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Cytokines serum levels in myocarditis and inflammatory dilated cardiomyopathy: A protocol for a systematic review and meta-analysis

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first attempt to summarize the studies on cytokine levels in myocarditis.
- This study will follow PRISMA-P guidelines, risk of bias and certainty of evidence assessment and will utilize meta-analysis approach to provide high quality results.
- The main limitation of this study could be a high heterogeneity of included studies and patient cohorts, and this may lead to inconsistent results.

Total words count: 2237

ABSTRACT

Background: Myocarditis is an inflammatory heart disease resulting from infections, toxic exposures, or autoimmune reactions. Irrespective of the factors responsible for the disease, cytokines play an important role in the regulation of immunological response involved in the disease development and progression. Accordingly, the aim of this protocol is to conduct systematic review and meta-analysis summarizing previous research on serum and plasma levels of cytokines in patients with myocarditis and inflammatory dilated cardiomyopathy.

Methods: Four scientific databases: PubMed, Embase, Scopus and Web of Science, will be searched. The estimated date of the search will be 30 March 2024. Each stage of the review, including the study section, data extraction, risk of bias and quality of evidence assessments, will be performed in duplicate. Studies meeting the following criteria will be eligible for inclusion: (1) studies must involve “myocarditis”, or “inflammatory dilated cardiomyopathy”, (2) and studies are required to report serum levels of any cytokine. Meta-analyses will be used to summarize the serum levels of each cytokine if possible. Subgroup analysis will be stratified by age, sex, sample size, NYHA scale, cardiac Troponin T, N-terminal prohormone of brain natriuretic peptide, C reactive protein, number of lymphocytes per mm^2 in the endomyocardial biopsy.

Discussion: The extensive research on cytokine serum levels in myocarditis and inflammatory dilated cardiomyopathy patients has highlighted their implication in the disease pathogenesis and clinical outcomes. Ongoing investigations into interleukin 1β inhibitors suggest a significant potential for cytokines as therapeutic targets and diagnostic markers in these conditions. This systematic review and meta-analysis will consolidate existing data on cytokine concentrations in myocarditis and inflammatory dilated cardiomyopathy.

Ethics approval and dissemination: This study does not require ethics approval. After completion results will be published as a peer reviewed paper. Data generated during study will be published in open access repository.

PROSPERO registration number: CRD42024519625

Keywords: myocarditis, dilated cardiomyopathy, cytokines, systematic review, meta-analysis, humans

BACKGROUND

Rationale of this study

Myocarditis (MCI) is an inflammatory heart disease that occurs as a consequence of infections, exposure to toxic substances, and autoimmune reactions[1-3]. The Global Burden of Disease Study estimated the incidence of MCI as 22 cases per 100,000 patients annually[4]. Furthermore, it is a relatively common cause of sudden cardiac death among young people (about 6% in autopsy-based series)[5]. Clinically, we distinguish two subtypes of MCI based on symptom duration: acute and chronic. Acute MCI is recognized when symptoms occur rapidly, regularly leading to early diagnosis (typically less than a month). Chronic MCI indicates myocardial inflammation with a longer duration of symptoms (usually defined as more than a month). Chronic MCI can lead to cardiac dysfunction and ventricular remodeling and may transition into inflammatory dilated cardiomyopathy (iDCM)[6 7].

The specific mechanism of pathogenesis of MCI and transition to iDCM is not fully understood. However, it is considered a multifactorial process, with several immunologic mechanisms contributing to disease development and progression. It is believed that auto-inflammatory reactions might have a crucial role in this disease. Inflammatory cells infiltrate cardiac tissue leading to heart damage and remodeling. One of the key factors regulating this process are cytokines[8].

Cytokines are low molecular weight (mainly ~40-80kD) soluble proteins, secreted by virtually all nucleated cells, although they are typically associated with immune cells (lymphocytes, macrophages, mast cells, and stromal cells, etc.). They engage in inflammation as a danger signal and also as a communication link between immunocompetent cells, overseeing the process. However, abnormalities in the production of pro-inflammatory cytokines such as during a cytokine storm are observed in various pathologies including MCI

and iDCM[9 10]. The role of cytokines in the beforementioned diseases is still an object of intensive research. Some scientific evidence suggests their potential significance in the etiology of MCI and iDCM. For example, IL-1 exerts pro-apoptotic and hypertrophic effects on cardiomyocytes, depressing cardiac contractility[11], and IL-6 overexpression correlates with a worse prognosis in MCI patients[12].

Interestingly, the usefulness of cytokine inhibitors in MCI and iDCM is currently being investigated. An example of such inhibitor is Anakinra, a recombinant human IL-1 receptor antagonist. Anakinra might be an effective method of treatment for pericarditis[13 14]. It was observed in the pediatric population that anakinra improves the myocardial function of patients with fulminant MCI[14]. On the other hand, the ARAMIS study results are less optimistic, revealing that there is no notable improvement in the condition of MCI patients[15 16].

Study objectives

The aim of this systematic review and meta-analysis is to summarize previous research on serum and plasma levels of cytokines in patients with myocarditis and inflammatory dilated cardiomyopathy. To this end, the proposed study will answer following questions:

(1) Which cytokines have already been evaluated in myocarditis and inflammatory dilated cardiomyopathy patients?

(2) Do the serum/plasma concentrations in myocarditis and inflammatory dilated cardiomyopathy patients differ compared to healthy volunteers?

(3) What clinical and methodological characteristics explain the heterogeneity in results (if heterogeneity is present)?

METHODS AND ANALYSIS

This protocol for the systematic review and meta-analysis was registered in PROSPERO International Prospective Register of Systematic Reviews. The methods for conducting and

describing the results of this systematic review and meta-analysis have been planned according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020)[17]. The protocol has been prepared according to PRISMA guidelines for reporting protocols (PRISMA-P)[18 19]. The PRISMA-P checklist is available as Supplementary materials S1.

Eligibility criteria

Study designs and participants

We will include prospective and retrospective observational studies and clinical trials (baseline data only). We will exclude case series and case reports. We will also include studies examining the general population.

Clinical diagnosis

We will include studies addressing myocarditis and inflammatory dilated cardiomyopathy. All studies describing "myocarditis", or "inflammatory dilated cardiomyopathy" will be included. Studies reporting "dilated cardiomyopathy" or "idiopathic dilated cardiomyopathy" will be included only if:

(1) inflammation was not excluded by endomyocardial biopsy;

(2) coronary artery disease was excluded;

(3) and authors did not identify other causes of DCM.

Studies involving the following diagnoses will be included: "active myocarditis", "acute myocarditis", "chronic inflammatory cardiomyopathy", "chronic myocarditis" and "fulminant myocarditis". The exclusion criteria involve the following diagnoses: "sarcoidosis", "amyloidosis", „eosinophilic myocarditis", "pericarditis", "drug-induced myocarditis" and "diabetic cardiomyopathy". Additionally, myocarditis caused by parasites (i.e. Trypanosoma cruzi) will be excluded. Study groups involving conditions / diseases leading to myocarditis or

known for abnormal cytokines expression also be excluded, i.e. heart transplant recipients, rheumatic diseases, COVID-19, and sepsis. Healthy volunteers will be included as controls. Included studies may or may not have a comparator group.

Outcomes

Eligible studies are required to report serum levels of any cytokine. The following proteins will be eligible as "cytokine": (1) interleukins, (2) interferons, (3) tumor necrosis factor alpha and beta, and (4) chemokines. Only direct proteins levels measurements will be valid. Measurements of mRNA levels or flow cytometry measurements of cells expressing cytokines will be excluded. Additionally, the following outcomes will be recorded (if available): New York Heart Association (NYHA) functional class, ejection fraction (EF), number of lymphocytes per mm^2 in endomyocardial biopsy, and serum levels of C reactive protein (CRP), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), cardiac troponin T(cTnT).

Information sources and search strategy

Literature search strategy will be performed using prepared search key using medical subjects' headings (MeSH) / Embase subject headings (Emtree) and text words related to myocarditis / dilated cardiomyopathy and cytokines. We will search four scientific databases: PubMed, Embase, Scopus and Web of Science. The search will be performed by two authors (MR and MB) with any disagreements resolved by discussion with the third author (PL). The search will not be limited by date or language of publication using search syntax presented in Supplementary Materials S2. All search results will be uploaded into Microsoft Excel worksheet.

Data management

One researcher (MR) will be responsible for data management. Records from all searches will be merged into one worksheet and each record will get unique ID (UID). Duplicates will be

removed using manual gold standard method described by Kwon et al[20]. Data manager will prepare files for title and abstract and full text screening, blinding, and keeping data integrity. All full texts of included records will be uploaded into OneDrive folder using predefined filename format: surname_year-of-publication.pdf. In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Selection of studies

Seven authors (MB, MZ, KK, PZ, JK, KL, JW) working as pairs of reviewers will independently screen the titles and abstracts of the retrieved articles. Then, full texts of potentially eligible records will be independently screened for eligibility by two reviewers (PL and MG). Any discrepancies during these steps will be resolved by a discussion with another author (RW). The results of the study selection, together with reasons for full-text article exclusion, will be presented using a PRISMA-compliant flow diagram. If more than one report from the study is available, all of them will be included unless data are redundant or discrepant.

Data extraction

Data extraction will be performed using standardized Excel worksheet to extract data for synthesis and risk of bias assessment. Seven authors (MB, MZ, KK, PZ, JK, KL, JW) working as pairs of reviewers will independently extract data from each record. Any differences will be resolved by two reviewers (PL and MG). To ensure consistency across reviewers, we will conduct calibration exercises before starting the review. The following data are planned to be extracted: first author, year of publication, country, patients demographic characteristics (age, sex, ethnicity), diagnosis, methodology of confirmation (i.e., cardiac MRI, endomyocardial biopsy), diagnosis criteria (i.e., Dallas criteria, ESC 2021), heart failure and general biomarkers (NYHA, EF, cTNT, NT-proBNP, CRP, number of lymphocytes per mm2 in endomyocardial

biopsy), cytokines concentrations and methods of measurement. For all quantitative data the standard deviation will be recorded if available.

Risk of bias assessment

To facilitate the assessment of the risk of bias within included studies, each record will be evaluated using Effective Public Health Practice (EPHPP)[21] tool by two independent reviewers (MB, KK). Any discrepancies during these steps will be resolved by discussion with another author (PL). To ensure consistency and reproducibility of each assessment Excel worksheet and criteria explanation manual will be prepared.

Data synthesis

We will conduct meta-analyses for all cytokines measured in at least two studies. Weighted mean serum concentration will be calculated for each cytokine for case and control group. For each record the standard mean difference and 95% CI of cytokine concentration between case and control group will be calculated. In case of studies without a control group, the mean difference will be calculated based on weighted mean of all included studies. The percentage variability across studies will be calculated using I^2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). If high levels of heterogeneity among the trials exist (I2 >=50% or P <0.1) the study design and characteristics in the included studies will be analyzed. We will try to explain the source of heterogeneity by subgroup analysis or sensitivity analysis. If the I^2 value is more than 50%, analysis will be performed using a random-effect model, otherwise a fixed-effect model will be used. To explore potential sources of inconsistency and heterogeneity, we will conduct subgroup and sensitivity analysis. Subgroup analysis will be stratified by age, sex, sample size, NYHA scale, cTNT, NT-proBNP, CRP, number of lymphocytes per mm^2 in endomyocardial biopsy. The

sensitivity analyses will include (1) studies with myocarditis confirmed by endomyocardial biopsy, (2) studies with low and moderate risk of bias. A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies. Additionally, the potential for reporting bias will be explored by funnel plots if ≥10 studies are available. All analyses will be performed in Python and PythonMeta package.

Certainty of evidence assessment

We will evaluate the credibility of evidence for all outcomes utilizing the methodology established by the Grading of Recommendations Assessment, Development, and Evaluation working group. We will scrutinize the quality of evidence across various dimensions including susceptibility to bias, coherence, relevance, accuracy, and potential publication biases. Additional aspects may be considered as deemed appropriate. The evaluation will categorize quality as either high (unlikely that additional research will significantly alter our confidence in the effect estimate), moderate (further research could substantially influence our confidence in the effect estimate and might lead to a different estimate), low (additional research is highly likely to impact our confidence in the effect estimate and could result in a different estimate), or very low (considerable uncertainty surrounding the effect estimate).

DISCUSSION

The preliminary searches have shown that cytokine serum levels have been extensively researched in patients with MCI and iDCM. It has also been demonstrated that certain cytokines are implicated in the pathogenesis of MCI or correlated with clinical outcomes. Clinical trials investigating the utilization of IL-1β inhibitors in myocarditis treatment are currently undergoing. Early results indicate that cytokines may play a significant role in the development of novel diagnostic and therapeutic strategies for MCI and iDCM.

The upcoming systematic review and meta-analysis will represent the first attempt to consolidate and analyze data on cytokine levels in the serum of MCI and iDCM patients. To ensure the provision of relevant and high-quality data, the meta-analysis will adhere to the PROSPERO guidelines. Given the diverse range of study types, including randomized controlled trials, case-control studies, and retrospective studies, we have chosen to evaluate the risk of bias using the EPHPP scale, as recommended by Mamikutty et al., which is suitable for multi-design studies. Additionally, considering the anticipated high heterogeneity among study groups, we will conduct further subgroup analyses[22].

Our findings will contribute to and consolidate the existing knowledge regarding cytokine levels in MCI and iDCM. These results may resolve the cause of observed diversity in MCI and iDCM trials conducted across various countries and time periods. Moreover, our results will help identify research gaps and limitations in previous trials, offering insights that may be addressed in future studies.

ETHICS APPROVAL AND DISSEMINATION

This study does not require ethics approval. After completion results will be published as a peer reviewed paper. Data generated during the study will be published in an open access repository.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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Funders are not involved in any aspects for the project and will have no input on the interpretation or publication of the study results.

REGISTRATION

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 16th March 2024 (registration number CRD42024519625)[23].

AUTHOR CONTRIBUTIONS

PL is the guarantor. PL, MG, MB, MR, MZ and RW drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. PL, MG, MB, and KK developed the search strategy. PL, MG, MR and JK provided statistical expertise. PL, MR and JK developed data management strategy. PL and RW were responsible for gathering funding. RW provided expertise on myocarditis and inflammatory dilated cardiomyopathy. All authors read, provided feedback, and approved the final manuscript.

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Not applicable.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1, 14
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2-3
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	10
Support			
Sources	#5a	Indicate sources of financial or other support for the review	13
Sponsor	#5b	Provide name for the review funder and / or sponsor	13
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	13
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	6-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

Supplementary materials S2 – search syntax

PubMed

("Myocarditis"[Mesh] OR myocarditis OR "Cardiomyopathy, Dilated"[Mesh] OR dilated cardiomyopathy OR dcm) AND ("Cytokines"[Mesh] OR cytokine* OR interleukin* OR chemokine* OR "chemokines"[Mesh] OR "Tumor Necrosis Factors"[Mesh] OR "Interferons"[Mesh] OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN OR ifnα OR ifnβ OR ifnε OR ifκ OR ifnτ OR ifnδ OR ifnζ OR ifnω OR ifnγ OR ifnλ*) AND (human* OR "humans"[Mesh] OR man OR men OR woman OR women OR person* OR "persons"[Mesh] OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*)

Embase

('myocarditis'/exp OR myocarditis OR 'dilated cardiomyopathy'/exp OR dilated cardiomyopathy OR dcm) AND ('cytokine'/exp OR cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) AND (human* OR man OR men OR woman OR women OR person* OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*)

Scopus

(myocarditis OR (dilated W/2 cardiomyopathy) OR dcm) AND (cytokine* OR interleukin* OR chemokine* OR il OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR

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Web of Science

(TS=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR TI=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR AB=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR AK=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR KP=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR SU=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR WC=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm)) AND (TS=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR TI=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR AB=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR AK=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR

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BMJ Open

How do serum cytokine levels change in myocarditis and inflammatory dilated cardiomyopathy relative to healthy individuals? A protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Immunology (including allergy)
Keywords:	Cardiomyopathy < CARDIOLOGY, CARDIOLOGY, IMMUNOLOGY, Systematic Review, Meta-Analysis

How do serum cytokine levels change in myocarditis and inflammatory dilated cardiomyopathy relative to healthy individuals? A protocol for a systematic review and meta-analysis

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Total words count: 2237

ABSTRACT

Introduction: Myocarditis is an inflammatory heart disease resulting from infections, toxic exposures, or autoimmune reactions. Irrespective of the factors responsible for this disease, cytokines play an important role in the regulating the immunological response involved in its development and progression. Accordingly, this protocol aims to conduct a systematic review and meta-analysis summarizing previous research on serum and plasma levels of cytokines in patients with myocarditis and inflammatory dilated cardiomyopathy.

Methods and analysis: Four scientific databases: PubMed, Embase, Scopus and Web of Science, will be searched. The estimated date of the search will be 30 March 2024. Each stage of the review, including the study selection, data extraction, risk of bias and quality of evidence assessments, will be performed in duplicate. Studies meeting the following criteria will be eligible for inclusion: (1) studies involving "myocarditis", or "inflammatory dilated cardiomyopathy" and (2) studies are required to report serum levels of any cytokine. Meta-analyses will be used to summarize serum levels of each cytokine if possible. Subgroup analysis will be stratified by age, sex, sample size, NYHA scale, cardiac Troponin T, N-terminal prohormone of brain natriuretic peptide, C reactive protein, number of lymphocytes per mm^2 in the endomyocardial biopsy.

Ethics approval and dissemination: This study does not require ethics approval. After completion the results will be published in a peer reviewed paper. Data generated during the study will be published in open access repository.

PROSPERO registration number: CRD42024519625

Keywords: myocarditis, dilated cardiomyopathy, cytokines, systematic review, meta-analysis, humans

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will follow PRISMA-P guidelines to ensure rigorous and transparent reporting of the systematic review protocol.
- A comprehensive risk of bias assessment and certainty of evidence evaluation will be conducted for all included studies.
- A meta-analysis approach will be used to synthesize quantitative data and identify patterns in cytokine levels.
- The main limitation of this study could be the high heterogeneity of included studies and patient cohorts, and this may lead to inconsistent results.

BACKGROUND

Rationale of this study

Myocarditis (MCI) is an inflammatory heart disease that occurs as a consequence of infections, exposure to toxic substances, and autoimmune reactions[1-3]. The Global Burden of Disease Study estimated the annual incidence of MCI to be 22 cases per 100,000 patients[4]. Furthermore, it is a relatively common cause of sudden cardiac death among young people (about 6% in autopsy-based series)[5]. Clinically, two subtypes of MCI based on the symptom duration: acute and chronic. Acute MCI is recognized when symptoms occur rapidly, regularly leading to an early diagnosis (typically less than a month). Chronic MCI indicates myocardial inflammation with a longer duration of symptoms (usually defined as more than a month). Chronic MCI can lead to cardiac dysfunction and ventricular remodeling and may transition into inflammatory dilated cardiomyopathy (iDCM)[6 7].

The specific mechanism of pathogenesis of MCI and transition to iDCM is not fully understood. However, it is considered a multifactorial process, with several immunologic mechanisms contributing to the disease development and progression. It is believed that auto-inflammatory reactions might have a crucial role in this disease. Inflammatory cells infiltrate cardiac tissue leading to the heart damage and remodeling. One of the key factors regulating this process are cytokines[8].

Cytokines are low molecular weight (mainly ~40-80kD) soluble proteins, secreted by virtually all nucleated cells, although they are typically associated with the immune cells (lymphocytes, macrophages, mast cells, and stromal cells, etc.). They engage in the inflammation as a danger signal and also as a communication link between the immunocompetent cells, overseeing the process. However, abnormalities in the production of pro-inflammatory cytokines storm are observed in various pathologies including MCI and

iDCM[9 10]. The role of cytokines in the beforementioned diseases is still an object of intensive research. Some scientific evidence suggests their potential significance in the etiology of MCI and iDCM. For example, IL-1 exerts pro-apoptotic and hypertrophic effects on cardiomyocytes, depressing cardiac contractility[11], and IL-6 overexpression correlates with a worse prognosis in MCI patients[12].

Interestingly, the usefulness of cytokine inhibitors in MCI and iDCM is currently being investigated. An example of such inhibitor is Anakinra, a recombinant human IL-1 receptor antagonis, which may effectively treat pericarditis[13 14]. In the pediatric population, it was observed that anakinra improves the myocardial function of patients with fulminant MCI[14]. On the other hand, the ARAMIS study results are less optimistic, revealing that there is no notable improvement in the condition of MCI patients[15 16].

Study objectives

The aim of this systematic review and meta-analysis is to summarize previous research on serum and plasma levels of cytokines in patients with myocarditis and inflammatory dilated cardiomyopathy. To this end, the proposed study will answer the following questions:

(1) Which cytokines have already been evaluated in acute / chronic myocarditis and inflammatory dilated cardiomyopathy patients?

(2) Do the serum/plasma concentrations in myocarditis and inflammatory dilated cardiomyopathy patients differ compared to healthy volunteers?

(3) Do serum/plasma cytokine concentrations differ between chronic myocarditis / inflammatory dilated cardiomyopathy and acute myocarditis patients?

(4) What is the relationship between cytokine concentrations and prognosis of myocarditis?

(5) What clinical and methodological characteristics explain the heterogeneity in results (if heterogeneity is present)?

METHODS AND ANALYSIS

This protocol for the systematic review and meta-analysis was registered in PROSPERO International Prospective Register of Systematic Reviews. The methods for conducting and describing the results of this systematic review and meta-analysis will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020)[17]. The protocol has been prepared according to PRISMA guidelines for reporting protocols (PRISMA-P)[18 19]. The PRISMA-P checklist is available as Supplementary materials S1. This systematic review and meta-analysis was started in March 2024. Estimated completion date is June 2025.

Eligibility criteria

Study designs and participants

We will include prospective and retrospective observational studies and clinical trials (baseline data only). We will exclude case series and case reports. Studies examining the general population will be included as a comparator.

Clinical diagnosis

We will include studies addressing myocarditis and inflammatory dilated cardiomyopathy. All studies describing “myocarditis”, or “inflammatory dilated cardiomyopathy” will be included. Studies reporting “dilated cardiomyopathy” or “idiopathic dilated cardiomyopathy” will be included only if:

(1) inflammation was not excluded by endomyocardial biopsy;

(2) coronary artery disease was excluded;

(3) and authors did not identify other causes of DCM.

Studies involving the following diagnoses will be included: “active myocarditis”, “acute myocarditis”, “chronic inflammatory cardiomyopathy”, “chronic myocarditis” and “fulminant

myocarditis". The exclusion criteria involve the following diagnoses: "sarcoidosis", "amyloidosis", „eosinophilic myocarditis", "pericarditis", "drug-induced myocarditis" and "diabetic cardiomyopathy". Additionally, myocarditis caused by parasites (i.e. Trypanosoma cruzi) will be excluded. Study groups involving conditions / diseases leading to myocarditis or known for abnormal cytokines expression will also be excluded, i.e. heart transplant recipients, rheumatic diseases, COVID-19, and sepsis. Healthy volunteers will be included as controls. Included studies may or may not have a comparator group.

Outcomes

Eligible studies are required to report serum levels of any cytokine. The following proteins will be eligible as "cytokine": (1) interleukins, (2) interferons, (3) tumor necrosis factor alpha and beta, and (4) chemokines. Only direct protein level measurements will be valid. Measurements of mRNA levels or flow cytometry measurements of cells expressing cytokines will be excluded. Additionally, the following outcomes will be recorded (if available): New York Heart Association (NYHA) functional class, ejection fraction (EF), number of lymphocytes per mm^2 in endomyocardial biopsy, and serum levels of C reactive protein (CRP), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), cardiac troponin T(cTnT).

Information sources and search strategy

Literature search strategy will be performed using prepared search key using medical subjects' headings (MeSH) / Embase subject headings (Emtree) and text words related to myocarditis / dilated cardiomyopathy and cytokines. We will search four scientific databases: PubMed, Embase, Scopus and Web of Science. The search will be performed by two authors (MR and MB) with any disagreements resolved by discussion with the third author (PL). The search will not be limited by date or language of publication using search syntax presented in

Supplementary Materials S2. All search results will be uploaded into a Microsoft Excel worksheet.

Data management

One researcher (MR) will be responsible for data management. Records from all searches will be merged into one worksheet and each record will get unique ID (UID). Duplicates will be removed using manual gold standard method described by Kwon et al[20]. The data manager will prepare files for title and abstract screening, full text screening, blinding, and maintaining data integrity. All full texts of included records will be uploaded into OneDrive folder using predefined filename format: surname_year-of-publication.pdf. In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Selection of studies

Seven authors (MB, MZ, KK, PZ, JK, KL, JW) working as pairs of reviewers will independently screen the titles and abstracts of the retrieved articles. Then, the full texts of potentially eligible records will be independently screened for eligibility by two reviewers (PL and MG). Any discrepancies during these steps will be resolved by a discussion with another author (RW). The results of the study selection, together with the reasons for full-text article exclusion, will be presented using a PRISMA-compliant flow diagram. If more than one report from the study is available, all of them will be included unless data are redundant or discrepant.

Data extraction

Data extraction will be performed using standardized Excel worksheet to extract data for synthesis and risk of bias assessment. Seven authors (MB, MZ, KK, PZ, JK, KL, JW) working as pairs of reviewers will independently extract data from each record. Any differences will be

resolved by two reviewers (PL and MG). To ensure consistency across reviewers, we will conduct calibration exercises before starting the review. The following data are planned to be extracted: first author, year of publication, country, patients demographic characteristics (age, sex, ethnicity), diagnosis, methodology of confirmation (i.e., cardiac MRI, endomyocardial biopsy), diagnosis criteria (i.e., Dallas criteria, ESC 2021), heart failure and general biomarkers (NYHA, EF, cTNT, NT-proBNP, CRP, number of lymphocytes per mm2 in endomyocardial biopsy), cytokine concentrations and methods of measurement. Additionally, if possible, we will extract data on the relationship between cytokine concentration and patient prognosis. Such data will include, for example: (1) hazard ratios for death with confidence interval per unit of cytokine concentration, (2) cytokine concentrations and their respective standard deviations in groups that survived and in groups that died during the follow-up, (3) diagnostic odds ratio, sensitivity, and specificity of cytokine testing in myocarditis for death prediction.

Risk of bias assessment

To facilitate the assessment of the risk of bias within included studies, each record will be evaluated using Effective Public Health Practice (EPHPP)[21] tool by two independent reviewers (MB, KK). Any discrepancies during these steps will be resolved by a discussion with another author (PL). To ensure consistency and reproducibility of each assessment, Excel worksheet and criteria explanation manual will be prepared.

Data synthesis

We will conduct meta-analyses for all cytokines measured in at least two studies. The weighted mean serum concentration will be calculated for each cytokine for case and control group. For each record the standard mean difference and 95% CI of cytokine concentration between case and control group will be calculated. In the case of studies without a control group, the mean difference will be calculated based on weighted mean of all control groups

in the included studies. The percentage variability across studies will be calculated using I^2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). If high levels of heterogeneity among the trials exist (I^2 >=50% or P <0.1) study design and characteristics of the included studies will be analyzed. We will try to explain the source of heterogeneity by subgroup analysis or sensitivity analysis. If the I^2 value is more than 50%, the analysis will be performed using a random-effect model, otherwise a fixed-effect model will be used. To explore potential sources of inconsistency and heterogeneity, we will conduct subgroup and sensitivity analysis. Subgroup analysis will be stratified variables such as age, sex, sample size, NYHA scale, cTNT, NT-proBNP, CRP, number of lymphocytes per mm^2 in endomyocardial biopsy. The sensitivity analyses will include (1) studies with myocarditis confirmed by endomyocardial biopsy, (2) studies with low and moderate risk of bias. A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and findings of the included studies. Additionally, the potential for reporting bias will be explored by funnel plots if ≥10 studies are available. All analyses will be performed in Python and PythonMeta package.

Certainty of evidence assessment

We will evaluate the credibility of evidence for all outcomes utilizing the methodology established by the Grading of Recommendations Assessment, Development, and Evaluation working group. We will scrutinize the quality of evidence across various dimensions including susceptibility to bias, coherence, relevance, accuracy, and potential publication biases. Additional aspects may be considered as deemed appropriate. The evaluation will categorize the quality as either high (unlikely that additional research will significantly alter our

confidence in the effect estimate), moderate (further research could substantially influence our confidence in the effect estimate and might lead to a different estimate), low (additional research is highly likely to impact our confidence in the effect estimate and could result in a different estimate), or very low (considerable uncertainty surrounding the effect estimate).

DISCUSSION

The preliminary searches have shown that cytokine serum levels have been extensively researched in patients with MCI and iDCM. Studies have demonstrated that certain cytokines are implicated in the pathogenesis of MCI or correlated with clinical outcomes. Clinical trials investigating the utilization of IL-1β inhibitors in myocarditis treatment are currently undergoing. Early results indicate that cytokines may play a significant role in the development of novel diagnostic and therapeutic strategies for MCI and iDCM.

The upcoming systematic review and meta-analysis will represent the first attempt to consolidate and analyze data on cytokine levels in the serum of MCI and iDCM patients. To ensure the provision of relevant and high-quality data, the meta-analysis will adhere to the PROSPERO guidelines. Given the diverse range of study types, including randomized controlled trials, case-control studies, and retrospective studies, we have chosen to evaluate the risk of bias using the EPHPP scale, as recommended by Mamikutty et al., which is suitable for multi-design studies[22]. Additionally, considering the anticipated high heterogeneity among study groups, we plan to conduct further subgroup analyses[22].

Our findings will enhance and consolidate the existing knowledge regarding cytokine levels in MCI and iDCM. These results may resolve the cause of observed diversity in MCI and iDCM trials conducted across various countries and time periods. Moreover, our results will help identify the gaps in research and limitations of previous trials, offering insights that may be addressed in the future studies.

ETHICS APPROVAL AND DISSEMINATION

This study does not require ethics approval. After completion results will be published as a peer reviewed paper. Data generated during the study will be published in an open access repository.

COMPETING INTERESTS

The authors declare that they have no competing interests.

Patient and Public Involvement

none

FUNDING

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REGISTRATION

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 16th March 2024 (registration number CRD42024519625)[23].

AUTHOR CONTRIBUTIONS

PL is the guarantor. PL, MG, MB, MR, MZ and RW drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. PL, MG, MB, and KK developed the search strategy. PL, MG, MR and JK provided statistical expertise. PL, MR and JK developed data management strategy. PL and RW were responsible for gathering funding. RW provided expertise on myocarditis and

inflammatory dilated cardiomyopathy. All authors read, provided feedback, and approved the final manuscript.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the author(s) used GPT 4.0 to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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Not applicable.

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1, 14
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2-3
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	14

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	10
Support			
Sources	#5a	Indicate sources of financial or other support for the review	13
Sponsor	#5b	Provide name for the review funder and / or sponsor	13
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	13
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	6-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9-10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

Supplementary materials S2 – search syntax

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("Myocarditis"[Mesh] OR myocarditis OR "Cardiomyopathy, Dilated"[Mesh] OR dilated cardiomyopathy OR dcm) AND ("Cytokines"[Mesh] OR cytokine* OR interleukin* OR chemokine* OR “chemokines”[Mesh] OR “Tumor Necrosis Factors”[Mesh] OR “Interferons”[Mesh] OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf OR “tumour necrosis factor*” OR “tumor necrosis factor*” OR interferon* OR IFN OR ifnα OR ifnβ OR ifnε OR ifκ OR ifnτ OR ifnδ OR ifnζ OR ifnω OR ifnγ OR ifnλ*) AND (human* OR “humans”[Mesh] OR man OR men OR woman OR women OR person* OR “persons”[Mesh] OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*)

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(‘myocarditis’/exp OR myocarditis OR ‘dilated cardiomyopathy’/exp OR dilated cardiomyopathy OR dcm) AND (‘cytokine’/exp OR cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR “tumour necrosis factor*” OR “tumor necrosis factor*” OR interferon* OR IFN*) AND (human* OR man OR men OR woman OR women OR person* OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*)

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(myocarditis OR (dilated W/2 cardiomyopathy) OR dcm) AND (cytokine* OR interleukin* OR chemokine* OR il OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR

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(TS=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR TI=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR AB=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR AK=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR KP=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR SU=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm) OR WC=(myocarditis OR (dilated NEAR/2 cardiomyopathy) OR dcm)) AND (TS=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR TI=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR AB=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR AK=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR

il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR KP=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR SU=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*) OR WC=(cytokine* OR interleukin* OR chemokine* OR il OR il1 OR il1a OR il1b OR il2 OR il3 OR il4 OR il5 OR il6 OR il7 OR il8 OR il9 OR il10 OR il11 OR il12 OR il13 OR il14 OR il15 OR il16 OR il17 OR il18 OR il19 OR il20 OR il21 OR il22 OR il23 OR il24 OR il25 OR il26 OR il27 OR il28 OR il28* OR il29 OR il30 OR il31 OR il32 OR il33 OR il35 OR il36 OR CCL1 OR CCL2 OR CCL3 OR CCL4 OR CCL5 OR CCL6 OR CCL7 OR CCL8 OR CCL9 OR CCL10 OR CCL11 OR CCL12 OR CCL13 OR CCL14 OR CCL15 OR CCL16 OR CCL17 OR CCL18 OR CCL19 OR CCL20 OR CCL21 OR CCL22 OR CCL23 OR CCL24 OR CCL25 OR CCL26 OR CCL27 OR CCL28 OR CXCL1 OR CXCL2 OR CXCL3 OR CXCL4 OR CXCL5 OR CXCL6 OR CXCL7 OR CXCL8 OR CXCL9 OR CXCL10 OR CXCL11 OR CXCL12 OR CXCL13 OR CXCL14 OR CXCL15 OR CXCL16 OR CXCL17 OR XCL1 OR XCL2 OR CX3CL1 OR tnf* OR "tumour necrosis factor*" OR "tumor necrosis factor*" OR interferon* OR IFN*)) AND (TS=(human* OR man OR men OR woman OR women OR person* OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*) OR TI=(human* OR man OR men OR woman OR women OR person* OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*) OR AB=(human* OR man OR men OR woman OR women OR person* OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*) OR AK=(human* OR man OR men OR woman OR women OR person* OR people OR individual* OR patient* OR child* OR adolescent* OR newborn* OR toddler* OR senior*) OR KP=(human* OR man OR men OR woman OR women OR person* OR people OR individual* OR patient* OR child* OR

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