JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
2023 August, XIV (02)

ORIGINAL ARTICLE

Urinalysis Profile of Dengue Viral Infection Patients in Dr. Soetomo General Academic Hospital, Surabaya, from 2019-2021

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ABSTRACT

Introduction: Dengue viral infection is still a burden in Indonesia. It often causes some kidney complications such as acute renal failure, proteinuria, hematuria, and glomerulonephritis. Urinalysis is an easy and useful examination of kidney complications. This study aimed to discover the most common profile of urinalysis in dengue viral infection.

Methods: This study used a cross-sectional method with medical records data of patients with dengue viral infection in Dr. Soetomo General Academic Hospital, Surabaya, in the 2019-2021 period. Purposive sampling techniques were used with inclusion and exclusion criteria. Data such as age, gender, dengue viral infection severity level, and dipstick urinalysis results were taken and analyzed using descriptive analysis in SPSS Statistics 25.

Results: A total of 276 patients were included. The sample was dominated by male patients (52.9%) and patients aged 17-45 years old (40.2%). Most patients suffered from dengue hemorrhagic fever/DHF (54.3%) followed by dengue fever (45.7%). DHF was categorized into grade I (28.3%), grade II (13.4%), grade III (8.3%), and grade IV (4.3%). Most urinalysis results were normal and followed by increased results of protein, blood/hemoglobin, bilirubin, urobilinogen, leukocytes esterase, and ketones in some patients.

Conclusion: Dengue viral infection was more common in male patients and 17-45 years old patients. The most common diagnosis was DHF. Urinalysis results in dengue viral infection were mostly normal. Follow-up research is needed to find the relation between the elevated urinalysis results and the severity of dengue viral infection.

Highlights:
1. Dengue viral infection patients were mostly male and aged 17-45 years old.
2. Dengue viral infection patients mostly have normal urinalysis results.
3. Some dengue viral infection patients can have elevated protein, blood, bilirubin, urobilinogen, leukocytes esterase, and ketones in the urine.

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JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
p-ISSN: 1907-3623; e-ISSN: 2684-9453
DOI: 10.20473/juxta.V14I22023.94-99

ARTICLE INFO

Article history:

Received 02-01-2023

Received in revised form 14-07-2023

Accepted 31-07-2023

Available online 10-08-2023

Keywords:
Dengue hemorrhagic fever,
Dengue viral infection,
Kidney disturbances,
Tropical disease,
Urinalysis.

Cite this as:
Rahardjo AR, Wardhani P. Urinalysis Profile of Dengue Viral Infection Patients in Dr. Soetomo General Academic Hospital, Surabaya, from 2019-2021. *JUXTA J Ilm Mhs Kedokt Univ Airlangga* 2023; 14: 94–99.

Introduction

Dengue viral infection is a systemic and dynamic infectious disease that can cause a decrease in platelet count resulting in plasma leakage called dengue hemorrhagic fever (DHF).[1,2] It is still a burden and continues to increase the number of cases in various countries, especially in tropical countries such as Indonesia. Globally, the number of cases of dengue viral infection in 2010 reached 2.4 million cases and in 2019 increased to 5.2 million cases.[3] The incidence rate of dengue viral infection in Indonesia was 77.96 cases per 100,000 people in 2017. The mortality rate due to DHF in Indonesia in 2017 reached 444 cases out of 59,047 cases.[4]

This infectious disease is caused by the Dengue virus, which is a ribonucleic acid (RNA) virus of the Flaviviridae group, genus Flavivirus.[5] RNA viruses are viruses that have RNA as their genetic material.[6] Dengue virus has an RNA genome of 11kb and is composed of 3 genes structural proteins that code for core protein (C), membrane-associated protein (M), enveloped protein (E), and seven non-membrane-associated proteins. (E) and seven non-structural proteins (NS) are NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5.[7] There are 4 serotypes of Dengue virus, DENV-1, DENV-2, DENV-3, DENV-4.5,8 The spread of Dengue virus to the human bloodstream was through the bite of an *Aedes sp* mosquito as a vector carrying Dengue virus.[8,9]

The clinical spectrum of dengue viral infection is quite broad with diverse clinical manifestations that appear after 4-10 days of incubation and can last for 2-7 days. The clinical manifestations of dengue viral infection begin after incubation and are divided into febrile phase, critical phase, and recovery phase. The World Health Organization (WHO) classifies dengue viral infection into asymptomatic dengue viral infection, dengue fever, and DHF with four grades of severity.[2] Early symptoms of dengue viral infection include high fever reaching 39-40°C and followed by severe headache, pain at the back of the eyes, muscle and joint pain, nausea, vomiting, swollen glands, sore throat, and rash.[10] Severe dengue viral infection has fatal complications such as plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ damage due to dengue viral infection.[3] Spontaneous bleeding, such as petechiae, epistaxis, and hematemesis, that occur in DHF is caused by vascular disorders, thrombocytopenia, platelet dysfunction, and coagulopathy.[7] These complications often resulted in organ disturbances such as the kidney.[10]

Previous studies have found some kidney complications in dengue viral infection, such as acute kidney failure, proteinuria, hematuria, and glomerulonephritis.[11] These complications can be detected through urinalysis examination. Urinalysis examined many urine properties such as color, clarity, specific gravity, pH, protein level, glucose level, blood/hemoglobin level, bilirubin level, urobilinogen level, leukocyte level, nitrite level, and ketone level.[12]

Normal urine has a yellow color due to the content of several color pigments, and the dominating pigment is urochrome pigment which gives a yellow color.[13] Normal urine is generally clear and contains no particulate matter.[14] Cloudy urine is caused by the precipitation of crystals or amorphous salts, the presence of body cells, leukocytes, erythrocytes, epithelial cells, sperm, excretion of mucus from the lower urinary tract, and other causes.[14] Normal urine specific gravity for adults is in the range of 1.016-1.022.[14] High specific gravity urine can be found in conditions of dehydration, adrenal insufficiency, liver disease, or congestive heart failure.[14] Normal urine in healthy adults has a pH range of 4.6-8.[14] Normal urine tested negative for protein, glucose, bilirubin, urobilinogen, leukocyte, nitrite, and ketone, while abnormal urine shows positive results caused by excretion increase or reduced reabsorption by the kidney.[12,14,15]

Research of urinalysis examination in patients with dengue viral infection has been rarely conducted although urinalysis is often used in monitoring dengue viral infected patients with electrolyte disturbances. Therefore, this study aimed to discover urinalysis profiles in patients with dengue viral infection and further find specific urinalysis results in different severity of dengue viral infection.

Methods

This was a cross-sectional study. The independent variable was the severity of dengue viral infection. The dependent variable was urinalysis results. This study had received approval of ethical clearance from the Ethics Commission of Dr. Soetomo General Academic Hospital, Surabaya.

The samples were obtained using a total sampling technique according to inclusion criteria which were samples collected from patients in Dr. Soetomo General Academic Hospital, Surabaya, with dengue viral infection diagnosed by the doctors and had urinalysis results. The data samples were obtained from digital and paper-based medical records. For the statistical analysis, there were some considerations such as the samples must be equipped by identity, diagnosis of dengue viral infection severity level, and the results of the urinalysis examination. Samples diagnosed without WHO 2011 dengue viral infection classification and patients with incomplete urinalysis results were excluded. The obtained data were recorded using Microsoft Excel spreadsheets and then analyzed using descriptive statistics in IBM SPSS Statistics 25.

Results

Characteristics of Dengue Viral Infection Patients

From 2019-2021, there were 1,278 patients with dengue viral infection admitted to Dr. Soetomo General Academic Hospital, Surabaya. However, this study included only 276 patients based on the inclusion-exclusion criteria. Based on Table 1, the dengue viral infection patients' age was ranging between 0 and 83 years old and were categorized into six age groups with the most in the 17-45 years old age group.

Table 1. Characteristics of dengue viral infection patients

Characteristics	n	%
Age (years old)		
0-5	56	20.3
6-11	66	23.9
12-16	23	8.3
17-45	111	40.2
46-65	17	6.2
>65	3	1.1
Total	276	100

Table 2. Continuation of characteristics of dengue viral infection patients

Characteristics	n	%
Gender		
Male	146	52.9
Female	130	47.1
Total	276	100
Dengue Viral Infections Severity		
Dengue Fever	126	45.7
DHF*	150	54.3
Grade I	78	28.3
Grade II	37	13.4
Grade III	23	8.3
Grade IV	12	4.3
Total	276	100

*Accumulations of all grades of DHF patients

The samples included, based on Table 2, consisted of 146 males (52.9%) and 130 females (47.1%). Based on dengue viral infection severity, 150 patients (54.3%) were diagnosed with DHF followed by dengue fever (126 patients, 45.7%).

Urinalysis Profile of Dengue Viral Infection Patients

A total of 12 properties of urine were examined and analyzed in Table 3 and Table 4. According to the obtained data, the most common urine colors found in patients with dengue viral infection were yellow (145 patients, 71.8%) and dark yellow (33 patients, 16.3%). Based on Table 3, the most common urine clarity found were clear urine (182 patients, 90.1%) and cloudy urine (13 patients, 6.4%). Most urine had a specific gravity of 1.007-1.016 (104 patients, 38.4%) and followed by a specific gravity of 1.016-1.022 (70 patients, 25.8%). The most common urine pH was 4.6-8 (26 patients, 97.5%). Most common urine protein levels were negative (148 patients, 53.6%) and 1+ (63 patients, 22.8%).

Most common urine glucose levels also were negative (260 patients, 94.2%) and 1+ (5 patients, 1.8%). Most common urine blood/hemoglobin levels were negative (183 patients, 66.3%) and 1+ (28 patients, 10.1%). Most common urine bilirubin levels were negative (207 patients, 75%) and 1+ (53 patients, 19.2%). The most common urine urobilinogen levels were 0.2 mg/dL (155 patients, 56.2%) and 1 mg/dL (85 patients, 30.8%). Most common urine leukocyte esterase levels were negative (192 patients, 69.6%) and 1+ (43 patients, 15.6%). The most common urine nitrate level was negative (201 patients, 93.9%). Most common urine ketone levels were negative (155 patients, 61.3%) and 1+ (39 patients, 15.4%).

Table 3. Urinalysis profile of dengue viral infection patients

Urinalysis	n	%
Color		
Yellow	145	71.8
Dark yellow	33	16.3
Amber	16	7.9
Orange	7	3.5
Brown	1	0.5
Total	202	100.0
Clarity		
Clear	182	90.1
Slightly cloudy	2	1.0
Cloudy	13	6.4
Turbid	5	2.5
Total	202	100.0
Specific Gravity		
<1.007	54	19.9
1.007-1.016	104	38.4
1.016-1.022	70	25.8
1.022-1.035	37	13.7
>1.035	6	2.2
Total	271	100.0
Urine pH		
4.6-8	269	97.5
>8	7	2.5
Total	276	100
Protein		
Negative	148	53.6
Trace	6	2.2
1+	63	22.8
2+	43	15.6
3+	11	4.0
4+	5	1.8
Total	276	100.0
Glucose		
Negative	260	94.2
±	4	1.4
1+	5	1.8
2+	4	1.4
3+	1	0.4
4+	2	0.7
Total	276	100.0

Table 4. Continuation of urinalysis profile of dengue viral infection patients

Urinalysis	n	%
Blood/Hemoglobin		
Negative	183	66.3
±	8	2.9
1+	28	10.1
2+	22	8.0
3+	19	6.9
4+	16	5.8
Total	276	100.0
Bilirubin		
Negative	207	75.0
1+	53	19.2
2+	15	5.4
3+	1	0.4
Total	276	100.0
Urobilinogen		
0.2 mg/dL	155	56.2
1 mg/dL	85	30.8
2 mg/dL	16	5.8
4 mg/dL	15	5.4
8 mg/dL	5	1.8
Total	276	100.0
Leukocyte Esterase		
Negative	192	69.6
±	21	7.6
1+	43	15.6
2+	13	4.7
3+	7	2.5
Total	276	100.0
Nitrite		
Negative	201	93.9
Positive	13	6.1
Total	214	100.0
Ketone		
Negative	155	61.3
±	20	7.9
1+	39	15.4
2+	14	5.5
3+	13	5.1
4+	12	4.7
Total	253	100.0

Discussion

Dengue viral infection can happen to everyone regardless of age and gender as the infection was spread through *Aedes sp* mosquitos.[2] WHO in their guideline estimated that 500,000 people with DHF were hospitalized annually and a very large proportion (around 90%) of the patients were children aged less than five years old.[2] This study found that dengue viral infection mostly happened in people in the age group of 17-45 years old. This is similar to the result of a study conducted by Haroon (2019), which found that dengue virus patients were mostly in the age group of 21-40 years old.[16] The results of this study are also similar to the study by Atique (2018), with the most dengue virus patients in the age group of 21-40 years old.[17] In Taiwan, Hsu (2017) found that the incidence of dengue viral infection was mostly at the age of 50-59 years old.[18]

Dengue viral infection can be detected using various methods such as clinical manifestation, immunoglobulin G and immunoglobulin M detection, thrombocytopenia, and detection of antigen non-structural 1 (NS1 antigen).[19] The clinical manifestation of dengue viral infection was spread in a wide spectrum of diseases which are dengue fever, DHF, dengue shock syndrome, and expanded dengue fever.[20] However, in the 2011 WHO guideline, dengue viral infection was divided into several severity grades from the mildest to the most severe by signs, symptoms, and laboratory results, namely dengue fever, DHF grade I, DHF grade II, DHF grade III, and DHF grade IV.[2] Dengue fever had sign and symptoms of high fever with 2 of the following, headache, retro-orbital pain, myalgia, arthralgia or bone pain, rash, and bleeding manifestations.[2] In dengue fever, there is no sign of plasma leakage, which differs from DHF.[2]

Signs and symptoms of DHF I are similar to dengue fever with the addition of bleeding manifestation and plasma leakage.[2] DHF grade II had additional symptoms of spontaneous bleeding.[2] DHF grade III has the same sign and symptoms to grade I and II, with circulatory failure shown by weak pulse, low pulse pressure (≤20 mmHg), hypotension, and restlessness.[2] The most severe was DHF grade IV whose signs and symptoms include episodes of severe shock and undetectable pulse and blood pressure.[2] The laboratory results of dengue fever according to WHO were leukopenia (leukocytes ≤5000 cells/mm3), thrombocytopenia (platelets <150,000 cells/mm3), and/or elevated hematocrit (5%-10%).[2] The laboratory results of DHF for all grades were thrombocytopenia (platelets <100,000 cells/mm3) and more elevated hematocrit (≥20%).[2]

Complications and sequelae of dengue viral infection are rare but may include the following, cardiomyopathy, seizures, encephalopathy, viral encephalitis, liver injury, depression, pneumonia, iritis, orchitis, oophoritis, metabolic abnormalities, and kidney diseases.[2,21] Complications on the kidneys found in cases of dengue viral infection include acute kidney injury (AKI), urine sedimentation, proteinuria, and nephropathy.[22] Those complications were mostly the results of severe dengue viral infection.

The number of samples diagnosed with DHF was higher than dengue fever. The number of patients with a lower severity grade of DHF was more than with a higher severity grade. These results could be caused by the dengue fever has mild symptoms that most patients were able to be cured in smaller medical facilities. These findings were similar to the results from the studies of Jayawinata (2017), Lumpaopong (2010), and Permatasari (2103).[23–25] However, the results of this study contradict the study of Nunthanid (2015), where the number of patients with dengue fever patients was higher than patients with DHF.[26] The urinalysis data collected for this study include the examination of 12 urine properties, which were color, clarity, specific gravity, pH, protein level, glucose level, blood/hemoglobin level, bilirubin level, urobilinogen level, leukocyte esterase level, nitrite level, and ketone level.[14]

Color and clarity used the physical examinations, while the others used the dipstick urinalysis method.[14] Microscopic urinalysis was not included since the data were not available in most samples' medical records.

This study showed that urine color and urine clarity in all grades of dengue viral infection tended to be normal. Urine color tends to be normal because urochrome pigments that give yellow color still dominate and are not dominated by other pigments such as blood in gross hematuria.[13,14] Urine clarity tends to be normal because, in cloudy urine, there is precipitation of crystals or salts, body cells, or proteinuria in large quantities.[14] Urine color and urine clarity tend to be normal in line with the results of urinalysis of other components, especially protein and blood levels in urine which tend to be negative.[14] Normal urine color and clarity show that dengue viral infection did not directly affect the production of urine at a macroscopic level.

The percentage for urine with specific gravity ≥1.020 was 15.9% of the samples in this study. This result contradicts the study conducted by Lumpaopong (2010), where the percentage of urine with specific gravity ≥1.020 was 61.4%.[25] Urine with high specific gravity can be found in conditions of dehydration, contamination, glucosuria, or iatrogenic causes.[14,15] In this study, glucosuria was found slightly in dengue viral infection, hence most urine-specific gravity tends to be lower. Dehydration mostly happened during the febrile phase of the infection due to high fever, vomiting, anorexia, and poor oral intake.[2] However, the hydration status of the patients was not recorded.

Urine with negative protein levels was found more often than positive protein levels in the sample. This is in accordance with the studies by Lumpaopong (2010) and Vachvanichsanong (2015).[25,27] Abnormal protein levels are an important indicator of kidney disease because only small-sized proteins can penetrate the capillary wall of nephron in the kidney and few of it is reabsorbed in the renal tubules.[14] Proteinuria is caused by an abnormal trans-glomerular pathway mechanism through which proteins pass due to increased permeability of the glomerular capillary wall and impaired reabsorption by proximal tubular epithelial cells.[28]

The results showed that the number of patients with negative urine glucose was obtained higher than positive urine glucose results. This is in line with the study by Vachvanichsanong (2015).[27] In the process of urine formation, glucose will be reabsorbed in the proximal tubules of the kidney, thus it is generally not found in the urine. If the amount of glucose exceeds the reabsorption capacity, the glucose will remain in the urine. The condition is referred to as glucosuria.[15] However, in dengue viral infections, there is no evidence of the virus's influence on glucose levels in the blood. Therefore, glucosuria was a rare finding. Most negative results in glucose urine were in line with ketone levels in urine. This was because the ketone body is usually detected in impaired carbohydrate absorption and/or metabolism.[15] However, some patients had positive ketone levels in urine (ketonuria) that could be caused by acute fever during dengue viral infection, diabetes, or other causes which were not recorded.[14]

Blood or hemoglobin is normally not found in urine. The condition of the existence of blood in urine is known as hematuria. Hematuria can be seen by using the naked eye with the color change of the urine to red, or by using microscope examinations.[14] Hemoglobinuria is the presence of free hemoglobin in the urine caused by increased production that exceeds the reabsorbing capacity of the proximal tubules of the kidneys. This increase occurs due to increased hemolysis due to red blood cell trauma, infection and organism toxins, erythrocyte enzyme deficiencies, hemoglobin imbalances, and stimulation of the immune system. This study found that most urine did not contain blood/hemoglobin.[14] This result is in accordance with the studies by Lumpaopong (2010) and Vachvanichsanong (2015).[25,27] Other urinalysis results, bilirubin levels in urine, urobilinogen levels, leukocyte levels, and nitrite levels were mostly normal based on urinalysis normal value guideline.[14]

Strength and Limitations

This study showed the urinalysis profile of patients with dengue viral infection. It can be used as a comparison in treating patients or further research related to dengue viral infection. However, this study could have a bias in the collected data as this study was a cross-sectional study and concomitant diseases of the patients were ignored.

Conclusion

Dengue viral infection was more common in male patients than in females. In this study, dengue viral infection occurred mostly in adult patients aged 17-45 years old. More patients were diagnosed with DHF than dengue fever. Urinalysis results in dengue viral infection for all urine properties were mostly normal and some were elevated such as protein, blood/hemoglobin, bilirubin, urobilinogen, leukocytes esterase, and ketones levels in urine. These results can be used for further research needed to find the relation between the severity of dengue viral infection and the elevated urinalysis results.

Acknowledgments

Special thanks to the teachers for their guidance during the research and writing process. Thanks to the student community for all the help and advice given during the making of this study. Thanks to the staff of the Department of Clinical Pathology, the Department of Pediatrics, and the Medical Records staff of Dr. Soetomo General Academic Hospital, Surabaya, for their assistance in this study.

Conflict of Interest

The authors declared there is no conflict of interest.

Funding

This study did not receive any funding.

Ethical Clearance

This study had received ethical clearance from the Ethical Committee for Health Research Dr. Soetomo General

Academic Hospital, Surabaya (no.0860/LOE/301.4.2/IV/2022) on 5 April 2022.

Authors' Contributions

Collecting and analyzing data: ARR. Analyzing and validating the collected data: PW. Writing the manuscript: ARR, PW.

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