REVIEW ARTICLE

Trigger receptor expressed in myeloid cell type-1 (TREM-1) as a biomarker of systemic inflammatory response syndrome (SIRS) in pediatrics

Receptor desencadeante expresso em células mieloides tipo-1 (TREM-1) como biomarcador da síndrome da resposta inflamatória sistêmica (SRIS) em pediatria

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ABSTRACT

Objective: to determine the validity of TREM-1 as a SIRS biomarker in pediatric patients. Method: systematic review, according to PRISMA, of studies published until October 2022 indexed in the VHL, Cochrane Library, PubMed/MEDLINE and Science Direct databases. The search strategy included the descriptors: TREM-1; SIRS; Child; Biomarker. Registration number PROSPERO CRD: 42022381838. Results: four studies comprising 2.353 patients aged 11 months to 18 years were included, with SIRS being present in 75% of these. Cutoff values ranged from 18.7 pg/mL to > 629 pg/mL. The results support a role for TREM-1 as a diagnostic tool for pediatric SIRS, but cannot be considered conclusive as a quantitative synthesis was not possible due to heterogeneity in study design. Conclusion: we conclude a potential use of TREM-1 in the pediatric population, specifically for the diagnosis of SIRS, with a good perspective in cardiac surgery through its elevation after surgery. However, it was not possible to establish a cut-off point, but rather to determine the possibility of its use for stratifying mortality risk, compared to baseline values, when the patient has SIRS.

Keywords: TREM-1, SIRS, Child, Biomarker.

RESUMO

Objetivo: determinar a validade do TREM-1 como biomarcador da SIRS em pacientes pediátricos. Método: revisão sistemática, segundo PRISMA, de estudos publicados até outubro de 2022 indexados nas bases de dados BVS, Cochrane Library, PubMed/MEDLINE e Science Direct. A estratégia de busca incluiu os descritores: TREM-1; SIRS; Criança; Biomarcador. Número de registro PROSPERO CRD: 42022381838. Resultados: foram incluídos quatro estudos com 2.353 pacientes de 11 meses a 18 anos, sendo que a SIRS esteve presente em 75% deles. Os valores de corte variaram de 18,7 pg/mL a > 629 pg/mL. Os resultados apoiam o papel do TREM-1 como uma ferramenta de diagnóstico para SIRS pediátrica, mas não podem ser considerados conclusivos, pois uma síntese quantitativa não foi possível devido à heterogeneidade no desenho do estudo. Conclusão: concluímos uma potencial utilização do TREM-1 na popu-

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lação pediátrica, especificamente para o diagnóstico de SIRS, com boas perspectivas em cirurgia cardíaca através da sua elevação após a cirurgia. No entanto, não foi possível estabelecer um ponto de corte, mas sim determinar a possibilidade de sua utilização para estratificar o risco de mortalidade, comparando com os valores basais, quando o paciente apresenta SIRS.

Palavras-chave: TREM-1, SRIS, Criança, Biomarcador.

INTRODUCTION

The Systemic Inflammatory Response Syndrome (SIRS) is well established to describe the inflammatory process triggered by infectious or non-infectious aggressions. SIRS results from the exacerbated stimulation of pro-inflammatory mediators and is characterized by immunohematological alterations, resulting in complications that, often, cause an increase in death rates[1] and remains a primary clinical problem that still lacks continuous approaches[2].

The trigger receptor expressed in myeloid cells type 1 (TREM-1) is a member of the immunoglobulin superfamily found on the surface of neutrophils, monocytes and macrophages, with a regulatory role in inflammation. Its activation induces the production of pro-inflammatory cytokines and chemokines, increases the expression of co-stimulatory molecules and increases neutrophil degranulation and phagocytic activity. TREM-1 has been studied as an important biomarker in different situations of acute inflammatory states, and its use in clinical practice demonstrates significant results in the diagnosis and prognosis of these conditions[3].

Major surgery induces, to varying degrees, an inflammatory response. Variations in volume, temperature, plasma composition and changes in tissue blood flow are present and result in important pathophysiological consequences[4]. Understanding the main events that induce tissue damage is certainly the first step in an attempt to optimize the diagnosis, management and prognosis of potentially serious conditions, especially in high-risk patients, such as critically ill children. Thus, this study aimed to describe the validity of TREM-1 as a SIRS biomarker in pediatric patients.

METHOD

This is a Systematic Literature Review according to the PRISMA[5] Protocol, aiming to describe whether TREM-1 is useful as a SIRS biomarker in pediatric patients. Based on the PICOS strategy, the following studies were considered eligible: P-population consisted of pediatric patients; I-with suspected/diagnosed SIRS; C-compare the validity of TREM-1 with other markers; O-presented an association of TREM-1 with the occurrence of complications and death; S-clinical and/or observational studies, published until October 2022 in the Virtual Health Library (VHL), Cochrane Library, National Library of Medicine, National Institutes of Health (PubMed / MEDLINE) and Science Direct.

The search strategy was guided by the Health Sciences Descriptors (DeCs), being performed their combination through the Boolean operators “and” and “or”. The descriptors used were: TREM-1; SIRS; Child; Biomarkers. There was no restriction

regarding period or language, as well as to the use of gray literature, as long as they were clinical and/or observational studies. Studies were selected by two independent researchers based on eligibility criteria. First, titles and abstracts were read, and discordant cases were discussed and submitted to the evaluation of a third researcher. Then, the selected articles were read in full. Figure 1 describes the flow of identification, selection, eligibility and inclusion of studies. The data extracted from the articles were of bibliometric and technical nature, based on a self-prepared form (Table 1).

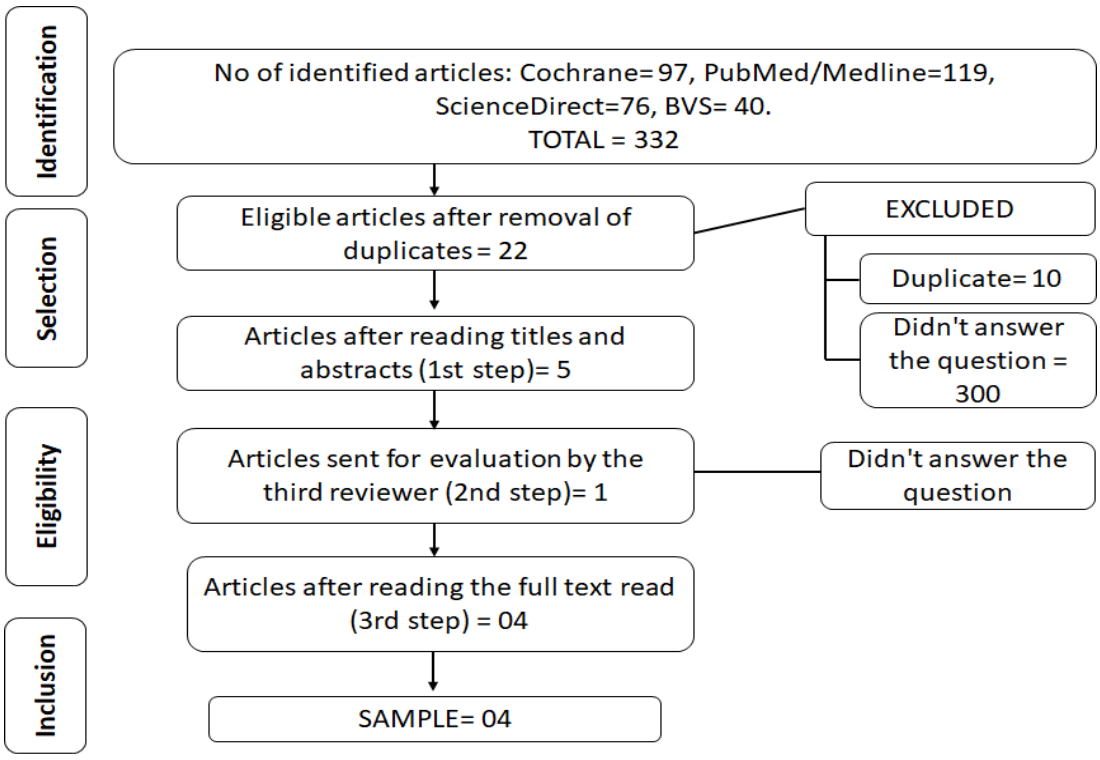

Figure 1 – Research Strategy Flow and Study Selection

The critical evaluation of the quality of the data of the studies was carried out according to the Oxford Center Evidence Based Medicine[6], as well as the evaluation of the methodological quality according to the GRADE recommendations. Aggregated data from the articles were used and a descriptive synthesis was performed. The methods section was published in the form of a protocol in the PROSPERO database – International Prospective Register of Systematic Reviews affiliated with the University of York, according to PROSPERO Code 2022 CRD42022381838, available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022381838. For the final critical evaluation of this review, the authors chose to use the AMSTAR tool.

RESULTS

A total of 332 studies were selected

from the search, 10 duplicates were excluded and the remaining 322 were read, of which 300 were ineligible. In the remaining 22 studies, further evaluation was performed and 18 articles were excluded. Four studies, with 2,353 patients, aged 11 months to 18 years, were included in this review, with SIRS present in 75% and mortality in 25% of these. Among the included studies, 02 were prospective cohort[7,9] and two were case-control[8,10]. TREM-1 cutoff values ranged from 18.7 pg/mL to > 629 pg/mL. The sample was stratified as B6 and had as main outcomes the use of TREM-1 for the diagnosis of SIRS, differentiation of SIRS, sepsis and septic shock and its use as a predictor of mortality (Table 1).

DISCUSSION

The diagnosis of SIRS and its differentiation from sepsis is still a challenge for clinical practice. Regarding the results, we observed heterogeneity in relation to the findings presented, as well as a scarcity of studies in the pediatric population, a fact that leads the discussion to be based, mostly, on research with adults. SIRS is often in the postoperative period of pediatric cardiac surgery, affecting almost one third of patients and resulting in a significant increase in hospitalization. Boehne et al., (2017)[11] lamented that SIRS was associated with organ dysfunction (HR: 2.69; 95% CI, 1.41; 5.12) and prolonged duration in the pediatric intensive care unit (PICU) (median: 168 vs. 96 hours; p = 0.007).

Table 1 – Studies on TREM-1 and its association with SIRS

Study and year of publication / LE / R / Type of study	Objective	Sample size and age	Outcomes	Cutoff points (pg/mL)	OR CI 95% and/or p-value	Conclusions
Da Rocha, 2012[7] 2B / B Prospective cohort	To study the kinetics of sTREM-1 in the postoperative period of cardiac surgery with CPB in children	31 / median de 11 months old	- 45.8% SIRS in admision - 94.5% SIRS in 1PO - 100% SIRS in 2PO	- Preop: 143.6 - IPO CPB: 96.9 - 24h after CPB: 140.2 - 48h after CPB: 19.5 - 72h after CPB: 193.5	p < 0.05, comparing only the value of sTREM-1 preoperatively and 24 and 48 hours after CPB. With 72h after CPB, there was no significant difference in the concentration of sTREM-1 in relation to the 48h result	Significant increase in sTREM-1 serum levels after CPB and increased diagnosis of SIRS on the 1st and 2nd postoperative day

Smok et al., 2020[8] 3B / B Case control	To assess the diagnostic and prognostic value of IL-6 and sTREM-1 in SIRS and sepsis in children with reference to CRP and procalcitonin	180 patients / 2 months old to 18 years old	- SIRS	- 18.7 to 27.3	- Median sTREM-1 was higher in the SIRS vs. control ($p < 0.05$)	Mean serum concentration of sTREM-1 was significantly higher in the SIRS group compared to the control group
Leligdowicz et al., 2021[9] 2B / B Prospective cohort	Identify a sepsis-linked mediator to predict mortality in febrile children	2.052 patients / 18,9 months old	- Death	- < 239.0 Low risk Risk (IEM 0.5%) - 239.0 to 629 Intermediary risk (IEM 3.9%) - > 629 High risk (IEM 32.8%)	**Derivation Cohort CI 95%** - EIDLR: 0.3% (0.0 to 0.7%) -EIDIR: 3.3% (1.7 to 4.8%) - EIHRD: 26.5% (18.5% to 34.6%) **Validation Cohort CI 95%** - EIDLR:0,8% (1.6% to 4,8%) - EIDIR: 3,3% (2,6% to 7,1%) - EIHRD: 38,8% (28,6 to 49,1%)	sTREM-1 measured at the first febrile clinical presentation had high predictive accuracy for in-hospital mortality
Duramaz et al., 2021[10] 3B / B Case control	To investigate the role of sTREM-1and IL-6 in distinguishing between SIRS, sepsis and septic shock in a pediatric intensive care unit	90 patients / median of 24,5 months old	-Differentiate SIRS, Sepsis, and Septic Shock	- 0h: 1106 ± 315 - 24h: 1188 ± 305 -72h: 1195 ± 216	- Control/ septic shock/ sepsis / SIRS ($p > 0.05$) - Septic shock/ Sepsis ($p > 0.05$) - Septic shock/ SIRS ($p > 0.05$) - Sepsis/ SIRS ($p > 0.05$)	sTREM-1 is not useful for diagnosing infection and for distinguishing between sepsis, septic shock and SIRS in the first 72h

Subtitle: NE/R: Level of evidence and Recommendation degree; CI: confidence interval; CPB: cardiopulmonary bypass; EID: Estimated Incidence of Death; EI-

DLR: Estimated Incidence of Death Low Risk; EIDIR: Estimated Incidence of Death Intermediate Risk; EIHRD: Estimated Incidence of High Risk Death; IL-6: Interleukin 6; PCR: CRP: C-reactive protein; preop: preoperative; PO: postoperative; POI: immediate postoperative;

Source: Cabral et al., (2022).

Da Rocha (2012)[7] demonstrated that there was a significant increase in sTREM-1 levels in relation to the post-CPB baseline level and in the other evaluated moments, as well as an increase in the diagnosis of SIRS on the 1st and 2nd postoperative days, with the median sTREM-1 of 96.9 pg/mL immediately after CPB; 140.2 pg/mL after 24 hours of CPB; 191.5 pg/mL after 48h ($p < 0.05$). Although the study did not associate sTREM-1 amplification with the diagnosis of SIRS, the findings are suggestive of possible locomotion.

Aiming to diagnose SIRS in febrile children, Smoke et al., (2020)[8] confirmed the usefulness of sTREM-1 for this purpose. The concentrations showed statistical significance with higher values when detected in the control group. The median of sTREM-1 was higher, comparing the SIRS group with the control group (AUROC 0.62, CI 95% 0.53 – 0.70, p 0.0012, cutoff 18.7 pg/mL, sensitivity 45.6%, specificity 75.5%, positive predictive value 8.9% and negative predictive value 96.3%). The authors also point out that the difference in the median of sTREM-1 was significant between the group of febrile patients without SIRS and those with SIRS/sepsis ($p = 0.048$).

As previously mentioned, most studies that determine the diagnostic validity of sTREM-1 have been carried out with adults, however, in those carried out with children, the results are promising. Adly et al., (2014)[12] found that in neonates, baseline levels of sTREM-1 were significantly elevated in those with positive culture (1461.1 ± 523 pg/mL) and SIRS (1194 ± 485 pg/mL) in compared with the control group, and that sTREM-1 values decreased within 48 hours after antibiotic therapy. The authors pointed out that the cutoff value of 310 pg/mL can be used for the diagnosis of neonatal sepsis, with 100% sensitivity and specificity (AUROC 1.0 - 0.696–1.015 - 95% CI), while the cutoff value of 1100 pg/mL was predictive of survival (100% sensitivity and 97% specificity, AUROC 0.978 - 0.853–1.13 - 95% CI).

Increases in sTREM-1 serum levels correlate with disease severity, prolonged clinical recovery, multiple organ dysfunction, and increased mortality rates among children and adults (BALANZA et al., 2020)[13].

Leligdowicz et al., (2021)[9] demonstrated that the sTREM-1 predictive performance for 7-day mortality in relation to the LODS (Logistic Organ Dysfunction System) criterion was statistically similar in the bypass cohort (AROC 0.894 - 0.843 - 0.944 CI 95 %) versus for LODS 0.907 (0.869 – 0.944 CI 95%), $p = 0.661$) and in the validation cohort (0.901 - 0.856 – 0.946 CI 95%) versus LODS 0.912 (0.875 – 0.949 CI 95%, $p = 0.628$). In this study, sTREM-1 was superior to ten other biomarkers in predicting mortality in febrile children aged 2 months to 5 years.

In a study from Thailand, with adults hospitalized with suspected infection, sTREM-1 showed a strong prognostic power for 28-day mortality (AUROC 0.81 - 0.77–0.85 95% CI) (WRIGHT et al.,

2020)[14]. These results are corroborated by Richard-Greenblatt et al., (2019)[15] who indicate sTREM-1 as a prognostic marker for 28-day mortality (AUROC 0.87 - 0.81–0.92 95% CI). The authors also showed that the prognostic utility of mortality of sTREM 1 was superior to C-Reactive Protein (CRP) and Procalcitonin ($p < 0.0001$).

Of the studies included in this article, only data from Duramaz et al., (2021)[10] demonstrated that sTREM-1 values were not useful for diagnosing infection and for distinguishing sepsis, septic shock, and SIRS. However, in a systematic review with meta-analysis carried out by Qin et al., (2021)[16] the results showed that circulating sTREM-1 showed high sensitivity (0.85 - 0.76-0.91 CI 95%) and moderate specificity (0.79 - 0.70-0.86 CI 95%) to differentiate sepsis from SIRS.

In a study with adults diagnosed with SIRS and sepsis, Oku et al., (2013)[17] found that patients diagnosed with sepsis had decreased TREM-1 expression in neutrophils and monocytes compared to patients with SIRS, however, the level of sTREM-1 in plasma in septic patients was significantly higher than in patients with SIRS ($p < 0.05$) and, in these cases, the level of sTREM-1 in plasma was positively correlated with the severity score and non-survivors had increased plasma sTREM-1 levels compared to survivors in all SIRS/sepsis patients ($p < 0.05$).

In the postoperative context, Li et al., (2013)[18] demonstrated that plasma levels of sTREM-1 were higher in patients with sepsis than in those with SIRS (111.7 versus 64.1 pg/mL, $p < 0.05$), with sensitivity, specificity and predictive value superior to those of procalcitonin.

In a study carried out with adult patients in an intensive care unit, subdivided into a group with sepsis and another with SIRS, Su et al., (2013)[19] found higher serum values of sTREM-1 in the group with sepsis compared to the group with SIRS ($p < 0.05$). The areas under the curve (AUROC) for these indicators were 0.868 (95% CI, 0.798–0.938), with 108.9 pg/mL as the cutoff point for sTREM-1, whose sensitivity was 0.83 and specificity was of 0.81. These data support the idea of using sTREM-1 to differentiate SIRS/sepsis, as well as to predict severity and mortality.

Among the potential biomarkers of the diagnosis and prognosis of severe infections the sTREM-1 is highlighted as a predictor of inflammation severity[20]. Jullien et al., demonstrate good prognostic accuracy of sTREM-1 with high-performance clinical features to generate simple algorithms for risk stratification in community and hospital settings [21].

However, it is highlighted that an important step and an imminent need is the incorporation of promising biomarkers, such as sTREM-1, into routine screening tests, aiming for speed, ease of use and low cost to be used in environments with few resources. Its hypothetical implementation in clinical practice could transform risk stratification and contribute to efforts to reduce mortality from inflammatory and infectious diseases, especially among the most vulnerable children[22].

Our study presented as limitations, a small number of works that sought to discuss the relationship between TREM-1 and SIRS, especially in the pediatric population. Furthermore, the methodological heterogeneity did not allow the performance of a meta-analysis.

CONCLUSION

The heterogeneity of the studies leads to different potential uses of TREM-1 in the pediatric population, specifically for diagnosing SIRS, with a good perspective in cardiac surgery through its elevation after surgery, however, it was not possible to establish a cutoff point, but rather demonstrate the possibility of mortality risk stratification and verification of its increase, compared to baseline values, when the patient has SIRS.

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