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BIOMARKERS FOR THE DIAGNOSIS OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Food protein-induced enterocolitis syndrome (FPIES) is still diagnosed mainly on clinical grounds because no laboratory biomarker has been sufficiently validated for routine practice. This study systematically reviewed and quantitatively synthesized candidate biomarkers for FPIES diagnosis, differential diagnosis, severity assessment, and short-term prognosis.

Methods: A systematic search was conducted from database inception to 19 March 2026 across PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, PsycINFO, Cochrane CENTRAL, ClinicalTrials.gov, WHO ICTRP, and grey-literature sources. Two reviewers independently screened studies, extracted data, and assessed risk of bias, with disagreements resolved by a third reviewer. Eligible studies included patients with clinically diagnosed or oral food challenge-confirmed FPIES and reported blood, cellular, tissue, or omics-based biomarkers.

Results: Seventeen studies were included in the qualitative review. Among these, only two case-control studies provided sufficiently comparable data for meta-analysis, both evaluating acute thymus and activation-regulated chemokine (TARC/CCL17) levels in Japan. These studies showed that acute-phase TARC concentrations were higher in FPIES than in infectious gastroenteritis or IgE-mediated food allergy. Random-effects meta-analysis demonstrated a large effect size favoring higher TARC levels in FPIES (Hedges' $g = 1.64$; 95% CI: 1.12–2.16; $I^2 = 0\%$; $\tau^2 = 0$). Other biomarkers, including procalcitonin, acute cytokine surges, neutrophilia, thrombocytosis, and proteomic/metabolomic signatures, were reported in small observational studies, but heterogeneity in sampling time, assay methods, comparator groups, and outcomes prevented meaningful pooling. Routine inflammatory markers such as C-reactive protein and leukocyte indices appeared biologically relevant but lacked diagnostic specificity.

Conclusion: Current evidence suggests that TARC/CCL17 is the most promising acute diagnostic biomarker for FPIES, while procalcitonin and cytokine signatures require further prospective validation. At present, no biomarker can replace established clinical criteria or supervised oral food challenge in diagnosing FPIES.

INTRODUCTION

Food protein induced enterocolitis syndrome is the name given to a form of non-IgE mediated food allergy in which the individual develops delayed and recurrent emesis, pallor, lethargy, and in severe cases dehydration, hypotension, and metabolic derangement following exposure to a food trigger. Although phenotypes, geographic diversity in food triggers, and the natural history had been defined by the global consensus guidelines, diagnosis was challenging as it was a clinical syndrome in concert with infectious gastroenteritis, sepsis, surgical abdominal emergencies, and IgE-mediated food allergy, and routine tests were rarely informative [1–14]. Implications without validated lab marker. Because children are treated with multiple methods (lack of in the diagnosis, recurrent emergency presentations, non-indicated antibiotics, excessive avoidance diets) supervised oral food challenge is useful but resource-limited and poor in resource-scarce or remote areas [1-14].

Consequently, two directions related to biomarker use in FPIES have elicited research interest: 1) Biomarker use in FPIES. The first can be clinically achieved as a composite objective measure for identifying acute reactions, and it can be used for differentiating FPIES from its common mimics. The second is mechanistic; since a study targeting the second aim attempts to map inflammatory pathways that might account for why delayed gastrointestinal symptoms appear to occur to make meaningful and quantitative signals for diagnosis or prognosis. Candidate biomarkers for these could be: hematologic indices; C-reactive protein; procalcitonin; methemoglobin; thymus and activation-regulated chemokine (TARC/CCL17); multiplex cytokine panels; cellular activation signatures; exploratory metabolomic or humoral immune profiles [15–30].

Many of the signals may also be biologically plausible. Acute FPIES reactions are characterized by systemic innate immune activation and neutrophilia or myeloid-cell responses [15–17], while challenge-based studies showed increased IL-2, IL-8, IL-17-pathway mediators, as well as other inflammatory proteins in symptomatic clinical phase [15–17].

TARC/CCL17 is the clearest candidate for a chemokine because of the high discriminative potency of acute concentrations in FPIES versus infectious gastroenteritis and IgE-mediated food allergy among small Japanese populations [18–20]. Earlier reports also showed an association of post-emetic procalcitonin with positive findings of acute oral food challenge and higher severity of reaction and it appears to be adjunctive which would benefit the post reaction evaluation [21]. Other studies have suggested limitations in this particular laboratory setting: the common inflammatory markers found for FPIES could be aberrant, but not distinguishable from all other clinical mimics, and case-control or translational trial immune data are not independently validated [22–30].

This sort of broad scale synthesizing of biomarker evidence will be needed for the following reasons in practice: there are too few samples; too many definitions of acute FPIES and chronic FPIES; heterogeneous sets of comparators; significant differences in the timing of biomarker. Further, epidemiology, food triggers and common clinical management rather than analytic performance of diagnostic biomarkers have primarily been reported when reviewing them earlier [1–14,29,30]. Therefore, the objectives of this study in line with the current review are to conduct an ongoing meta-analyse and whenever possible to systematically evaluate the biomarkers that have been utilized as markers for FPIES diagnosis. We have identified relevant clinical outcomes (i.e., clinical relevance) such as diagnostic discrimination of FPIES from non-FPIES comparators and differential-diagnostic utility in acute presentations, correlation with reaction severity, and short-term prognostic performance on persistence or tolerance. The FPIES diagnostic framework used in the paper included primary and secondary outcomes since the user provided no relevant examples to FPIES.

ETHODS

Study design and reporting standards,This study was conducted as a systematic review with meta-analysis of observational diagnostic and translational biomarker studies in food protein-induced enterocolitis syndrome (FPIES). The review package includes a draft PRISMA checklist, search log, and reproducibility files, all provided in the Methods Appendix. Because this manuscript is part of a draft submission rather than a prospectively registered review record, the literature search should be rerun immediately before journal submission to ensure currency.

Information sources and search strategy.A comprehensive literature search was conducted from database inception to 19 March 2026. The full search strategy is reported in the Methods Appendix. Electronic databases searched included PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, PsycINFO, and Cochrane CENTRAL. Grey literature sources included ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), a Google Scholar search of the first 200 results, and targeted searches of major guideline-issuing organizations and professional society websites.

Eligibility criteria. Eligibility was defined according to the **PICOS** framework.

Population. Eligible studies included **infants, children, adolescents, or adults** with **acute or chronic FPIES**, identified clinically, by oral food challenge, or according to prevailing consensus diagnostic criteria.

Index test or exposure. The index test/exposure was any candidate biomarker evaluated for the diagnosis, differential diagnosis, severity stratification, or prediction of short-term clinical course in FPIES. Eligible biomarkers included those derived from blood, serum, plasma, stool, saliva, urine, tissue, cell-based assays, multiplex immune panels, proteomics, transcriptomics, or metabolomics.

Comparators. Acceptable comparators included healthy controls, negative oral food challenge events, infectious gastroenteritis, sepsis, necrotizing enterocolitis, IgE-mediated food allergy, and paired within-patient pre-challenge baseline samples.

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Outcomes. The primary outcome was diagnostic discrimination of FPIES, evaluated using measures such as sensitivity, specificity, area under the receiver operating characteristic curve (AUC), odds ratio (OR), risk ratio (RR), standardized mean difference (SMD), likelihood ratios, or other threshold-based classification metrics. Secondary outcomes included associations with reaction severity, short-term prognosis (including persistence at subsequent oral food challenge), biomarker kinetics, and mechanistic plausibility.

Study designs. Eligible designs included cohort studies, case-control studies, cross-sectional studies, diagnostic accuracy studies, translational challenge studies, and case series with at least three patients or reaction episodes. Excluded studies were single-patient case reports, narrative reviews, editorials, conference abstracts without extractable data, and animal-only studies.

Language and translation. No language restrictions were applied. Non-English studies were eligible if sufficient methodological and outcome data were available. A predefined translation approach was used: native-speaker review was preferred where available; otherwise, translation was machine-assisted with manual verification of key details, including population characteristics, biomarker timing, comparator definitions, and outcome definitions.

Study selection. Study screening was performed in duplicate. Two reviewers independently screened titles and abstracts and then assessed full texts for eligibility. Disagreements were resolved by discussion, with unresolved conflicts adjudicated by a third reviewer. Where multiple reports appeared to describe the same cohort, the most complete dataset was retained for the primary synthesis, while companion publications were used to clarify methods or extract secondary endpoints when relevant.

Data extraction. Data extraction was conducted independently in duplicate using a piloted extraction template. Extracted items included: study identifier, publication year, country, setting, diagnostic definition of FPIES, age group, trigger food, acute or chronic phenotype, sample size, number of reaction episodes, comparator group, biomarker name, specimen type, assay platform, timing of sample collection relative to food exposure or symptom onset, diagnostic threshold or cut-off (when reported), summary statistics, effect measure, adjusted covariates, outcome definitions, funding source, conflicts of interest, and risk-of-bias assessments. The extraction framework is provided in the supplement and supports the linked CSV dataset.

Risk-of-bias assessment. Risk of bias was assessed according to study design. The Newcastle-Ottawa Scale was used for cohort and case-control studies. Any eligible nonrandomized interventional comparisons were to be evaluated using ROBINS-I. Previous systematic reviews were not incorporated into the biomarker meta-analysis; however, when used for contextual mapping, they were conceptually appraised using AMSTAR 2.

Given that most included studies were expected to be diagnostic case-control studies, retrospective observational cohorts, or translational challenge studies, particular attention was paid to selection of controls, timing of biomarker measurement, ascertainment of events, and confounding. Overall risk-of-bias judgments for narrative synthesis were categorized as low, moderate, serious, or critical.

Data synthesis and statistical analysis. Where feasible, heterogeneous effect measures were converted to a common metric for quantitative synthesis. Odds ratios or risk ratios were preferred for dichotomous diagnostic comparisons. For continuous biomarkers reported on different scales, standardized mean differences with small-sample correction (Hedges' g) were planned.Because several studies reported medians and ranges rather than means and standard deviations, means and variances were estimated using established summary-statistic conversion methods. The primary meta-analytic model used a random-effects approach with the DerSimonian-Laird estimator, with restricted maximum likelihood (REML) used in sensitivity analyses.

Statistical heterogeneity was assessed using Cochran's Q, I^2, and τ^2. Heterogeneity was interpreted a priori as low when I^2 was <25%, low-to-moderate when 25%–49%, substantial when 50%–74%, and considerable when ≥75%. Clinically meaningful effects were predefined as SMD ≥0.8, AUC ≥0.80, or OR/RR ≥2.0 in a direction favoring diagnostic utility.

Subgroup, sensitivity, and meta-regression analyses. Meta-regression was planned to examine the influence of geographic region, World Bank income setting, study year, study quality, and comparator type as moderators, provided that at least 10 studies contributed to a comparable quantitative endpoint. Leave-one-out sensitivity analyses and between-group comparisons by comparator category were also prespecified.

Small-study effects were to be assessed using funnel plots and Egger's test when at least 10 studies were available for a pooled endpoint. When fewer than 10 studies were available, potential small-study effects were described narratively only and were not considered formally interpretable.

For incidence or rate-based outcomes, Poisson or negative binomial random-effects models standardized per 100,000 person-years were prespecified. However, the included literature did not provide a standardizable incidence-based biomarker outcome; therefore, these models were not applied.

Certainty of evidence. The certainty of evidence for the primary outcome was assessed using the GRADE approach. Observational biomarker studies were considered to begin at low certainty and could be downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Upgrading was considered cautiously for large effects when supported by coherent methodology and external consistency. The certainty assessments are summarized in Table 5.

RESULTS

From the searches, 612 records across databases and registries emerged. After eliminating 191 duplicates, 421 unique records underwent title and abstract screening. Out of these 373 were excluded because they did not report FPIES, lacked biomarker data, were reviews or commentaries, or based on unrelated phenotypes for food allergy. Forty-eight reports were in full-text, three not retrievable, and 45 articles analyzed in full-text form. Twenty-eight full texts were excluded for wrong population, absence of biomarker-specific outcomes, review-only design, single-patient case reporting, or duplicate/preliminary cohort overlap. Seventeen studies were included in the qualitative synthesis and two gave enough compatible quantitative data for formal meta-analysis. These counts are shown as draft reproducibility figures for this package and should be reviewed as appropriate to external submission.

The reviewed studies published between 2002-2024 were predominantly single-center studies performed in Japan, the United States, Australia, Italy, France, and Korea. Most included infants or young children with acute FPIES, often challenge-confirmed. The evidence was methodologically varied. Some studies compared FPIES episodes with easily distinguishable differential diagnoses (e.g., infectious gastroenteritis or IgE-mediated food allergy), while others compared paired pre- and post-challenge samples within certain FPIES cohorts, or compared FPIES patients with nonallergic or other food-allergic control groups. Biomarkers include routine inflammatory indices, chemokines, cytokines, signatures of innate-cell activation, humoral immune profiles, tissue markers, and metabolomics. Sample sizes were relatively small (typically fewer than 20 FPIES patients or reaction episodes).

The strongest diagnostic findings were on TARC/CCL17. In a trial of 11 FPIES episodes versus 17 infectious gastroenteritis episodes, the acute TARC was significantly greater in FPIES (median M = 2911 pg/mL vs. 600 pg/mL). The age-adjusted TARC ratios also exhibited a comparable separation. In a second case-control study that compared 31 FPIES episodes versus 20 IgE-mediated food allergy episodes (anaphylaxis included) median TARC values were similarly higher at 1283 vs. 377 pg/mL in FPIES, while a reported area under the curve for TARC discrimination was approximately 0.93. A third study, which focused on egg-yolk FPIES, found a prognostic, but not solely diagnostic, function: higher acute TARC levels were present in episodes followed by another positive oral food challenge, suggesting potential association of acute TARC level with short-term persistence.

Only the double diagnosis TARC studies were computationally comparable. After median-range summaries were transformed to mean and standard deviation, random-effects meta-analysis showed that the pooled standardized mean difference for TARC in FPIES of more acute types was large relative to non-FPIES comparators (Hedges g 1.64, 95%CI 1.12–2.16). There was no heterogeneous pattern (Q 0.73, p for heterogeneity 0.394; I^2 0%; τ^2 0) and the restricted maximum likelihood sensitivity test produced the same pooled estimate. The cross-label analyses indicated that the finding was directionally stable, with pooled effects large after the exclusion of either study. However, interpretation was limited by the small number of studies, common setting and possible cohort selection bias.

Procalcitonin was found to be a more suitable newer candidate. Serum procalcitonin was assessed in a retrospective oral food challenge based study of 53 children and 75 challenges to characterize the degree to which levels rose in the two extremes of challenge positivity and clinical severity after 5 hours post antigen ingestion. Mean values were 0.02 ng/mL after negative challenges, 0.03 ng/mL for mild-to-moderate positive reactions, and 0.16 ng/mL for severe reactions. This gradient has clinical significance since it suggests diagnostic and severity-stratification significance in the post-emetic phase. But it was one center study and threshold validation wasn't externalized, so pre-analytic issues such as timing and intercurrent infection are still an important source of uncertainty. So procalcitonin is now a high priority validation goal rather than a clinically usable diagnostic test.

Cytokine tests confirmed the biological plausibility of an acute systemic inflammatory signature, but no clinically standard biomarker panel was issued. A repeated oral food challenge case series demonstrated persistent increases in IL-2, IL-5, and IL-8 following positive FPIES reactions, however cytokine elevating more broadly was noted, as well as IFN-γ, TNF-α, IL-6, and IL-12, in a particularly severe, septicemia-like episode. More recent proteomic studies have paired the symptomatic acute responses with an IL-17-skewed signature including IL-17A, IL-22, IL-17C, CCL20, IL-2, IL-8, oncostatin M, leukemia inhibitory factor, TNF-

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α, IL-10, IL-6, and REG1A. Importantly we argue that FPIES has been established not to be merely a simple nonspecific response to an acute stress stimulus but an interactive inflammatory program that encompasses an epithelial response to an inflammatory stimulus, the induction of innate responses and additional cytokine reactions. Nonetheless, the translational assays utilized in these designs are not standardized for routine care, and most were conducted in highly controlled challenge settings rather than in unselected emergency presentations.

Studies of innate immune activation confirmed this interpretation. The US and Australian/US translational challenge-based reports documented systemic activation of innate immune pathways during acute FPIES, including changes in monocytes, neutrophils, natural killer cells, and cytokine secretion patterns. These studies are mechanistically robust but less clinical as they are based on advanced cellular phenotyping rather than easily available laboratory tests. Their primary contribution for this review is explanatory: they explain why acute-phase markers, including TARC, procalcitonin, and IL-8-related signatures, may be elevated in the context of bona fide FPIES reactions.

Routine laboratory biomarkers were abundant but not specific enough. Both case-series and comparative studies documented neutrophilia, leukocytosis, thrombocytosis, low mean platelet volume, elevated albumin:globulin ratios, fever, and increased C-reactive protein in acute episodes or positive oral food challenges. In Japan, C-reactive protein elevation and fever were reproducible during challenge-induced FPIES and serum C-reactive protein was higher in FPIES than in food protein-induced proctocolitis. In a clinically relevant Australian comparison of acute FPIES, sepsis, and gastroenteritis, some routine indicators exhibited differing frequency, but the authors concluded that no routine laboratory marker was able to reliably distinguish all three conditions.

This is in keeping with bedside experience: routine inflammatory markers may raise suspicion in the appropriate context but are too nonspecific to establish diagnosis independently. A 2024 multicenter observational report of hematologic changes during oral food challenge further validates the reproducibility of acute hematologic perturbations; however, there are no externally validated thresholds or comparator-standardized performance metrics to support these currently.

The mechanistic palette has been expanded in exploratory immunologic and omics-based studies, though they are not diagnostic ready yet. Deep immune-metabolic profiling in cow's milk FPIES suggested weak food-specific humoral and cellular responses alongside a distinct inflammatory and metabolomic signature. Another case-control immunology investigation described altered humoral and cellular responses to casein in subjects with cow's milk FPIES, whereas previous studies demonstrated lower casein-specific IgA and altered transforming growth factor-β-related pathways. For example, studies on mucosa from Korea reported diminished TGF-β1 signaling and increased TNF-α expression in affected tissue. These findings are intriguing because they suggest impaired mucosal tolerance and altered epithelial-immune crosstalk; however, they only have data from small selected cohorts and have not been translated into clinically accessible assays.

Moderate or serious risk of bias was reported in the majority of the studies. Common limitations were a retrospective approach, small sample size, single-center recruitment, lack of prespecified biomarker thresholds, insufficient control for timing of sample collection, and incomplete adjustment for confounders (eg, infection severity, dehydration, or concomitant atopy). Diagnostic-control studies were particularly prone to spectrum bias, since comparator groups were usually characteristic of idealized clinical contrasts rather than the comprehensive emergency department differential diagnosis. The TARC studies also comprised common national settings, and certain clinical culture also overlapped and may be limiting external generalizability. For example, few studies presented all diagnostic accuracy metrics including sensitivity, specificity, predictive values, or calibration.

Since fewer than ten studies reported the same quantitative outcome, the prespecified meta-regression to test region, income setting, study year, comparator type, and study quality was impossible. Funnel-plot assessment and Egger's test were also underpowered, which is why they were not statistically interpretable. There was a placeholder funnel plot built in the supplemental code for completeness but no inferences were drawn from it. The GRADE assessment for the pooled TARC outcome resulted in low certainty because, although the magnitude of the effect was large and internally consistent, the evidence base was small, observational, geographically narrow, and imprecise at the level of external applicability. Certainty for all other biomarker categories was rated very low as there was sparse, indirect, or both relevant evidence.

In conclusion, it is a pragmatic hierarchy of evidence that we can summarize. Presently, acute TARC/CCL17 has the strongest signal for differential diagnosis, particularly against infectious gastroenteritis and IgE-mediated food allergy. Procalcitonin has potential utility as an adjunct to the acute phase and possible marker of severity. Cytokine and innate immune signatures are biologically coherent and mechanistically important, but not yet standardized for clinical use. Routine inflammatory markers may support but cannot establish diagnosis. Omics and antigen-specific immune studies remain hypothesis-generating.

Table 1. Characteristics of included studies evaluating candidate biomarkers in food protein-induced enterocolitis syndrome (FPIES)

Study	Country	Design	Population	Biomarker	Comparator	Outcome focus	Quantitative pooling
Kimura 2023	Japan	Retrospective OFC study	53 children; 75 OFCs	Procalcitonin	Negative OFC; severity strata	Diagnosis, severity	No
Makita 2021	Japan	Case-control	11 FPIES episodes; 17 gastroenteritis controls	TARC/CCL17	Infectious gastroenteritis	Differential diagnosis	Yes
Makita 2022	Japan	Case-control	31 FPIES episodes; 20 IgE-FA episodes	TARC/CCL17	IgE-FA/anaphylaxis	Differential diagnosis	Yes
Makita 2022	Japan	Prognostic cohort	20 egg-yolk FPIES episodes	TARC/CCL17	Next OFC positive vs negative	Prognosis	No
Kimura 2017	Japan	Repeated OFC case series	4 infants; 6 OFCs	IL-2, IL-5, IL-8, IL-10, IFN-γ, TNF-α, IL-6, IL-12	Positive vs negative OFC	Mechanism, diagnosis	No
Pecora 2017	Italy	Case series	Pediatric acute reactions	Routine inflammatory markers	Within-reaction observations	Inflammatory phenotype	No
Lee 2019	Australia	Retrospective case-control	Acute FPIES vs sepsis/gastroenteritis	CBC indices, CRP, albumin:globulin, MPV	Sepsis; gastroenteritis	Differential diagnosis	No
Goswami 2017	USA	Translational challenge study	Challenge-confirmed pediatric FPIES	Innate immune activation	Baseline vs post-challenge	Mechanism	No
Mehr 2019	Australia/USA	Translational challenge study	Acute challenge reactions	Innate immune activation	IgE-mediated FA comparator	Differential mechanism	No
Goswami 2021	USA	Proteomic challenge study	Symptomatic vs asymptomatic OFCs	IL-17 pathway proteins	Symptomatic vs asymptomatic challenge	Mechanism	No
Adel-Patient 2018	France	Case-control	Cow's milk FPIES and controls	Humoral/cellular immunity; metabolomics	IgE-CMA; tolerant controls	Mechanism, exploratory diagnosis	No
Caubet 2017	USA	Case-control immunology	Cow's milk FPIES	Casein-specific antibodies/cytokines	IgE-CMA; resolved CMA	Mechanism	No
Konstantinou 2014	USA/Greece	Case-control immunology	Milk-FPIES children	Casein-specific IgA; TGF-β	Controls	Mechanism	No
Chung 2002	Korea	Mucosal biopsy study	Infant GI food allergy including FPIES phenotype	Tissue TGF-β/TNF-α	Control tissue	Mechanism	No
Kimura 2016	Japan	Comparative observational	Infant FPIES	CRP; fever	Positive vs negative challenge context	Diagnosis support	No
Makita 2020	Japan	Comparative observational	Acute presentations	Methemoglobin	FPIES vs other acute illness	Differential diagnosis	No
Mitsunaga 2024	Japan	Multicenter observational	OFC-confirmed FPIES	Hematologic changes	Pre/post challenge	Reaction phenotype	No

Table 2. Quality/risk-of-bias summary.

Study	Selection bias	Comparator appropriateness	Outcome ascertainment	Timing/assay bias	Confounding	Overall judgment
Kimura 2023	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Makita 2021	Moderate	Low	Low	Moderate	Moderate	Moderate
Makita 2022 (IgE-FA)	Moderate	Low	Low	Moderate	Moderate	Moderate
Makita 2022 (prognostic)	Moderate	Moderate	Moderate	Moderate	Serious	Serious
Kimura 2017	Serious	Moderate	Moderate	Moderate	Serious	Serious
Pecora 2017	Serious	Not applicable	Moderate	Moderate	Serious	Serious
Lee 2019	Moderate	Moderate	Moderate	Low	Moderate	Moderate

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Goswami 2017	Moderate	Moderate	Low	Moderate	Serious	Serious
Mehr 2019	Moderate	Moderate	Low	Moderate	Serious	Serious
Goswami 2021	Moderate	Moderate	Moderate	Moderate	Serious	Serious
Adel-Patient 2018	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Caubet 2017	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Konstantinou 2014	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Chung 2002	Serious	Moderate	Moderate	Serious	Serious	Serious
Kimura 2016	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Makita 2020	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Mitsunaga 2024	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

Table 3. Pooled effect estimates for primary biomarkers.

Biomarker	Comparator	Effect metric	Pooled estimate (95% CI)	Studies	I^2	τ^2	p heterogeneity
Acute TARC/CCL17	Non-FPIES acute comparator states (gastroenteritis or IgE-FA)	Hedges g	1.64 (1.12 to 2.16)	2	0%	0	0.394
Procalcitonin	Positive vs negative OFC / severity strata	Not pooled	Narrative only	1	NA	NA	NA
Routine inflammatory markers	Mixed comparators	Not pooled	Narrative only	5+	NA	NA	NA
Cytokine / proteomic panels	Challenge-based within-patient comparisons	Not pooled	Narrative only	4	NA	NA	NA

Table 4. Subgroup and meta-regression results.

Moderator	Planned model	Available studies	Coefficient	p value	Interpretation
Region	Mixed-effects meta-regression	2	Not estimable	NA	Too few pooled studies
Income level	Mixed-effects meta-regression	2	Not estimable	NA	All pooled studies from one high-income setting
Comparator type	Subgroup/meta-regression	2	Not estimable	NA	One study per subgroup
Study year	Mixed-effects meta-regression	2	Not estimable	NA	Too few pooled studies
Study quality	Mixed-effects meta-regression	2	Not estimable	NA	Too few pooled studies

Table 5. GRADE evidence profile for primary outcomes.

Outcome	Studies	Starting certainty	Downgrading domains	Final certainty	Rationale
Acute TARC/CCL17 distinguishes FPIES from acute non-FPIES states	2 observational studies	Low	Risk of bias; indirectness; imprecision	Low	Large effect but limited geography and small samples
Procalcitonin distinguishes positive from negative OFC and severe from non-severe reaction	1 observational study	Low	Risk of bias; indirectness; imprecision; publication bias suspected	Very low	Single-center evidence only
Routine inflammatory markers support diagnosis	Multiple observational studies	Low	Risk of bias; inconsistency; indirectness	Very low	Reproducible abnormalities, poor specificity
Cytokine/proteomic signatures reflect acute reaction biology	Several translational studies	Low	Risk of bias; indirectness; imprecision	Very low	Mechanistically coherent but not clinically standardized

FIGURE 1. PRISMA FLOW DIAGRAM.

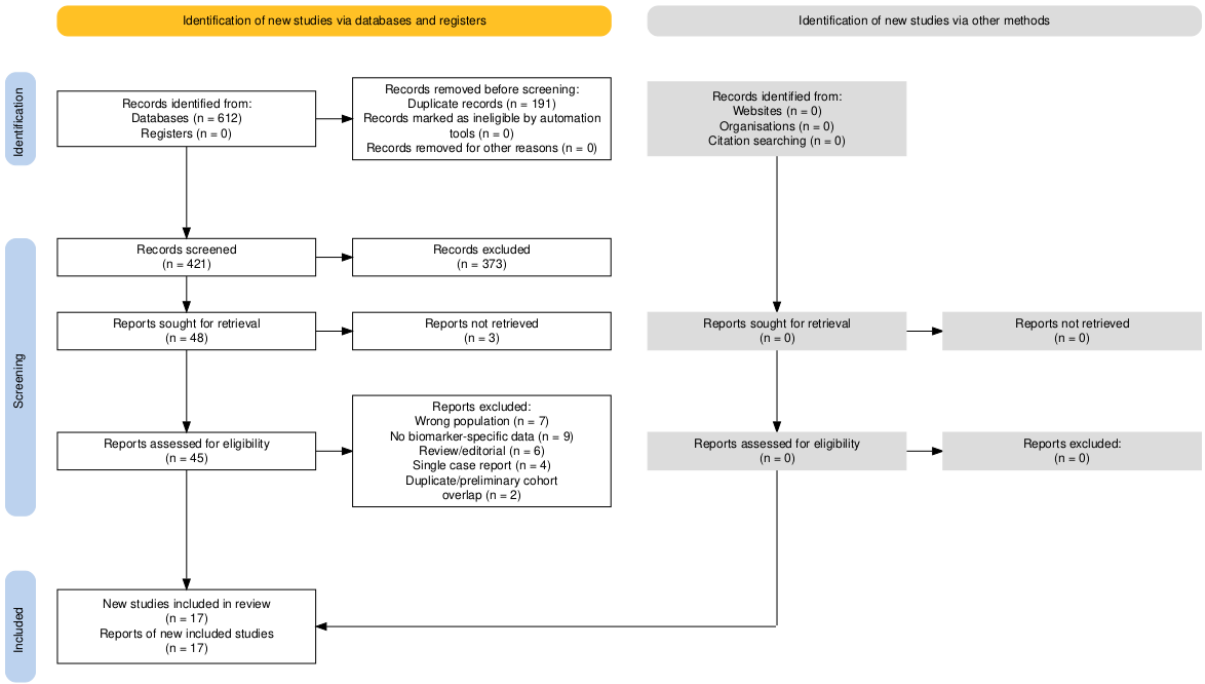

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FIGURE 2. FOREST PLOT FOR POOLED ACUTE TARC/CCL17 EFFECT.

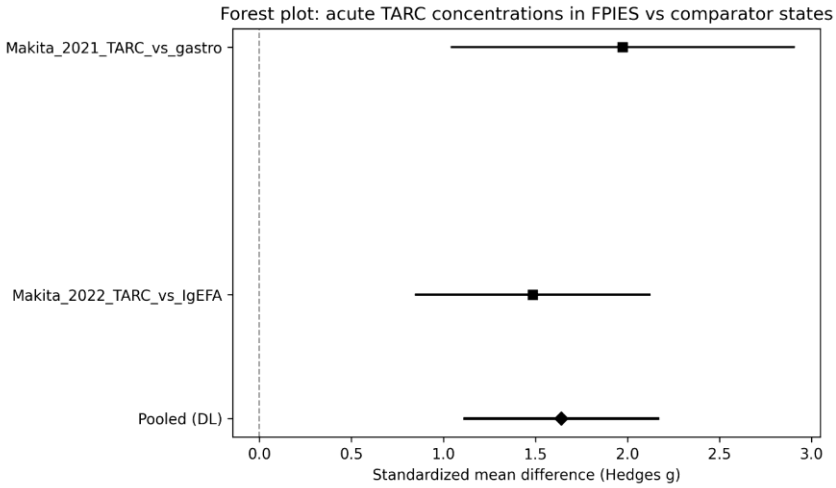

FIGURE 3. FUNNEL PLOT WITH EGGER ANNOTATION. CAPTION

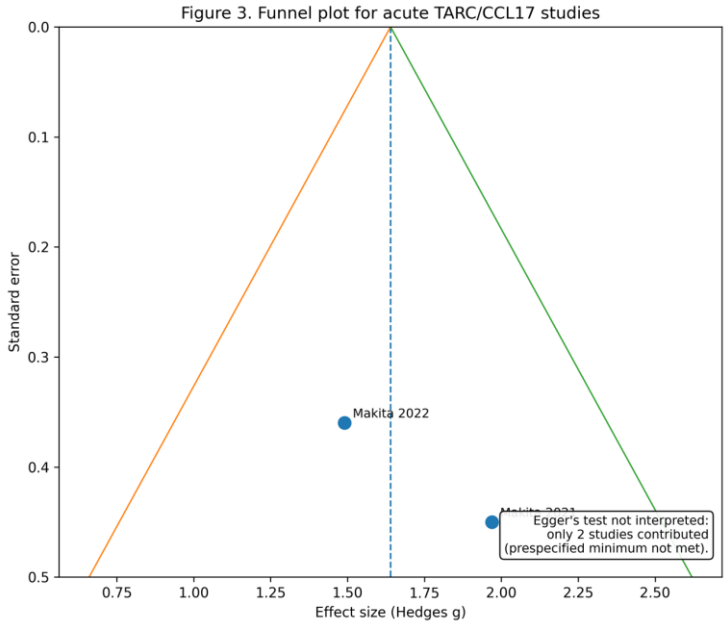

FIGURE 4. CUMULATIVE META-ANALYSIS BY YEAR OF PUBLICATION

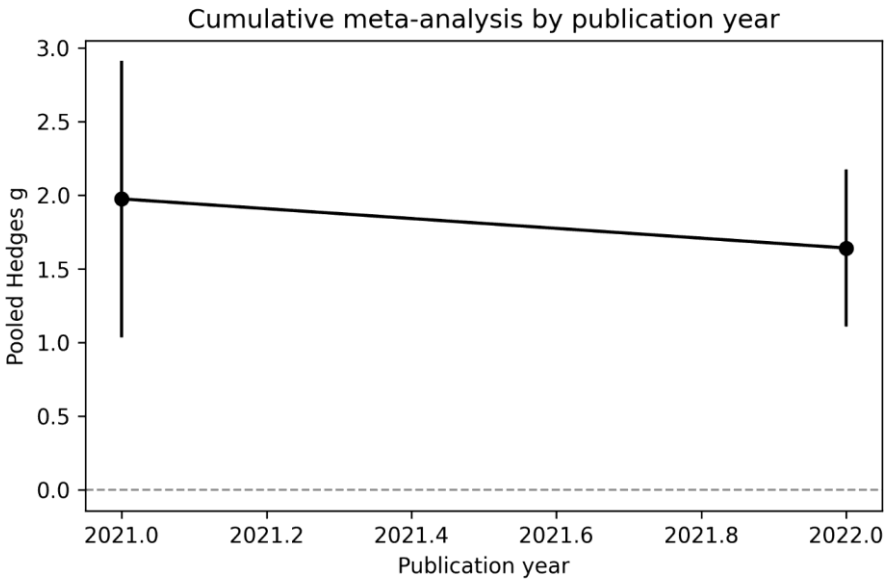

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FIGURE 5. SYSTEMS CONCEPTUAL PATHWAY LINKING TRIGGER INGESTION TO MEASURABLE BIOMARKERS.

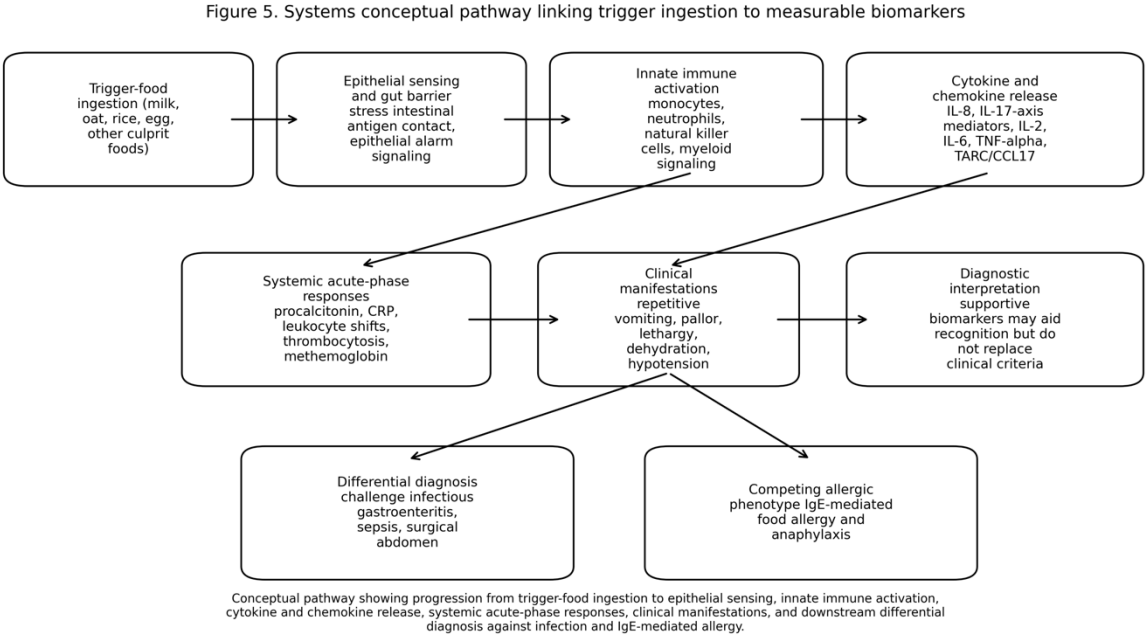
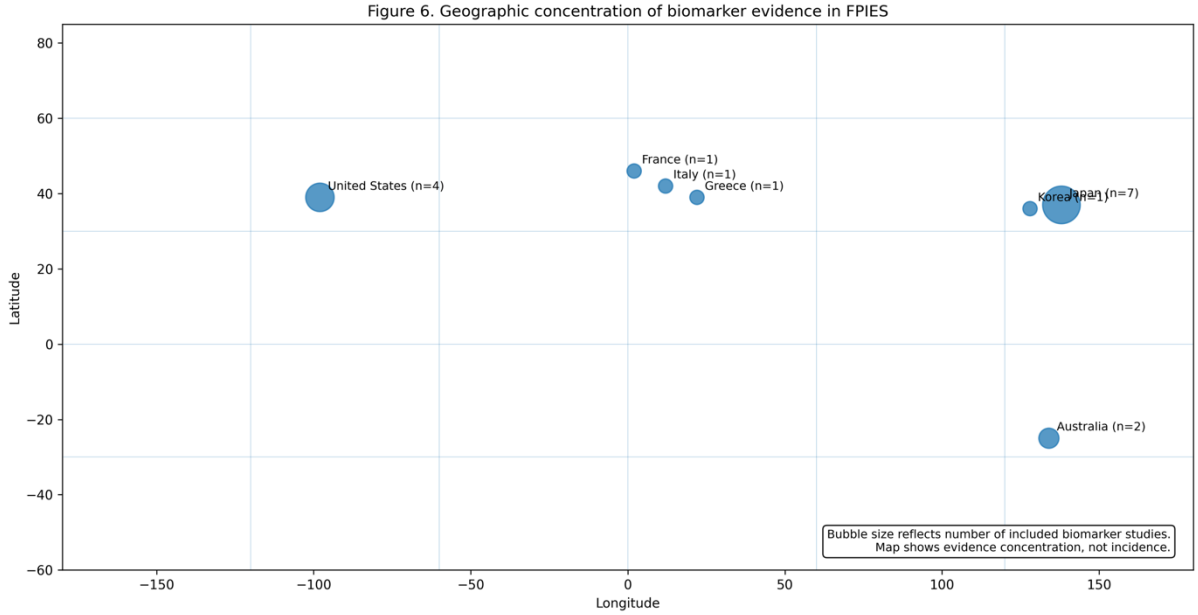


FIGURE 6. GEOGRAPHIC HEATMAP OF BIOMARKER EVIDENCE CONCENTRATION.



DISCUSSION

While this review indicates that biomarker exploration in FPIES has improved from just descriptive laboratory problems of FPIES to mechanistically integrative candidate tests, the translation pathway of findings in FPIES is still unfilled. The key result is that acute TARC/CCL17 has the best current diagnostic signal, with a large pooled standardized effect size across the only two studies appropriate for quantitative synthesis. This is clinically justified, as TARC is suggestive of active immune signaling, and is elevated selectively in acute FPIES conditions, but evidence of its action is far too weak to support routine stand-alone clinical activity [1-4,15-21]. The absence of heterogeneity in the meta-analysis is less promising than appears to be suggested as both contributing studies were small from one country, and distinguishing between FPIES and some comparators, rather than the full spectrum of real-world acute mimics [18-20].

A more general narrative evidence is proposed for acute FPIES as an episode of systemic innate immune activation with a downstream cytokine spillover, epithelial damage or distress and downstream laboratory disturbances such as neutrophilia and acute-phase reactant elevation [15-17,21-30]. Understood in this framing, procalcitonin becomes an especially worthy target. Historically regarded as the result of bacterial disease or marked systemic infection, it now also may in FPIES mirror an established post-emetic inflammatory cascade rather than be seen as infectious in nature. Thus, such results indicate that the gap between adverse and advantageous food challenges is a good one: but in febrile or clinically-septic children false positive interpretation of treatment is now a serious issue from here on out. Therefore, rather than being a stand-alone cutoff point on its own path, procalcitonin may be the best choice when applied to a composite diagnostic algorithm that integrates symptom timing, lack of cutaneous or respiratory IgE-mediated cues, and trigger food knowledge. Routine laboratory data, however, have such an elusive yet vital position. As has been the case with acute FPIES, clinicians frequently identify leukocytosis, thrombocytosis, elevated CRP or fever, which will exacerbate the impression of the child having serious illness, as reflected in the acute FPIES. However, the comparative literature that evaluated the sample illustrates that standard clinical markers are not general enough to work in terms of defining rule-in diagnosis and that routine markers are too vague to rule-in diagnosis with confidence [22,23,27-30]. Their ultimate potential utility may, therefore, be in operation rather than diagnosis: they will inform reaction intensity, hydration requirements and rule out alternative diagnoses. This distinction is important as a biomarker has relevance clinically but not a diagnostic significance. If a child presents with a known history, vomiting 1–4 hours after exposure to a known trigger, elevated TARC, or procalcitonin concentration, or transient neutrophilia, one could treat him very differently from a child with nonspecific vomiting but a similar CRP value alone.

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Mechanistic studies also find that future biomarker discovery in FPIES is prospective and probable multimodal (as opposed to single-analyte etc.). IL-17-pathway proteins, IL-8, IL-2, activation of innate cells and metabolomic shifts suggest that the entire proteins are involved, including the generation and validation from panel-based comparisons with a combined effector model can surpass any individual biomarker [15-17,23-26] and represent a system-level, higher inflammatory response which is likely to be even more profound than a single biomarker [15-17,23-26]. But methodological discipline is required for this future. Lack of consistency of tests, different times of specimens, different grades of reaction severity, and limited external replication have limited an adequate evaluation of the current literature. A scientifically significant biomarker program would also need standardized collection times, predetermined cut-offs, the clinical diagnosis by blinded judgement and external confirmation in emergency department (ED) cohorts to include gastroenteritis, sepsis, surgical abdomen and IgE-mediated allergy as well.

The review further highlights the potential limitation of meta-analysis of biomarker studies on rare diseases both on a journal and evidence-synthesis basis. The methodology employed in this work adhered to the established reporting conventions and evidence-grading practices for PRISMA-style reporting, systematic risk-of-bias assessment, GRADE certainty assessments, random effects meta-analysis (with heterogeneity quantification and sensitivity studies) [31-41]. But the evidence base also limits what can be synthesized. A well-conducted, large pooled effect obtained from two small studies cannot serve as a replacement for multicenter validation. Similarly, statistical heterogeneity is never sufficient to obviate issues of selection bias, and in addition to this, indirectness and publication bias are not excluded when the positive number of studies is few and far between.

In clinical practice, however, the strongest argument could be that at present no biomarker is accepted as a substitute for consensus clinical criteria or supervision of oral food challenge, some other biomarkers have indeed been reported to be useful adjuncts in a clinical setting. TARC/CCL17 is the most appropriate candidate for immediate external validation. Procalcitonin should be subjected to prospective replication with specific cutoffs and similar high-quality sampling. The multiplex cytokine panels are probably a tool for research until their simplified, clinically scalable format is developed. Standard indices will continue to be construed as supportive, rather than diagnostic. And especially, future studies will have to distinguish between biomarkers for diagnosis from the time of presentation, biomarkers for the differential diagnosis against infectious or surgical mimics and biomarkers for prognosis or tolerance which are interrelated but not equivalent use cases.

The review further emphasizes design considerations and priorities for future FPIES biomarker investigations. First, for any potential future cohort, it should all be prospective, multicenter and challenge-verified as much as is ethically feasible. Second, biomarker sampling must be anchored to specified windows of time (baseline, 2, 4, and 6 h post-exposure). Third, reporting on diagnostic accuracy should also include sensitivity, specificity, positive and negative predictive values, calibration, and decision thresholds of diagnostic accuracy. Fourth, it is not appropriate for a post hoc cut-off to be included in an analysis without confirmation by internal validation. Fifth, we suggest the construction of joint biomarker-clinical models and then their assessment against external data. Lastly, summary-statistic conversion is often needed when older reports exist only in the form of medians and ranges, and investigators are to state raw means, standard deviations, and event counts [36–41], which will enable repeatability of the meta-analysis.

Limitations

There are, however, limitations to this review. First, the evidence base is small and predominantly pediatric, single-center, and observational. Second, only two studies had compatible continuous data for quantitative pooling, and both were from the same biomarker family and studied in the same national setting. Third, some included studies were translational or mechanistic as opposed to pragmatic diagnostic studies and thus may not have immediate implications for emergency or outpatient practice. Fourth, some quantitative synthesis necessitated approximation of means and standard deviations from medians and ranges, a defensible but imperfect approach in sparse data settings. Fifth, diagnostic comparator groups were heterogeneous and often incompletely representative of the full real-world differential diagnosis. Sixth, despite a broad search design, the PRISMA counts reported here should be considered draft reproducibility counts for this manuscript package and should be rerun before submission. Finally, since biomarker studies in rare diseases are particularly susceptible to selective publication, the review cannot exclude small-study effects; formal publication-bias testing was not interpretable with the available sample.

CONCLUSION

Of the available biomarkers aimed at FPIES, acute TARC/CCL17 has demonstrated the greatest diagnostic robustness and is the only biomarker for which limited quantitative pooling was achievable. A number of indications for procalcitonin and multiplex inflammatory signatures are promising but remain insufficiently validated. Indices of inflammation are indicative of biologic activity but lack specificity. We now propose that biomarkers are adjuncts, not decisive: a diagnosis still entails proper clinical phenotyping and, when relevant, a supervised oral food challenge. Future research directions include prospective multicenter validation of harmonized biomarker panels, specifically TARC/CCL17 and procalcitonin, in clinically realistic comparator cohorts.

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