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ORIGINAL ARTICLE

# Evaluation of immune dysfunction in a pediatric intensive care unit: an observational study

## *Evaluación de la disfunción inmunológica en una unidad de cuidado intensivo pediátrico: un estudio observacional*

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## Abstract

**Introduction:** *Immune dysfunction in critical patients has not been clearly defined and has been insufficiently researched, particularly in pediatrics. Guidelines to standardize the immune system assessment and for routine use in clinical practice are lacking.* **Objective:** *To determine the association between immune dysfunction (here understood as the reduction of immunoglobulins and/or of the absolute count or populations of lymphocytes) and the outcome of patients admitted to the pediatric intensive care unit.* **Materials and method:** *This was an observational, analytical, descriptive, and retrospective study conducted over four years. The records of all patients who were admitted to the pediatric intensive care unit and had an immunity profile were included in the database. Demographic and clinical variables were compared between patients with and without immune dysfunction.* **Results:** *A total of 188 patients with an immune profile were identified; 83% of the patients had immune dysfunction and 65% had heart disease. The presence of immune dysfunction was associated with worse outcomes measured in mortality (37 vs. 9% p = 0.0021), length of stay greater than 14 days (46 vs. 14%; p < 0.0001) and multiple organ dysfunction syndrome (72 vs. 25%; p < 0.0001).* **Conclusion:** *Immune dysfunction is frequent in patients with a difficult disease course and in our study sample. It was found to be associated with increased mortality, duration of invasive mechanical ventilation and length of stay in the pediatric intensive care unit. Further prospective studies with other biomarkers are needed to determine the immune compromise and its impact on outcomes in critically ill children.*

***Keywords:*** *Immune dysfunction. Pediatrics, heart disease. Pediatric intensive care unit. Lymphopenia. Hypogammaglobulinemia.*

## Resumen

**Introducción:** *La disfunción inmunológica en el paciente críticamente enfermo es un compromiso de un sistema muy poco estudiado; adicionalmente, en la población infantil aún faltan guías que orienten la evaluación del sistema inmunológico.* **Objetivo:** *Determinar la asociación de disfunción inmunológica y los desenlaces en los pacientes que ingresan a la unidad de cuidado intensivo pediátrico.* **Materiales y método:** *Estudio observacional, con componente analítico, llevado a cabo durante cuatro años, en el que se revisaron los expedientes de todos los pacientes pediátricos consecutivos con estancia en la unidad de cuidados intensivos a quienes, por criterios médicos, se les realizó perfil inmunológico.*

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**Resultados:** *Durante el período de estudio se reportaron 188 pacientes quienes cumplieron con los criterios de inclusión. Se presentó disfunción inmunológica en el 83% de los casos y enfermedad cardiaca en el 65%. La disfunción inmunológica se asoció con peores desenlaces medidos en mortalidad (37 vs. 9%; p = 0.0021), tiempo de estancia mayor a 14 días (46 vs. 14%; p < 0.0001) y disfunción multiorgánica (72 vs. 25%; p < 0.0001).* **Conclusión:** *La disfunción inmunológica es frecuente en los pacientes que ingresan a la unidad de cuidado intensivo pediátrico y se asocia con un aumento de la mortalidad, la duración de la ventilación mecánica invasiva y la duración de la estancia en la unidad de cuidado intensivo pediátrico. Muchos factores se asociaron con el desarrollo de disfunción inmunológica en esta población. Se necesitan estudios prospectivos para dilucidar el manejo óptimo de la disfunción inmunológica en el paciente crítico.*

***Palabras clave:*** *Disfunción inmunológica. Pediatría. Cardiopatía. Unidad de cuidado intensivo pediátrico. Linfopenia. Hipogammaglobulinemia.*

## Introduction

Immune dysfunction is seen in intensive care in situations which cause stress and lead to an imbalance between the proinflammatory and anti-inflammatory responses[1-3]. Some authors have suggested that immune dysfunction is related to prolonged lymphopenia and abnormalities in the lymphocyte population counts, the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR) and immunoglobulin levels, among other biomarkers[4-6]. This immune dysfunction increases susceptibility to infection, multiple organ dysfunction and death[5-8].

While this has not traditionally been a major research topic, there is greater interest today in analyzing and understanding the immune processes that lead to immune dysfunction in critically ill patients. In this vein, different tools have been used for diagnosis, but, so far, none of the biomarkers used to diagnose the different immune dysfunction states has been ideal[3], and these tests are not always available for clinical use.

Therefore, a screening strategy to identify patients with immune dysfunction must be evaluated using laboratory tests which are accessible to most institutions. Consequently, the objective of this study was to determine the association between immune dysfunction (defined as a reduction in immunoglobulins, lymphocytes and their subpopulations) and outcomes in patients admitted to the pediatric intensive care unit (PICU) who have not progressed as expected.

## Materials and method

This was an observational study with an analytical, descriptive, and retrospective component, which included patients admitted to the PICU at Hospital Cardiovascular de Cundinamarca between January 1, 2017, and May 31, 2021, for whom the attending physicians ordered a screening immune study due to their degree of severity on admission, sluggish clinical course, resistance to treatment or complete blood count (CBC) abnormalities such as lymphopenia, and relevant history such as serious or recurrent infections. The study was approved by the research ethics committee at Hospital Cardiovascular de Cundinamarca, through Memorandum No. 15-06-2021. Data was collected from the medical charts. Sample size calculation was not required.

## Definition of terms

Immune dysfunction: immune dysfunction was defined as abnormalities in immunoglobulins and/or absolute lymphocyte or subpopulation counts on flow cytometry.

Multiple organ dysfunction (MOD): involvement of two or more systems, according to the 2005 Goldstein criteria[9].

Mortality: defined as patients who died while hospitalized in the PICU.

Inclusion criteria: patients under the age of 18, hospitalized in the PICU, who had an immune profile ordered during their PICU stay.

Exclusion criteria: patients with diagnosed immunodeficiencies.

## Data collection

Demographic data was collected, including age, sex, PICU stay, Pediatric Risk of Mortality (PRISM) score, admission diagnoses, and laboratory tests taken during their stay, such as CBC and leukocyte, lymphocyte, platelet and neutrophil counts. Likewise, information was collected on the values of CD3, CD4, CD8, CD19 and CD20 lymphocyte subpopulations, the CD4/CD8 ratio and NKCD3/CD16/CD56 cells. Finally, information was gathered on the status of the different immunoglobulin (Ig) classes: IgG, IgM, and IgA. The NLR and PLR were calculated, and culture results were also included[4].

## Outcome variables

The outcome variables were length of stay greater than 14 days, MOD and mortality.

## Data analysis

A descriptive analysis was conducted using measures of central tendency according to the variables' normality distribution. Means were reported with their standard deviations or medians with interquartile ranges, as appropriate. Categorical variables were reported in frequencies and percentages. For the comparative analysis between groups with and without immune dysfunction, a p value less than 0.05 was considered significant, and a two-tailed test was performed. The analysis of these comparisons considered whether the variables were categorical or quantitative and, depending on their distribution, used parametric (Student's t) and nonparametric (Mann-Whitney U, Kruskall-Wallis, Wilcoxon T, $Chi^2$) tests. Then, the variables which were significant in the bivariate analysis were taken to construct a multivariate analysis followed by logistic regression, in which the outcome variables (mortality, PICU stay and MOD) were the dependent variables. The model was adjusted by the PRISM value. The IBM SPSS® version 23 statistical program was used for the analyses.

## Results

### *Clinical characteristics of the patients*

During the study period, 1,709 patients were hospitalized and 188 met the inclusion criteria, having undergone immune screening for clinical reasons. The age ranged from 7 days to 18 years, with a mean of 26 months and a standard deviation (SD) of 46; 52% were male, 59% had congenital heart disease, and 42.6% underwent hemodynamic or surgical procedures; of these, 35% had extracorporeal circulation (ECC). Twenty-six percent had respiratory diseases, 7.4% had other infections, 4.8% had nonsurgical neurological diseases, and 2.6% had other diseases. The mean PRISM score was 22, with an SD of 12.5 points, for an expected and observed mortality of 33.27 and 32.4%, respectively, and a standardized mortality ratio of 0.97 (Table 1 and Fig. 1).

Immune screening consisted of measuring the levels of immunoglobulin G (182 patients), immunoglobulin M (181 patients) immunoglobulin A (29 patients) and CBC on admission (188 patients). Subsequently, absolute lymphocytes and subpopulations were measured: CD3 (155 patients), CD4 (156 patients), CD8 (154 patients), CD19 and 20 (150 patients), and NK (20 patients) (Table 1).

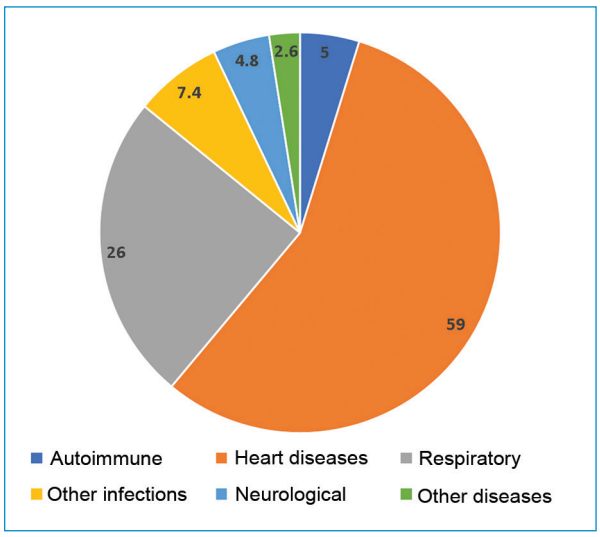


**Figure 1.** Admitting diagnosis. Reasons for admission to the pediatric intensive care unit, showing that 59% were post-cardiovascular surgery.

Table 1 shows the bivariate analysis of the population's characteristics and laboratory tests. It lists the variables that showed a significant difference when patients with and without immune dysfunction were compared. Of the 188 patients, 156 (83%) had immune dysfunction (defined as decreased immunoglobulins or lymphocytes or both) and, of these, 40% (75 patients) were found to have a reduction in both evaluated parameters (immunoglobulins and lymphocytes).

### *Analysis of the outcome variables*

Table 2 shows a bivariate analysis in which the outcome variables with and without immune dysfunction are compared. Here, immune dysfunction was associated very significantly with increased length of PICU stay (32 vs. 10; p = 0.0023), the onset of MOD (72 vs. 25%; p = 0.0001), the use of mechanical ventilation (91 vs. 59%; p = 0.0001), the use of inotropic medications (88 vs. 66%; p = 0.0019), more days on antibiotics (19 vs. 8; p = 0.0001), increased mortality (37 vs. 9%; p = 0.0021) and more isolated germs during the stay (1.26 vs. 0.66; p = 0.002).

**Table 1.** A comparison of the demographic, diagnostic and laboratory characteristics of the children included in the study

| | With immune dysfunction | Without immune dysfunction | p value |
|---|---|---|---|
| | 156/188 (83) | 32/188 (17) | |
| Sex (male) (%) | 78/156 (50) | 20/32 (62) | 0.2170 |
| Age months *m ± (SD) | 22 (39) | 48 (65) | 0.0029 |
| PRISM* | 21 (12) | 11 (11) | < 0.0001 |
| Heart disease (%) | 102/156 (65) | 9/32 (28) | 0.0001 |
| Heart disease surgery (%) | 72/156 (46) | 8/32 (25) | 0.0290 |
| ECC (%) | 60/156 (38) | 6/32 (19) | 0.0403 |
| Isolation (%) | 84/156 (54) | 12/32 (37) | 0.0805 |
| Immunoglobulin interpretation n (%) | | | |
| Low | 141/156 (91) | 0 | < 0.0001 |
| Normal | 14/156 (9) | 32/32 (100) | < 0.0001 |
| Lymphocyte interpretation n (%) | | | |
| Low | 90/156 (59) | 0 | < 0.0001 |
| Normal | 41/156 (41) | 32/32 (100) | < 0.0001 |
| Low immunoglobulins and lymphocytes | 75/156 (40) | 0 | < 0.0001 |
| Laboratory tests* m ± (SD) | | | |
| IgG mg | 381 (288) | 560 (727) | 0.0015 |
| Neutrophils | 4.646 (3.550) | 8.850 (7.992) | < 0.0001 |
| Lymphocytes | 2.218 (2.008) | 4.220 (2.630) | < 0.0001 |
| CD3 | 1.154 (891) | 2.432 (1.637) | < 0.0001 |
| CD4 | 750 (565) | 1.452 (995) | < 0.0001 |
| CD8 | 391 (414) | 901 (728) | < 0.0001 |
| CD19 AND 20 | 577 (520) | 1.271 (1207) | < 0.0001 |
| NK | 47 (44) | 487 (477) | < 0.0001 |
| NLR | 1.73 (2.58) | 3.88 (3.88) | 0.0001 |
| PLR | 110 (107) | 118 (76) | 0.6880 |

*The data are presented as m (mean) and standard deviation (SD).
n: number; %: percentage; PRISM: Pediatric Risk of Mortality score; ECC: extracorporeal circulation; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

**Table 2.** Comparison of the outcomes in patients with and without immune dysfunction

| Variable | With immune dysfunction | Without immune dysfunction | p* |
|---|---|---|---|
| | 156/188 (83) | 32/188 (17) | |
| Stay (days) m ± (SD) | 32 (40) | 10 (7) | 0.0023 |
| Respiratory failure (%) | 142/156 (91) | 19/32 (59) | < 0.0001 |
| MOD > two organs (%) | 112/156 (72) | 8/32 (25) | < 0.0001 |
| Mortality (%) | 58/156 (37) | 3/32 (9) | 0.0021 |
| Isolation (#) | 1.26 | 0.66 | 0.002 |
| Time on antibiotics (days) m ± (SD) | 18 (14) | 8 (7) | 0.0001 |
| Use of inotropic medications (%) | 137/156 (88) | 21/32 (66) | 0.0019 |

*$Chi^2$ p value.
m: mean; SD: standard deviation; MOD: multiple organ dysfunction; PICU: pediatric intensive care unit.

Immune dysfunction was not found to be associated with abnormal values or worse PICU outcomes between total leukocyte count, abnormal platelets or C-reactive protein levels, nor the NLR (1.73 vs. 3.88) and PLR (110 vs. 118; p = 0.68) levels seen in Table 1. There were no differences in immunoglobulin levels

or other CBC data in patients with heart disease or those who underwent ECC, nor was there a significant difference between diagnoses other than heart disease and having immune dysfunction, nor in the total number of leukocytes, platelets or C-reactive protein levels.

### *Multivariate analysis*

A logistic regression was run (Table 3) in which the outcome variables like mortality, PICU stay > 14 days and MOD > two organs were taken as dependent variables, and the model was adjusted to the PRISM score. This analysis found a significant association between respiratory failure (OR: 14; 95% CI: 1.7-119; p = 0.01) and the use of inotropic medications (OR: 76; 95% CI: 7-778; p = 0.000), as predictors of these outcomes. Furthermore, microbiological isolations (OR: 3; 95% CI: 1.5-7; p = 0.002), were predictors of hospital stays longer than 14 days.

**Table 3.** Logistic regression for predicting outcomes like mortality, PICU stay and MODS adjusted by the PRISM score

| | Sig. | OR | 95% CI for the OR | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Respiratory failure | 0.014 | 14.349 | 1.718 | 119.847 |
| Use of inotropic medications | 0.000 | 76.409 | 7.495 | 778.920 |
| Isolations | 0.002 | 3.456 | 1.557 | 7.670 |

Logarithm of the likelihood -2 = 142,554. Cox and Snell R2 = 0.423. Nagelkerke R2 = 0.580. MODS: multiple organ dysfunction syndrome; PICU: pediatric intensive care unit.

## Discussion

This study showed how immune dysfunction was associated with worse outcomes, greater mortality, MOD syndrome, hospital stay and the susceptibility to more microbiological isolation during the hospital stay. The group with the most abnormalities was that of children with congenital heart disease. However, the sample was made up of seriously ill patients, evidenced by their high PRISM score and high expected mortality. Likewise, the group with the clinical indication for ordering screening studies consisted of patients with sluggish progress, severe illness on admission and risk factors in their history, such as recurrent hospitalizations.

While this was not one of the study objectives, we also found that inexpensive bedside laboratory tests in intensive care patients can provide information about the distribution of lymphocytes and immunoglobulins and their subgroups in critically ill patients. In addition, lymphopenia and hypogammaglobulinemia, especially affecting IgG, were found more often in patients with immune dysfunction.

In another vein, immune dysfunction in patients with congenital heart disease who have undergone correction has been described in the literature. Hauser et al.[10] found a greater prevalence of cellular and humoral dysfunction, mainly in the first 24 hours after surgery, with a tendency to recover after seven days in the PICU. The authors reported changes in the $CD3^+$ and $CD4^+$ lymphocyte subpopulations, but no $CD8^+$ disorders, along with reduced levels of IgG, IgM and IgA, especially in patients with ECC, unrelated to hemodilution. This study also showed a reduction in all lymphocyte populations, as well as their absolute counts, in patients with congenital heart disease and those who had undergone surgery with ECC.

Hypogammaglobulinemia associated with the use of ECC has been described as secondary to the destruction of immunoglobulins by the circuit and extravasation into the interstitial space due to the marked inflammatory response and capillary leak, which, in itself, has been related to worse clinical outcomes like longer time on mechanical ventilation, longer PICU stays and the risk of secondary infections[10,11]. However, this study did not find a significant difference in the absolute values of immunoglobulins in patients with congenital heart disease with or without surgery or ECC, possibly because this screening could not be performed on 100% of the population.

Immune dysfunction is not only associated with the use of ECC, but also with factors like hypothermia or sudden temperature changes, aortic clamping, the metabolic response to trauma, hypoxia and changes in the regulatory mechanisms of genetic response, including disorders in the stress response genes which affect the hematopoietic cells and accelerate or induce apoptosis, probably secondary to high cortisol and catecholamine levels[11-13]. These immune disorders, like lymphopenia, have been associated with a higher risk of death following cardiovascular surgery, especially in children under the age of two, leading to longer hospital stays and a higher risk of predisposition to postoperative infections and sepsis[14], correlating with this study's findings. This data suggests that this population group requires special

attention in immune function monitoring, because this has an important effect on critical outcomes like the risk of infections and secondary sepsis.

The separate analysis of lymphopenia is strongly associated with the outcomes and is, therefore, an important biomarker for immune dysfunction, a process attributed not only to recruitment at the inflammation or infection site, but also to apoptosis or suppression of the myeloid precursos[15,16]. It is known in the literature as a risk factor for nosocomial infections, MOD and higher mortality secondary to apoptosis of T and B lymphocytes, as it alters the organism's ability to eradicate infections[15]. The degree of lymphocyte apoptosis has also been related to persistent multiple organ failure, longer duration of mechanical ventilation and death[17].

Furthermore, patients with hypo-IgG in critical care have been associated with a higher need for vasopressors, more likelihood of developing acute respiratory distress syndrome and higher mortality[18,19]. This data, however, differs from a study carried out in the PICU of Hospital Universitario Clínica San Rafael in Bogotá[20], which found no association between immunoglobulin levels and the progression of patients with sepsis in regard to mortality or the severity of sepsis. In the current study, the hypogammaglobulinemia results are probably influenced by the prevalence of patients with congenital heart disease and the use of ECC in the participating population.

The process of immune dysfunction can be differentiated not only by the degree of lymphopenia, but also by the analysis of lymphocyte subpopulations, a condition which reflects the involvement of the adaptive immune response and is related to the severity and clinical course of the disease[21]. Despite this, lymphocyte subpopulation screening could not be performed on 100% of the sample in our study; thus, it could not be analyzed. The prognostic value of elevated PLR and NLR in PICU patients, used as mortality markers in this study, did not prove to be a predictor of mortality.

It is important to highlight that patients with immune dysfunction were significantly associated with microbiological findings on blood cultures, which confirms the risk of and predisposition to secondary infections and affects the secondary outcomes, like prolonged stay, sepsis and MOD[15,22]. This was also found in our population's results and was a predictor of length of stay greater than 14 days.

## Strengths

This study contributes information on immune dysfunction in critically ill pediatric patients and its results have internal validity for the PICU studied. Furthermore, they encourage the performance of a more rigorous study of lymphopenia and immunoglobulin levels, to consider looking for prognostic markers and treatment strategies that can help improve intensive care in this population.

Likewise, it highlights the importance of suspecting immune dysfunction with inexpensive, bedside laboratory tests which can provide information to begin complementary studies early, with timely treatment, especially in countries like Colombia in which, many times, the diagnosis of immune dysfunction is delayed until costly tests are run, which are not easily accessible in all hospitals. Therefore, these tests are always delayed, many times requiring that empirical treatment be started with IgG supplementation, without timely certainty that the patients have this particular disorder, and with no diagnosis even at the time of their death.

## Limitations

This was a retrospective, single center study, with a population selected at the discretion of the attending specialists based on the patients' characteristics and disease progression, which limits the development of an extensive analysis of the subgroups such as, for instance, relating variables like age, type of disease or reason for PICU admission to each of the outcomes. Due to all this, immune dysfunction could only be suspected in 11% of the treated population. In addition, lymphocyte subpopulation screening could not be performed on all patients included in the study.

On the other hand, most of the patients with congenital heart disease had immunodeficiency studies taken after their surgical procedure, when their clinical condition could be considered most critical, and this may have affected the clinical outcomes found.

Finally, the patients in this study did not have a prior immunodeficiency test; only those who already had a confirmed diagnosis of immunodeficiency were excluded.

Therefore, these results cannot be generalized to other populations.

## Conclusions

Immune dysfunction, defined in this study as lymphopenia and/or hypogammaglobulinemia, was associated with worse outcomes such as longer PICU stay, MOD and mortality. We found that the degree of lymphopenia can differentiate the immunological dysfunction process and determine a relationship with the clinical course prognosis.

Many factors were associated with the onset of immune dysfunction in this population, and therefore prospective studies are needed to clarify the optimal treatment for this dysfunction in critically ill patients.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Human and animal protection.** The authors declare that no experiments in humans or animals were conducted for this study.

**Data confidentiality.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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