Review Article

Biomarkers associated with postoperative cardiac surgery clinical outcomes in pediatric intensive care

Biomarcadores associados à defechos clínicos pós-cirurgia cardíaca em terapia intensiva pediátrica

Biomarcadores relacionados con resultados clínicos en el posoperatorio de cirugía cardíaca en cuidados intensivos pediátricos

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How to cite:
Souza AR, Lima RA, Lopes-Júnior LC. Biomarkers associated with postoperative cardiac surgery clinical outcomes in pediatric intensive care. Acta Paul Enferm. 2021;34:eAPE00171.

DOI
http://dx.doi.org/10.37689/acta-ape/2021AR00171

Keywords
Biomarkers; Stress; Pediatric intensive care units; Congenital heart surgery; Pediatric nursing

Descritores
Biomarcadores; Unidades de terapia intensiva pediátrica; Cirurgia cardíaca congênita; Enfermagem pediátrica

Descriptores
Biomarcadores; Estrés; Unidades de cuidados intensivos pediátricos; Cirugía congénita del corazón; Enfermería pediátrica

Submitted
February 4, 2020

Accepted
June 1, 2020

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Abstract

Objective: To summarize and critically analyze the literature on potential biomarkers associated with clinical outcomes in the postoperative cardiac surgery period in infants and children under intensive care.

Methods: Integrative review, whose search was carried out in September and December 2019 in the databases MEDLINE, ISI Web of Knowledge, Cochrane Central Register of Controlled Trials, Embase, Cumulative Index to Nursing and Allied Health Literature, Science Direct, and Latin America and Caribbean Center on Health Sciences Information to answer the following guiding question: "What is the scientific evidence on potential biomarkers associated with clinical outcomes in the postoperative cardiac surgery period in infants and children under intensive care?". Original articles published between 2000 and 2019 in English, Spanish, or Portuguese were included. Gray literature was excluded.

Results: Eight articles made up the final sample (six descriptive observational prospective studies and two prospective cohort studies). Most studies, pediatric patients were submitted to the intraoperative cardiopulmonary bypass technique during congenital heart disease surgeries. The potential biomarkers analyzed were molecules that participate in immune-inflammatory processes, mainly proinflammatory cytokines such as IL-1β, IL-6, IL-8, and tumor necrosis factor-alpha and its receptor, as well as anti-inflammatory cytokines such as IL-10.

Conclusion: The IL-6, IL-8, and IL-10 cytokines, cortisol, and lactate showed as promising molecules for elucidating mechanisms underlying clinical outcomes in the postoperative cardiac surgery period in infants and/or children under intensive care. These molecules can take on a preventive role by being used as a diagnostic and prognostic tool in the future in a protocol that allows to identify patients with high risk to develop clinical complications during the postoperative period.

Resumo

Objetivo: Sintetizar e analisar criticamente a literatura a respeito de potenciais biomarcadores associados à desfechos clínicos no pós-operatório de cirurgia cardíaca em lactentes e crianças em cuidados intensivos.

Métodos: Revisão integrativa, cuja busca ocorreu nos meses de setembro e dezembro de 2019, nas bases de dados MEDLINE, ISI of Knowledge, CENTRAL Cochrane, EMBASE, CINAHL, Science Direct e LILACS para responder à questão norteadora: "Quais as evidências científicas acerca de potenciais biomarcadores relacionados à desfechos clínicos no pós-operatório de cirurgia cardíaca de lactentes e crianças em cuidado intensivo?" Foram incluídos artigos originais publicados entre 2000 e 2019, nos idiomas inglês, português ou espanhol. Excluiu-se toda a literatura cinzenta.

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Conflicts of interest: none to declare.

Resultados: A amostra final foi constituída por oito artigos, sendo seis estudos observacionais prospectivos descritivos e dois coortes prospectivas. Na maioria dos estudos os pacientes pediátricos foram submetidos à técnica de *Bypass Cardiopulmonar* (BCP) intraoperatória durante cirurgia de cardiopatia congênita. Os potenciais biomarcadores analisados foram moléculas participantes de processos imune-inflamatórios, predominantemente citocinas pró-inflamatórias tais como IL-1β, IL-6, IL-8 e o fator de necrose tumoral-α (TNF-α) e seu receptor, ou citocinas anti-inflamatórias como a IL-10.

Conclusão: As citocinas IL-6, IL-8 e IL-10, o cortisol e o lactato, apresentaram-se como moléculas promissoras para elucidação de mecanismos subjacentes a desfechos clínicos no pós-operatório de cirurgia cardíaca em lactentes e/ou crianças em cuidado intensivo. Tais moléculas podem assumir um caráter preventivo, podendo futuramente ser utilizadas como ferramentas diagnósticas e prognósticas alternativas para um regime que permita identificar pacientes sob alto risco de desenvolver complicações clínicas nos pós-operatórios.

Resumen

Objetivo: Sintetizar y analizar críticamente la literatura sobre potenciales biomarcadores relacionados con resultados clínicos en el posoperatorio de cirugía cardíaca de lactantes y niños en cuidados intensivos.

Métodos: Revisión integradora, cuya búsqueda ocurrió en los meses de septiembre y diciembre de 2019, en las bases de datos MEDLINE, ISI of Knowledge, CENTRAL Cochrane, EMBASE, CINAHL, Science Direct y LILACS para responder la pregunta orientadora: "¿Cuáles son las evidencias científicas sobre potenciales biomarcadores relacionados con resultados clínicos en el posoperatorio de cirugía cardíaca de lactantes y niños en cuidados intensivos?". Se incluyeron artículos originales publicados entre los años 2000 y 2019, en idioma inglés, portugués o español. Se excluyó toda la literatura gris.

Resultados: La muestra final fue formada por ocho artículos, de los cuales seis eran estudios observacionales prospectivos y dos cohortes prospectivas. En la mayoría de los estudios, los pacientes pediátricos fueron sometidos a la técnica de *bypass cardiopulmonar* (BCP) intraoperatoria durante la cirugía de cardiopatía congénita. Los potenciales biomarcadores analizados fueron moléculas participantes de procesos inmunoinflamatorios, predominantemente citocinas proinflamatorias tales como IL-1β, IL-6, IL-8 y el factor de necrosis tumoral-α (TNF-α) y su receptor, o citocinas antinflamatorias como la IL-10.

Conclusión: Las citocinas IL-6, IL-8 e IL-10, el cortisol y el lactato, se presentaron como moléculas promisorias para explicar mecanismos subyacentes de los resultados clínicos en el posoperatorio de cirugía cardíaca de lactantes o niños en cuidados intensivos. Estas moléculas pueden asumir un carácter preventivo y, en un futuro, pueden utilizarse como herramientas alternativas de diagnóstico y pronóstico para un régimen que permita identificar pacientes con alto riesgo de presentar complicaciones clínicas en el posoperatorio.

Introduction

Pediatric cardiac surgery is considered one of the most complex subspecialties in medicine.[1] Specifically, congenital heart disease is a relatively common disorder worldwide, affecting between 4 and 14 people per 1,000 live births.[1,2] Around one third of the infants and children affected by the problem need surgery during first childhood.[3,4] There are many reasons for the complications that occur in the postoperative cardiac surgery recovery, and those related to extracorporeal circulation support, including cardiopulmonary bypass (CPB), stand out.[5,6]

Infants and children submitted to congenital heart disease surgeries, in combination with experiencing post-CPB hemodynamic instability, face one of the causes associated with higher morbidity and mortality rates in infants and children in pediatric intensive care units (PICU).[7] Additionally, CPB can lead to systemic endotoxemia, alterations in capillary permeability, release of cytokines and their soluble receptors in the bloodstream, and activation of the complement cascade, which results in an exacerbated inflammatory response.[8-10] This response involves the activation of lymphocytes, monocytes, macrophages, endothelial cells, and heart myocytes that can express several proinflammatory cytokines, including the tumor necrosis factor (TNF-α), interleukins (ILs) such as IL-1β, IL-6, and IL-8, anti-inflammatory cytokines such as IL-4 and IL-10, and the transforming growth factor.[11-14] In addition, the release of corticoids as part of the physiological response of the body to surgical stress plays several roles in the post-CPB acute response, which modulates the host's inflammatory response, stimulates the release of anti-inflammatory cytokines, and has a function in the limitation of capillary permeability, as well as in the sensitization of adrenergic receptors in the myocardium.[15,16]

These biologically active factors have been implied after cardiac surgery complications, including pulmonary dysfunction and depressed cardiac contractile activity.[17,18] Additionally, the deregulation originating in homeostatic routes that control inflammation, metabolism, and the endocrine system has important clinical consequences, such as poor surgical recovery, persistent low cardiac output, and risk of infection, among other secondary morbidities, with the possibility of evolution

toward systemic inflammatory response syndrome (SIRS) or even multiple organ dysfunction syndrome (MODS).[4,6,19-22]

Several studies have shown that the activation of the complement cascade, the release of endotoxins, and the production of altered cytokine levels occur during and after CPB.[9,10,23-26] However, the capacity of these studies to evaluate the correlation of these events with a higher number of mediators of inflammation has been limited, because of both the small sample size and patients' age and diagnosis variability.[4,27,28]

A better understanding of the interaction between this homeostatic imbalance in pediatric patients submitted to cardiac surgeries under intensive care can help increase diagnosis accuracy and stratify patients who show high risk to develop postoperative complications by allowing the use of clinically relevant biomarkers.[4,29] In this sense, the need for diagnostics and prediction of clinical outcomes in infants and children can be overcome by routinely applying molecular technologies such as the use of clinically relevant biomarkers in postoperative pediatric intensive care. Hence, the purpose of the present integrative review was to analyze the use of potential biomarkers associated with clinical outcomes in the postoperative cardiac surgery period in infants and children under intensive care.

Methods

An integrative literature review was carried out.[30] The authors defined the following outline for the study design: subject identification and research question formulation; establishment of the inclusion and exclusion criteria; definition of the information to be extracted from the selected studies; evaluation of the studies included in the integrative review; results interpretation; review presentation, and qualitative synthesis.[31]

The review subject was defined as potential biomarkers associated with clinical outcomes in the postoperative cardiac surgery period in infants and children under intensive care in order to answer to the following guiding question: What is the scientific evidence on potential biomarkers associated with postoperative cardiac surgery clinical outcomes in infants and children under intensive care? The PECO[32] strategy was applied to formulate the research question to address the studied clinical question, in which "P" referred to "population" (infants and/or children in the postoperative cardiac surgery period), "E" to "exposure" (cardiac surgery), "C" to "comparison" (does not apply), and "O" indicated "outcome" (clinical outcomes in the postoperative cardiac surgery period in PICU).

The studies were identified in seven electronic databases: Medical Literature Analysis and Retrieval System Online - MEDLINE via PubMed, ISI Web of Knowledge via Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL Cochrane), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Science Direct, and Latin America and Caribbean Center on Health Sciences Information (LILACS). In addition to these electronic databases, other sources were consulted for secondary searches, for instance clinical trial registry websites, including ClinicalTrials.gov (National Institutes of Health, United States) and the Brazilian Registry of Clinical Trials website (via the ReBEC platform). The lists of references of the identified primary studies were examined to find additional relevant articles (crossed references). This advanced search strategy was carried out in September and December 2019.

The studies retrieved from the search strategy were limited to the publication period between 2000 and December 2019 in order to focus on the contemporary clinical practice. The search was restricted to full articles published in English, Spanish, or Portuguese in scientific journals that adopt peer reviewing. To guarantee the systematization of the qualified search regarding the organization and management of all the references retrieved from the databases, the EndNote (https://www.myendnoteweb.com/) bibliographic tool was used. The results of the search were stored and managed online.[33]

Initially, descriptors extracted from controlled vocabularies of each database, such as MeSH terms (MEDLINE), CINAHL headings (CINAHL),

Emtree terms (Embase), and Health Sciences Descriptors (LILACS) and noncontrolled descriptors (keywords) for Web of Science, CENTRAL Cochrane, and Science Direct were selected. Subsequently, all the controlled and noncontrolled descriptors were combined, as well as their synonyms, in each set of terms, by using advanced search tools in the respective databases with the Boolean operators "AND" and "OR".[34]

In this sense, the main descriptors adopted in the search strategy were ("Biomarkers" OR "Biomarkers, Pharmacological" AND "Stress") AND ("Child" OR "Infant" OR "Pediatrics") AND ("Intensive Care Units, Pediatrics" OR "Critical Care" OR "Critical Illness") AND ("Congenital Heart Disease" OR "Cardiac Surgery" OR "Cardiopulmonary Bypass").

The inclusion criteria were: original studies whose subject answered the guiding question, published in English, Spanish, or Portuguese, over the last 20 years (from 2000 to 2019); studies carried out with infants (defined as people between 1 and 23 months old according to the MeSH terms) and/or children (defined as people between 2 and 12 years old according to the MeSH terms) under intensive care and submitted to cardiac surgery; and studies whose evaluated outcomes were related to potential biomarkers associated with clinical outcomes in the postoperative cardiac surgery period. Gray literature (publications such as literature review, dissertations, theses, editorials, clinical guidelines, and specialist consensus) was excluded.

A comprehensive reading of the studies' titles and abstracts was performed by two researchers independently to ensure that the texts addressed the review guiding question and met all the inclusion criteria. When doubts arose during selection, the researchers opted to include the article in the initial phase of the study and decide over its definitive inclusion after the reading of its full text and evaluation by a third reviewer.

An adapted version[36] of a previously designed form[35] was used to extract data. It can be used to collect study information from four domains: i) study identification (title, journal, journal impact factor, publication year, volume, number, authors, country, language, and institution where the study was carried out); ii) objective and methodological characteristics (research question, objective, tested hypotheses, design, sample characteristics, including sample calculation, description of the data collection protocol, description of losses, instruments for data collection and evaluated measurements, and statistical analyses); iii) primary and secondary results/outcomes; and iv) conclusion and clinical-epidemiological relevance.

The level of evidence of each study was based on its design. Level I was attributed to systematic reviews and meta-analyses of randomized clinical trials; level II to randomized clinical trials; level III to nonrandomized clinical trials; level IV to case-control or cohort studies; level V to systematic reviews of qualitative or quantitative studies; level VI to qualitative or descriptive studies; and level VII to authorities' reports and/or specialist committee reports. This hierarchy classifies levels I and II as strong, levels III to V as moderate, and levels VI and VII as weak.[37] It must be emphasized that level VII was not considered in the present review, given that gray literature was excluded.

Regarding the evaluation of internal validity and the risk of bias in the selected studies, two assessment scales were applied, depending on the study design. Studies with a cohort design (prospective or retrospective) were evaluated by using the Newcastle-Ottawa Scale,[38] which assesses three domains: i) patient selection (0 to 4 stars); ii) comparability of patients in the cohorts (0 to 2 stars); and iii) outcomes (0 to 3 stars). Satisfactory answers get 1 star, and the maximum possible score is 9 stars. The closer to the maximum the score is, the higher the methodological quality of the study is and, consequently, the lower the risk of bias.

The methodological quality of the descriptive observational studies was assessed by applying the generic quantitative evaluation tool.[39] This modified tool has 12 criteria that evaluate methodological elements in the studies. A point is attributed to each affirmative answer, and the total score, whose maximum value is 12 points, is converted into a percentage (0 to 100%). The closer to 12 points or 100% the score is, the better the methodological

quality of the study is. It is noteworthy that all the evaluations relative to the internal validity of the included studies were carried out and confirmed independently by two reviewers.

Data analysis was designed to be descriptive. A chart created by the authors was used to summarize data extracted from each primary study included in the review shows the following information: citation/publication year and origin country, objectives, sample/average participant age, evaluated biomarkers, blood collection protocol, analyzed clinical variables, main results/conclusions, and level of evidence. This chart facilitated data comparison and organization according to their differences, similarities, and the response they provided to the research question. Data were then critically analyzed and integrated.

Results

Firstly, 839 articles were identified in the seven databases, and another six articles were included in the search result after manual secondary searchers on Google Scholar, ClinicalTrials.gov, the ReBEC platform and/or the references in the selected primary articles (crossed references). Consequently, the search in the databases resulted in 833 studies after the removal of 12 duplicates. Most of the publications (804) were excluded during the first screening, because the reading of titles and abstracts indicated that they did not meet the eligibility criteria. Twenty-nine articles were fully read, among which eight met all the inclusion criteria and made up the final sample for data extraction and qualitative synthesis (Figure 1).

Regarding the methodological quality of the studies, it was found that the scores ranged from moderate to high, that is, the studies were classified as good quality ones. The assessment performed with the Newcastle-Ottawa Scale[38] indicated that the two prospective cohort studies had good methodological quality, with one of them obtaining a score of 5 points[7] and the other a score of 6 points.[4] The other prospective descriptive observational studies received a considerable score according to the ge-

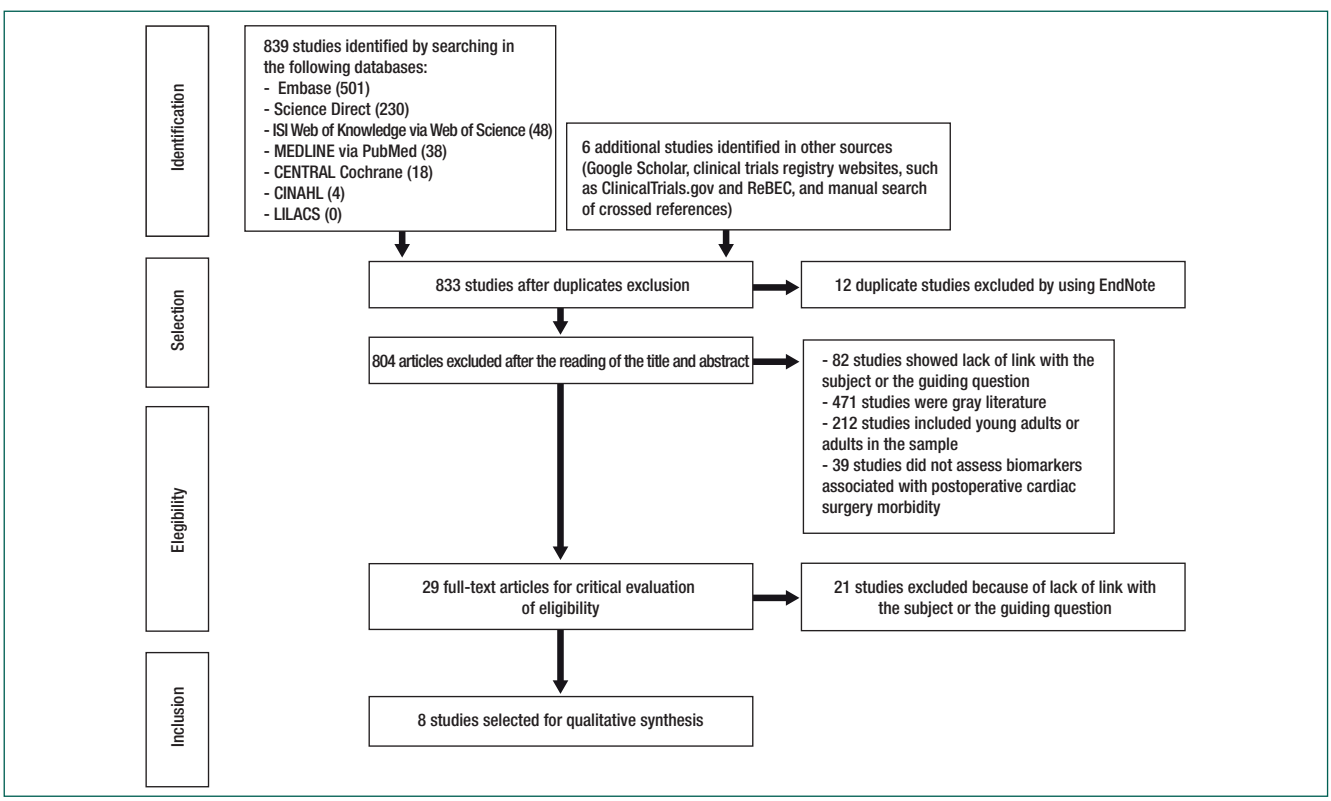

Figure 1. Flowchart showing the selection of the studies that were included in the integrative review.

Chart 1. Methodological appraisal of the studies included in the integrative review

Study/ Design	Criteria														Level of evidence
	1	2	3	4	5	6	7	8	9	10	11	12	Score	%	
Trotter et al.[40] (PDO)	Y	Y	Y	N	Y	Y	NR	Y	Y	Y	NR	Y	[a]9/12	75	VI
ElBarbary et al.[41] (PDO)	Y	Y	Y	N	Y	Y	NR	Y	Y	Y	NR	Y	[a]9/12	75	VI
Madhok et al.[42] (PDO)	Y	Y	Y	N	Y	Y	NR	Y	Y	Y	NR	Y	[a]9/12	75	VI
Allen et al.[43] (PDO)	Y	Y	Y	N	Y	Y	NR	Y	Y	Y	NR	Y	[a]9/12	75	VI
Allan et al.[44] (PDO)	Y	Y	Y	N	Y	Y	NR	Y	Y	Y	NR	Y	[a]9/12	83	VI
Crow et al.[45] (PDO)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NR	Y	[a]10/12	75	VI

	Selection				Comparability	Outcomes			Score	Level of evidence
	Selection of the exposed cohort	Selection of the nonexposed cohort	Exposure	Result of interest was not present at the beginning	Comparability of cohorts based on the design or analysis	Outcome evaluation	Follow-up time	Follow-up adequacy		
Correia et al.[4] (PC)	★	★	★		★	★	★		[b]6/9	IV
Wald et al.[7] (PC)	★	★	★			★	★		[b]5/9	IV

PDO = prospective descriptive observational; PC = prospective cohort; N = no; NR = not reported; Y = yes. Criteria: 1 = reported study objective; 2 = relevant literature background; 3 = sample description; 4 = sample size justification; 5 = reliable and valid results measurements; 6 = intervention description; 7 = contamination and cointervention; 8 = statistical significance; 9 = appropriate analysis method(s); 10 = clinical significance; 11 = drop-outs; 12 = appropriate conclusions. [a]Scale modified by Machotka et al. (2009).[39] This modified tool has 12 criteria that assess methodological elements of the studies. In this tool, each affirmative answer gets a score of 1 point, and the total score, which can reach 12 points, is converted into a percentage (0 to 100%). [b]Newcastle-Ottawa Scale,[38] which is specific for study type. This scale evaluates three great domains: patient selection (0 to 4 stars); comparability of patients in the cohorts (0 to 2 stars); and outcomes (0 to 3 stars). The maximum possible score is 9 points. Scores for cohort studies and for prospective observational studies are not directly comparable.

neric evaluation scale adapted by Machotka et al.,[39] with five studies obtaining a score of 9 points[26,40-43] and one showing a score of 10 points[44] out of 12 possible points (Chart 1). Regarding the risk of bias in the selected studies, it was observed that the reliability of the studies can be slightly questioned in all of them, given the presence of uncertain risk of bias or high risk of bias, especially regarding selection (not informing about drop-outs or not recruiting an adequate control group), confusion biases, and incomplete outcomes data.

Chart 2 shows a synthesis of the main characteristics of the studies included in the qualitative analysis, in publication chronological order.[4,7,40-45]

The selected studies were published between 2001 and 2015.[4,7,26,40-43] Half of the investigations were carried out in the United States,[7,42,43,44] two in the United Kingdom,[4,42] one in Germany,[40] and one in Saudi Arabia.[41] Each one of the studies were performed in only one center or institution.[4,7,26,40-44]

Regarding methodological design, there was a predominance of prospective descriptive observational studies (six),[26,40-44] of which only one was randomized.[26] The other two studies were prospective cohorts.[4,7] The sample size of the included studies ranged from 18 to 93 patients, who were infants or children of both genders.[4,7,26,40-44] The age of the infants/children evaluated in the studies was between two days and 15 years, and all the participants were submitted to surgeries to fix congenital heart disease and received postoperative intensive care in PICU.

In most of the studies (seven),[7,26,40-44] the pediatric patients were submitted to the intraoperative CPB technique during a surgery to treat congenital heart disease. This technique was not applied in only one study in the sample.[4] Several congenital heart diseases were examined in the studies, both those with a cyanotic and an acyanotic clinical profile, such as: ventricular septal defect, pulmonary artery insufficiency, double-outlet right ventricle, tetralogy of Fallot, atrioventricular canal, pulmonary artery stenosis, mitral regurgitation, pulmonary atresia, transposition of the great vessels, heterotaxy (presence of a single ventricle), double-inlet

Chart 2. Characteristics of the studies included in the integrative review.

Reference/ Country	Objectives	Sample/ Average age	Evaluated biomarkers	Blood collection protocol	Analyzed clinical variables	Main results
Trotter et al.[40] (Germany)	To investigate the plasma levels of progesterone, IL-8, and IL-10 during and after CPB in infants/children according to gender and PO cardiac morbidities	n = 18 (10M;8F)/ 19 months (2 months to 15 years)	Progesterone, IL-8, and IL-10	Immediately before surgery; after anesthesia induction and heparin administration; ten minutes after the beginning of CPB; after disconnecting the protamine administration circuit; six hours, one day, three days, and seven days after surgery	CPB time; aortic clamp; mechanical ventilation; days in the PICU; and MOD**	After CPB, all the patients showed an increase in the levels of progesterone, IL-8, and IL-10, with the IL-10 level being considerably higher in girls ($p < 0.05$). Six out of ten boys and no girl showed MOD ($p = 0.01$)
ElBarbary et al.[41] (Saudi Arabia)	To examine the behavior of the TNF-α p55 receptor before and after CPB and its relationship with the development of cytokinemia and clinical complications such as SIRS and MOD**	n = 20 (12M;8F)/ 4.4 years	IL-1β, TNF-α p55 and p75 receptors, TNF-α, IL-6, and IL-8	Immediately before CPB; two hours and one day after the beginning of CPB	Hypotension; coagulopathy; liver dysfunction; kidney dysfunction; respiratory dysfunction; and capillary leak	The levels of the TNF p55 receptor increased considerably two hours after CPB and remained stable up to one day after the procedure, showing a positive correlation with the presence of SIRS ($r = 0.74$, $p = 0.0001$) and MOD ($r = 0.84$, $p = 0.0007$). The preoperative levels of the TNF p55 receptor were predictors of hypotension, respiratory dysfunction, and coagulopathy in the patients ($p < 0.005$)
Madhok et al.[42] (United States)	To measure cytokine levels in the PO period of surgeries to treat congenital heart disease and correlate them with intraoperative variables and PO outcomes	n = 20 (11M;9F) 15 months (0.1 to 180)	TNF-α, IL-1β, IL-12, IL-6, IL-8, and IL-10	Preoperative (after anesthesia induction); one to three days in the PO period	Diagnosis; CPB time; aortic clamp; days in the PICU; mechanical ventilation; days in the hospital; inotropic score; venous oxygen saturation; and lactate	The levels of IL-6, IL-8, and IL-10 increased considerably in the first PO period ($p < 0.01$), and the IL-8 level showed a positive correlation with the need for inotropic support ($r = 0.470$, $p = 0.057$) and an inverse correlation with the IL-6 ($r = -0.575$; $p = 0.016$) and IL-8 ($r = -0.614$, $p = 0.009$) level and with the venous oxygen saturation
Allen et al.[43] (United Kingdom)	To determine the relationship between IL-10 observed levels, the genetic polymorphism that influences these levels, and the occurrence of severe hyperresponsiveness to endotoxin in children submitted to heart surgery with the use of CPB	n = 36 (21M;15F) 6.5 months (9 days to 24 months)	IL-10, IL-1 receptor antagonist, IL-6, IL-8, and TNF-α	After anesthesia induction and insertion of the arterial catheter; during the aortic clamp release; at the end of CPB; after ultrafiltration; when arriving at the PICU; and 2, 4, 8, 14,18, 24, and 48 hours after admission to the PICU	Duration of mechanical ventilation; days in the PICU; presence of sepsis; immunoparalysis; SIRS; and death	The response of blood IL-10 ($p < 0.001$), TNF-α ($p < 0.001$), and IL-6 ($p < 0.05$) to a lipopolysaccharide was reduced up to 50% in the first PO period in comparison with the response found in the preoperative period. Immunoparalysis was partially related to high circulating levels of IL-10 ($p < 0.001$), which exposed the patients to high risk of complications in the PO period. In addition, the IL-10 GCC genotype seemed to be a marker for risk of immunoparalysis ($p < 0.01$)
Allan et al.[26] (United States)	To evaluate the relationship between inflammatory status and clinical outcomes in infants submitted to CPB	n = 93 (61M;32F) 37 days (2 to 264)	CRP, IL-6, IL-8, IL-10, TNF-α, and IL-1β	Before CPB; immediately after CPB; and 6, 12, and 24 hours after CPB	Preoperative: use of inotropes and mechanical ventilation, for example; intraoperative: CPB, aortic clamp, administered hemoderivatives; PO: duration of intubation, days in the PICU and the hospital, and lactate concentration	The pre-CPB IL-6 and CRP levels were higher in young infants ($p < 0.001$). The levels of IL-6, IL-8, and IL-10 increased in the PO period, but only IL-6 ($r = 0.29$, $p = 0.006$) and IL-8 ($r = 0.30$, $p = 0.004$) showed a correlation with a longer PICU stay and the need for hemoderivatives administration. There was a positive correlation between IL-8 and lactate concentration 24 hours after surgery ($r = 0.44$, $p < 0.001$)
Wald et al.[7] (United States)	To examine the effect of CPB on the HPA axis, specifically on the adrenal responsiveness, of infants/children with congenital heart disease submitted to surgeries to treat the problem	n = 52 (25M;27F) 1.6 years (0.4 to 6.5)	Total cortisol, globulin-bound cortisol, free serum cortisol, and albumin	Preoperative (immediately after the central catheter incision); PO: 30 minutes after surgery and 60 minutes after administration of cosyntropin	Inotropic score*; hemodynamic indexes and use of supplementary corticoids; heart surgery adjusted score risk; duration of mechanical ventilation; days in the PICU	Decreased levels of globulin-bound cortisol were associated with a considerable increase in free cortisol levels. After stimulation with CPB, they were associated with worse clinical outcomes, such as a longer PICU stay ($p = 0.02$), higher inotropic scores ($p = 0.05$), greater requirement for isotonic solutions ($p = 0.007$), and a longer period on mechanical ventilation ($p = 0.013$)
Crow et al.[44] (United States)	To evaluate whether there was variability in blood dexamethasone levels after the administration of a dosage of 1 mg/kg before CPB in infants	n = 32 (13M;19F) 199±114 days (group with a low dexa level) and 225±363 days (group with a high dexa level)	Dexamethasone, cortisol, ACTH, IL-6, IL-8, and IL-10	After anesthesia induction; after ultrafiltration; at the admission to the PICU; 4, 8, 12, and 24 hours after surgery	Congenital heart disease surgery adjusted score risk; time of CPB; aortic clamp; inotropic score; duration of mechanical ventilation; days in the PICU	The administration of 1 mg/kg of dexamethasone before CPB originated different levels of the drugs in the infants at the arrival at the PICU, which were highly correlated with the magnitude of the response to stress/cortisol in the PO period ($p < 0.05$). Patients with high dexamethasone levels had lower cortisol levels in the PO period in comparison with the baseline levels (pre-CPB) ($p = 0.018$)

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Continuation.

Reference/ Country	Objectives	Sample/ Average age	Evaluated biomarkers	Blood collection protocol	Analyzed clinical variables	Main results
Correia et al.[4] (United Kingdom)	To evaluate the change in key metabolite levels after the surgery and examine the potential of a metabolic profile in the stratification of patients regarding expected clinical outcomes	n = 28 (15M;13F) 6.6 months (4.4 to 15.5)	IL-1 receptor antagonist, IL-6, IL-8, IL-10, and main metabolites	Preoperative (during anesthesia induction); PO: at the admission to the PICU (zero hour), 6, 24, and 28 hours after surgery	Congenital heart disease surgery adjusted score risk; pediatric organs dysfunction score at the admission to the PICU; inotropic score; lactate; arteriovenous oxygen saturation; days outside the PICU	A rigorous glycemic control did not change the response profile of the patients in the PO period considerably. Eight metabolites were associated with the disease severity and the surgery severity (3-d-hydroxibutirate, acetone, acetoacetate, citrate, lactate, creatine, creatinine, and alanine). The concentration of IL-6 (r = -0.73, p = 0.026) and IL-8 (r = -0.76, p = 0.017) showed an inverse correlation with the number of days outside the PICU, and the IL-6/IL-10 ratio showed a positive correlation with the plasma lactate level ($p < 0.05$)

Abbreviations: PO = Postoperative; CPB = cardiopulmonary bypass; CRP = C-reactive protein; IL = interleukine; TNF = tumor necrosis factor; PICU = pediatric intensive care unit; HPA = hypothalamic-pituitary-adrenal axis; ACTH = adrenocorticotropic hormone; SIRS = systemic inflammatory response syndrome.
*Inotropic score = dopamine x 1 + dopamine x 1 + milrinone x 15 + epinephrine x 100 + norepinephrine x 100 + phenylephrine x 100.
**DMO = multiple organ dysfunction (renal, respiratory, liver, heart, hematologic, and neurological).

left ventricule, hypoplastic left heart syndrome, anomalous coronary artery, sinus venosus atrial septal defects, aortic insufficiency/stenosis, total anomalous pulmonary venous return, myxoma, truncus arteriosus, pulmonary artery loop, aortic valve stenosis, complete atrioventricular block, coarctation of the aorta, foramen ovale, patent arterial duct, endocardial cushion defect, and rheumatic heart disease.[4,7,26,40-44]

In most of the studies (seven),[4,26,40-44] the potential biomarkers analyzed were molecules that participate in immune-inflammatory processes, mostly proinflammatory cytokines such as IL-1β, IL-6, IL-8, and IL-12, as well as TNF-α and its receptor, or anti-inflammatory cytokines, for instance IL-10. Only one study assessed a single hormonal biomarker for stress (cortisol) to examine the responsiveness of the HPA axis.[7] Two other studies evaluated both inflammatory and endocrine biomarkers, such as ACTH[44] and progesterone.[40]

The biomarkers were assessed in blood samples in all the selected studies. The researchers followed the preoperative and postoperative collection protocol at regular time intervals up to three days after surgery to carry out comparative analysis. This temporal analysis was performed to evaluate what the best time to estimate a clinical worsening in patients experiencing heart surgery stress is and predict possible clinical complications and worse prognoses.

Some of the postoperative clinical outcomes and prognoses that were mentioned and correlated with the evaluated biomarkers were: MODS;[40,41] iatrogenic kidney disease;[44] worsening in the venous oxygen saturation;[42] greater need for therapeutic intervention (higher therapeutic intervention scores);[42] higher inotropic score;[7,42] high risk of developing SIRS;[41] longer PICU stay;[7,26] greater fluid requirement;[7] longer use of mechanical ventilation;[7] variation in the number of days outside the PICU;[4] increased plasma lactate level;[4,26] need for the administration of hemoderivatives;[26] and immunoparalysis and higher susceptibility to hospital-acquired infections.[43]

Discussion

Surgical stress triggers a series of hormonal, metabolic, and immune responses by means of the activation of psychoneuroimmunoendocrine pathways that affect homeostasis in patients submitted to this event. Over the past decades, it has been shown that surgical procedures can activate the HPA axis, causing an increase in the level of systemic glucocorticoids.[45] In addition, recent studies have reported the presence of considerably deregulated levels in a series of proinflammatory and anti-inflammatory cytokines in the postoperative period, which are directly involved in the initiation of an acute inflammatory reaction and the modulation of immune responses.[46,47] Among these cytokines, some stand out, such as IL-6, a representative of proinflammatory mediators that regulate acute inflammatory response positively, and IL-10, which acts as a typical anti-inflammatory cytokine, inhibiting the proinflammatory response.[12]

Surgeries to treat congenital heart diseases are among the causes of greater stress in the pediatric population in the hospital setting. The challenge of dealing with this major surgery type, combined with the exposure to invasive intraoperative procedures, such as CPB, triggers susceptibility to several physiological disorders that impact the postoperative stability in infants and children remarkably. Regarding the CPB procedure specifically, researchers have put efforts developing studies that address the physiological disorder caused by this stress to the body and the risk of developing postoperative complications, leading to worse patient prognoses and increasing the rates of unfavorable clinical outcomes.[7,26,44,48,49] Multiple factors associated with CPB use contribute to originating immune deregulation and favoring an acute inflammatory condition, including cellular activation resulting from the contact with the CPB "foreign" components;[50] mechanical shear;[51] reperfusion and tissue ischemia;[52] hypotension;[53] nonpulsatile perfusion;[54] hemodilution with relative anemia;[55] administration of hemocomponents and/or hemoderivatives;[56] administration of heparin and protamine;[57] and hypothermia.[58]

In our review, we verified the predominance of studies that addressed CPB as an inducer of immune-inflammatory alterations, which were related to unfavorable clinical conditions, such as: longer PICU stay;[4,7,26] need for administration of hemoderivatives;[26] increase in the postoperative lactate level;[4,26] higher inotropic scores;[7,42] greater requirement for fluid transfusion;[7] prolonged period on mechanical ventilation;[7] impairment of the cardiopulmonary function;[42] immunoparalysis and increased risk of developing hospital-acquired infections;[43] hypotension, respiratory dysfunction, and coagulopathy;[41] and even severe health problems, including SIRS[41] and MODS.[40,41] The relevance of these studies was focused on the identification of potential biomarkers for clinical alterations caused by the cardiac surgery procedure and CPB as a predictive tool of clinical outcomes.

Regarding immunological imbalance caused by surgical stress, the cytokines IL-6, IL-8, and IL-10 stood out in five analyzed studies[4,26,40,42,43] as key molecules in the response to stressors. Analysis of these studies indicated the important role of postoperative clinical condition worsening signaling that these cytokines modulate, given that there was an increase in the level of the proinflammatory cytokines IL-6 and IL-8 after CPB, which significantly correlated with a longer PICU stay, the need for administration of hemoderivatives, the increase in plasma lactate levels, the need for a greater inotropic support, and a greater impairment of the pulmonary function.[4,26,42] The exacerbated IL-10 response, in turn, predisposed the patients to a state of multiple organ dysfunction[40] and immunoparalysis.[43]

In addition, tumor necrosis factor-α completed the set of proinflammatory cytokines evaluated for having the potential to predict postoperative cardiac surgery complications.[26,41-43] However, it was its soluble receptor with a mass of 55 kD (p55sR), found in high concentrations in the postoperative period, that effectively showed to be involved in unfavorable clinical outcomes in children submitted to surgeries to fix congenital heart disorders combined with CPB. High levels of this soluble receptor were associated with predisposition to cytokinemia (increase in the number of cytokines and their receptors in the circulation) and the development of SIRS and MODS. When in high levels in the preoperative period, this soluble receptor correlated with complications such as hypotension, respiratory dysfunction, and coagulopathy.[41]

Regarding the alterations in the metabolism of patients submitted to stressful conditions, several studies highlighted metabolites in altered levels that hinder the body from recovering from some diseases and surgeries and may even lead to clinical conditions that pose risk of death.[59-63] A study[4] emphasized the need to show specifically which metabolites are involved in the clinical conditions in children submitted to intraoperative CPB to make it possible to predict worse clinical outcomes for intervention. In this study, the authors found that eight metabolites were associated with the heart disease severity and the surgical severity (3-d-hydroxibutirate, acetone, acetoacetate, citrate, lactate, creatine, creatinine, and alanine). These metabolites were directly associated with the number of days during which

the patients received pediatric intensive care outside the PICU, as well as with the inotropic score of each patient. Overall, ketone bodies seemed to be related to better surgical outcomes, whereas citrate, lactate, alanine, and the creatinine/creatine ratio showed an inverse profile. The researchers suggested, from the reported results, that a metabolic profile could be a clinically relevant tool to stratify patients regarding their capacity to respond positively or negatively to a surgery to treat a congenital heart disease.[4]

With regards to endocrine alterations and their effects on the body as a response to stressors, the selected studies examined hormones whose participation in neuroendocrine pathways that play a role when the body is experiencing stress has been well established, such as cortisol and its stimulator, ACTH,[7,45] as well as progesterone[40] and its relationship with heart surgery postoperative clinical outcomes. These studies demonstrated that these molecules can be used as important biomarkers in the preventive detection of physiological complications.

When the body is reacting to surgical stress, glucocorticoids play several roles in the aggression caused by CPB. They modulate the body's inflammatory answer, stimulate the release of anti-inflammatory cytokines, limit capillary permeability, promote vasomotor tone, and sensitize adrenergic receptors in the myocardium.[15,16] Crow et al.[44] questioned the indiscriminate use of corticoid-based drugs in the prevention of post-CPB inflammatory processes after showing that alterations in postoperative cortisol levels were observed when a standard dosage of 1 mg/kg of dexamethasone was administered before heart surgery and CPB. This study reported that high levels of dexamethasone were associated with cortisol response suppression in the postoperative period, which predisposed the patients to a period of adrenal insufficiency that could impact postsurgical stability and recovery because of an exacerbated inflammatory response of the body. As found in another study analyzed in the present review, high serum free cortisol concentrations after stimulation with CPB were associated with worse postoperative clinical outcomes in infants and children, including a longer PICU stay, higher inotropic scores, greater requirement for fluids, and a longer period on mechanical ventilation.[7]

Interestingly, progesterone, a sexual steroid with potential to suppress the production of proinflammatory cytokines, was analyzed when in association with IL-10 to verify a possible sexual difference in the response to multiple organ dysfunction.[40] However, this study found no statistically significant correlation between the hormone and the multiple organ dysfunction condition, probably because of the small sample size. In contrast, it was observed that increased IL-10 levels in girls conferred them a protection factor for the disease in comparison with the result obtained for the boys, given that no girl had multiple organ dysfunction while six out of ten boys had this postoperative clinical complication.

The present review identified the predominance of prospective descriptive observational studies (six articles)[39-44], classified as having a level of evidence equal to IV (weak).[37] This draws attention to the need to carry out randomized controlled trials that are properly designed and have representative samples, with high internal validity and low risk of bias, to allow the evidence concentrated on the identification of potential biomarkers that are clinically important for predicting clinical outcomes to be extrapolated to the population of infants and children submitted to heart surgeries and intensive care.

Most of the studies included in the present review had reduced samples ($n < 30$), which did not represent the population, and did not show how the sample calculation was performed. To minimize type I and type II errors and increase the accuracy of the results found, the authors suggest that new studies be carried out, mainly randomized clinical trials with adequate sample size. In addition, most studies did not have a control group and did not provide a description of the patients who were excluded or dropped-out in their methodology section, which indicates a selection bias. Together with the methodological limitations, the risks of uncertain bias found in the analyzed studies reduce the reliability of the evidence gathered in the present review, pointing out the need to carry out new experimental studies to confirm these results. Other limitations of the present review include the restriction

in the studies' publication year (between 2000 and 2019), because there could be studies that preceded heart surgeries and that were designed when the discussions about the clinical outcomes in the postoperative period had already begun. Consequently, the results of the present review must be evaluated with caution, because a considerable diversity of biomarkers, protocols, and number of participants was found, which makes the result generalization difficult.

Despite the limitations shown in each study, the present review was able to gather the main publications that reported findings on potential biomarkers that are clinically relevant for a possible management of postoperative cardiac surgery clinical outcomes in infants and/or children under intensive care. These studies contribute to diagnostic and prognostic progresses as they can allow health professionals who work in PICU to deal with the prediction of preventable physiological stresses and postoperative complications more effectively, delivering more safety as well as timely recovery to patients.

Conclusion

Cardiac surgery and CPB, often required in the repair of congenital heart problems in infants and children, are a stress to the body and originate physiological stress, with immunological, metabolic, and endocrine alterations. Analysis of potential biomarkers, especially cytokines IL-6, IL-8, and IL-10, cortisol, and lactate suggested that these molecules can be protagonists in the elucidation of the mechanisms underlying postoperative cardiac surgery clinical outcomes in infants and children under intensive care and identify patients showing a high risk of developing postoperative clinical complications. These molecules can take on a protective role that is suitable in these situations and may be used in the future as alternative diagnostic and prognostic tools in a preventive protocol by health professionals who provide pediatric intensive care. However, further studies, especially well-designed randomized clinical trials, must be performed to bridge the gap in the scientific literature, focusing on the effectiveness, sensitivity, and specificity of the clinically relevant potential biomarkers mentioned in the present review.

References

1. Hoffman JI. The global burden of congenital heart disease. Cardiovasc J Afr. 2013;24(4):141–5.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890–900.
3. Qu Y, Liu X, Zhuang J, Chen G, Mai J, Guo X, et al. Incidence of Congenital Heart Disease: The 9-Year Experience of the Guangdong Registry of Congenital Heart Disease, China. PLoS One. 2016;11(7):e0159257.
4. Correia GD, Wooi Ng K, Wijeyesekera A, Gala-Peralta S, Williams R, MacCarthy-Morrogh S, et al. Metabolic profiling of children undergoing surgery for congenital heart disease. Crit Care Med. 2015;43(7):1467–76.
5. Brown KL, Ridout DA, Goldman AP, Hoskote A, Penny DJ. Risk factors for long intensive care unit stay after cardiopulmonary bypass in children. Crit Care Med. 2003;31(1):28–33.
6. Pagowska-Klimek I, Pychynska-Pokorska M, Krajewski W, Moll JJ. Predictors of long intensive care unit stay following cardiac surgery in children. Eur J Cardiothorac Surg. 2011;40(1):179–84.
7. Wald EL, Preze E, Eickhoff JC, Backer CL. The effect of cardiopulmonary bypass on the hypothalamic-pituitary-adrenal axis in children. Pediatr Crit Care Med. 2011;12(2):190–6.
8. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003;107(7):996–1002.
9. Tárnok A, Schneider P. Pediatric cardiac surgery with cardiopulmonary bypass: pathways contributing to transient systemic immune suppression. Shock. 2001;16 Suppl 1:24–32.
10. Paśnik J. [The significance of neutrophil in inflammatory response after cardiac surgery with cardiopulmonary bypass]. Wiad Lek. 2007;60(3-4):171–7.
11. Gessler P, Pfenninger J, Pfammatter JP, Carrel T, Baenziger O, Dahinden C. Plasma levels of interleukin-8 and expression of interleukin-8 receptors on circulating neutrophils and monocytes after cardiopulmonary bypass in children. J Thorac Cardiovasc Surg. 2003;126(3):718–25.
12. Gessler P, Pretre R, Hohl V, Rousson V, Fischer J, Dahinden C. CXC-chemokine stimulation of neutrophils correlates with plasma levels of myeloperoxidase and lactoferrin and contributes to clinical outcome after pediatric cardiac surgery. Shock. 2004;22(6):513–20.
13. Qing M, Schumacher K, Heise R, Wöltje M, Vazquez-Jimenez JF, Richter T, et al. Intramyocardial synthesis of pro- and anti-inflammatory cytokines in infants with congenital cardiac defects. J Am Coll Cardiol. 2003;41(12):2266–74.
14. Goldszmid RS, Trinchieri G. The price of immunity. Nat Immunol. 2012;13(10):932–8.
15. Suominen PK, Dickerson HA, Moffett BS, Ranta SO, Mott AR, Price JF, et al. Hemodynamic effects of rescue protocol hydrocortisone in neonates with low cardiac output syndrome after cardiac surgery. Pediatr Crit Care Med. 2005;6(6):655–9.

16. Kilger E, Weis F, Briegel J, Frey L, Goetz AE, Reuter D, et al. Stress doses of hydrocortisone reduce severe systemic inflammatory response syndrome and improve early outcome in a risk group of patients after cardiac surgery. Crit Care Med. 2003;31(4):1068–74.

17. de Mendonça-Filho HT, Gomes RV, de Almeida Campos LA, Tura B, Nunes EM, Gomes R, et al. Circulating levels of macrophage migration inhibitory factor are associated with mild pulmonary dysfunction after cardiopulmonary bypass. Shock. 2004;22(6):533–7.

18. Stayer SA, Diaz LK, East DL, Gouvion JN, Vencill TL, McKenzie ED, et al. Changes in respiratory mechanics among infants undergoing heart surgery. Anesth Analg. 2004;98(1):49–55.

19. Brown MD, Wernovsky G, Mussatto KA, Berger S. Long-term and developmental outcomes of children with complex congenital heart disease. Clin Perinatol. 2005;32(4):1043–57.

20. Snookes SH, Gunn JK, Eldridge BJ, Donath SM, Hunt RW, Galea MP, et al. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. Pediatrics. 2010;125(4):e818–27.

21. Horeczko T, Green JP, Panacek EA. Epidemiology of the Systemic Inflammatory Response Syndrome (SIRS) in the emergency department. West J Emerg Med. 2014;15(3):329–36.

22. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):762–74.

23. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg. 2002;21(2):232–44.

24. Ben-Abraham R, Weinbroum AA, Dekel B, Paret G. Chemokines and the inflammatory response following cardiopulmonary bypass—a new target for therapeutic intervention?—A review. Paediatr Anaesth. 2003;13(8):655–61.

25. Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg. 2003;75(2):S715–20.

26. Allan CK, Newburger JW, McGrath E, Elder J, Psoinos C, Laussen PC, et al. The relationship between inflammatory activation and clinical outcome after infant cardiopulmonary bypass. Anesth Analg. 2010;111(5):1244–51.

27. Alcaraz AJ, Manzano L, Sancho L, Vigil MD, Esquivel F, Maroto E, et al. Different proinflammatory cytokine serum pattern in neonate patients undergoing open heart surgery. Relevance of IL-8. J Clin Immunol. 2005;25(3):238–45.

28. Schumacher K, Korr S, Vazquez-Jimenez JF, von Bernuth G, Duchateau J, Seghaye MC. Does cardiac surgery in newborn infants compromise blood cell reactivity to endotoxin? Crit Care. 2005;9(5):R549–55.

29. Goddard SL, Adhikari NK. The Challenging Task of Improving the Recovery of ICU Survivors. JAMA. 2016;315(24):2671–2.

30. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs. 2005;52(5):546–53.

31. Mendes KD, Silveira RC, Galvão CM. Revisão integrativa: método de pesquisa para a incorporação de evidências na saúde e na enfermagem. Texto Contexto Enferm. 2008;17(4):758–64.

32. Morgan RL, Whaley P, Thayer KA, Schünemann HJ. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ Int. 2018;121(Pt 1):1027–31.

33. Carlos L. Lopes-Júnior, Cruz LA, Leopoldo VC, Campos FR, Almeida AM, Silveira RC. Effectiveness of traditional chinese acupuncture versus sham acupuncture: a systematic review. Ver Lat Am Enfermagem. 2016;24:e2762.

34. Lopes-Júnior LC, Rosa MA, Lima RA. Psychological and Psychiatric Outcomes Following PICU Admission: A Systematic Review of Cohort Studies. Pediatr Crit Care Med. 2018;19(1):e58–67.

35. Ursi ES, Gavão CM. [Perioperative prevention of skin injury: an integrative literature review]. Rev Lat Am Enfermagem. 2006;14(1):124–31. Portuguese.

36. Lopes-Júnior LC, Bomfim EO, Nascimento LC, Nunes MD, Pereira-da-Silva G, Lima RA. Non-pharmacological interventions to manage fatigue and psychological stress in children and adolescents with cancer: an integrative review. Eur J Cancer Care (Engl). 2016;25(6):921–35.

37. Melnyk BM, Fineout-Overholt E. Evidence-based practice in nursing & healthcare. A guide to best practice. China: Wolters Kluwer/Lippincott Williams & Wilkins; 2011.

38. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in metaanalyses. Ottawa (ON): Ottawa Hospital Research Institute; 2011. [cited 2015 Sep 30]. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

39. Machotka Z, Kumar S, Perraton LG. A systematic review of the literature on the effectiveness of exercise therapy for groin pain in athletes. Sports Med Arthrosc Rehabil Ther Technol. 2009;1(1):5.

40. Trotter A, Mück K, Grill HJ, Schirmer U, Hannekum A, Lang D. Gender-related plasma levels of progesterone, interleukin-8 and interleukin-10 during and after cardiopulmonary bypass in infants and children. Crit Care. 2001;5(6):343–8.

41. el-Barbary M, Khabar KS. Soluble tumor necrosis factor receptor p55 predicts cytokinemia and systemic inflammatory response after cardiopulmonary bypass. Crit Care Med. 2002;30(8):1712–6.

42. Madhok AB, Ojamaa K, Haridas V, Parnell VA, Pahwa S, Chowdhury D. Cytokine response in children undergoing surgery for congenital heart disease. Pediatr Cardiol. 2006;27(4):408–13.

43. Allen ML, Hoschtitzky JA, Peters MJ, Elliott M, Goldman A, James I, et al. Interleukin-10 and its role in clinical immunoparalysis following pediatric cardiac surgery. Crit Care Med. 2006;34(10):2658–65.

44. Crow SS, Oliver WC Jr, Kiefer JA, Snyder MR, Dearani JA, Li Z, et al. Dexamethasone levels predict cortisol response after infant cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2014;147(1):475–81.

45. Nakamura M, Suita S, Yamanouchi T, Masumoto K, Ogita K, Taguchi S, et al. Cortisol and cytokine responses after surgery in different age groups of pediatric patients. Pediatr Surg Int. 2003;19(3):194–9.

46. Li Y, Yuan Q, Huang J, Li YP, Pan J, Feng X, et al. Assessment of plasma B7-H3 levels in pediatric patients with different degrees of surgical stress. BMC Pediatr. 2016;16(1):110.

47. Gentile LF, Moldawer LL. HMGB1 as a therapeutic target for sepsis: It's all in the timing. Expert Opin Ther Targets. 2014; 18(3:243–245.

48. Checchia PA, Bronicki RA, Costello JM, Nelson DP. Steroid use before pediatric cardiac operations using cardiopulmonary bypass: an international survey of 36 centers. Pediatr Crit Care Med. 2005;6(4):441–4.

49. Kozik DJ, Tweddell JS. Characterizing the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg. 2006;81(6):S2347–54.

50. Brix-Christensen V. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. Acta Anaesthesiol Scand. 2001;45(6):671–9.

51. Seghaye MC. The clinical implications of the systemic inflammatory reaction related to cardiac operations in children. Cardiol Young. 2003;13(3):228–39.

52. Chugani HT. Biological basis of emotions: brain systems and brain development. Pediatrics. 1998;102(5 Suppl E):1225–9.

53. Vidal Melo MF. Clinical respiratory physiology of the neonate and infant with congenital heart disease. Int Anesthesiol Clin. 2004;42(4):29–43.

54. Bestic M, Reed MD. The ontogeny of human kidney development: influence on neonatal diuretic therapy. Neoreviews. 2005;6(8):e363–8.

55. Ulrichs F, Speer CP. Neutrophil function in preterm and term infants. Neoreviews. 2004;5(10):e417–30.

56. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med. 1981;304(9):497–503.

57. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1983;86(6):845–57.

58. Kirklin JK, Chenoweth DE, Naftel DC, Blackstone EH, Kirklin JW, Bitran DD, et al. Effects of protamine administration after cardiopulmonary bypass on complement, blood elements, and the hemodynamic state. Ann Thorac Surg. 1986;41(2):193–9.

59. Suhre K. Metabolic profiling in diabetes. J Endocrinol. 2014;221(3):R75–85.

60. Mirnezami R, Kinross JM, Vorkas PA, Goldin R, Holmes E, Nicholson J, et al. Implementation of molecular phenotyping approaches in the personalized surgical patient journey. Ann Surg. 2012;255(5):881–9.

61. Mickiewicz B, Vogel HJ, Wong HR, Winston BW. Metabolomics as a novel approach for early diagnosis of pediatric septic shock and its mortality. Am J Respir Crit Care Med. 2013;187(9):967–76.

62. Langley RJ, Tsalik EL, van Velkinburgh JC, Glickman SW, Rice BJ, Wang C, et al. An integrated clinico-metabolomic model improves prediction of death in sepsis. Sci Transl Med. 2013;5(195):195ra95.

63. Mickiewicz B, Duggan GE, Winston BW, Doig C, Kubes P, Vogel HJ; Alberta Sepsis Network. Metabolic profiling of serum samples by 1H nuclear magnetic resonance spectroscopy as a potential diagnostic approach for septic shock. Crit Care Med. 2014;42(5):1140–9.