Published Online: 2025 April 29 **Research Article**

D-dimer as a Marker of Clinical Outcome in Children with Sepsis: A Tertiary Care Centre Experience

Shrikiran Aroor [#1], Arthi Palanichamy [#2], Sandeep Kumar [1], Ramesh Bhat Y [1], Suneel C Mundkur [1], Pushpa Kini [1], Koushik Handattu [1,*]

[1] Department of Paediatrics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, 576104, Karnataka, India
[2] SG Institute of Medical Sciences and Research, Coimbatore, 641004, Tamil Nadu, India

[*] ***Corresponding Author:*** Department of Paediatrics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, 576104, Karnataka, India. Email: koushik.h@manipal.edu
# These authors have contributed equally

Received: 3 August, 2024; **Revised:** 27 January, 2025; **Accepted:** 25 February, 2025

Abstract

Background: Emerging infections, sepsis, and disseminated intravascular coagulation (DIC) carry a high risk of morbidity and mortality in children. Elevated D-dimer levels indicate ongoing thrombosis and thrombolysis, which are hallmarks of DIC. Hence, D-dimer can be used as a prognostic marker in sepsis.

Methods: A prospective single-center observational study was conducted at the Department of Pediatrics, Kasturba Medical College, Manipal. Children aged between 1 month and 18 years with sepsis were included to determine the level of D-dimer and to correlate D-dimer levels with outcomes.

Results: Among the 80 consecutive children included in the study, the incidence of sepsis was highest in the 1 month to 6 years age group (55%). Lower respiratory tract infection (LRTI) was the most common etiology (25%) for sepsis. D-dimer was elevated in 64 out of 80 children (80%), and C-reactive protein (CRP) was elevated in 66 children (82%). About 6 children with sepsis had multi-organ dysfunction, with D-dimer elevated in 4 of these children. Three patients (4%) succumbed in our cohort. When elevated D-dimer levels were compared with the primary outcomes, statistical significance was not found. However, elevated D-dimer was found to be fairly sensitive (74 - 85%) in predicting outcomes, though with poor specificity. Data were analyzed using the Statistical Package for the Social Sciences version 23. The mean ± standard deviation, median, and interquartile ranges were used based on the normality of data. The chi-square test/Fisher's exact test and Mann-Whitney tests were used for the analysis of categorical and continuous-discrete data, respectively, to determine statistical significance.

Conclusions: This study reiterates that D-dimer is a sensitive tool for identifying various outcome parameters, though not statistically significant.

Keywords: Disseminated Intravascular Coagulation, Child, Fibrinolysis, Sepsis

1. Background

Sepsis is a syndromic reaction to infection that can result in organ dysfunction caused by a defect in the host's immune response. In 2017, globally, about 50% of sepsis cases occurred in children, constituting approximately 20 million cases and leading to 2.9 million deaths in children below five years of age (1). A recent report indicated that the prevalence of severe sepsis was 8.2% in hospitalized children, with a mortality rate of 25% among those with severe sepsis (2). Previously, different scoring systems were used to stratify sepsis patients and predict mortality (3). However, these scoring systems did not include biochemical tests for diagnosis and prognostication (3). Biomarkers like C-reactive protein (CRP) and procalcitonin help differentiate between infectious and non-infectious causes and also assist in monitoring the response to antimicrobials (3, 4).

Recently, infection and inflammation have been linked to derangement in the coagulation cascade. D-

How to Cite: Aroor S, Palanichamy A, Kumar S, Bhat Y R, C Mundkur S, et al. D-dimer as a Marker of Clinical Outcome in Children with Sepsis: A Tertiary Care Centre Experience. J Compr Ped. 2025; 16 (2): e152358. https://doi.org/10.5812/jcp-152358.

dimer and other biomarkers related to coagulation are significantly increased during sepsis due to disseminated intravascular coagulation (DIC) (5). D-dimer is a biomarker used to diagnose DIC and pulmonary embolism. In patients without obvious evidence of bleeding manifestations, D-dimer can signify microvascular thrombosis and fibrinolysis, indicating the severity and complexity of the disease (6-8).

2. Objectives

Although many studies have examined the role of D-dimer in predicting the severity and mortality of sepsis, only a few have explored its role in predicting outcomes such as the length of ICU stay, need for inotropes, and mechanical ventilation. Hence, we aimed to study the role of D-dimer in predicting the severity and detailed outcome measures of children with sepsis.

3. Methods

This is a single-center, prospective, observational study conducted in the Department of Paediatrics, Kasturba Medical College, Manipal, India, among children with a diagnosis of sepsis aged between 1 month and 18 years, from May 2021 to July 2022. Approval for the study was obtained from the Institutional Ethics Committee (IEC number 866 - 2020) and registered with the Clinical Trial Registry of India (CTRI) (CTRI/2021/04/032592). Informed written consent was obtained from the parents of the study participants, indirect identifiers were used, and patient-related data were kept confidential.

Children were recruited to the study if they satisfied the Systemic Inflammatory Response Syndrome (SIRS) criteria according to the International Consensus Conference on Pediatric Sepsis 2005 (9). SIRS was diagnosed when at least two of the following four criteria were present, one of which must be an abnormal temperature or leukocyte count: Core body temperature of > 38.5°C or < 36°C, tachycardia/bradycardia, tachypnea, or leukocytosis/leukopenia. Sepsis is defined as SIRS in the presence of or as a result of a suspected or proven infection. Severe sepsis is defined as sepsis plus one of the following: Cardiovascular organ dysfunction, acute respiratory distress syndrome, or two or more other organ dysfunctions. Septic shock is when sepsis is associated with cardiovascular or organ dysfunction (9).

The following children were excluded from the study: Those on anticoagulants or procoagulants before admission, those diagnosed with malignancies, those with a history of recent fibrinolytic therapy/stroke/pulmonary embolism/deep vein thrombosis, those diagnosed with sickle cell disease, those with snake envenomation, those with a history of recent blood transfusion, or those who refused consent. Baseline clinical, laboratory, and treatment data were documented in the proforma designed for the study. Plasma samples for D-dimer levels were sent along with routine investigations within 24 hours of admission among children with sepsis. D-dimer levels were measured by the Rosch Cobas c702 model plasma enhanced immunoturbidometric method with a range of detectability of 0.15 - 9.0 microgram FEU/mL. The following normal values of D-dimer (microgram FEU/mL) were considered for analysis: 1 month-1 year: 0.22 (0.11 - 0.42), 1 year-5 years: 0.25 (0.09 - 0.53), 6 years-10 years: 0.26 (0.10 - 0.56), 11 years-16 years: 0.27 (0.16 - 0.39), Adult: 0.18 (0.05 - 0.42) (10).

D-dimer levels of patients were compared with outcomes, namely, length of hospital stay, length of ICU stay, need for oxygen and/or mechanical ventilation, inotropes requirement, and mortality. Based on the estimation that D-dimer has a 72% prognostic ability and 10% absolute precision, the sample size required was 80. Out of 87 consecutive children who fulfilled the SIRS criteria during the study period, 80 children were recruited. Four children with acute lymphoblastic leukemia, one child with a recent history of blood transfusion, one child with aspirin usage, and one child who had post-cardiac surgery were excluded from the study.

Data were analyzed using the Statistical Package for the Social Sciences version 23. For parameters where the scatter was uniform, the mean and standard deviation were considered, and where the distribution was skewed, the median and interquartile ranges were considered for statistical assessment. The chi-square test and Fisher's exact test were used for the analysis of categorical data, and the Mann-Whitney test was used for continuous, discrete data to determine statistical significance. Sensitivity and specificity were calculated by receiver operating characteristic (ROC) curve analysis.

4. Results

Table 1. Demographic Profile and Etiology of Sepsis (N = 80)

Characteristics	No. (%)
Age	
1 (mo) - 5 (y)	45 (56.3)
> 5 - 12 (y)	16 (20)
> 12 (y)	19 (23.7)
Gender	
Male	43 (53.7)
Female	37 (46.3)
Etiology of sepsis	
Pneumonia	20 (25)
Dengue-like illness/dengue fever	11 (12)
Meningoencephalitis/meningitis	10 (14)
Scrub typhus	9 (12)
Urinary tract infection	6 (8)
Acute gastroenteritis	6 (7)
COVID-19 infection	4 (5)
Pyrexia of unknown origin	3 (4)
Sinusitis/URTI	3 (4)
Kawasaki's disease	2 (3)
Viral exanthematous illness	2 (3)
Typhoid fever	1 (1)
Pulmonary TB	1 (1)
Cellulitis	1 (1)

We studied the role of D-dimer in identifying and predicting outcomes in 80 children aged between 1 month and 18 years with sepsis. The male-to-female ratio was 1.1:1. Table 1 shows the demographic details and etiology of sepsis among the study participants. The most common clinical presentation of sepsis was fever, observed in 95% of the cases. Pneumonia was the most common etiology for sepsis, accounting for 25% of the cases.

Details of the severity of sepsis and absolute D-dimer levels among the study participants are described in Tables 2 and 3. The majority of study participants belonged to the sepsis category, and D-dimer was elevated in 80% of the cases included. Children were categorized based on the severity of sepsis according to the Systemic Inflammatory Response Syndrome (SIRS) criteria into sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) (Table 2). The maximum D-dimer level found was > 9 µg FEU/mL, observed in 8 cases, with 4 cases categorized under MODS. Out of 64 children with elevated D-dimer, only 2 children exhibited bleeding manifestations (endotracheal bleeding and hematuria).

The primary outcomes of the study participants are described in Table 4. The median duration of hospital stay in the study was 8 days, with the maximum hospital stay being 30 days and the minimum hospital stay being 2 days.

When elevated D-dimer levels were compared against primary outcomes (Table 5), statistical significance was not obtained. However, elevated D-dimer was found to be fairly sensitive in predicting outcomes using the ROC curve. The sensitivity of D-dimer to predict the requirement for ICU care, prolonged hospital stay, oxygen requirement, mechanical ventilation requirement, and inotrope requirement was 74%, 77%, 85%, 80%, and 83%, respectively. Specificity for these outcomes was poor, ranging from 14% to 22%. Among the 3 deaths in children with sepsis, all had elevated D-dimer levels, with the maximum D-dimer level being > 9 µg FEU/mL. Overall mortality in children with sepsis in our study was 3.7%. The sensitivity of D-dimer to predict mortality was 100%, whereas specificity was only 20%.

5. Discussion

The highlight of our study is the finding that D-dimer is a highly sensitive marker for predicting outcomes. D-

Table 2. Categorization of Cases Based on Severity of Sepsis (N = 80)

Variables	Number of Cases (%)
Sepsis	60 (76)
Severe sepsis	13 (16)
Septic shock	7 (9)

Table 3. D-dimer Levels in Children with Sepsis

D-Dimer	Number of Cases (%)
Normal (0 - 0.5 μg FEU/mL)	16 (20)
Elevated (> 0.5 μg FEU/mL)	64 (80)

dimer is a biomarker used to diagnose DIC and pulmonary embolism. It is an easily obtainable test that signifies the stimulation of the coagulation pathway and the complexity of the body's response and outcome (6-8). Sepsis is the most common etiologic factor for DIC in children, with DIC present in almost 30 - 60% of sepsis cases. The sustained activation of the inflammatory and coagulation processes leads to microvascular thrombosis, thereby causing DIC, which can lead to multiple organ dysfunction syndrome (MODS) and mortality. Hence, it becomes important to detect DIC early and intervene. D-dimer, a marker of coagulation and fibrinolysis, is being studied in children with sepsis (11).

In a study conducted by Weiss et al. (12), the highest incidence of sepsis was seen in children under 5 years (43%), followed by those aged 6 - 12 years (26%) and 12 - 18 years (23%), similar to our study. This possibly explains the high mortality rate in children under 5 years of age due to sepsis. Nademi et al. (13) studied the source of fever in children and found that 41 (29%) children had a serious infection. The most common cause of infection was pneumonia (22%), followed by meningitis. This observation is similar to our study, where the most common cause of sepsis was pneumonia, constituting 25% of the cases.

In our cohort, blood cultures were performed in 66 children, out of which 2 cultures were positive for *Streptococcus pneumoniae*, 1 for *Candida*, and 1 for *Escherichia coli*. Out of the 4 culture-positive sepsis cases, 3 had elevated D-dimer levels. In a study by Alvaro-Meca et al. (14) on epidemiological trends of sepsis, it was found that the length of hospital stay was high in infants and children under 5 years (21.8 days), compared to older children (5 - 9 years) (10.2 days). Nonetheless, in our study, the median duration of hospital stay in children with sepsis was 8 days, with the maximum stay being 30 days and the minimum stay being 2 days. However, there was no significant difference in the median duration of hospital stay between those with elevated D-dimer (8 days) and those with normal D-dimer (7 days).

In our study, MODS led to mortality in 33% of cases (2 out of 6 MODS cases), which is comparable to another similar study where the mortality was 30% (15). In 2012, Sharma et al. (16) conducted a pilot study to determine D-dimer and fibrinogen levels in 50 children with sepsis. It was found that both D-dimer and fibrinogen were significantly increased in patients compared to controls, even though no patient had any clinical features of DIC at admission. Sridhar et al. (17) conducted a case-control study to determine the role of D-dimer as a marker of DIC in children with dengue hemorrhagic fever (DHF). They found that D-dimer levels were significantly higher among those who presented with shock, irrespective of the severity of thrombocytopenia.

In a study done by Li et al. (18) in elderly patients with sepsis, a combination of D-dimer levels, PaO2/FiO2 levels, and the Sequential Organ Failure Assessment (SOFA) score were used as prognostic markers in terms of 28-day mortality. It was concluded that each of these variables is a good marker for the prognosis of sepsis.

In the present study, elevated D-dimer levels were compared with outcomes, namely length of hospital stay, length of ICU stay, need for oxygen, mechanical ventilation, mortality, and inotrope requirement, however statistical significance was not evident. However, it is noteworthy that Sharma et al. (16) studied only the D-dimer positivity rate in patients compared to

Table 4. Outcomes in Children with Sepsis

Variables	Number of Cases (%)
Hospital stay (d)	
≤ 14	71 (89)
≥ 14	9 (11)
ICU care requirement	39 (49)
Oxygen requirement	27 (34)
Inotropes requirement	12 (15)
Need for mechanical ventilation	5 (6)
Mortality	3 (4)

Table 5. Comparison of D-dimer Levels with the Primary Outcomes in Children with Sepsis [a]

Outcome	D-Dimer		P-Value
	Normal	Elevated	
Duration of hospital stay > 14 (d); (n = 71)	16 (20)	64 (80)	0.4 [b]
ICU care (n = 39)	10 (26)	29 (74)	0.1 [b]
Requirement of oxygen (n = 27)	4 (15)	23 (85)	0.407 [b]
Mechanical ventilation (n = 5)	1 (20)	4 (80)	1 [b]
Inotrope requirement (n = 12)	2 (17)	10 (83)	0.75 [b]
Mortality (n = 3)	0	3 (100)	0.5 [c]

[a] Values are expressed as No. (%).

[b] Chi-square test.

[c] Fisher's exact test.

controls and not the levels. Similarly, in the study by Li et al. (18), D-dimer levels in association with other factors like PaO_2/FiO_2 levels and the Sequential Organ Failure Assessment (SOFA) score were studied as outcome predictors, not D-dimer alone. The sensitivity of D-dimer to predict each of the above-mentioned outcomes varied between 70% and 85%; however, it had poor specificity. Therefore, it is better to study D-dimer in association with other biochemical tools or in conjunction with illness severity scores like the pediatric SOFA (pSOFA) to predict outcomes. This approach will ensure early identification of sepsis and its complications and ensure appropriate timely intervention (19, 20).

The limitation of our study was that a large proportion of cases were in the less severe category — sepsis (76%) — which might have lead to selection bias. The total number of cases in the serious categories (severe sepsis, septic shock, and MODS) constituted 24%. This would have led to falsely low levels of D-dimer, considering the milder illness of the participants. The lack of logistic regression analysis to adjust for confounding variables is also a limitation of our study. We recommend larger studies with more power to better predict outcomes before generalizing our findings and also explore the role of low molecular weight heparin or plasma exchange in improving the outcomes of children with sepsis.

5.1. Conclusions

Coagulation abnormalities are consistently present in the pathophysiology of the host inflammatory response to infection. Hence, it has been found that D-dimer can be studied as a marker of DIC in sepsis. This study reiterates that D-dimer is a sensitive tool to identify various outcome parameters, though not statistically significant. Higher D-dimer levels at admission may alert the clinician to the possible need for a longer hospital stay, ICU care, and inotrope requirements.

Acknowledgements

We would like to extend our heartfelt thanks to the study participants, faculty members and residents of the Department of Paediatrics, Kasturba Medical College, Manipal.

Footnotes

Authors' Contribution: Study concept and design: S. A., K. H., and A. P.; Acquisition of data: A. P.; Analysis and interpretation of data: A. P., K. H., S. A., S. K., R. Y., S. M., and P. K.; Drafting of the manuscript: S. A., K. H., and A. P.; Critical revision of the manuscript for important intellectual content: A. P., K. H., S. A., S. K., R. Y., S. M., P. K.; Statistical analysis: A. P., K. H.; Administrative, technical, and material support: S. A. and K. H.; Study supervision: S. A. and K. H.

Clinical Trial Registration Code: CTRI/2021/04/032592.

Conflict of Interests Statement: The authors declared no conflict of interests.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to ethical concerns.

Ethical Approval: This study is approved under the ethical approval code of IEC number- 866-2020 Institutional Ethics Committee of Kasturba Medical College, Manipal.

Funding/Support: This study was not funded by any agency.

Informed Consent: Informed consent was from all participants/ parents as applicable before enrolling to study.

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;**395**(10219):200-11. [PubMed ID: 31954465]. [PubMed Central ID: PMC6970225]. https://doi.org/10.1016/S0140-6736(19)32989-7.
2. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Erratum: Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study. *Am J Respir Crit Care Med*. 2016;**193**(2):223-4. [PubMed ID: 26771421]. [PubMed Central ID: PMC5464250]. https://doi.org/10.1164/rccm.1932erratum.
3. Rodelo JR, De la Rosa G, Valencia ML, Ospina S, Arango CM, Gomez CI, et al. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. *Am J Emerg Med*. 2012;**30**(9):1991-9. [PubMed ID: 22795996]. https://doi.org/10.1016/j.ajem.2012.04.033.
4. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2004;**39**(2):206-17. [PubMed ID: 15307030]. https://doi.org/10.1086/421997.
5. Amaral A, Opal SM, Vincent JL. Coagulation in sepsis. *Intensive Care Med*. 2004;**30**(6):1032-40. [PubMed ID: 15148567]. https://doi.org/10.1007/s00134-004-2291-8.
6. Shilon Y, Shitrit AB, Rudensky B, Yinnon AM, Margalit M, Sulkes J, et al. A rapid quantitative D-dimer assay at admission correlates with the severity of community acquired pneumonia. *Blood Coagul Fibrinolysis*. 2003;**14**(8):745-8. [PubMed ID: 14614354]. https://doi.org/10.1097/00001721-200312000-00009.
7. Hesselvik JF, Blomback M, Brodin B, Maller R. Coagulation, fibrinolysis, and kallikrein systems in sepsis: relation to outcome. *Crit Care Med*. 1989;**17**(8):724-33. [PubMed ID: 2502362]. https://doi.org/10.1097/00003246-198908000-00002.
8. Goebel PJ, Williams JB, Gerhardt RT. A Pilot Study of the Performance Characteristics of the D-dimer in Presumed Sepsis. *West J Emerg Med*. 2010;**11**(2):173-9. [PubMed ID: 20823968]. [PubMed Central ID: PMC2908653].
9. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;**6**(1):2-8. [PubMed ID: 15636651]. https://doi.org/10.1097/01.PCC.0000149131.72248.E6.
10. McDaniel L. Blood chemistry and body fluids. In: Anderson CC, Kapoor S, Mark TE, editors. *The Harriet Lane Handbook E-Book*. 22nd ed. Amsterdam, Netherlands: Elsevier; 2021. p. 640-52.
11. Oren H, Cingoz I, Duman M, Yilmaz S, Irken G. Disseminated intravascular coagulation in pediatric patients: clinical and laboratory features and prognostic factors influencing the survival. *Pediatr Hematol Oncol*. 2005;**22**(8):679-88. [PubMed ID: 16251173]. https://doi.org/10.1080/08880010500278749.
12. Weiss SL, Balamuth F, Chilutti M, Ramos MJ, McBride P, Kelly NA, et al. Identification of Pediatric Sepsis for Epidemiologic Surveillance Using Electronic Clinical Data. *Pediatr Crit Care Med*. 2020;**21**(2):113-21. [PubMed ID: 32032262]. [PubMed Central ID: PMC7008717]. https://doi.org/10.1097/PCC.0000000000002170.
13. Nademi Z, Clark J, Richards CG, Walshaw D, Cant AJ. The causes of fever in children attending hospital in the north of England. *J Infect*. 2001;**43**(4):221-5. [PubMed ID: 11869058]. https://doi.org/10.1053/jinf.2001.0920.
14. Alvaro-Meca A, Jimenez-Sousa MA, Micheloud D, Sanchez-Lopez A, Heredia-Rodriguez M, Tamayo E, et al. Epidemiological trends of sepsis in the twenty-first century (2000-2013): an analysis of incidence, mortality, and associated costs in Spain. *Popul Health Metr*. 2018;**16**(1):4. [PubMed ID: 29433513]. [PubMed Central ID: PMC5809921]. https://doi.org/10.1186/s12963-018-0160-x.
15. Khan MR, Maheshwari PK, Masood K, Qamar FN, Haque AU. Epidemiology and outcome of sepsis in a tertiary care PICU of Pakistan. *Indian J Pediatr*. 2012;**79**(11):1454-8. [PubMed ID: 22392263]. https://doi.org/10.1007/s12098-012-0706-z.
16. Sharma A, Sikka M, Gomber S, Sharma S. Plasma Fibrinogen and D-dimer in Children With Sepsis: A Single-Center Experience. *Iran J*

Pathol. 2018;**13**(2):272-5. [PubMed ID: 30697298]. [PubMed Central ID: PMC6339482].

17. Sridhar A, Sunil Kumar BM, Rau A, Rau ATK. A Correlation of the Platelet Count with D-Dimer Levels as an Indicator for Component Therapy in Children with Dengue Hemorrhagic Fever. *Indian J Hematol Blood Transfus*. 2017;**33**(2):222-7. [PubMed ID: 28596655]. [PubMed Central ID: PMC5442049]. https://doi.org/10.1007/s12288-016-0686-7.
18. Li T, Hu WQ, Li X, Zhang JP, Tan LZ, Yu LX, et al. Prognostic value of PaO(2)/FiO(2), SOFA and D-dimer in elderly patients with sepsis. *J Int Med Res*. 2022;**50**(6):300060522110760. [PubMed ID: 35751423]. [PubMed Central ID: PMC9234855]. https://doi.org/10.1177/03000605221100755.
19. Zeerleder S, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. *Chest*. 2005;**128**(4):2864-75. [PubMed ID: 16236964]. https://doi.org/10.1378/chest.128.4.2864.
20. Kotake K, Hongo T, Tahira A, Niimi N, Haisa I, Kawakami Y. Factors Determining the Efficacy of Recombinant Human Thrombomodulin in the Treatment of Sepsis-Induced Disseminated Intravascular Coagulation. *Biol Pharm Bull*. 2021;**44**(5):605-10. [PubMed ID: 33612566]. https://doi.org/10.1248/bpb.b20-00371.