URF PUBLISHERS
connect with research world

Journal of Cell Science and Regenerative Medicine

https://urfpublishers.com/journal/cell-science-regenerative-medicine

Vol: 1 & Iss: 2

Research Article

Diagnostic Aspect of Ferritin Level in Acquired Heart Failure in Children: A Retrospective Study in Covid-19 Patients

Running title: Ferritin blood level in Covid-19 children

Amir Hasabi[1], Sajjad Farrokhpour[2], Mahsa Fallahi[2], Masome Tavanayan[3], Samira Zakeri Shahvari[3] and Mohammad Satarzadeh[4]*

[1]Department of Pediatrics, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[2]School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[3]Department of Pediatrics, School of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

[4]Student Research Committee, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

Citation: Satarzadeh M. Diagnostic Aspect of Ferritin Level in Acquired Heart Failure in Children: A Retrospective Study in Covid-19 Patients. *J Cell Sci Regenerative Med 2025;* 1(2): 61-66.

Received: 14 April, 2025; **Accepted:** 30 April, 2025; **Published:** 02 May, 2025

***Corresponding author:** Satarzadeh M, School of Medicine, Arak University of Medical Sciences, Iran, Arak, Iran. Tel: 09058447124; Email: m.satarzadeh78@gmail.com

ABSTRACT

Background: Managing the consequences of Covid-19 on vital organs is more crucial than the infection itself. This respiratory illness can significantly alter various biomarkers, impacting vital organs such as the heart. This study aims to investigate the relationship between serum ferritin levels and acquired heart diseases in children who suffered from Covid-19.

Methods: This retrospective study examined ferritin levels measured in children with a positive PCR result. It also examined children who underwent echocardiography from March 2019 to one year later. The research evaluated the age, gender, echocardiography results and ferritin levels of these children.

Results: Among 116 patients with COVID-19 examined, 62 (53.45%) were female and 54 (46.55%) were male. The highest ferritin levels were found in patients aged six months to one year, followed by those aged one to three years. Of the children studied, 90% had normal cardiac health. However, 4.3% presented with mild tricuspid regurgitation (TR), 2.6% with both mild TR and mitral regurgitation (MR) and another 2.6% with moderate TR, severe MR and right and left ventricular hypertrophy. Ferritin was lower in female infants and children infected with COVID-19. Statistical analysis revealed a significant association between ferritin and cardiac complications in female COVID-19 patients, but not in males. In addition, ferritin levels were significantly greater in COVID-19 patients younger than six months old with cardiac disease, even though the correlation was negligible in other age groups.

Conclusion: Serum ferritin levels can predict acquired cardiovascular disorders. Higher ferritin levels significantly correlate with the severity of heart diseases, making it a strong prognostic indicator, especially in children affected by Covid-19.

Keywords: Covid-19, Ferritin, Heart Failure, Pediatric Diagnosis

1. Introduction

Acquired heart failure (AHF), which frequently has its o rigins during childhood, continues to be a significant cause of public health in developing countries[1]. The types of childhood AHF are variable worldwide and include idiopathic cardiomegaly, endomyocardial fibrosis (EMF), rheumatic heart disease (RHD) and infectious pericarditis as the most common types of acquired heart disease (AHD)[2-4]. COVID-19 affects numerous body systems, especially the cardiovascular and respiratory systems. COVID-19-infected children have demonstrated an increased prevalence of AHF[5,6]. Furthermore, previous CVD has the potential to aggravate disease severity and impact patient mortality[7].

As of mid-October 2020, the globe had over 50 million confirmed COVID-19 cases and one million fatalities[8]. COVID-19 is an extremely contagious illness with an initial presentation of an acute respiratory infection[9]. While numerous studies have examined cardiovascular complications of COVID-19, significant gaps remain in current understanding, especially for pediatric cardiac manifestations. Of the various iron biomarkers studied, serum ferritin (SF) has been particularly significant as it is the most widely used marker of body iron status[10,11].

As established, COVID-19 patients typically exhibit decreased hemoglobin levels alongside elevated ferritin levels, enhancing diagnostic potential. A U.S. study of 5,700 hospitalized COVID-19 patients found pathologically high ferritin levels in this population[12]. Iron is a crucial micronutrient for human cells and pathogens; the innate immune system can restrict iron turnover to deprive pathogens during infection[13]. This protective reaction paradoxically causes anemia, which can cause hypoxia and organ failure later on, particularly cardiac tissue. The correlation of anemia with hyper-ferritinemia is a significant prognostic mortality factor irrespective of the history of patients[14]. Elevated ferritin may either predate impending inf lammatory responses in COVID-19 or be correlated with viral dissemination and resultant disturbances in iron metabolism[15].

The current research attempts to investigate the relationship between hyperferritinemia and acquired heart failure (AHF) in children suffering from COVID-19. In an attempt to learn about such a relationship, we performed a retrospective study assessing ferritin level and AHF occurrence in southern Iranian children.

2. Methods

The STROBE checklist has improved this retrospective, cross-sectional article this retrospective, cross-sectional article[16].

- Study design
- Study Design and Setting

This cross-sectional study was carried out at Bandar Abbas Children's Hospital, Iran, from March 2019 to March 2020, with ethical permission from the Ethics Committee of Hormozgan University of Medical Sciences. This study specifically examined the relationship of serum ferritin levels with acquired cardiac conditions in pediatric cases of COVID-19 in all hospital departments. The research recruited all 0-14-year-old patients with clinically confirmed COVID-19 diagnosis and underwent both echocardiographic evaluation and ferritin level testing.

2.1. Participants

Newborns to 14-year-olds who tested positive for Covid-19 via PCR and received a confirmed diagnosis at the hospital were included in the study. These patients underwent echocardiography and had their ferritin levels measured. The following exclusion criteria were applied for selection:

- Patients with cyanotic congenital heart disease
- Cases with family refusal to participate
- Patients with comorbid chronic conditions (chronic kidney disease, hypertension, diabetes mellitus or malignancy)
- COVID-19 patients without concurrent cardiac involvement

Researchers examined acquired heart diseases using the ICD-11 guidelines. At Bandar Abbas Children's Hospital, all tests are conducted following clinical standards and promptly sent to the hospital's lab. One limitation of this study was ensuring the accuracy of ferritin measurements. In this study, a high ferritin level was considered 140 ng/mL, while a low level was 50 ng/mL.

2.2. Data and outcome

In the first phase, patients with confirmed COVID-19 diagnoses were chosen. Next, ferritin levels were measured to screen for acquired heart disease. Patient selection was made regardless of gender, race, skin color or native status. Demographic data such as age, sex and weight were obtained on standardized forms. Treatment protocols such as ferritin level monitoring were used. The checklist was validated by Hormozgan University of Medical Sciences' Children's Department as reliable and valid. Structured interviewing, examination of medical records and a questionnaire designed by the researcher and answered under pediatricians' supervision with expertise in hematology, cardiology, infectious diseases and statisticians was used for collecting data. The study protected patient data confidentiality (by collecting data anonymously), ensured methodological fidelity, honest reporting, objective analysis of results and adherence to research ethics principles.

2.2.1. Data synthesis and analysis: The gathered data were analyzed using SPSS software version 23. Descriptive statistics indicators such as frequency, frequency percentage, mean and standard deviation were used to evaluate all the gathered data. The required number of individuals for the study was calculated to be 116 individuals (form in Appendix 1). The 95% level of normal distribution for p=0.10 was estimated to be d=0.036. Patients were selected by convenience sampling from children with COVID-19 referring and following the application of exclusion criteria. Thus, the sampling continued until the end of the group of 116 eligible children and was traced in a non-random manner.

2.2.2. Participant and demographic data: The research team initially identified all patients with PCR-confirmed COVID-19 diagnoses, with results verified by a pediatric infectious disease specialist. Subsequently, the study focused on patients who had undergone echocardiography, with findings carefully reviewed by a pediatric cardiologist to confirm acquired heart failure (AHF) diagnoses. For eligible patients meeting discharge criteria, comprehensive medical histories and laboratory results were compiled **(Figure 1)**.

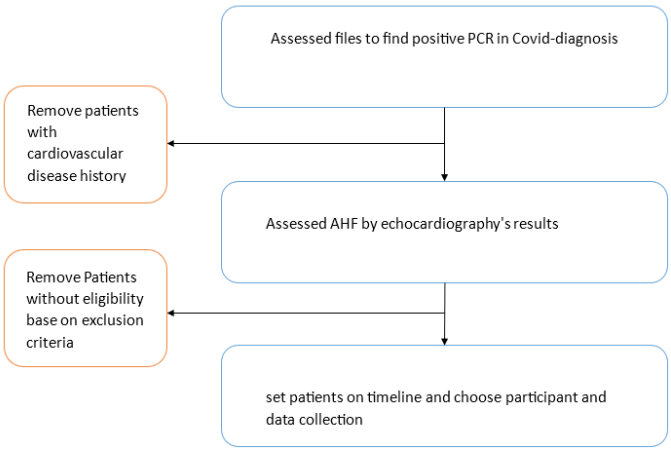

Figure 1: patients selection steps and exclusion criteria.

Patient selection followed reverse chronological order, with the 116 most recent hospital admissions included in the analysis. The cohort was stratified into age-specific categories, with detailed age distribution data presented in **(Figure 2)**.

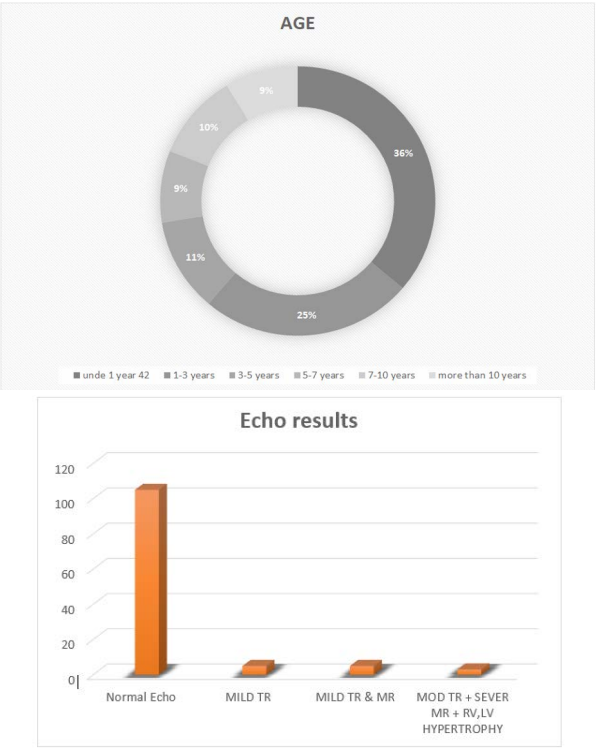

Figure 2: patients' distributions, the upper one shows the normal age distribution among the participants, the lower one shows the classification of children based on their echo results. TR: Tricuspid regurgitation, MR: mitral regurgitation, RV: Right ventricle, LV: left ventricle.

2.3. AHF in children with Covid-19 is a function of the child's weight but is not affected by age

No correlation was found between age and cardiac complications ($p>0.05$), which suggests that post-COVID-19 acquired heart disease prevalence in children cannot be explained by normal developmental health or physiology at birth. Infants less than one year old did have the most severe manifestations of disease, though this trend was not statistically significant **(Table 1)**.

A strong inverse correlation was also observed between patient weight and cardiac involvement ($p<0.05$), with disease severity being significantly reduced as weight increased. Patients with the lowest weights also had the most severe manifestations of the heart. While female patients had a tendency toward higher baseline weights, males were predominantly represented in the mild tricuspid regurgitation (MILD TR) group. This small but possibly important pattern deserves particular attention to viral infection screening in female children **(Table 1)**.

Table 1: this table show relation of Weight, Sex and Age by Echo results.

	MOD TR + SEVER MR + RV, LV HYPERTROPHY	MILD TR & MR	MILD TR	Normal	-P value
Age					
under 1 year	3	·	1	38	0.06
1-3 years	·	·	1	28	
3-5 years	·	1	2	10	
5-7 years	·	1	·	9	
7-10 years	·	·	·	12	
more than 10 years	·	1	1	8	
Sex					
Daughter	3	2	2	55	0.357
Boy	0	1	3	50	
Weight					
Numerus	3	3	5	105	
Weight (mean ± standard deviation) Kg	4/160/28±	15/503/50±	14/686/58±	13/288/16±	0.03

2.4. Ferritin levels in children with Covid-19 are different between males and females

Female children with COVID-19 and no heart disorders had significantly elevated ferritin levels than males, a pattern that persisted in the MILD TR category even though boys were higher in the MILD TR & MR group. There was a significant association between ferritin levels and cardiac status in female COVID-19 patients and children as a whole, with significantly elevated ferritin in females with heart disease. Significantly, this ferritin-cardiac disease correlation was observed in both genders, as male COVID-19 patients' cases of heart-disease also presented with increased levels of ferritin. This indicates the diagnostic value and possible therapeutic significance of ferritin in COVID-19 patients below the age of one with acquired cardiac diseases **(Table 2)**.

Table 2: ferritin blood level in male and female patients, based on their Echo results.

	Ferritin (mean ± standard deviation) ng/mL	Numerus	P-value
Female			
Normal	239/38218/74 ±	55	0.00
MILD TR	37/47228/50 ±	2	
MILD TR & MR	196/57565/00 ±	2	
MOD TR + SEVER MR + RV, LV HYPERTROPHY	188/211110/66 ±	3	
Male			
Normal	178/43162/94 ±	50	0.15
MILD TR	103/34208/33 ±	3	
MILD TR & MR	833/00	1	
MOD TR + SEVER MR + RV, LV HYPERTROPHY	-	-	

2.4.1. Ferritin level in children with Covid-19 is a function of the child's age: Results in **(Table 3)** present age-specific relations between ferritin levels and cardiac involvement in COVID-19 patients. The statistically significant correlation was observed in infants younger than six months, while this tendency was absent in children younger than one year. The most powerful, though statistically nonsignificant, relation was seen in the six-month to one-year age group with cardiac disorders. Across other age categories, this correlation existed but was limited by low sample sizes. Notably, all ages were uniform in showing that heightened cardiac damage was linked to more highly elevated ferritin levels. These findings support the measurement of ferritin levels as a uniform criterion for ascertaining risk of acquired heart failure, particularly for children less than one year old.

Table 3: The relationship between ferritin and heart diseases in covid patients at different ages.

	MOD TR + SEVER MR + RV, LV HYPERTROPHY	MILD TR & MR	MILD TR	Normal	P-value
Age					
under 1 year	Under 6 months=1002/00	-	255/00	Under 6 month = 246/12167/27±	0.06
	Upper 6 month = 132800			Upper 6 month = 253/70238/00±	
1-3 years	-	-	89/00	118/89143/26±	
3-5 years	-	426/00	268/00	147/20103/84±	
5-7 years	-	704/00	-	142/11159/48±	
more than 7 years	٠	833/00	202/00	66/7569/27±	

3. Discussion

The analysis of the current research findings indicates a notable correlation between ferritin levels and the prevalence of cardiovascular conditions (P<0.05). Following the onset of Covid-19 infection among individuals, the likelihood of developing cardiovascular issues rises, aligning with the outcomes of this investigation. The findings demonstrate that ferritin levels in COVID-19 patients serve as a predictive biomarker for disease complications and cardiac failure development in pediatric cases. Both age and gender significantly influenced the relationship between ferritin and acquired cardiovascular disorders (P<0.05). The highest infection rates occurred among females under six months of age[17]. Ahmed's research confirmed ferritin's significant association with COVID-19 complications and cardiac issues, particularly in younger patients and females[18]. While no significant correlation emerged between Z Score, weight and cardiovascular risk in COVID-19 patients, Reyes' study found that elevated serum ferritin levels during follow-up indicated higher coronary heart disease risk[19]. The results clearly revealed that heavier children had reduced heart failure susceptibility. Furthermore, ferritin serves as an inflammatory marker for predicting disease severity and cardiac complications, showing differential relationships based on age and gender[20].

Ferritin, the major intracellular iron storage protein and acute-phase reactant, becomes elevated in inflammatory conditions including infections, hyperferritinemia syndromes (macrophage activation syndrome, antiphospholipid syndrome) and septic shock[21,22]. Recent evidence establishes ferritin as a predictor of ischemic heart disease mortality[23,24]. while Liu's work extends this association to heart failure and cardiac ischemia[25]. Our findings confirm this cardiac-ferritin relationship, particularly noting ferritin's role in cardiac cellular mechanisms. Elevated ferritin with other inflammatory markers (CRP, IL-6) predicts worse COVID-19 outcomes[26,27] and links to aortic valve calcification via TNF-α-associated inflammation[28]. Additionally, these element concentrations in patients with Covid-19 hyperferritinemia (ferritin level greater than 400 ng/ml) are associated with disease severity in patients[29]. COVID-19 hyperferritinemia (>400 ng/ml) directly correlates with disease severity[29]. Proposed mechanisms for COVID-19 cardiac complications include direct cardiotoxicity, inflammatory responses, supply-demand mismatch, thromboembolism, drug effects, DIC and electrolyte disturbances[30-33]. with escalating risk as disease progresses, making critically ill patients particularly vulnerable to cardiac involvement.

Eventually, ferritin levels have a high value for the prognosis of heart disorders in pediatric patients with Covid-19. The increase in ferritin is related to the child's weight and shows a higher sensitivity for heart diseases in children under one year of age. The obtained results showed that serum ferritin levels is a predictive factor for acquired cardiovascular disorders, although they cannot reliably predict their severity.

4. Conclusion

Measuring ferritin levels in children, particularly those under one year, is strongly advised as a prognostic indicator for heart diseases, as ferritin is a biomarker associated with iron. Despite the limited sample size, this study proposes further clinical investigations to explore the significance of this marker. Future studies are anticipated to help reconcile any discrepancies observed in the current research findings.

4.1. Ethics approval and consent to participate

All study procedures involving human participants complied with the ethical standards of our institutional review board, national research regulations and the 1964 Helsinki Declaration with its subsequent amendments. This animal-free research represents part of an M.D. dissertation in social work (Ethics Code: IR.HUMS.REC.1400.392) approved by Hormozgan University of Medical Sciences, with legal guardians providing authorization for minors (<18 years) through LAR (Legally Authorized Representative) protocols.

4.2. Consent for publication

Not applicable.

4.3. Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

4.4. Conflict of Interests

The authors declared no conflict of interests.

4.5. Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

4.6. Authors' contributions

A.H. and S. F. writhed manuscript. M.F, M.T and S.Z.H are gathered data. M.S. edited manuscript. All authors reviewed the manuscript.

4.7. Acknowledgment

The authors sincerely thankful the counselors in the Clinical Research Development Center of Bandar Abbas Children's Hospital.

5. References

1. Loss KL, Shaddy RE, Kantor PF. Recent and upcoming drug therapies for pediatric heart failure. Frontiers in Pediatrics, 2021;9: 681224.
2. Abdel-Haq N, Moussa Z, Farhat MH, et al. Infectious and noninfectious acute pericarditis in children: An 11-year experience. International Journal of pediatrics, 2018;2018: 5450697.
3. Nkoke C, Menanga A, Boombhi J, et al. A new look at acquired heart diseases in a contemporary sub-Saharan African pediatric population: the case of Yaoundé, Cameroon. Cardiovasc Diagn Ther, 2015;5: 428-434.
4. Agarwal N, Taneja S. Acquired heart disease in children is not necessarily rheumatic. Tropical Doctor, 2019;49: 181-184.
5. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol, 2020;17: 259-260.
6. Li JW, Han TW, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis. Prog Cardiovasc Dis, 2020;63: 518-524.
7. Aggarwal G, Cheruiyot I, Aggarwal S, et al. Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) severity: a meta-analysis. Current problems in cardiology, 2020;45: 100617.
8. Jafri L, Ahmed S, Siddiqui I. Impact of COVID-19 on laboratory professionals-A descriptive cross sectional survey at a clinical chemistry laboratory in a developing country. Annals of medicine and surgery, 2020;57: 70-75.
9. Ahmed S, Jafri L, Majid H, et al. Challenges amid COVID-19 times - Review of the changing practices in a clinical chemistry laboratory from a developing country. Ann Med Surg (Lond), 2020;55: 300-304.
10. Daru J, Colman K, Stanworth SJ, et al. Serum ferritin as an indicator of iron status: what do we need to know? The American journal of clinical nutrition, 2017;106: 1634-1639.
11. De Carli E, Dias GC, Morimoto JM, et al. Dietary iron bioavailability: agreement between estimation methods and association with serum ferritin concentrations in women of childbearing age. Nutrients, 2018;10: 650.
12. Fan BE. Hematologic parameters in patients with COVID-19 infection: a reply. Am J Hematol, 2020;95: 215.
13. Wessling-Resnick M. Crossing the Iron Gate: Why and How Transferrin Receptors Mediate Viral Entry. Annu Rev Nutr, 2018;38: 431-458.
14. Sloniewsky D. Anemia and transfusion in critically ill pediatric patients: a review of etiology, management and outcomes. Crit Care Clin, 2013;29: 301-317.
15. Bianconi V, Mannarino MR, Figorilli F, et al. The detrimental impact of elevated Ferritin to Iron ratio on in-hospital prognosis of patients with COVID-19. Expert Review of Molecular Diagnostics, 2022;22: 469-478.
16. Gallo V, Egger M, McCormack V, et al. STrengthening the Reporting of OBservational studies in Epidemiology--Molecular Epidemiology (STROBE-ME): an extension of the STROBE Statement. PLoS Med, 2011;8: 1001117.
17. Silvestre OM, Gonçalves A, Nadruz Jr W, et al. Ferritin levels and risk of heart failure-the Atherosclerosis Risk in Communities Study. European journal of heart failure, 2017;19: 340-347.
18. Ahmed S, Ahmed ZA, Siddiqui I, et al. Evaluation of serum ferritin for prediction of severity and mortality in COVID-19-A cross sectional study. Annals of medicine and Surgery, 2021;63: 102163.
19. Reyes C, Pons NA, Reñones CR, et al. Association between serum ferritin and acute coronary heart disease: a population-based cohort study. Atherosclerosis, 2020;293: 69-74.
20. Lanser L, Fuchs D, Kurz K, et al. Physiology and inflammation driven pathophysiology of iron homeostasis-mechanistic insights into anemia of inflammation and its treatment. Nutrients, 2021;13: 3732.
21. Mahroum N, Alghory A, Kiyak Z, et al. Ferritin-from iron, through inflammation and autoimmunity, to COVID-19. Journal of autoimmunity, 2022;126: 102778.
22. Rosário C, Zandman-Goddard G, Meyron-Holtz EG, et al. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC medicine, 2013;11: 1-11.
23. Liu S, Chen M, Tang L, et al. Association between Serum Ferritin and Prognosis in Patients with Ischemic Heart Disease in Intensive Care Units. Journal of Clinical Medicine, 2023;12: 6547.
24. Dhondge RH, Agrawal S, Kumar S, et al. A Comprehensive Review on Serum Ferritin as a Prognostic Marker in Intensive Care Units: Insights Into Ischemic Heart Disease. Cureus, 2024;16.
25. Liu F, Liu Y, Xu S, et al. Mendelian randomization study reveals a causal relationship between serum iron status and coronary heart disease and related cardiovascular diseases. Frontiers in Cardiovascular Medicine, 2023;10: 1152201.
26. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. The Journal of clinical investigation, 2020;130: 2620-2629.
27. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell host & microbe, 2020;27: 992-1000.
28. Sikura KÉ, Potor L, Szerafin T, et al. Potential role of H-ferritin in mitigating valvular mineralization. Arteriosclerosis, thrombosis and vascular biology, 2019;39: 413-431.
29. Gómez-Pastora J, Weigand M, Kim J, et al. Hyperferritinemia in critically ill COVID-19 patients-is ferritin the product of inflammation or a pathogenic mediator? Clinica Chimica Acta; International Journal of Clinical Chemistry, 2020;509: 249.
30. Bandyopadhyay D, Akhtar T, Hajra A, et al. COVID-19 pandemic: cardiovascular complications and future implications. American Journal of Cardiovascular Drugs, 2020;20: 311-324.
31. Zhu H, Rhee J-W, Cheng P, et al. Cardiovascular Complications in Patients with COVID-19: Consequences of Viral Toxicities and Host Immune Response. Current Cardiology Reports, 2020;22: 32.
32. Chang W-T, Toh HS, Liao C-T, et al. Cardiac involvement of COVID-19: a comprehensive review. The American journal of the medical sciences, 2021;361: 14-22.
33. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. International journal of hematology, 2021;113: 45-57.

34. Baraff LJ. Management of infants and young children with fever without source. Pediatric annals, 2008;37: 673.