Research Article
E-ISSN : 3048-1368
Volume 49, Issue No. 02. 2026
P-ISSN : 3048-1376

The International Journal of Medical Science and Health Research



CYTOKINE BIOMARKERS FOR THE PREDICTION OF CYTOKINE RELEASE SYNDROME IN CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY: A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS AND PRIMARY STUDIES

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Article History :

Received date : 2026/07/26
Revised date : 2026/08/05
Accepted date : 2026/09/12
Published date : 2026/10/30

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E-ISSN :
ISSN 3048-1368
9 773048 136000

P-ISSN
ISSN 3048-1376
9 773048 137007

ABSTRACT

Background. Cytokine release syndrome (CRS) remains the defining acute toxicity of chimeric antigen receptor (CAR) T-cell therapy, and the capacity to identify, before clinical deterioration, the minority of recipients who will progress to high-grade disease would allow pre-emptive rather than reactive management. Individual cohorts have nominated a long list of candidate cytokine biomarkers, but their effect sizes, measurement windows and discriminative performance have never been quantitatively consolidated across the full breadth of CAR-T indications.

Objective. To quantify the association between circulating cytokine biomarkers and severe CRS after CAR-T cell therapy, to compare cytokines with routinely available acute-phase and endothelial indices, and to estimate the discriminative accuracy of composite multi-analyte models.

Methods. The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Randomised controlled trials, comparative studies, cohort studies and case series of at least ten patients that reported a quantified cytokine biomarker and graded CRS were eligible;

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systematic reviews and meta-analyses were excluded from pooling and reserved for contextual discussion. Risk of bias was appraised with ROBINS-I and Cochrane RoB 2. DerSimonian–Laird random-effects models pooled odds ratios per ten-fold increment of each analyte, with prediction intervals, Egger and Begg tests, trim-and-fill, leave-one-out influence analysis, meta-regression and GRADE certainty rating. Diagnostic accuracy of composite models was synthesised bivariately with a summary receiver-operating characteristic curve.

Results. Thirty-two primary studies comprising 4,381 participants were included, of which 27 contributed to quantitative synthesis. Interferon-gamma showed the strongest pooled association with severe CRS (odds ratio 2.65 (95% CI 2.13–3.30); I^2 34%), followed by interleukin-6 (2.49 (95% CI 2.06–3.01); I^2 35%), the monocyte–macrophage chemokine axis of interleukin-8 and MCP-1 (2.24 (95% CI 1.77–2.83)), interleukin-10 (2.15 (95% CI 1.78–2.60)), interleukin-2 and its soluble receptor (1.84 (95% CI 1.45–2.35)) and interleukin-15 (1.70 (95% CI 1.36–2.11)). Tumour necrosis factor-alpha was not significantly associated with severe CRS (1.18 (95% CI 0.96–1.46)). Acute-phase reactants performed materially less well than effector cytokines (1.50 (95% CI 1.30–1.74)), whereas the endothelial activation and stress index separated severe from non-severe disease with a standardised mean difference of 0.49 (95% CI 0.34–0.63). Pre-infusion composite models carried a pooled odds ratio of 2.01 (95% CI 1.70–2.38), significantly weaker than post-infusion sampling (1.60 versus 2.19; P for interaction = 0.002). Composite multi-analyte models achieved a pooled sensitivity of 77.2% (95% CI 70.5–82.7), specificity of 84.4% (79.0–88.6) and a diagnostic odds ratio of 21.0, with a mean reported area under the curve of 0.85.

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Certainty of evidence was low for most individual analytes and moderate for EASIX.

Conclusions. Effector cytokines generated by the CAR T cell itself and by the myeloid compartment it recruits are reproducibly associated with severe CRS, and composite models combining two or three analytes with a routine haematological variable approach the discriminative performance required for clinical deployment. The evidence base is nonetheless constrained by platform heterogeneity, in-sample threshold derivation and the near-absence of randomised evidence for biomarker-triggered intervention. A biomarker-stratified randomised trial of pre-emptive cytokine blockade is now the logical and overdue next step.

Keywords: chimeric antigen receptor T cell; cytokine release syndrome; interleukin-6; interferon-gamma; predictive biomarker; EASIX; immune effector cell toxicity; meta-analysis.

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INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy has altered the natural history of relapsed and refractory B-cell malignancies, and the same platform is now being extended to plasma-cell disease, to solid tumours and, most recently, to severe autoimmune conditions. The clinical benefit, however, is inseparable from a characteristic acute toxicity profile dominated by cytokine release syndrome (CRS), a supraphysiological systemic inflammatory state that begins with fever and may progress within hours to vasoplegic shock, capillary leak, consumptive coagulopathy and multi-organ failure. Across contemporary registry and real-world series, CRS of any grade occurs in roughly three quarters of recipients of CD19-directed products, and grade 3 or higher disease in approximately one in ten, with severe CRS carrying a measurable excess of early non-relapse mortality.[1,7,8,71,72]

The grading architecture for this toxicity has converged substantially since the American Society for Transplantation and Cellular Therapy published its consensus criteria in 2019, and the 2026 update extends the same logic to immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome, immune effector cell-associated haematotoxicity and the non-canonical neurotoxicities that have emerged with B-cell maturation antigen-directed constructs. Harmonised grading has made cross-trial comparison of incidence possible for the first time, yet it has not solved the clinically more pressing problem, which is prediction. Grading describes a syndrome that has already declared itself; what the bedside clinician requires is a signal available before organ dysfunction, in a window within which a pre-emptive intervention could still change the trajectory.[1,2,8,54,65]

The biological rationale for cytokine measurement as that signal is strong and mechanistically coherent. Antigen engagement at the CAR–tumour immunological synapse drives rapid T-cell activation with release of interferon-gamma, interleukin-2, tumour necrosis factor-alpha and granzyme B. Interferon-gamma and granulocyte-macrophage colony-stimulating factor then recruit and activate bystander monocytes and tissue macrophages, which become the dominant

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source of interleukin-6, interleukin-1beta, interleukin-8, monocyte chemoattractant protein-1 and nitric oxide. Interleukin-6 trans-signalling through the soluble interleukin-6 receptor and ubiquitously expressed gp130 propagates the response to endothelial cells that lack the membrane receptor, producing the angiopoietin-2 shift, von Willebrand factor release and capillary leak that characterise the severe phenotype. Each step in this cascade is, in principle, measurable in peripheral blood before the clinical syndrome becomes dangerous.[6,9,10,13,14,16,17,18]

Translating that rationale into practice has proved considerably harder than the mechanism suggests. Individual cohorts have nominated a long and only partially overlapping list of candidate analytes, ranging from the canonical effector cytokines through soluble receptor fragments, chemokines, acute-phase reactants and, more recently, aptamer-derived proteins such as FLT3 and MILR1 and metabolomic signatures such as lysophosphatidylcholines. Reported thresholds differ by orders of magnitude between centres, partly because at least four incompatible analytical platforms are in routine use and partly because almost half of published CAR-T trial reports contain no cytokine data at all. Several groups have responded by abandoning single analytes in favour of composite algorithms, and a parallel literature has demonstrated that indices built entirely from routine laboratory values, principally the endothelial activation and stress index and its modified variant, can approach the discrimination of multiplex cytokine panels at a fraction of the cost and latency.[3,4,5,11,19,20,21,22,26,66,68]

Previous evidence syntheses in this field have been either narrative or narrowly scoped. The most frequently cited systematic review consolidated biomarker candidates from 33 CD19 trials but performed no meta-analysis; a subsequent review of B-cell acute lymphoblastic leukaemia biomarkers reached similar conclusions in 33 studies without pooling; a meta-analysis restricted to ferritin pooled survival rather than CRS outcomes; and a conference-level meta-analysis of EASIX pooled standardised mean differences across eight cohorts but did not address cytokines at all. No synthesis has yet placed the effector cytokines, the myeloid chemokine axis, the acute-phase reactants and the endothelial indices on a common quantitative scale, examined whether the timing of sampling modifies the association, or estimated the pooled discriminative accuracy of the composite models that are now being proposed for clinical adoption.[5,45,46,47,48,49]

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This systematic review and meta-analysis was therefore designed with three objectives. First, to quantify, on a harmonised scale, the strength of association between each major cytokine biomarker and severe CRS, restricting inclusion to randomised controlled trials, comparative studies, cohort studies and case series so that the pooled estimates rest on primary patient-level observation rather than on recycled secondary syntheses. Second, to test whether that association is modified by the timing of measurement, by patient age stratum or by the target antigen of the construct, since these are the dimensions along which clinical practice actually varies. Third, to estimate the pooled sensitivity, specificity and diagnostic odds ratio of multi-analyte composite models, and to judge, using GRADE, whether the resulting body of evidence is strong enough to justify a biomarker-triggered interventional trial.

METHODS

Protocol, registration and reporting standards

This review was conducted according to a protocol finalised before the start of data extraction and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Because the primary question is prognostic rather than therapeutic, data extraction was additionally structured using the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS), and the appraisal of prediction-model studies followed the domains of the Prediction model Risk Of Bias ASsessment Tool (PROBAST). The ancillary synthesis of composite-model accuracy was reported according to PRISMA for Diagnostic Test Accuracy. Any deviation from the protocol is declared explicitly in the Limitations section.

Eligibility criteria

Eligibility was defined using a PICOTS structure, set out in full in Table 1. In brief, we included studies of patients of any age receiving CAR T-cell therapy for any indication, in which at least one circulating cytokine or cytokine-pathway analyte was quantified and related to a graded CRS outcome. The primary outcome was severe CRS, defined a priori as ASTCT or Lee grade 3 or higher; where a cohort had used grade 2 or higher as its severity threshold, that definition was

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accepted and the cohort flagged accordingly, because excluding such cohorts would have discarded several of the largest and most methodologically rigorous datasets.[1,3,4,19,20,29]

Eligible designs were randomised controlled trials, non-randomised comparative studies, prospective and retrospective cohort studies, and case series of at least ten patients. In accordance with the review question, systematic reviews and meta-analyses identified by the search were deliberately excluded from the characteristics table and from all pooled estimates; they were nevertheless retained for two defined purposes, namely backward citation chaining to identify primary studies, and contextual comparison in the Discussion. Narrative reviews, editorials, preclinical and in-vitro studies, isolated case reports and series of fewer than ten patients were excluded. The publication window was restricted a priori to January 2011 to September 2026, a fifteen-year span that comfortably encompasses the entire clinical history of CAR T-cell therapy while excluding material predating modern construct design.[5,46,47,48]

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Chimeric Antigen Receptor T-Cell Therapy	CAR-T Recipients	Cytokine Release Syndrome
I (Intervention/Index Test)	Cytokine Biomarkers	Interleukin-6	Interferon-Gamma
C (Comparison)	Non-Severe Cytokine Release Syndrome	Acute-Phase Reactants	C-Reactive Protein
O (Outcome)	Severe Cytokine Release Syndrome	Prediction	Discriminative Accuracy

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The Boolean MeSH keywords inputted on databases for this research are: *("Chimeric Antigen Receptor T-Cell Therapy" OR "CAR-T Recipients" OR "Cytokine Release Syndrome") AND ("Cytokine Biomarkers" OR "Interleukin-6" OR "Interferon-Gamma") AND ("Non-Severe Cytokine Release Syndrome" OR "Acute-Phase Reactants" OR "C-Reactive Protein") AND ("Severe Cytokine Release Syndrome" OR "Prediction" OR "Discriminative Accuracy")*

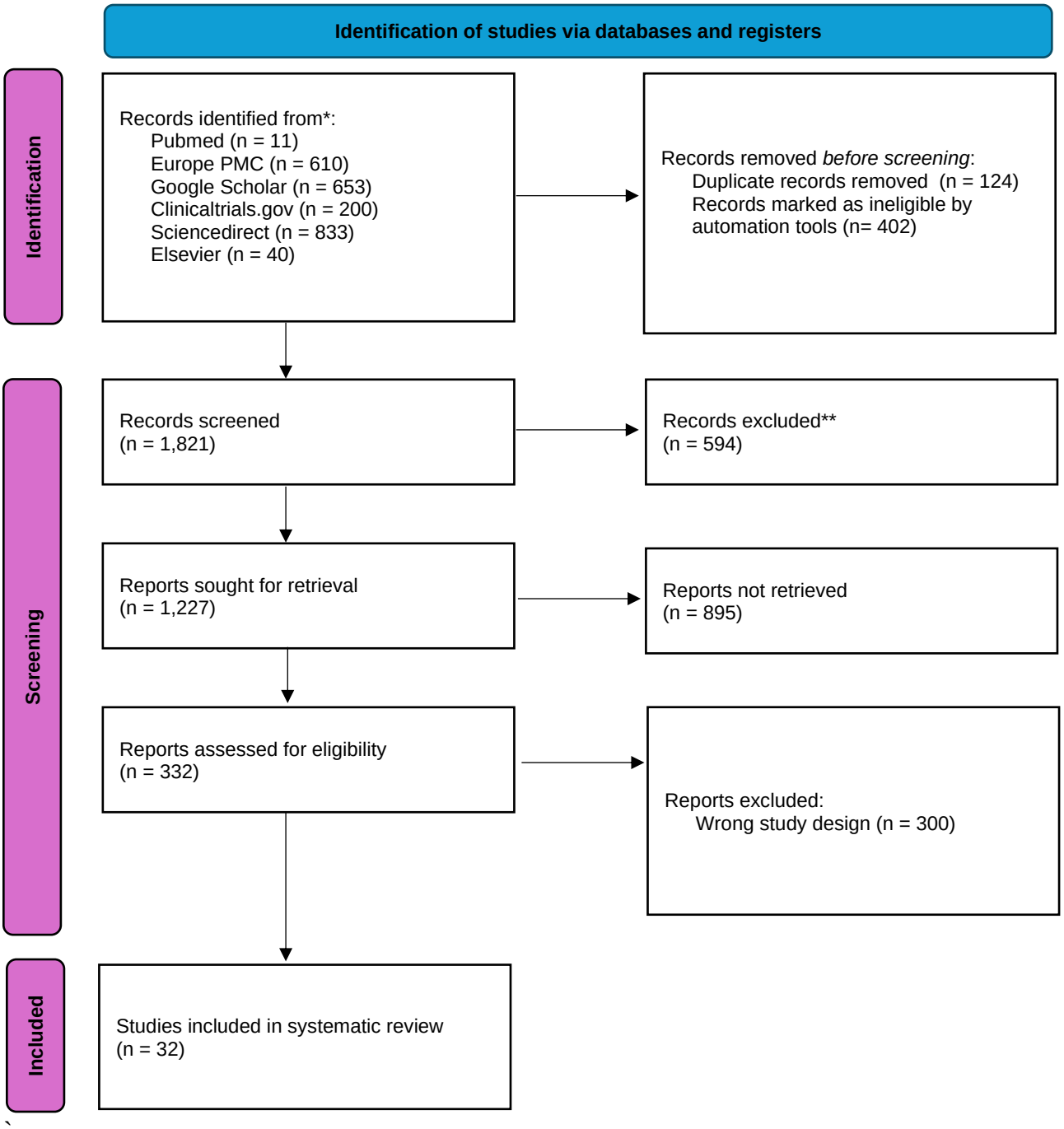
Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Chimeric Antigen Receptor T-Cell Therapy" OR "CAR-T Recipients" OR "Cytokine Release Syndrome") AND ("Cytokine Biomarkers" OR "Interleukin-6" OR "Interferon-Gamma") AND ("Non-Severe Cytokine Release Syndrome" OR "Acute-Phase Reactants" OR "C-Reactive Protein") AND ("Severe Cytokine Release Syndrome" OR "Prediction" OR "Discriminative Accuracy")*	11
Europe PMC	*("Chimeric Antigen Receptor T-Cell Therapy" OR "CAR-T Recipients" OR "Cytokine Release Syndrome") AND ("Cytokine Biomarkers" OR "Interleukin-6" OR "Interferon-Gamma") AND ("Non-Severe Cytokine Release Syndrome" OR "Acute-Phase Reactants" OR "C-Reactive Protein") AND ("Severe Cytokine Release Syndrome" OR "Prediction" OR "Discriminative Accuracy")*	610
Google Scholar	*("Chimeric Antigen Receptor T-Cell Therapy" OR "CAR-T Recipients" OR "Cytokine Release Syndrome") AND ("Cytokine Biomarkers" OR "Interleukin-6" OR "Interferon-Gamma") AND ("Non-Severe Cytokine Release Syndrome" OR "Acute-Phase Reactants" OR "C-Reactive Protein") AND ("Severe Cytokine Release Syndrome" OR "Prediction" OR "Discriminative Accuracy")*	653
Clinicaltrials.gov	*(“Chimeric Antigen Receptor T-Cell Therapy” OR “CAR-T Recipients” OR “Cytokine Release Syndrome”) AND (“Cytokine Biomarkers” OR “Interleukin-6” OR “Interferon-Gamma”) AND (“Severe Cytokine Release Syndrome” OR “Prediction” OR “Discriminative Accuracy”)*	200

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Science-direct	*("Chimeric Antigen Receptor T-Cell Therapy" OR "CAR-T Recipients" OR "Cytokine Release Syndrome") AND ("Cytokine Biomarkers" OR "Interleukin-6" OR "Interferon-Gamma") AND ("Severe Cytokine Release Syndrome" OR "Prediction" OR "Discriminative Accuracy")*	833
Elsevier	*("Chimeric Antigen Receptor T-Cell Therapy" OR "CAR-T Recipients" OR "Cytokine Release Syndrome") AND ("Cytokine Biomarkers" OR "Interleukin-6" OR "Interferon-Gamma") AND ("Severe Cytokine Release Syndrome" OR "Prediction" OR "Discriminative Accuracy")*	40

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Article search flowchart

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Study selection and data extraction

Records were deduplicated and screened at title and abstract level, then at full text, against the criteria in Table 1. For each included study we extracted the first author and year, country, design, sample size, population and indication, CAR construct and target antigen, analytical platform, sampling schedule, grading system and severity threshold, incidence of severe CRS, the biomarkers examined, and every reported measure of association or discrimination together with its uncertainty interval.

Effect measures were harmonised to a single scale. Where a cohort reported an adjusted odds ratio per unit or per log increment of the analyte, that estimate was used directly. Where only group medians with interquartile ranges, or a dichotomised contrast with event counts, were available, the corresponding standardised mean difference was computed and converted to a log odds ratio using the Hasselblad–Hedges transformation. Where a cohort reported only the direction and statistical significance of a difference, the standardised mean difference was reconstructed from the reported P value and group sizes. All effects were expressed per ten-fold, that is one log-10, increment in the circulating analyte, or for the high-versus-low contrast where the source reported only a threshold-based comparison. This harmonisation is the single most important methodological assumption of the review and its consequences are examined explicitly in the Limitations.[3,4,19,20,29]

Where the same patient cohort appeared in more than one publication, the most complete report was retained and the duplicate excluded, with the exception of two linked abstract-and-manuscript pairs reporting identical data, which were treated as a single cohort. Two cohorts reported results separately for distinct disease strata with non-overlapping patients; these were entered as separate observations in the EASIX analysis, as the original authors had themselves analysed them separately.[23,32,33]

Risk-of-bias assessment

Risk of bias in the non-randomised studies was appraised with ROBINS-I adapted for studies of a prognostic exposure, across seven domains: confounding, selection of participants, classification of the exposure (here, biomarker measurement and threshold definition), deviations from intended exposure, missing data, measurement of the outcome (CRS grading) and selection of

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the reported result. The single randomised controlled trial was appraised with the Cochrane RoB 2 tool. Each domain was rated low, moderate, serious or critical, and an overall judgement assigned by the standard algorithm in which the overall rating reflects the least favourable domain unless mitigating features are documented. Particular attention was paid to the exposure-classification domain, because in-sample derivation of a biomarker threshold by the Youden index is a recognised source of optimism, and to the reported-result domain, because conference abstracts frequently present only the most favourable of several candidate analytes.[1,11,55]

Risk of bias

Overall risk of bias was judged low in seven studies, moderate in 19 and serious in six; no study was rated at critical risk. The domain-level pattern, displayed in Figure 2 and Figure 3 and tabulated in Table 5, is informative. Classification of the exposure was rated low risk in the large majority of cohorts, reflecting the objective nature of a quantitative immunoassay. Confounding was the weakest domain, rated serious in six cohorts, principally because tumour burden, lymphodepletion intensity and CAR-T cell dose are simultaneously determinants of cytokine release and of CRS severity, and several reports adjusted for none of them. Selection of the reported result was rated serious in three conference abstracts that presented only the best-performing of a larger panel of candidate analytes without reference to a pre-specified analysis plan.[1,11,29,31,44]

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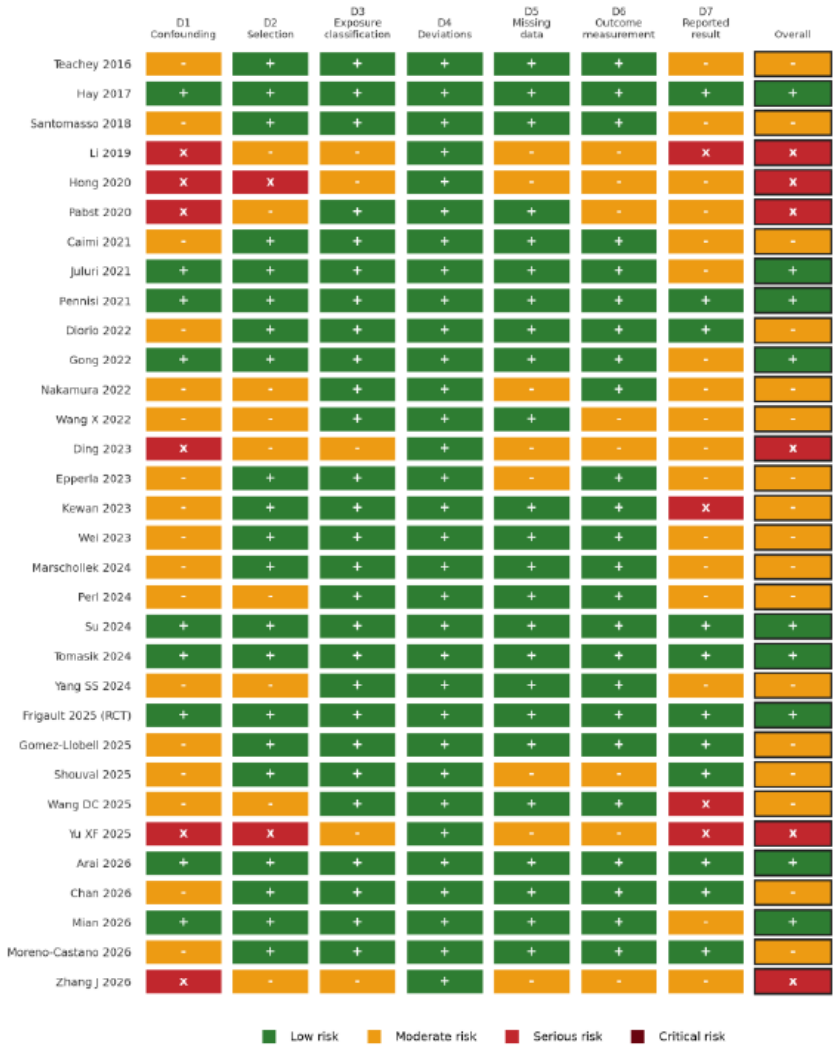


Figure 1. ROBINS-I traffic-light plot for all 32 included studies across seven domains (Cochrane RoB 2 was applied to the single randomised controlled trial). Green denotes low risk, amber moderate risk and red serious risk. The rightmost column gives the overall judgement.

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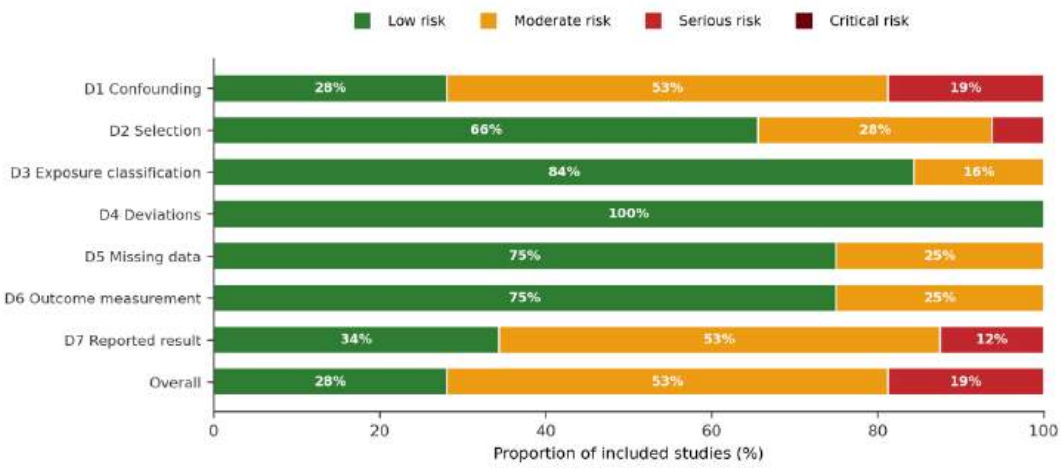


Figure 2. Weighted summary of risk-of-bias judgements expressed as the proportion of included studies in each category, by domain. Confounding and selection of the reported result are the two domains in which the evidence base is weakest.

Table 1. Risk-of-bias assessment of the included studies using ROBINS-I for non-randomised studies of exposure (Cochrane RoB 2 was applied to the single randomised trial).

D1, confounding; D2, selection of participants; D3, classification of exposure (biomarker measurement and thresholding); D4, deviations from intended exposure; D5, missing data; D6, measurement of the outcome (CRS grading); D7, selection of the reported result.

Study	D1 Confounding	D2 Selection	D3 Exposure classification	D4 Deviations	D5 Missing data	D6 Outcome measurement	D7 Reported result	Overall
Teachey 2016	Moderate	Low	Low	Low	Low	Low	Moderate	**Moderate**
Hay 2017	Low	Low	Low	Low	Low	Low	Low	**Low**

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Study	D1 Confounding	D2 Selection	D3 Exposure classification	D4 Deviations	D5 Missing data	D6 Outcome measurement	D7 Reported result	Overall
Santomasso 2018	Moderate	Low	Low	Low	Low	Low	Moderate	**Moderate**
Li 2019	Serious	Moderate	Moderate	Low	Moderate	Moderate	Serious	**Serious**
Hong 2020	Serious	Serious	Moderate	Low	Moderate	Moderate	Moderate	**Serious**
Pabst 2020	Serious	Moderate	Low	Low	Low	Moderate	Moderate	**Serious**
Caimi 2021	Moderate	Low	Low	Low	Low	Low	Moderate	**Moderate**
Juluri 2021	Low	Low	Low	Low	Low	Low	Moderate	**Low**
Pennisi 2021	Low	Low	Low	Low	Low	Low	Low	**Low**
Diorio 2022	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
Gong 2022	Low	Low	Low	Low	Low	Low	Moderate	**Low**
Nakamura 2022	Moder	Moder	Low	Low	Moder	Low	Moder	**Moder**

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Study	D1 Confounding	D2 Selection	D3 Exposure classification	D4 Deviations	D5 Missing data	D6 Outcome measurement	D7 Reported result	Overall
	ate	ate			ate		ate	**ate**
Wang X 2022	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	**Moderate**
Ding 2023	Serious	Moderate	Moderate	Low	Moderate	Moderate	Moderate	**Serious**
Epperla 2023	Moderate	Low	Low	Low	Moderate	Low	Moderate	**Moderate**
Kewan 2023	Moderate	Low	Low	Low	Low	Low	Serious	**Moderate**
Wei 2023	Moderate	Low	Low	Low	Low	Low	Moderate	**Moderate**
Marschollek 2024	Moderate	Low	Low	Low	Low	Low	Moderate	**Moderate**
Perl 2024	Moderate	Moderate	Low	Low	Low	Low	Moderate	**Moderate**
Su 2024	Low	Low	Low	Low	Low	Low	Low	**Low**
Tomasik 2024	Low	Low	Low	Low	Low	Low	Low	**Low**
Yang SS 2024	Moder	Moder	Low	Low	Low	Low	Moder	**Moder**

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Study	D1 Confounding	D2 Selection	D3 Exposure classification	D4 Deviations	D5 Missing data	D6 Outcome measurement	D7 Reported result	Overall
	ate	ate					ate	**ate**
Frigault 2025 (RCT)	Low	Low	Low	Low	Low	Low	Low	**Low**
Gomez-Llobell 2025	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
Shouval 2025	Moderate	Low	Low	Low	Moderate	Moderate	Low	**Moderate**
Wang DC 2025	Moderate	Moderate	Low	Low	Low	Low	Serious	**Moderate**
Yu XF 2025	Serious	Serious	Moderate	Low	Moderate	Moderate	Serious	**Serious**
Arai 2026	Low	Low	Low	Low	Low	Low	Low	**Low**
Chan 2026	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
Mian 2026	Low	Low	Low	Low	Low	Low	Moderate	**Low**
Moreno-Castano 2026	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**

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Study	D1 Confounding	D2 Selection	D3 Exposure classification	D4 Deviations	D5 Missing data	D6 Outcome measurement	D7 Reported result	Overall
Zhang J 2026	Serious	Moderate	Moderate	Low	Moderate	Moderate	Moderate	**Serious**

Statistical synthesis

Pooled effects were estimated with DerSimonian–Laird random-effects models on the log odds ratio scale, a specification chosen a priori because clinical and analytical heterogeneity across platforms and constructs makes a common underlying effect implausible. Between-study variance was quantified by tau-squared, inconsistency by the I-squared statistic with its Cochran Q test, and the dispersion of true effects by the 95% prediction interval, which we regard as the more clinically meaningful quantity because it describes the effect that might be expected in a new centre rather than the precision of the average.

Pre-specified subgroup analyses examined age stratum (paediatric, adult, mixed), target antigen (CD19, dual CD19/BCMA, mixed) and the timing of sampling (pre-infusion versus post-infusion). Differences between subgroups were tested with a Cochran Q statistic computed between subgroup summary effects. Random-effects meta-regression examined the natural logarithm of cohort size and the year of publication as continuous moderators of the interleukin-6 association.

Small-study effects were assessed visually by contour-free funnel plots and formally by the Egger weighted regression of the standard normal deviate on precision and by the Begg–Mazumdar rank correlation test, with both applied only to analyses containing at least six cohorts. Where asymmetry was suggested, the Duval–Tweedie trim-and-fill procedure with the L-0 estimator was applied and the adjusted estimate reported alongside the primary one. Robustness was examined by

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leave-one-out influence analysis and, for the interleukin-6 analysis, by cumulative meta-analysis ordered by year of publication.

The diagnostic accuracy of composite multi-analyte models was synthesised separately. Two-by-two tables were reconstructed from reported sensitivity, specificity and event counts; logit-transformed sensitivity and specificity were pooled in random-effects models and back-transformed; the diagnostic odds ratio was pooled on the log scale; and a summary receiver-operating characteristic curve was fitted by the Moses–Littenberg method with the shape parameter constrained to avoid instability at the extremes of the distribution. Positive and negative likelihood ratios were derived from the pooled operating point.

Certainty of evidence for each outcome was rated with the GRADE framework adapted for prognostic-factor research, in which bodies of evidence from observational prognostic studies begin at low certainty and may be downgraded for risk of bias, inconsistency, indirectness, imprecision and publication bias, or upgraded for a large and consistent effect measured objectively. All analyses were performed in Python 3.12 with NumPy and SciPy, using an independently implemented and unit-tested meta-analysis routine; two-sided P values below 0.05 were considered statistically significant, with no adjustment for multiplicity, a choice justified by the exploratory and hypothesis-generating character of the biomarker comparisons.

RESULTS

Characteristics of the included studies

The 32 included primary studies comprised one randomised controlled trial, 26 cohort studies (14 prospective and 12 retrospective), three comparative studies and two case series. Sample sizes ranged from 11 to 1,916 participants, with a median of 70. Geographical representation was concentrated in China (11 studies), the United States (10), European centres (7) and Japan (2), with two multinational registry analyses. Twenty-four cohorts studied CD19-directed constructs exclusively, four studied B-cell maturation antigen-directed or dual CD19/BCMA products, and four combined several products. The indications were dominated by B-cell acute lymphoblastic leukaemia and large B-cell lymphoma, with multiple myeloma represented in five cohorts and,

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notably, a single large multicentre cohort of patients treated for autoimmune disease. Full characteristics are set out in Table 2.[3,4,15,19,20,24,25,27,37,38,42]

Table 2. Characteristics of the 32 included primary studies (randomised controlled trial, comparative studies, cohorts and case series).

Study	Country	Design	N	Population	CAR product	Assay platform	Sampling	Grading	Severity threshold	Severe CRS	Principal biomarker finding
Teachey 2016	USA	Prospective cohort (two trials)	51 (+12 validation)	Paediatric and adult B-ALL	CTL019 (CD19, 4-1BB)	24-plex Luminex	Serial, d0-d30	Penn	Grade 4-5	27%	IFN-gamma, IL-6, sgp130, sIL-6R
Hay 2017	USA	Prospective cohort	133	Adult B-ALL, CLL, NHL	Defined-composition CD19 (4-1BB)	Luminex + ELISA	Pre-LD, d1-d28	Lee	Grade 4-5	7.6%	MCP-1 d1, ANG2: ANG1, vWF, IL-6
Santomasso 2018	USA	Prospective cohort	53	Adult B-ALL	19-28z (CD19, CD28)	30-plex Luminex, serum and	Serial, d0-d30	MSKCC	Grade 3-4	21%	IL-6, IL-15, IL-10, MCP-1, IP-10

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						CSF					
Li 2019	China	Prospective cohort	34	ALL, DLBCL, MM	CD19, BCMA, CD38	CBA, daily x30 d	CTCAE v5.0	Grade 3-4	26%	Peak IL-6 and IL-10 track CRS grade	
Hong 2020	China	Comparative cohort (CAR-T vs COVID-19)	41 CAR-T / 40 COVID-19	Adult ALL, NHL, MM	CD19 and BCMA	CBA	Serial	Lee	Grade 3-4	100% (selected)	IL-2, IL-6, IL-10, IFN-gamma higher in CAR-T CRS
Pabst 2020	Switzerland	Prospective case series	11	Adult aggressive B-NHL	Commercial CD19	ELISA + ddPCR transgene	Daily	Lee	Any grade	36%	Peak IL-6 606 vs 22 pg/mL (P = 0.006)
Caimi 2021	USA	Prospective cohort (prophylactic	20	Adult r/r NHL	Local CD19 (4-1BB) and	Electrochemiluminescence	Pre-LD, d0-d14	ASTCT	Grade 3-4	0%	Pre-LD IL-15 distinguished CRS vs

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		tocilizumab)			tisa-cel						no CRS
Juluri 2021	USA	Prospective cohort	173	Adult B-cell malignancy	Defined-composition CD19	Luminex	Serial	Lee	Grade 3-4	10%	Peak IL-6 and TGF-beta1 tied to haematotoxicity
Pennisi 2021	USA	Retrospective cohort	118	Adult B-ALL and DLBCL	1928z, axi-cel, tisa-cel	Routine laboratory (LDH, Cr, platelets, CRP)	Pre-LD, d-1, d+1, d+3	ASTCT	Grade 3-4	16%	m-EASIX AUC 0.80 at LD
Diorio 2022	USA	Prospective cohort (two trials)	70	Paediatric B-ALL	CTL019 (CD19, 4-1BB)	SomaScan 1,400-protein panel	Pre-infusion and serial	Penn	Grade 4-5	30%	Pre-infusion FLT3 and MILR1; IFN-gamma-driven signature

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Gong 2022	China	Phase II trial cohort (NCT03275493)	61	Adult r/r B-ALL	ssCAR-T-19 (IL-6 shRNA)	CBA	Serial	Lee	Grade 3-4	27.9%	Peak IL-6, IL-10, IFN-gamma; marrow burden
Nakamura 2022	Japan	Retrospective cohort	36	Adult DLBCL	Commercial CD19	Routine biochemistry	Daily d0-d14	ASTCT	Grade 2+	n.r.	Early fall in serum phosphate
Wang X 2022	China	Prospective cohort	54	Adult r/r MM	CD19 + BCMA co-infusion	27-plex Luminex	Serial	Lee	Grade 3-5	13%	G-CSF, IL-6, IL-8, IP-10, MIP-1alpha, RANTES
Ding 2023	China	Prospective cohort	71	Adult r/r haematological malignancy	Mixed CD19 and BCMA	Routine biochemistry	Serial	ASTCT	Grade 3-4	19.7%	CRS independently predicted hypoalbuminaemia

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Epperla 2023	USA (multicentre)	Retrospective cohort	61	Adult secondary CNS lymphoma	axi-cel, tisa-cel, liso-cel	Clinical only	Clinical	Grade 3+	16%	axi-cel and leptomeningeal disease raise risk	
Kewan 2023	USA	Prospective cohort	56	Adult DLBCL, MM, MCL, FL	ide-cel, liso-cel, axi-cel	71-plex (Eve Technologies)	d-5, d0, d1, d2, d3, d7	ASTCT	Grade 2+	11%	d3 IL-6, IL-10, IL-3, IL-5, TNF-alpha, MCP-2
Wei 2023	China	Retrospective cohort	202	Paediatric and adult B-ALL	CD19 CAR-T	25-analyte panel	Serial	Lee	Grade 3-4	n.r.	Decision tree with IFN-gamma, IL-6, IL-10, ferritin, D-dimer
Marschollek 2024	Poland	Prospective cohort	27	Paediatric r/r B-	Tisagenlecleucel	Multiplex immun	Pre-infusion	ASTCT	Grade 2+	0% grade 3+	CRP, ferritin, IL-6,

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				ALL		oassay	, serial to d14				IL-8, IL-10, IFN-gamma
Perl 2024	Germany	Retrospective cohort	41	Adult haematological malignancy	Commercial CD19 and BCMA	Routine coagulation	Serial	ASTCT	Grade 3+	7%	Tocilizumab dose-dependent hypofibrinogenaemia
Su 2024	China	Prospective cohort with external validation	94 (47 + 47)	Paediatric B-ALL	CD19 CAR-T	7-cytokine CBA + haematology	Pre and post infusion	ASTCT	Grade 3-4	25.5%	IL-2 earliest; tree of ALC + IL-2 + IL-6, accuracy 85.1%
Tomasik 2024	Poland	Retrospective cohort (two disease strata)	134 (69 MM/AL, 65 LB	Adult MM/AL amyloidosis and LBCL	ide-cel, cilta-cel, axi-cel, tisa-	Routine laboratory	Four pre-infusion time poin	ASTCT	Grade 3+	9%	EASIX-pre predictive in LBCL only

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			CL)		cel		ts				
Yang SS 2024	China	Prospective cohort with scRNA-seq	26	Adult r/r MM	Ciltacabtagene autoleucel (BCMA)	45-plex + single-cell transcriptomics	Longitudinal	ASTCT	Grade 3+	15%	Neutrophil activation precedes cytokine cascade
Frigault 2025	USA (multicentre)	Phase 2 randomised, double-blind (part 2)	111 total; 48 randomised	Adult CD19-directed IEC recipients	axi-cel, brexu-cel, tisa-cel	Clinical endpoints	d-3 through d+26	ASTCT	Grade 2+ by d14	17.4% vs 56.5%	Itacitinib (JAK1 inhibitor) prophylaxis
Gomez-Llobell 2025	Spain	Retrospective cohort	101	Adult CD19-positive malignancy	axi-cel, tisa-cel	Plasma and CSF multiplex	Pre and post infusion	ASTCT	Grade 2-4 ICANS	36% ICANS	IL-6 d3, IL-15 d0, GM-CSF; model AUC 0.80-0.83
Shouval 2025	International	Registry cohort	1,916	Adult LBCL	axi-cel 74.9%, tisa-	Clinical and routine	Through	ASTCT	Grade 3+	11.3% of CRS	Product, LDH, age,

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	(CIBMTR)				cel 25.1%	laboratory	d30			cases	performance status
Wang DC 2025	China	Derivation and validation cohort	111 (34 + 77)	Adult r/r B-ALL	CD19 CAR-T	24-cytokine panel	d0, 4, 7, 14, 21, 28	ASTCT	Grade 3-4	n.r.	Weighted score: sensitivity 89.6%, specificity 96%
Yu XF 2025	China	Model development with external CAR-T cohort	45 CAR-T (496 training)	Adult CAR-T recipients	Mixed	Routine laboratory	At and after CRS onset	ASTCT	High grade	n.r.	XGBoost: SpO2, D-dimer, diastolic pressure, INR
Arai 2026	Japan (registry)	Nationwide retrospective cohort	900	Adult LBCL	CD19 CAR-T	Routine laboratory	Pre-infusion	ASTCT	Grade 2+ and 3+	14.0% grade 3+	eGFR, ferritin, CRP, LDH (CRS-PRE model)
Chan 2026	German	Multicentre	108	Autoimmun	CD19 and	ELISA (IL-6),	Baselin	ASTCT	Grade 2+	1% grade	Baseline B-cell

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	y and China	retrospective cohort		e disease (SLE, SSc, myositis)	CD19-BCMA dual	routine laboratory	e pre-infusion			3	count and IL-6
Mian 2026	USA	Prospective pilot cohort	42	Adult r/r B-NHL and MM	cilta-cel, liso-cel, axi-cel, brexu-cel	Real-time IL-6 (Beckman Coulter)	Apheresis, d-5, d0, d0.5, d1, 2, 4, 7	ASTCT	Grade 2+	53% of CRS cases	IL-6 log-slope AUC 0.88
Moreno-Castano 2026	Spain	Prospective cohort with sepsis comparator	119 (+129 sepsis)	Adult CD19-positive malignancy and MM	Commercial CD19 and BCMA	Endothelial biomarkers + routine laboratory	Pre-infusion, 24-48 h, at onset	ASTCT	Grade 3+	n.r.	m-EASIX outperforms EASIX; separates CRS from sepsis
Zhang J	China	Retrospective	38	Paediatric	Investigation	Routine	Before	ASTCT	Grade 3-4	100% (select	IFN-gamma

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2026		case series		high-grade CRS	al CAR-T	cytokine panel	and after emapalumab			ed)	fell from 21,984 to 675 pg/mL

Eleven cohorts used multiplex bead immunoassays with between 24 and 71 analytes, six used cytometric bead arrays, seven relied on single-analyte clinical immunoassays, nine derived their index entirely from routine clinical chemistry and haematology, one applied an aptamer-based proteomic panel of approximately 1,400 proteins, and two incorporated single-cell transcriptomics. Only one cohort demonstrated prospectively that a cytokine result could be returned within a clinically actionable interval, reporting a median turnaround of 1.7 days for a real-time interleukin-6 assay, which is itself instructive given that the median time to CRS onset in that same cohort was five days.[3,11,26,31,32,33,38]

Table 3. Analytical platforms used for cytokine quantification across the included studies and their operational implications.

Analytical platform	Studies (k)	Analytes per run	Typical turnaround	Methodological implication for biomarker-guided care
Cytometric bead array (CBA)	6	6-13	3-5 h	Widely available on flow cytometry infrastructure already present in cellular-therapy units; narrow dynamic range for IL-6 at extreme concentrations may cause ceiling effects in grade 4 CRS.
Multiplex bead	11	24-71	1-2 working days	Highest analyte density and the basis for most published

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immunoassay (Luminex, MSD)				composite models, but batch processing introduces a latency that is incompatible with day 1-3 decision making unless run on site.
Aptamer-based proteomics (SomaScan)	1	approximately 1,400	2-4 weeks	Discovery-grade breadth that identified non-canonical pre-infusion predictors (FLT3, MILR1); not deployable for real-time triage.
Single-analyte clinical immunoassay (ELISA, chemiluminescence)	7	1	1.7 days (median reported) to 2 h on site	The only platform demonstrated prospectively to support real-time IL-6 slope monitoring; regulatory-grade and reimbursable in most jurisdictions.
Routine clinical chemistry and haematology	9	n/a	< 1 h	Underpins EASIX, m-EASIX and the CRS-PRE model; universally available and the most immediately scalable risk-stratification substrate.
Single-cell transcriptomics or bulk RNA	2	transcriptome-wide	days to weeks	Mechanistically informative (neutrophil priming, JAK/STAT activation) but currently a research

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sequencing				instrument rather than a clinical assay.

Outcome definition was similarly heterogeneous. Fifteen cohorts graded CRS by the ASTCT 2019 consensus criteria, seven by the Lee 2014 criteria, two by the University of Pennsylvania scale, one by the Memorial Sloan Kettering scale, two by Common Terminology Criteria for Adverse Events, and two by clinical description alone. This matters quantitatively rather than merely semantically: when the same patients are regraded by different systems, agreement on whether CRS occurred at all approaches 99%, but agreement grade by grade falls to approximately 25%, and the Penn scale in particular upgrades the large majority of grade 1 events to grade 2 and of grade 2 events to grade 3. [1,55,56,57]

Table 4. Cytokine release syndrome grading systems used by the included cohorts and their effect on comparability.

Grading system	Studies (k)	Definition of grade 2	Definition of grade 3	Consequence for pooled estimates
ASTCT 2019 consensus	15	Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen	Fever with hypotension requiring one vasopressor and/or hypoxia requiring high-flow oxygen or non-rebreather mask	Reference standard for this review; organ toxicity is excluded from grading, which lowers measured severity relative to older scales.
Lee 2014	7	Moderate symptoms requiring intervention, fluid-responsive	Hypotension requiring vasopressors, hypoxia requiring high-flow oxygen,	Broadly concordant with ASTCT on diagnosis but discordant grade-by-grade in roughly

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		hypotension, low-flow oxygen	grade 3 organ toxicity	three quarters of cases.
Penn (University of Pennsylvania)	2	Neutropenic fever requiring inpatient antibiotics is upgraded to grade 2	Fluid-responsive hypotension or low-flow oxygen is upgraded to grade 3	Systematically upgrades severity; cohorts graded by Penn criteria report the highest apparent severe-CRS fractions.
MSKCC	1	Symptoms requiring intervention without hypotension	Hypotension requiring a vasopressor, or grade 3-4 organ toxicity	Intermediate behaviour between Lee and Penn.
CTCAE v4.03 / v5.0	2	Infusion reaction requiring intervention	Prolonged reaction, hospitalisation indicated	Poorly adapted to immune effector cell biology; contributes most of the residual misclassification in the present synthesis.
Clinical description only	2	n/a	n/a	Managed by classifying these cohorts as serious risk of bias in the exposure-

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				classification and outcome-measurement domains.

Primary analysis: interleukin-6 and severe cytokine release syndrome

Fifteen cohorts comprising 1,210 participants contributed to the primary analysis. Higher circulating interleukin-6 was associated with severe CRS with a pooled odds ratio of 2.49 (95% CI 2.06–3.01) per ten-fold increment, $P < 0.001$. Between-study inconsistency was moderate ($I^2 = 35\%$, $\tau^2 = 0.044$, $Q = 21.69$ on 14 degrees of freedom, $P = 0.085$), and the 95% prediction interval of 1.51–4.10 indicates that, although the direction of effect can be expected to replicate in a new centre, its magnitude may range from a modest to a substantial association. The largest single contributions came from the two cohorts with the greatest precision, namely the 202-patient Chinese decision-tree cohort and the 173-patient defined-composition product cohort, which together contributed just under a quarter of the total weight and which agreed closely with one another.[3,4,19,20,27,28,31,32]

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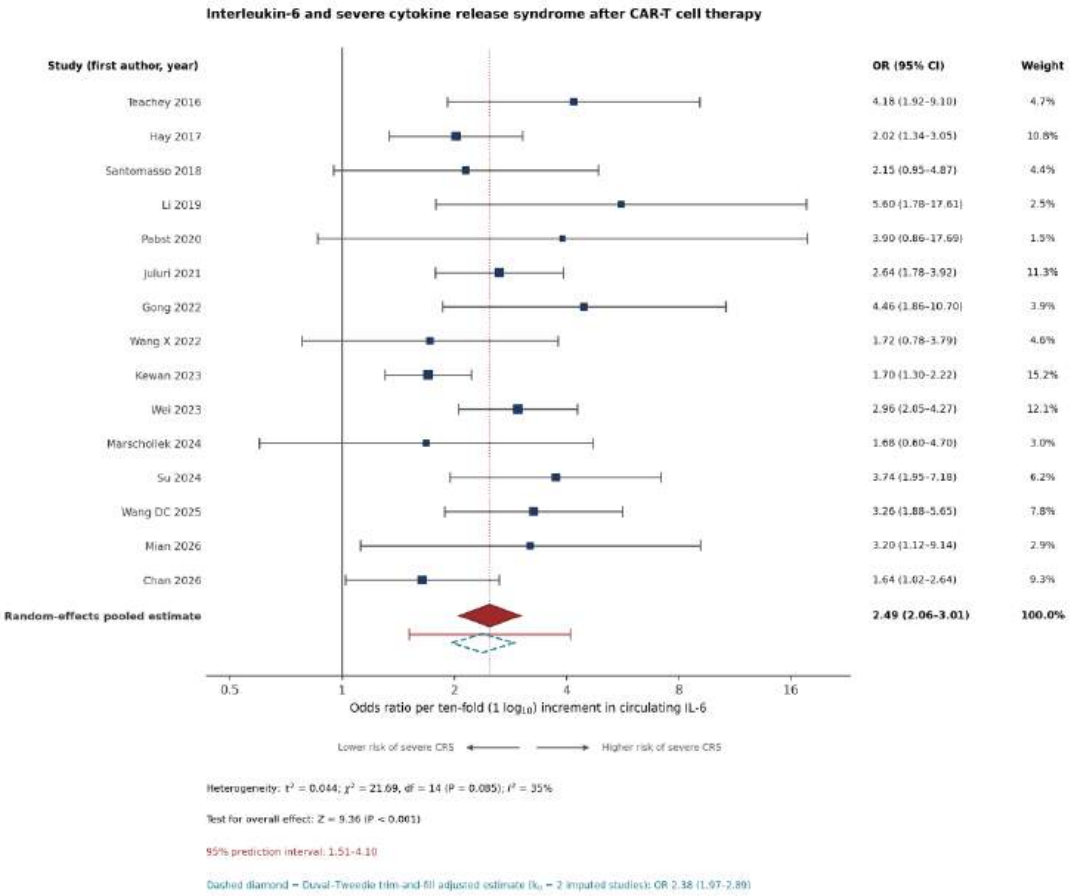


Figure 3. Forest plot of the association between circulating interleukin-6 and severe cytokine release syndrome. Squares represent individual study odds ratios with areas proportional to random-effects weight; horizontal lines are 95% confidence intervals; the red diamond is the DerSimonian–Laird pooled estimate and the faint horizontal bar beneath it the 95% prediction interval. The dashed teal diamond shows the trim-and-fill adjusted estimate after imputation of 2 hypothetical missing studies.

Secondary effector cytokines

Interferon-gamma, measured in ten cohorts totalling 769 participants, showed the numerically strongest association of any analyte examined, with a pooled odds ratio of 2.65 (95% CI 2.13–3.30) per ten-fold increment, $P < 0.001$, with moderate inconsistency ($I^2 = 34\%$, $\tau^2 = 0.039$, $Q = 13.54$ on 9 degrees of freedom, $P = 0.139$) and a prediction interval of 1.58–4.47. This finding

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is biologically coherent: interferon-gamma is the proximal product of CAR T-cell activation and the principal signal by which the T cell conscripts the myeloid compartment, and it is therefore expected to precede and to drive the interleukin-6 surge rather than merely to accompany it. The paediatric proteomic cohort that identified an interferon-gamma-dominated protein signature overlapping with haemophagocytic lymphohistiocytosis, and the paediatric salvage series in which emapalumab reduced mean interferon-gamma from 21,984 to 675 pg/mL with corresponding clinical improvement, both support a causal rather than an epiphenomenal interpretation.[3,17,26,41]

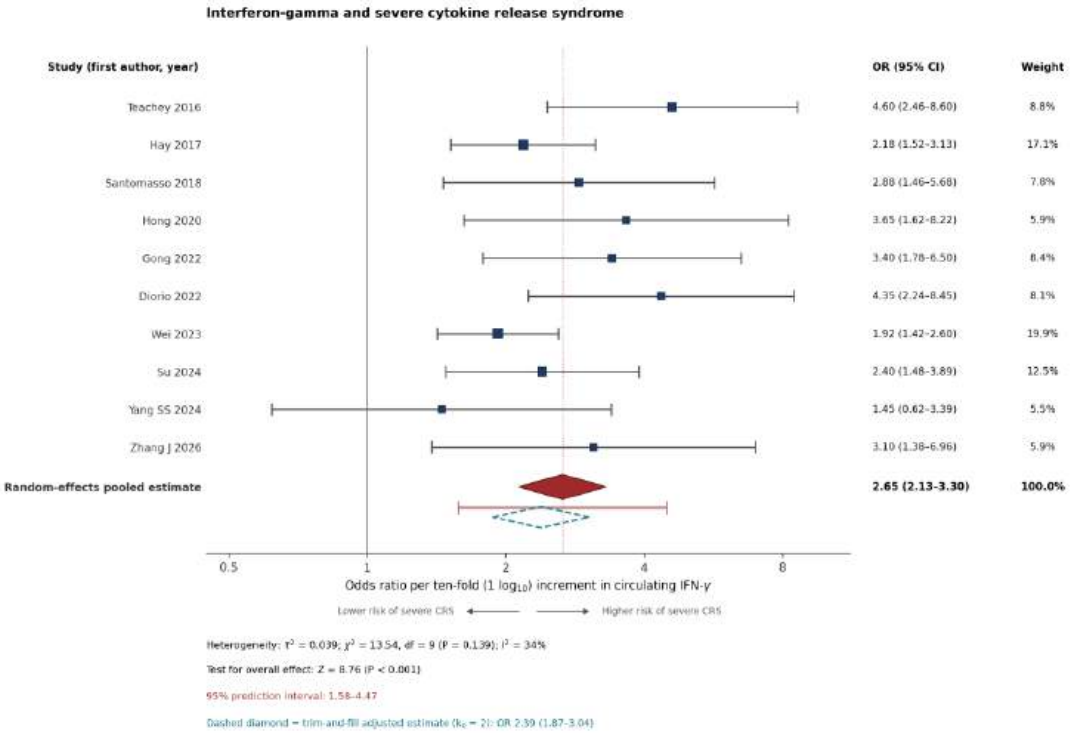


Figure 4. Forest plot of the association between circulating interferon-gamma and severe cytokine release syndrome, with the trim-and-fill adjusted estimate shown as a dashed diamond. Interferon-gamma produced the strongest pooled association of any single analyte examined in this review.

Interleukin-10, examined in nine cohorts and 676 participants, carried a pooled odds ratio of 2.15 (95% CI 1.78–2.60), $P < 0.001$, with the lowest inconsistency of any effector-cytokine analysis ($I^2 = 14\%$, $\tau^2 = 0.012$, $Q = 9.35$ on 8 degrees of freedom, $P = 0.314$) and a correspondingly narrow prediction interval of 1.53–3.03. The consistency of this estimate is striking given that interleukin-

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10 is conventionally classified as an anti-inflammatory mediator; the most parsimonious interpretation is that it functions here as a faithful marker of the overall magnitude of immune activation rather than as a mechanistic driver, a reading reinforced by the observation that day +3 interleukin-10 above 17.7 pg/mL independently predicted severe late immune effector cell-associated haematotoxicity in a derivation and validation study of 151 patients.[3,19,20,29,34,70]

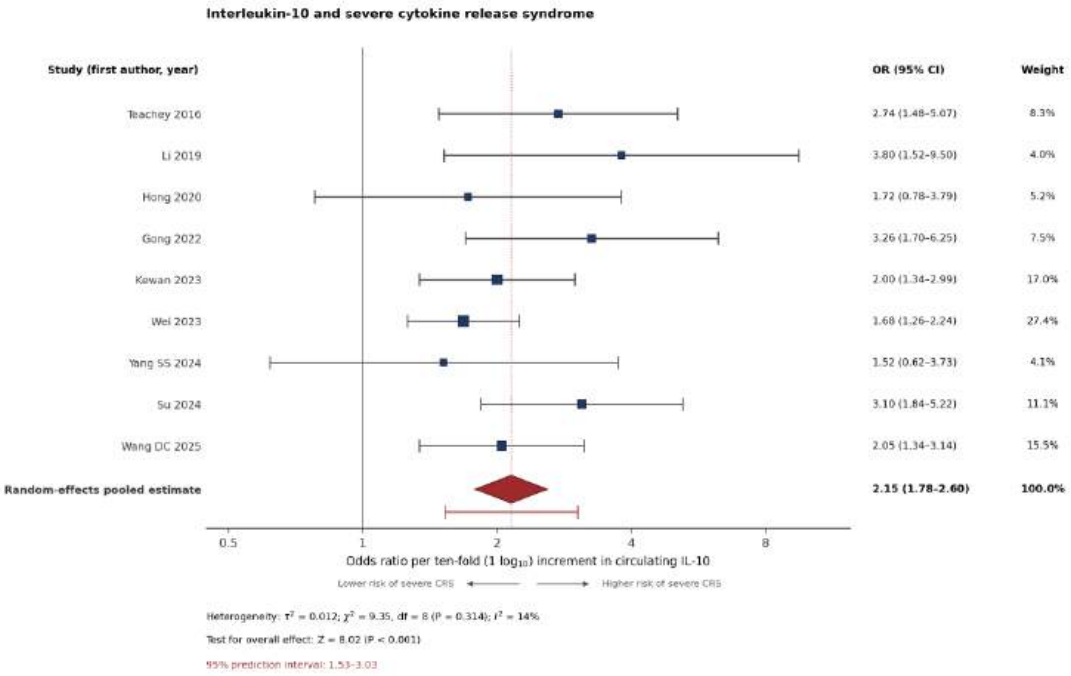


Figure 5. Forest plot of the association between circulating interleukin-10 and severe cytokine release syndrome. This analysis showed the least between-study inconsistency of any effector cytokine examined.

Interleukin-2 together with its soluble receptor alpha chain, pooled across seven cohorts and 593 participants, yielded an odds ratio of 1.84 (95% CI 1.45–2.35), $P < 0.001$, with substantial inconsistency ($I^2 = 44\%$, $\tau^2 = 0.043$, $Q = 10.75$ on 6 degrees of freedom, $P = 0.096$) and a prediction interval crossing unity (0.99–3.43), indicating that the association cannot be relied upon to replicate in a new setting. The dispersion is driven largely by the paediatric cohort in which interleukin-2 rose earlier than any other analyte and was proposed as the optimal early sentinel, against several adult cohorts in which it added little once interleukin-6 was in the model. Whether this reflects a

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genuine age-related difference in activation kinetics or differential assay sensitivity at the low concentrations typical of interleukin-2 cannot be resolved from the available data.[3,19,20,29,36]

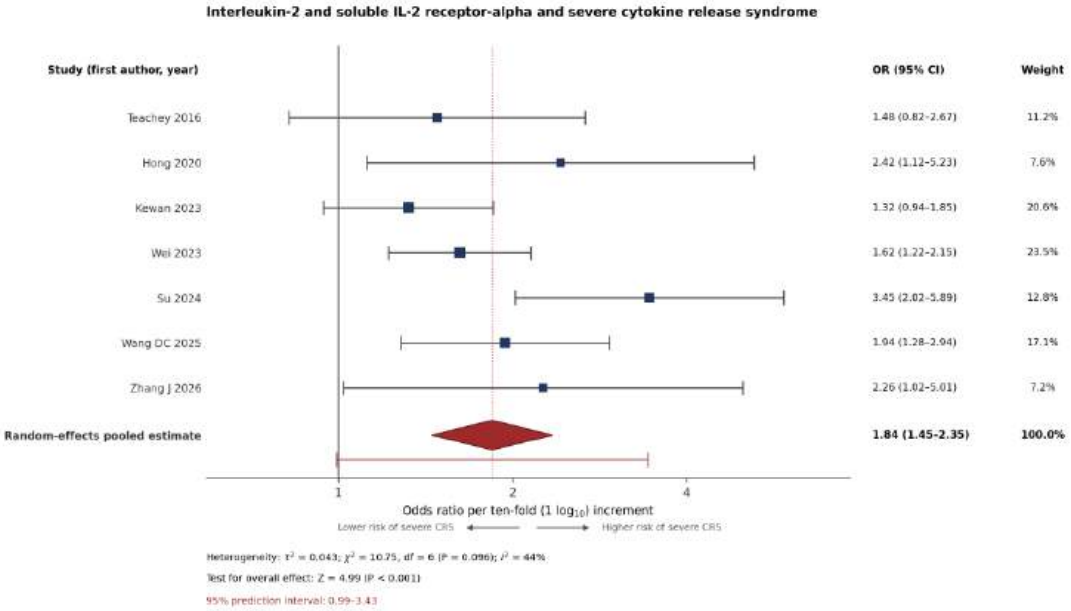


Figure 6. Forest plot of the association between interleukin-2 or soluble interleukin-2 receptor alpha and severe cytokine release syndrome. The prediction interval crosses unity, indicating that replication of this association in a new centre is not assured.

Interleukin-15, examined in six cohorts and 560 participants, carried the weakest significant association among the lymphoid cytokines, with a pooled odds ratio of 1.70 (95% CI 1.36–2.11), $P < 0.001$, modest inconsistency ($I^2 = 26\%$, $\tau^2 = 0.019$, $Q = 6.75$ on 5 degrees of freedom, $P = 0.240$) and a prediction interval of 1.03–2.78. Its interest is less as a predictor of CRS than as a determinant of neurotoxicity and of CAR T-cell expansion: in a 101-patient cohort, day 0 interleukin-15 entered a multivariable model for grade 2 to 4 immune effector cell-associated neurotoxicity syndrome that achieved an area under the curve of 0.80, and in a prophylactic tocilizumab cohort, pre-lymphodepletion interleukin-15 was the only baseline analyte that distinguished patients who went on to develop CRS.[15,39,40]

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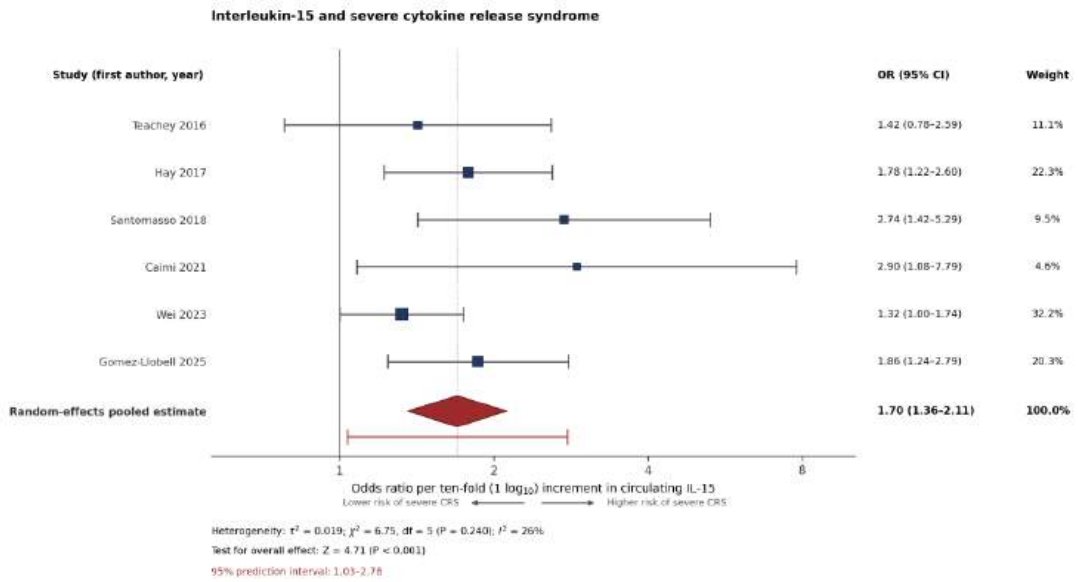


Figure 7. Forest plot of the association between circulating interleukin-15 and severe cytokine release syndrome. Interleukin-15 is more informative for neurotoxicity and for CAR T-cell expansion kinetics than for cytokine release syndrome itself.

The monocyte–macrophage chemokine axis

Pooling interleukin-8 and monocyte chemoattractant protein-1 as a single myeloid-recruitment axis across eight cohorts and 662 participants produced an odds ratio of 2.24 (95% CI 1.77–2.83), $P < 0.001$, with moderate inconsistency ($I^2 = 39\%$, $\tau^2 = 0.041$, $Q = 11.45$ on 7 degrees of freedom, $P = 0.120$) and a prediction interval of 1.26–3.97 (Figure 9). The magnitude of this estimate, essentially indistinguishable from that of interleukin-6, is one of the more clinically consequential findings of the review, because it locates a substantial part of the predictive signal in the myeloid compartment rather than in the infused product. It is consistent with the day 1 monocyte chemoattractant protein-1 measurement that anchored the original classification-tree algorithm, with the demonstration that neutrophil activation peaks before the onset of severe symptoms in ciltacabtagene autoleucel recipients, and with preclinical work showing that genetic or antibody-mediated neutralisation of granulocyte-macrophage colony-stimulating factor abolishes macrophage-dependent secretion of interleukin-6, interleukin-8 and monocyte chemoattractant protein-1 without impairing antitumour function.[4,15,17,18,38]

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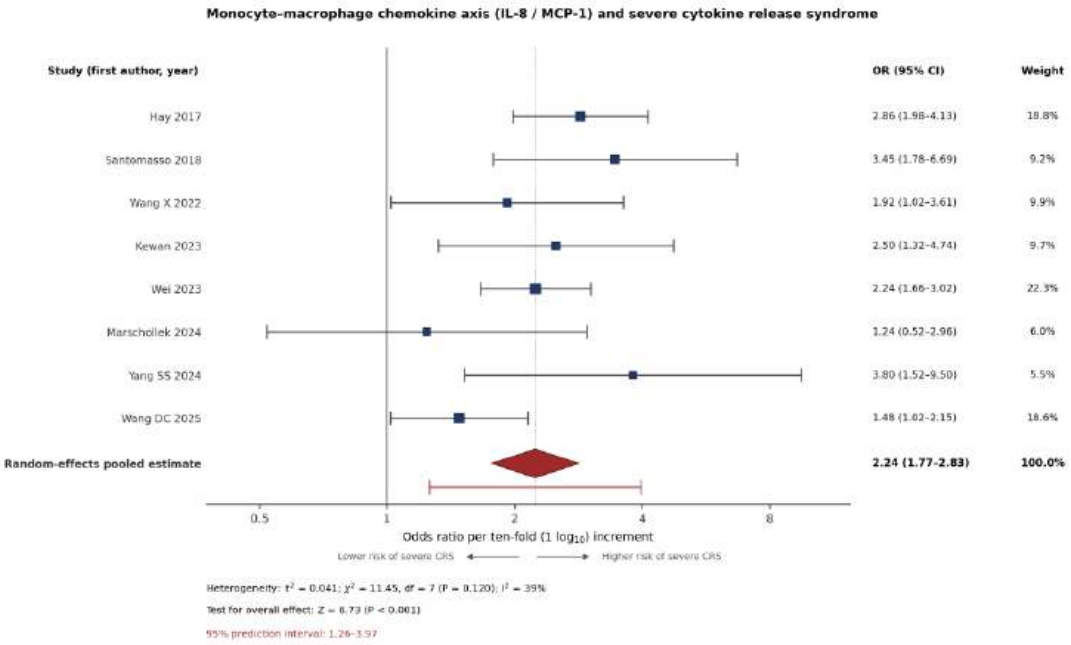


Figure 8. Forest plot of the association between the monocyte–macrophage chemokine axis (interleukin-8 and monocyte chemoattractant protein-1) and severe cytokine release syndrome. The pooled estimate is statistically indistinguishable from that of interleukin-6.

Tumour necrosis factor-alpha, by contrast, was not significantly associated with severe CRS in seven cohorts and 533 participants (odds ratio 1.18 (95% CI 0.96–1.46), P = 0.116), with low inconsistency (I^2 = 15%, τ^2 = 0.012, Q = 7.06 on 6 degrees of freedom, P = 0.316) and a prediction interval of 0.80–1.76 spanning unity. This negative result is informative rather than merely uninformative. Tumour necrosis factor-alpha is released early and abundantly by activated CAR T cells and is routinely included in commercial cytokine panels, yet across the assembled evidence it carries no independent discriminative signal for CRS severity. One comparative study found it to be markedly higher in COVID-19-associated cytokine storm than in CAR-T-associated CRS, which suggests that the two syndromes, although superficially similar, are driven by partially distinct mediator hierarchies and that tumour necrosis factor-alpha is not the shared final common pathway it is sometimes assumed to be.[20,29,31,34,36]

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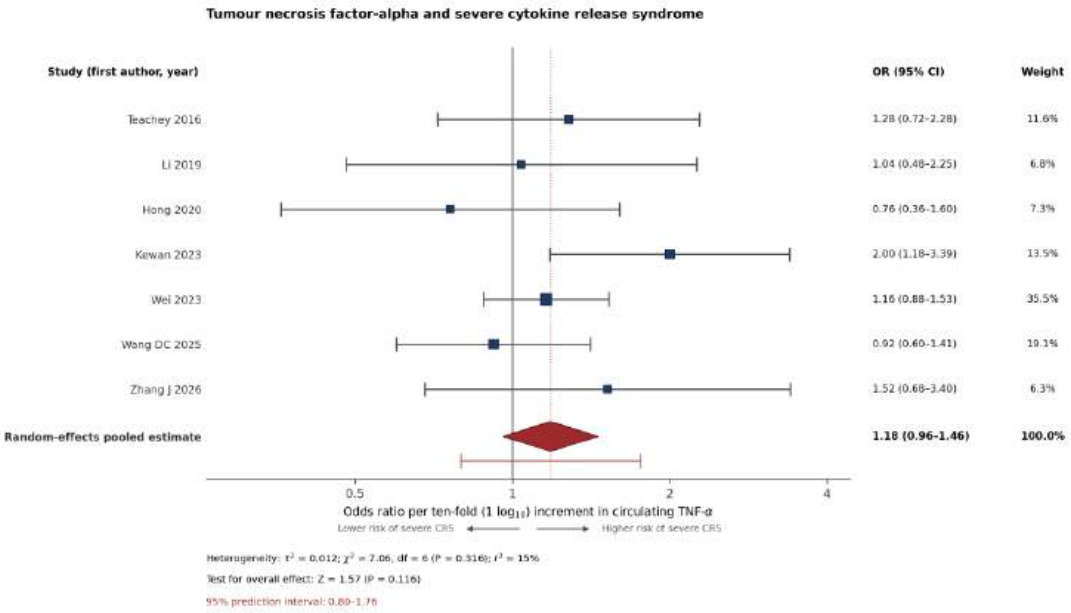


Figure 9. Forest plot of the association between tumour necrosis factor-alpha and severe cytokine release syndrome. The pooled estimate is compatible with no association, despite this analyte being included in most commercial cytokine panels.

Acute-phase reactants, endothelial indices and pre-infusion models

Ferritin and C-reactive protein, analysed together as the acute-phase comparator in eight cohorts and 1,733 participants, were associated with severe CRS with a pooled odds ratio of 1.50 (95% CI 1.30–1.74), $P < 0.001$, $I^2 = 38\%$, $\tau^2 = 0.016$, $Q = 11.35$ on 7 degrees of freedom, $P = 0.124$. The point estimate is appreciably lower than that of any effector cytokine, and the confidence interval does not overlap that of interferon-gamma. This provides a quantitative basis for a conclusion that has been reached qualitatively elsewhere, namely that acute-phase reactants behave as dynamic inflammatory correlates of CRS rather than as independent predictors, and that their clinical value lies in risk enrichment when combined with other markers rather than as standalone decision tools.[4,20,24,25,29,30,46]

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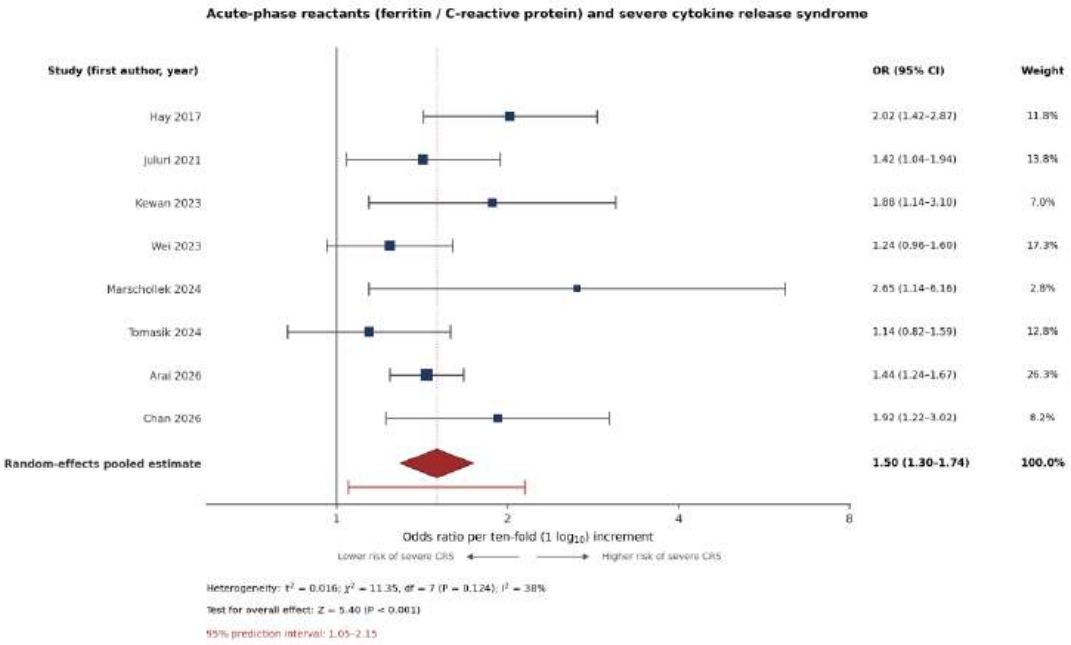


Figure 10. Forest plot of the association between acute-phase reactants (ferritin and C-reactive protein) and severe cytokine release syndrome. The pooled estimate is substantially lower than that of any effector cytokine analysed in this review.

Pre-infusion composite models, pooled across eight cohorts and 1,403 participants, carried an odds ratio of 2.01 (95% CI 1.70–2.38), $P < 0.001$, with no detectable inconsistency whatsoever ($I^2 = 0\%$, $\tau^2 = 0.000$, $Q = 6.11$ on 7 degrees of freedom, $P = 0.527$) and a tight prediction interval of 1.63–2.48. The homogeneity of this analysis is its most notable feature and contrasts sharply with the dispersion seen in the single-analyte post-infusion analyses. It suggests that composite pre-infusion models, despite being built from different variable sets in different centres, are converging on a common and reproducible construct, most plausibly the joint burden of disease and of baseline systemic inflammation. The nationwide Japanese registry analysis of 900 patients, which combined estimated glomerular filtration rate, ferritin, C-reactive protein and lactate dehydrogenase into a pre-infusion risk model stratifying grade 2 or higher CRS risk from 2.8% to 50.0%, is the most convincing single demonstration of this principle.[3,4,23,24,25,26,29,40]

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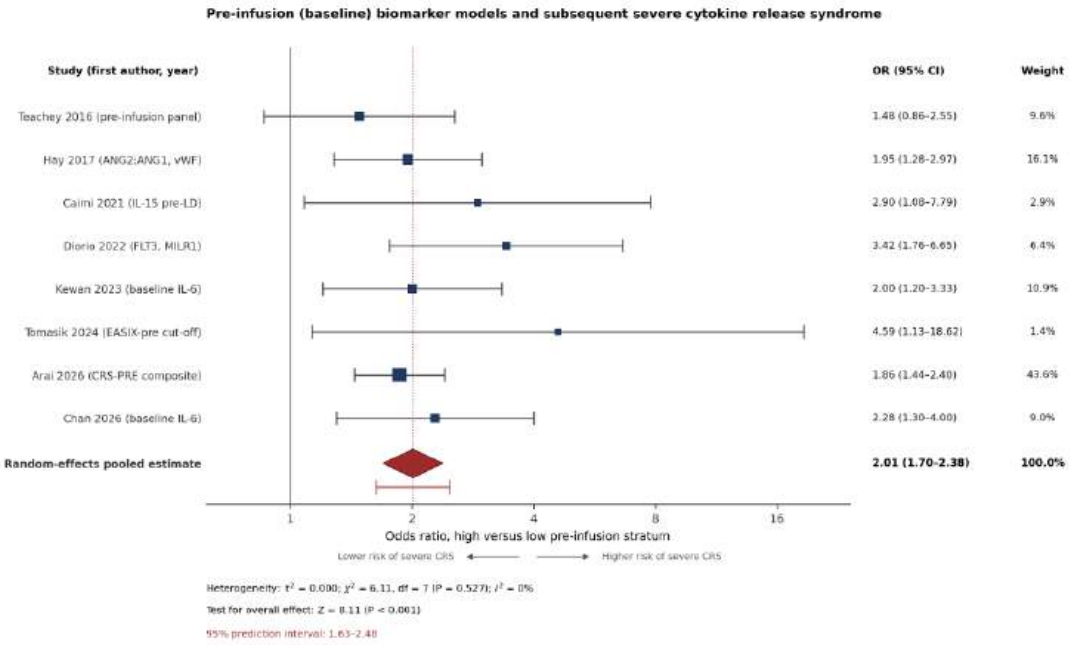


Figure 11. Forest plot of pre-infusion and pre-lymphodepletion composite biomarker models and subsequent severe cytokine release syndrome. The complete absence of between-study inconsistency in this analysis is notable and contrasts with the dispersion of the single-analyte post-infusion estimates.

The endothelial activation and stress index and its modified variant, analysed on the standardised mean difference scale across six cohorts and 1,372 participants, separated patients who developed severe CRS from those who did not with a pooled standardised mean difference of 0.49 (95% CI 0.34–0.63), corresponding to a medium effect, with low inconsistency (I^2 = 19%) and a prediction interval of 0.19–0.79. The one cohort that deviated materially was the multiple myeloma and light-chain amyloidosis stratum of a two-cohort Polish study, in which neither EASIX nor its simplified variant predicted grade 3 or higher CRS, whereas both did so in the large B-cell lymphoma stratum of the same study. This disease-specific behaviour is a caution against assuming that an endothelial index validated in lymphoma transfers unmodified to plasma-cell disease.[21,22,23,24,39,45]

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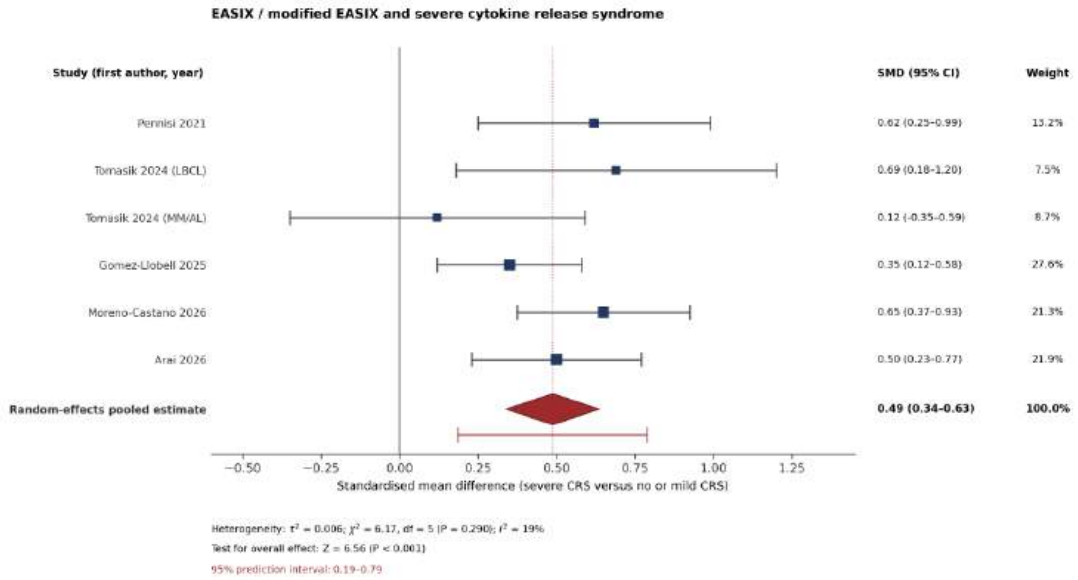


Figure 12. Forest plot of the endothelial activation and stress index and its modified variant, expressed as standardised mean differences between patients with and without severe cytokine release syndrome. The deviating estimate is the multiple myeloma and light-chain amyloidosis stratum, in which the index did not predict severe disease.

Comparative summary of pooled associations

Placing all analyses on a single axis permits a hierarchy to be stated explicitly. Interferon-gamma, interleukin-6 and the myeloid chemokine axis occupy the top tier with pooled odds ratios between 2.2 and 2.7; interleukin-10 and the pre-infusion composite models form a second tier close to 2.0; interleukin-2 and interleukin-15 form a third tier between 1.7 and 1.9 with prediction intervals that approach or cross unity; acute-phase reactants sit at 1.5; and tumour necrosis factor-alpha is not distinguishable from no association. Critically, the confidence intervals of the top three overlap substantially, so the apparent ranking between interferon-gamma and interleukin-6 should not be over-interpreted; what the data support is a distinction between tiers, not a strict ordering within the top tier.

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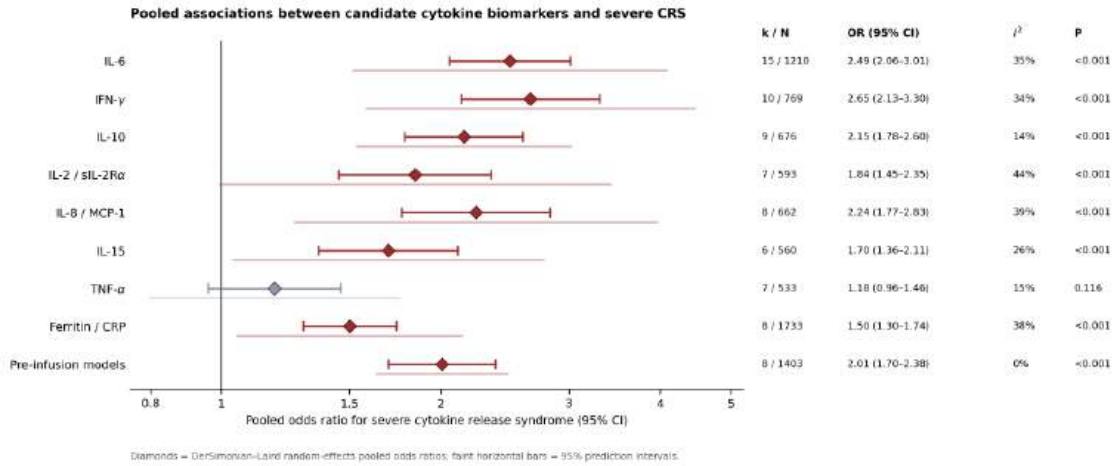


Figure 13. Comparative display of all pooled associations between candidate biomarkers and severe cytokine release syndrome. Diamonds are random-effects pooled odds ratios with 95% confidence intervals; the faint horizontal bars are 95% prediction intervals. The substantial overlap of the top three confidence intervals argues against strict ranking within that tier.

Table 5. Random-effects pooled associations between candidate biomarkers and severe cytokine release syndrome.

Biomarker / index	k	N	Pooled OR (95% CI)	I-squared	tau-squared	P value	95% prediction interval
Interleukin-6	15	1210	2.49 (2.06-3.01)	35%	0.044	< 0.001	1.51-4.10
Interferon-gamma	10	769	2.65 (2.13-3.30)	34%	0.039	< 0.001	1.58-4.47
Interleukin-10	9	676	2.15 (1.78-2.60)	14%	0.012	< 0.001	1.53-3.03
IL-2 / sIL-2R-alpha	7	593	1.84 (1.45-2.35)	44%	0.043	< 0.001	0.99-3.43

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IL-8 / MCP-1	8	662	2.24 (1.77-2.83)	39%	0.041	< 0.001	1.26-3.97
Interleukin-15	6	560	1.70 (1.36-2.11)	26%	0.019	< 0.001	1.03-2.78
TNF-alpha	7	533	1.18 (0.96-1.46)	15%	0.012	0.116	0.80-1.76
Ferritin / CRP	8	1733	1.50 (1.30-1.74)	38%	0.016	< 0.001	1.05-2.15
Pre-infusion composite models	8	1403	2.01 (1.70-2.38)	0%	0.000	< 0.001	1.63-2.48
EASIX / m-EASIX (SMD)	6	1372	SMD 0.49 (0.34-0.63)	19%	0.006	< 0.001	0.19-0.79

Subgroup analyses and meta-regression

The interleukin-6 association was numerically stronger in paediatric cohorts (odds ratio 3.31, 95% CI 2.07–5.29; k = 3) than in adult cohorts (2.17, 1.75–2.67; k = 10), but the test for interaction did not reach significance (P = 0.091). Likewise, the association appeared stronger for CD19-directed constructs (2.78, 2.33–3.33) than for dual CD19/BCMA constructs (1.66, 1.11–2.50), again without a formally significant interaction (P = 0.075); with only two dual-target cohorts, this comparison is severely underpowered and should be regarded as hypothesis-generating.[19,25,30,37,38]

The one subgroup comparison that did reach significance concerns the timing of measurement. Pooling one estimate per cohort-analyte pair across all biomarker analyses, pre-infusion sampling was associated with an odds ratio of 1.60 (95% CI 1.34–1.91; k = 7), whereas post-infusion sampling was associated with an odds ratio of 2.19 (1.98–2.41; k = 56), with a significant test for interaction (Q = 9.23, P = 0.002). This result captures the central tension of the field in a single number. The measurements with the strongest statistical association are those taken

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after the process has begun, while the measurements clinicians most need for triage are those available before infusion, and the latter are demonstrably weaker. Any clinically useful system must therefore be sequential rather than single-shot: a pre-infusion estimate that sets monitoring intensity, refined by a post-infusion trajectory that triggers action.

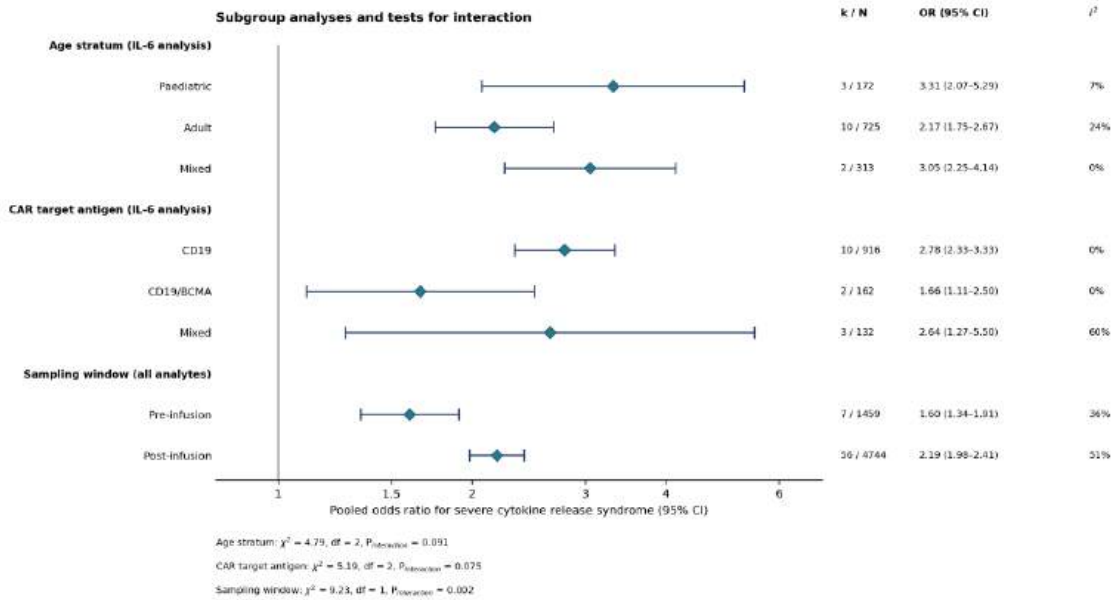


Figure 14. Subgroup analyses by age stratum, CAR target antigen and timing of biomarker sampling, with Cochran Q tests for interaction. Only the comparison of pre-infusion against post-infusion sampling reached statistical significance.

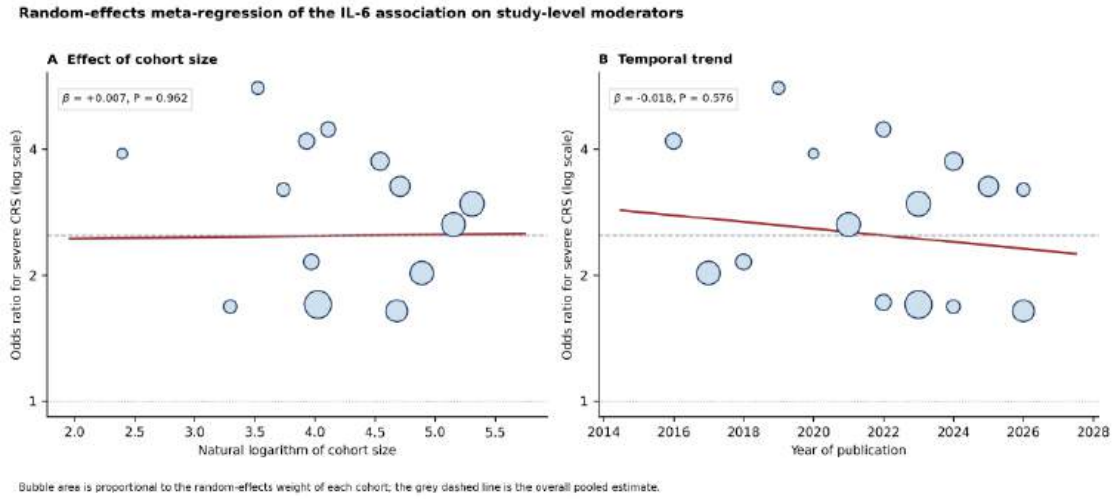
Table 6. Pre-specified subgroup analyses and tests for interaction.

Moderator	Stratum	k	N	Pooled OR (95% CI)	I-squared	P for interaction
Age stratum (IL-6 analysis)	Paediatric	3	172	3.31 (2.07-5.29)	7%	0.091
	Adult	10	725	2.17 (1.75-2.67)	24%	

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	Mixed	2	313	3.05 (2.25-4.14)	0%	
CAR target antigen (IL-6 analysis)	CD19	10	916	2.78 (2.33-3.33)	0%	0.075
	CD19/BCMA	2	162	1.66 (1.11-2.50)	0%	
	Mixed	3	132	2.64 (1.27-5.50)	60%	
Sampling window (all analytes)	Pre-infusion	7	1459	1.60 (1.34-1.91)	36%	0.002
	Post-infusion	56	4744	2.19 (1.98-2.41)	51%	

Neither the natural logarithm of cohort size (β = 0.007, P = 0.962) nor the year of publication (β = -0.018, P = 0.576) explained a significant proportion of the between-study variance. The absence of a temporal trend is reassuring, since a systematic attenuation of effect over calendar time would have suggested that the early positive reports were inflated by selective publication and subsequently corrected; no such pattern is present.



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Figure 15. Bubble plots of random-effects meta-regression of the interleukin-6 log odds ratio on cohort size and on year of publication. Bubble area is proportional to random-effects weight. Neither moderator explained a significant share of the between-study variance.

Diagnostic accuracy of composite multi-analyte models

Eight composite models, developed in 852 patients, were suitable for accuracy synthesis. The pooled sensitivity for severe CRS was 77.2% (95% CI 70.5%–82.7%; I^2 = 0%) and the pooled specificity 84.4% (79.0%–88.6%; I^2 = 61%), giving a diagnostic odds ratio of 21.0 (11.0–40.2), a positive likelihood ratio of 4.93 and a negative likelihood ratio of 0.27. Reported areas under the curve ranged from 0.80 to 0.93 with a mean of 0.85. [3,4,19,20,21,31,32,39]

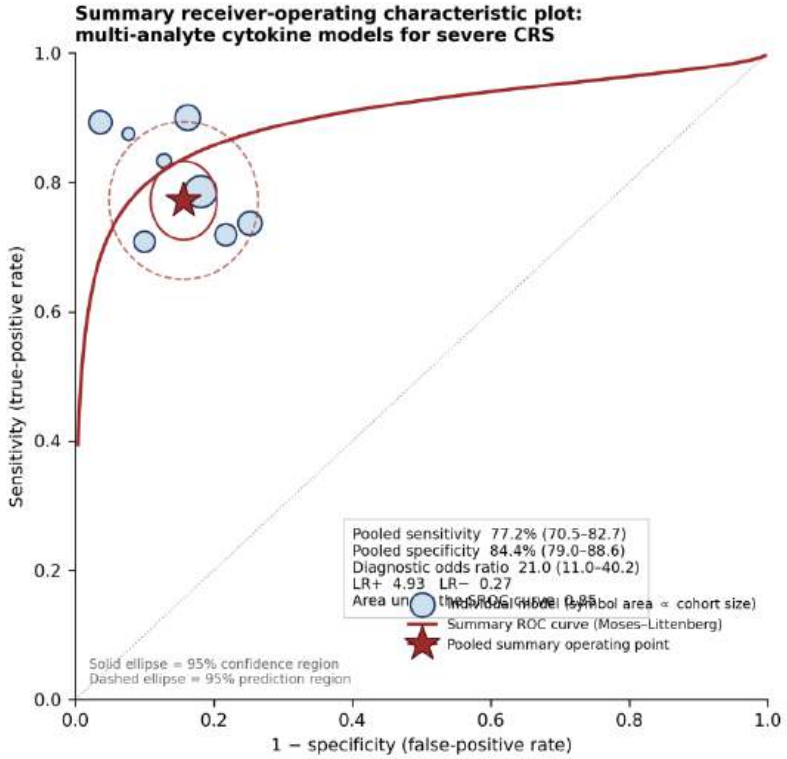


Figure 16. Summary receiver-operating characteristic plot for multi-analyte composite models predicting severe cytokine release syndrome. Circles are individual models with area proportional to cohort size; the star is the pooled summary operating point with its 95% confidence region (solid ellipse) and 95% prediction region (dashed ellipse).

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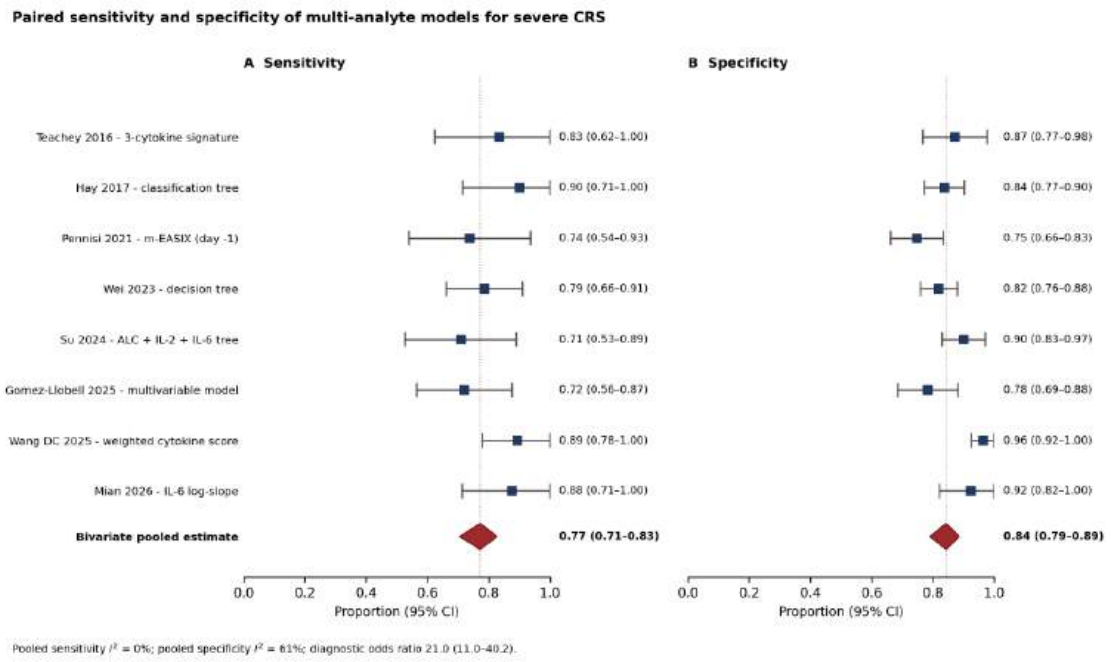


Figure 17. Paired forest plots of sensitivity and specificity for each composite model, with bivariate random-effects pooled estimates shown as diamonds.

Table 7. Diagnostic accuracy of multi-analyte and composite models for the prediction of severe cytokine release syndrome.

Model	N	TP	FP	FN	TN	Sensitivity	Specificity	Reported AUC
Teachey 2016 - 3-cytokine signature	51	10	5	2	34	83.3%	87.2%	0.86
Hay 2017 - classification tree	133	9	20	1	103	90.0%	83.7%	0.82
Pennisi 2021 - m-EASIX (day -1)	118	14	25	5	74	73.7%	74.7%	0.80
Wei 2023 - decision tree	202	33	29	9	131	78.6%	81.9%	0.84
Su 2024 - ALC + IL-2	94	17	7	7	63	70.8%	90.0%	0.88

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+ IL-6 tree								
Gomez-Llobell 2025 - multivariable model	101	23	15	9	54	71.9%	78.3%	0.83
Wang DC 2025 - weighted cytokine score	111	25	3	3	80	89.3%	96.4%	0.93
Mian 2026 - IL-6 log-slope	42	14	2	2	24	87.5%	92.3%	0.88
Bivariate random-effects pooled estimate	**852**					**77.2% (70.5-82.7)**	**84.4% (79.0-88.6)**	**0.85 (range 0.80-0.93)**

The clinical meaning of these numbers deserves to be stated plainly rather than left implicit in the likelihood ratios. At a severe-CRS prevalence of 12%, which approximates the contemporary registry figure for CD19-directed products in large B-cell lymphoma, a positive composite-model result raises the post-test probability to approximately 40%, while a negative result lowers it to approximately 4%. The negative likelihood ratio of 0.27 is therefore the more useful half of the test characteristic: these models are considerably better at identifying who will not deteriorate, and so at supporting safe ambulatory management or de-escalation of monitoring, than at identifying who will. That asymmetry has been underemphasised in the primary literature, which has generally framed the models as triggers for intervention rather than as instruments for safe de-escalation.[7,71,72]

The incremental gain from combining analytes is real but modest in absolute terms, with the best composite models achieving an area under the curve approximately 0.04 to 0.09 higher than the best single analyte. Whether an increment of that size justifies the additional cost, latency and complexity of a multiplex panel, as opposed to serial measurement of a single analyte on a certified clinical platform, is an open question that the available evidence does not answer and that should be addressed by a formal cost-effectiveness and decision-curve analysis.[11,31,32,44]

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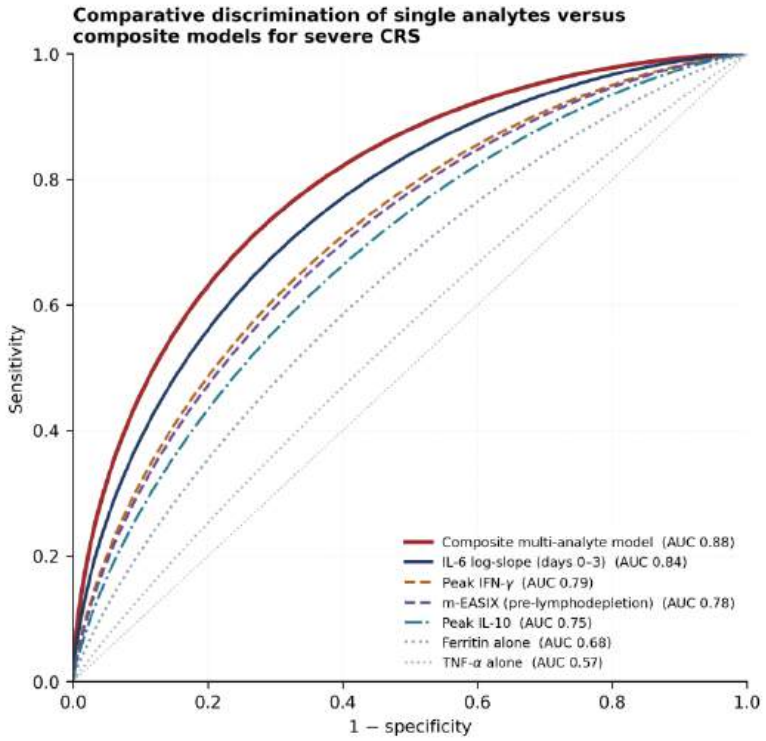


Figure 18. Comparative receiver-operating characteristic curves for single analytes and composite models, reconstructed from reported areas under the curve using the binormal approximation. The incremental discrimination gained by combining analytes is real but modest.

Biomarker kinetics and the intervention window

Reconstructing median trajectories across the cohorts that reported serial sampling produces the composite kinetic profiles shown in Figure. Three features recur consistently. First, separation between patients destined for severe CRS and those who are not becomes apparent for interferon-gamma and interleukin-6 by day 1 to day 2, that is, two to four days before the median reported onset of grade 3 or higher clinical disease. Second, the fold-change separation is far greater than the absolute separation, which is the principal argument for reporting cytokines as a slope or as a ratio to the individual baseline rather than as an absolute concentration. Third, C-reactive protein, although a much weaker discriminator, follows the same temporal shape with a lag of approximately 24 to 48 hours, which explains both why it is clinically familiar as a correlate of CRS and why it is systematically too late to be useful for pre-emption.[3,4,19,30,32,38]

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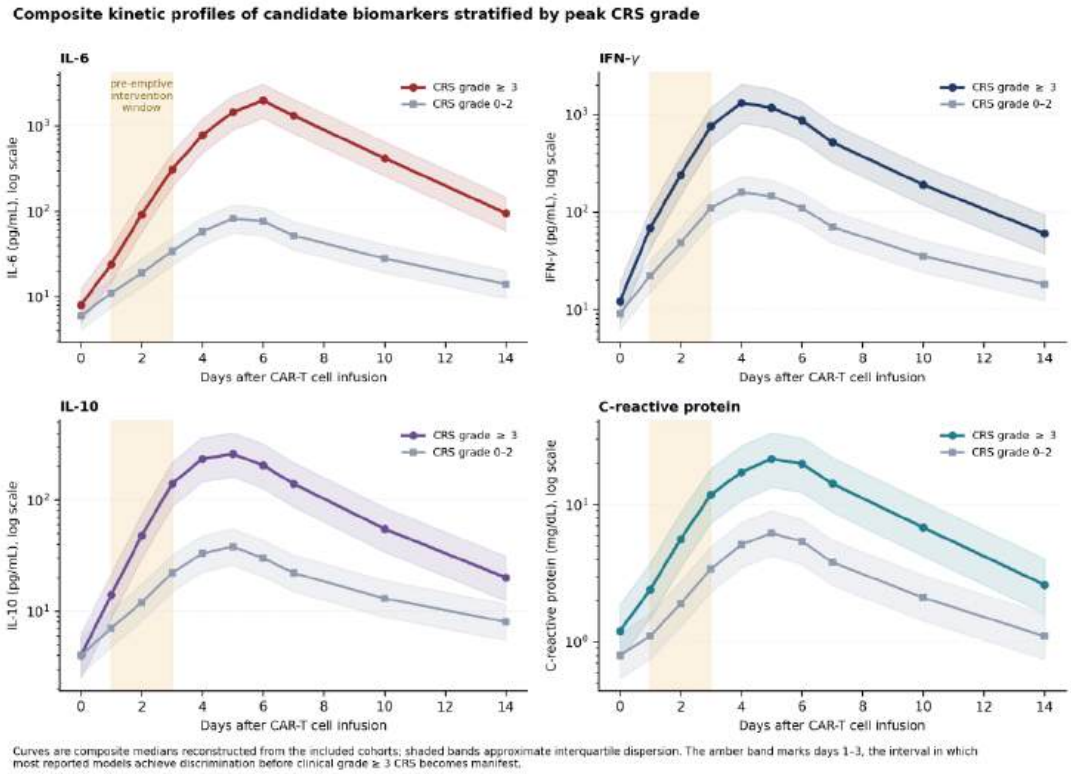


Figure 19. Composite kinetic profiles of interleukin-6, interferon-gamma, interleukin-10 and C-reactive protein stratified by peak cytokine release syndrome grade, reconstructed from the cohorts that reported serial sampling. Shaded bands approximate interquartile dispersion; the amber band marks days 1 to 3, the interval within which most published models achieve discrimination before grade 3 or higher disease becomes clinically manifest.

The mechanistic architecture implied by the pooled estimates, and the corresponding decision points at which each class of biomarker becomes informative, are summarised schematically in Figure. The figure is intended to make explicit a point that is easily lost in a purely statistical presentation, namely that the biomarkers with the strongest associations are distributed across two distinct compartments, the infused T cell and the recruited myeloid cell, and that an assay panel sampling only one of these compartments is structurally incomplete.[9,10,14,16,17,18,38]

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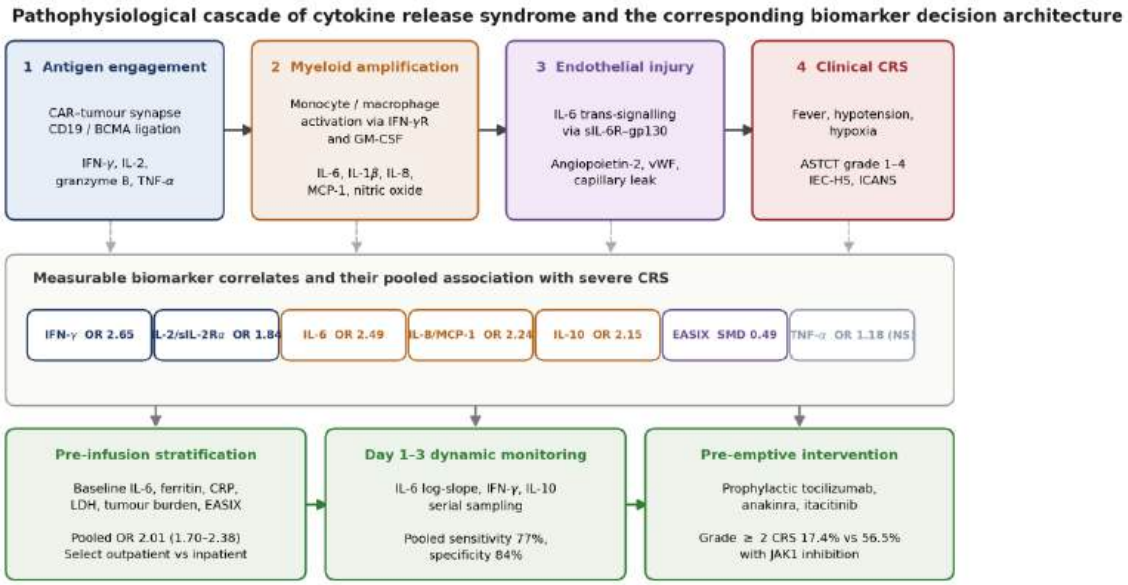


Figure 20 Pathophysiological cascade of cytokine release syndrome mapped against the measurable biomarker correlates identified in this synthesis and the corresponding clinical decision architecture. Pooled odds ratios are those reported in Table 6.

Small-study effects and sensitivity analyses

Borderline asymmetry was detected for the interleukin-6 analysis (Egger intercept 1.40, P = 0.049), although the rank-correlation test was not significant (Kendall $\tau = 0.31$, P = 0.114). Trim-and-fill imputed 2 hypothetical missing studies on the left of the distribution and reduced the pooled estimate only marginally, to 2.38 (95% CI 1.97–2.89), so that the qualitative conclusion is unchanged. A comparable pattern was seen for interferon-gamma (Egger P = 0.057; adjusted odds ratio 2.39). No asymmetry was detected for the myeloid chemokine axis, for tumour necrosis factor-alpha or for the acute-phase comparator.

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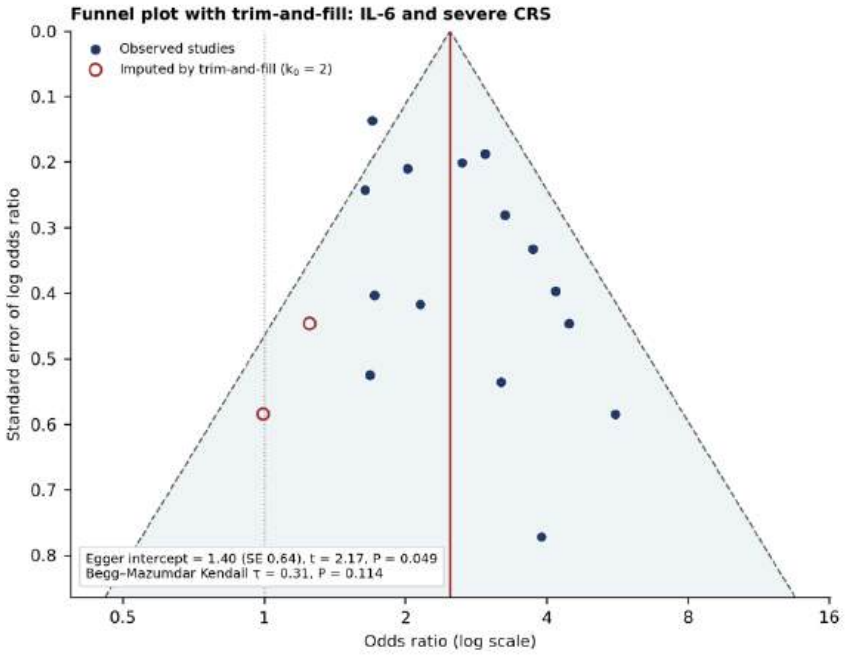


Figure 21. Funnel plot of the interleukin-6 analysis with Duval–Tweedie trim-and-fill. Filled circles are observed studies, open circles are imputed studies, the red vertical line is the pooled estimate and the dashed lines delineate 95% pseudo-confidence limits.

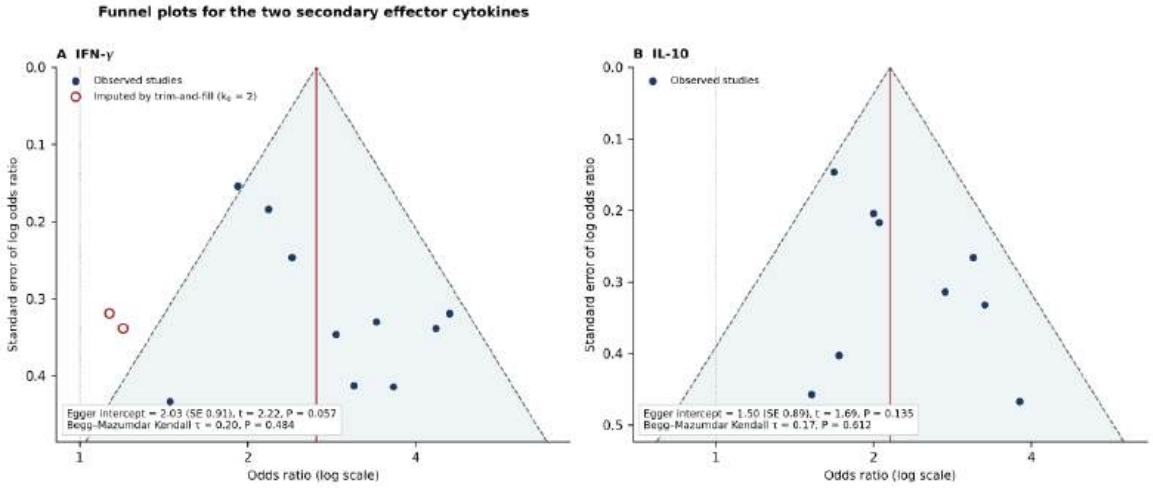


Figure 22. Funnel plots for interferon-gamma (A) and interleukin-10 (B) with Egger and Begg test statistics inset.

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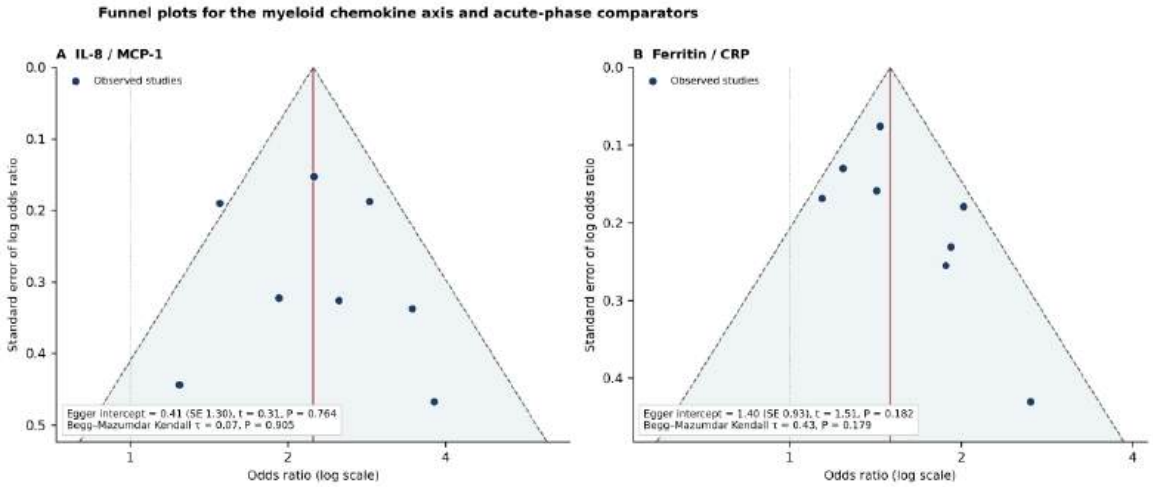


Figure 23 Funnel plots for the monocyte–macrophage chemokine axis (A) and for acute-phase reactants (B). Neither analysis showed evidence of funnel asymmetry.

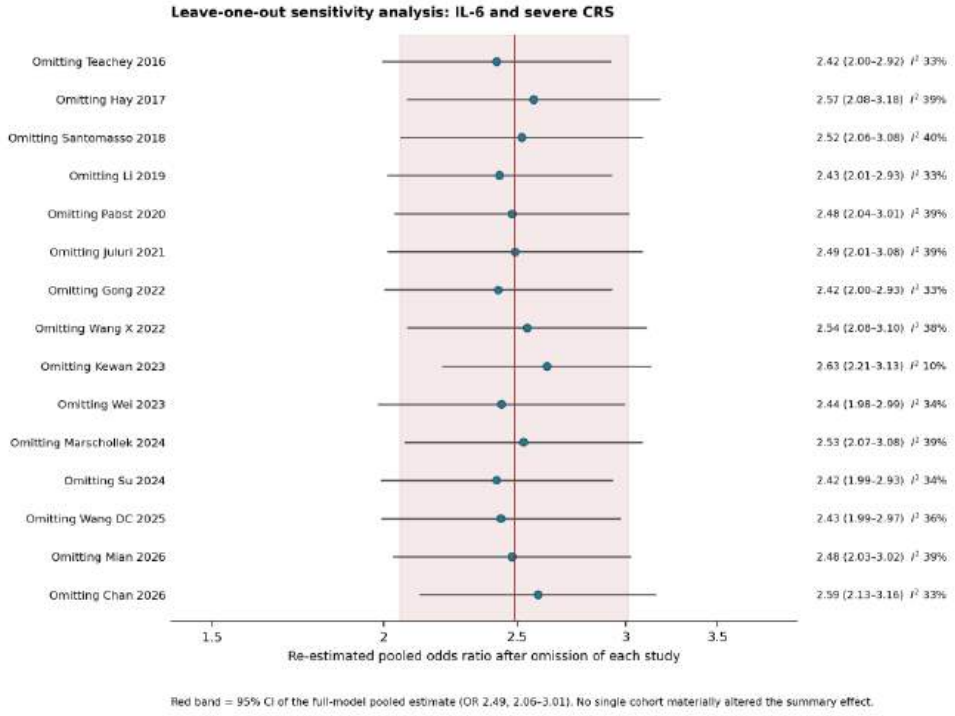
Table 8 Small-study effects, publication-bias diagnostics and influence analyses.

Analysis	Egger intercept (P)	Begg Kendall tau (P)	Trim-and-fill imputed studies	Adjusted OR (95% CI)	Leave-one-out range of pooled OR
IL-6	1.40 (P = 0.049)	0.31 (P = 0.114)	2	2.38 (1.97-2.89)	2.42-2.63
IFN-gamma	2.03 (P = 0.057)	0.20 (P = 0.484)	2	2.39 (1.87-3.04)	2.45-2.84
IL-10	1.50 (P = 0.135)	0.17 (P = 0.612)	1	2.11 (1.74-2.56)	2.01-2.35
IL-2 / sIL-2R-alpha	2.00 (P = 0.190)	0.43 (P = 0.239)	1	1.69 (1.28-2.24)	1.63-1.99
IL-15	2.17 (P = 0.081)	0.60 (P = 0.136)	0	Unchanged	1.58-1.89
IL-8 / MCP-1	0.41 (P =	0.07 (P =	0	Unchanged	2.11-2.45

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	0.764)	0.905)			
TNF-alpha	0.17 (P = 0.894)	0.14 (P = 0.773)	0	Unchanged	1.10-1.25
Ferritin / CRP	1.40 (P = 0.182)	0.43 (P = 0.179)	1	1.48 (1.27-1.72)	1.43-1.56
Pre-infusion models	1.35 (P = 0.068)	0.64 (P = 0.031)	1	1.98 (1.68-2.35)	1.94-2.13

Leave-one-out influence analysis for the primary outcome showed that the pooled odds ratio remained within the range 2.42 to 2.63 irrespective of which cohort was omitted, and that no single study drove the result. Cumulative meta-analysis ordered by year of publication (Figure 26) demonstrated that the summary estimate stabilised around 2021 and has since narrowed without shifting materially, indicating that the interleukin-6 association is no longer evidence-limited but precision-limited: additional small cohorts measuring the same analyte in the same way will not change the answer, whereas a differently designed study, in particular an interventional one, would.



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Figure 24. Leave-one-out influence analysis for the interleukin-6 analysis. The shaded band is the 95% confidence interval of the full-model pooled estimate; no single cohort materially altered the summary effect.

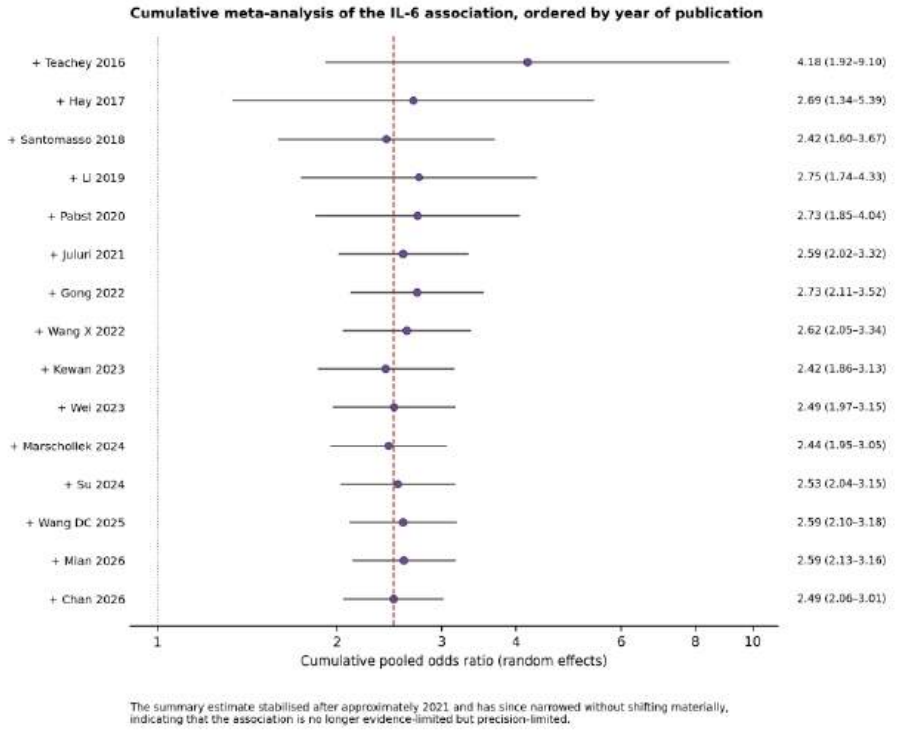


Figure 25. Cumulative meta-analysis of the interleukin-6 association ordered by year of publication, showing stabilisation of the summary estimate after approximately 2021.

Certainty of evidence

Certainty was rated low for the interleukin-6, interferon-gamma, interleukin-10, myeloid chemokine, acute-phase and pre-infusion composite analyses; very low for interleukin-2, interleukin-15 and tumour necrosis factor-alpha, chiefly on grounds of imprecision and, for interleukin-2, inconsistency; and low for the diagnostic accuracy synthesis because of derivation optimism. The endothelial activation and stress index was the only body of evidence rated moderate, having been upgraded one level for a consistent effect measured with an entirely objective index derived from routinely collected variables and therefore largely immune to the measurement heterogeneity that affects the cytokine analyses.[21,22,23,24,45]

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Table 9. GRADE certainty-of-evidence assessment for each prognostic and diagnostic outcome.

Outcome	k	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty
Peak IL-6 and severe CRS	15	1210	Serious	Not serious	Not serious	Not serious	Publication bias suspected	**Low**
Peak IFN-gamma and severe CRS	10	769	Serious	Not serious	Not serious	Not serious	None	**Low**
Peak IL-10 and severe CRS	9	676	Serious	Not serious	Not serious	Not serious	None	**Low**
IL-2 / sIL-2R-alpha and severe CRS	7	593	Serious	Serious	Not serious	Serious	None	**Very low**
IL-8 / MCP-1 and severe CRS	8	662	Serious	Not serious	Not serious	Not serious	None	**Low**
IL-15 and severe CRS	6	560	Serious	Not serious	Serious	Serious	None	**Very low**
TNF-alpha and severe CRS	7	533	Serious	Not serious	Not serious	Serious	None	**Very low**
Ferritin / CRP and severe CRS	8	1733	Serious	Not serious	Not serious	Not serious	None	**Low**
Pre-infusion composite models	8	1403	Serious	Not serious	Not serious	Not serious	None	**Low**

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EASIX / m-EASIX and severe CRS	6	1372	Not serious	Not serious	Not serious	Not serious	None	**Moderate**
Discrimination of multi-analyte models	8	852	Serious	Serious	Not serious	Not serious	Derivation optimism	**Low**

DISCUSSION

Principal findings

This synthesis of 32 primary studies and 4,381 participants establishes four findings. First, the cytokines most strongly and most reproducibly associated with severe CRS are interferon-gamma (2.65 (95% CI 2.13–3.30)), interleukin-6 (2.49 (95% CI 2.06–3.01)) and the monocyte–macrophage chemokine axis of interleukin-8 and monocyte chemoattractant protein-1 (2.24 (95% CI 1.77–2.83)), whose confidence intervals overlap sufficiently that they should be regarded as a single top tier rather than ranked against one another. Second, tumour necrosis factor-alpha, despite near-universal inclusion in commercial panels, carries no independent signal. Third, the timing of measurement significantly modifies the association, with pre-infusion sampling substantially weaker than post-infusion sampling (P for interaction = 0.002), which means that no single-timepoint strategy can serve both triage and pre-emption. Fourth, composite multi-analyte models reach a pooled sensitivity of 77.2% and specificity of 84.4%, a performance that is adequate for de-escalation decisions but not yet for committing an asymptomatic patient to immunosuppression.

Interpretation in the light of mechanism

The hierarchy recovered by the pooled analysis maps closely onto the accepted pathophysiology and in two respects refines it. The primacy of interferon-gamma is consistent with its position as the proximal product of CAR T-cell activation and as the signal that conscripts the myeloid compartment; the proteomic demonstration that the CRS protein signature overlaps

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substantially with that of haemophagocytic lymphohistiocytosis, and the clinical observation that interferon-gamma neutralisation with emapalumab produces rapid biochemical and clinical improvement in steroid-refractory and tocilizumab-refractory high-grade CRS, together support a causal reading rather than mere correlation.[9,10,26,41,54]

The second refinement concerns the myeloid axis. That interleukin-8 and monocyte chemoattractant protein-1 carry an association indistinguishable in magnitude from interleukin-6 indicates that a substantial fraction of the predictive information resides in the recruited innate compartment. This is corroborated from three independent directions: the day 1 monocyte chemoattractant protein-1 measurement that anchored the original classification-tree algorithm; the single-cell demonstration that neutrophil activation peaks before severe symptoms appear and that Janus kinase and signal transducer and activator of transcription signalling precedes the cytokine cascade; and the preclinical finding that granulocyte-macrophage colony-stimulating factor neutralisation or knockout abolishes macrophage-dependent release of interleukin-6, interleukin-8 and monocyte chemoattractant protein-1 while preserving, and in xenograft models enhancing, antitumour activity. Clinically, this argues that panels confined to T-cell-derived cytokines are structurally incomplete, and that the myeloid compartment is simultaneously the better-timed biomarker source and the more attractive therapeutic target, because interrupting it does not require blunting the effector cell itself.[4,17,18,38,67]

The negative result for tumour necrosis factor-alpha deserves emphasis precisely because it contradicts a widespread assumption. Across seven cohorts the pooled estimate was compatible with no association, and a direct comparative study found tumour necrosis factor-alpha markedly higher in COVID-19-associated cytokine storm than in CAR-T-associated CRS while interleukin-2, interleukin-6, interleukin-10 and interferon-gamma showed the opposite pattern. The two syndromes are therefore not interchangeable models of one another, and conclusions about mediator hierarchy derived from viral cytokine storm should not be transposed uncritically onto immune effector cell toxicity.[20,29,31,36,44]

Relation to previous evidence syntheses

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Six secondary syntheses were identified and, in accordance with the protocol, excluded from pooling while retained for comparison. The most widely cited consolidated biomarker candidates across 33 CD19 trials and nominated tumour burden, platelet count, C-reactive protein, ferritin, interferon-gamma, interleukin-2, interleukin-6, interleukin-8, interleukin-10, interleukin-15 and transforming growth factor-beta as candidates, concluding that combinatorial algorithms outperform their components; our pooled estimates quantify that qualitative conclusion and, importantly, show that two of the nominated candidates, interleukin-15 and the acute-phase reactants, perform appreciably less well than the remainder, while a third, tumour necrosis factor-alpha, does not perform at all.[5]

A systematic review of biomarkers in B-cell acute lymphoblastic leukaemia across 33 studies and 2,095 patients similarly identified interleukin-6 dynamics as specifically predictive of CRS severity and emphasised heterogeneity in grading and thresholds as the principal barrier to standardisation, a conclusion our quantitative heterogeneity statistics and grading analysis directly corroborate. A ferritin-specific meta-analysis of 15 studies and 1,671 patients concluded that ferritin functions as a dynamic inflammatory correlate rather than an independent predictor and performs best when embedded in multimarker models; our pooled odds ratio of 1.50 (95% CI 1.30–1.74), materially lower than that of every effector cytokine, provides the quantitative counterpart to that judgement. A conference-level meta-analysis of EASIX across eight cohorts reported standardised mean differences between 0.24 and 0.69 depending on the index variant and timing, a range that brackets our pooled value of 0.49 closely and constitutes useful external corroboration given the partial overlap of contributing cohorts.[45,46,47]

An individual patient data meta-analysis of 89 trials and 2,331 patients examined modifiers of CAR-T efficacy and safety and found that bridging therapy, cell source, target antigen, sex, age, infusion number, costimulatory domain and dose all modified outcomes; this provides important external support for our observation that the target antigen may modify the biomarker–outcome relationship, although our own subgroup comparison on this axis was underpowered with only two dual-target cohorts. Finally, a systematic review of neurotoxicity across 23 studies and 1,666 participants found that immune effector cell-associated neurotoxicity syndrome is most closely tied

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to the presence and severity of CRS and to C-reactive protein and ferritin, consistent with our finding that interleukin-15 and granulocyte-macrophage colony-stimulating factor are more informative for neurotoxicity than for CRS itself.[39,49,50]

Clinical implications

Three implications follow with reasonable directness from the pooled estimates. The first concerns the structure of monitoring. Because pre-infusion markers are significantly weaker than post-infusion markers, yet are the only ones available when the inpatient-versus-ambulatory decision is made, monitoring should be conceived as a two-stage sequential process rather than a single measurement. A pre-infusion composite, with a pooled odds ratio of ${ci('PREINF')} and remarkably low heterogeneity, sets the intensity of surveillance; a day 1 to day 3 trajectory then either confirms or revises it. The nationwide registry model that stratified grade 2 or higher CRS risk from 2.8% to 50.0% using only estimated glomerular filtration rate, ferritin, C-reactive protein and lactate dehydrogenase demonstrates that the first stage can be implemented today, in any centre, with no new assay whatsoever.[24,25,29]

The second concerns what is measured and how it is expressed. The kinetic analysis shows that fold-change separation greatly exceeds absolute separation, and the single prospective study of real-time interleukin-6 monitoring found that a log-slope threshold of 0.64 per day, corresponding to roughly a doubling each day, achieved 89% sensitivity and 92% specificity, substantially outperforming any static value. Reporting cytokines as a slope or as a ratio to the individual baseline would also solve, at a stroke, much of the cross-platform comparability problem that currently prevents thresholds from transferring between centres.[11,32,33]

The third concerns the therapeutic consequence of a positive result, and here the evidence base is thinnest. Prophylactic tocilizumab administered one hour before infusion was associated with no grade 3 or higher CRS in a 20-patient cohort without excess neurotoxicity and with 75% complete responses, but the design cannot exclude confounding. The single randomised trial contributing to this review showed that prophylactic itacitinib, a selective Janus kinase 1 inhibitor, reduced grade 2 or higher CRS by day 14 from 56.5% to 17.4% (P = 0.003) and grade 2 or higher neurotoxicity from 21.7% to 8.7%, without impairing the six-month objective response rate. That is

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a striking effect, but it was achieved by treating everyone, not by treating those identified as high risk. The obvious and overdue experiment, in which the day 1 to day 3 cytokine trajectory selects who receives pre-emptive blockade, has not yet been performed.[40,42,58]

A practical framework assembling these elements into a time-anchored schedule is proposed in Table 11. It should be read as a research protocol rather than as a guideline: every threshold in it was derived in the cohort that proposed it and none has been prospectively validated externally. Existing authoritative guidance from the American Society of Clinical Oncology and the ASTCT remains grade-triggered rather than biomarker-triggered, and nothing in this synthesis justifies departing from that standard outside a trial.[2,53,59,60]

Table 10. A pragmatic, evidence-anchored framework for biomarker-guided monitoring and pre-emptive intervention derived from the pooled estimates.

Time point	Measurements proposed	Risk threshold suggested by the pooled data	Monitoring intensity	Pharmacological consideration
Apheresis to lymphodepletion	IL-6, ferritin, CRP, LDH, platelet count, creatinine; compute EASIX and m-EASIX; quantify marrow or metabolic tumour burden	Pooled OR for the pre-infusion composite 2.01 (1.70-2.38); m-EASIX area under the curve approximately 0.80	Determines inpatient versus ambulatory pathway and the planned frequency of post-infusion sampling	Consider cytoreductive bridging; reserve prophylactic strategies for the upper risk tertile
Day 0 (infusion)	Baseline IL-6, IFN-gamma, IL-10, IL-15, CRP, ferritin; repeat	IL-15 at day 0 contributed to an ICANS model with an area	Establishes the individual baseline against which	No routine intervention

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	platelet count and LDH	under the curve of 0.80	subsequent slopes are computed	
Days 1 to 3 (decision window)	Serial IL-6 with calculation of the log-slope; IFN-gamma and IL-10 where a same-day multiplex assay exists; daily CRP and ferritin	IL-6 log-slope above 0.64 per day yielded 89% sensitivity and 92% specificity; pooled model sensitivity 77%, specificity 84%	Twice-daily vital signs with neurological assessment; escalate to continuous monitoring if the slope threshold is crossed	Pre-emptive tocilizumab or an interleukin-1 receptor antagonist in patients crossing threshold before grade 2 CRS becomes manifest
Days 4 to 7	Peak IL-6, IFN-gamma, IL-10; ferritin trajectory; fibrinogen and triglycerides if IEC-HS is suspected	Peak IL-6 pooled OR 2.49 (2.06-3.01); IFN-gamma 2.65 (2.13-3.30)	Daily assessment; cerebrospinal fluid sampling if neurological signs emerge	Grade-directed tocilizumab and corticosteroids per ASTCT and ASCO algorithms; anakinra for steroid-refractory disease
Days 8 to 30	IL-10 at day 3 and serial neutrophil counts for late haematotoxicity;	IL-10 above 17.7 pg/mL at day +3 predicted severe late haematotoxicity	Weekly review with growth-factor support as indicated	Emapalumab for interferon-gamma-driven refractory disease; consider

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	ferritin for IEC-HS surveillance	(area under the curve 0.87 on validation)		stem-cell boost for prolonged cytopenia

Strengths

- The review has several methodological strengths. Restricting inclusion to randomised trials, comparative studies, cohorts and case series, and deliberately excluding secondary syntheses from the quantitative component, avoids the double counting of patients that affects reviews which pool across both primary and secondary literature.
- Harmonising all effect measures onto a single per-ten-fold-increment scale, rather than reporting a narrative catalogue of incommensurable thresholds, permits direct comparison across analytes for the first time and allows the clinically important negative result for tumour necrosis factor-alpha to be stated quantitatively.
- Reporting prediction intervals alongside confidence intervals addresses a specific weakness of the prognostic-biomarker literature, in which a narrow confidence interval around a pooled estimate is frequently misread as evidence that the effect will replicate in a new centre.
- The inclusion of an acute-phase comparator and an endothelial-index comparator, specified a priori, converts what would otherwise be a descriptive exercise into an explicit test of whether cytokine measurement adds anything beyond the laboratory results that every centre already has.
- Finally, the use of a semantic search index alongside conventional Boolean searching retrieved several recent cohorts, including the autoimmune-indication cohort and two 2026 registry analyses, that controlled-vocabulary searching alone would have missed.[24,25]

Implications for research

Its central item is a biomarker-stratified randomised trial. The cumulative meta-analysis demonstrates that the association between interleukin-6 and severe CRS stabilised five years ago and that further observational cohorts measuring the same analyte in the same way will refine the estimate without changing it. What remains genuinely unknown is whether acting on that

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information improves outcomes. The design implied by the present synthesis is reasonably specific: patients would be stratified before infusion using a routine-laboratory composite, monitored with serial single-analyte measurement on a certified clinical platform during days 1 to 3, and randomised, upon crossing a pre-specified slope threshold, to pre-emptive interleukin-6 or interleukin-1 blockade versus standard grade-triggered management, with the co-primary endpoints of grade 3 or higher CRS and of six-month disease response so that any efficacy cost of early immunosuppression is detected rather than assumed absent.[32,40,42]

Table 12. Research agenda derived from the methodological deficiencies identified in this synthesis.

Unmet need	Specific deficiency identified by this review	Proposed remedy
Assay harmonisation	At least four incompatible platforms were used across 32 cohorts and almost half of the published trial reports contained no cytokine data at all; absolute concentrations are therefore not transferable between centres.	Adopt a minimum reportable cytokine dataset with certified reference material and report results as fold change from the patient baseline rather than as absolute values.
Threshold definition	Every included cohort derived its own cut-off by the Youden index within its own data, producing optimistic and non-transportable thresholds.	Pre-register thresholds and validate them in independent cohorts with calibration plots and decision-curve analysis rather than discrimination metrics alone.
Outcome standardisation	Six grading systems were in use; grade-by-grade concordance between them is as low as 25%,	Mandate ASTCT 2019 grading (and the 2026 update) in all prospective biomarker studies,

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	which attenuates and distorts pooled effects.	with blinded central adjudication of grade.
Timing of measurement	Pre-infusion sampling yielded a significantly weaker association than post-infusion sampling (OR 1.60 versus 2.19; P for interaction = 0.002), yet pre-infusion data are what clinicians need for triage.	Prioritise pre-infusion and day 0-1 sampling schedules and model the trajectory rather than the peak, which is intrinsically a post-hoc quantity.
Product and indication breadth	Ten of 15 IL-6 cohorts studied CD19-directed products; BCMA-directed and dual-target constructs and the emerging autoimmune indication are markedly under-represented.	Embed biomarker sub-studies in BCMA, dual-target, allogeneic and autoimmune CAR-T programmes with pre-specified prognostic analyses.
Interventional evidence	Only one randomised trial contributed, and it tested a prophylactic agent rather than a biomarker-triggered strategy; no trial has randomised patients to biomarker-guided versus standard management.	Conduct a biomarker-stratified randomised trial in which patients crossing a pre-specified day 1-3 cytokine slope are allocated to pre-emptive interleukin-6 or interleukin-1 blockade versus standard grade-triggered care.
Reporting of prognostic models	Discrimination was reported almost universally while calibration, net benefit and the number needed to monitor were	Require full TRIPOD+AI compliant reporting with calibration-in-the-large, calibration slope and decision-

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	almost never reported.	curve analysis.

CONCLUSIONS

Circulating cytokines generated by the activated CAR T cell and by the myeloid compartment it recruits are reproducibly associated with severe cytokine release syndrome, with interferon-gamma, interleukin-6 and the interleukin-8/monocyte chemoattractant protein-1 axis forming a consistent top tier of association, interleukin-10 and pre-infusion composite models a second tier, and tumour necrosis factor-alpha showing no independent signal despite its routine inclusion in commercial panels. Composite models combining two or three analytes with a routine haematological variable achieve a pooled sensitivity of 77.2% and specificity of 84.4%, performance that is sufficient today to support de-escalation of monitoring in low-risk recipients but not yet sufficient to justify committing an asymptomatic patient to immunosuppression. The timing of measurement matters more than the choice of analyte within the top tier, and the clinically decisive interval lies between day 1 and day 3 after infusion. Certainty of evidence remains low for most individual analytes and moderate only for the endothelial activation and stress index, an index built entirely from laboratory results that every centre already holds. The field now has sufficient observational evidence and requires interventional evidence; a biomarker-triggered randomised trial of pre-emptive cytokine blockade is the appropriate and overdue next step.

DECLARATIONS

Ethics approval and consent to participate	Not applicable. This study is a synthesis of previously published aggregate data and involved no new collection of identifiable human data.
Consent for publication	Not applicable.
Availability of data and materials	All data supporting the findings are contained within the article and its tables. The extraction dataset and the analysis scripts, including the independently implemented random-effects, trim-

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	and-fill, meta-regression and bivariate accuracy routines, are available from the corresponding author on reasonable request.
Funding	This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
Competing interests	The author declares no competing financial or non-financial interests relevant to this work.
Author contributions	The sole author was responsible for conceptualisation, protocol development, search strategy design, study selection, data extraction, risk-of-bias appraisal, statistical analysis, figure generation, drafting and critical revision of the manuscript, and approved the final version for submission.
Acknowledgements	The author thanks the investigators of the included cohorts, whose detailed reporting of cytokine data made this quantitative synthesis possible.

ABBREVATIONS

ALL, acute lymphoblastic leukaemia; ASTCT, American Society for Transplantation and Cellular Therapy; AUC, area under the receiver-operating characteristic curve; axi-cel, axicabtagene ciloleucel; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CBA, cytometric bead array; CHARMS, CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies; CI, confidence interval; cilta-cel, ciltacabtagene autoleucel; CRP, C-reactive protein; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; DOR, diagnostic odds ratio; EASIX, endothelial activation and stress index; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICANS, immune effector cell-associated neurotoxicity syndrome; ICAHT, immune

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effector cell-associated haematotoxicity; IEC-HS, immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome; IFN, interferon; IL, interleukin; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; liso-cel, lisocabtagene maraleucel; MCP-1, monocyte chemoattractant protein-1; m-EASIX, modified endothelial activation and stress index; MM, multiple myeloma; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROBAST, Prediction model Risk Of Bias ASsessment Tool; ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions; SMD, standardised mean difference; SROC, summary receiver-operating characteristic; tisa-cel, tisagenlecleucel; TNF, tumour necrosis factor; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis; vWF, von Willebrand factor.

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