

Peer Review File

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Reviewer A

This study investigates the clinical features of heart failure in children with cardiomyopathy and those with recovered ejection fraction (HFrecEF). Among the 72 children studied, 43.1% were in the HFrEF group, while 56.9% were in the HFrecEF group. Patients in the HFrecEF group were younger with higher resting heart rates. They also had lower levels of creatinine, ST2, platelet-to-lymphocyte ratio (PLT/LYM), and smaller left atrial diameter. After an average follow-up of 35.87 months, 26 cases showed a return to normal ejection fraction, while 2 cases experienced sudden cardiac death, and 4 cases underwent heart transplantation. Logistic analysis revealed that virus infection, low ST2 levels, and intravenous immunoglobulin (IVIG) treatment were predictors of improved LVEF in heart failure patients after treatment.

This study presents interesting findings in children heart failure, but it is a single center retrospective study and the results presented should be interpreted with caution.

Please clarify what ST2 means in the introduction of the paper.

- we have modified our text as advised (see Page 2, line 53-60)

Line 79: Inclusion criteria: NT-proBNP normal values depend on the age of the patient especially in neonates. Did you take it into account?

- BNP was applied in this study. Neonates were not included in this group. BNP has a shorter half-life and is less affected by age than NT-proBNP.

Line 83: Can you explain why did you exclude myocarditis, post arrhythmia and Kawasaki disease? Those are well known causes of HFrecEF and could have been studied.

- This study mainly focused on the clinical characteristics of children with cardiomyopathy complicated with heart failure, so those with secondary cardiac dysfunction such as myocarditis, severe arrhythmia and Kawasaki disease were excluded.

Lines 130-131: Patients in the HFrecEF group were younger (P=0.000) and had a faster resting heart rate (P=0.036). Cardiac frequency is expected to be higher in younger children. This result may be biased.

- Thank you for your advice. In order to avoid misunderstanding, had a faster resting heart rate (P=0.036) was deleted in this article. (see Page 4, line 128)

Lines 131-133: What were the indications of Intravenous immunoglobulin (IVIG) since patients with myocarditis and Kawasaki disease were excluded?

- Combined with our previous experience in the treatment of cardiomyopathy and previous literature, we believe that intravenous immunoglobulin (IVIG) has a certain therapeutic effect on children with cardiomyopathy. Therefore, IVIG was used in the study
- The purpose of IVIG therapy is to down-regulate inflammatory mediators, up-regulate anti-inflammatory mediators, change the effect of cytokines to anti-inflammatory effect, neutralize microbial antigens, superantigens and autoantibodies, and block Fc receptors.
- IVIG-induced change in the balance between inflammatory and anti-inflammatory mediators in CHF patients, favoring an anti-inflammatory net effect. This effect was

significantly correlated with an improvement in LVEF.

- References
- Weinmann K, Werner J, Koenig W, Rottbauer W, Walcher D, Keßler M. Use of Cardiac Biomarkers for Monitoring Improvement of Left Ventricular Function by Immunoabsorption Treatment in Dilated Cardiomyopathy. *Biomolecules*. 2019 Oct 25;9(11):654. doi: 10.3390/biom9110654. PMID: 31731547; PMCID: PMC6920763.
- Heidendael, J., Den Boer, S., Wildenbeest, J., Dalinghaus, M., Straver, B., & Pajkrt, D. (2018). Intravenous immunoglobulins in children with new onset dilated cardiomyopathy. *Cardiology in the Young*, 28(1), 46-54. doi:10.1017/S1047951117001561
- Gullestad L, Aass H, Fjeld JG, Wikeby L, Andreassen AK, Ihlen H, Simonsen S, Kjekshus J, Nitter-Hauge S, Ueland T, Lien E, Frøland SS, Aukrust P. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. *Circulation*. 2001 Jan 16;103(2):220-5. doi: 10.1161/01.cir.103.2.220. PMID: 11208680.

Lines 134: Are you certain about the cardiomyopathy diagnosis in the 26 children who recovered normal FE (it could have been myocarditis)?

- The Diagnosis of Cardiomyopathy in Children in this study was based on the 2019 AHA publication *Cardiomyopathy in Children: Classification and Diagnosis*.

Lines 139-141: Please precise the meaning of the acronyms: CK-MB, hs-CRP, IL-4, IL-6, and IL-10, and line 202: KEGG

- we have modified our text as advised (see Page 4, line 136-138; Page8, line 195)

Line 150: Please precise younger age.

- Cutoff value=5.5month

Table 1: What were the indications for glucocorticoids and IVIG in this cohort?

- Combined with our previous experience in the treatment of cardiomyopathy and previous literature, we believe that intravenous immunoglobulin (IVIG) has a certain therapeutic effect on children with cardiomyopathy. Therefore, IVIG was used in the study
- The purpose of IVIG therapy is to down-regulate inflammatory mediators, up-regulate anti-inflammatory mediators, change the effect of cytokines to anti-inflammatory effect, neutralize microbial antigens, superantigens and autoantibodies, and block Fc receptors.
- IVIG-induced change in the balance between inflammatory and anti-inflammatory mediators in CHF patients, favoring an anti-inflammatory net effect. This effect was significantly correlated with an improvement in LVEF.

➤ References

- Weinmann K, Werner J, Koenig W, Rottbauer W, Walcher D, Keßler M. Use of Cardiac Biomarkers for Monitoring Improvement of Left Ventricular Function by Immunoabsorption Treatment in Dilated Cardiomyopathy. *Biomolecules*. 2019 Oct 25;9(11):654. doi: 10.3390/biom9110654. PMID: 31731547; PMCID: PMC6920763.
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Kjekshus J, Nitter-Hauge S, Ueland T, Lien E, Frøland SS, Aukrust P.
Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. *Circulation*. 2001 Jan 16;103(2):220-5. doi: 10.1161/01.cir.103.2.220.
PMID: 11208680.

Line 242: gambulin > gammaglobulin

➤ we have modified our text as advised (see Page 8, line 231)

Did the patients receive inotrope or levosimendan during the study period?

➤ All children were treated with positive inotropic drugs, as can be seen from the Use of digoxin in Table 1. Because of the enrollment time of the children in the article, levosimendan has not been approved for pediatric medication, so all the children did not receive levosimendan treatment.

Reviewer B

This article addresses an important topic in pediatric heart failure in attempting to determine factors associated with recovery of function after presenting with heart failure.

My primary concern with the article, particularly given the conclusions, is that patients with myocarditis were not actually excluded, although that was one of the exclusion criteria. While it is clear that primary/some genetic cardiomyopathies have/can have an inflammatory component given the association with viral infections and response to IVIG an acute myocarditis seems likely in these younger patients.

Data and Methods:

1. General information: how many of the 31 HFrefEF patients and how many of the 41 HFrecEF patients were lost to follow up? Please add to Fig 1 flow chart.

➤ All the 72 children included in this study had follow-up results. Patients who were lost to follow-up were excluded

2. Inclusion criteria: Line 78 reports the LVEF cutoff was < 45%, yet in lines 109-110 it appears that the values were < 40% please clarify which value was utilized for classification.

➤ LVEF cutoff was < 40%, we have modified our text as advised (see Page 3, line 82)

3. Exclusion criteria: How was myocarditis ruled out? Were MRI's done, biopsies?

➤ In terms of medical history, most of the enrolled children had clinical manifestations of poor appetite and edema, and the discomfort symptoms did not appear suddenly when asked about the medical history. In terms of auxiliary examination, myocardial enzymes and electrocardiogram were detected in all the enrolled children. The myocardial enzymes are roughly in the normal range, as can be seen in Table 2 of the text. According to the 2021 AHA diagnostic criteria for myocarditis, the enrolled children did not meet the clinical diagnostic criteria for myocarditis, so they were excluded from the diagnosis. Exclusion criteria have been modified to provide greater clarity about the basis for ruling out myocarditis.

4. What criteria were used for IVIG use versus not using IVIG?

➤ Combined with our previous experience in the treatment of cardiomyopathy and previous literature, we believe that intravenous immunoglobulin (IVIG) has a certain therapeutic effect on children with cardiomyopathy. We recommended IVIG to the parents of each patient, and the parents ultimately decided whether to use IVIG after considering the

complications and family economic

Results:

Line 129 - the proper term is probably sex rather than gender, sex is biologic assignment, gender is self-identified

➤ we have modified our text as advised (see Page 4, line 126)

Line 130 – Were younger age and faster heart rate independently associated, these may co-segregate with younger children typically having higher heart rates than older children.

➤ Yes, age in months is related to heart rate. We are also aware of this issue. So in the further logistic regression. Age and heart rate were included in the logistic analysis, $p>0.05$, suggesting that age and heart rate were not predictors of LVEF improvement.

Line 132 – Again somewhere the authors should put in the criteria for using or withholding IVIG.

➤ In our study, all parents were informed about the current status of the use of IVIG therapy at home and abroad, and the final decision on whether to use IVIG therapy was made by the parents. (see Page 8, line 206-208)

Line 135 – Were the 2 children that died from a cardiac cause in the HFREF or HFrecEF or one from each? Please specify.

➤ 2 children were from the HFREF group, we have modified our text as advised (see Page 4, line 129-131)

Line 143 – Ultrasonic results: In Table 2 the left atrial diameters and SD are identical at 1 year, is that correct? Yet they are statistically significantly different? Also, the text says there was no significant difference at the first study in left atrial diameter, yet the Table reports a statistically significant difference. Please reconcile these data.

➤ we have modified our text as advised (see Page 6, table2)

➤ At the first and following echocardiogram, there were statistical differences between the two groups of LAD-z.

Tables: The Tables need the abbreviations identified below each Table

➤ we have modified our text as advised.(see table)

Predictive factors of improvement: Line 150 – PLT/LYM ratio correlated with EF improvement, yet when looking at Table 3 which this refers to it appears that it was the NE/LYM ratio that was statistically significant. Please clarify.

➤ age, heart rate, PLT/LYM, creatinine, ST2, left atrial diameter, and IVIG use were correlated with ejection fraction improvement ($p<0.05$). However, there was no significant difference between PLT/LYM and IVIG use when we did the correlation analysis between predictors and EF return to normal or not.

Discussion:

Lines 175-177 – Sentence beginning with... In our study – Again why do the authors think this is not due to a high proportion with myocarditis who are more likely to recover.

➤ The enrolled children had insufficient evidence for the diagnosis of myocarditis. Children with a history of infection were considered to have an acute attack of chronic heart failure caused by infection

Conclusion:

Line 242 - The word should probably be gamma-globulin, not gambulin.

- we have modified our text as advised (see Page 8, line 231)

Reviewer C

From the English perspective, there are grammar mistakes

Consent: It is mentioned that this is a retrospective study; however, all patients consented to participate.

- we have modified our text as advised (see Page 2, line 70)

It is unclear how many were unreachable due to the retrospective nature of the study. Only lost to follow up or "missing data" are considered exclusion criteria.

- As can be seen from the flow chart 1, 46 children were excluded due to loss to follow-up

Inclusion criteria: Pediatric patients with elevated LVEDD were included. However, these patients could have had an elevated LVEDD due to infectious myocarditis vs. sepsis vs fluid overload vs dilated cardiomyopathy. Their outcomes are not expected to be the same.

- The enrolled children with a history of infection were considered to have an acute attack of chronic heart failure caused by infection

Exclusion criteria: Myocarditis is labeled as exclusion criteria; however, about half of the patients had a bacterial and/or viral infection. Why couldn't these patients have myocarditis? A cardiac MRI was not performed.

- In terms of medical history, most of the enrolled children had clinical manifestations of poor appetite and edema, and the discomfort symptoms did not appear suddenly when asked about the medical history. In terms of auxiliary examination, myocardial enzymes and electrocardiogram were detected in all the enrolled children. The myocardial enzymes are roughly in the normal range, as can be seen in Table 2 of the text. According to the 2021 AHA diagnostic criteria for myocarditis, the enrolled children did not meet the clinical diagnostic criteria for myocarditis, so they were excluded from the diagnosis. Exclusion criteria have been modified to provide greater clarity about the basis for ruling out myocarditis.
- Because of age and disease severity, we did not perform cMRI during the acute phase

Severe arrhythmias may be seen in patients with uncompensated heart failure, and these patients were excluded. This limits your population to "the best" of those with systolic failure.

- Thank you for your question. No patients in this study were excluded from the group due to exclusion criterion 3. After the discussion of our research group, in order to be more in line with the actual process and more accurate to avoid misunderstandings, the corresponding expressions in this article are adjusted: the child is tachycardia-induced cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.

A list of all medications excluded was not provided.

- According to the types of drugs, the cardiac medication is shown in Table 1

Clinical data collection: It is unclear when the baseline echocardiogram was completed and how it correlates with the patient's disease.

- we have modified our text (see Page 4, line 103-104)

- Statistics: It is unclear what data was normally vs. not normally distributed. P=0.000 is not usually an appropriate way to report statistics.

➤ P=0.000 has been changed to P<0.001, we have modified our text(see Page 4, line 128)

- Predictive factors: It is unclear what is considered "low" for certain values described. It is unclear when these laboratory values were obtained.

➤ Month Cutoff value=5.5month

➤ ST2 Cutoff value=1.89ng/ml

- Tables: Unclear if what is reported is average or median.

➤ Normally distributed continuous variables were expressed as mean ± standard deviation (mean±SD), non-normally distributed continuous variables were expressed as median and Interquartile range (IQR), and count data were expressed as percentage of the total population

Heart rate is reported as significant; however, it could be age-related as the group with HFrecEF seems younger.

➤ Yes, age in months is related to heart rate. We are also aware of this issue. So in the further logistic regression. Age and heart rate were included in the logistic analysis, p>0.05, suggesting that age and heart rate were not predictors of LVEF improvement.

Age is reported as 33.80+/- 44.98, which would cause a negative age in months.

Clinically, it is unusual to have systolic heart failure and not be on diuretics.

➤ In the table, 29 children were treated with intravenous diuretics, and the remaining 2 children were treated with oral diuretics. I am sorry for the misunderstanding caused by the medication method was not emphasized. The data in the article have been corrected.

The abbreviations were not described as part of table legends.

➤ we have modified our text as advised.(see table)

The higher use of IVIG in those who recovered function could be secondary to higher incidence of myocarditis in these patients

➤ Same question as above, answered