



Biomarkers for atopic dermatitis: a systematic review and meta-analysis

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Purpose of review

A large number of studies investigating the correlation between severity of atopic dermatitis and various biomarkers have been published over the past decades. The aim of this review was to identify, evaluate and synthesize the evidence examining the correlation of biomarkers with disease severity in atopic dermatitis patients, something that has not been performed previously.

Recent findings

Three electronic databases were systematically searched and relevant studies were selected for inclusion. A total of 222 articles, reporting on 115 different biomarkers in 30 063 patients, were critically appraised. Studies were divided into two main groups. The first group consisted of longitudinal randomized controlled trials and cohort studies, which reported measurements at multiple time points. The second contained cross-sectional studies that reported only one measurement per patient. Out of 222 articles, 108 articles reported sufficient data for meta-analysis. Only four biomarkers were eligible for meta-analysis in the longitudinal group, and nine in the cross-sectional group.

Summary

Serum thymus and activation-regulated chemokine (TARC) was found to be the most reliable biomarker studied, showing pooled correlation coefficients of 0.60 [95% confidence interval (95% CI) 0.48–0.70] and 0.64 (95% CI 0.57–0.70) in longitudinal and cross-sectional studies, respectively. Additional biomarkers that could prove useful but require additional research include serum cutaneous T-cell attracting chemokine (CTACK), sE-selectin, macrophage-derived chemokine (MDC), lactate dehydrogenase (LDH) and interleukin (IL)-18.

Keywords

atopic dermatitis, biomarkers, cutaneous T-cell attracting chemokine, disease severity measures, interleukin-18, lactate dehydrogenase, macrophage-derived chemokine, sE-selectin, thymus and activation-regulated chemokine

INTRODUCTION

Atopic dermatitis is a common, chronic inflammatory skin disease that is frequently associated with a personal or family history of allergic asthma and/or rhinitis. Atopic dermatitis can have profound effects on quality of life and imposes a high socioeconomic burden [1]. There has been an increasing interest in atopic dermatitis over the past decades, reflected in an exponential increase in publications. However, the use of different criteria for the diagnosis of atopic dermatitis and different outcome measurements hampers study comparability [2].

Quantifying disease severity using severity measurement tools such as the SCORing of Atopic Dermatitis (SCORAD) and Eczema Area Severity Index (EASI) is time-consuming and may be subject

to intra and interobserver variation [3]. In addition, many severity measurement tools that are used in clinical trials have not been validated. A systematic

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review of atopic dermatitis severity measurement tools found that 91% of atopic dermatitis clinical trials used an objective severity measure, but less than one-third of these scales had been previously published [4]. In addition, Schmitt *et al.* [5] assessed the validity and reliability of the 20 most commonly used severity measures for atopic dermatitis and found that only three performed adequately. To address these deficiencies in reporting, leading experts in the field have established the Harmonizing Outcome Measurements in Eczema (HOME) initiative, an attempt to ensure that investigators employ a core set of outcome measures to enhance comparability between studies [5]. We suggest that in addition to improvements in clinical outcome reporting, an objective serological measure for disease severity would be of great value for clinical research.

Over the past decades, a number of serum and plasma parameters (biomarkers) have been found to correlate with disease severity in atopic dermatitis patients. These include a variety of proteins, such as cytokines, chemokines, adhesion molecules and growth factors. In addition, numerous studies investigating the efficacy of various treatments for atopic dermatitis patients have also reported biomarker levels in their patients. To the best of our knowledge, a systematic review of this sprawling literature has not yet been performed. Our aim was to identify, evaluate and synthesize the evidence examining the correlation of known biomarkers with disease severity in atopic dermatitis patients.

MATERIALS AND METHODS

Search strategy

This systematic review was performed according to the criteria of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA)

statement [6]. Three electronic databases (PubMed, EMBASE and the Cochrane Library) were systematically searched from inception until October 2014. The electronic search was designed to provide optimal coverage for the targeted domain ‘atopic dermatitis’, ‘biomarkers’ as the determinant and ‘disease severity’ as the outcome and synonyms (Table 1). No language or publication restrictions were used, but studies were limited to research in humans.

Inclusion and exclusion criteria

All publications on serum and/or plasma biomarkers in atopic dermatitis patients that provided correlations with disease severity were considered. We did not discriminate between randomized controlled trials, cohorts or case series. Case reports were excluded, as were publications reporting data on fewer than five patients. All study titles and abstracts obtained from the database searches were screened and reviewed by at least two independent reviewers (J.T., T.K. or D.J.H.). An additional assessment was performed on the basis of the full-text versions of all selected articles and those with insufficient information in the title and abstract.

Data extraction

A data extraction sheet was developed, pilot-tested on the first included studies and refined accordingly. The adapted version (Table S1, <http://links.lww.com/COAI/A14>) was applied to all subsequent studies and retrospectively to the initially identified subset. The data items extracted from each study are listed in Table S1, <http://links.lww.com/COAI/A14>. In this review, only reported data on biomarker levels with corresponding severity scores in atopic dermatitis patients and the correlation coefficients were extracted for analysis. Because biomarkers were not

Table 1. Search performed on 25 September 2014 in PubMed, EMBASE and the Cochrane Library databases

Search
PubMed
'atopic eczema'[tiab] OR 'atopic dermatitis'[tiab]) AND (soluble*[tiab] OR plasma*[tiab] OR serum*[tiab] OR sera[tiab] OR cytokine[tiab] OR chemokine[tiab] OR serologic*[tiab] OR marker*[tiab]) AND (severity[tiab] OR scor*[tiab] OR measur*[tiab] OR index[tiab] OR activity[tiab] OR symptom*[tiab] OR correlat*[tiab])
EMBASE
'atopic eczema':ab,ti OR 'atopic dermatitis':ab,ti AND (soluble*:ab,ti OR plasma*:ab,ti OR serum*:ab,ti OR sera:ab,ti OR cytokine:ab,ti OR chemokine:ab,ti OR serologic*:ab,ti OR marker*:ab,ti) AND (severity:ab,ti OR scor*:ab,ti OR measur*:ab,ti OR index:ab,ti OR activity:ab,ti OR symptom*:ab,ti OR correlat*:ab,ti) NOT ('medline'/exp OR 'medline')
Cochrane library
'atopic eczema' OR 'atopic dermatitis') AND (soluble* OR plasma* OR serum* OR sera OR cytokine OR chemokine OR serologic* OR marker*) AND (severity OR scor* OR measur* OR index OR activity OR symptom* OR correlat*) in Title, Abstract, Keywords in Trials'

primary study outcomes in the vast majority of studies, we did not evaluate the risk of bias in individual studies on the basis of whether randomization, concealment of allocation or the use of control groups was used, as these were less relevant to this investigation. The selected studies were appraised for diagnostic criteria, preferably according to the Hanifin and Rajka criteria [7] or the U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis [8] and for severity scores at the time of blood sampling. In addition, reporting of missing data and loss to follow-up were also assessed.

Data analysis

The principal summary measures of interest were the correlation between the reported biomarker(s) and severity measurement tools, the corresponding *P* values and Pearson/Spearman rank correlation coefficients [9]. A meta-analysis was carried out for biomarkers for which correlation coefficient and sample size were reported by at least four studies.

The meta-analysis was performed using the R statistical environment version 3.2.0 (R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2015, <http://www.R-project.org/>), using the metaphor package version 1.9-7 [10]. For each biomarker, the correlation coefficients were transformed using Fisher's *r*-to-*z* transformation, to produce the *z* value. These were then pooled using a standard random-effects model [11], regardless of heterogeneity. Heterogeneity was assessed using the *I*² statistic [12], and by visual inspection of funnel plots of the included studies [13]. The *I*² was considered acceptable if below 60% and the funnel plot was considered unbiased if upon visual inspection, the distribution of studies was approximately symmetrical. Forest plots of the included studies and the random-effects pooled estimates were generated and back-transformed to the original correlation coefficients for improved interpretability.

RESULTS

Characteristics of included studies

Figure 1 summarizes the results of the search strategy. A total of 222 publications, examining 115 different biomarkers (Table S2, <http://links.lww.com/COAI/A14>), were included. Studies from all 222 publications were divided into two groups. The first group comprised randomized controlled trials and cohort studies, which reported multiple measurements in the same patient over time (further referred to as

longitudinal studies). Studies that reported only one measurement per patient are referred to as cross-sectional studies. We included 173 longitudinal studies with data from a total of 5328 patients and an average follow-up between 4 and 3650 days. A total of 56 biomarkers were reported in longitudinal studies. Cross-sectional studies comprised 148 publications with data from a total of 15 471 patients, reporting on 65 biomarkers. Some publications describing longitudinal studies also presented cross-sectional study data resulting in an overlap between the groups. SCORing of Atopic Dermatitis (SCORAD) was used in 132 studies (59.4% of studies) and was thereby the most commonly used severity score for atopic dermatitis. Other disease severity measures included the Eczema Area and Severity Index (EASI) in 11 studies (5.0%), the Costa score in nine studies (4.1%) and the Six Area Six Sign Atopic Dermatitis (SASSAD) in six studies (2.7%). In total, over 30 different clinical severity scores were used.

One hundred and eight articles, examining 64 biomarkers, reported sufficient data for meta-analysis. Four biomarkers were eligible for meta-analysis in the longitudinal group. In the cross-sectional group, nine biomarkers were eligible for meta-analysis.

Meta-analysis

Thirty biomarkers have been investigated in 29 longitudinal studies providing sufficient data for meta-analysis. Out of 30 biomarkers, only the correlation coefficients of levels of serum thymus and activation-regulated chemokine (TARC/CCL17), serum total IgE, serum eosinophil cationic protein (ECP) and serum sE-selectin were reported by at least four studies and were therefore eligible for meta-analysis according to our inclusion criteria. The results of the meta-analysis of longitudinal studies are shown in Fig. 2. Eighty-four cross-sectional studies, investigating 49 biomarkers, provided sufficient data for meta-analysis. Biomarkers that were reported by at least four studies and thus included in the meta-analysis included serum levels of TARC, ECP, total IgE, cutaneous T-cell attracting chemokine (CTACK/CCL27), CD30, interleukin (IL)-18, lactate dehydrogenase (LDH), macrophage-derived chemokine (MDC) and vitamin D. The results of the meta-analysis of cross-sectional studies are shown in Fig. 3a–c.

Total serum IgE was found as the most frequently studied biomarker. However, pooling of data from the longitudinal studies resulted in a weak correlation coefficient of 0.33 (95% CI 0.08–0.64). Meta-analysis of the cross-sectional studies showed only a moderate pooled correlation to disease

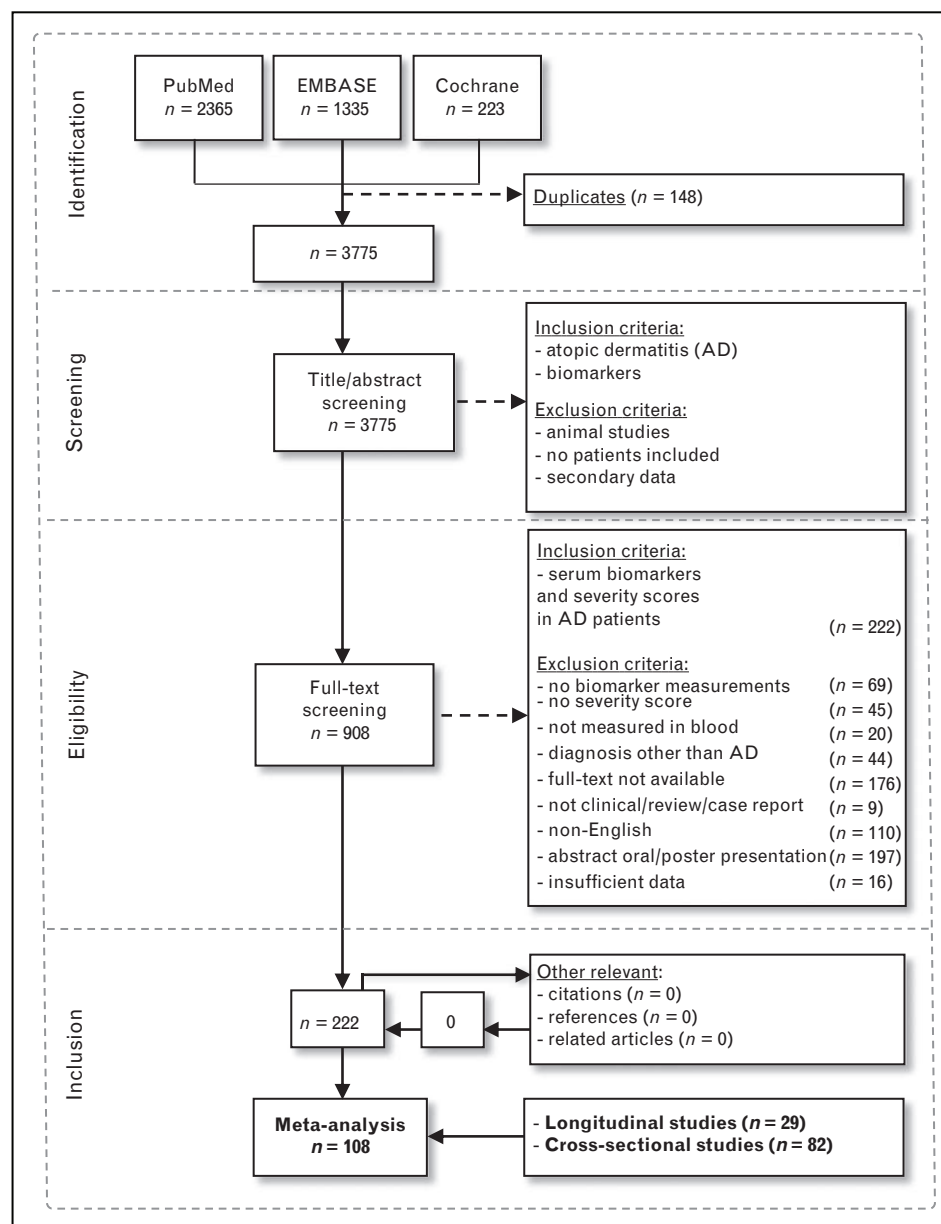


FIGURE 1. Flowchart of the study selection process.

severity of 0.45 (95% CI 0.32–0.57). Funnel plot asymmetry was present in funnel plots for both longitudinal and cross-sectional studies (Figures S1 and S2). Hence, we conclude that total serum IgE levels are not an appropriate biomarker for the follow-up of disease severity in atopic dermatitis and correlate only moderately to disease severity on a single time point.

TARC/CCL17 is one of the key chemokines involved in homing of chemokine (C-C motif) receptor 4 (CCR4)-expressing T cells to the skin [14]. Serum TARC levels were found to significantly correlate to disease severity in atopic dermatitis patients from four longitudinal studies and in patients from 16 cross-sectional studies. Pooled

correlation coefficients showed a strong correlation in both longitudinal [$r=60$, 95% confidence interval (95% CI) 0.48–0.70] and cross-sectional studies ($r=0.64$, 95% CI 0.57–0.70). This suggests that serum TARC/CCL17 could potentially be a valuable biomarker for assessing disease severity in atopic dermatitis as well as evaluating the course of the disease. Although less frequently investigated, reports on plasma TARC levels also show promising results, but require further investigation.

CTACK/CCL27 is another T-cell attracting chemokine that is suggested to play an important role in skin inflammation in atopic dermatitis. CTACK is being produced by keratinocytes and binds to its receptor CCR10 that is expressed on skin-homing T

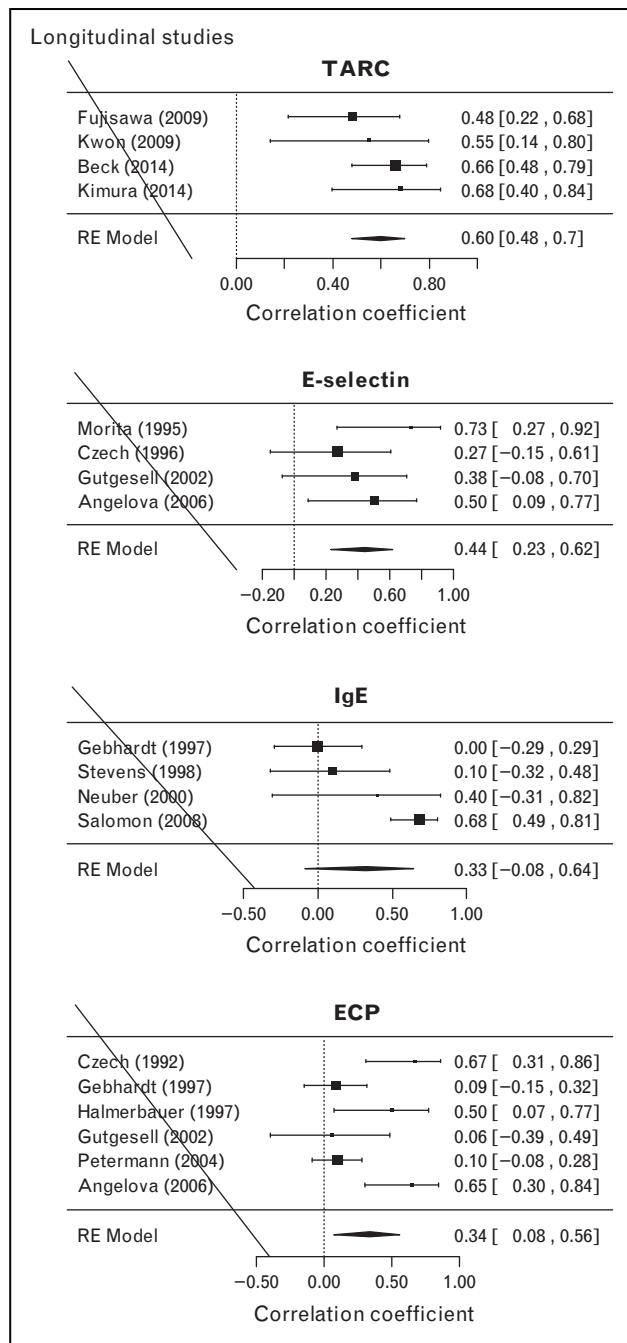


FIGURE 2. Forest plots of meta-analysis of longitudinal studies. The heterogeneity (I^2) for TARC was 0%; E-selectin: 0%; IgE: 78%; and ECP: 74%.

cells [15]. Serum CTACK levels have only been reported in two studies, reporting on follow-up in 16 patients. However, a large number of cross-sectional studies reported serum CTACK levels, and meta-analysis showed a strong correlation to disease severity ($r=0.68$, 95% CI 0.47–0.82). Inspection of the funnel plot revealed asymmetry. Additional data are needed to determine its usability in the follow-up of atopic dermatitis patients.

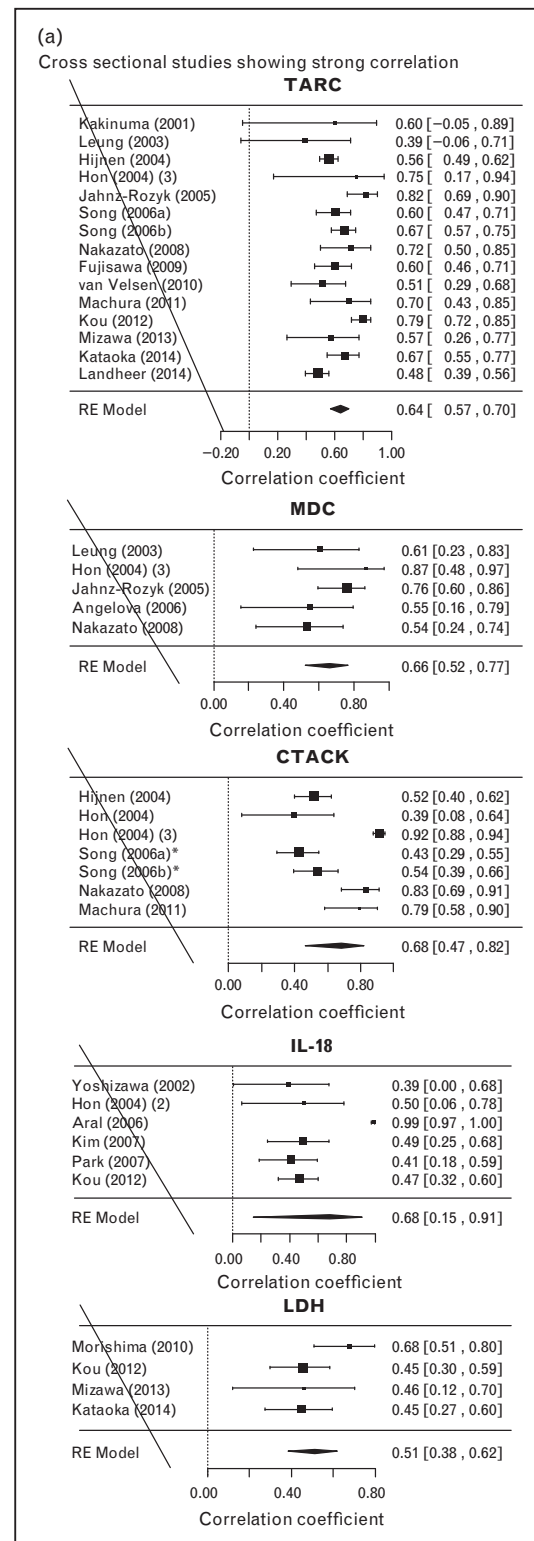


FIGURE 3. (a) Biomarkers showing a strong correlation with disease severity [heterogeneity (I^2) for TARC: 70%; MDC 22%; CTACK: 93%; IL-18: 97%; LDH: 43%]. (b) Biomarkers showing a moderate correlation with disease severity [heterogeneity (I^2) IgE: 92%; ECP: 67%]. (c) Biomarkers showing a weak correlation with disease severity [heterogeneity (I^2) for CD30: 93%; vitamin D: 94%].

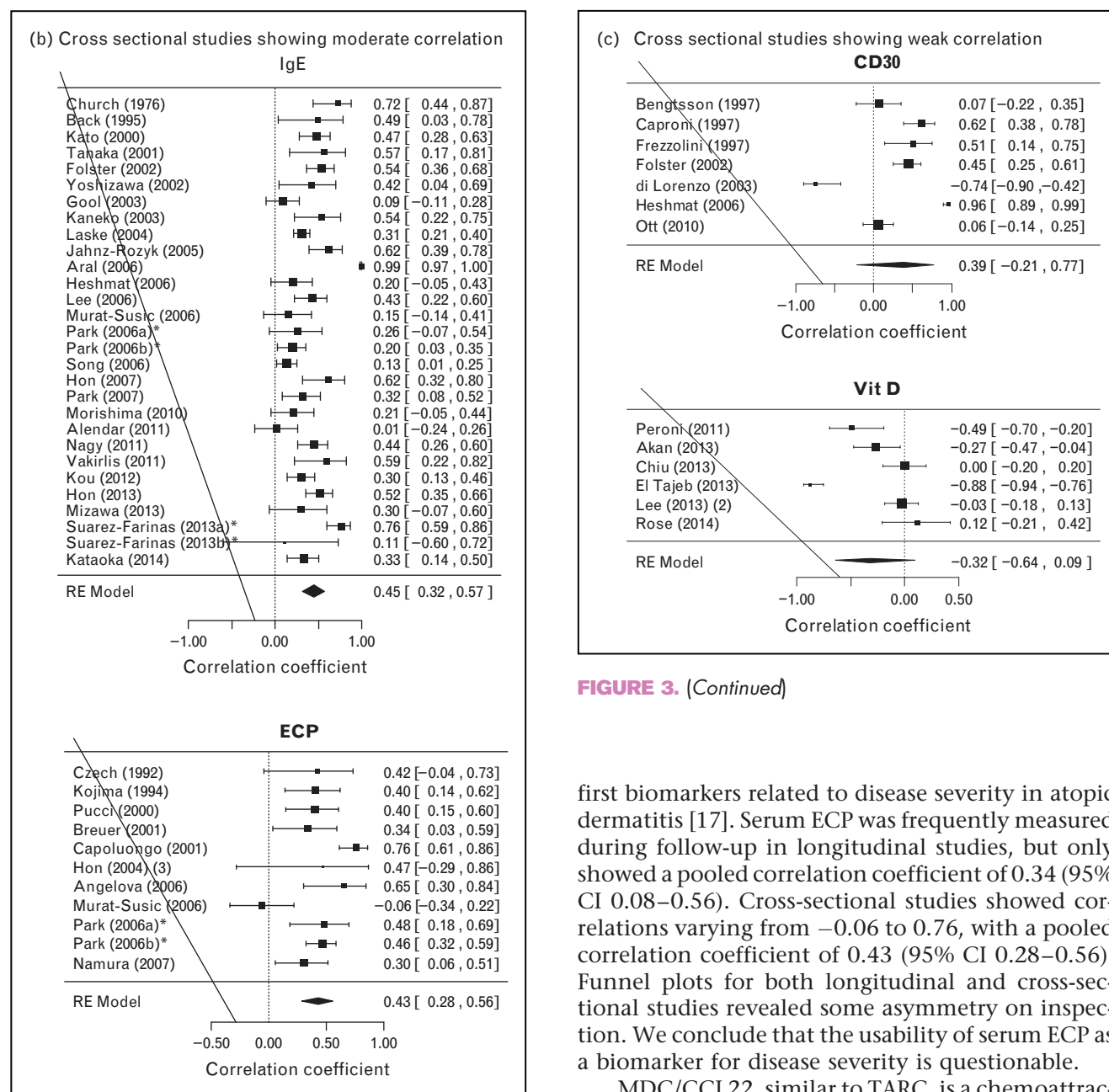


FIGURE 3. (Continued)

FIGURE 3. (Continued)

Serum sE-selectin is a cell adhesion molecule expressed on vascular endothelium, important for the migration of inflammatory cells from blood to tissue [16]. Four longitudinal studies reported correlation coefficients, resulting in a pooled correlation coefficient of 0.44 (95% CI 0.23–0.62), indicating a moderate correlation. Serum sE-selectin might be a good candidate as a biomarker for disease severity, but requires further investigation.

ECP is a protein that is released during degranulation of eosinophils. Serum ECP was one of the

first biomarkers related to disease severity in atopic dermatitis [17]. Serum ECP was frequently measured during follow-up in longitudinal studies, but only showed a pooled correlation coefficient of 0.34 (95% CI 0.08–0.56). Cross-sectional studies showed correlations varying from –0.06 to 0.76, with a pooled correlation coefficient of 0.43 (95% CI 0.28–0.56). Funnel plots for both longitudinal and cross-sectional studies revealed some asymmetry on inspection. We conclude that the usability of serum ECP as a biomarker for disease severity is questionable.

MDC/CCL22, similar to TARC, is a chemoattractant for CCR4-expressing skin-homing T cells [18]. Serum MDC levels showed a strong pooled correlation coefficient in the meta-analysis of cross-sectional studies of 0.66 (95% CI 0.52–0.77). Correlation coefficients have only been reported in two longitudinal studies; therefore, a meta-analysis on longitudinal studies was not possible. We conclude that serum MDC is a suitable biomarker for measuring disease severity at a single time point, but additional data are needed to determine its usability in the follow-up of atopic dermatitis patients.

LDH is an enzyme found in nearly all tissue cells and catalyzes the conversion of pyruvate to lactate. LDH is released during tissue damage and is

therefore commonly used as a marker for malignancies, cardiac diseases and haemolysis. Four cross-sectional studies reported correlation coefficients of serum LDH levels to disease severity, and pooling resulted in a correlation coefficient of 0.51 (95% CI 0.38–0.62). Inspection of the funnel plot revealed some asymmetry. This makes serum LDH a potential candidate as a biomarker for disease severity.

IL-18 is a member of the IL-1 family and induces production of Interferon-gamma by T cells. Furthermore, it stimulates Th1 cells to produce IL-13, and synergistically with IL-12 stimulates the production of IgE and Th2 cytokines [19–21]. A meta-analysis of cross-sectional studies reporting IL-18 as a marker for disease severity showed a strong pooled correlation coefficient of 0.68 (95% CI 0.15–0.91). The funnel plot showed asymmetry, but as only four cross-sectional studies reported IL-18, it is hard to distinguish chance from real asymmetry, making the interpretation of a funnel plot rather unreliable. Only one longitudinal study [22] reported a significant correlation between serum IL-18 levels and disease severity. We conclude that serum IL-18 might be a possible biomarker for disease severity, but requires further investigation.

Serum soluble CD30 levels have been investigated for use in several immune-mediated inflammatory diseases. Correlation coefficients of serum CD30 levels with disease severity in atopic dermatitis ranged widely, from an inversed correlation (–0.74) to a very strong correlation (0.96). Pooling the data resulted in a correlation coefficient of 0.39 (95% CI –0.21 to 0.77), with a fairly asymmetric funnel plot. Serum vitamin D has also been studied as a biomarker in atopic dermatitis. Although some studies showed promising data regarding an inversed correlation with disease severity, there was a wide range of correlation coefficients (0.12 to –0.88). Meta-analysis resulted in a pooled correlation of –0.32 (95% CI –0.64 to 0.09). Visual inspection of the funnel plot revealed asymmetry. We conclude that neither CD30 nor vitamin D are suitable as biomarkers for disease severity in atopic dermatitis.

Biomarkers found to show a good correlation to disease severity, but studied only in small numbers of studies, include serum levels of IL-2R, IL-4R and IL-31. The remaining biomarkers have been reported in even smaller patient series and show variable or inconclusive results.

DISCUSSION

In search of an objective biomarker for disease severity, this review aimed to synthesize results from all available publications, not limited to studies focusing on the identification of a biomarker.

Meta-analysis of both longitudinal and cross-sectional studies revealed that currently serum TARC levels perform best as an objective biomarker for disease severity, showing strong pooled correlation coefficients in both longitudinal and cross-sectional studies. Although serum sE-selectin was reported by only four longitudinal studies, it showed a moderate correlation to disease severity and might also be a good candidate as a biomarker for disease severity. Meta-analysis of cross-sectional studies reporting serum levels of CTACK, MDC, LDH and IL-18 showed that these markers are potentially good biomarkers for disease severity. However, these biomarkers were less frequently studied in longitudinal studies, and additional data are needed to determine their usability in the follow-up of atopic dermatitis patients. Although total serum IgE was found to be the most frequently studied biomarker, we conclude that it is not an appropriate biomarker for longitudinal studies.

Limitations of this study are the occurrence of potential selection and publication bias. The initial search yielded 222 relevant publications reporting on 93 different biomarkers. Only 16% of longitudinal studies, and 57% of cross-sectional studies provided sufficient data for inclusion in our meta-analysis. The occurrence of selection bias in the results of the meta-analyses is therefore inevitable. Funnel plot asymmetry was present in a fairly large number of the meta-analysed biomarkers, indicating publication bias. Publication bias may have caused overestimation of the correlation coefficients of the biomarkers reported in this article. Publication of biomarker data might be influenced by the direction and statistical significance of the correlation between a biomarker and disease severity, as nonsignificant study outcomes might be less likely to be published. Although we did not limit our search on language, it was not possible to retrieve data from 110 non-English publications. In addition, 176 out of 908 publications selected for screening were not available at our institutions. Despite these caveats, our synthesis of the disparate and prolific literature has yielded interesting new insights into several promising biomarkers.

Most studies included in this review reported on one or only a limited number of biomarkers. Because atopic dermatitis is known to be a highly heterogeneous disease and different clinical phenotypes have been described, we hypothesized that it may be useful to simultaneously investigate a panel of biomarkers. From our own experience, we know, for example that a small subset of patients with severe atopic dermatitis have serum TARC levels in the normal range. These patients may represent a distinct immunological subtype for which biomarkers other than TARC may have an additional value.

Indeed, we recently reported that a combination of serum biomarkers shows a better correlation with disease severity than single biomarkers in atopic dermatitis patients [23[■]].

CONCLUSION

We conclude that serum TARC is the most reliable biomarker currently available. Serum TARC levels have been determined in relatively large numbers of patients from different studies, showing pooled correlation coefficients of 0.60 (95% CI 0.48–0.70) and 0.64 (95% CI 0.57–0.70) in longitudinal and cross-sectional studies, respectively. Additional biomarkers that could prove useful but require additional research include serum CTACK, serum sE-selectin, serum MDC, serum LDH and serum IL-18. In addition to clinical outcome reporting, an objective serological measure for disease severity would be of great value for clinical research in atopic dermatitis. Serum TARC is the most reliable biomarker currently available.

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Conflicts of interest

There are no conflict of interests.

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- of special interest
- of outstanding interest

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This study shows that a combination of serum biomarkers is more suitable for assessing disease severity than a single biomarker.