Role of triggering receptor expressed on myeloid cells-1 (TREM-1) in COVID-19 and other viral pneumonias: a systematic review and meta-analysis of clinical studies

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Abstract

Background Triggering receptor expressed on myeloid cells-1 (TREM-1) has emerged as an important inflammatory marker of immune response associated with severity and mortality outcomes in infection diseases, including viral pneumonias.

Aim (1) To evaluate the expression of TREM-1 in patients with COVID-19 and other viral pneumonias compared to healthy individuals; and (2) to analyze the levels of these biomarkers according to disease severity.

Materials and methods This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Searches were performed in PubMed, Scopus, Embase, and Google Scholar. Studies were considered eligible if they were observational studies that provided data on the levels of TREM-1 in humans with viral pneumonia compared to healthy controls. The results of the meta-analysis were expressed as standardized mean difference (SMD) and an effect size of 0.8 was considered a large effect. A subgroup analysis was performed according to the disease severity.

Results Seven studies were included in this systematic review. Four studies included patients with COVID-19 and three analyzed patients with different viruses. The meta-analysis was performed only with patients with COVID-19, which showed increased levels of soluble form of TREM-1 (sTREM-1) among patients with COVID-19 compared to healthy controls (SMD 1.53; 95% CI 0.53–2.52; \( p < 0.01 \)). No differences were found between patients with mild-to-moderate COVID-19 and healthy controls, but higher levels of sTREM-1 were shown among patients with severe COVID-19 (SMD 1.83; 95% CI 0.77–2.88; \( p < 0.01 \)). All three studies including patients with other viral pneumonias showed that TREM-1 levels were significantly elevated in infected patients compared with controls.

Conclusion These findings may provide evidence on the pro-inflammatory role of TREM-1 in these infections, contributing to the inflammatory profile and disease progression.

Keywords Viral infections · Coronavirus disease-2019 · COVID-19 · SARS-CoV-2 · Viral pneumonia · TREM-1

Introduction

Viral pneumonias are one of the most causes of morbidity and mortality worldwide. Currently, there is an emergence of new respiratory viral pathogens including influenza A virus, hantavirus, avian H5N1 influenza, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with the coronavirus disease-2019 (COVID-19) (Hodgens and Gupta 2022). In clinical practice, a wide range of biomarkers has been used to assess disease severity and mortality. In the last years, several studies have suggested that the Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) is an important biomarker in the diagnosis and
The TREM-1 consists of an innate immune system receptor expressed on innate immune cells and is present in two forms, as a membrane-bound receptor (mTREM-1) and as a soluble protein (sTREM-1) (Bouchon et al. 2000; Kerget et al. 2021). The mTREM-1 has three domains in its structure: one that resembles Ig responsible for binding the ligand, one transmembrane-bound, and a cytoplasmic portion that associates with the DAP12 protein (Colonna 2003; Tammaro et al. 2017). This complex, when activated, increases the expression of pro-inflammatory cytokines including IL-6, IL-8, IL-1β, and TNF-α (de Oliveira Matos et al. 2020), promotes cell survival through the inactivation of pro-apoptotic factors (Yuan et al. 2016; Tammaro et al. 2017), and blocks the synthesis of anti-inflammatory cytokines, such as IL-10 (Dubar et al. 2018).

The soluble form of TREM-1 may originate from the proteolytic cleavage of mTREM-1 through the action of metalloproteinases (Gómez-Piña et al. 2007) or from the translation of an alternative splicing of TREM-1 mRNA (Gingras et al. 2002). Studies have shown that sTREM-1 negatively regulates mTREM-1 signaling by neutralizing its ligands (Yuan et al. 2016; Du et al. 2016). The sTREM-1 has been measured in body fluids, including serum, cerebrospinal fluid, and bronchoalveolar lavage fluid from patients with various inflammatory conditions (de Sá Resende et al., 2021). It has been found that increased levels of sTREM-1 are associated with poor clinical outcomes in infectious and non-infectious diseases (Gibot 2005; Bomfim et al. 2017; de Oliveira Matos et al. 2020).

Some studies have suggested that the broad spectrum of clinical symptoms in viral diseases reflects increased activation of the immune system, characterized by elevated levels of inflammatory cytokines (Martins-Filho et al. 2020; Yang et al. 2020). Although sTREM-1 is a promising inflammatory biomarker (Bellos et al. 2018; de Sá Resende et al. 2021), there is no systematic evidence comparing the levels of this biomarker between patients with viral pneumonia and healthy controls. Thus, the aim of this systematic review and meta-analysis was (1) to evaluate the expression of mTREM-1 and its soluble form in patients with COVID-19 and other viral pneumonias compared to healthy individuals; and (2) to analyze the levels of these biomarkers according to disease severity.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al. 2010).

Search strategy

Searches were performed in PubMed, Scopus, Embase, and Google Scholar, and were limited to studies published in full-text versions, without language restriction. The reference lists of all eligible studies and reviews were scanned to identify additional studies for inclusion. The main keywords used in the search strategies were as follows: ‘triggering receptor expressed on myeloid cells-1’, ‘soluble triggering receptor expressed on myeloid cells-1’, ‘TREM-1’, ‘sTREM-1’, ‘respiratory tract infections’, ‘viral pneumonia’, ‘COVID-19’, ‘SARS-CoV-2’, ‘coronavirus’, ‘respiratory distress syndrome’, and ‘severe acute respiratory syndrome’. Search strategies were adapted for each database (Supplementary Table 1) and were performed on December 1, 2021.

Eligibility criteria

Studies were considered eligible if they were observational studies that provided data on the levels of TREM-1 in humans with viral pneumonia [respiratory syncytial virus, influenza, parainfluenza, adenovirus, severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV), metapneumovirus, rhinovirus, bocavirus, and parechovirus] compared to healthy controls. We excluded co-infections with bacteria and studies that did not provide clear information about the microorganisms involved in the infections. Reviews, letters, correspondences, editorials, commentaries, expert opinions, case reports, conference abstracts, and in vitro or animal experiments were also excluded. In addition, authors were contacted via e-mail or using the ResearchGate for missing data in potentially eligible studies. The response time for the requested data was 3 weeks, and those who did not respond were excluded.

Study selection and risk of bias assessment

Two investigators (Y. L. M. O. and A. S. R.) independently screened the search results based on title and abstracts. Relevant studies were read in full and selected according to the eligibility criteria. Disagreements were resolved by a third reviewer (P. R. M-F.).

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (NIH) (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) was used to grade the quality of included studies by two investigators (Y. L. M. O. and A. S. R.).
Data extraction

Two independent investigators (Y. L. M. O. and A. S. R.) extracted the following data: author’s name, year of publication, journal, country, study design, information about eligibility criteria, clinical setting, groups, sample size, age, sex distribution, diagnosis of viral pneumonia and microorganisms involved, disease severity, and TREM-1 values. When TREM-1 values were not reported in tables or text and authors could not be reached, data were extracted using the WebPlotDigitizer (Web Plot Digitizer, V.3.11. Texas, USA: Ankit Rohatgi 2017). If the means and standard deviations were also not reported in the article, indirect methods of extracting estimates were used (Hozo et al. 2005; Wan et al. 2014).

Data analysis

The results of the meta-analysis were expressed as standardized mean difference (SMD). An effect size of 0.2 was considered a small effect, a value of 0.5 a medium effect, and a value of 0.8 a large effect (Colen et al. 2018). We used either a fixed or random-effects model to pool the results of individual studies depending on the presence of heterogeneity. Statistical heterogeneity was quantified by the I² index using the following interpretation: 0%, no between-study heterogeneity; < 50%, low heterogeneity; 50–75%, moderate heterogeneity; > 75%, high heterogeneity (Higgins and Thompson 2002). In the case of heterogeneity, we used the random-effects model, otherwise, the fixed-effects model was used.

A subgroup analysis was performed according to the disease severity. Although funnel plots may be useful tools in investigating small study effects in meta-analyses, they have limited power to detect such effects when there are few studies (Simmonds 2015). Therefore, because we had a small number of studies included, we did not perform a funnel plot analysis. Forest plots were used to present the effect sizes and 95% confidence interval (CI), and p < 0.05 was used to determine significance. Analyses were conducted using Review Manager, version 5.3 (Cochrane IMS).

Results

Study selection

The search strategy retrieved 285 records and 72 duplicates were deleted. Two additional records were identified in the gray literature. After screening titles and abstracts, 54 full-text articles were assessed for eligibility, and seven (Rohde et al. 2012; Arriaga-Pizano et al. 2015; Zhong and Zhao 2016; Yaşar et al. 2021; de Nooijer et al. 2021; Youngs et al. 2021; Kerget et al. 2021) studies were finally included in this systematic review (Fig. 1).

Study characteristics

The included studies were published from 2012 to 2021 and the main characteristics are listed in Table 1. Three studies were conducted in Europe (Rohde et al. 2012; de Nooijer et al. 2021; Youngs et al. 2021), two studies in Turkey (Yaşar et al. 2021; Kerget et al. 2021), one study in Asia (Zhong and Zhao 2016), and one study in Latin America (Arriaga-Pizano et al. 2015). Only one study was conducted including the pediatric population (Zhong and Zhao 2016).

Four studies included patients with COVID-19 (Yaşar et al. 2021; de Nooijer et al. 2021; Youngs et al. 2021; Kerget et al. 2021) and three studies analyzed patients with different viruses (Rohde et al. 2012; Arriaga-Pizano et al. 2015; Zhong and Zhao 2016). All studies reported that viral infections were confirmed by polymerase chain reaction (PCR). All studies presented a healthy control group consisting of individuals with similar age and sex distribution.

Data synthesis

Due to the small number of studies and the clinical heterogeneity in the study population, the meta-analysis was performed only with patients with COVID-19. All studies including patients with COVID-19 provided data on disease severity. Results from studies including patients with other viral pneumonias were reported descriptively.

SARS-CoV-2 infection and TREM-1

This meta-analysis included 366 individuals, 246 individuals with COVID-19, and 120 healthy controls. Among the COVID-19 patients, 135 were men and 111 were women with a mean age between 51 and 65 years. Among the infected patients, 103 were diagnosed with mild-to-moderate COVID-19 and 143 with severe COVID-19. All four studies have measured the soluble form of TREM-1 in serum (Yaşar et al. 2021; de Nooijer et al. 2021; Youngs et al. 2021; Kerget et al. 2021).

The overall results of the meta-analysis showed increased levels of sTREM-1 among patients with COVID-19 compared to healthy controls (SMD 1.53; 95% CI 0.53–2.52; p < 0.01; I² = 93%) and the effect size was considered very large (Fig. 2). In the subgroup analysis evaluating sTREM-1 expression according to disease severity, no differences were found between patients with mild-to-moderate COVID-19 and healthy controls (SMD 1.17; 95% CI −0.61 to 2.95; p = 0.20; I² = 97%), but higher levels of sTREM-1 were shown among patients with severe COVID-19 (SMD 1.83; 95% CI 0.77–2.88; p < 0.01; I² = 91%) (Fig. 3).
Table 2 shows the quality assessment tool that resulted in a moderate-to-high risk of bias. Although research question and outcome measures were clearly stated in all studies, important questions on the study design were not clearly described, such as exposure measures of the control group,
| Author and year       | Country    | Study design | Viral pneumonia | Main characteristics | TREM-1 data | Control group | Mean (SD) | Sample | Assay method | Main characteristics | TREM-1 data | Assay method |
|----------------------|------------|--------------|-----------------|----------------------|-------------|---------------|-----------|--------|--------------|----------------------|-------------|--------------|
| Arriaga-Pizano et al. (2015) | Mexico    | Cross-sectional | H1N1 1st wave, H1N1 2nd wave, ILI | N: 9 | Virus: H1N1 1st wave, Sex: Mo and Se, Age (y): 5M 4F, Mean (SD): 41 (15–49)*, Sample: Blood, Assay method: Flow cytometry | TREM-1: 7,150.99 (2,678.06), Blood monocytes: 2,792.02 (455.84) | N: 23 | Virus: H1N1 2nd wave, Sex: 13M 10F, Age (y): 48 (18–76)*, Sample: Blood, Assay method: Flow cytometry | TREM-1: 2,165 (398.86), Blood monocytes: 2,792.02 (284.9) | N: 10 | Assay method: Flow cytometry |
| Kerget et al. (2021) | Turkey    | Cross-sectional | SARS-CoV-2 | Mo: 68, Se: 53 | Virus: SARS-CoV-2, Sex: Mo and Se, Age (y): 73M 48F, Mean (SD): 55 (14.3), Sample: Serum, Assay method: ELISA | TREM-1: 162 (49.6) pg/ml, Mo: 0.24 (0.08) ng/ml, Se: 0.29 (0.07) ng/ml | N: 24 | Virus: SARS-CoV-2, Sex: 18M 6F, Age (y): 63 (58–71)*, Sample: Serum, Assay method: ELISA | TREM-1: 21 9M 12F, Virus: 42 (22–48.5)*, Sample: Serum, Assay method: ELISA | N: 50 | Assay method: ELISA |
| Rhode et al. (2012) | Germany   | Cross-sectional | RSV, FLU and Rhinovirus | Mo: 118, Se: 53 | Virus: RSV, FLU and Rhinovirus, Sex: Mo and Se, Age (y): 95M 23F, Mean (SD): 66 (13), Sample: Serum, Assay method: ELISA | TREM-1: 87.5 (97.3) pg/ml | N: 118 | Virus: RSV, FLU and Rhinovirus, Sex: 13M 13F, Age (y): 51.3 (13.5), Sample: Serum, Assay method: ELISA | TREM-1: 13 7M 6F, Virus: 47.5 (4), Sample: Serum, Assay method: ELISA | N: 13 | Assay method: ELISA |
| Yasar et al. (2021) | Turkey    | Cross-sectional | SARS-CoV-2 | Mo: 26, Se: 25 | Virus: SARS-CoV-2, Sex: Mo, Age (y): 13M 13F, Mean (SD): 51.3 (13.5), Sample: Machine learning, Assay method: ELISA | TREM-1: 2.33 (0.51) pg/ml | N: 26 | Virus: SARS-CoV-2, Sex: 13M 6F, Age (y): 64.8 (12.8), Sample: Machine learning, Assay method: Machine learning | TREM-1: 33 17M 16F, Virus: 61.1 (18.2), Sample: Machine learning, Assay method: Machine learning | N: 33 | Assay method: Machine learning |
| Youngs et al. (2021) | United Kingdom | Cross-sectional | SARS-CoV-2 | Mo: 41, Se: 17 | Virus: SARS-CoV-2, Sex: Se, Age (y): 26M 15F, Mean (SD): 57.7 (11), Sample: Luminex, Assay method: ELISA | TREM-1: 608.57 (512.35) pg/ml | N: 41 | Virus: SARS-CoV-2, Sex: 6M 24F, Age (y): 6 (2.3), Sample: ELISA, Assay method: ELISA | TREM-1: 36 17M 13F, Virus: 6.3 (2.2), Sample: ELISA, Assay method: ELISA | N: 36 | Assay method: ELISA |

*Data presented as median (interquartile range)

ELISA enzyme-linked immunosorbent assay, FLU influenza, H1N1 influenza A (H1N1) pandemic, ILI influenza-like illness, RSV respiratory syncytial virus, M men, F female, Mi. mild, Mo moderate, Se severe, N sample size, NR not reported.
sample size justification, blinding of outcome assessors, and adjustment for confounders.

Other viral pneumonias and TREM-1

Three studies have investigated differences in TREM-1 levels among patients with other viral pneumonias and healthy individuals. Only one study evaluated TREM-1 expression on monocytes (Arriaga-Pizano et al. 2015), while two studies have analyzed the soluble form of TREM-1 (Rohde et al. 2012; Zhong and Zhao 2016). Zhong and Zhao (2016) included children in the study population and Rohde et al. (2012) have focused on adults with smoking habits. All three studies showed that TREM-1 levels were significantly elevated in infected patients compared with controls.

Discussion

Viral respiratory infections are a burden on the public health system due to their rapid transmissibility among people and poor capacity for control and recovery. Since the outbreak of the SARS-CoV-2 infection in December 2019, there is urgency in identifying biomarkers of severity to improve diagnosis and predict the clinical course of patients (de Nooijer et al. 2021; Kerget et al. 2021). In this context, systematic reviews have consistently demonstrated an association between high levels of sTREM-1 and worse clinical outcomes in patients with infectious diseases. However, these studies have summarized the available evidence based on infections caused by different microorganisms, which limits the understanding of the role of TREM-1 in specific infections (Jiyong et al. 2009; Ye et al. 2014; Su et al. 2016). Thus, to the best of our knowledge, this is the first meta-analysis performed to assess the levels of TREM-1 in viral infections of lower respiratory tract, especially from COVID-19 patients.

Diagnosis in the early stages of infection can be challenging due to the lack of specificity of clinical features and the limited effectiveness of conventional inflammatory markers, such as C-reactive protein (CRP) (Ansar and Ghosh 2016). In viral infections, including COVID-19, the patient can progress to a critical condition called cytokine storm, which is characterized by a significant elevation of inflammatory markers that can lead to hyperinflammation and multiple organ failure (Tang et al. 2020; Luo et al. 2021). In this regard, TREM-1 is early activated on the surface of myeloid cells, including neutrophils and monocytes, to
promptly trigger the innate immune response. These cells, in turn, release various cytokines and inflammatory proteins to prevent the spread of the virus, improve its elimination, and recruit more immune cells. However, flaws in TREM-1 suppression mechanisms may contribute to the cytokine storm. As a feedback mechanism, surface-bound TREM-1 is cleaved in its soluble form sTREM-1, which is suggested to act as a regulator of the inflammatory status. Soluble TREM-1 originates through proteolysis by metalloproteinases or alternative splicing (Gao et al. 2019) after stimulation of TREM-1 by inflammatory molecules (Van Singer et al. 2021). Elevated sTREM-1 levels, mainly as a result of neutrophil activation, correlate with other inflammatory mediators, such as IL-6 and TNF-α, and indicate the occurrence of cell damage associated with the inflammatory process and the release of proteinases by necrotic cells or pathogens (Dubar et al. 2018). In our meta-analysis, we found an increase in sTREM-1 in infected patients compared to healthy individuals, demonstrating the involvement of this inflammatory biomarker in COVID-19. In the subgroup analysis, we found evidence that patients with severe COVID-19 have higher levels of sTREM-1 than patients with mild or moderate disease. In addition, individual results have shown elevated levels of TREM-1 in other viral respiratory-tract infections. These results indicate that TREM-1 may be useful in predicting clinical outcomes in patients with viral pneumonia.

A few studies have investigated whether TREM-1 can be a sensitive and specific biomarker of general infections to predict mortality (Su et al. 2016; Jedynak et al. 2018; Wright et al. 2020). Considering respiratory infections, a meta-analysis by Su et al. (2016) demonstrated a sensitivity of 0.75 (95% CI 0.61–0.86) and specificity of 0.66 (95% CI 0.54–0.75) suggesting a moderate prognostic value of sTREM-1 to predict mortality. However, the between-study heterogeneity was high mainly due to variability in the type of infections, including cases of sepsis. Although it was not possible to measure the sensitivity and specificity of sTREM-1 in the present meta-analysis, our study showed the behavior of sTREM-1 in viral pneumonias including COVID-19. Despite these findings, further studies are needed to confirm the prognostic value and clinical significance of TREM-1 in viral infections.

Our study has some major limitations: (1) relatively small number of studies that evaluated TREM-1 function in respiratory viral infections; (2) different methods of TREM-1 detection; and (3) difficulty in summarizing TREM-1 levels in patients with other viral infections due to heterogeneity.

Table 2 Risk of bias assessment

| Question                                                                 | de Nooijer et al. (2021) | Kerget et al. (2021) | Yasar et al. (2021) | Youngs et al. (2021) |
|------------------------------------------------------------------------|-------------------------|---------------------|--------------------|---------------------|
| 1. Was the research question or objective in this paper clearly stated? | Y                       | Y                   | Y                  | Y                   |
| 2. Was the study population clearly specified and defined?             | Y                       | Y                   | N                  | N                   |
| 3. Was the participation rate of eligible persons at least 50%?         | CD                      | CD                  | N                  | N                   |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | N                       | Y                   | N                  | N                   |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | N                       | N                   | N                  | N                   |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | NA                      | NA                  | NA                 | NA                 |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | NA                      | NA                  | NA                 | NA                 |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | N                       | Y                   | Y                  | N                   |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Y                       | Y                   | Y                  | Y                   |
| 10. Was the exposure(s) assessed more than once over time?             | NA                      | NA                  | NA                 | NA                 |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Y                       | Y                   | Y                  | Y                   |
| 12. Were the outcome assessors blinded to the exposure status of participants? | CD                      | CD                  | CD                 | CD                 |
| 13. Was loss to follow-up after baseline 20% or less?                  | NA                      | NA                  | NA                 | NA                 |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | N                       | N                   | N                  | Y                   |

*CD cannot determine, N no, NA not applicable, NR not reported, Y yes*
between studies. Although these limitations, this is the first study to synthesize the available evidence on TREM-1 levels in patients with COVID-19 and other viral pneumonias. These findings may provide evidence on the pro-inflammatory role of TREM-1 in these infections, contributing to the inflammatory profile and disease progression.

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Data availability Data were directly retrieved from published original articles or by authors upon request by the reviewers.

Declarations

Conflict of interest The authors declare that there is no competing interest. All authors have approved the manuscript for submission.

Ethical approval Not applicable.

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