Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.3 (2024). p.258-63; DOI: https://doi.org/10.14238/pi64.3.2024.258-63

Original Article

Evaluation of performance of *2021 Indonesian Sepsis National Guidelines* in diagnosing pediatric bacterial sepsis

Lilis Siti Asiyani, Tunjung Wibowo, Eggi Arguni, Ratni Indrawanti, Desy Rusmawatiningtyas, Nurnaningsih

Abstract

Background Sepsis remains one of the causes of child morbidity and mortality worldwide. The reference standard diagnosis of sepsis is blood culture, but its false negative is relatively high. Therefore, a validated triage tool is needed for rapid diagnosis. In Indonesia, diagnosis and management of pediatric sepsis are based on *Pedoman Nasional Pelayanan Kesehatan Manajemen Sepsis pada Anak 2021/PNPK Sepsis 2021 (2021 Indonesian Sepsis National Guidelines)*.

Objective To evaluate the performance of *2021 Indonesian Sepsis National Guidelines* in diagnosing pediatric bacterial sepsis in PICU.

Methods This cross-sectional study was conducted in the PICU unit of Dr. Sardjito Hospital, Yogyakarta, using subject's medical records. All patients with suspected bacterial infection who were admitted to the PICU, had complete evaluation of PELOD-2 score, and the blood culture results were included in this study. Sepsis was assessed with *2021 Indonesian Sepsis National Guidelines*. Performance analysis of the guidelines was conducted with *SPSS version 25*, by assessing sensitivity, specificity, accuracy, positive predictive value, negative predictive value, and likelihood ratio.

Results Two hundred subjects were enrolled in this study, of whom 52.5% were males. Most subjects aged under one year (40.5%), and the most common infection was respiratory system (49%). A total of 63.5% were referral cases, with the length of stay in the previous hospital more than 48 hours (69.7%). There were 77% of subjects had antibiotics treatment at the previous hospital. As for outcomes, 63.5% survived and 36.5% died. The positivity rate of blood culture in this study was 19%. Performance evaluation of *2021 Sepsis Indonesian Sepsis National Guidelines* revealed sensitivity 28.95%, specificity 87.65%, accuracy 76.5%, positive predictive value 35.48%, negative predictive value 84.02%, positive likelihood ratio 2.34 (95%CI 1.28 to 4.32) and negative likelihood ratio 0.81 (95%CI 0.7 to 0.94).

Conclusion *2021 Indonesian Sepsis National Guidelines* (*PNPK Sepsis 2021*) has low sensitivity and high specificity in diagnosing pediatric bacterial sepsis. **[Paediatr Indones. 2024;64:258-63; DOI: 10.14238/pi64.3.2024.258-63].**

Keywords: *sepsis; 2021 Indonesian Sepsis National Guidelines; performance, blood culture*

Sepsis is still one of the leading causes of morbidity and mortality in children in all parts of the world. Based on the *World Health Organization* (WHO) data, the number of deaths in children under 5-year-old due to sepsis is estimated to reach 10% of all deaths. The incidence of septic shock in developed countries ranges from 2-3%, while in developing countries, it is 18-46%.[1] A study on critically ill children treated at the pediatric intensive care unit (PICU) of Dr. Cipto Mangunkusumo Hospital in 2019, stated that the sepsis mortality rate reached 10.7%.[2] Another study at the PICU of Dr. Sardjito Hospital showed that the incidence of sepsis was 25.08%, with a mortality of 57.8%.[3]

The definitive diagnosis of sepsis is blood culture, but it has low sensitivity and positivity rate. The polymerase chain reaction (PCR) allows rapid and accurate diagnosis of the presence of blood infection in infants and children with suspected sepsis.[4] However, availability of the PCR test is still limited to referral hospitals, and the examination cost is expensive.

From the Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Central Java, Indonesia.

Contributing author: Lilis, Department of Child Health, Gadjah Mada University, Jalan Kesehatan no. 1 Sekip Yogyakarta 55284, Indonesia. Telp. +62-271-712779. Email: lilis8.sa@gmail.com.

Submitted October 12, 2022. Accepted June 4, 2024.

The limitations of blood culture and PCR lead to delays in the diagnosing and managing sepsis, thereby increasing the risk of organ dysfunction and death. Thus, the triage tools/validated diagnostic tests for pediatric sepsis assessment are being developed. This diagnosis is made using clinical assessment, supported by laboratory testing.

In Indonesia, the diagnosis and management of sepsis are based on *Pedoman Nasional Pelayanan Kesehatan "Manajemen Sepsis pada Anak" 2021/ PNPK Sepsis 2021 (2021 Indonesian Sepsis National Guidelines)*, published by the *Indonesian Ministry of Health*.[5] This guidelines refers to *The 2016 Surviving Sepsis Campaign International*, which establishes the diagnosis of sepsis, evidence of infection, and signs of organ dysfunction.[6] Assessment of organ dysfunction with PELOD-2 score, in which the diagnosis of sepsis is established when the PELOD-2 score is ≥10. The international system still uses *Goldstein Criteria* to diagnose pediatric sepsis, based on the evidence of infection with 2 of 4 signs of systemic inflammatory response (SIRS).[7] We conducted this study to evaluate the performance of *2021 Indonesian Sepsis National Guidelines* in diagnosing pediatric bacterial sepsis.

Methods

This cross-sectional study was conducted in the PICU of Dr. Sardjito Hospital, Yogyakarta, using subject's medical record data. We included all patients with suspected of bacterial infections who were treated from October 2019 to October 2021, has complete evaluation of PELOD-2 score, and the blood culture results conducted in the first 24 hours of PICU admission. Subjects with incomplete medical record were excluded from the study.

The bacterial infections criteria were the presence of focus infection, accompanied by the clinical findings of SIRS (temperature, pulse rate, and respiratory rate abnormalities) and abnormalities of the laboratory evaluation including white blood cells (WBC) count, platelet count, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin, urine, stool, and cerebrospinal fluid (CSF) analysis, as well as abnormalities of the radiological finding. All data related to PELOD-2 score which include mean arterial pressure (MAP), pediatric coma scale (PCS), pupillary reactions, use of mechanical ventilation, blood gas analysis, lactate serum, creatinine level, WBC, and platelet count were recorded for this study. We assessed sepsis diagnosis based on *2021 Indonesian Sepsis National Guidelines*. According to the guidelines, the diagnosis of sepsis is established if there is a suspected or proven infection, along with PELOD-2 score ≥10.[5]

We collected subject's demographic data, which include sex, age, nutritional status, diagnosis, length of stay (LoS) in the PICU, referral status, previous length of treatment, previous use of antibiotics, indications for PICU care, and outcomes.

Data were analyzed using *SPSS version 25*. Performance assessment was carried out by analyzing sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) of *2021 Indonesian Sepsis National Guidelines* compared to the standard reference of the blood culture. This study has received permission from the Research Ethics Committee from the Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University Yogyakarta, and was approved by Dr. Sardjito Hospital.

Results

A total of 366 subjects were admitted with suspected of bacterial infections during the study period, of whom 200 subjects met the inclusion and exclusion criteria.The baseline characteristics data of our subjects are shown in **Table 1**.

From the assessment of sepsis diagnosis according to *2021 Indonesian Sepsis National Guidelines*, 31 (15.5%) subjects were diagnosed with sepsis, and 169 (84.5%) were not sepsis (**Table 2**). Furthermore, the performance of *2021 Indonesian Sepsis National Guidelines* was assessed to calculate the sensitivity, specificity, PPV, NPV, positive LR, and negative LR of *2021 Indonesian Sepsis National Guidelines* compared to blood culture (**Table 3**).

The post-test probability assessment after the use of *2021 Indonesian Sepsis National Guidelines* with a pretest probability (prevalence) of sepsis at Dr. Sardjito Hospital from a previous study was 50.3%, using Fagan's nomogram (**Figure 1**).[8]

Fagan's nomogram shows that with *2021 Indonesian Sepsis National Guidelines*, on a positive test (LR+2.35; 95%CI 1.28-4.32), it will increase the pretest probability from 50% to 70% in the post-test probability (blue color), demonstrating moderate clinical importance. Meanwhile, a negative test result (LR- 0.81; 95%CI 0.7-0.94) will change the pretest probability from 50% to 45% in the post-test probability (red color), indicating low clinical importance.

Table 1. The subject's characteristic data

Characteristics	N=200
Age, n (%)	
1 m.o - < 1 y.o	81 (40.5)
1 y.o - < 5 y.o	50 (25)
5 y.o - < 12 y.o	42 (21)
12 y.o - ≤ 18 y.o	27 (13.5)
Sex, n (%)	
Male	105 (52.5)
Female	95 (47.5)
Nutritional status, n (%)	
Overweight & obesity	6 (3)
Well-nourished	82 (41)
Mild-moderate malnourished	61 (30.5)
Severe malnourished	51 (25.2)
Admission diagnosis of PICU, n (%)	
Respiration system	98 (49)
Central nervous system	49 (24.5)
Gastrointestinal system	45 (22.5)
Genitourinary system	8 (4)
Referral status, n (%)	
Referral case	127 (63.5)
Not referral case	73 (36.5)
Previous length of treatment (n=172),* n (%)	
<24 hours	36 (20.9)
24- 48 hours	16 (9.3)
>48 hours	120 (69.7)
Previous use of antibiotics, n (%)	
Yes	154 (77)
No	46 (23)
LOS at PICU, mean (SD), day	9.5 (9.4)
Outcomes, n (%)	
Survive	73 (36.5)
Death	127 (63.5)
PNPK sepsis (positive), n (%)	31 (15.5)
Positive blood culture, n (%)	38 (19.0)

*28 subjects had no previous treatment

Discussion

There has not been any study yet that assessed the performance of the *2021 Indonesian Sepsis National Guidelines* in diagnosing pediatric bacterial sepsis. This study found that *2021 Indonesian Sepsis National Guidelines* has a sensitivity 28.95%, specificity 87.65%, accuracy 76.5%, PPV 35.48%, NPV 84.02%. These indicate that *2021 Indonesian Sepsis National Guidelines* has high specificity with low sensitivity and good accuracy.

From our analysis, the low sensitivity of *2021 Indonesian Sepsis National Guidelines* in diagnosing pediatric bacterial sepsis due to the large false negative blood culture as a standard reference, which also results in a low positivity rate. Several studies revealed that imperfect standard reference will lead to bias in the sensitivity, specificity, and accuracy of a diagnostic test. This bias can be positive or negative.[9] Even when a diagnostic test has excellent sensitivity and specificity, but the standard reference is imperfect, there can still be substantial bias in the accuracy of the diagnostic test. The degree of bias in the assessment of sensitivity and specificity reflects the covariance between the diagnostic test and an imperfect standard reference.[10] The type and magnitude of bias of a diagnostic test depend on several components, such as disease prevalence, false negative, and false

Table 3. Performance evaluation of *2021 Indonesian Sepsis National Guidelines*

Parameters	*2021 Indonesian Sepsis National Guidelines* diagnostic test
Sensitivity	28.95%
Spesificity	87.65%
Accuracy	76.5%
PPV	35.48%
NPV	84.02%
Positive LR	2.34
Negative LR	0.81

Table 2. *2021 Indonesian Sepsis National Guidelines* compared to blood culture

2021 Indonesian Sepsis National Guidelines	The blood culture		Total (N=200)
	Positive (n=38)	Negative (n=162)	
Positive, n(%)	11 (35.5)	20 (64.5)	31
Negative, n(%)	27 (16.0)	142 (84.0)	169

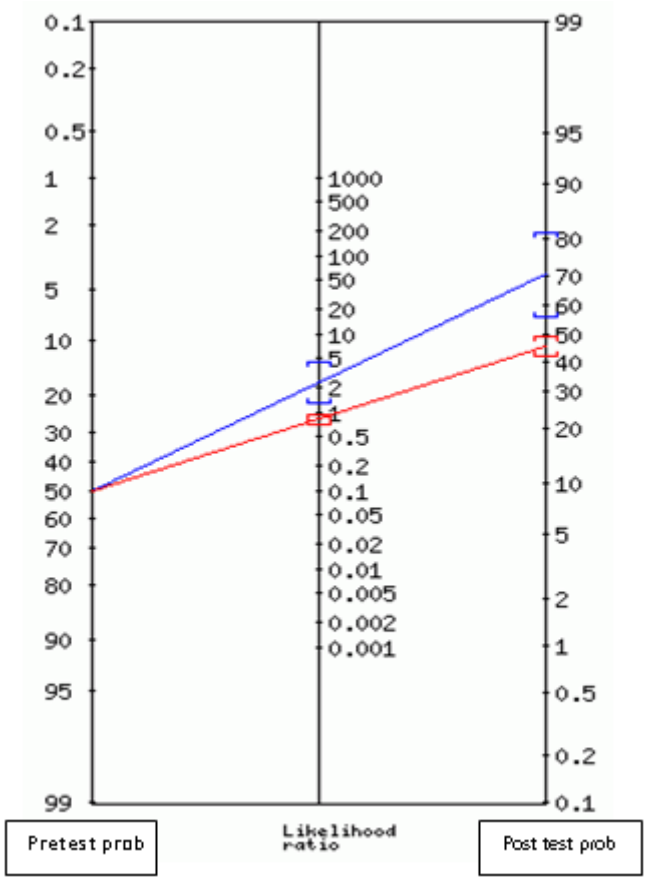

Figure 1. Fagan's nomogram of *2021 Indonesian Sepsis National Guidelines* compared to blood culture

positive covariance between the diagnostic test and the standard reference.[9,10]

Blood culture is the standard reference for detecting bacteremia conditions, but the positivity rate is low.[11] In this study, the positivity rate of blood culture was only 19%. The positivity rate of blood culture reported in the previous studies conducted in Dr. Sardjito Hospital was 23.8% and 18.6%.[3,12] Another study showed that the positivity rate of blood cultures was only 6%.[13] Meanwhile, another study on the evaluation of the use of blood cultures in academic hospitals in Europe, found blood culture positivity rate of 13.9%.[14]

The high false negatives and the low positivity rate of blood culture are caused by several factors, such as previous use of antibiotics, types of transient or intermittent bacteremia, small blood volumes, or microbial patterns (incubation and bacteremia period).[14] A total of 77% of our study subjects had received antibiotics in the previous hospitalization, and 69.7% of the subjects underwent treatment for more than 48 hours. The length of previous hospitalization and the microbial pattern (incubation and bacteremia period) are related to the time of taking blood specimens and affecting the blood culture results. Time to positive blood cultures are generally found within 36-48 hours of an episode of sepsis.[13,15] The low positivity rate of the blood cultures from most studies indicates that the blood cultures are inefficient in detecting bacteremia conditions. The blood culture in the first 24 hours of admission will give a greater positive result. The significant variation in the epidemiology of blood cultures, particularly in terms of time and cost efficiency, suggests the need re-evaluate of the use of blood cultures in detecting bacteriemia conditions.[14]

Given the low sensitivity of blood culture in detecting bacteremia conditions, other modalities such as PCR are needed, or the combination of clinical assessment with several inflammatory parameters such as procalcitonin (PCT), C-reactive protein (CRP), interleukins (IL-6, IL-8, IL-10), TNFα, or other

infection parameters such as absolute neutrophil count (ANC), leukocyte count, and neutrophil to lymphocyte ratio (NLR).[16] Polymerase chain reaction (PCR) can immediately identify bloodstream infections, compensating for the low sensitivity of blood culture. A study in an Italian children's hospital, which compared PCR performance with blood cultures in children with suspected sepsis, showed that PCR had a sensitivity of 85.0% and a specificity of 93.5%.[4] However, the use of PCR itself is still limited, and has not yet been available in all health facilities.

Most of our study subjects are male, with an age distribution under 1-year-old. This is in line with the previous study in 2015, which showed that 52.2% of pediatric sepsis patients were male.[17] Male sex hormones suppress the immune system, but the incidence in male infants has not been explained yet, and still requires further study.[18] The previous study revealed that the incidence of sepsis was most commonly found in the infant group (57.1%).[19] The other study showed that the incidence of sepsis in infants was 58.9%. It is due to an immature immune system that causes a higher risk of sepsis. This study also revealed no difference in nutritional status with the incidence of bacterial sepsis in children.[20]

The most common focus infections in this study were respiratory system (49%), followed by central nervous system (24.5%), gastrointestinal system (22.5%), and genitourinary system (4%). Our findings are analogous to previous studies, which reported that respiratory infection is the most common infection in PICU.[21-25] However, these findings are different from a previous study on the use of the PELOD-2 score as a predictor of pediatric sepsis mortality in the PICU of Dr. Sardjito Hospital, in which the primary infection is the central nervous system (29.1%).[21]

Our study was conducted at a referral hospital, whereas most of the referral patients had received antibiotics from previous hospitalization, which affected the positivity rate of the blood culture. In addition, most subjects (69.7%) had a previous LoS in the hospital of more than 48 hours, thus lead to the blood sampling for the blood cultures after incubation period. Furthermore, it causes false negative blood culture results and bias in the sensitivity and specificity values of *2021 Indonesian Sepsis National Guidelines*.

The limitation of molecular diagnostic technology usage causes researchers unable to prove sepsis caused by virus, which is the second common cause of sepsis after bacteria. Thus, the population of this study was limited to children with suspected bacterial infection which enables the researchers to identify bacteriemia by examining blood cultures. Another limitation of this study is the diagnosis of sepsis was made by the doctor in charge using various types of sepsis triage tools, and not all of them used the *2021 Indonesian Sepsis National Guidelines*.

The strength of this study is that this was the first study assessing the performance of the *2021 Indonesian Sepsis National Guidelines* and provided data of administration of antibiotics in the previous hospital, which are factors affecting the blood culture results. In conclusion, this study revealed that *2021 Indonesian Sepsis National Guidelines* performance in diagnosing pediatric bacterial sepsis have low sensitivity and high specificity. Further study should be carried out in primary health care setting, where blood cultures are taken before administer the antibiotic to patient with suspected sepsis. Studies on assessing the cut-off PELOD-2 score ≥10 according to the *2021 Indonesian Sepsis National Guidelines* in diagnosing sepsis in children in Indonesia, evaluating the use of blood culture as a standard reference to identify bacteremia condition, as well as developing the use of molecular diagnostic technologies such as PCR, miRNAs, and presepsin as another standard reference in detecting the condition of bloodstream infection in the diagnosis of sepsis are required.

Conflict of interest

None declared.

Funding acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. de Souza DC, Machado FR. Epidemiology of Pediatric Septic Shock. J Pediatr Intensive Care. 2019;8:3-10. DOI: https://doi.org/10.1055/s-0038-1676634
2. Dewi R, Fatimatuzzuhroh. Profil pasien sakit kritis yang dirawat di

PICU RSCM berdasarkan sistem skoring PELOD-2. Sari Pediatr. 2019;21:37-43.

3. Rusmawatiningtyas D, Rahmawati A, Makrufardi F, Murni KI, Uiterwaal CSPM, Savitri AI, *et al*. Factors associated with mortality of pediatric sepsis patients at the pediatric intensive care unit in a low- resource setting. BMC Pediatr. 2021;21:471-81. DOI: https://doi.org/10.1186/s12887-021- 02945-0.
4. Lucignano B, Ranno S, Liesenfeld O, Pizzorno B, Putignani L, Bernaschi P, *et al*. Multiplex PCR allows rapid and accurate diagnosis of bloodstream infections in newborns and children with suspected sepsis. J Clin Microbiol. 2011;49:2252-8. DOI: https://doi.org/10.1128/JCM.02460-10
5. Kementerian Kesehatan Republik Indonesia. Keputusan Menteri Kesehatan no HK.01.07/KEMKES/44722/2021 tentang Pedoman Pelayanan Kedokteran Tata Laksana Sepsis pada Anak. [cited 2022 Sept 10]. Available from: https://id.scribd.com/document/560848432/KMK-No-HK-01-07-MENKES-4722-2021-ttg- Pedoman-Nasional-Pelayanan
6. Gotts JE, Matthay MA. Sepsis: Pathophysiology and clinical management. BMJ. 2016;353:1-20.DOI: https://doi.org/10.1136/bmj.i1585
7. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatric Crit Care Med. 2005;6:2-8.DOI: https://doi.org/10.1097/01.PCC.0000149131.72248.E6
8. Patriawati K, Nurnaningsih N, Suryantoro P. Serial blood lactate levels as a prognostic factor for sepsis mortality. Paediatr Indones. 2014;54:168-73. DOI: https://doi.org/10.14238/pi54.3.2014.168-73
9. Umemneku CCM, Wilson KJ, Allen AJ, Vale L. Comparative diagnostic accuracy studies with an imperfect reference standard - a comparison of correction methods. BMC Med Res Methodol. 2021;21:67-86. DOI: https://doi.org/10.1186/s12874-021- 01255-4
10. Walter SD, Macaskill P, Lord SJ, Irwig L . Effect of dependent errors in the assessment of diagnostic or screening test accuracy when the reference standard is imperfect. Stat Med. 2012;31:1129-38. DOI: https://doi.org/10.1002/sim.4444
11. Khan MS, Kareem A, Fatima K, Rauf S, Khalid A, Bashir MS. Microbial patterns and antibiotic susceptibility in blood culture isolates of septicemia suspected children in the pediatrics ward of a tertiary carehospital. J Lab Physicians. 2021;13: 64-69. DOI: https://doi.org/10.1055/s-0041-1726271
12. Murni IK, Duke T, Daley AJ, Kinney S, Soenarto Y. True pathogen or contamination: Validation of blood cultures for the diagnosis of nosocomial infections in a developing country. J Trop Pediatr. 2018:64:389-94. DOI: https://doi.org/10.1093/tropej/fmx081
13. Tran CA, Zschaebitz JV, Spaeder MC. Epidemiology of blood culture utilization in a cohort of critically ill children. J Pediatr Intensive Care. 2019;8:144-7. DOI: https://doi.org/10.1055/s-0038- 1676993
14. Nannan Panday RS, Wang S, van de Ven PM, Hekker TAM , Alam N, Nanayakkara PWB. Evaluation of blood culture epidemiology and efficiency in a large European teaching hospital. PLoS One. 2019;14:1-11. DOI: https://doi.org/10.1371/journal.pone.0214052
15. Dierig A, Berger C, Agyeman PKA, Bernhard-Stirnemann S, Giannoni E, Stocker M, *et al*. Time-to-positivity of blood cultures in children with sepsis. Front Pediatr. 2018; 6:e222-32. DOI: https://doi.org/10.3389/fped.2018.00222
16. Aygün F, Durak C, Varol F, Çokuğraş H, Camcıoğlu Y, Çam H, *et al*. Evaluationof complete blood count parameters for diagnosis in children with sepsis in the pediatric intensive care unit. J Pediatr Inf. 2020;2:e55-e62. DOI: https://doi.org/10.5578/ced.68886
17. Dewi R, Rahayu T. Kadar C-peptida dan skor PELOD-2 sebagai prediksi prognosis pasien sepsis dengan hiperglikemia. J Indonesian Med Assoc. 2015;596-600.
18. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: Cardiovascular and immunological aspects. Virulence. 2014;5:12-9. DOI: https://doi.org/10.4161/viru.26982
19. Wati DK, Hartawan INB, Suparyatha IBG, Mahalini DS, Pratiwi IGAPE, Utama IMGDL. Profil sepsis anak di pediatric intensive care unit Rumah Sakit Umum Pusat Sanglah Denpasar - Bali. Sari Pediatr. 2019;21:152-8. DOI: https://doi.org/10.14238/sp21.3.2019.152-8
20. Supit P, Mandei JM, Rampengan NH. profil anak dengan sepsis dan syok sepsis yang dilakukan kultur darah periode Januari 2010-Juni 2015 DI RSUP Prof. Dr. R. Kandou Manado. e-CliniC. 2016;4. DOI: https://doi.org/10.35790/ecl.4.1.2016.10982
21. Salim, HBSI, Nym, BHI. Penggunaan skor pediatric logistic organ dysfunction harian Sebagai prediktor mortalitas anak yang dirawat di unit perawatan intensif anak. Sari Pediatr. 2016;1:143-8. DOI: https://doi.org/10.14238/sp16.2.2014.141- 6
22. Wulandari A, Pudjiastuti P, Martuti S. Severe sepsis criteria, PELOD-2, and pSOFA as predictors of mortality in critically ill children with sepsis. Paediatr Indones. 2019;59:318-24. DOI: https://doi.org/10.14238/pi59.6.2019.318-24
23. Simajuntak YR, Saputra I, Triratna S, Bakri A, Iriani Y. Validation of PELOD-2 score as a predictor of life-threatening organ dysfunction in pediatric sepsis. Paediatr Indones. 2020;60:227-32. DOI:https://doi.org/10.14238/pi60.5.2020.227-32
24. Sovira N, Ism, J, Trisnawati Y, Lubis M, Yusuf S. Profil penyakit kritis di ruang rawat intensif anak RSUD Dr. Zainoel Abidin Banda Aceh. Sari Pediatr. 2020;22:92-7. DOI: https://doi.org/10.14238/sp22.2.2020.92-7
25. Melda M, Triasih R, Nurnaningsih. Modifying the pelod-2 score to predict mortality in critically ill patients. Paediatr Indones. 2021;61:61-8. DOI: https://doi.org/10.14238/pi61.2.2021.61-8