) in 344 cases (56.5%), followed by antibiotic use without indications (Gyssens V) in 164 cases (26.9%), and inappropriate antibiotic use (Gyssens I-IV) in 100cases (16.7%).

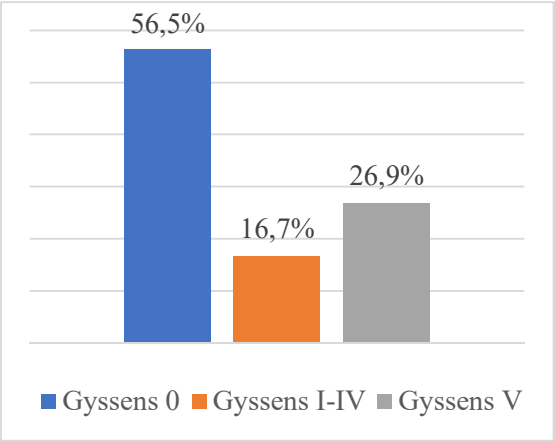



**Figure 1.** Appropriateness of Antibiotic Use. The use of antibiotics at Dr. M. Djamil General Hospital was appropriate (Gyssens 0) in 56.5% of cases, 26.9% of cases without indications (Gyssens V), and inappropriate (Gyssens I-IV) in 16.7% of cases.

The details and appropriateness of the antibiotics used in 608 cases can be seen in **Figure 2.** Based on the results presented in **Figure 2**, ceftriaxone and levofloxacin were the two most commonly used antibiotics, with 199 and 142 of the total 608 antibiotics used, respectively. Appropriate antibiotic use (Gyssens 0) was found to be 344, with ceftriaxone and levofloxacin accounting for 120 and 99 of the total antibiotics used in the Gyssens 0 category, respectively. In terms of antibiotic use without indications (Gyssens V), ceftriaxone and levofloxacin were found in 68 and 29 out of 164 antibiotics used in the Gyssens V category, respectively.

The Gyssens categories based on departments are presented in **Figure 3**. Antibiotic use without indications (Gyssens V) was mostly found in the Surgery Department (59 cases), followed by the Internal Medicine Department (22 cases), and the ICU (17 cases). The appropriate antibiotic use (Gyssens 0) was found in the Internal Medicine Department (108 cases), followed by surgery (95 cases) and the ICU (29 cases).

**Table 2** shows that there was a significant relationship between the appropriateness of

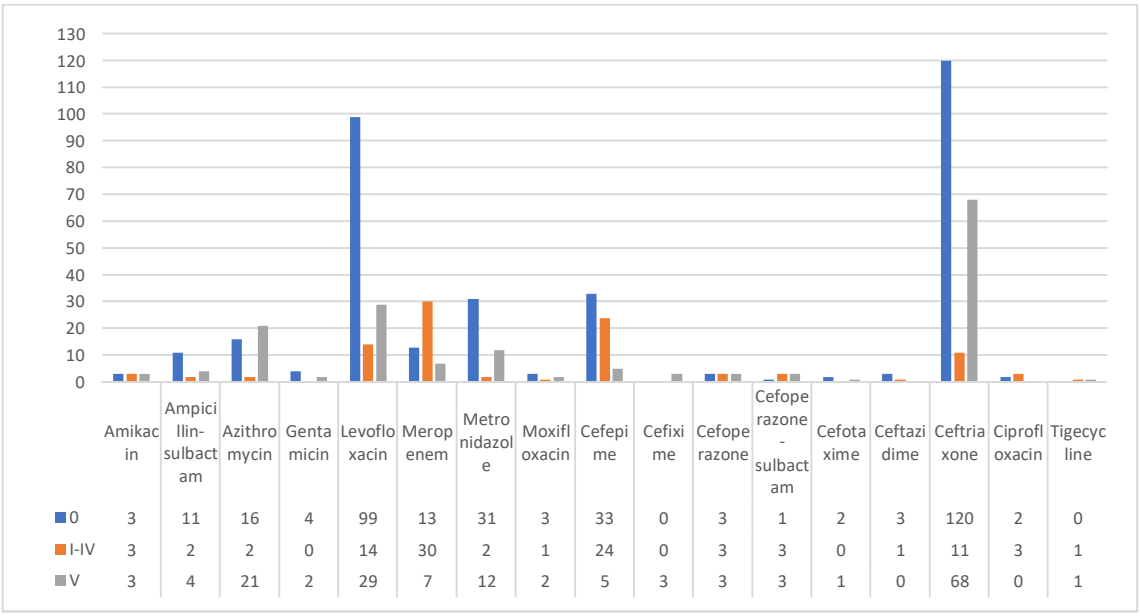



**Figure 2.** Types of Antibiotics Based on Gyssens Categories. Ceftriaxone and levofloxacin were the two most commonly used antibiotics. Appropriate antibiotic use (Gyssens 0) was found to be 344, with ceftriaxone as much as 120 and levofloxacin as much as 99 of the total antibiotics in the Gyssens 0 category used. While for antibiotics use without indications (Gyssens V), ceftriaxone was found to be 68 and levofloxacin was 29 out of a total of 164 antibiotics in the Gyssens V category. The use of inappropriate antibiotics (Gyssens I-IV), such as meropenem, had a fairly high distribution, which was 30 out of a total of 100 antibiotics.

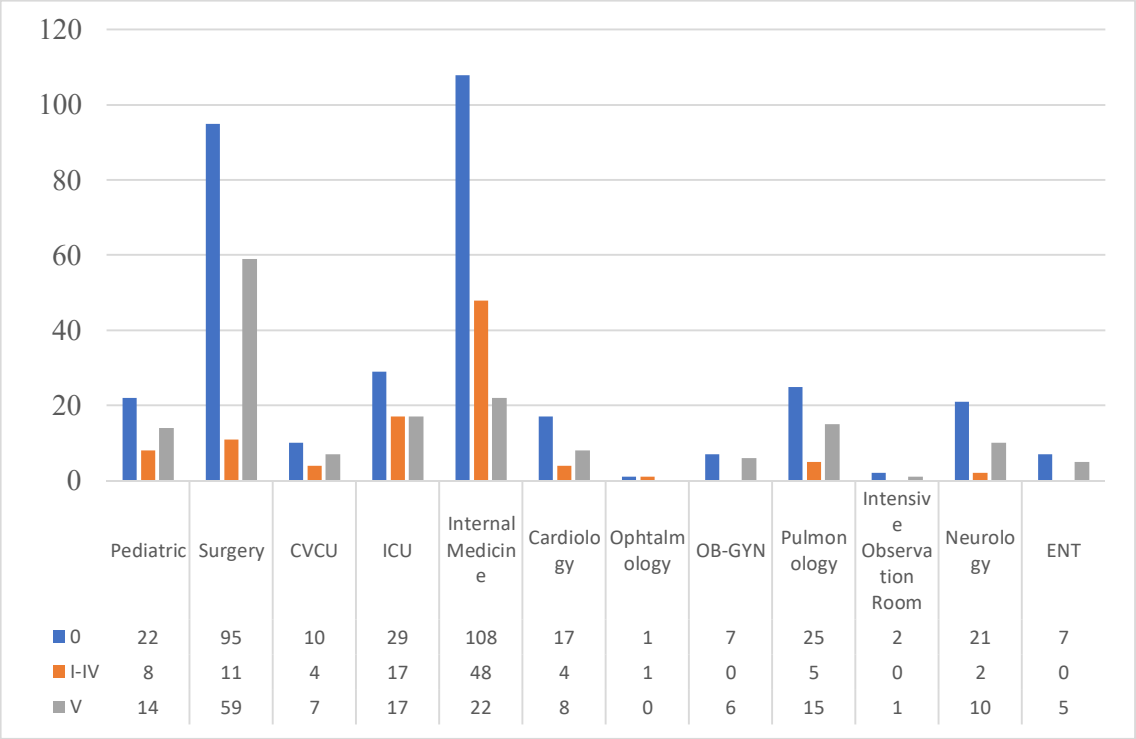



**Figure 3.** Gyssens categories based on the department. The use of antibiotics without indications (Gyssens V) was mostly found in the surgery department, internal medicine, and the ICU. Rational and appropriate antibiotic use (Gyssens 0) was found in internal medicine, surgery, and the ICU. Inappropriate antibiotic use (Gyssens I-IV) was mostly found in internal medicine, the ICU, and surgery

**Table 2.** Outcome of hospital discharge based on appropriateness of antibiotic use.

| Gyssens Category | Patient's Outcome | | Total | p-value | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| | Recovery n (%) | Dead n (%) | | | |
| 0 | 216 (62.8) | 128 (37.2) | 344 (100) | Ref[1] | Ref[1] |
| I-IV | 45 (45) | 55 (55) | 100 (100) | 0.002 | 1.965 (1.286-3.001) |
| V | 126 (76.8) | 38 (23.2) | 164 (100) | 0.000 | 4.053 (2.372-6.923) |
| Total | 387 (63.7) | 221 (36.3) | 608 (100) | | |

[1]Ref, Reference

antibiotic use and the patient's condition upon discharge from the hospital. The analysis also showed that patients with inappropriate antibiotic use (Gyssens I-IV) had increased mortality risk by 1.96 times, and patients with antibiotic use without indication (Gyssens V) had increased by 4.05 times mortality risk.

## DISCUSSION

This study showed that male patients were more common (59.2%) than female patients. This finding is similar to that of a study by Rohmah et al., which showed that the patients were mostly male (62.5%). This could be due to the differences in the lifestyle and behavior of women and men who are at risk.[9] Contrary to the study by Masyrifah et al., which showed that the patients were predominantly female (52.7%). Based on the age group, most patients in this study were adults. Masyrifah et al., also showed that the largest patients of the study were patients in the age group of 19-65 years (66.4%).[9] The differences in the results of this study are thought to be caused by the total sampling technique and different inclusion criteria. There were differences in the length of hospitalization between this study and previous observational studies at Fatmawati General Hospital Jakarta. Most of the patients in this study spent more than 14 days of hospitalization, whereas in the

study at Fatmawati General Hospital Jakarta, most of the patients only spent less than 14 days of hospitalization (85.5%).[10] The reason for this difference may be that Dr. M. Djamil Central General Hospital is the only final referral hospital for the West Sumatra region. Thus, generally, the patients treated are those with multiple comorbidities that require longer treatment. This is supported by Fadrian et al., research in 2022 showed that many patients treated at Dr. M. Djamil Central General Hospital with more than one comorbidity, with the highest presentations such as chronic kidney disease (28%), type 2 diabetes mellitus (19.2%), and malignancy (12.4%).[11] Another research in 2021 regarding comorbidities and outcomes in patients also showed that the percentage of patients with comorbidities >1 had poor outcomes with deaths of 93.1%, compared to only 6.9% who lived (OR = 10.97, 95% CI 2.19-54.96).[12]

Most of the patients in this study were discharged from the hospital in an improved condition after receiving antibiotics, which is in contrast to the results of a study by Chen et al., which showed that the study patients were more likely to die (63.8%) than to recover (36.2%).[13] A similar finding was also reported by Masyrifah et al., who showed that patients who used antibiotics according to the Gyssens algorithm had a higher mortality rate (71.8%) than those who recovered (28.2%). The high mortality in the study by Masyrifah et al. was due to various causative factors, including the number of comorbid diseases that the patient had, the source of infection, the use of ventilators, and other causative factors.[10] However, this study is in line with another study in 2023 which showed that patients who were given antibiotics were more likely to recover (95.8%) than die (4.2%).[9]

In terms of infectious diseases, the majority of the patients in this study were diagnosed with pneumonia. The results of this study are in line with a study in 2022 that reported that the patients were more likely to have a diagnosis of pneumonia (66.4%), followed by intra-abdominal infections (10%), and skin and soft tissue infections (8.2%).[10]

Furthermore, this study showed that antibiotic use was appropriate. Meanwhile, research by Ma'rifah et al., in the internal medicine department, found that there was 40% appropriate use of antibiotics (Gyssens 0), 7.27% inappropriate use (Gyssens I-IV), and 52.73% use of antibiotics without indication (Gyssens V).[14] Different result can happen because the study only focuses in two departments. The study by Sukmawati et al. showed that 40% of the study patients in the Gyssens 0 category received intravenous ceftriaxone, intravenous levofloxacin, and oral levofloxacin antibiotics and those in the Gyssens I-IV categories were 60% of the study patients, dominated by those in category IIIA (40%).[15] The antibiotics most commonly used in this study were ceftriaxone and levofloxacin. Fadrian et al., also found that ceftriaxone was the most commonly used initial empirical antibiotic alone, followed by cefepime and meropenem.[16] This is due to the most common disease in those study was pneumonia. Ceftriaxone is recommended as first-line antibiotic treatment with the addition of fluoroquinolone /macrolides for pneumonia.[17,18]

Patients referred to Dr. M. Djamil Central General Hospital were clinically severe with significant comorbidities, making it a consideration for clinicians to provide early antibiotic therapy for better patient outcomes. In addition, the risk of nosocomial bacterial infection in hospitals is another factor that needs to be considered by clinicians when providing antibiotic therapy to patients. The antibiotic use policy is a strategy of the Antibiotic Resistance Control Program. Appropriate antibiotic use can reduce the risk of antibiotic resistance in patients which has an impact on patient outcomes.[19]

This study showed that antibiotic use without indication (Gyssens V) is common in the surgical department. This is likely due to the large number of cases of postoperative antibiotic use in patients without a diagnosis of infection. Appropriate antibiotic use (Gyssens 0) was most prevalent in the Internal Medicine Department, and inappropriate antibiotic use (Gyssens I-IV) was most prevalent in the Internal Medicine Department. A study by Hadi et al., of 999 patients who used appropriate

antibiotics (Gyssens 0) was predominantly found in the Internal Medicine Department (49 cases). Inappropriate antibiotic use (Gyssens I-IV) was found mostly in the pediatric department (48 cases).[6] The difference in the results of this study is considered because there are only 4 departments used for the study. In contrast, our study includes all departments and uses a preliminary proportion system, so there were differences in the proportion of the pediatric department.[6]

In this study, 241 patients who used 387 antibiotics were discharged after improvement. This was also consistent with the statistically significant relationship ($p<0.05$) between the appropriateness of antibiotic use and the patient's condition at discharge. Patients with inappropriate antibiotic use (Gyssens I-IV) had increased mortality risk by 1.96 times, and those with antibiotic use without indication (Gyssens V) had increased mortality risk by 4.05 times. A study by Adani et al., on 48 sepsis patients in the ICU of Dr. Hasan Sadikin Hospital showed 81.3% of death cases, and most of them (56.3%) had a history of inappropriate antibiotic use (Gyssens I-IV).[20] Another study by Masyrifah et al., also reported that inappropriate antibiotic use had a high mortality rate, which was 80.6%.[10] In addition, Dhillon et al., who conducted a study at the Persahabatan Central General Hospital, found that there was a statistically significant relationship between inappropriate empirical antibiotic use, which could increase the risk of mortality by 4.2 times, and patient outcomes.[21] In those studies that have carried out inappropriate antibiotic use, Gyssens I-V is not described more specifically. Therefore, our study divides Gyssens I-IV and Gyssens V because there is more antibiotic use without indication at 26.9% (Gyssens V) than those with inappropriate antibiotic use at 16.7% (Gyssens I-IV). Although our study provides the same results as several previous studies regarding increased mortality, we described 2 groups to see the differences in mortality between groups with inappropriate antibiotic use (Gyssens I-IV) and antibiotic use without indication (Gyssens V).

## CONCLUSION

Antibiotic use at Dr. M. Djamil General Hospital was appropriate (Gyssens 0) in 343 cases (56.5%). On the other hand, we found antibiotic use without indications (Gyssens V) in 164 cases (26.9%), and inappropriate antibiotic use (Gyssens I-IV) in 101 cases (16.7%). The analysis also showed that patients with inappropriate antibiotic use (Gyssens I-IV) had an increased mortality risk of 1.96 times and patients with antibiotic use without indication (Gyssens V) had an increased by 4.05 times mortality risk. The increased risk of death from inappropriate and the usage of antibiotics without indication should be a concern. Therefore, education regarding appropriate antibiotic use is necessary.

## ACKNOWLEDGMENTS

The authors thank the Education and Research Department of Dr. M. Djamil Central General Hospital for supporting this study by providing input and consultation throughout the study. We would also like to thank the Medical Record Department of Dr. M. Djamil Central General Hospital for their support and assistance in providing data and information for the study.

## REFERENCES

1. Afekouh H, Baune P, Abbas R, De Falvelly D, Guermah F, Haber N. Antibiotic prescription evaluation in the rehabilitation ward of a geriatric hospital. Med Mal Infect. 2015;45(11–12):427–35.
2. Cusini A, Rampini SK, Bansal V, et al. Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: A prevalence survey. PLoS One. 2010;5(11):e14011.
3. Luciana T, Andrajati R, Rianti A, Khan A. Rational antimicrobial use in an intensive care unit in Jakarta, Indonesia: A Hospital-Based, Cross-Sectional Study. Tropical Journal of Pharmaceutical Research. 2015 May 6;14(4):707.
4. Katarnida SS, Murniati D, Katar Y. Evaluasi penggunaan antibiotik secara kualitatif di RS Penyakit Infeksi Sulianti Saroso, Jakarta. Sari Pediatri. 2016 Nov 9;15(6):369.

5. Sihite EN, Ramadhan AM, Samsul E. Evaluasi penggunaan antibiotik secara kuantitatif dan kualitatif pada pasien bedah digestif di RSUD Abdul Wahab Sjahranie Samarinda. Proceeding of Mulawarman Pharmaceuticals Conferences. 2021;14:214–21.
6. Hadi U, Duerink DO, Lestari ES, Nagelkerke NJ, Keuter M, In't Veld DH, Suwandojo E, Rahardjo E, van den Broek P, Gyssens IC. Audit of antibiotic prescribing in two governmental teaching hospitals in Indonesia. Clinical microbiology and infection. 2008;14(7):698-707.
7. Sundariningrum RW, Setyanto DB, Natadidjaja RI. Evaluasi kualitatif antibiotik metode gyssens dengan konsep regulasi antimikroba sistem prospektif RASPRO pada pneumonia di Ruang Rawat Intensif Anak. Sari Pediatri. 2020;22(2):109.
8. Sitompul F, Radji M, Bahtiar A. Evaluasi penggunaan antibiotik dengan metode Gyssens pada pasien stroke rawat inap di RSUD Koja secara retrospektif (Periode KJS Dan BPJS). Indonesian Pharmaceutical Journal. 2016;6(1):30–8.
9. Rohmah SD, Andrajati R, Yudhorini LT. Qualitative evaluation of antibiotic use in bacterial meningitis patients using the Gyssens method. Jurnal Aisyah: Jurnal Ilmu Kesehatan. 2023;8(S1):169–78.
10. Masyrifah M, Andrajati R, Yudhorini LT. Qualitative evaluation of antibiotics use with Gyssens method in sepsis patients at Fatmawati Central General Hospital Jakarta. Pharmaceutical Sciences and Research. 2022;9(2).
11. Chen LK, Nathanael J, Shakinah S, et al. Association between early antibiotic administration and in-hospital mortality in moderate and severe COVID-19 patients. Jurnal Penyakit Dalam Indonesia. 2022;9(4).
12. Fadrian F, Linosefa L, Ridhwan F. M, Hasnah H, Syafa Ayuni A. Multidrug-resistant organisms and determinant factors in sepsis patients. Iran. Iran J Med Microbiol. 2023;17(5):596-605.
13. Elly U, Yusticia K. The role of age and comorbidities on the outcome of confirmed clinically critical Covid-19 patients treated with Remdesivir At Indonesia's National Referral Hospital. Afr J Infect Dis. 2022;17(1):55-59.
14. Ma'rifah N, Hasmono D, Hadi U, Kuntaman K. Analysis of quality of antibiotic usage on patient with internal and surgical service. FMI. 2021;57(1):1-5.
15. Sukmawati IGAND, Adi Jaya MK, Swastini DA. Evaluasi Penggunaan antibiotik pada pasien tifoid rawat inap di salah satu rumah sakit pemerintah Provinsi Bali dengan metode Gyssens dan ATC/DDD. Jurnal Farmasi Udayana. 2020;26:37.
16. Fadrian F, Chen K, Kumalawati J, Rumende CM, Shatri H, Nelwan EJ. The validation of drug resistance in pneumonia (DRIP) score in predicting infections due to drug-resistant pathogens in community-acquired pneumonia at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Acta Med Indones. 2021;53(4):416–22.
17. Barcha M, Steinberg Y, Kozlovsky D, Gvili AG. Ceftriaxone versus ampicillin for the treatment of community-acquired pneumonia. A propensity-matched cohort study. Clin Microbiol Infect. 2023;29(1):70-6.
18. Metlay JP, Watere GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):45-67.
19. Ibrahim AM, Widyati W, Prasetyadi FOH. Analisis Kualitatif penggunaan antibiotik pada pasien rujukan dengan metode analisis alur Gyssen di RSPAL Dr. Ramelan Surabaya. MPI (Media Pharmaceutica Indonesiana). 2020 Dec 22;3(2):88–95.
20. Adani SD, Zulfariansyah A, Santoso PTR. Quality assessment of antibiotic prescription for sepsis treatment in intensive care unit at top referral hospital in West Java, Indonesia. Althea Medical Journal. 2017 Jun;4(2):286–92.
21. Dhillon J, Agustin H, Burhan E, et al. Evaluation of antibiotics use based on gyssens method and their relationship to the outcome of hospitalized community-acquired pneumonia patients in Persahabatan General Hospital Jakarta. [Jakarta]: Universitas Indonesia; 2020.

# Early Experience of Left Bundle Branch Pacing with Lumenless Lead in a Single Center: A Case Series

***Evan Jim Gunawan[1], Johan [1], Dian Andina Munawar[1,2], Dian Larasati Munawar[1], Beny Hartono[1], Muhammad Munawar[1,2]****

[1]Binawaluya Cardiac Center, Jakarta, Indonesia.
[2]Department of Cardiovascular Medicine, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

***Corresponding Author:***
*Muhammad Munawar, MD, PhD. Binawaluya Cardiac Center. Jl. TB Simatupang 71, Jakarta 13750, Indonesia. Email: muna@cbn.net.id; muna286@gmail.com.*

## ABSTRACT

*Left bundle branch pacing (LBBP) has been subject to increasing interest over the last few years due to its capacity for physiological conduction and its advantages compared to His bundle pacing. His bundle pacing has certain limitations, such as a small pacing area for the His bundle, a high threshold that leads to battery depletion, a low R-wave amplitude that may result in atrial or His oversensing, and ventricular signal undersensing. In this case series, four patients (two female and two male) aged 62.2 ± 8.4 years old with symptomatic sick sinus disease and no scar tissue in the interventricular septum underwent LBBP. All LBBPs were done with standard LBBP using a lumenless SelectSecure 3830 lead (Medtronic®, Minneapolis, USA) with a fixed helix. The lead parameters showed a good R-wave amplitudes (13 ± 7.4 mV) and a low threshold (0.77 ± 0.17 V @ 0.4 ms). All patients were discharged on the next day. During follow-up period of 13.3 ± 12.9 months, all patients were well and no complications were noted. In conclusion, LBBP may be as an alternative of novel conduction pacing techniques and can be done relatively easy and safe, even with limited experience center.*

***Keywords****: Left bundle branch pacing, novel conduction system pacing, sick sinus syndrome, pacemaker.*

## INTRODUCTION

Left bundle branch pacing (LBBP) is a novel conduction system pacing (CSP) approach that can bypass an abnormal conduction system more distal to the left-sided His bundle and capture the left bundle branch to produce near physiological conduction.[1] LBBP has advantages compared to His bundle pacing, such as a lower threshold, larger R wave, and larger area for LBBP.[2,3] The first LBBP in humans was reported by Huang et al. in 2017.[4] In our center, the first LBBP was performed in December 2021. This report describes our four LBBP cases and provides an overview of the implantation technique. To our knowledge, this is the first published case series of LBBP in Indonesia.

## CASE ILLUSTRATION

Four patients with symptomatic bradycardia due to sick sinus syndrome were scheduled for permanent pacemakers. All patients had normal ejection fraction and no scar tissue in the interventricular septum (IVS) (**Table 1**). The ECGs showed normal QRS width, with no bundle branch block (BBB), and only one patient had paroxysmal AF but successful PVI ablation . During the procedure, we used intravenous sedation and local anesthesia. Our LBBP technique was using a lumenless SelectSecure 3830 lead (Medtronic®, Minneapolis, USA) and a delivery sheath of fixed-curve 315-HIS (Medtronic®, Minneapolis, USA). Only in the first case we used a His quadripolar catheter

for His mapping (**Figure 1A**). After gaining more experience, we did not use this technique in in the subsequent cases (**Figure 1B**). After implantation, the pacing QRS showed a Qr pattern and a relatively narrow QRS in v1, a larger R wave in lead II than in lead III, a negative R wave in aVR and a positive in aVL lead. The pacemaker mode setting was AAI, with a mode switch to DDD. No complications occurred related to the LBBP procedure in any of the patients.

## IMPLANTATION TECHNIQUE

Preprocedural assessments and implantation tools should be well prepared. The assessments in this case series included determining the thickness of the basal IVS and the presence or absence of a septal scar. The general approach for LBBP lead implantation in our center was to use a lumenless SelectSecure 3830 lead (Medtronic®, Minneapolis, USA) with a fixed helix for LBBP and a delivery sheath using a fixed-curve 315-HIS sheath (Medtronic®, Minneapolis, USA) or Selectsite C304-HIS deflectable sheath (Medtronic®, Minneapolis, USA). A standard 12-lead ECG, a pacing system analyzer (PSA), and an intracardiac electrogram were used for pacing lead recording and implantation.

Our implantation technique was a standard approach for LBBP and can be found anywhere .[5,6] Basically, our approach was either cutting-down from the left side of cephalic vein or puncturing from the axillary vein. We used a 7-Fr introducer for the C315 sheath or a 9-Fr introducer for the C304 sheath (Medtronic®, Minneapolis, USA).

His bundle potential was recorded with a quadripolar catheter or a SelectSecure 3830 lead (Medtronic®, Minneapolis, USA). The His bundle location was mapped from the right anterior oblique (RAO) fluoroscopic view using a delivery sheath and a SelectSecure 3830 lead (Medtronic®, Minneapolis, USA). However, in some cases, it was difficult to record the His signal. Therefore, we used the tricuspid annulus as an anatomical landmark (fluoroscopic) (**Figure 1A, B**) or recorded it electrically with A and V waves based on an intracardiac electrogram.[6]

To locate the left bundle branch area, we used the RAO position, and the delivery sheath was turned clockwise and advanced 1.5–2 cm apico-inferiorly from the His bundle area into the RV cavity (**Figure 1A**). Unipolar pacing was performed to find the optimal lead site and the paced morphology of the QS complex, with a notch in the nadir or a "w" pattern in lead V1, R wave in lead II larger than in lead III, a negative aVR, and a positive aVL (**Figure 2B**).[5]

For fixation of the lead, the delivery sheath was rotated (typically counter-clockwise) to make the lead and tip of the sheath perpendicular to the septum at approximately 3 o'clock in the LAO view (**Figure 1C**) and 1 o'clock in the RAO view (**Figures 1A** and **1B**). If the above ECG criteria were met, the lead was subject to several rotations.[6] Due to the floppiness of the 3830 lead, in our experience, the rotation number could vary from eight turns up to more than 12 turns depending on the tissue characteristics. Clockwise rotation was performed until the paced QRS morphology resembled the RBBB pattern in lead V1 (qR or rSR') (**Figure 2D**). During the clockwise rotation, the impedance would gradually increase, and after reaching the left bundle branch (LBB) area, the impedance would gradually drop by 100 Ω.[6]

A contrast injection of approximately several milliliters through the delivery sheath port was performed in the LAO view (**Figure 1C**) to define the RV septal wall and to confirm the lead depth inside the RV septum. When the tip of the lead was approximately 6–8 mm inside the IVS, the fulcrum sign was observed in fluoroscopy. As the lead was advanced inside the septum, the notch on the S wave in lead V1 moved up, and after additional rotation, the end of the QRS became r' in V1.[5] During fixation, "fixation beats" were observed when the lead was already near the left bundle branch (**Figure 2C**).[7] We continuously monitored the unipolar pacing morphology and the impedance to ensure a value > 500 Ω. The lead rotation was stopped when a low threshold (< 1.5 V at 0.5 ms) was confirmed for the LBB capture.[5]

The final step consisted of removing the sheath and confirming the proper slack. The delivery sheath was pulled back to the right atrium, and the

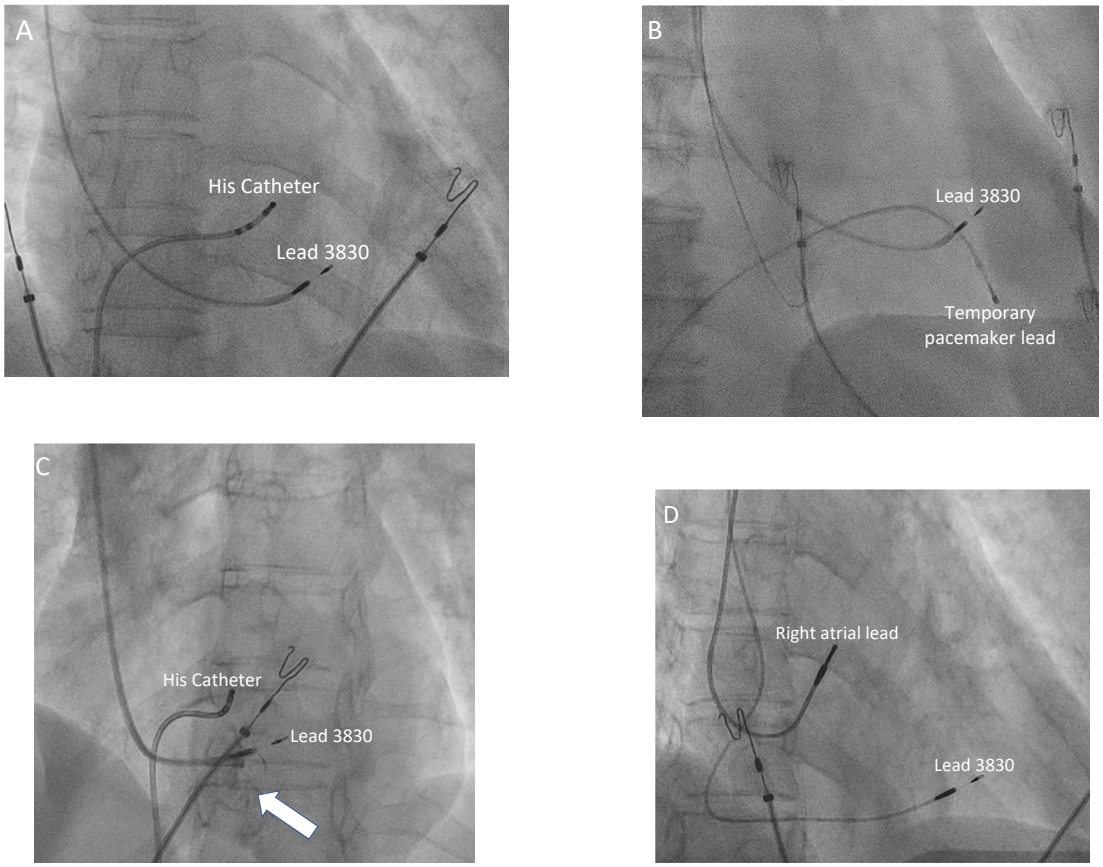



**Figure 1.** Fluoroscopy of the pacemaker lead 3830.
A. RAO view, His quadripolar catheter, and lead 3830 with sheath C315 pointing 1 -2 o'clock. B. RAO view, lead 3830 with sheath C315 without mapping the His bundle. C. Left anterior oblique (LAO) view, His quadripolar catheter, and lead 3830 pointing 3 o'clock with contrast injection (arrow). D. RAO view, final fluoroscopy lead RA, and LBBP lead (lead 3830).

lead was slightly advanced to allow for adequate slack. Adequate slack is very important to avoid lead dislodgement after slitting the sheath. In this case series, there were no complications related to LBBP. All patients had left bundle branch capture. The mean procedure time was 142.5 ± 55 minutes, and the mean fluoroscopic time was 16.7 ± 9.3 minutes. The lead parameters, such as threshold for LBBP and impedance, remained stable and within the normal range during follow-up (**Table 1**). Generally, the symptoms related to bradycardia were improved.

## DISCUSSION

LBBP is relatively new compared to RVA or RVOT and His bundle pacing in clinical practice. This modality shows promising results regarding safety, success rates, and resulting narrow QRS.[8] LBBP and His bundle pacing can be used for patient with symptomatic bradycardia with or without BBB, especially patient with reduced ejection fraction. The overall success rate varies for LBBP between 80–94% and His bundle pacing between 56-95%.[6] The implantation technique is relatively easier to perform compared to His bundle pacing. Other advantages of LBBP compared to His bundle pacing include a larger anatomic target site of pacing, shorter procedural and fluoroscopic times, a lower threshold , stable lead parameters during follow-up, and longer battery life.[6] The benefit of LBBP pacing for the patient is preservation or restoring the LV synchrony.[6]

To obtain a narrow QRS and improve LV synchrony, the LBB must be captured during pacing. Rotating the lead and penetrating the IVS does not mean it will capture the LBB, because some patients only have IVS pacing. Therefore,

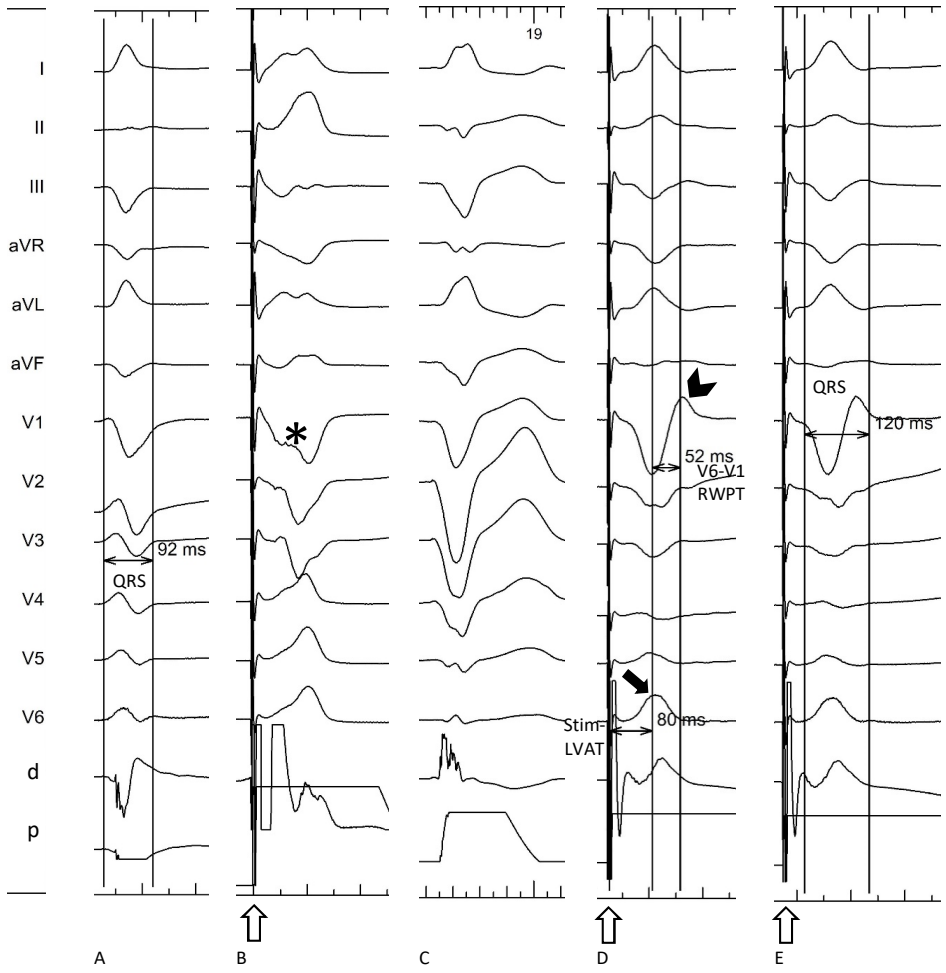



**Figure 2.** ECG prior to procedure and during LBBP implantation.

A. QRS morphology pre-implantation. B. Paced morphology of QS complex with a notch in the nadir or "w" pattern in V1 (asterisk), an R wave in lead II larger than lead III, a negative aVR, and a positive aVL. C. PVC during rotation called a fixation beat. D. QRS morphology resembling RBBB pattern in lead V1. Pacing stimulus (hollow arrow) to left ventricular activation time (Stim-LVAT) is an interval from pacing stimulus (hollow arrow) to the peak R wave in lead V6 (solid arrow). In this case, the Stim-LVAT is 80 ms. V6-V1 interpeak interval is an interval between R-wave peak time (RWPT) in V1 (arrow head) and V6 (solid arrow). R-wave peak time in V6-V1 interpeak interval is 52 ms. E. qR morphology in lead V1 and QRS duration of 120 ms. Stim-LVAT: stimulus to left ventricular activation time, V6-V1 RWPT: R-wave peak time in V6-V1.

Huang et al. proposed criteria to determine LBB capture,[5] which include paced morphology of the RBBB pattern (qR or rSR'), the presence of LBB potential, left ventricular activation time measured from stimulus to peak of the R wave in lead V5/V6 (Stim-LVAT) ≤ 80 ms, and evidence for direct LBB capture.[5] [9]Jastrzębski et al. reported additional novel criteria for left bundle branch capture to differentiate the technique from ventricular septal pacing. The different combinations of R-wave peak time (RWPT) in the V6-V1 interpeak interval with a cut-off value > 44 ms are specific for diagnosing left bundle branch capture.[10] (**Figure 2.D**). Recently, the European Heart Rhythm Association (EHRA) published a clinical consensus statement on CSP, including LBBP and an algorithm for confirming LBBP capture.[11] In this case series, the Stim-LVAT was ≤ 80 ms, and the V6-V1 interpeak interval was > 44 ms (only one patient had < 44 ms). During implantation, only one patient with left bundle potential was observed. Based on the EHRA consensus, LBBP capture may be obtained even without the presence of left bundle potential. Therefore, during implantation, it is very important to understand the techniques and criteria for LBBP. In early experience for LBBP, it is better and safer to have proctor that can guide

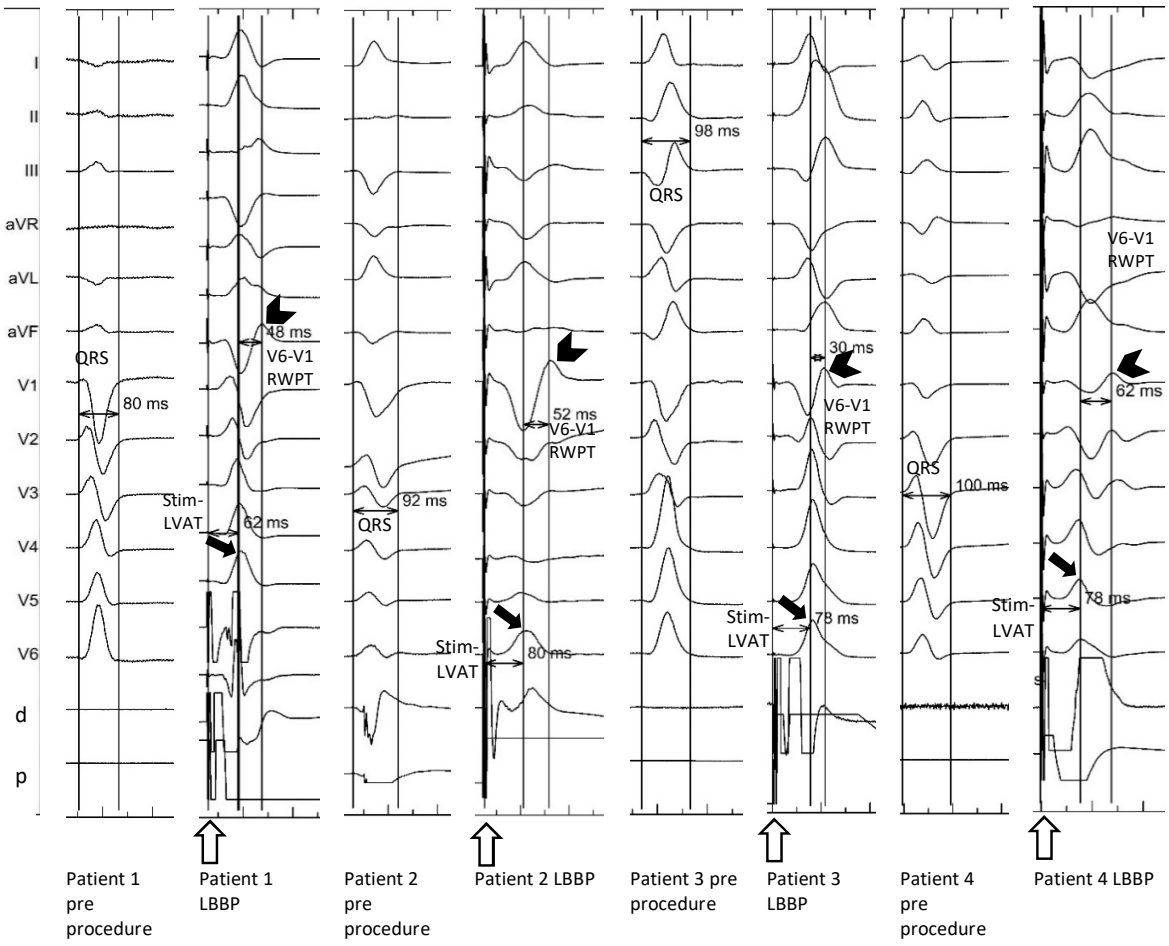



**Figure 3.** ECG patients pre- and post-LBBP.

Left ventricular activation time (Stim-LVAT) is an interval from pacing stimulus (hollow arrow) to the peak R wave in lead V6 (solid arrow). V6-V1 interpeak interval is an interval between R-wave peak time (RWPT) in V1 (arrow head) and V6 (solid arrow). *LBBP: left bundle branch pacing, Stim*-LVAT: stimulus to left ventricular activation time, V6-V1 RWPT: R-wave peak time in V6-V1.

the procedure, and without adding any cost for the pacemaker implantation.

## CONCLUSION

Although we had limited experience with the procedure , we successfully implanted LBBP without any difficulties or complications, and we therefore conclude that it is a relatively easy and safe approach.

## REFERENCES

1. Glikson M. ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021; 42:3427–520.
2. Ponnusamy SS, Vijayaraman P. How to implant his bundle and left bundle pacing leads: Tips and pearls. Card Fail Rev 2021;7.
3. Cabrera J-Á., Porta-Sánchez A., Tung R, Sánchez-Quintana D. Tracking down the anatomy of the left bundle branch to optimize left bundle branch pacing. JACC Case Rep. 2020;2:750.
4. Huang W. A novel pacing strategy with low and stable output: Pacing the left bundle branch immediately beyond the conduction block. Can J Cardiol. 2017;33: 1736.e1-1736.e3.
5. Huang W. A beginner's guide to permanent left bundle branch pacing. Heart Rhythm. 2019;16:1791–6.
6. Padala SK, Ellenbogen KA. Left bundle branch pacing is the best approach to physiological pacing. Heart Rhythm O. 2020;2(1):59–67.
7. Jastrzębski M. Fixation beats: A novel marker for reaching the left bundle branch area during deep septal lead implantation. Heart Rhythm. 2021;18:562–9.
8. Li Y. Left bundle branch pacing for symptomatic bradycardia: Implant success rate, safety, and pacing characteristics. Heart Rhythm. 2019;16:1758–65.

**Table 1.** Patient data, procedure duration, and lead parameters

| Patient | Age | Sex | Diagnosis | QRS | IVS (mm) | QRS width pre LBBP | QRS width post LBBP | LB potential | Stim-LVAT | V6-V1 RWPT inter-peak interval | Procedure time (min) | Fluoro time (min) | Contrast (ml) | During implantation | | | | During follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | R wave (mV) | Threshold (V at 0.4 ms) | Impedance (Ω) | R wave (mV) | Threshold (V at 0.4 ms) | Impedance (Ω) | Complication |
| 1 | 60 | F | SSS | Normal QRS | 13 | 80 | 116 | Yes | 62 | 48 | 190 | 14 | 25 | 24,8 | 0,8 | 602 | 22,4 | 0.7 | 608 | No |
| 2 | 73 | M | SSS | Normal QRS | 15 | 92 | 120 | No | 80 | 52 | 50 | 5 | 10 | 6,1 | 0,8 | 934 | 9.1 | 1.0 | 475 | No |
| 3 | 66 | F | SSS, post AF ablation | Normal QRS | 9 | 98 | 116 | No | 78 | 30 | 180 | 17 | 20 | 14 | 0,5 | 1211 | 11.2 | 0.6 | 804 | No |
| 4 | 50 | M | SSS | Normal QRS | 9 | 100 | 156 | No | 78 | 72 | 150 | 31 | 20 | 7.4 | 1.0 | 753 | 16.2 | 0.75 | 772 | No |
| Average | 62.5±8.4 | | | | 11.5±2.5 | 92.5±7.8 | 127±16.8 | | 74.5±7.2 | 50.5±14.9 | 142.5±55 | 16.7± 9.3 | 18.7± 5.4 | 14.9±7.6 | 0.7±0.14 | 875±226 | 22.4 | 0.76±0.14 | 664±132 | | |

SSS: sick sinus syndrome, AF: atrial fibrillation, IVS: interventricular septum, LB: left bundle; LBBP: left bundle branch pacing; Stim-LVAT: stimulus to left ventricular activation time, V6-V1 RWPT: R-wave peak time in V6-V1.


9. Jastrzębski M. Physiology-based electrocardiographic criteria for left bundle branch capture. Heart Rhythm. 2021;18:935–43.
10. Jastrzębski M. The V6-V1 interpeak interval: a novel criterion for the diagnosis of left bundle branch capture. Europace. 2022;24:40–7.
11. Burri H. EHRA clinical consensus statement on conduction system pacing implantation: executive summary. Endorsed by the Asia-Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS) and Latin-American Heart Rhythm Society (LAHRS). Europace. 2023;25:1237–48.

# Factors Associated with Hepatitis B and Hepatitis C among Infected Patients in Indonesia and Their Knowledge and Attitude: A Multicenter Observational Study

*Juferdy Kurniawan[1*], Gita Aprilicia[1], Hery Djagat Purnomo[2], Cecilia O. Permatawedi[2], Ulfa Kholili[3], Tehar Karo-Karo[4], Haris Widita[5], Aritantri Darmayani[6], Arif Nur Widodo[7], Nenny Agustanti[8], Saptino Miro[9], Suyata[10], Fauzi Yusuf[11], Catharina Triwikatmani[12], Syifa Mustika[13], Rini R. Bachtiar[14], Fandy Gosal[15], I Ketut Mariadi[16], Irsan Hasan[1]*

[1]Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Diponegoro - Kariadi Hospital, Semarang, Indonesia.
[3]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Airlangga - Soetomo Hospital, Surabaya, Indonesia.
[4]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Abdul Moeloek Hospital, Lampung, Indonesia.
[5]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Kota Mataram Hospital, Mataram, Indonesia.
[6]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Sebelas Maret, Moewardi Hospital, Surakarta, Indonesia.
[7]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Ulin Hospital, Banjarmasin, Indonesia.
[8]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Padjadjaran, Hasan Sadikin Hospital, Bandung, Indonesia.
[9]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Andalas - M.Djamil Padang Hospital, Padang, Indonesia.
[10]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Sriwijaya, Mohammad Hoesin Hospital, Palembang, Indonesia.
[11]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Syiah Kuala - Dr. Zainoel Abidin Hospital, Aceh, Indonesia.
[12]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Gadjah Mada - Sardjito Hospital, Yogyakarta, Indonesia.
[13]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Brawijaya - Syaiful Anwar Hospital, Malang, Indonesia.
[14]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Hasanuddin - Wahidin Sudirohusodo Hospital, Makassar, Indonesia.
[15]Division of Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Sam Ratulangi - RD Kandau Hospital, Manado, Indonesia.
[16]Division Gastroenterology-Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Udayana - Sanglah Hospital, Bali, Indonesia.
Indonesian Association for the Study of the Liver (Ina ASL/PPHI) Member of Research Committee.

***Corresponding Author:***
*Juferdy Kurniawan, MD., PhD. Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: juferdy.k@gmail.com , juferdy.kurniawan@ui.ac.id*

## ABSTRACT

***Background:*** *Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections are global health problems, including in Indonesia. The purpose of this study was to assess the knowledge and attitudes about HBV and HCV infection among infected patients in Indonesia.* ***Methods:*** *This cross-sectional study used a questionnaire survey . The questionnaire was adapted and translated into Indonesian language, and trialed with 27 HBV and 27 HCV patients. The final validated questionnaire was later used in the target population. Patients diagnosed with Hepatitis B or Hepatitis C were included. The patients were enrolled from November 2019 until February 2020 in sixteen multicenter locations. Multivariate analysis with logistic regression was conducted to determine the factors that are associated with the knowledge and attitude among HBV and HCV patients toward their illness.* ***Results:*** *A total of 931 HBV patients and 254 HCV patients were included in this survey. The proportion of infected patients with adequate knowledge of Hepatitis B and Hepatitis C was 72.1% and 53.9%, respectively. Positive attitudes about Hepatitis B and Hepatitis C were 28.5% and 41.3%, respectively. Multivariate analysis revealed that higher education level, higher income level, diagnosis duration of more than 5 years, and receiving of antiviral therapy were independent factors associated with adequate knowledge about Hepatitis B among HBV patients. Among HCV patients, independent factors associated with adequate knowledge about Hepatitis C were being married, higher education level, higher income level, and receiving antiviral therapy. Moreover, older age and receiving of antiviral therapy were independent factors associated with positive attitudes towards Hepatitis B among HBV patients. However, only higher education level was found to be an independent factor associated with positive attitudes towards Hepatitis C among HCV patients.* ***Conclusion:*** *The knowledge and attitude of patients regarding HBV and HCV were quite low among infected patients in Indonesia.*

***Keywords*****:** *Knowledge, Attitude, Hepatitis B, Hepatitis C.*

## INTRODUCTION

Hepatitis B virus (HBV) and Hepatitis C virus (HCV) are global health problems, including in Indonesia. According to a national study of Basic Health Research 2013 in Indonesia, the prevalence of chronic hepatitis B and C in Indonesia was 7.1% and 1%, respectively.[1] Within 10-20 years, 20-50% of chronic hepatitis B patients and 10-20% of chronic hepatitis C patients may develop cirrhosis.[2,3] In the long term, chronic hepatitis B and C can result in severe liver problems, such as liver cirrhosis, decompensation of liver cirrhosis (esophageal variceal, hepatic encephalopathy, hepatorenal syndrome), liver cancer, and death.[4]

HBV and HCV pathogens are transmitted through blood and certain body fluid, primarily through blood contact with an infected person's blood, sexual contact, sharing of needles, or from an infected mother to her baby during vaginal birth, which is more common in Hepatitis B.[5] Patients with inadequate knowledge tend to have misconceptions about their disease, which can contribute to the continued transmission of the virus, missed opportunities for medical treatment, and poor health outcomes.[6] Chronic hepatitis B and C require long-term anti-viral medication. Forcmost HBV patients, therapy of antiviral requires lifelong therapy and reactivation may occur after discontinuation of the medication. Inadequate knowledge about medication can lead to poor adherence to treatment, resulting in disease progression.[7] Despite clinical medication, psychosocial issues are a rising concern as an important component of the quality of life for patients. Patients with chronic HBV and HCV might involve serious aspects of psychosocial impairment such as fear, anxiety, stigma, and

a lack of social support .[8] Psychosocial issues related to knowledge and attitudes about chronic HBV and HCV greatly affect patients' quality of life. Misunderstandings can lead to fear, anxiety, and stigma, while lack of social support worsens the situation.

Studies examining the knowledge and attitudes of individuals living with chronic hepatitis B and C in Indonesia are currently limited. This scarcity of data underscores the importance of conducting research to better understand the specific challenges faced by patients in Indonesia. Local data is essential for developing targeted interventions aimed at improving education, support, and the overall quality of life for individuals affected by these conditions in Indonesian context. A study of 520 patients in India who tested positive for HBsAg and anti-HCV revealed that only two-thirds of the respondents were knowledgeable about transmission and prevention. Additionally, only one-third of the respondents provided correct answers about the consequences of chronic HBV and HCV infection.[9] Addressing inadequate knowledge is essential not only to prevent the spread of these infections but also to improve the quality of life for those affected.[10] The purpose of this study was to evaluate the knowledge and attitude about HBV and HCV infection in infected patients. The findings of this study could serve as evidence to provide education and interventions for improving the quality of life of infected patients.

## METHODS

### Setting and Participants

A cross-sectional study with a questionnaire survey was used to perform this study. A pilot study was conducted to pretest the questionnaire. The reliability of the questionnaire was evaluated with Cronbach Alpha, while validity was evaluated with Pearson correlation . Patients aged above 18 years who were diagnosed with Hepatitis B/Hepatitis C (proven by HBsAg/ Anti-HCV positive) and voluntarily agreed to participate in the survey were included. The study was conducted between November 2019 and February 2020, with a member of Ina ASL/PPHI in each region acting as the study investigator. Each center had a research assistant who was trained by the study investigator to collect survey data through face-to-face interviews and conducted interviews in the native Indonesian language.

### Co-variates

Age is categorized into two groups: participants who are younger than 40 years old (< 40 years) and those who are 40 years old or older (≥ 40 years) according to the mean age of the subjects. Sex is classified as either women or men. Marital status includes three categories: married, single, and divorced. Education status is divided into primary (0-9 years of formal education), secondary (10-12 years of formal education), and tertiary (more than 12 years of formal education, including college or university degrees). Income level is divided into low (below Rp 3.000.000), middle (Rp 3.000.000 – 7.000.000), and high (above Rp 7.000.000) based on the income of patients from the 1st to the 3rd quartile. The years of diagnosis are classified into two groups based on the third quartile data, which aligns with Mohamed et al's[11] findings that the longer a patient has been diagnosed with hepatitis B, the lower their level of worry about the disease. Participants are categorized as diagnosed less than 5 years ago (< 5 years) and those diagnosed 5 years ago or more (≥ 5 years) from the time they were initially diagnosed as positive for hepatitis B or C. Anti-viral therapy is defined as a patient who already nucleotide analog for HBV patients and direct-acting antivirals for HCV patients. Cirrhosis was determined based on ultrasound results or transient elastography indicating a fibrosis stage above F4, as reported by patient interviews.

### Survey Instrument

Patients with HBV and HCV in each center who agreed to participate in this study were informed about the aim of this survey and sign the informed consent. Participants of the study were asked to fill out a questionnaire containing the demography, knowledge, and attitude about HBV and HCV. The questionnaire was adapted and translated into Indonesian language and trialed with 10% of minimal sample sizes. The final validated questionnaire was later used in

the target population. The section of knowledge consists of 17 items. One score was given for each correct answer, while zero score was given for each wrong or does not know the answer. The participants were classified in two group (non-adequate vs. adequate knowledge) based on the mean of the overall knowledge score (11 out of 17). A participant's score of less than 50% (1 – 7 score) was considered as non-adequate knowledge, while a score of more than 50% (8-11 score) was considered as adequate knowledge. The section on attitude consists of 12 items. Score range from -2 to +2. A participant was classified into two groups (negative vs. positive attitude) based on the overall attitude score. A participant with more positive score was defined as positive attitude, while a less or negative score was defined as negative attitude. The cut-off values of variables knowledge and attitude were set based on the median scores from the study result.

### Statistical Analysis

The data that has been collected was analyzed with SPSS 25 IBM Corporation United States. Demographic data were processed descriptively. Numerical data was displayed as mean with a standard deviation and categorical data was displayed as percentage. Multivariate analysis with logistic regression was conducted to determine the factors that associate with the knowledge and attitude among HBV and HCV patients towards their illness. Variable with p value below 0.05 was considered as statistically significant.

### Ethical Statement

The authors declare that all procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Faculty Medicine Universitas Indonesia, with the registered protocol number 19-10-1205. All participants signed the informed consent before the study. All data collected in this study were kept confidential and can only be accessed by the principal investigator and co-investigator.

## RESULTS

### Characteristic of Study Population

Out of 980 HBV patients and 286 HCV patients were sampled consecutively for the study. Out of those assessed, 931 HBV patients and 254 HCV patients agreed to participate in this survey. The participant rate was 94.9% for HBV patients and 88.8% for HCV patients. **Figure 1**.

The mean age of HBV patients was 43 ± 12.74 years and that of HCV patients was 48 ± 12.98 years. Major of HBV and HCV patients were male (57.6%, 62.6%, respectively). Most of level education were secondary education in HBV patients (54.4%), while most of level education were tertiary education in HCV patients (44.5%). Most of them in low-income category (60.4% in HBV patients and 58.7% in HCV patients). Characteristic of study population were summarized in **Table 1**.

### Knowledge of Hepatitis B and Hepatitis C Among Infected Patients

A 29-item questionnaire assessing knowledge and attitude was evaluated in the patients. For HBV patients, the reliability of the knowledge and attitude sections showed Cronbach's alpha values of 0.920 and 0.830, respectively. For HCV patients, these values were 0.808 and 0.813, respectively. Regarding the questionnaire's validity, 10% of the questions demonstrated a moderate correlation (r = 0.4 – 0.6), while the remaining 90% showed a strong correlation (r > 0.6).

Out of the 931 HBV patients, 808 (86.8%) patients were aware that the etiology of Hepatitis B was a viral infection. Most HBV patients knew

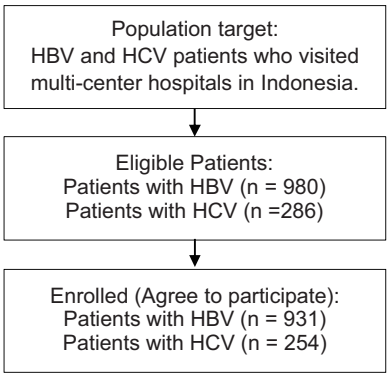



**Figure 1**. Flowchart of sample selection

**Table 1.** Characteristic of study population.

| Variables | HBV Patients (n = 931) | HCV Patients (n = 254) |
|---|---|---|
| Age, mean ± SD | 43 ± 12.74 | 48 ± 12.98 |
| Age, n (%) | | |
| < 40 years | 387 (41.6) | 68 (26.8) |
| ≥ 40 years | 544 (58.4) | 186 (73.2) |
| Sex, n (%) | | |
| Women | 395 (42.4) | 95 (37.4) |
| Men | 536 (57.6) | 159 (62.6) |
| Marital status, n (%) | | |
| Married | 760 (81.6) | 206 (81.1) |
| Single | 128 (13.7) | 20 (7.9) |
| Divorced | 43 (4.6) | 28 (11.0) |
| Education status, n (%) | | |
| Primary (0 – 9 years) | 107 (11.5) | 35 (13.8) |
| Secondary (10-12 years) | 506 (54.4) | 106 (41.7) |
| Tertiary (above 12 years) | 318 (34.2) | 113 (44.5) |
| Income level, n (%) | | |
| Low | 562 (60.4) | 149 (58.7) |
| Middle | 327 (35.1) | 66 (26.0) |
| High | 42 (4.5) | 39 (15.4) |
| Years of Diagnosis, n (%) | | |
| < 5 years | 747 (80.2) | 187 (73.6) |
| ≥ 5 years | 184 (19.8) | 67 (26.4) |
| Has received anti-viral therapy, n (%) | | |
| No | 386 (41.5) | 148 (58.3) |
| Yes | 545 (58.5) | 106 (41.7) |
| Has diagnosed cirrhosis, n (%) | | |
| No | 756 (81.2) | 204 (80.2) |
| Yes | 175 (18.8) | 50 (19.8) |

that Hepatitis B might cause chronic inflammation of the liver 773 (83.0%), liver failure 697 (74.9%), and liver cancer 717(77.0%). Poor knowledge of transmission of Hepatitis B was found in sharing personal food equipment 352 (37.8%), coughing and sneezing 528 (56.7%). Only 639 (68.6%) patients knew that antiviral for Hepatitis B was available for therapy. Of 734 (78.8%) patients knew that the hepatitis B vaccine can prevent of HBV infection.

Overall, HBV patients have better knowledge than HCV patients. Out of the 254 HCV patients, only 202 (79.5%) patients knew the etiology of Hepatitis C is viral infection. HCV patients knew Hepatitis C can cause chronic inflammation of the liver 191 (75.2%), liver failure 168 (66.1%), and liver cancer 170 (66.9%). Similar to HBV patients, poor knowledge of transmission of Hepatitis C among HCV patients was found in sharing personal food equipment 90 (35.4%), coughing and sneezing 139 (54.7%). Only 165 (65.0%) patients knew that an antiviral for Hepatitis C was available for therapy. The knowledge of item HBV and HCV infection among infected patients was summarized in **Table 2**.

### Attitude of Hepatitis B and Hepatitis C Among Infected Patients

The attitudes of infected patients toward HBV and HCV infection are summarized in **Table 3**. Emotional instability among HBV patients was dominated by fear of developing liver cancer 779 (83.6%), fear of transmitting the disease to other people 779 (83.6%), and fear that Hepatitis B disease will worsen and damage the liver 771 (82.8%). Most HBV patients believed that Hepatitis B could be controlled with medication 812 (87.2%) and could be cured 808 (86.8%). Of 468 (50.3%) patients who were unlike to talk about hepatitis B to others, 327 (35.2%) patients were kept thinking about their disease all the time, while 416 (44.6%) patients saw life differently after diagnosed with hepatitis

**Table 2.** Knowledge of Hepatitis B and Hepatitis C among infected patients.

| Knowladge (N = 931) | Correct Answer, n (%) | Knowledge (N = 254) | Correct Answer, n (%) |
|---|---|---|---|
| **Hepatitis B etiology** | | **Hepatitis C etiology** | |
| Viral infection | 808 (86.8) | Viral infection | 202 (79.5) |
| **Hepatitis B effect** | | **Hepatitis C effect** | |
| Chronic inflammation of the liver | 773 (83.0) | Chronic inflammation of the liver | 191 (75.2) |
| Liver failure | 697 (74.9) | Liver failure | 168 (66.1) |
| Liver cancer | 717 (77.0) | Liver cancer | 170 (66.9) |
| **Hepatitis B transmission** | | **Hepatitis C transmission** | |
| Blood | 788 (84.6) | Blood | 202 (79.5) |
| Sexual intercourse | 737 (79.2) | Sexual intercourse | 172 (67.7) |
| Unsterilized needles | 812 (87.2) | Unsterilized needles | 193 (76.0) |
| Tattoo | 690 (74.1) | Tattoo | 178 (70.1) |
| Mother to child during childbirth | 706 (75.8) | Mother to child during childbirth | 156 (61.4) |
| Sharing personal food equipment | 352 (37.8) | Sharing personal food equipment | 90 (35.4) |
| Coughing and sneezing | 528 (56.7) | Coughing and sneezing | 139 (54.7) |
| Casual contact with infected person | 616 (66.2) | Casual contact with infected person | 170 (66.9) |
| Sharing toothbrush or razor | 631 (67.8) | Sharing toothbrush or razor | 149 (58.7) |
| **Hepatitis B symptom** | | **Hepatitis C symptom** | |
| Tiredness | 781 (83.9) | Tiredness | 184 (72.4) |
| Asymptomatic | 697 (74.9) | Asymptomatic | 169 (66.5) |
| **Hepatitis B therapy** | | Hepatitis C therapy | |
| Available antiviral for hepatitis B | 639 (68.6) | Available antiviral for hepatitis C | 165 (65.0) |
| **Hepatitis B prevention** | | | |
| Vaccination hepatitis B | 734 (78.8) | | |

B. As a result of having Hepatitis B, patients felt difficult to get a job or school 296 (31.8%) and made them ostracized from their environment 154 (16.5%).

Similar to HBV patients, emotional instability among HCV patients was dominated by fear of developing liver cancer 197 (77.5%), fear of transmitting the disease to other people 188 (74%), and fear that Hepatitis C disease will worsen and damage the liver 197 (77.6%). Most HCV patients believed that Hepatitis C could be controlled with medication 210 (82.7%) and could be cured 211 (83.1%). Of 127 (50%) patients who were unlike to talk about hepatitis C to others, 86 (33.8%) patients were kept thinking about their disease all the time, while 98 (38.6%) patients saw life differently after diagnosed with hepatitis C. As a result of having Hepatitis C, patients felt difficult to get a job or school 53 (20.9%), and made them ostracized from their environment 40 (15.7%).

### Knowledge and Attitudes Scores of Hepatitis B and Hepatitis C

Among HBV patients, mean scores for knowledge about Hepatitis B was 12 ± 4 out of 17. Patients with adequate knowledge of Hepatitis B was 671(72.1%). Only 265 (28.5%) patients have a positive attitude towards Hepatitis

**Table 3.** Attitude of Hepatitis B and Hepatitis C among infected patients.

| Attititudes | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|
| **In patients with HBV (n = 931)** | | | | | |
| **Hepatitis B – related emotional instability** | | | | | |
| Worried about suffering from liver cancer due to hepatitis | 342 (36.7%) | 431 (46.3%) | 84 (9.0%) | 58 (6.2%) | 16 (1.7%) |
| Worried about transmitting my disease to others | 357 (38.3%) | 422 (45.3%) | 71 (7.6%) | 66 (7.1%) | 15 (1.6%) |
| Worried that my illness will worsen and damage the liver | 362 (38.9%) | 409 (43.9%) | 70 (7.5%) | 66 (7.1%) | 24 (2.6%) |
| Hepatitis B makes me feel guilty | 105 (11.3%) | 238 (25.6%) | 219 (23.5%) | 316 (33.9%) | 53 (5.7%) |
| Often feel sad and helpless because of hepatitis B | 114 (12.2%) | 249 (26.7%) | 202 (21.7%) | 319 (34.3%) | 47 (5.0%) |

| Attititudes | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
|---|---|---|---|---|---|
| **Hepatitis B – related confidence** | | | | | |
| Believe hepatitis B can be controlled with medication | 308 (33.1%) | 504 (54.1%) | 86 (9.2%) | 24 (2.6%) | 9 (1.0%) |
| Sure there will be a cure for hepatitis B | 400 (43.0%) | 408 (43.8%) | 85 (9.1%) | 32 (3.4%) | 6 (0.6%) |
| **Hepatitis B – related fear of deprivation** | | | | | |
| Do not like to talk about my hepatitis B to others | 143 (15.4%) | 325 (34.9%) | 236 (25.3%) | 184 (19.8%) | 43 (4.6%) |
| Thinking about hepatitis B all the time | 88 (9.5%) | 239 (25.7%) | 249 (26.7%) | 296 (31.8%) | 59 (6.3%) |
| Seeing life differently since I was diagnosed with hepatitis B | 127 (13.6%) | 289 (31.0%) | 195 (20.9%) | 279 (30.0%) | 41 (4.4%) |
| **Hepatitis B – related social withdrawal** | | | | | |
| Hepatitis B makes it difficult for me to get a job/school | 106 (11.4%) | 190 (20.4%) | 192 (20.6%) | 349 (37.5%) | 94 (10.1%) |
| Hepatitis B made me ostracized from my environment | 42 (4.5%) | 112 (12.0%) | 189 (20.3%) | 425 (45.6%) | 163 (17.5%) |
| **In patients with HCV (n = 254)** | | | | | |
| **Hepatitis C – related emotional instability** | | | | | |
| Worried about suffering from liver cancer due to hepatitis C | 88 (34.6%) | 109 (42.9%) | 37 (14.6%) | 16 (6.3%) | 4 (1.6%) |
| Worried about transmitting my disease to others | 88 (34.6%) | 100 (39.4%) | 37 (14.6%) | 24 (9.4%) | 5 (2.0%) |
| Worried that my illness will worsen and damage the liver | 99 (39.0%) | 98 (38.6%) | 36 (14.2%) | 16 (6.3%) | 5 (2.0%) |
| Hepatitis C makes me feel guilty | 32 (12.6%) | 73 (28.7%) | 58 (22.8%) | 76 (29.9%) | 15 (5.9%) |
| Often feel sad and helpless because of hepatitis C | 36 (14.2%) | 63 (24.8%) | 59 (23.2%) | 74 (29.1%) | 22 (8.7%) |
| **Hepatitis C – related confidence** | | | | | |
| Believe hepatitis B can be controlled with medication | 99 (39.0%) | 111 (43.7%) | 27 (10.6%) | 16 (6.3%) | 1 (0.4%) |
| Sure there will be a cure for hepatitis C | 118 (46.5%) | 93 (36.6%) | 31 (12.2%) | 10 (3.9%) | 2 (0.8%) |
| **Hepatitis C – related fear of deprivation** | | | | | |
| Do not like to talk about my hepatitis C to others | 41 (16.1%) | 86 (33.9%) | 76 (29.9%) | 43 (16.9%) | 8 (3.1%) |
| Thinking about hepatitis B all the time | 27 (10.6%) | 59 (23.2%) | 78 (30.7%) | 79 (31.1%) | 11 (4.3%) |
| Seeing life differently since I was diagnosed with hepatitis C | 32 (12.6%) | 66 (26.0%) | 75 (29.5%) | 67 (26.4%) | 14 (5.5%) |
| **Hepatitis C – related social withdrawal** | | | | | |
| Hepatitis C makes it difficult for me to get a job/school | 21 (8.3%) | 32 (12.6%) | 79 (31.1%) | 87 (34.3%) | 35 (13.8%) |
| Hepatitis C made me ostracized from my environment | 11 (4.3%) | 29 (11.4%) | 67 (26.4%) | 97 (38.2%) | 50 (19.7%) |

B. Meanwhile among HCV patients, mean scores for knowledge about Hepatitis C was lower than HBV patients 10 ± 4 out of 16. Patients with adequate knowledge of Hepatitis C was 137 (53.9%). Positive attitude towards Hepatitis C was observed higher in HCV patients than HBV patients 105 (41.3%) (**Table 4**).

### Factor Associated with Knowledge and Attitudes of Hepatitis B

In multivariate analysis, independent factors associated with adequate knowledge Hepatitis B among HBV patients were education level (AOR high education level 9.25 (CI 95%: 5.18 – 16.5, p-value <0.001) and AOR middle education level = 3.92 (CI 95%: 2.46 – 6.26), p-value <0.001), income level (AOR high-income level = 5.56 (CI 95%: 1.24 – 25.1, p-value <0.025) and AOR middle-income level = 1.52 (CI 95%: 1.04 – 2.23), p-value 0.033), diagnosis above 5 years (AOR = 1.82 (CI 95%: 1.13 – 2.93), and has received antiviral therapy (AOR = 1.89 (CI 95%: 1.36 – 2.63, p-value <0.001). Independent factors associated with positive attitude Hepatitis B among HBV patients were age older (AOR= 1.99 (CI 95%: 1.42 – 2.80, p-value <0.001) and received antiviral therapy (AOR = 1.59 (CI 95%:

**Table 4.** Knowledge and Attitudes Scores of Hepatitis B and Hepatitis C

| Variables | |
|---|---|
| **In patients with HBV (n = 931)** | |
| Knowledge about Hepatitis B | |
| Number of correct answers | 0-17 |
| Overall Score, mean ± SD | 12 ± 4 |
| Knowledge about Hepatitis B, n (%) | |
| Adequate | 671 (72.1) |
| Non-Adequate | 260 (27.9) |
| Attitude about Hepatitis B, n (%) | |
| Positive | 265 (28.5) |
| Negative | 666 (71.5) |
| **In patients with HCV (n = 254)** | |
| Knowledge about Hepatitis C | |
| Number of correct answers | 0-16 |
| Overall Score, mean ± SD | 10 ± 4 |
| Knowledge about Hepatitis C, n (%) | |
| Adequate | 137 (53.9) |
| Non-Adequate | 117 (46.1) |
| Attitude about Hepatitis C, n (%) | |
| Positive | 105 (41.3) |
| Negative | 149 (58.7) |

1.16 – 2.18, p-value <0.004). (**Table 5**)

### Factor Associated with Knowledge and Attitudes of Hepatitis C

In multivariate analysis, independent factors associated with adequate knowledge of Hepatitis C among HCV patients were marital status (AOR single = 0.25 (CI 95%: 0.08 - 0.78, p-value 0.017), an education level (AOR high education level 7.45 (CI 95%: 2.50 – 22.19, p-value <0.001) and AOR middle education level = 4.34 (CI 95%: 1.55 – 12.19), p-value 0.005), income level (AOR high-income level = 2.68 (CI 95%: 1.02 – 6.99, p-value <0.045, and has received antiviral therapy (AOR = 1.97 (CI 95%: 1.09 – 3.58, p-value <0.025). Independent factors associated with positive attitude Hepatitis C among HCV patients was only education level (AOR middle education level= 3.25 (CI 95%: 1.32 – 7.99, p-value 0.010). (**Table 6**)

**Table 5.** Multivariate factorstitudes of Hepatitis B

| Variables | Knowledge | | AOR (95% CI) | P value | Attitude | | AOR (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|
| | Non-Adequate | Adequate | | | Negative | Positive | | |
| Age, n (%) | | | | | | | | |
| < 40 years | 97 (25.1) | 290 (74.9) | Ref | | 308 (79.6) | 79 (20.4) | Ref | |
| ≥ 40 years | 163 (30.0) | 381 (70.0) | 0.93 (0.65 – 1.33) | 0.684 | 358 (65.8) | 186 (34.2) | 1.99 (1.42 – 2.80) | <0.001 |
| Sex, n (%) | | | | | | | | |
| Female | 112 (28.4) | 283 (71.6) | 1 | | 292 (73.9) | 103 (26.1) | 1 | |
| Male | 148 (27.6) | 388 (72.4) | 0.76 (0.55 – 1.07) | 0.112 | 374 (69.8) | 162 (30.2) | 1.14 (0.83 – 1.55 | 0.412 |
| Marital status, n (%) | | | | | | | | |
| Married | 215 (28.3) | 545 (71.7) | Ref | | 535 (70.4) | 225 (29.6) | Ref | |
| Single | 32 (25.0) | 96 (75.0) | 1.16 (0.71 – 1.91) | 0.557 | 100 (78.1) | 28 (21.9) | 0.99 (0.61 – 1.62) | 0.981 |
| Divorced | 13 (30.2) | 30 69.8) | 1.15 (0.55 – 2.43) | 0.707 | 31 (72.1) | 12 (27.9) | 0.83 (0.41 – 1.68) | 0.607 |
| Education level, n (%) | | | | | | | | |
| Primary (0 – 9 years) | 70 (65.4) | 37 (34.6) | Ref | | 78 (72.9) | 29 (27.1) | Ref | |
| Secondary (10-12 years) | 151 (29.8) | 355 (70.2) | 3.92 (2.46 – 6.26) | <0.001 | 356 (70.4) | 150 (29.6) | 1.32 (0.81 – 2.16) | 0.260 |
| Tertiary (above 12 years) | 39 (12.3) | 279 (87.7) | 9.25 (5.18 – 16.5) | <0.001 | 232 (73.0) | 86 (27.0) | 1.19 (0.68 – 2.09) | 0.529 |
| Income level, n (%) | | | | | | | | |
| Low | 199 (35.4) | 363 (64.6) | Ref | | 400 (71.2) | 162 (28.8) | Ref | |
| Middle | 59 (18.0) | 268 (82.0) | 1.52 (1.04 – 2.23) | 0.033 | 240 (73.4) | 87 (26.6) | 0.77 (0.54 – 1.10) | 0.154 |
| High | 2 (4.8) | 40 (95.2) | 5.56 (1.24 – 25.1) | 0.025 | 26 (61.9) | 16 (38.1) | 1.25 (0.61 – 2.54) | 0.539 |
| Years of Diagnosis, n (%) | | | | | | | | |
| < 5 years | 234 (31.1) | 513 (68.7) | Ref | | 545 (73.0) | 202 (27.0) | Ref | |
| ≥ 5 years | 26 (14.1) | 158 (85.9) | 1.82 (1.13 – 2.93) | 0.014 | 121 (65.8) | 63 (34.2) | 1.21 (0.84 – 1.75) | 0.301 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Has received anti-viral therapy, n (%) | | | | | | | | |
| No | 139 (36.0) | 247 (64.0) | Ref | | 301 (78.0) | 85 (22.0) | Ref | |
| Yes | 121 (22.2) | 424 (77.8) | 1.89 (1.36 – 2.63) | <0.001 | 365 (67.0) | 180 (33.0) | 1.59 (1.16 – 2.18) | 0.004 |
| Has diagnosed cirrhosis, n (%) | | | | | | | | |
| No | 207 (27.4) | 549 (72.6) | Ref | | 548 (72.5) | 208 (27.5) | Ref | |
| Yes | 53 (30.3) | 122 (69.7) | 0.75 (0.94 – 0.62) | 0.750 | 118 (67.4) | 57 (32.6) | 0.95 (0.65 – 1.38) | 0.773 |

AOR: Adjusted Odd Ratio; CI: Confidence Interval

**Table 6.** Multivariate factors associated with Knowledge and Attitudes of Hepatitis C

| **Variables** | **Knowledge** | | **AOR (95% CI)** | **P value** | **Attitude** | | **AOR (95% CI)** | **P value** |
|---|---|---|---|---|---|---|---|---|
| | **Non Adequate** | **Adequate** | | | **Negative** | **Positive** | | |
| Age, n (%) | | | | | | | | |
| < 40 years | 20 (29.4) | 48 (70.6) | Ref | | 44 (64.7) | 24 (35.3) | Ref | |
| ≥ 40 years | 97 (52.2) | 89 (47.8) | 0.26 (0.12 – 0.58) | 0.001 | 105 (56.5) | 81 (43.5) | 1.11 (0.57 – 2.17) | 0.763 |
| Sex, n (%) | | | | | | | | |
| Female | 46 (48.4) | 49 (51.6) | Ref | | 58 (61.1) | 37 (38.9) | Ref | |
| Male | 71 (44.7) | 88 (55.3) | 0.74 (0.40 – 1.39) | 0.351 | 91 (57.2) | 68 (42.8) | 0.85 (0.47 – 1.55) | 0.603 |
| Marital status, n (%) | | | | | | | | |
| Married | 89 (43.2) | 117 (56.8) | Ref | | 115 (55.8) | 91 (44.2) | Ref | |
| Single | 10 (50) | 10 (50) | 0.25 (0.08 – 0.78) | 0.017 | 16 (80.0) | 4 (20.0) | 0.34 (0.09 – 1.20) | 0.093 |
| Divorced | 18 (64.3) | 10 (35.7) | 0.57 (0.22 – 1.48) | 0.248 | 18 (64.3) | 10 (35.7) | 0.62 (0.25 – 1.55) | 0.304 |
| Education level, n (%) | | | | | | | | |
| Primary (0 – 9 years) | 29 (82.9) | 6 (17.1) | Ref | | 26 (74.3) | 9 (25.7) | Ref | |
| Secondary (10-12 years) | 54 (50.9) | 52 (49.1) | 4.34 (1.55 – 12.19) | 0.005 | 48 (45.3) | 58 (54.7) | 3.25 (1.32 – 7.99) | 0.010 |
| Tertiary (above 12 years) | 34 (30.1) | 79 (69.9) | 7.45 (2.50 – 22.19) | <0.001 | 75 (66.4) | 38 (33.6) | 1.04 (0.39 – 2.80) | 0.933 |
| Income level, n (%) | | | | | | | | |
| Low | 82 (55.0) | 67 (45.0) | Ref | | 90 (60.4) | 59 (39.6) | Ref | |
| Middle | 27 (40.9) | 39 (59.1) | 1.26 (0.63 – 2.52) | 0.508 | 37 (56.1) | 29 (43.9) | 1.54 (0.77 – 3.05) | 0.219 |
| High | 8 (20.5) | 31 (79.5) | 2.68 (1.02 – 6.99) | 0.045 | 22 (56.4) | 17 (43.6) | 1.75 (0.75 – 4.07) | 0.194 |
| Years of Diagnosis, n (%) | | | | | | | | |
| < 5 years | 24 (35.8) | 43 (64.2) | Ref | | 33 (49.3) | 34 (50.7) | Ref | |
| ≥ 5 years | 93 (49.7) | 94 (50.3) | 0.68 (0.35 – 1.32) | 0.252 | 116 (62.0) | 71 (38.0) | 0.60 (0.33 – 1.09) | 0.092 |
| Has received anti-viral therapy, n (%) | | | | | | | | |
| No | 78 (52.7) | 70 (47.3) | Ref | | 87 (58.8) | 61 (41.2) | Ref | |
| Yes | 39 (36.8) | 67 (63.2) | 1.97 (1.09 – 3.58) | 0.025 | 62 (58.5) | 44 (41.5) | 1.03 (0.59 – 1.81) | 0.905 |
| Has diagnosed cirrhosis, n (%) | | | | | | | | |
| No | 97 (47.5) | 107 (52.5) | Ref | | 122 (59.8) | 82 (40.2) | Ref | |
| Yes | 20 (40.0) | 30 (60.0) | 1.34 ( 0.64 – 2.82) | 0.444 | 27 (54.0) | 23 (46.0) | 1.04 (0.52 – 2.07) | 0.915 |

AOR: Adjusted Odd Ratio; CI: Confidence Interval

## DISCUSSION

Characteristics of education in Indonesia were a little different from the result of Indonesia Education Statistics 2020. National data suggested that 50.9% of residents had completed secondary education, while only 9.5% had completed tertiary education .[12] In this study, we found that 34.2% of HBV patients and 44.5% of HCV patients had completed tertiary education, which is higher than the data in the census. It might reflect that individuals person with higher education have more awareness and accessibility to healthcare service utilization and seek medical treatment than the population in general.[13] The discrepancy in education levels between the general population and the Hepatitis B (HBV) and Hepatitis C (HCV) patients in the study may influence the applicability of the results to the broader population. In this study, HBV and HCV patients with higher education levels are overrepresented compared to the general population due to the use of consecutive sampling techniques.

However, this study obtained the proportion of HBV patients with adequate knowledge of Hepatitis B was 72.1%, while adequate knowledge of Hepatitis C in HCV patients was 53.9%. Dwiartama reported that the knowledge level among the HBV respondents in four cities in Indonesia was very high, with an average index level of knowledge was 86.7.[14] This variation might happened as a result of differences in geographical study locations. Compared to other countries, the overall average scores of knowledge HBV patients in Indonesia were higher than Malaysia and Gambia (12/17 ± 4 vs. 12.57/20 ± 4.4 in Malaysia, 11.09/20 ± 4.89 in the Gambia), but lower than Singapore and Canadian (12/17 ± 4 vs. 10.4/14 ± 0.1 in Singapore, 10/14 in Canadian).[11,15,16,17] There's no data of knowledge Hepatitis C in Indonesia. In this study, we found that patients with adequate knowledge were slightly low in Hepatitis C compared to Hepatitis B patients. All the thought HCV patients in thibeingbeing s studying have a level of income comparable to HBV patients, however, there was a difference oof of the level of knowledge amfrom from ong these professionals Consultation with healthcare professionals as reliable sources was essential to provide knowledge about evidence-based Hepatitis B and Hepatitis C, especially in patients with newly diagnosed. A study from Ul Haq[18,] Pak A[19,] Velvzhi G [20,] and Gambhir R [21] reports a similar finding, which underscores the importance of implementing extensive health educational campaigns in a diverse research population, including the healthy population [18], medical students [19,20], and healthcare workers[21] .

In this study, we found that HBV and HCV patients have good knowledge about etiology and the consequences of HBV and HCV Hepatitis, but less knowledge of transmission in items of sharing personal food equipment, coughing, and sneezing. The common myths about HBV and HCV transmission such as mosquito bites, sharing toilets, and sharing cup was also observed among patients in Poland.[22] The myth of transmission in patients could be a barrier to social interaction because of fear of spreading the virus to others. Public health education might have a role in preventing the myth of HBV and HCV transmission, especially in the general population.

The differential attitudes towards HBV and HCV have significant impacts. The result data showed differing attitudes between HBV and HCV patients, impacting their emotional well-being and social interactions. While both express worry about transmission and health consequences, HCV patients, on the other hand, display slightly more confidence in treatment outcomes. Before the availability of DAA medication, Enescu et al.'s[23] study reported that more drop was seen in HCV patients than in HBV patients regarding psychiatric components. However, this study found the opposite, which may be linked to the high effectiveness of DAA in treating hepatitis C patients.[24] Socially, both groups report difficulties in employment or education, with HBV patients experiencing slightly more challenges. This is also consistent with a systematic review of Asian populations, which reported that up to 30% of patients with HBV experience workplace discrimination.[25]

Our study revealed that education level, income level, and antiviral therapy were factors linked to contributing adequate knowledge in

patients, while marital status was only found significant for contributing adequate knowledge in Hepatitis C patients. Several studies support this result. A study in Malaysia also reported that tertiary education level was a significant factor in the higher knowledge of patients. HBV and HCV patients with higher degrees of education might have an easier understanding of information regarding their health status.[11] A study in Europe revealed that people with lower education and low socio-economic were vulnerable to having limited health literacy.[26] Ever received antiviral therapy in HBV and HCV patients also associated with higher knowledge of patients. The possibility of duration consultation with doctors perhaps can be explained that the patients who have received antiviral therapy have better knowledge compared with not yet received anti-viral therapy.[27] Being single is associated with less knowledge of hepatitis C. Ministry of Health Indonesia reported that the distribution of HCV is concentrated in injecting drug users (IDU), hemodialysis, and blood donors. The prevalence of HCV among IDUs in Indonesia was reported high accounting for 13.8 % - 31.1%.[28] The IDUs in Indonesia were relatively high in young adults with initiation of injecting occurring in age 15-34 years old.[29] It might explain why single patients have less knowledge of Hepatitis C. The young adult likes to explore the risk behavior, including the use of IDUs. Pre-marital screening and counseling for hepatitis might be important to get a person tested and informed about the transmission of hepatitis.[30]

Hepatitis B/C-related concerns was qualitative explored in this study. This study demonstrates the perspective of patients toward life since being diagnosed with hepatitis. Above 80% of subjects in this study have a fear of developing liver cancer, fear of transmitting the disease to other people, and fear that Hepatitis B will worsen and damage the liver. These results are similar to the most common concern of patients related to fear and worries about having Hepatitis B in Australia.[31] HBV and HCV patients, especially newly diagnosed patients might be shocked for the first time knowing diagnosed with hepatitis. Counseling services from healthcare professionals were urgently needed to provide emotional support to this group of patients. This service should be available to reduce the psychological stressor the first time diagnosed and the entire time during the treatment. This study provides information that patients with HBV and HCV might have social implications. About 30-50% of patients were unlike to talk about their hepatitis to others, kept thinking about their disease all the time, and seeing life differently after being diagnosed with hepatitis. That perspective could lead them to become self-isolated and avoid social life.

This study also revealed that 20 – 30% of HBV and HCV patients found it difficult to get a job or school as a consequence of social withdrawal due to having hepatitis. Patients with HBV and HCV often face discrimination during the selection of students or employment.[32,33] Many companies in Indonesia have a trend to conduct HBsAg testing as a tool for selecting employees to be accepted, where a person with positive HBsAg is considered an unhealthy person to be employed. Meanwhile the Labor laws from Director Labor number NO. SE-07/B MW/1997 already exists to guarantee the legal rights of hepatitis patients in Indonesia. The companies should provide guidance and workplace programs for HBV and HCV workers rather than avoid them from working in their companies. A person with Hepatitis B/C-related illness may have the ability to work and be productive as long as they are medically performed and fit to work. The government has the responsibility to protect the HBV and HCV workers from stigma by giving education to the companies.

In this study, fears and anxiety were less found in increasing age and patients who have ever received antiviral therapy among Hepatitis B patients. The increasing age might linger with obtaining information from medical treatment and already not worried about a job since they were already employed at a young age. Among patients with Hepatitis C, the level of education was associated with less fear and anxiety. Education might strengthen the knowledge. The knowledgeable patients seem not to worry about their illness because they already know the

characteristics of the disease and how to prevent their illness for not getting worse by obtaining medical treatment.

## CONCLUSION

Despite the relatively high prevalence of HBV and HCV in Indonesia, the knowledge and attitude of patients regarding HBV and HCV were quite low. The myth of transmission and social discrimination against HBV and HCV also exists in Indonesia. As a suggestion, the physician should have a package program to educate patients about the route of transmission and treatment, especially in patients with newly diagnosed. Counseling service is also needed to reduce anxiety and social implications related to HBV and HCV. Discrimination about not hiring HBV and HCV patients to work is not following the Labor laws in Indonesia. The government has implications to protect HBV and HCV workers from stigma by giving eduimplicationshe companto ies. For non-modfollowingch such as marital status, education level, and income level take into account these socio-economic variables to ensure equitable access to healthcare and improve knowledge and attitudes towards HBV and HCV.

## ACKNOWLEDGMENTS

The authors would like to thanks for patients and research assistant who contribute in this study

## ABBREVIATIONS

AOR: Adjusted Odds Ratio; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; CI: Confidence Interval; Ina ASL/PPHI: The Indonesian Association for the Study of the Liver

## REFERENCES

1. Muljono DH. Epidemiology of Hepatitis B and C in the Republic of Indonesia. Euroasian J Hepato-Gastroenterology [Internet]. 2017;7(1):55–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5663775/
2. Hasan I. Konsensus nasional penatalaksanaan Hepatitis B. Jakarta: Perhimpunan Peneliti Hati Indonesia; 2017.
3. Hasan I. Konsensus nasional penatalaksanaan Hepatitis C. Jakarta: Perhimpunan Peneliti Hati Indonesia; 2017.
4. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016. Hepatology. 2017;65(1):310–35.
5. Beltrami EM, Williams IT, Shapiro CN, Chamberland ME. Risk and management of blood-borne infections in health care workers. Clin Microbiol Rev. 2000;13(3):385–407.
6. Colvin HM, Mitchell AE. A National Strategy for Prevention and. Prevention and Control. 2010.
7. Bitton Alaluf M, Shlomai A. New therapies for chronic hepatitis B. Liver Int. 2016;36(6):775–82.
8. Sonzogni A, Previtali G, Seghezzi M, et al. Liver histopathology in severe COVID-19 respiratory failure is suggestive of vascular alterations. Liver Int. 2020;40(9):2110–6.
9. Mukherjee PS, Dutta E, Das DK, Ghosh S, Neogi S, Sarkar A. Knowledge about hepatitis B and hepatitis C virus infection and consequences: a cross-sectional assessment of baseline knowledge among infected patients in West Bengal, India. Hepatol Med Policy [Internet]. 2017;2(1):1–9. Available from: http://dx.doi.org/10.1186/s41124-016-0014-8
10. Shah HA, Abu-Amara M. Education provides significant benefits to patients with hepatitis b virus or hepatitis C virus infection: A systematic review. Clin Gastroenterol Hepatol [Internet]. 2013;11(8):922–33. Available from: http://dx.doi.org/10.1016/j.cgh.2013.04.024
11. Mohamed R, Ng CJ, Tong WT, Abidin SZ, Wong LP, Low WY. Knowledge, attitudes, and practices among people with chronic hepatitis B attending a hepatology clinic in Malaysia: A cross-sectional study. BMC Public Health [Internet]. 2012;12(1):1. Available from: BMC Public Health
12. Badan Pusat Statistik. Potret Sensus Penduduk 2020 Menuju Satu Data Kependudukan Indonesia. 2020.
13. Raghupathi V, Raghupathi W. The influence of education on health: An empirical assessment of OECD countries for the period 1995-2015. Arch Public Heal. 2020;78(1):1–18.
14. Dwiartama A, Nirbayati WF, Giri-Rachman EA, Niloperbowo W, Tan MI, Anin A. Knowledge, attitude, and practice towards Hepatitis B infection prevention and screening among Indonesians. Int J Environ Res Public Health. 2022;19(8).
15. Jarju L, Bittaye SO, Keita A, Tamba S, Njie R. Knowledge and attitude of hepatitis B infection among patients with the infection in the main liver clinic in The Gambia. Pan Afr Med J. 2022;42.
16. Wai CT, Mak B, Chua W, et al. Misperceptions among patients with chronic Hepatitis B in Singapore. World J Gastroenterol. 2005;11(32):5002–5.
17. Wu H, Yim C, Chan A, Ho M, Heathcote J. Sociocultural factors that potentially affect the institution of prevention and treatment strategies for hepatitis B in Chinese Canadians. Can J Gastroenterol. 2009;23(1):31–6.

18. Ul Haq N, Hassali MA, Shafie AA, Saleem F, Farooqui M, Aljadhey H. A cross-sectional assessment of knowledge, attitude, and practice towards Hepatitis B among the healthy population of Quetta, Pakistan. BMC Public Health [Internet]. 2012;12(1):1. Available from: BMC Public Health
19. Pak A, Raza W, Tariq W, et al. Knowledge, attitude and practices (KAP) of medical students towards Hepatitis B and C. Inst Med Sci. 2008;4(2):116–20.
20. Velvzhi G, Senthil K, Sucilathangam G, Revathy C. Knowledge and attitude of medical students towards Hepatitis B infection. Int J Curr Microbiol Appl Sci. 2016;5(6):570–6.
21. Gambhir R, Kapoor V, Jindal G, Garg S, Setia S, Setia S. Attitudes and awareness regarding Hepatitis B and Hepatitis C amongst healthcare workers of a tertiary Hospital in India. Ann Med Health Sci Res. 2013;3(4):551.
22. Ganczak M, Dmytrzyk-Daniłów G, Korzeń M, Drozd-Dąbrowska M, Szych Z. Prevalence of HBV infection and knowledge of Hepatitis B among patients attending primary care clinics in Poland. J Community Health. 2016;41(3):635–44.
23. Enescu A, Mitrut P, Balasoiu M, Turculeanu A, Enescu AS. Psychosocial issues in patients with chronic hepatitis B and C. Curr Health Sci J. 2014;40(2):93-6. doi: 10.12865/CHSJ.40.02.02. Epub 2014 Mar 29. PMID: 25729588; PMCID: PMC4340448.
24. Brzdęk M, Zarębska-Michaluk D, Invernizzi F, Cilla M, Dobrowolska K, Flisiak R. Decade of optimizing therapy with direct-acting antiviral drugs and the changing profile of patients with chronic hepatitis C. World J Gastroenterol. 2023;29(6):949–66.
25. Smith-Palmer J, Cerri K, Sbarigia U, Chan EK, Pollock RF, Valentine W, et al. Impact of stigma on people living with chronic Hepatitis B. Patient Relat Outcome Meas. 2020;11:95–107.
26. Sørensen K, Pelikan JM, Röthlin F, et al. Health literacy in Europe: Comparative results of the European health literacy survey (HLS-EU). Eur J Public Health. 2015;25(6):1053–8.
27. Cowan ML, Thomas HC, Foster GR. Therapy for chronic viral hepatitis: Current indications, optimal therapies and delivery of care. Clin Med J R Coll Physicians London. 2011;11(2):184–9.
28. RI KK. Rencana aksi nasional pengendalian Hepatitis 2020-2024. Jakarta; 2020.
29. Trickey A, Hiebert L, Perfect C, Thomas C, Luc El Kaim, Vickerman P, Schütte C, Hecht R. Hepatitis C virus elimination in Indonesia: Epidemiological, cost, and cost-effectiveness modeling to advance advocacy and strategic planning. Liver Int [Internet]. 2020;40(2):0–3. Available from: https://pubmed.ncbi.nlm.nih.gov/31454466/
30. Alharbi IM, Aljarallah BM. Premarital hepatitis screening: Attitude towards screening and the risk factors for transmission. Saudi Med J. 2018;39(12):1179–85.
31. Hajarizadeh B, Richmond J, Ngo N, Lucke J, Wallace J. Hepatitis B-related concerns and anxieties among people with chronic hepatitis B in Australia. Hepat Mon. 2016;16(6).
32. Valizadeh L, Zamanzadeh V, Negarandeh R, Zamani F, Hamidia A, Zabihi A. Psychological reactions among patients with chronic Hepatitis B: a qualitative study. J Caring Sci [Internet]. 2016;5(1):57–66. Available from: http://dx.doi.org/10.15171/jcs.2016.006
33. Ng CJ, Low WY, Wong LP, Sudin MR, Mohamed R. Uncovering the experiences and needs of patients with chronic hepatitis B infection at diagnosis: A qualitative study. Asia-Pacific J Public Heal. 2013;25(1):32–40.

# High-Dose Vitamin D3 and Tonsillectomy as Therapeutic Management in Henoch–Schönlein Purpura Following Hepatitis B Vaccination: A Rare Case Report

*Agus Joko Susanto[1,2*], Felizia Alika Yusman[2], Fatna Andika Wati[1,2], Yeremia Suryo Pratama[2]*

[1]Division of Clinical Allergy and Immunology, Department of Internal Medicine, Dr. Moewardi Hospital, Surakarta, Indonesia.
[2]Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia.

**** Corresponding Author:***
*Agus Joko Susanto, MD. Department of Internal Medicine, Faculty of Medicine, Sebelas Maret University. Jl. Kolonel Soetarto no. 132, Jebres, Surakarta 57126, Indonesia. E-mail address: agusjoko.susanto4@gmail.com.*

## ABSTRACT

*Henoch–Schönlein purpura (HSP) is an immunoglobulin A (IgA)-mediated systemic vasculitis, which is one of the rare adverse reactions to hepatitis B vaccination. Low vitamin D levels were found to be present in the majority of HSP patients.*

*A 19-year-old woman was admitted with a purpuric rash on bilateral lower limbs and joint pain on her left index finger in January 2020. A previous history of rash occurred one week after the patient received her first dose of recombinant hepatitis-B vaccination. Routine hematological examination, creatinine, urinalysis, C3, and C4 showed normal results. HBsAg, Anti-HCV, and ANA tests were negative, and anti-HBs were elevated. Vitamin D is very low. The patient was diagnosed with HSP and given mycophenolate mofetil, methylprednisolone, vitamin D3, and folic acid. Within 1 month of therapy, the rash still occurred frequently, so mycophenolate mofetil was changed to mycophenolic acid, the dose of methylprednisolone was increased and fexofenadine was administered. In the next 3 months, the rash has improved. However, patients reported knee joint pain and hair loss. In May 2021, the patient underwent tonsillectomy due to acute exacerbation of chronic tonsillitis. Thereafter, the patient reported that the rash had completely resolved and never worsened, and the vitamin D assay was normal.*

*Hepatitis B vaccination is one of the etiologies of HSP, although it is rare, so it is important to ask about the vaccination history in patients with suspected HSP. Correction of vitamin D and performing tonsillectomy provide better treatment results in HSP cases in this patient.*

***Keywords**: Vitamin D3, tonsillectomy, Henoch–Schönlein purpura, hepatitis B vaccination.*

## INTRODUCTION

Henoch–Schönlein purpura (HSP) is an immunoglobulin A (IgA)-mediated systemic vasculitis defined by the clinical triad of nonthrombocytopenic palpable purpura, abdominal discomfort, and arthritis.[1] This is the most prevalent form of systemic vasculitis in children, with an incidence rate of between 6 and 22 per 100,000 person-years Clicktaps. This vasculitis was more uncommon in adults, with an incidence rate between 3.4 and 14.3 per 100,000 person–years.[1] The incidence of this vasculitis does not differ between genders; however, the recurrence rate is nearly twice as high in males.[2] HSP is a rare complication of infectious diseases, and a significant percentage of HSP patients have

a recent history of upper respiratory infection. More rare predisposing factors include exposure to insect bites, immunizations, medications, or dietary allergies.[3]

Vitamin D exhibits a range of immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant properties in addition to its calcium homeostasis regulator activities.[4,5] Vitamin D or 1,25 dihydroxy vitamin D has immune regulatory effects on innate and adaptive immune responses,[6] and low vitamin D may decrease self-tolerance in genetically susceptible individuals by impairing the control of dendritic cells, regulatory T-lymphocytes, and Th1 cells.[7] Several autoimmune disorders were associated with low vitamin D levels, such as multiple sclerosis, systemic scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and rheumatic heart disease.[6] In several studies, low vitamin D levels were found to be present in the majority of HSP patients.[8,9]

Type B viral hepatitis is a severe and potentially fatal disease that is easily prevented by vaccination. Hepatitis B vaccines are extraordinarily safe, and infrequently mild and transient adverse reactions to hepatitis B vaccination are observed.[10] Vasculitis, including HSP,[11] is one of the rare adverse reactions, and it has been scarcely reported in the past decade.[12–14] There were only 8 cases of cutaneous vasculitis previously reported, namely 4 cases of cryoglobulinemia detected with 1 patient type II (mixed) and 1 case of transient proteinuria.[15] The purpose of this case report was to describe the first case of HSP in a 19-year-old Indonesian woman following hepatitis B vaccination, which was successfully treated with a high dose of vitamin D3 and tonsillectomy.

## CASE ILLUSTRATION

In January 2020, a 19-year-old Indonesian woman was admitted to an outpatient care unit with a sudden purpuric rash on her bilateral lower legs (**Figure 1A**) and joint pain on her left index finger. The rash was palpable, painful, and not itchy. This was the second time the rash appeared in the lower extremities; the first one occurred 1 week after the first dose of recombinant hepatitis B (Euvax B) vaccination 3 months prior accompanied by acute abdominal pain and fresh bloody stool. The previous rash was treated with a symptomatic regimen, including topical and oral steroids, and resolved. Her medical history included multiple allergies and chronic tonsillitis that have been treated conservatively by an otorhinolaryngologist.

Routine hematological, glucose, HbA1c, lipid profile, creatinine, uric acid, and urinalysis were performed and showed unremarkable results. Antistreptolysin O titer, anti-human

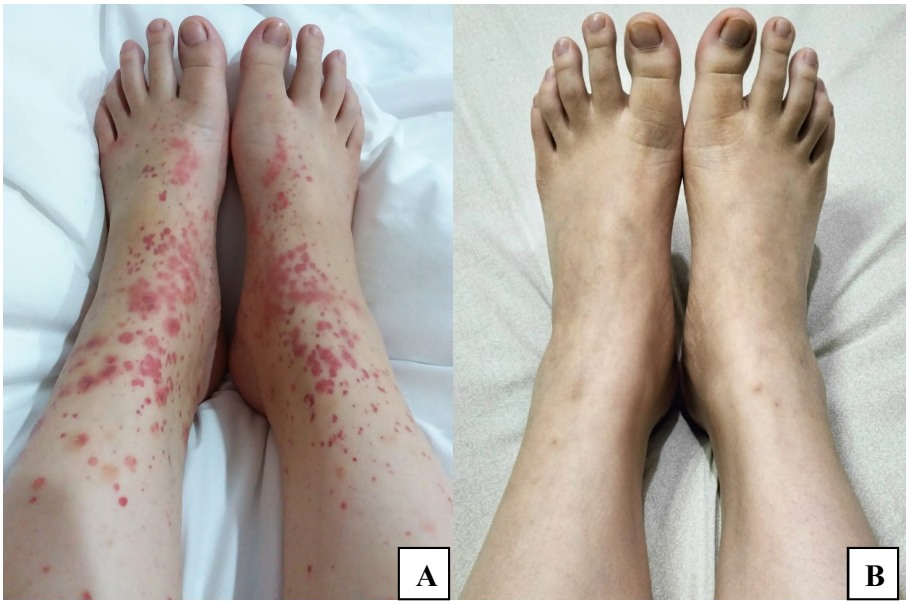



**Figure 1.** Clinical picture of the bilateral purpuric palpable rash of the patient. A, on presentation; B, bilateral rash resolution following 19 months of follow up period.

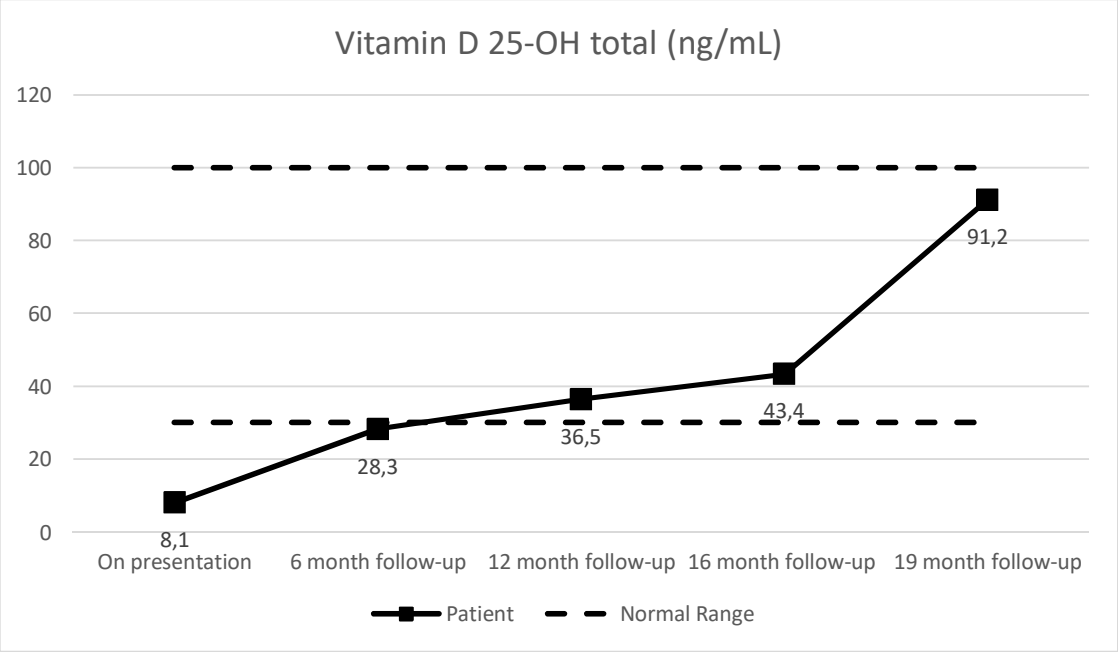



**Figure 2.** Vitamin D examination of the patient from presentation to the last follow-up visit. The vitamin D continued to increase gradually. It reached the normal range on the 12-month follow-up and continued to increase on the 19-month follow-up.

immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and anti-hepatitis C virus (HCV) showed negative results, and anti-HBs were elevated. C3 and C4 were in the normal range, but the vitamin D was remarkably low (8.1 ng/mL). ANA IF and profile test showed negative results, but the serum IgE panel test confirmed the multiple allergies in the patient (**Table 1**).

HSP then was established based on clinical criteria (**Table 2**), and the patient was given mycophenolate mofetil 500 mg/day, methylprednisolone 8 mg/day, vitamin D3 1000 IU b.i.d., and folic acid 400 µg/day.

During the 1-month follow-up, the patient reported frequent exacerbations of the rash, and the drug regimen was changed to as follows: fexofenadine 120 mg/day, mycophenolic acid

**Table 1.** Results of laboratory and immunology investigations in the patient at presentation

| Parameter | Value |
|---|---|
| Hemoglobin (g/dL) | 13.2 |
| Platelets ($10^3$/µL) | 333 |
| WBC ($10^3$/µL) | 7.5 |
| Creatinin (mg/dL) | 0.55 |
| Fasting glucose (mg/dL) | 76 |
| HbA1C (%) | 4.6 |
| Cholesterol LDL (mg/dL) | 161 |
| Triglycerides (mg/dL) | 60 |
| Uric acid (mg/dL) | 5.3 |
| Urinalysis | |
| Color | Light yellow |
| Appearance | Clear |
| pH | 7.0 |
| Specific gravity | 1.004 |
| Leukocyte esterase | – |
| Nitrit | – |
| Albumin | – |
| Glucose | – |
| Keton | – |
| Urobilinogen | – |
| Bilirubin | – |
| Blood | – |
| Casts | – |
| Cell/epithelium | – |
| Bacteria | – |
| Crystal | – |
| Antistreptolysin O | <200 |
| Anti-HIV | Nonreactive |
| HBsAg | Nonreactive |
| Anti-HCV | Nonreactive |
| Anti-HBs (mIU/mL) | 94.42 |
| C3 (mg/dL) | 96.8 |
| C4 (mg/dL) | 19.9 |
| Vitamin D 25-OH total (ng/mL) | 8.1 |
| ANA IF | Negative |
| ANA profile | Negative |
| Serum IgE panel | |
| Tyrophagus putrescentiae | ++ |
| Cockroach | +++++ |
| Shellfish | ++++ |

**Table 2.** Diagnostic criteria for HSP as developed by EULAR/PRINTO/PRES

| Criteria | Description |
|---|---|
| Mandatory criteria | Purpura or petechiae with lower limb predominance |
| Minimum 1 out of 4 criteria | Diffuse abdominal pain with acute onset |
| | Histopathology showing leukocytoclastic vasculitis or proliferative glomerulonephritis, with predominant IgA deposits |
| | Arthritis or arthralgia of acute onset |
| | Renal involvement in the form of proteinuria or hematuria |

EULAR/PRINTO/PRES: the European League Against Rheumatism, the Paediatric Rheumatology International Trials Organization, and the Paediatric Rheumatology European Society[20]

180 mg b.i.d., and methylprednisolone 8 mg b.i.d. Vitamin D3 and folic acid supplementation remained the same.

Observations over the next 3 months revealed that the rash became infrequently exacerbated, leaving hyperpigmented and unpalpable patches. However, the patient reported moderate knee joint pain and moderate hair loss. The diagnosis of osteoarthritis of the knee and telogen effluvium was considered, and the patient was referred to a medical rehabilitation department and dermatologist. The rehabilitation program included cryotherapy and a routine stationary cycling program. A combination of minoxidil 5% and mometasone furoate 0.1% was prescribed by the dermatologist for topical scalp application. The dose of methylprednisolone was then reduced to 4 mg/day.

The complication was resolved, and the rash was also rarely exacerbated in 2 months of follow-up. Additional laboratory assessment showed low vitamin D (28.3 ng/mL) and normal renal function. The drug regimen was adjusted to mycophenolic acid 180 mg at the one-day interval, and methylprednisolone 4 mg two times a week. Then, the patient was scheduled for monthly monitoring. Another vitamin D laboratory finding in December 2020 showed a normal result (36.5 ng/mL).

In May 2021, the rash was still persistent, albeit rarely exacerbated, and her vitamin D showed a normal result (43.4 ng/mL). This improvement in vitamin D was deemed unremarkable; thus, the vitamin D dose was adjusted to 15.000 IU/day paired with 90 mcg of vitamin K2/day for the next 3 months. Concurrently, the patient had an episode of acute exacerbation of chronic tonsillitis. The patient was then referred to an otorhinolaryngologist, and a tonsillectomy was performed. At the next follow-up, the patient reported that the rash was completely resolved and never exacerbated, and the vitamin D examination showed a normal result (91.2 ng/mL).

## DISCUSSION

A 19-year-old woman was admitted with a purpuric rash on bilateral lower limbs and joint pain on her left index finger in January 2020. A previous history of rash occurred one week after the patient received her first dose of recombinant hepatitis-B vaccination. Routine hematological examination, creatinine, urinalysis, C3, and C4 showed normal results. HBsAg, Anti-HCV, and ANA tests were negative, and anti-HBs were elevated. Vitamin D is very low. The patient was diagnosed with HSP and given mycophenolate mofetil, methylprednisolone, vitamin D3, and folic acid. Within 1 month of therapy, the rash still occurred frequently, so mycophenolate mofetil was changed to mycophenolic acid, the dose of methylprednisolone was increased and fexofenadine was administered. In the next 3 months, the rash has improved. However, patients reported knee joint pain and hair loss. In May 2021, the patient underwent tonsillectomy due to acute exacerbation of chronic tonsillitis. Thereafter, the patient reported that the rash had completely resolved and never worsened, and the vitamin D assay was normal.

Immunization against hepatitis B is crucial as hepatitis B virus (HBV) role in liver carcinoma and is a substantial source of morbidity and death globally. Currently, the vaccine for hepatitis B contains recombinant HBsAg protein (5–40 μg) and adjuvants such as aluminum phosphate or aluminum hydroxide. Primary doses are administered twice a month apart, with the third dose as a booster 6 months later. The vaccine is injected intramuscularly at the anterior thigh or deltoid muscle.[10] In this case, the patient's left deltoid muscle was injected intramuscularly with

the first dose of recombinant hepatitis B vaccine (Euvax B; containing 20 µg purified HBsAg and 0.5 mg aluminum hydroxide gel).

Vaccines against hepatitis B are safe. The vaccination is associated with uncommon, typically mild, and temporary adverse events. The Global Advisory Committee on Vaccine Safety has confirmed the hepatitis B vaccine's excellent safety profile and continues to monitor this vaccine's safety.[10] However, the patient, in this case, experienced undesirable events after receiving the first dose of the recombinant hepatitis B vaccine and she was finally diagnosed with HSP. A similar case was reported in 2003 where a 28-year-old healthcare worker suffered from HSP after receiving a booster dose of recombinant hepatitis B vaccine (Engerix B; SmithKline Beecham).[11] Other cases of vasculitis after receiving the hepatitis B vaccine that have been reported so far include cutaneous vasculitis,[14] lymphocytic vasculitis,[15] cutaneous polyarteritis nodosa,[16] large artery vasculitis.[12] periarteritis nodosa,[17] and hypersensitivity vasculitis.[18]

Since it was feared that the condition would get worse, the patient was not given a second dose. This decision is based on a study conducted in 1999 in which, among 22 patients who developed rheumatic disorders following hepatitis B vaccination, the next hepatitis B vaccine inoculation was administered to 10 patients despite their complaints, and in eight cases, the complaints worsened.[19] This decision-making was strengthened by the results of anti-HBs of 94.42 mIU/mL. Anti-HBs could be measured to determine the immunity after B vaccination, with levels over 10 mIU/mL in 1 month after the last dose of the primary vaccination series considered reliable indicators of HBV protection. When immunocompetent kids and adults had anti-HBs concentrations of 10 mIU/mL or higher after vaccination, they were completely protected against both acute diseases and chronic infections (documented for 30 years), even if anti-HBs concentrations eventually dropped to less than 10 mIU/mL.[10]

Upper respiratory tract infections preceded many HSP cases, and a correlation between virtually all respiratory pathogens and HSP is suggested. The most frequently associated pathogens are Streptococcus strains and Parainfluenza virus.[20] In this instance, the ASTO result was less than 200, so it can be inferred that upper respiratory tract infection is not the culprit. Additionally, drugs prescribed by an otorhinolaryngologist have always been effective in controlling chronic tonsillitis that has been experienced thus far. Before receiving the hepatitis B vaccine, the patient had never experienced this before; thus, the vaccine is the most plausible explanation for this occurrence.

Vasculitis induced by antiviral vaccines and drugs is less common and less well-known.[21] The deposition of IgA1-dominant immune complexes in target organs is essential to the pathophysiology of HSP.[22] It is believed that IgA depositions in the blood vessel walls of the affected organs, especially the skin, digestive system, joints, and kidneys, cause clinical symptoms. However, the pathophysiology of HSP is not yet completely understood.[20] Sensitivity to one of the vaccine components, pseudoallergic reactions that frequently arise after hyperimmunization, and worsening of atopic disease or vasculitis can be categorized as vaccine-specific allergic reactions.[23] The question arises, namely, why the patient did not experience any untoward events after she received the hepatitis B vaccine at birth.

HSP diagnosis is based on clinical criteria.[20] The condition is uncommon in adults but has a more severe course.[22] The new EULAR/PRINTO/PRES criteria were published in 2010 and represent the gold standard for the diagnosis of HSP (**Table 2**). In children, the sensitivity is 100% and the specificity is 87%. One study analyzed the application of these criteria to adults and showed that they have a diagnostic sensitivity of 99.2% and a specificity of 88%, thus validating their usage for all patients with HSP.[20]

This patient met the mandatory criteria for making the diagnosis, namely purpura or petechiae with predominance in the lower limbs, and the presence of acute diffuse abdominal pain and arthralgia was also found. Gastrointestinal symptoms typically develop within a week of the appearance of the rash.[22] However, in this

patient, gastrointestinal symptoms manifested 5 days after the appearance of the rash as diffuse abdominal pain and fresh bloody stools. Joint involvement is transient and only involves the index finger of the patient's left hand. A skin biopsy, which is the gold standard for diagnosing cutaneous vasculitis, was not performed. This is because IgA-dominant vascular deposits are characteristic of HSP but are not sufficient to diagnose HSP, as these deposits could be found in other vasculitis syndromes, erythema nodosum, and conditions associated with venous stasis.[22]

The treatment of HSP in adults is still a subject of debate.[22] The patient in this case was treated with corticosteroids and mycophenolate. The utilization of corticosteroids in HSP patients is contentious. Mycophenolate is an immunosuppressive medication that can impede T and B cell growth and reduce antibody production. Its toxicological profile is excellent. Mycophenolate + low-dose prednisone is superior to full-dose prednisone, with the same remission rate, fewer adverse effects, and fewer relapses.[22] Additionally, the patient received folic acid and vitamin D3 supplements. Folate is necessary for regular cell reproduction and proliferation. Folate analogs have been and remain useful as antibiotics and cytotoxic medications in various diseases. Folate (vitamin B9) is an essential and underappreciated element having substantial direct and indirect effects on the body and a putative regulatory role in autoimmune and chronic inflammation.[25] Although the role of vitamin D in autoimmunity remained controversial, vitamin D has been widely recognized for reducing the risk of diabetes mellitus, depression, dementia, cancer, cardiovascular diseases, allergies, and asthma, as well as chronic infections.[26] In two case reports, vitamin D proved to be beneficial in autoimmune cases, namely helping to achieve remission of severe myasthenia gravis[27] and minimizing exacerbations of graves disease.[28]

In the course of treatment, the patient developed knee osteoarthritis, which was thought to be due to steroid use. In osteoarthritis itself, six major categories of modifiable risk factors have been identified: (1) obesity and overweight, (2) comorbidity, (3) occupational factors, (4) physical activity, (5) biomechanical factors, and (6) diet exposures.[29] Looking deeper, things that can also trigger the onset of osteoarthritis, in this case, are patients who are overweight, have a comorbidity, and have high physical activity. Therefore, the patient was sent to the medical rehabilitation department and underwent cryotherapy. Additionally, the patient is asked to routinely do stationary cycling. This combination gives better results than cryotherapy alone.[30] Stationary cycling may reduce pain and enhance the patient's athletic performance.[31]

Telogen effluvium that occurs in this patient is thought to be caused by an autoimmune condition suffered along with low levels of vitamin D in the blood. As it is known that vitamin D is essential for cell growth, its deficiency may also be a cause.[32] In addition to continuing treatment, minoxidil and topical corticosteroids were administered to help improve this condition. Minoxidil inhibits or induces the catagen phase of the hair follicles, whereas topical corticosteroid was administered because they have been proven to be an effective adjuvant therapy.[32]

Due to the insignificant increase in vitamin D3 yield, the patient was given 15.000 IU of vitamin D3 together with 90 mcg of vitamin K2 daily. We use the "Coimbra Protocol," in which vitamin D3 is administered at high levels to improve autoimmune illnesses. Orally administered vitamin D3 up to 1000 IU per kilogram of body weight is safe for calcium metabolism and renal function when strict dietary and fluid intake requirements are adhered to for up to 3.5 years. Vitamin K2 (menaquinone) has been described as a bone cofactor for mineralization, circulatory, and endothelial protective factors. Moreover, antioxidative effects have been outlined. Vitamin K2 is added to the "Coimbra Protocol" in quantities ranging from 100 to 800 mcg per day, to minimize the risk of calcification of arteries[26]. Because levels of serum calcium and urinary calcium excretion were not measured in this patient, we decided to use 90 mcg of K2. After 3 months of using high-dose vitamin D3 accompanied by K2, the level of serum vitamin D3 in this patient increased significantly until it reached optimal levels. Together with optimal

levels of vitamin D in the blood, the patient's complaints and allergies dissipate.

Based on several studies, tonsillectomy has also been proposed as a therapy and preventative measure for HSP, which is frequently precipitated by an upper respiratory tract infection.[20] In a retrospective study[33], from 78 children diagnosed with HSP, an upper respiratory tract infection was reported to occur in 32/78 (41%) children. It has been shown that HSP associated with chronic tonsillitis is mainly associated with streptococcal infection.[34] Because the patient had a history of chronic tonsillitis and had experienced exacerbations, she was referred to the ENT department, where a tonsillectomy was performed. After undergoing the surgery, the recurrence of HSP in our patient was eliminated. This is in line with a study where, compared with those of the non-surgery group, the complaints of the surgery group improved significantly after surgery.[34] Furthermore, there was a case of HSP nephritis that was successfully treated with tonsillectomy and steroid pulse therapy.[35] Moreover, there was a case report of clinical remission of HSP nephritis after a monotherapeutic tonsillectomy.[36]

## CONCLUSION

Hepatitis B vaccination is one of the etiologies of HSP, although it is rare, so it is important to ask about the vaccination history in patients with suspected HSP. Correction of vitamin D and performing tonsillectomy provide better treatment results in HSP cases in this patient.

## ACKNOWLEDGMENTS

The authors thank Fata Prihatsari and Dyah Rohmania Agustina for their indispensable assistance in manuscript preparation.

## CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

## FUNDING

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

## REFERENCES

1. López Meiller MJ, Cavallasca JA, Maliandi MDR, Nasswetter GG. Henoch-SchöNlein purpura in adults. Clinics (Sao Paulo) [Internet]. 2008 [cited 2022 Nov 29];63(2):273. Available from: /pmc/articles/PMC2664214/
2. Lei W te, Tsai PL, Chu SH, et al. Incidence and risk factors for recurrent Henoch-Schönlein purpura in children from a 16-year nationwide database. Pediatr Rheumatol Online J [Internet]. 2018 Apr 16 [cited 2022 Nov 29];16(1). Available from: /PMC/articles/PMC5902957/
3. Rigante D, Castellazzi L, Bosco A, Esposito S. Is there a crossroad between infections, genetics, and Henoch–Schönlein purpura? Autoimmun Rev. 2013;12(10):1016–21.
4. Jain SK, Micinski D. Vitamin D upregulates glutamate cysteine ligase and glutathione reductase, and GSH formation, and decreases ROS and MCP-1 and IL-8 secretion in high-glucose exposed U937 monocytes. Biochem Biophys Res Commun. 2013;437(1):7–11.
5. Beyazit Y, Kocak E, Tanoglu A, Kekilli M. Oxidative stress might play a role in low serum vitamin D associated liver fibrosis among patients with autoimmune Hepatitis. Digestive Diseases and Sciences 2015 60:4 [Internet]. 2015 Jan 14 [cited 2022 Nov 29];60(4):1106–8. Available from: https://link.springer.com/article/10.1007/s10620-015-3526-y
6. Murdaca G, Tonacci A, Negrini S, et al. Emerging role of vitamin D in autoimmune diseases: An update on evidence and therapeutic implications. Autoimmun Rev. 2019;18(9):102350.
7. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun Rev. 2012;12(2):127–36.
8. Fan L, Liu H, Wang YC, Chen L, Zhou JJ, Cui YX. [Association of serum vitamin D level with severity and treatment in children with Henoch-Schönlein purpura]. Zhongguo Dang Dai Er Ke Za Zhi [Internet]. 2017 Jul 1 [cited 2022 Nov 29];19(7):796–9. Available from: https://europepmc.org/articles/PMC7389916
9. Dong X, Zhong T, Huang Y, Yi L, Zeng H, Zhong X. A case-control study on the relationship between serum 25-hydroxy vitamin D and the risk of Henoch-Schonlein purpura. Chongqing Medicine [Internet]. 2017 [cited 2022 Nov 29];1076-8,81. Available from: http://dx.doi.org/10.3969/j.issn.1671-8348.2017.08.022
10. Pattyn J, Hendrickx G, Vorsters A, van Damme P. Hepatitis B vaccines. J Infect Dis [Internet]. 2021;224(12 Suppl 2):S343–51. Available from: http://dx.doi.org/10.1093/infdis/jiaa668
11. Chave TA, Neal C, Camp R. Henoch-Schönlein purpura following hepatitis B vaccination. http://dx.doi.org/101080/09546630310004199 [Internet].

2009 Sep [cited 2022 Nov 29];14(3):179–81. Available from: https://www.tandfonline.com/doi/abs/10.1080/09546630310004199
12. Zaas A, Scheel P, Venbrux A, Hellmann DB. Large artery vasculitis following recombinant hepatitis B vaccination: 2 cases. J Rheumatol [Internet]. 2001;28(5):1116–20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11361200
13. Allen MB, Cockwell P, Page RL. Pulmonary and cutaneous vasculitis following hepatitis B vaccination. Thorax [Internet]. 1993;48(5):580–1. Available from: http://dx.doi.org/10.1136/thx.48.5.580
14. Bui-Quang D, Thomas E, Riols M, et al. Cutaneous vasculitis after Hepatitis B vaccination with recombinant vaccine in a renal transplant patient. Presse Med [Internet]. 1998;27(26):1321–3. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9779046
15. Chave T, Neal C, Camp R. Henoch-Schönlein purpura following Hepatitis B vaccination. J Dermatolog Treat [Internet]. 2003;14(3):179-81. Available from: http://dx.doi.org/ 10.1080/09546630310004199
16. Drucker Y, Prayson RA, Bagg A, Calabrese LH. Lymphocytic vasculitis presenting as diffuse subcutaneous edema after Hepatitis B virus vaccine. J Clin Rheumatol [Internet]. 1997;3(3):158–61. Available from: http://dx.doi.org/10.1097/00124743-199706000-00010
17. Bourgeais AM, Dore MX, Croue A, Leclech C, Verret JL. Cutaneous polyarteritis nodosa following hepatitis B vaccination. Ann Dermatol Venereol [Internet]. 2003;130(2 Pt 1):205–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12671586
18. Saadoun D, Cacoub P, Mahoux D, Sbai A, Piette JC. Postvaccine vasculitis: a report of three cases. Rev Med Interne [Internet]. 2001;22(2):172–6. Available from: http://dx.doi.org/10.1016/s0248-8663(00)00307-6
19. Masse I, Descoffres MC. Hypersensitivity vasculitis after Hepatitis B vaccination. Presse Med [Internet]. 1998;27(20):965–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9767839
20. Maillefert JF, Sibilia J, Toussirot E, et al. Rheumatic disorders developed after hepatitis B vaccination. Rheumatology (Oxford) [Internet]. 1999;38(10):978–83. Available from: http://dx.doi.org/10.1093/rheumatology/38.10.978
21. Hetland LE, Susrud KS, Lindahl KH, Bygum A. Henoch-Schönlein Purpura: A literature review. Acta Derm Venereol [Internet]. 2017;97(10):1160–6. Available from: http://dx.doi.org/10.2340/00015555-2733
22. le Hello C. Vasculitis associated with antiviral vaccines and antiviral agents. Pathol Biol (Paris) [Internet]. 1999;47(3):252–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10214618
23. Maritati F, Canzian A, Fenaroli P, Vaglio A. Adult-onset IgA vasculitis (Henoch-Schönlein): Update on therapy. Presse Med [Internet]. 2020;49(3):104035. Available from: http://dx.doi.org/10.1016/j.lpm.2020.104035
24. Barbaud A, Deschildre A, Watson J, Raison-Peyron N, Tréchot P. Hypersensitivity and vaccines: an update. Eur J Dermatol [Internet]. 2013;23(2):135–41. Available from: http://dx.doi.org/10.1684/ejd.2012.1842
25. Kamen B. Folate and antifolate pharmacology. Semin Oncol [Internet]. 1997;24(5 Suppl 18):S18-30-S18-39. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9420019
26. Mölzer C, Wilson HM, Kuffova L, Forrester JV. A role for folate in microbiome-linked control of autoimmunity. J Immunol Res [Internet]. 2021;2021:9998200. Available from: http://dx.doi.org/10.1155/2021/9998200
27. Amon U, Yaguboglu R, Ennis M, Holick MF, Amon J. Safety data in patients with autoimmune diseases during treatment with high doses of vitamin D3 according to the "Coimbra protocol". Nutrients [Internet]. 2022;14(8):1575. Available from: http://dx.doi.org/10.3390/nu14081575
28. Cadegiani FA. Remission of severe myasthenia gravis after massive-dose vitamin D treatment. Am J Case Rep [Internet]. 2016;17:51–4. Available from: http://dx.doi.org/10.12659/ajcr.894849
29. Alhuzaim ON, Aljohani N. Effect of vitamin D3 on untreated graves' disease with vitamin D deficiency. Clin Med Insights Case Rep [Internet]. 2014;7:83–5. Available from: http://dx.doi.org/10.4137/CCRep.S13157
30. Georgiev T, Angelov AK. Modifiable risk factors in knee osteoarthritis: treatment implications. Rheumatol Int [Internet]. 2019;39(7):1145–57. Available from: http://dx.doi.org/10.1007/s00296-019-04290-z
31. Dantas LO, Moreira R de FC, Norde FM, Mendes Silva Serrao PR, Alburquerque-Sendín F, Salvini TF. The effects of cryotherapy on pain and function in individuals with knee osteoarthritis: a systematic review of randomized controlled trials. Clin Rehabil [Internet]. 2019;33(8):1310–9. Available from: http://dx.doi.org/10.1177/0269215519840406
32. Luan L, Bousie J, Pranata A, Adams R, Han J. Stationary cycling exercise for knee osteoarthritis: A systematic review and meta-analysis. Clin Rehabil [Internet]. 2021;35(4):522–33. Available from: http://dx.doi.org/10.1177/0269215520971795
33. Asghar F, Shamim N, Farooque U, Sheikh H, Aqeel R. Telogen effluvium: A review of the literature. Cureus [Internet]. 2020;12(5):e8320. Available from: http://dx.doi.org/10.7759/cureus.8320
34. Gonzalez-Gay MA, Calviño MC, Vazquez-Lopez ME, et al. Implications of upper respiratory tract infections and drugs in the clinical spectrum of Henoch-Schönlein purpura in children. Clin Exp Rheumatol [Internet]. 2004;22(6):781–4. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15638057
35. Yan M, Wang Z, Niu N, Zhao J, Peng J. Relationship

between chronic tonsillitis and Henoch-Schonlein purpura. Int J Clin Exp Med [Internet]. 2015;8(8):14060–4. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26550368

36. Iwamoto M, Wakabayashi M, Hanada S, Kobayashi N, Hata T, Ando R. Case of Henoch-Schönlein purpura nephritis successfully treated with tonsillectomy and steroid pulse therapy. Nihon Jinzo Gakkai Shi [Internet]. 2009;51(4):484–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19601558
37. Iwazu Y, Akimoto T, Muto S, Kusano E. Clinical remission of Henoch–Schönlein purpura nephritis after a monotherapeutic tonsillectomy. Clin Exp Nephrol [Internet]. 2011;15(1):132–5. Available from: http://dx.doi.org/10.1007/s10157-010-0345-5.

# Risk Factors and Survival Analysis of COVID-19 Among Health Care Workers in West Jakarta Hospital

*Virmandiani[1,2]*, Asri C. Adisasmita[2], Febby Elvanesa Sandra Dewi[1]*

[1]Harapan Kita Hospital, Jakarta, Indonesia.
[2]Department of Epidemiology, Universitas Indonesia, Jakarta, Indonesia.

***Corresponding Author:***
*Virmandiani, MD. Harapan Kita Hospital. Jl. Letjen S.Parman Kav 87, Slipi, Jakarta 11420, Indonesia. Email: drvirmandiani@gmail.com.*

## ABSTRACT

***Background:*** *The first two cases of Coronavirus Disease 2019 (COVID-19) were identified in Indonesia on March 2nd, 2020. Health Care workers (HCWs) are at risk of contracting COVID-19 infection. This study analyzed the risk factors, compared the prevalence rate of COVID-19 between HCWs and non-HCWs, and investigated survival analysis describing the time risk of COVID-19.* ***Methods:*** *This prospective cohort study retrieved data from the Hospital Surveillance Team (one of the largest hospitals in West Jakarta) which were analyzed using descriptive, bivariate analysis, Survival Analysis through the Kaplan-Meier method, and multivariate Cox analysis.* ***Results:*** *Observations were conducted on 1,080 employees from March 2021 to March 2022. There were 192 employees (17.78%) of 40±11 years tested positive for COVID-18, of which 126 cases (16.84%) were HCWs of ≤ 40 years of age, with females dominating. There was no difference between HCW and Non-HCW; ARR=1.08; [95% IK, 0.83-1.43]; p=0.591. Workers on shift work (> 38 hours in a week) were likely to be affected by COVID-19 with RR=1.37; [95% IK, 1.06-1.78]; p=0.018. Kaplan–Meier method and the log-rank test showed the difference between Shift and Non-shift groups HR=1.43; [95% IK 1.06-1.94]; p=0.019. Asthma or Chronic Obstructive Pulmonary Disease appeared as the independent factor of COVID-19 infection with RR=1.82; [95% IK, 1.10-3.02]; p=0.031.* ***Conclusion:*** *The probability of contracting COVID-19 was found equal to HCW and Non-HCW. Employees who are on shifts have a greater probability of contracting COVID-19. Survival analysis showed a statistically different Hazard Ratio between shifts with Non-shift workers.*

***Keywords****: COVID-19; Health Care Workers*

## INTRODUCTION

COVID-19 was first identified in China in December 2019 due to coronavirus SARS-CoV-2 infection that is believed to have originated from bats and was transmitted to humans before spreading among humans it is a global endemic, a public health emergency and a national disaster in Indonesia.[1] Indonesia reported its first COVID-19 cases on March 2nd, 2020 which number then rapidly increased. By December 31st, 2020,[2] there were 743,196 cases, requiring optimizing health resources to support COVID-19 patient care. Health workers played important roles in maintaining and improving community health. The number of COVID-19-positive health workers has increased tenfold since the initial report, highlighting the need to protect the health and safety of this workforce.

Health workers were grouped into: medical personnel (general practitioners, dentists, specialists, and dentist specialists), clinical psychology personnel, nursing staff, midwifery staff, pharmaceutical personnel, public health personnel, environmental health personnel,

nutritionists, physical therapy personnel, medical technicians, biomedical engineering personnel, traditional health workers and other health workers.[3] In April 2020, the Centers for Disease Control and Prevention (CDC) reported that health workers made up 3% of all COVID-19 cases in the US, but only 16% of these cases were reported through standard forms.[4] The number of health workers infected by COVID-19 increased tenfold. This condition shows the high transmission rate among health workers, thereby their health and safety need to be further protected.[5]

COVID-19 mortality rate among health worker was one of the highest in Asia and top three worldwide based on testing and population statistics and based on the data released by Indonesian Doctors Association (PB-IDI) Mitigation Team, the Indonesian Dentist Association (PDGI), the Indonesian National Nurses Association (PPNI), the Indonesian Midwives Association (IBI), the Association of Indonesian Medical Laboratory Technologists (PATELKI), and the Indonesian Pharmacists Association (IAI) In January 2021, 647 health workers confirmed positive for COVID-19, including 289 doctors, 27 dentists, 221 nurses, 84 midwives, 11 pharmacists, and 15 medical lab staff from 26 provinces and 116 cities/districts.[6]

With a higher risk of exposure to infectious diseases due to high exposure to pathogens, the death rate of health workers in Indonesia is among the highest in Asia and the top three worldwide. The death rate of health workers in Indonesia is the third highest worldwide and one of the highest in Asia. The literature about health workers and COVID-19 which highlights the importance of examining the risk of exposure between those on shifts versus those off shifts at health facilities is limited. This study aims to analyze the risk factors and survival outcomes for the workers in a hospital in the West Jakarta area as an evaluation to improve their survival rate for the next pandemic and its management, especially in the national referral hospital.

## METHODS

### Design Study

This is a prospective cohort study on health workers and non-health workers in a maternal and children national referral hospital, in Jakarta, Indonesia from March 2nd, 2020 to March 2nd, 2021.

### Population and Sampling

The population of this study is hospital workers (health workers and non-health workers). A sample size of 1.080 was involved in the study. Employees at this hospital were regarded as Health Workers (according to Law of the Republic of Indonesia No. 36 of 2014, concerning Health Workers). They need to interact and touch the patients. Among health workers in this hospital, managerial staff were included in Non-Health Employees. Non-health employees are those not included in the operational definition of health workers. Employees who work in shifts have longer working hours (>38 hours a week).

### Statistical Analysis

The baseline data (age, sex, comorbidities, and job) was obtained. The continuous data was expressed as mean $\pm$ SD and the categorical data as frequency (percentage [%]). A confidence interval (CI) of 95% was used in this study. Cox Regression analyzed the estimated risk of COVID-19 infection. It will be expressed as a Hazard ratio, a *p*-value of under 0.05 is indicated as statistically significant.

To obtain HR with Cox Regression, when a violation of the PH assumption occurred, an approach would be taken to evaluate the Proportional Hazard (PH) assumption of the Cox model, using a graphical procedure (both with log-log survival curves and expected-observed graphs). Goodness-of-fit (GOF) approach was also used to see the test results and p-values to assess PH assumptions, therefore researchers will be able to make more objective decisions.[7]

## RESULTS

The study analyzed the risk factors and survival for COVID-19 between health workers and non-health workers in a hospital in West Jakarta. The results show that out of 1080 hospital

workers, 671 (62.13%) were health workers and 126 (18.78%) of them were confirmed positive for COVID-19. Meanwhile, 409 (37.87%) were non-health workers and 66 (16.83%) of them were confirmed positive for COVID-19 cases. No significant correlation was found between being a health worker or non-health worker and COVID-19 incidence (RR=1.16, 95% CI 0.88-1.53, p=0.270). The study also found that working as a shift worker was significantly correlated with COVID-19 incidence (RR=1.37, 95% CI 1.06-1.78, p=0.018). However, after stratification analysis for the shift variable, there was no significant correlation between health workers and COVID-19 incidence (RR=1.08, 95% CI 0.83-1.43, p=0.591). The presence of comorbidities was present in 40 workers (22.60%) and was not significantly correlated with COVID-19 incidence (RR=1.34, 95% CI 0.99-1.82, p=0.066).

However, employees with comorbid respiratory system disorders such as asthma or obstructive pulmonary disease (COPD) are at greater risk of getting infected with RR=1.82; [95% CI, 1.10-3.02]; p=0.031. Employees with hematological disorders also risk being affected by COVID-19 with RR = 2.84; [95%; IK 1.26-6.39]; p=0.038.

Employees with comorbid hypertension showed RR=1.43; [95% CI, 1.00-2.00]; p=0.063 and comorbid Diabetes Mellitus (DM) with RR=1.34; [95% CI, 0.99-1.82]; p=0.06; showing a statistically insignificant correlation with the COVID-19 prevalence.

Employees in outpatient and inpatient settings seem to be at greater risk of being exposed to COVID-19, with RR=1.52; [95% CI, 1.08-2.14]; p=0.01. After controlling for the health worker variable, we obtain ARR=1.64; [95% CI, 1.07-2.53]; p=0.204.

**Table 1.** Respondents' characteristics, risk factors, and the transmission risk of COVID-19.

| Variables | Total N = 1080 | COVID-19 n = 192 | Non-COVID19 n = 888 |
|---|---|---|---|
| **Age (**year), Mean (±SD) | 39.5 ±11 years | 40 ± 11 years | 39 ± 10 years |
| ≤ 40 years | 665 (61.57) | 112 (16.84) | 553 (83.16) |
| >40 years | 415 (38.43) | 80 (19.28) | 335 (80.72) |
| **Sex, n (%)** | | | |
| Male | 276 (25.56) | 48 (17.39) | 228 (82.61) |
| Female | 804 (74.44) | 144 (17.91) | 660 (82.09) |
| **Type of Work, n (%)** | | | |
| **Shift** | | | |
| Shift | 564 (52.22) | 115 (20.39) | 449 (79.61) |
| Non-Shift | 516 (47.78) | 77 (14.92) | 439 (85.08) |
| **Profession, n (%)** | | | |
| Health Worker | 671 (62.13) | 126 (18.78) | 545 (81.22) |
| Non-Health Worker | 409 (37.87) | 66 (16.14) | 343 (83.86) |
| **Comorbid, n (%)** | | | |
| Comorbid | 177 (16.39) | 40 (22.60) | 137 (77.40) |
| Non-Comorbid | 903 (83.61) | 152 (16.83) | 751 (83.17) |
| **Asthma/PPOK, n (%)** | | | |
| Yes | 35 (3.24) | 11 (31.43) | 24 (68.57) |
| No | 1045 (96.76) | 864 (82.68) | 181 (17.32) |
| **Hematological Disorder, n (%)** | | | |
| Yes | 6 (0.56) | 3(50) | 3 (50) |
| No | 1074 (99.44) | 189(17.60) | 885 (82.40) |
| **Hypertension, n (%)** | | | |
| Yes | 107 (9.91) | 26 (24.30) | 81 (75.70) |
| No | 973 (90.09) | 166 (17.06) | 807 (82.94) |
| **Diabetes Mellitus (DM), n (%)** | | | |
| Yes | 26 (2.41) | 2 (7.69) | 24 (92.31) |
| No | 1054 (97.59) | 190 (18.03) | 864 (81.97) |

*adjusted for shift worker variable; **adjusted for health worker variable.

**Table 2** presents that health workers and non-health workers have a similar average age of (40 ± 10 years) and (41 ± 12 years), respectively. They also have similar positive duration (from positive PCR to negative PCR duration) of a mean of 23 ± 20 days for health workers and 21 ± 23 days for non-health workers. However, health workers were more likely to require hospital treatment (73.85% of confirmed cases) compared to non-health workers (26.15% of confirmed cases). None of the subjects died and only one required intensive care. Health workers had symptoms such as fever 23 (76.67%), respiratory system disorders 37 (69.81%), and anosmia 30 (81.08%) at higher rates compared to non-health workers. The results of multivariate analysis showed shift work was the only factor affecting COVID-19 transmission among health workers with RR=1.45 [95% CI, 1.06-1.99].

The study analyzed the survival rate of 1080 hospital workers from March 2nd, 2020 to March 2nd, 2021 as shown in **Table 3**. The study found that 192 workers were diagnosed with COVID-19 with an incident rate of 0.0005149 per day. The incidence rate was higher for health workers (0.0005471) than for non-health workers (0.0004629). The study observed the workers for 365 days; the average observation time was 345.2593 days. No median survival rate was found because the number of COVID-19 cases did not reach 25% of the total employees at the end of the observation period. 192 subjects tested positive, with a Prevalence Rate of 0.0005149 per day, or 5 cases per 10,000 person-days. If 10,000 people were observed in 1 year there would be 5 workers who tested COVID-19 positive. Health workers have a 0.0005471 higher incidence rate compared to non-health workers 0.0004629. There was no median survival rate in this study because, until the end of observation, the number of subjects with an event (COVID-19) from all employees (observation subjects) did not reach 25%.

The survival probability of the non-shift workers until the end of the observation results was higher, namely 84.93% [95% CI, 0.81-0.87] compared to Shift Workers at 79.61% [95% CI, 0.76-0.82] was regarded as statistically significant (p=0.023). Employees' profession variable (Health Worker or Non-Health Worker) shows cumulative survival probability of non-health workers until the end of the observation results was higher i.e.: 83.86% [95% CI, 0.79-0.87] compared to Health Workers at 81.22% [95% CI, 0.78-0.83], with p=0.240, indicating no statistical difference. For the age group variable, employees aged up to 40 years until the end of the observation showed slightly higher i.e.: 83.16% [95% CI, 0.80-0.85]; compared to employees aged over 40 years 80.72% [95%

**Table 2.** Data by profession of respondents.

| Variables | Health Worker n = 126 (65.62%) | Non Health Worker n = 66 (34.38%) |
|---|---|---|
| **Age, Mean ± SD** | 40±10 years | 41±12 years |
| ≤ 40 years | 73 (65.18%) | 39 (34.82%) |
| >40 years | 53 (66.25%) | 27 (33.75%) |
| **Positive mean duration** | 23±20 days | 21±23 days |
| **Needed hospital care, n (%)** | 48 (73.85) | 17 (26.15) |
| **Complaints, n (%)** | | |
| Fever | 23 (76.67) | 7 (23.33) |
| Respiratory disorder | 37 (69.81) | 16 (30.19) |
| Anosmia | 30 (81.08) | 7 (18.92) |
| Myalgia | 9 (75) | 3 (25) |
| **Comorbid, n (%)** | 25 (19.84) | 15 (22.73) |
| Hypertension | 15 (42.31) | 11 (57.69) |
| DM | 2 (100) | 0 (0) |
| Asthma/PPOK/Allergy | 8 (72.73) | 3 (27.27) |
| Hematological disorder | 1 (33.33) | 2 (66.67) |
| **Reason for PCR, n (%)** | 66 (61.68) | 41 (38.32) |
| Close contact at the hospital | 13 (61.9) | 8 (38.1) |
| Close contact with the family Suspect | 42 (75) | 14 (25) |
| Hospital routine screening | 5 (62.5) | 3 (37.5) |

CI, 0.76-0.84]. However, the difference was not statistically significant (p=0.296). Analysis was not carried out for the gender variable since most of them were female. The Cox Regression risk analysis resulted in HR = 1.43 [95% CI, 1.06-1.94] p=0.019 for the Work Shift variable, implying the presence of a statistically significant difference in risk between the Shift Workers group and non-Shift workers. For employee profession variables (health workers vs. non-health workers), HR=1.11; [95% CI, 0.82-1.51]; p = 0.476 shows that there is no statistically significant difference in the risk of COVID-19 transmission rate between the groups.

In the age group variable, HR = 1.26 [95% CI, 0.94-1.70] p = 0.112 indicates that there is no statistically significant difference in the risk of COVID-19 infection among employees aged below and older than 40 years. The Goodness-of-Fit (GOF) results as shown in Table 3 conform to the proportional hazards (PH) assumption with p>0.05 proportional hazards (PH) values: Shift variable p=0.079 (p-value>0.05), health worker variable p=0.101 (p-value>0.05), age group variable p-value=0.947 (p-value>0.05).

The survival plot graph above shows that the cumulative probability of survival for the Non-Shift Workers and non-health workers groups was higher than for the Shift Workers and health workers.

The Log-log Survival curve and the expected-observed graph of three variables are parallel, thereby PH assumption is fulfilled based on the shift variable, health worker variable, and the age group variable.

Similar to the results of the Kaplan-Meier (KM) approach, the Log-log Survival curve of the Shift variable (shift code) and age group variable (usage) is parallel (consistent), showing that the assumptions based on the results of the Goodness-of-fit graph (**Figure 3**) are fulfilled. Whilst the health worker variable may not meet the PH assumption, Extended Cox analysis was used.

The Extended Cox model found that the health worker variable did not meet the Proportional Hazard (PH) assumption with a function of time or ln(t) based on the 210th day time cut point (t=210) determined from Kaplan Meier Log-log Survival Curves. A double Heaviside analysis was performed and followed by exponential calculations. The hazard ratio (HR) for Health Workers (1) versus Non-Health Workers (0) of <210 days g1(t) = 1, while g2(t) = 0

**HR =exp[0.036*g1(t)+ 0.128*g2(t)]**

HR = exp[0.036] = 1.03, that employees in the Healthcare group have a risk of 1.03 times higher [95%CI; 0.58-1.88] than the Non-Health Workers group on less than 210 days of observation.

HR Health Workers (1) vs Non-Healthcare Workers (0) at <210 days at >=210 days g1(t)=0, while g2(t)=1

**HR = exp[0.036*g1(t)+ 0.128*g2(t)]**

HR = exp [0.128] = 1.13 shows that employees in the health care group are at

**Table 3.** Survival probability based on patients' characteristics.

| Variables | Survival Cumulative | LogRank | PH Assumption | Hazard ratio |
|---|---|---|---|---|
| **Type of worker** | | | | |
| Shift Worker | 79.61% [95% CI; 0,76 – 0,82] | p=0.023 | 0.079 | HR=1.43; [95% IK 1.06-1.94]; p=0.019 |
| Non-Shift Worker | 84.93%, [95%IK; 0.81-0.87] | | | |
| **Profession** | | | | |
| Health Worker | 81.22%, [95%IK; 0.78-0.83] | p=0.240 | 0.101 | HR=1.11; [95%IK 0.82-1.51]; p=0.476 |
| Non-Health Worker | 83.86%, [95%IK; 0.79-0.87] | | | |
| **Age** | | | | |
| ≤ 40 years | 83.16%, [95%IK; 0.80-0.85] | p=0.296 | 0.947 | HR=1.26; [95%IK 0.94-1.70]; p=0.112] |
| >40 years | 80.72%, [95%IK; 0.76-0.84] | | | |

1.13 times higher risk [95%CI; 0.81-1.62] of contracting COVID-19 compared to the Non-Health Workers group for more than 210 days of observation and so on.

Even though the GOF graph indicates a non-parallel figure, after calculating double Heaviside, it turns out that the risk before and after 210 days was not significantly different. It can be understood that the exposure to COVID-19 based on the health worker variable remained constant during the 1 year observation period.

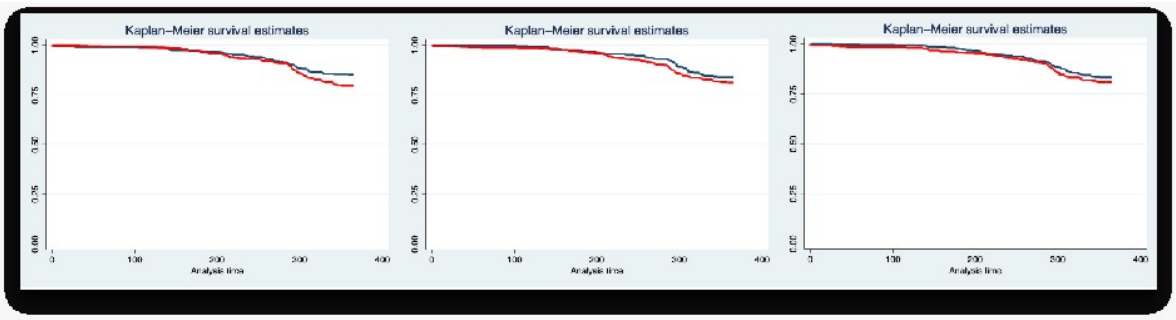



**Figure 1.** Graph of the cumulative probability for the incidence of COVID-19 survival on the shift variable (figure 1a), profession variable or health worker vs. non-health worker (figure 1b), and age group up to 40 years and over 40 years old

Description of images from left to right,
Figure 1a shift variable, the blue line Non-Shift worker, the red line Shift worker Figure 1b profession variable, the blue line Non-HCWs, the red line HCWs
Figure 1c age group variable

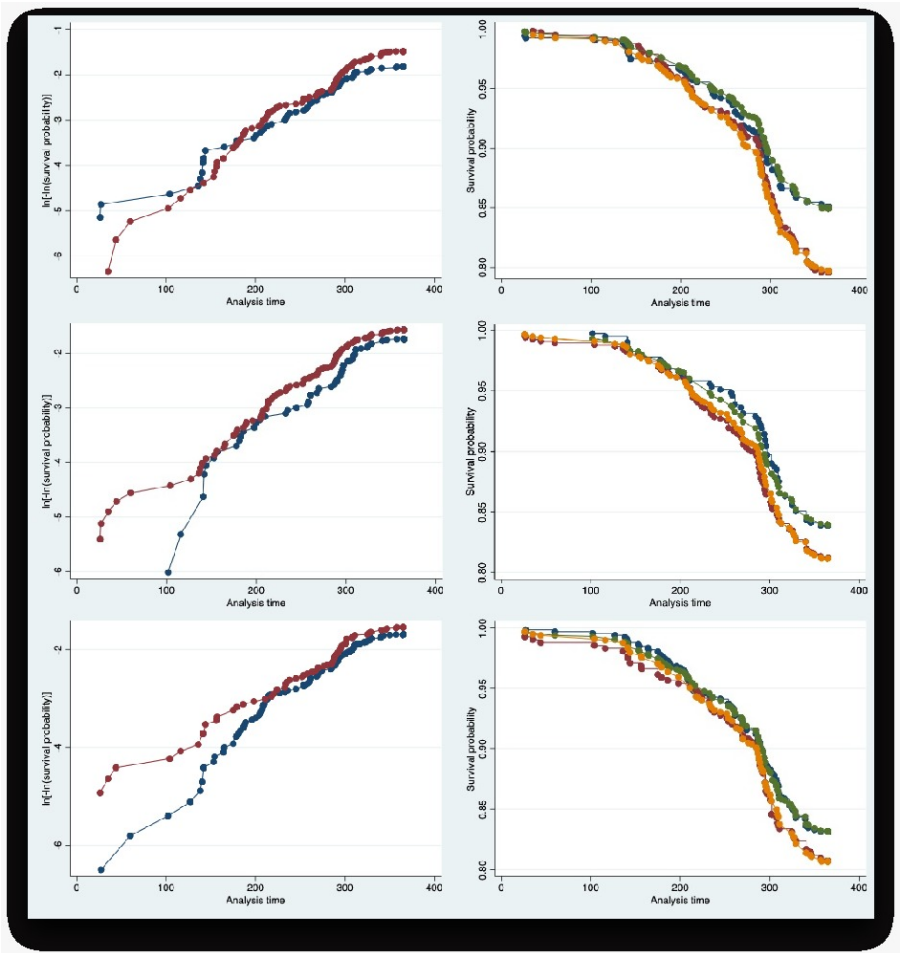



**Figure 2**. Log-log graph and The Expected-Observed graph.

Description of images from left to right, top to bottom
Figure 2(a) The Log-log Survival curve (aii) The Expected-Observed graph of shift variable, the blue line Non-Shift worker, the red line Shift worker
Figure 2(bi) The Log-log Survival curve (bii) The Expected-Observed graph of profession variable, the blue line Non-HCWs, the red line HCWs
The Log-log Survival curve and the Expected-Observed graph of three variables are parallel which shows that the PH assumption is fulfilled based on the Shift variable (figure 2a), profession or HCW variable (figure2b), and the age group variable (figure 2c)
Figure 2(ci) The Log-log Survival curve (cii) The Expected-Observed graph of age group variable, the blue line up to 40 years, the red line over 40 years old

## DISCUSSION

Most of the confirmed COVID-19 cases were employees at the age of <40. This finding is similar to the one of Diana, et.al and the prevalence of COVID-19 cases in Indonesia where almost one-third are in the 31-45 years age group (29.3%).[8] Female health workers have a higher transmission rate.[4,9,10] CDC also reported the median age of health workers confirmed COVID-19 is 42 years (interquartile range [IQR] = 32-54 years), 6,603 (73%) of whom were female. The data also confirmed that most of the health workers (6,760, 90%) were not hospitalized and the course of the disease appears to be milder, where only 1 person required intensive care.[5] Results of our study showed that health workers and non-health workers have the same probability of contracting COVID-19. Moreover, health workers and non-health workers who work in shifts with longer working hours (>38 hours a week) have a greater risk of contracting COVID-19. Employees with comorbid respiratory system disorders such as asthma, and chronic obstructive pulmonary disease are also at higher risk.

Although several studies have shown that major comorbidities such as hypertension and DM have a greater risk of being affected by COVID-19.[8,11,12] The Systematic Review results showed 372 articles that described comorbidities of 161,271 confirmed COVID-19 patients, where asthma was reported as a premorbid condition in only 2,623 patients or 1.6% of all patients. From a global asthma prevalence of 4.4%, the article concluded that asthma is not a major premorbid that contributes to the rise in COVID-19 cases. It is also possible that researchers or clinicians may lack detail or description about the pre-morbidities in COVID-19 patients.[13]

Our study found that employees with comorbid hematological disorders such as Thalassemia Beta Minor (3 people) and Hypercoagulation (3 people) are at greater risk of being impacted by COVID-19. Three of the 6 employees were confirmed positive for COVID-19. COVID-19 patients with hematologic disease can experience substantial morbidity and mortality. The annual meeting of the American Society of Haematology (ASH) reported an overall mortality of 28% for the first 250 patients admitted to ASH. Research Collaborative COVID-19 Registry for Haematology that the mortality or morbidity of COVID-19 stated that patients with hematological disorders had worse prognosis and most often were in acute leukemia, non-Hodgkin's lymphoma, and myeloma or amyloidosis. Overall, these findings support the consensus that mortality and morbidity related to COVID-19 significantly indicate the presence of withhold intensive therapies in patients with hematological disorders, therefore further studies are needed following the change in the direction

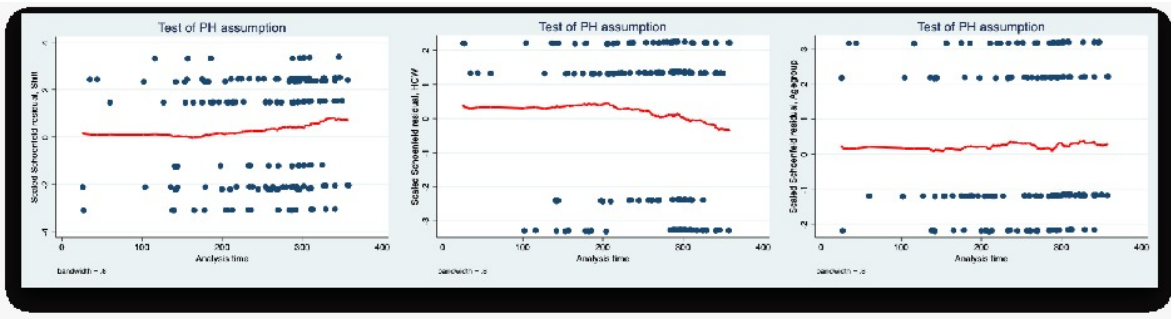



**Figure 3**. Goodness-of-fit graph.
Description of images from left to right, Figure 3a Goodness-of-fit graph of shift variable, Figure 3b, Goodness-of-fit graph of profession variable, Figure 3c Goodness-of-fit graph of age group variable

of treatment for underlying diseases. The findings of this registry are important to better understand how SARS-CoV-2 affects not only patients with hematological disease but also individuals who develop hematological complications related to COVID-19. However, it was also mentioned that the findings were limited due to the heterogeneity of the disease, symptoms, and treatments registered in the registry data. There is a need for research with more data to clarify these findings.[14]

Health workers confirmed with COVID-19 have different characteristics compared to the general population. A meta-analysis found that of 3,111,714 global COVID-19 cases, men have higher odds of being admitted to the ICU and of dying from COVID-19, even though the proportion of men and women confirmed with the disease was similar. Men have almost 3 times the odds compared to women and they need to be admitted to the Intensive Care Unit (ICU) with a higher risk of mortality. Gender differences will have important implications in clinical management and mitigation strategies. Since the location of this study is a maternity and children's hospital, male patients or male employees who tested positive for COVID-19 were referred to the COVID-19 Referral Hospital. In the United States, several pieces of literature show that the majority of confirmed health workers were female nurses and female nurse assistants.[4] Research shows that health workers have higher morbidity and mortality rates than non-health workers.[4] Yet, this finding should be confirmed in other studies involving more hospitals in Indonesia. All employees, both health workers and non-health workers must apply the appropriate Personal Protective Equipment (PPE) as they are often in close contact with COVID-19 patients. Health protocol adherence is crucial, especially when people are not at home. Health protocol compliance is a major factor that can help hold back the transmission of COVID-19.

Our study identified some common characteristics between health workers and non-health workers who were confirmed positive for COVID-19. One characteristic was the duration of positivity, with an average of 23 days for health workers and 21 days for non-health workers, from the time they received a positive PCR result to a negative result. Although the number of health workers confirmed with COVID-19 in Indonesia is high due to their potential exposure, the data showed that the possibility of infection was similar for both groups. Employees who provide direct medical services had the highest proportion of COVID-19 impacts. This highlights the importance of proper use and disposal of Personal Protective Equipment (PPE) in hospitals, as all patients, visitors, and employees have the potential to become asymptomatic confirmed cases. The 5M protocol must be mandatory for all hospital employees and visitors to ensure their safety, which includes wearing masks, washing hands with soap and running water, maintaining distance, avoiding crowds, and limiting mobility and interaction. The study also found that most cases were detected through contact tracing or close contact at the workplace and that most employees were confirmed to be asymptomatic. The majority of symptomatic employees reported fever and respiratory system disorders, with a higher incidence among health workers compared to non-health workers, which is in line with research by Dionita et al. in the general population of Indonesia.[8] Comorbidities such as hypertension and diabetes mellitus were dominating, similar to results from other studies conducted in the general population and among health workers.[8–10,15]

A Cox proportional hazards regression model analysis was performed, indicating no significant difference in cumulative survival between health workers and non-health workers, or between employees aged 40 and under and those over 40. However, a difference was observed between shift and non-shift workers, where longer working hours related to a higher likelihood of contracting COVID-19. Social-behavioral and cultural factors may also affect this condition. The longer an individual stays outside their home, the higher their risk of contracting the virus. However, with a better understanding of COVID-19 transmission and the vaccination since February 2021, the number of infected health workers has reportedly decreased. Further

research is necessary to compare the number of infections before and after vaccination.

Most COVID-19 infection cases in health workers are severe and the scarcity of personal protective equipment (PPE) is the most infection-related factor. The other risk factors of COVID-19 infection in health workers are work overload, inadequate or non-usage of PPE and poor hand hygiene, close contact with potentially infected people, the risk of aerosol-generating procedures, and late diagnosis of COVID-19, and inadequate air renovation in the negative pressure room. Also, the overload of the health system is an important factor for COVID-19 infection. As an example, the occupational medicine department in Spain was overwhelmed due to the COVID-19 pandemic, therefore both physicians and nurses from the different departments had to manage the pandemic. The survival rate was affected by several factors. Another study stated that age, gender, body mass index, and three respiratory symptoms affect the speed of negativisation of the PCR result The presence of dry cough and dyspnea can decrease the negativitasion rate of positive PCR result. Therefore, it is important to make strategies for the usage of PPEs, adequate training, and reinforcement of PPE usage, eye protection, and the adoption of standard precautions.[15,16]

Our study has several limitations including a potential non-differential information bias due to insufficient information and the inability to distinguish between different types of work that may have direct patient contact, such as cleaning staff who are non-health workers but have close contact with patients. It is also not possible to specifically determine the impact of health workers who do not have direct contact with patients, such as doctors in supporting services. More detailed data on subgroups of health workers is needed, such as non-health workers who have daily direct patient contact. Additionally, this study is limited to maternity and children's hospitals that are located in the epicenter of the COVID-19 pandemic in Indonesia. Hence, the findings of this study may not be generalized to other healthcare facilities. Finally, this study also excluded outsourced employees who may also have direct contact with patients.

## CONCLUSION

In summary, health workers and non-healthcare workers have the same probability of being infected by COVID-19. Employees who work in shifts (work duration 38 hours/ week) have a greater probability of contracting COVID-19.

The results of the 1-year survival analysis showed no significant difference in the hazard ratio between health workers and non-health workers. However, workers who worked in shifts with an average working hour of 38 hours per week, showed a statistically significant difference in hazard ratio compared to non-shift workers. It is therefore crucial that surveillance programs at all health facilities are strengthened with adequate and sustainable strategies, such as timely testing and close contact tracing to test pre-symptomatic or asymptomatic cases, especially for employees who work in high-risk areas or are vulnerable (e.g. elderly or those with comorbidities). Establishing a standard protocol of PPE and PPE and personal hygiene training is necessary to decrease the transmission rate and increase the survival rate of infectious diseases in the hospital.

## ACKNOWLEDGMENTS AND FUNDING

We would like to thank Harapan Kita Hospital for allowing us to conduct the research there. The researcher declared having no conflict of interest. This research is an observational study using secondary data from a hospital.

## REFERENCES

1. Burhan E, Susanto AD, Nasution SA, et al. Pedoman tatalaksana COVID-19. 3rd ed. Jakarta: Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia; 2020. 149 p.
2. Kim J, Zhang J, Cha Y, et al. Advanced bioinformatics rapidly identifies existing therapeutics for patients with coronavirus disease-2019 (COVID-19). J Transl Med. 2020;18(1):257.
3. Presiden Republik Indonesia. Undang-Undang Republik Indonesia Nomor 36 Tahun 2014 Tentang Tenaga Kesehatan. Dewan Perwakilan Rakyat; 2014.
4. Kim R, Nachman S, Fernandes R, Meyers K, Taylor M, LeBlanc D, et al. Comparison of COVID-19 infections among healthcare workers and non-healthcare workers. Lazzeri C, editor. PLoS ONE. 2020;15(12):e0241956.

5. Burrer SL, De Perio MA, Hughes MM, et al. Characteristics of health care personnel with COVID-19 — United States, February 12–April 9, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(15):477–81.
6. Aditya NR, Prabowo D. IDI : Kematian tenaga medis Indonesia 3 besar di dunia. Kompas. 2021;15003431.
7. Kleinbaum D, Klein M. Survival analysis: A self-learning text. 3rd ed. New York: Springer; 2012. p. 700.
8. Karyono DR, Wicaksana AL. Current prevalence, characteristics, and comorbidities of patients with COVID-19 in Indonesia. J Community Empowerment for Health. 2020;3(2):77.
9. Lahner E, Dilaghi E, Prestigiacomo C, et al. Prevalence of Sars-Cov-2 infection in health workers (HWs) and diagnostic test performance: The experience of a teaching hospital in Central Italy. IJERPH. 2020;17(12):4417.
10. Teleman MD, Boudville IC, Heng BH, Zhu D, Leo YS. Factors associated with transmission of severe acute respiratory syndrome among health-care workers in Singapore. Epidemiol Infect. 2004;132(5):797–803.
11. Guan W jie, Liang W hua, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547.
12. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069–76.
13. Mendes NF, Jara CP, Mansour E, Araújo EP, Velloso LA. Asthma and COVID-19: a systematic review. Allergy Asthma Clin Immunol. 2021;17(1):5.
14. MDedge Hematology and Oncology. COVID–19–related outcomes are poor for patients with hematologic disease in the ASH registry. MDedge Hematology and Oncology. 2021;2.
15. Mahajan NN, Mathe A, Patokar GA, et al. Prevalence and clinical presentation of COVID-19 among healthcare workers at a dedicated hospital in India. Journal of The Physicians of India. 2020;68:16=21.
16. González Martin-Moro J, Chamorro Gómez M, Dávila Fernández G, et al. Survival analysis of time to SARS-CoV-2 PCR negativisation to optimise PCR prescription in health workers: the Henares COVID-19 healthcare workers cohort study. Occup Environ Med. 2021;78(9):638–42.

# Kikuchi-Fujimoto Disease Preceding Overlap Syndrome of Sjögren's Syndrome and Systemic Lupus Erythematosus: Literature Review Based on a Case Report

*Cindy[1]*, Suryo Anggoro Kusumo Wibowo[2], Anna Ariane[2], Rudy Hidayat[2]*

[1]Fellow of Rheumatology, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Corresponding Author**:
*Cindy, MD. Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: cindy_oey@yahoo.com.*

## ABSTRACT

*Kikuchi-Fujimoto disease (KFD) is a benign, self-limiting histiocytic necrotizing lymphadenitis systemic disorder with unknown etiology. KFD has been known for half a century, but difficulties in distinguishing it remain. Its diagnostic significance is related to the increasing prevalence of KFD with autoimmune diseases in various timeframes. Systemic lupus erythematosus (SLE) is the most prevalent autoimmune connective tissue disease (AICTD) appearing alongside KFD. An 18-year-old female presented with acute muscle weakness, shortness of breath, fever, and significant weight loss for 5 months before admission. Pain and morning joint stiffness had been felt for 9 months. One year ago, she lumped her right neck and was diagnosed with KFD from the excision biopsy and immunohistochemical staining (CD68). Creatine-kinase enzymes and C-Reactive protein were elevated with a high anti-Ku and anti-Jo-1 negative level. There was a low level of complements, high anti-nuclear antibody titer, with positive anti-SS-A. Sialometry and Schirmer test showed reduced salivary and lacrimal gland production. We diagnosed this patient as having an overlap syndrome preceded by KFD. The AICTD involved was Sjögren's syndrome and SLE. Although KFD is considered a self-limiting disease, its occurrence should be noticed regarding the possibility of other autoimmune conditions. KFD usually coincides with AICTD, although it could also precede or occur afterward. This case is reported to raise awareness of the overlap syndrome preceded by KFD.*

***Keywords:*** *Kikuchi-Fujimoto disease, Overlap Syndrome, Sjögren's Syndrome, Systemic Lupus Erythematosus, Inflammatory Myositis.*

## INTRODUCTION

Kikuchi-Fujimoto disease (KFD) has an unknown etiology.[1,2] There were difficulties in distinguishing KFD from other lymph node diseases.[3] The occurrence of KFD should increase our awareness since it could coincide (preceding, simultaneous, or after) with autoimmune diseases.[4] Systemic lupus erythematosus (SLE) is the most prevalent AICTD with KFD.[5] Still, there are also other AICTDs such as Sjögren's syndrome (SjS), polymyositis, vasculitis, and other autoimmune diseases, such as thyroiditis, antiphospholipid syndrome, which have been reported with KFD.[6–8] Our patient had an overlap syndrome consisting of Sjögren's syndrome and SLE preceded by KFD. There is no specific treatment for KFD; corticosteroid treatment was necessary in only 16% of the cases; and

immunosuppressants have been recommended as an adjunct to corticosteroids in severe, life-threatening diseases.[5] However, there would be a huge therapeutic difference if AICTD is diagnosed in KFD patients. Thus, we reported this case to raise the awareness of AICTD preceded by KFD beyond SLE. The physicians should notice the occurrence of KFD regarding the possibility of autoimmune diseases that will lead to further investigation to obtain the right diagnosis and treatment.

## CASE ILLUSTRATION

An 18-year-old female was admitted to the hospital due to muscle weakness since three weeks before admission. She also complained about fever, cough, shortness of breath, swallowing difficulty, and weight loss (6 kg in the last 5 months). Nine months before, she began to feel dryness in her eyes and mouth, and pain on her wrists, elbows, and fingers accompanied with morning stiffness. In the four months before admission, she was prescribed 8 grams of methylprednisolone thrice daily. The patient has no other known comorbidities nor a similar family history.

One year before admission, she had a painful lump on her right neck with no other symptoms, as seen in **Figure 1**. She underwent surgery and received no further treatment because it was considered benign and self-limiting. The result of the biopsy followed by histologic and immunohistochemistry smear showed reactive chronic granulomatous lymphadenitis (non-neoplastic) lesion, positive for CD 3, CD 68, CD 10, and KI-67 supporting Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis) like seen in **Figure 2**.

Our patient was underweight and had a motoric weakness (tetraparesis), especially on her proximal limbs (motoric examination of upper limbs 4433/3344 and lower limbs 4432/2344). There was tenderness in her metacarpophalangeal joints (MCP 2-4 bilateral) as seen in **Figure 3** and metatarsophalangeal joints (MTP 2-5 bilateral), right elbow joint,

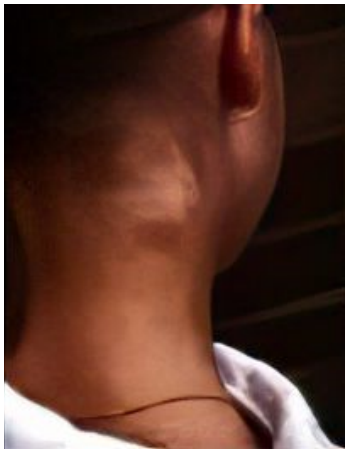


**Figure 1. L**ump on the patient's right neck

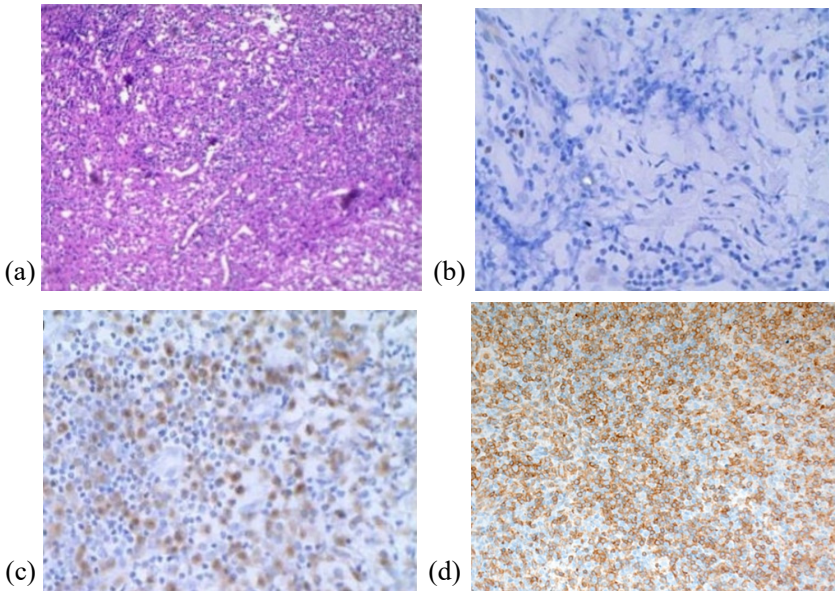



**Figure 2.** Immunohistochemical staining of cervical lymph node demonstrating (a) hematoxylin-eosin staining (b) Ki67, (c) CD68 (adapted from Khan et al[9]), and (d) CD3 (adapted from Alshieban et al[10])

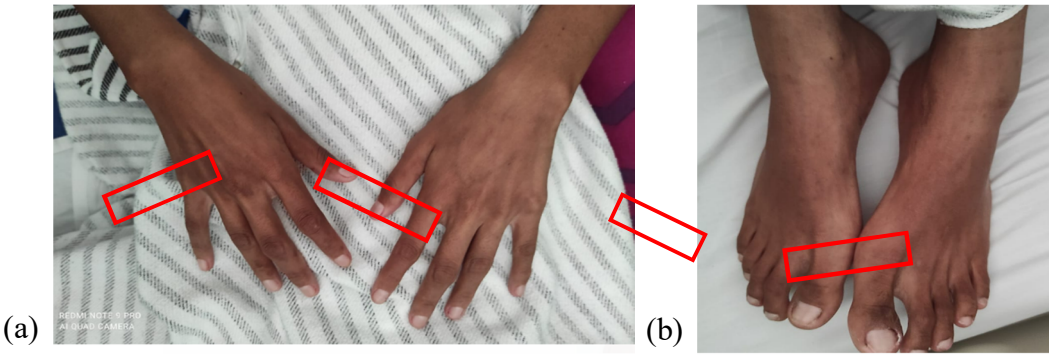


**Figure 3.** Joint tenderness in (a) metacarpophalangeal and (b) metatarsophalangeal (b)

right shoulder joint, and both knees. Pain and hypertonus were felt in her upper quadrants and periumbilical abdomen area, without spasticity. Contracture and atrophy of upper and lower limb muscles can be seen in **Figure 4.**

Transaminase enzymes (Aspartate aminotransferase 103 U/L; Alanine aminotransferase 373 U/L), Lactate Dehydrogenase / LDH (1280 U/L), C-Reactive Protein (29.8 mg/L), Creatine-kinase (1970 U/L) were elevated with a high level of anti-Ku (167 U, strong positive). Electromyography and nerve velocity test examination found a myogenic lesion without overt myotonic and cramps. A muscle biopsy at her right hamstring muscle revealed fibrous tissue partly fibrotic and lipoid, and no striated muscle was found. Blood complements (C3 and C4) were lower than normal (32 and 8 mg/dL), but anti-ds-DNA was within the normal limit (9.4 IU/ml). D-dimer was elevated (8700 ug/L), with Anti Cardiolipin antibody IgM positive in 2 examinations (12 weeks interval), and Anti-nuclear antibody immunofluorescent (ANA IF) positive (>1/1000, nuclear membrane/rim pattern) with a positive result of anti-SS-A (++) and a borderline result of anti-ribosomal protein (+). She also had xerostomia (unstimulated salivary flow rate (USSFR) < 0.02 ml/min) and xerophthalmia (Schirmer test on her right eye 0 mm, left eye 2 mm).

Chest CT scan with IV-contrast showed multiple lymphadenopathies in the mediastinum (around 2.4 cm), bilateral pleural effusion, partial atelectasis at bilateral inferior lobes, minimal ground glass opacity, and consolidation at bilateral posterobasal, fibrosis at left lung (segment 5&9) and cardiomegaly accompanied with pericardial effusion as seen in **Figure 5**.

Echocardiography also confirmed mild pericardial effusion with normal ejection fraction. The fiberoptic evaluation of swallowing (FEES) result was moderate-severe neurogenic dysphagia at the pharyngeal phase with

**Figure 4.** Contracture and atrophy of (a) upper limb muscle and (b) lower limb muscle.

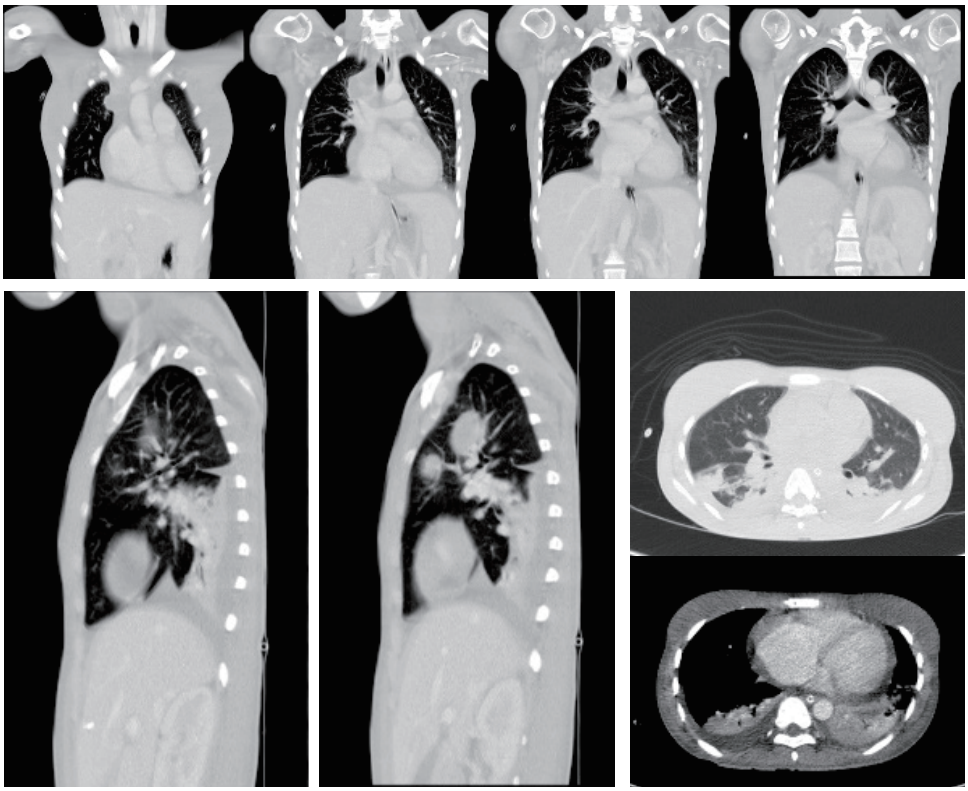


**Figure 5.** Chest CT Scan with IV contrast showed multiple lymphadenopathies in the mediastinum (around 2.4 cm), bilateral pleural effusion, partial atelectasis at bilateral inferior lobes, minimal ground glass opacity, and consolidation at bilateral posterodorsal, fibrosis at left lung (segment 5&9) and cardiomegaly accompanied with pericardial effusion

laryngopharyngeal reflux. She had a positive antiphospholipid antibody and a high probability of a thromboembolic event (Padua Score[11] 4).

We considered that inflammatory myositis, interstitial lung disease, dysphagia, and serositis in this patient were part of an overlap syndrome. Thus, we diagnosed this patient with an Overlap Syndrome (Sjögren's Syndrome and Systemic Lupus Erythematosus) preceded by Kikuchi-Fujimoto Disease. She was treated with 500 mg IV methylprednisolone on 3 consecutive days, 500 mg IV cyclophosphamide every 2 weeks (6 cycles), hydroxychloroquine 200 mg o.d., cotrimoxazole 960 mg o.d. on alternate days, and other symptomatic therapies including artificial tears and mouthwash. We also gave her clopidogrel 75 mg o.d oral and tapered the steroid dose to 35 mg (1 mg/kgBW) o.d oral prednisone for two weeks. Neurologists gave baclofen 10 mg b.i.d oral and she had a routine program for muscle strengthening, mobilization training, and orometer physiotherapy.

One month later, her condition gradually improved, and was able to eat orally. Her joint and muscle pain had also resided. After being treated with 6 doses of cyclophosphamide, her motoric became fully recovered in four extremities with Creatine-kinase level decreasing to 657 U/L, C-Reactive Protein 15 mg/L, and SLEDAI score 4 (low disease activity).

## DISCUSSION

Kikuchi-Fujimoto disease (KFD) was first reported in Japan in 1972 and manifested as cervical subacute necrotizing lymphadenitis.[1,2] This disease misdiagnosis rate is up to 40%.[3] KFD is characterized by regional lymphadenopathy with tenderness, predominantly in the cervical region, accompanied by mild fever and night sweats. Posterior cervical nodes are affected in about 80% of cases.[12] Fever (35%), fatigue (7%), joint pain (7%), erythematous rashes (10%), arthritis (5%), hepatosplenomegaly (3%), leucopenia (43%), high acute phase reactants (40%), and anemia (23%) are the most common findings.[5] Diagnostic laboratory and radiologic

test findings are nonspecific.[13] Predominantly 77% were female and 70% were younger than 30 years old.[5]

The cause of KFD is unknown and might be an exaggerated T cell-mediated immune response in genetically susceptible people to nonspecific stimuli. The incidence of DPA1*01 and DPB1*0202 alleles of HLA antigen LAHLA is significantly higher in patients with KFD than in healthy controls. These genes are extremely rare among Caucasians but relatively common among Asians. The tubular-reticular structures in the cytoplasm of stimulated lymphocytes and histiocytes have been seen in patients with KFD, which are described in endothelial cells and lymphocytes of patients with SLE and other autoimmune disorders.[13]

KFD is diagnosed based on an excisional biopsy of affected lymph nodes showing necrosis and karyorrhexis with paucity or absence of granulocytes.[5,13] The histiocytes express histiocyte-associated antigens, such as lysozyme, myeloperoxidase (MPO), and CD68.[13] This patient has had a typical clinical presentation of right single cervical lymphadenopathy proven by immunohistochemical staining showing histiocytic necrotizing lymphadenitis, reactive chronic granulomatous lymphadenitis (non-neoplastic) lesion, positive for CD 3, CD 68, CD 10, and KI-67 supporting Kikuchi-Fujimoto disease 1 year before muscle weakness and 7 months before other AICTD symptoms.

The differential diagnosis of KFD may include toxoplasmic lymphadenitis, infectious mononucleosis, cat-scratch disease, and Hodgkin's lymphoma.[5] Tuberculosis, plasmacytoid T-cell leukemia, Kawasaki disease, and myeloid tumor are also included in the differential diagnosis.[14] There is no specific treatment for KFD, and it mostly lasts 1 to 3 months, up to 1 year.[3] The disease was self-limiting in 156 cases (64%), and corticosteroid treatment was necessary in 16 cases (16%).[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate lymph node tenderness and fever. Indications for corticosteroids include neurologic involvement, hepatic involvement, and severe lupus-like syndrome. Immunosuppressants can be used as an adjunct to corticosteroids in severe disease. Intravenous immunoglobulin (IVIG) is chosen in a few cases of refractory KFD.[13] The mortality rate of KFD alone is 2.1%.[5]

KFD is not an independent condition and most likely develops due to an autoimmune mechanism.[15,16] The diagnosis of KFD can precede, postdate, or coincide with the diagnosis of SLE.[13] Zaccarelli et al. found out that autoimmune disease may be "preceding" (11 cases) "simultaneous" (20 cases) or "post" (8 cases) KFD. Also, the autoimmune disease can be present with a complete clinical picture or only with the presence of autoantibodies.[4] Sopena et al. followed 20 KFD patients and autoimmune diseases were detected in 9 women (53%): 2 patients with SLE before, 1 patient simultaneous, and 1 patient after KFD, 2 patients developed primary SjS after KFD, 1 thyroiditis before KFD, 1 SLE-like, and 1 antiphospholipid antibodies after KFD. Leukocytoclastic vasculitis was found in 2 patients; one of them eventually developed SLE. In females, painful adenopathies, and cytopenias are significantly associated with autoimmune diseases.[8] There was a case reported by Radfar et al. of a patient with KFD who developed SjS 8 years after diagnosis of KFD.[6] There is also a report from China of two patients, a 14-year-old boy with SLE and secondary SjS, and a 9-year-old boy with primary SjS who was diagnosed after 3 years of disease duration. Both had KFD.[6,17] Jun et al. have also found 7 case reports in which KFD and SjS were diagnosed simultaneously in 1 patient, KFD preceding SjS (312 months latency) in 1 patient, and KFD after SjS (2-120 months latency) in 5 patients.[18] We found only one case of KFD and PM reported by Wilkinson and Nichol of a 41-year-old Indian woman diagnosed with KFD who subsequently developed polymyositis with pulmonary involvement.[7] There are two cases of KFD preceding Mixed Connective Tissue Disease (MCTD) reported by Cheng et al. and Ogata et al.[15,19]

We found a case report of an overlap syndrome (RA and SLE) that concurred with KFD, reported by Campbell et al.[21] We report a case of KFD preceding overlap syndrome that consists of Sjögren's Syndrome, SLE, and

inflammatory myositis.

When the patient was admitted to our hospital, she had tetraparesis especially on her proximal limbs, accompanied by pain and hypertonus on her upper quadrants and periumbilical area of the abdomen, without spasticity. Stiff-person syndrome (SPS), characterized by progressive rigidity and muscle spasms affecting the axial and limb muscles, has been ruled out by neurologists. Most patients with SPS have antibodies directed against the glutamic acid decarboxylase.[21] The patient was checked for that antibody and was negative (<5 IU/mL). Electromyography and nerve velocity test examination were conducted, supporting inflammatory myositis that did not fulfill the criteria for Polymyositis (Anti-Jo-1 negative, EULAR/ACR classification criteria for IIM 2017 score 4.4).[22,23] Idiopathic inflammatory myopathy (IIM) is the umbrella term that includes dermatomyositis (DM), polymyositis (PM), overlap myositis (OM), inclusion body myositis (IBM), and necrotizing autoimmune myopathy (NAM), also known as immune-mediated necrotizing myopathy.[24] PM and DM are relatively rare (<10 per 100,000 individuals).[25] An analysis of six large cohorts showed that 6.5-36.7 % of IIM presented as overlap syndrome (OS).[26] Patients with myositis overlap syndrome are almost always responsive to steroids.[25] Regarding the high level of anti-Ku in our patient, Sifuentes Giraldo et al. found out that Anti-Ku Antibodies are more common in overlap syndromes especially when myositis is present, and are associated with severe and corticoresistant ILD.[23]

This patient had Sjögren's syndrome (SjS) (ACR/EULAR 2016 classification criteria for Primary Sjögren's syndrome score 5).[26] Sjögren's syndrome (SjS) is a systemic autoimmune disease with antinuclear antibodies that are frequently detected (specifically anti-Ro/SS-A) and hypocomplementaemia. The symptoms are dominated by sicca syndrome caused by immune-mediated glandular involvement, accompanied by fatigue, musculoskeletal pain, and systemic features, complicated by lymphoma in 2-5% of patients.[26] The ACR/EULAR 2016 classification criteria for Primary SjS were fulfilled/scored 5 (Anti-SS-A positive, xerostomia, and xerophthalmia) in this patient.[12] The management is symptomatic treatment and broad-spectrum immunosuppression.[26]

The differentiation of KFD from SLE can be problematic because both can show similar clinical features.[27] In KFD, although there may be a decrease in C4, the RF and ANA studies are generally negative.[14] She had a history of fever, arthritis, serositis, ANA IF positive, and hypocomplementemia (ACR/EULAR 2019 SLE classification criteria scored 20).[28] SLE and SjS are related clinically and serologically. Anti-Ro (anti-SS-A) and anti-La (anti-SS-B) are found in both diseases.[6] Anti-U1RNP in this case was negative; and Systemic lupus erythematosus (SLEDAI 19, ACR/EULAR 2019 SLE classification criteria score 20).[28] Thus, she was diagnosed as OS with SjS and SLE as the AICTD involved. Inflammatory myositis, interstitial lung disease, dysphagia, and serositis also existed in this case as part of the overlap syndrome. The concept of OS implies the occurrence of two or more well-defined AICTDs in the same patient.[29] Patients may be presented with evidence of more than one disease simultaneously or they may develop different diseases sequentially.[26] OS is not frequent, and its descriptions in the literature are limited to a few case reports.[29] The management was based on its clinical features.[25]

The treatment of our case was aimed at severe SLE (serositis), inflammatory myositis, and interstitial lung disease; hence, we gave cyclophosphamide and a pulse dose of steroids, accompanied by symptomatic treatments.[30] We also have a special caution about the high risk of a thromboembolic event (immobilization state, high d-dimer, prolongation of aPTT, Padua score 4) and antiphospholipid antibody positive (in 2 examinations with a 12-week interval). Thus, we gave a prophylactic dose of unfractionated heparin and then switched to clopidogrel when discharged.

## CONCLUSION

KFD is a self-limiting disease whose occurrence should get special attention regarding the possibility of autoimmune conditions. Individuals with KFD should be examined

systemically, and they must be under regular follow-up to monitor the manifestations of AICTD. Although KFD usually co-occurs with AICTD, it could also occur before or after it. Systemic lupus erythematosus (SLE) is the most common AICTD found with KFD. This case is reported to raise the awareness of AICTD associated with KFD beyond SLE.

## REFERENCES


1. Kikuchi M. Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytes: a clinicopathological study. Acta Hematol Jpn. 1972;35:379-80.
2. Fujimoto, Y. Kozima, Y. Yamaguchi K. Cervical subacute necrotizing lymphadenitis: a new clinicopathologic entity. Naika. 1972;20:920-7.
3. Xu S, Sun W, Liu J. Kikuchi-Fujimoto disease: A case report and the evaluation of diagnostic procedures. BMC Oral Health. 2019;19(1):1-5. doi:10.1186/s12903-019-0920-4
4. Zaccarelli F, de Vincentiis M, D'Erme G, Greco A, Natalucci F, Fusconi M. Kikuchi-Fujimoto disease: a distinct pathological entity but also an "overlap" autoimmune syndrome - a systematic review. Curr Rheumatol Rev. 2022;(3 Sep).
5. Kucukardali Y, Solmazgul E, Kunter E, Oncul O, Yildirim S, Kaplan M. Kikuchi-Fujimoto disease: analysis of 244 cases. Clin Rheumatol. 2007;26(1):50-54. doi:10.1007/s10067-006-0230-5
6. Radfar L, Radfar M, Moser KL, Scofield RH. Kikuchi-Fujimoto disease in patients with Sjögren ' s syndrome. 2013;2013(January):32-36.
7. Wilkinson CE, Nichol F. Kikuchi-Fujimoto disease associated with polymyositis. Rheumatology. 2000;39(11):1302-1304. doi:10.1093/rheumatology/39.11.1302
8. Sopeña B, Rivera A, Vázquez-Triñanes C, et al. Autoimmune manifestations of Kikuchi disease. Semin Arthritis Rheum. 2012;41(6):900-906. doi:10.1016/j.semarthrit.2011.11.001
9. Khan AM, Ahmad M, Muhammad O, Taj S, Shiza ST. Kikuchi-Fujimoto disease in a young female: A case report and literature review. Cureus. 2021;13(11):11–4.
10. AlShieban S, Masuadi E, Alghamdi R, et al. Pathological features and clinical characteristics of Kikuchi-Fujimoto disease: A tertiary hospital experience in Riyadh, Saudi Arabia. Cureus. 2023;15(1).
11. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The Padua Prediction Score. J Thromb Haemost. 2010;8(11):2450-7. doi:10.1111/j.1538-7836.2010.04044.x
12. Bottai M, Tjärnlund A, Santoni G, et al. EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: A methodology report. RMD Open. 2017;3(2):1-10. doi:10.1136/rmdopen-2017-000507
13. Sifuentes Giraldo W., Bouruncel Alaluna C, Roy Ariño G, García Villanueva M., de La Puente Bujidos C, Gámir Gámir M. Autoimmune diseases associated with anti-ku antibodies: A retrospective case series. Ann Rheum Dis. 2016;75(Suppl 2):544-5. doi:10.1136/annrheumdis-2016-eular.2478
14. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol. 2017;69(1):35-45. doi:10.1002/art.39859
15. Amin R. Review Article Kikuchi -Fujimoto Disease-a Comprehensive Review. Bangladesh J Med. 2013;24:70-7.
16. Salah A, Al-Fadhli A. Kikuchi-fujimoto disease. Kuwait Med J. 2014;46(4):340-1. doi:10.5858/134.2.289
17. Ogata S, Bando Y, Saito N, Katsuoka K, Ishii M. Kikuchi-Fujimoto disease developed into autoimmune disease: A report of two cases. Mod Rheumatol. 2010;20(3):301-305. doi:10.1007/s10165-009-0269-7
18. Ghadiri N, Stanford M. Case of vaso-occlusive retinopathy in Kikuchi-Fujimoto and lupus overlap syndrome. BMJ Case Rep. 2021;14(5).
19. Lu, S. Zhang, J. Zhou, W. Wang X. Histiocytic necrotic lymphadenitis as an initial presentation in two children with Sjogren's syndrome and/or systemic lupus erythematous. Chinese J Contemp Pediatr. 2010;12(4):311-312.
20. Jun Z, Jun Y, Weng WW, Zhu YJ, Qiu H, Dong MJ. Kikuchi-Fujimoto disease associated with Sjogren's syndrome: A case report and review of the literature. Int J Clin Exp Med. 2015;8(10):17061-6.
21. Cheng CY, Sheng WH, Lo YC, Chung CS, Chen YC, Chang SC. Clinical presentations, laboratory results and outcomes of patients with Kikuchi's disease: Emphasis on the association between recurrent Kikuchi's disease and autoimmune diseases. J Microbiol Immunol Infect. 2010;43(5):366-371. doi:10.1016/S1684-1182(10)60058-8
22. Campbell T, Auer I, Martin L. A case of concurrent Kikuchi-Fujimoto disease and neuropsychiatric lupus in a patient with rheumatoid arthritis and systemic lupus erythematosus overlap syndrome. McMaster Univ Med J. 2019;16(1):1-5. doi:10.15173/mumj.v16i1.2026
23. Baizabal-Carvallo JF, Jankovic J. Stiff-person syndrome: Insights into a complex autoimmune disorder. J Neurol Neurosurg Psychiatry. 2015;86(8):840-8. doi:10.1136/jnnp-2014-309201
24. Ashton C, Paramalingam S, Stevenson B, Brusch A, Needham M. Idiopathic inflammatory myopathies: a review. Intern Med J. 2021;51(6):845-852. doi:10.1111/

imj.15358
25. Firestein GS. Firestein & Kelley's Textbook of Rheumatology. 10th ed. Elsevier; 2017.
26. Pepmueller PH. Undifferentiated connective tissue disease, mixed connective tissue disease, and overlap syndromes in Rheumatology. Mo Med. 2016;113(2):136-40.
27. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis. 2020;79(1):3-18. doi:10.1136/annrheumdis-2019-216114
28. Bosch X, Guilabert A. Kikuchi-Fujimoto disease. Orphanet J Rare Dis. 2006;1(1):3-5. doi:10.1186/1750-1172-1-18
29. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019;71(9):1400-12. doi:10.1002/art.40930
30. Aguila LA, Lopes MRU, Pretti FZ, et al. Clinical and laboratory features of overlap syndromes of idiopathic inflammatory myopathies associated with systemic lupus erythematosus, systemic sclerosis, or rheumatoid arthritis. Clin Rheumatol. 2014;33(8):1093-8. doi:10.1007/s10067-014-2730-z
31. Mok CC, Hamijoyo L, Kasitanon N, et al. The Asia-Pacific league of associations for rheumatology consensus statements on the management of systemic lupus erythematosus. Lancet Rheumatol. 2021;9913(21):1-15. doi:10.1016/s2665-9913(21)00009-6

# Spontaneous Rupture of Abdominal Aorta Pseudoaneurysm: a Case Report

*Dono Antono[1]*, David Hutagaol[2], Nindya PBS Utami[3], Jatmiko Gustinanda[3]*

[1]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Cardiothoracic Surgery, Department of Surgery, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Independent Scholar, Indonesia.

***Corresponding Author*:**
*Dono Antono, MD. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: dantonos@yahoo.com.*

## ABSTRACT

*Pseudoaneurysms are false aneurysms that mostly occur at the site of arterial injury. Pseudoaneurysm is the most frequent complication after catheter-associated interventions and occurs because of an insufficient closure of the puncture site. However, there are several reported cases of patients with pseudoaneurysm without a prior history of vascular intervention. We described a case of ruptured giant abdominal aortic pseudoaneurysm in a patient with no prior history of vascular intervention, with an initial complaint of abdominal pain. The patient successfully received EVAR therapy using a kissing graft*

***Keywords**: pseudoaneurysm, abdominal aorta, rupture.*

## INTRODUCTION

Pseudoaneurysms are false aneurysms that mostly occur at the site of arterial injury. Besides hematomas and arteriovenous fistulas, pseudoaneurysm is the most frequent complication after catheter-associated interventions and occurs because of an insufficient closure of the puncture site. The rate of pseudoaneurysm occurrence after diagnostic intervention varies between 0.06% and 0.18%. On the other side, the occurrence of pseudoaneurysm following therapeutic intervention ranges from 0.7% to 6.25%.[1] Pseudoaneurysm has pulsatile in and outflow of blood through the neck, thus providing risk to growth and rupture.

Here, we report a rare case of ruptured abdominal aortic pseudoaneurysm with no prior history of catheter-based intervention. This report aims to report the case with rare nature to give readers a new perspective.

## CASE ILLUSTRATION

A 48-year-old man with a history of diabetes mellitus and hypertension was referred to the emergency department by a peripheral hospital with the suspicion of an abdominal aortic aneurysm. The patient works as a police officer. Two weeks before admission, the patient presented with abdominal pain. The patient was hospitalized for twelve days and was observed with a suspected abdominal aortic aneurysm before being referred. At admission to the emergency department, the patient tested positive on the SARS-CoV2 screening swab test and was admitted to the isolation unit.

The patient underwent laboratory examination and CT angiography. Laboratory examination revealed normocytic normochromic anemia suspected to be caused by chronic disease, and hypoalbuminemia with bilateral pitting edema on lower extremities. CT angiography reported the finding of a giant abdominal aortic pseudoaneurysm rupture with the size of the sac 5.5 x 10.7 x 7.7 cm. The giant sac was pushing the middle part of the left ureter and resulted in left hydroureter and hydronephrosis.

Endovascular aneurysm repair (EVAR) was planned but after multidisciplinary discussion, it was decided to wait for the patient to test negative for SARS-CoV2 before doing the procedure. The patient underwent an angiography examination before the EVAR procedure. Angiography examination shows contrast leakage in the abdominal aorta.

The procedure was started with a cut down of the right and left femoral arteries, and continued with the insertion of a 6F sheath on the right femoral artery and 7F on the left femoral artery. The Pigtail 5F catheter was inserted through the left femoral artery and pushed into the abdominal aorta. Aortography and pressure measurement was conducted. Aortography revealed a leakage lesion on the distal abdominal aorta. The 6F sheath from the right femoral artery was changed into a SENTRANT 16F sheath, and an Amplatz extra stiff wire was inserted. Graft stent EVAR ENDURANT IL sized 16x13x82 mm was then inserted with the help of extra stiff wire Amplatz, and positioned throughout the lesion. The graft stent was deflated right at the lower bound of the left renal artery. Evaluation with aortography showed endo-leakage and the distal part of the graft stent which was not deployed perfectly in the bifurcation of the common iliac artery. Dilatation of the proximal and distal parts of the stent was performed using balloon RELIANT 12F. The procedure was continued with the insertion of stent BEGRAFT 7.0x57 mm throughout the right common iliac artery and BEGRAFT 8.0x57 mm in the left common iliac artery, both overlapping with the previous EVAR stent graft. BEGRAFT stents were deflated each at 13 atm and 12 atm for 60 seconds respectively (kissing graft). Aortography was performed and showed no endo-leakage. The procedure was ended with the suture of the right femoral area.

The patient showed stable condition with decreased bilateral pitting edema. However, the patient still suffered from flank pain suspected to be caused by a retroperitoneal abscess due to a hematoma, thus the patient was planned to undergo open abdominal surgery to evacuate the hematoma. Upon open abdominal surgery, the patient was stable and moved to the general ward.

## DISCUSSION

Pseudoaneurysm is frequently associated with arterial injury following a catheter-based diagnostic or therapeutic intervention. The rate of pseudoaneurysm occurrence after diagnostic intervention varies between 0.06% and 0.18%, meanwhile, rate of pseudoaneurysm following therapeutic intervention ranges from 0.7% to 6.25%. The most common site of pseudoaneurysm is femoral pseudoaneurysm due

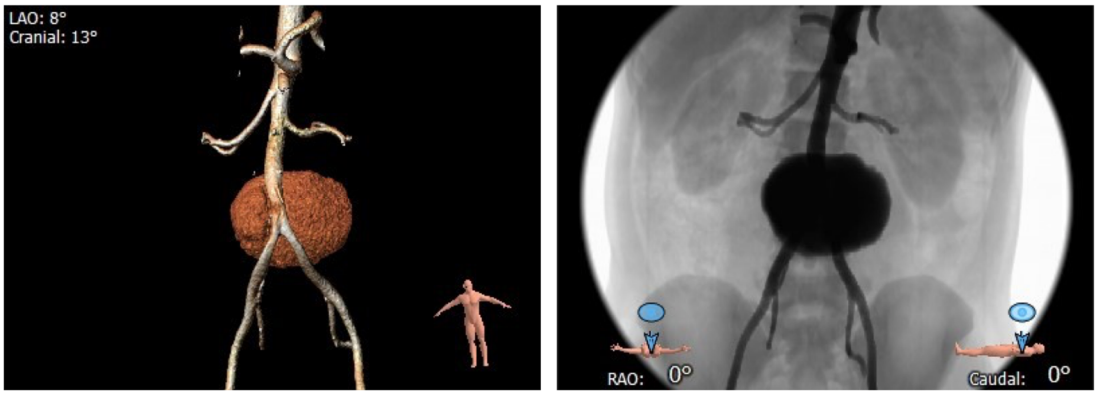



**Figure 1.** CT angiography showed a giant abdominal aortic pseudoaneurysm rupture with the size of the sac 5.5 x 10.7 x 7.7 cm.

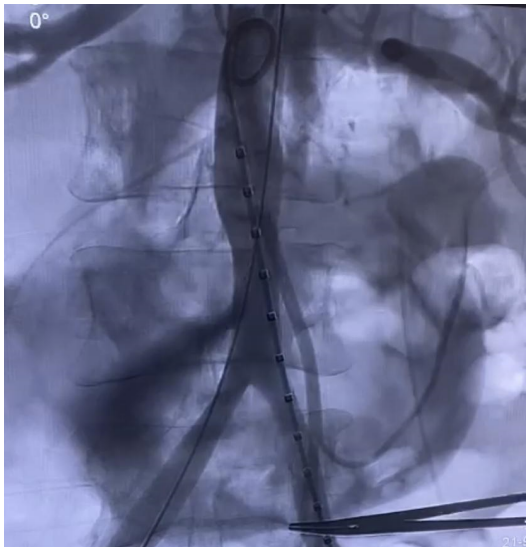



**Figure 2.** Angiography showed a giant abdominal aortic pseudoaneurysm rupture with the size of a sac 5.5 x 10.7 x 7.7 cm.

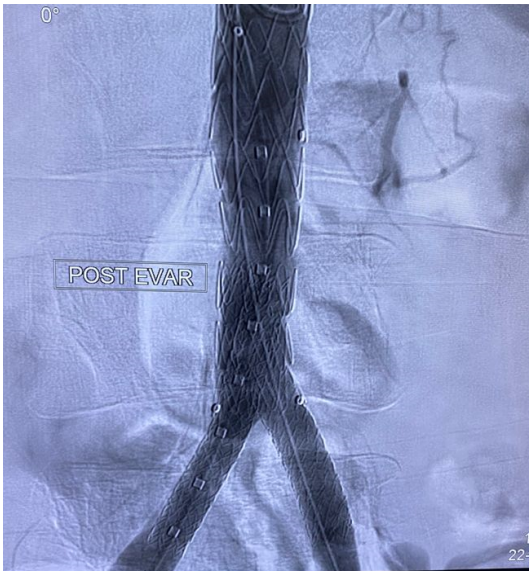



**Figure 3.** Angiography showing well-positioned graft stent upon EVAR procedure.

to its role as the primary access for endovascular procedures. The clinical sign that can be found in patients with pseudoaneurysm includes swelling, pain, large or growing hematoma, and audible bruit upon the lesion location. The main difference between a pseudoaneurysm and an aneurysm is that a pseudoaneurysm has a "to-and-fro curve" depicting the systolic and diastolic inflow and outflow of blood. The gold standard for diagnosing pseudoaneurysm is duplex sonography, with sensitivity and specificity of 94-99% and 94-97% respectively.

In this case, the patient had no prior history of vascular intervention. This patient had a prior history of controlled hypertension and diabetes mellitus. However, the association of hypertension and diabetes mellitus with the occurrence of abdominal aortic pseudoaneurysm are still lacking. One of the risk factors that may cause pseudoaneurysms is penetrating or blunt trauma.[2] Compression of the abdominal aorta against the rigid vertebral column increases the intra-aortic pressure, which may cause vascular damage and aortic rupture.[3] Dual platelet inhibition along with the use of additional anti-coagulants (triple-therapy) are also relevant risk factors of pseudoaneurysm.

A small pseudoaneurysm can close spontaneously and thus does not need further treatment. In some cases, pausing the current anticoagulant therapy is sufficient to prevent further growth of the pseudoaneurysm. Spontaneous thrombosis of the cavum mostly occurs in cases of small pseudoaneurysm. In 88–93% of cases, the pseudoaneurysm closes spontaneously after bed rest or compression with bandages or other systems. However, a growing pseudoaneurysm increases the risk of rupture and compression to the surrounding organ, thus altering the patient's hemodynamics. Pseudoaneurysms sized more than 2-4 cm, those increasing in size or those associated with a large surrounding hematoma should be treated. The treatment options for pseudoaneurysm comprise ultrasound-guided compression therapy, ultrasound-guided thrombin injection, operative therapy, and transcatheter intervention. Until 1990, operative therapy was the primary treatment for pseudoaneurysm, with a success rate of 100%. However, operative therapy has intraprocedural and post-procedural complications up to 21%. The complications included bleeding, infections, healing disorders, thrombosis, edema, permanent neuralgia, and lymphatic fistulas, thus operative therapy was not primarily preferable. Endovascular methods are nowadays available to treat pseudoaneurysms, such as the implantation of a stent or coil. In this case, the patient was previously planned to receive open repair surgery due to a lack of

EVAR stent with precise size. The doctor in charge then modified the use of BE graft stent. The patient received percutaneous transcatheter EVAR limb extensions that were connected to BE graft stent in both branches of common iliac arteries.

Studies explaining the comparison between EVAR and operative therapy for pseudoaneurysm were still lacking. However, a systematic review and meta-analysis conducted by Antoniou *et al*[4] concluded that EVAR results in a better outcome during the first six months but carries an increased risk of aneurysm-related mortality after eight years compared to surgery for patients with abdominal aortic aneurysm. This study included seven RCTs reporting a total of 2.983 patients. The result of this study shows significantly lower odds of 30 days (OR, 0.36; 95% CI 0.20-0.66) and in-hospital mortality with EVAR (RD -0.03; 95% CI -0.04 to 0.02). Results found no significant difference in all-cause mortality at any time between EVAR and operative therapy (HR 1.02; 95% CI 0.93-1.13; p = 0.62). The hazard of all causes (HR 0.62; 95% CI 0.42-0.91) and aneurysm-related death within six months (HR 0.42; 95% CI 0.24-0.75) was significantly lower in patients who underwent EVAR. With further follow-up, the pooled hazard estimate moved in favor of open surgery; in the long term (>8 years) the hazard of aneurysm-related mortality was significantly higher after EVAR (HR 5.12; 95% CI 1.59-16.44).

## CONCLUSION

Abdominal aortic pseudoaneurysms are mostly caused by endovascular intervention. However, spontaneous abdominal aortic pseudoaneurysm may occur due to blunt trauma, penetrating trauma, or consumption of dual antiplatelet therapy in combination with one anticoagulant. Pseudoaneurysm may rupture and cause hemodynamic instability due to internal hemorrhage, thus it needs to be treated properly. A pseudoaneurysm can be treated with ultrasound-guided compression therapy, ultrasound-guided thrombin injection, operative therapy, or transcatheter intervention. Pseudoaneurysms occurring in these patients do not commonly happen in the absence of prior vascular intervention or surgery. Therefore, adequate interventional therapy is needed to prevent fatal rupture complications. EVAR compared to operative therapy has a better outcome, thus may be the treatment of choice to treat pseudoaneurysm.

## REFERENCES

1. Peters S, Braun-Dullaeus R, Herold J. Pseudoaneurysm incidence, therapy and complications. Hamostaseologie. 2018;38(3):166–72.
2. Massara M, Prunella R, Gerardi P, et al. Infrarenal abdominal aortic pseudoaneurysm: Is it a real emergency? Ann Vasc Dis. 2017;10(4):423–5.
3. Potts RiG, Alguire PC. Pseudoaneurysm of the abdominal aorta: A case report and review of the literature.pdf. American Journal of The Medical Science; 1991. p. 265–8.
4. Antoniou GA, Antoniou SA, Torella F. Editor's choice – endovascular vs. open repair for abdominal aortic aneurysm: Systematic review and meta-analysis of updated peri-operative and long term data of randomised controlled trials. Eur J Vasc Endovasc Surg [Internet]. 2020;59(3):385–97. Available from: https://doi.org/10.1016/j.ejvs.2019.11.030.