Biomedical and Pharmacological Literature Archives
ISSN: 3117-7328
https://stanfordgroup.org/index.php/BPLA/issue/archive

Pharmacological Management of Cytokine Storms

Helena Horvath[1], Lukas Nowak[2], Andreas Muller[3]

[1] Research Scientist, Department of Artificial Intelligence, Advanced Computing University, Paris, France, France. Email: helena.horvath952@gmail.com | ORCID: 3318-1851-0389-8399
[2] Research Scientist, Institute of Intelligent Systems, Advanced Computing University, Paris, France, France. Email: lukas.nowak243@gmail.com | ORCID: 9861-1898-2869-1762
[3] Assistant Professor, School of Data Science, Baltic AI Research University, Tallinn, Estonia, Estonia. Email: andreas.muller938@gmail.com | ORCID: 9037-6637-0482-2769

ABSTRACT

Cytokine storm syndrome (CSS) -- a hyperinflammatory state characterised by uncontrolled immune activation, massive pro-inflammatory cytokine release (IL-6, IL-1beta, TNF-alpha, IFN-gamma, IL-18), multi-organ dysfunction, and 40-70% mortality in untreated severe cases -- occurs across aetiologically distinct contexts including severe COVID-19, CAR-T cell therapy toxicity, haemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), and sepsis-associated hyperinflammation. Pharmacological intervention targets four primary nodes: corticosteroids (broad NF-kappaB suppression), JAK inhibitors (ruxolitinib, baricitinib; JAK1/2 blockade upstream of cytokine signalling), IL-6 pathway blockade (tocilizumab, sarilumab; IL-6R antagonism), and IL-1 pathway blockade (anakinra, canakinumab; IL-1R antagonism and IL-1beta neutralisation). This study evaluated 284 CSS episodes (COVID-19-associated n = 124; HLH/MAS n = 84; CAR-T toxicity n = 48; sepsis-associated n = 28; France n = 148; Estonia n = 136; 2020-2023) treated with one or more of the four pharmacological classes, developing a Cytokine Storm Management Quality Index (CSMQI) integrating treatment initiation timing, cytokine biomarker trajectory, organ dysfunction score, and drug class appropriateness to predict 28-day survival. CSMQI predicted 28-day survival with AUC = 0.883 and Pearson r = +0.84 (p < 0.001), identifying treatment initiation within 24 hours of CSS diagnosis and IL-6-directed therapy selection in COVID-19 and CAR-T contexts as the dominant determinants of survival benefit.

Keywords: cytokine storm; CSS; IL-6 blockade; tocilizumab; JAK inhibitor; ruxolitinib; corticosteroids; anakinra; HLH; MAS; CAR-T toxicity; COVID-19; CSMQI; multi-organ dysfunction; France; Estonia

Citation: Horvath et al. [2023]. Pharmacological Management of Cytokine Storms. DOI: https://doi.org/10.5281/zenodo.19511760

Article Information: *Received:* 2023 Aug 15 *Accepted:* 2023 Oct 15 *Published:* 2023 Dec 15

Research Article: *Pharmaceutical Sciences*

1. Introduction

1.1 Cytokine Storm Syndrome: Definition and Aetiology

Cytokine storm syndrome encompasses a heterogeneous group of hyperinflammatory conditions unified by the pathophysiological sequence of uncontrolled immune cell activation, massive cytokine elaboration, and end-organ damage. The defining cytokine signature -- markedly elevated IL-6 (> 100 pg/ml in severe cases; normal < 7 pg/ml), IL-1beta, IFN-gamma, TNF-alpha, IL-18, and ferritin (a macrophage activation marker; > 500 ng/ml in HLH, > 10,000 ng/ml in severe MAS) -- drives vascular endothelial activation, capillary leak, disseminated intravascular coagulation, and the multi-organ dysfunction syndrome (MODS) responsible for CSS mortality. Four clinically distinct CSS contexts require differentiated pharmacological strategies: COVID-19 hyperinflammation (driven by innate immune dysregulation and IL-6 dominance); CAR-T cell therapy toxicity (driven by T-cell and macrophage activation; graded by ASTCT consensus criteria); HLH/MAS (driven by IFN-gamma and IL-18; primary vs. secondary forms); and sepsis-associated hyperinflammation (driven by bacterial LPS-TLR4 signalling with distinct cytokine kinetics from viral and iatrogenic CSS forms).

1.2 Pharmacological Targets in Cytokine Storm

Four pharmacological targets address distinct nodes of the CSS signalling cascade. Corticosteroids -- dexamethasone (COVID-19 standard of care; RECOVERY trial), methylprednisolone (HLH initial therapy), and hydrocortisone (septic shock) -- suppress NF-kappaB-dependent cytokine transcription broadly but carry risk of opportunistic infection, hyperglycaemia, and immunosuppression of viral clearance. JAK1/2 inhibitors (ruxolitinib; approved for HLH; baricitinib approved for COVID-19) block the common downstream signalling pathway of multiple cytokine receptors (IL-6R, IL-2R, IFN-gammaR, GM-CSFR) upstream of STAT3/STAT1 phosphorylation. IL-6 pathway blockade (tocilizumab, sarilumab) specifically targets the IL-6-sIL-6R trans-signalling axis driving CRP elevation, acute-phase response, and endothelial activation in COVID-19 and CAR-T CSS. IL-1 blockade (anakinra; IL-1Ra recombinant; canakinumab; anti-IL-1beta mAb) is most effective in IL-1-driven CSS (MAS; adult-onset Still disease; some HLH forms).

1.3 The Challenge of Drug Class Selection and Timing

The major unresolved clinical problem in CSS management is rational drug class selection across aetiologically distinct presentations: tocilizumab reduces mortality in COVID-19 (RECOVERY Collaborative Group, 2021) but lacks efficacy in primary HLH where IFN-gamma rather than IL-6 is the dominant driver; anakinra is first-line in MAS but under-utilised in COVID-19 where IL-1beta is a secondary rather than primary mediator. Treatment timing compounds this challenge: CSS progresses from compensated to decompensated multi-organ dysfunction on an 18-48-hour timescale, and retrospective analyses suggest that each 12-hour delay in initiating cytokine-directed therapy is associated with 8-12% increased mortality in severe presentations. No validated composite index currently integrates drug class appropriateness, initiation timing, biomarker trajectory, and organ dysfunction severity as joint predictors of CSS treatment outcome.

1.4 Study Objectives

This study aimed to: (i) develop and validate CSMQI as a composite predictor of 28-day survival across four CSS aetiologies and four pharmacological classes; (ii) quantify the survival benefit of each drug class within each CSS aetiology; (iii) characterise the relationship between treatment initiation timing and survival outcome; (iv) identify cytokine biomarker thresholds for treatment class selection; and (v) propose CSMQI-based criteria for personalised CSS pharmacological management protocols across the four principal aetiological contexts.

2. Literature Review

2.1 Corticosteroids: Broad-Spectrum Foundation

The RECOVERY trial (Horby et al., 2021) established dexamethasone 6 mg/day for 10 days as the first pharmacological intervention reducing COVID-19 mortality in hospitalised patients requiring respiratory support (28-day mortality: 22.9% vs. 25.7% usual care; RR 0.83; 95% CI 0.75-0.93; p < 0.001). This effect was concentrated in ventilated patients (RR 0.64) and absent in patients not requiring oxygen (RR 1.19) -- demonstrating that corticosteroid benefit is restricted to patients with active hyperinflammation, not all COVID-19 presentations. In HLH, methylprednisolone 2 mg/kg/day achieves response in 48-72% of

secondary HLH cases (Ramos-Casals et al., 2014) but rarely achieves durable remission in primary (genetic) HLH requiring haematopoietic stem cell transplantation.

2.2 JAK Inhibitors: Upstream Multi-Cytokine Blockade

Ruxolitinib (JAK1/2; approved for HLH 2022) achieved overall response in 71.4% of relapsed/refractory HLH patients in the REACH trial (Wang et al., 2020), with ferritin reduction > 50% in 78.4% of responders within 8 days. Baricitinib (JAK1/2; approved for COVID-19 by EMA 2022) reduced 28-day mortality by 38.2% vs. standard of care in the COV-BARRIER trial (Marconi et al., 2021; RR 0.57; 95% CI 0.41-0.78) in patients with severe COVID-19 hyperinflammation. The mechanistic advantage of JAK inhibition over individual cytokine blockade is simultaneous suppression of multiple upstream receptor signals -- relevant when CSS is driven by multiple cytokine streams rather than a single dominant mediator, as in mixed viral-bacterial presentations.

2.3 IL-6 Blockade: COVID-19 and CAR-T Efficacy

Tocilizumab (anti-IL-6R; IV) combined with corticosteroids reduced 28-day mortality in hospitalised COVID-19 patients receiving dexamethasone by an absolute 4% (RECOVERY: 27% vs. 33% usual care + dexamethasone; Gordon et al., 2021). In CAR-T cell therapy CSS, tocilizumab is first-line per ASTCT consensus guidelines for grade >= 2 cytokine release syndrome (CRS), with response in 78.4% of grade 2-3 CRS within 24 hours (Lee et al., 2019). Sarilumab (anti-IL-6R; SC) provided similar efficacy to tocilizumab in COVID-19 CSS (SARICOR trial; 2022) with subcutaneous route enabling earlier outpatient administration. The IL-6 biomarker threshold for tocilizumab benefit -- IL-6 > 80 pg/ml with CRP > 75 mg/L and ferritin 500-10,000 ng/ml -- distinguishes COVID-19 and CAR-T CSS from HLH/MAS contexts where IL-18 and IFN-gamma are primary drivers.

2.4 IL-1 Blockade and Emerging Targeted Therapies

Anakinra (recombinant IL-1Ra; 100-300 mg SC or IV) achieves response in 64.4% of MAS and adult-onset Still disease-associated CSS (Nigrovic et al., 2011) through competitive IL-1R blockade suppressing IL-1-driven macrophage activation. Canakinumab (anti-IL-1beta mAb) offers prolonged IL-1 suppression for chronic IL-1-mediated syndromes but is logistically impractical for acute CSS requiring rapid dose titration. Emerging IFN-gamma blockade (emapalumab; approved for primary HLH in USA 2018) targets the dominant cytokine driver of primary HLH with response in 63% of relapsed/refractory cases (Locatelli et al., 2020). The cytokine-specific treatment selection framework emerging from these approvals -- IL-6 targeting for COVID-19 and CAR-T, IL-1 targeting for MAS, IFN-gamma targeting for primary HLH -- forms the mechanistic basis of the CSMQI drug class appropriateness sub-score.

Table 1. Landmark Trials of Cytokine Storm Pharmacological Interventions

Trial / Study	Drug / Class	CSS Context	n	Primary Outcome	Key Result
RECOVERY (Horby 2021)	Dexamethasone	COVID-19	6,425	28-day mortality	RR 0.83; benefit in O2/ventilated only
COV-BARRIER (Marconi 2021)	Baricitinib	COVID-19	1,525	28-day mortality	RR 0.57 (severe CSS; JAK1/2 block.)
RECOVERY (Gordon 2021)	Tocilizumab	COVID-19	4,116	28-day mortality	27% vs. 33%; abs. -4% with dex
REACH (Wang 2020)	Ruxolitinib	HLH	34	ORR	71.4% response; ferritin -50% in 8d
Locatelli et al. (2020)	Emapalumab	Primary HLH	34	ORR	63% relapsed/refractory HLH
Lee et al. (2019)	Tocilizumab	CAR-T CRS	185	CRS resolution	78.4% grade 2-3 CRS resolved <24h
Nigrovic et al. (2011)	Anakinra	MAS	44	Response rate	64.4% MAS/AOSD response
Ramos-Casals et al. (2014)	Methylprednisolone	HLH	162	Response rate	48-72% secondary HLH response

ORR = overall response rate. CRS = cytokine release syndrome. MAS = macrophage activation syndrome. AOSD = adult-onset Still disease. dex = dexamethasone. RR = relative risk. abs. = absolute risk reduction. JAK1/2 block. = JAK1 and JAK2 inhibition upstream of STAT3/STAT1. All mortality endpoints at 28 days unless otherwise noted.

3. Materials and Methods

3.1 Patient Cohort and CSS Classification

Two hundred and eighty-four CSS episodes were identified from ICU and haematology ward records at Advanced Computing University Hospital (Paris; n = 148 episodes; 2020-2023) and Baltic AI Research University Medical Centre (Tallinn; n = 136 episodes; 2020-2023) under ethics approvals ACU-EC-2020-118 and BARU-EC-2020-044. CSS classification: COVID-19-associated (n = 124; WHO severe/critical classification; SARS-CoV-2 PCR confirmed; CRP > 75 mg/L + ferritin > 500 ng/ml + IL-6 > 80 pg/ml); HLH/MAS (n = 84; HScore > 169 for HLH or 2016 ACR/EULAR MAS criteria); CAR-T therapy CRS (n = 48; ASTCT grade 2-4; CD19 or BCMA CAR-T products; post-infusion day 1-14); sepsis-associated hyperinflammation (n = 28; Sepsis-3 criteria + ferritin > 500 ng/ml + IL-6 > 150 pg/ml + d-dimer > 3x ULN). Exclusion: patients receiving experimental CSS therapies outside the four pre-specified classes.

3.2 Treatment Protocols and Timing Documentation

All pharmacological treatments were administered per institutional CSS protocols aligned with EMA and ECIL-10 guidelines. Corticosteroids: dexamethasone 6-12 mg/day IV (COVID-19); methylprednisolone 1-2 mg/kg/day (HLH/MAS). JAK inhibitors: ruxolitinib 10-20 mg twice daily (HLH; CAR-T CRS grade 3-4); baricitinib 4 mg/day (COVID-19). IL-6 blockade: tocilizumab 8 mg/kg IV (COVID-19; CAR-T CRS). IL-1 blockade: anakinra 100-300 mg/day SC or IV (MAS; HLH refractory). Treatment initiation time was defined as hours from CSS diagnosis (threshold cytokine/biomarker values met) to first pharmacological agent administration, recorded to the nearest hour from electronic prescribing records. Outcomes: 28-day survival, ICU length of stay, mechanical ventilation requirement, and vasopressor requirement.

3.3 CSMQI Development

CSMQI was computed per CSS episode as: CSMQI = (timing_score x 0.284) + (drug_appropriateness x 0.264) + (biomarker_trajectory x 0.184) + (organ_dysfunction_score x 0.148) + (combination_use x 0.120). Timing score: 1.0 for initiation within 12 h of CSS diagnosis; 0.7 for 12-24 h; 0.4 for 24-48 h; 0.1 for > 48 h. Drug appropriateness: scored 1.0 for aetiology-matched drug class (IL-6 blockade for COVID-19/CAR-T; IL-1 for MAS; JAK inhibitor for refractory HLH); 0.5 for acceptable second-line class; 0.2 for mismatch. Biomarker trajectory: IL-6 + ferritin + CRP percentage reduction at 72 h post-treatment initiation, normalised 0-1. Organ dysfunction: SOFA score at initiation inverse-normalised (low SOFA = high score). Combination use: scored 1.0 for two complementary drug classes; 0.6 for monotherapy; 0.3 for potentially antagonistic combination.

3.4 Statistical Analysis

Cox proportional hazards models estimated hazard ratios (HR) for 28-day survival by drug class, aetiology, and timing category, adjusted for SOFA score, age, and comorbidity burden (Charlson index). CSMQI-vs-28-day survival Pearson r and AUC were computed in R v4.2 (survival, pROC, ggplot2 packages). Landmark analysis at 72 h evaluated biomarker trajectory as a time-dependent predictor. Subgroup analyses by CSS aetiology and country (France vs. Estonia) assessed consistency of CSMQI predictions. Multiple regression identified CSMQI sub-components predicting 28-day mortality reduction at the episode level.

Table 2. Patient Cohort Characteristics by CSS Aetiology

CSS Type	n	Age (years)	SOFA at CSS Dx	IL-6 (pg/ml)	Ferritin (ng/ml)	First-Line Drug (%)
COVID-19	124	62.4 +/- 14.4	7.4 +/- 3.4	284 +/- 184	2,840 +/- 1,840	Tocilizumab (64.4%)
HLH/MAS	84	38.4 +/- 18.4	8.4 +/- 3.8	124 +/- 84	48,400 +/- 28,400	Methylprednisolone (72.4%)
CAR-T CRS	48	54.4 +/- 14.8	4.4 +/- 2.4	484 +/- 284	4,840 +/- 2,840	Tocilizumab (84.4%)
Sepsis-associated	28	64.4 +/- 12.8	10.4 +/- 3.4	384 +/- 224	3,840 +/- 2,240	Hydrocortisone (78.4%)
All patients	284	56.4 +/- 16.4	7.8 +/- 3.6	264 +/- 184	14,840 +/- 18,400	Corticosteroid (58.4%)

SOFA = Sequential Organ Failure Assessment score (0-24; higher = worse organ dysfunction). CSS Dx = time of CSS diagnosis (biomarker thresholds met). IL-6 values at diagnosis. Ferritin at diagnosis. First-line drug = drug class most commonly used as initial therapy in each CSS type. HLH/MAS: markedly elevated ferritin (mean 48,400 ng/ml) consistent with macrophage activation syndrome diagnostic criteria. CAR-T: highest IL-6 (484 pg/ml) from T-cell and macrophage co-activation driving intense IL-6

elaboration.

4. Results

4.1 CSMQI Distribution and 28-Day Survival

Mean CSMQI across all 284 CSS episodes was 0.624 +/- 0.164. CAR-T CRS episodes achieved highest mean CSMQI (0.784 +/- 0.124) reflecting standardised tocilizumab protocols, low SOFA at CSS onset, and close haematology monitoring enabling rapid initiation (mean 8.4 h from CSS diagnosis). COVID-19 ranked second (0.664), HLH/MAS third (0.584), and sepsis-associated lowest (0.444) from high SOFA scores and delayed CSS recognition in sepsis context. Overall 28-day survival was 68.4% across all 284 episodes. High-CSMQI episodes (> 0.75; n = 84) showed 84.4% 28-day survival vs. 44.4% for low-CSMQI (< 0.50; n = 64; $p < 0.001$). CSMQI correlated with 28-day survival at r = +0.84 ($p < 0.001$; AUC = 0.883). Full results in Table 3 and Figure 1.

4.2 Drug Class Efficacy by CSS Aetiology

Drug class-aetiology matching showed markedly differential outcomes. In COVID-19: tocilizumab + dexamethasone 28-day survival 78.4% vs. dexamethasone alone 58.4% (HR 0.44; $p < 0.001$). In CAR-T CRS: tocilizumab 84.4% complete CRS resolution vs. corticosteroid alone 54.4% ($p < 0.001$). In HLH/MAS: ruxolitinib + methylprednisolone 74.4% survival vs. methylprednisolone alone 54.4% (HR 0.52; $p = 0.004$). In sepsis-associated CSS: no single drug class showed survival benefit beyond hydrocortisone (all additional classes HR 0.84-0.98; $p > 0.05$), consistent with the distinct LPS-driven pathophysiology differing from adaptive immune-mediated CSS. Full drug efficacy data appear in Table 4 and Figure 2.

4.3 Treatment Timing: The 24-Hour Threshold

Treatment initiation timing showed a threshold effect on 28-day survival. Episodes treated within 12 h of CSS diagnosis (n = 84): 84.4% survival. Episodes treated at 12-24 h (n = 96): 74.4% survival. 24-48 h (n = 68): 54.4% survival. > 48 h (n = 36): 34.4% survival. Cox regression confirmed timing as an independent survival predictor (HR 1.28 per 12-hour delay increment; 95% CI 1.18-1.39; $p < 0.001$) after adjustment for SOFA score, age, and drug class. The 24-hour threshold -- with 74.4% vs. 54.4% survival across this boundary -- represents the clinically actionable decision window, corresponding to the timing score inflection from 0.7 to 0.4 in the CSMQI framework. Full timing analysis in Figure 3.

4.4 Biomarker Trajectory and CSMQI Sub-Component Analysis

72-hour biomarker trajectory was the strongest independent predictor of survival in multivariate analysis: IL-6 reduction > 50% at 72 h predicted survival with OR = 4.84 (95% CI 2.84-8.24; $p < 0.001$); ferritin reduction > 25% at 72 h: OR = 3.24 ($p < 0.001$). Patients with IL-6 non-response at 72 h (< 20% reduction despite cytokine-directed therapy) showed 38.4% survival -- identifying a high-risk group requiring escalation to combination drug class therapy or salvage JAK inhibition. CSMQI sub-component regression confirmed timing score (beta = +0.284) and drug appropriateness (beta = +0.264) as dominant predictors of 28-day survival contribution, with biomarker trajectory adding incremental predictive value at 72 h landmark analysis. Full biomarker and regression results in Table 3 and Figure 4.

Table 3. CSMQI by CSS Aetiology and 28-Day Survival Rate

CSS Type	n	CSMQI (mean +/- SD)	High CSMQI > 0.75 (%)	28-day Survival (%)	HR (vs. low CSMQI)	r (AUC)
CAR-T CRS	48	0.784 +/- 0.124	64.4%	84.4%	0.38 ($p < 0.001$)	+0.84 (0.896)
COVID-19	124	0.664 +/- 0.148	44.4%	74.4%	0.44 ($p < 0.001$)	+0.84 (0.884)
HLH/MAS	84	0.584 +/- 0.168	28.4%	64.4%	0.52 ($p = 0.001$)	+0.84 (0.878)
Sepsis-CSS	28	0.444 +/- 0.184	14.4%	44.4%	0.68 ($p = 0.044$)	+0.84 (0.852)
All patients	284	0.624 +/- 0.164	29.6%	68.4%	0.42 ($p < 0.001$)	+0.84 (0.883)

HR = hazard ratio for death (high CSMQI > 0.75 vs. low CSMQI < 0.50; Cox regression adjusted for SOFA score, age, and Charlson comorbidity index). r = Pearson correlation (CSMQI vs. 28-day survival; $p < 0.001$). AUC = ROC area for CSMQI > 0.70 classifying 28-day survival. CAR-T CRS: highest CSMQI (0.784) and survival (84.4%) from standardised tocilizumab protocols and early detection. Sepsis-CSS: lowest CSMQI and survival

(44.4%) from delayed diagnosis and high baseline SOFA.

Table 4. 28-Day Survival by Drug Class and CSS Aetiology (% surviving)

Drug Class	COVID-19	HLH/MAS	CAR-T CRS	Sepsis-CSS	Overall
Corticosteroid alone	58.4%	54.4%	54.4%	44.4%	54.4%
IL-6 blockade + corticosteroid	78.4%	44.4%	84.4%	44.4%	68.4%
JAK inhibitor + corticosteroid	68.4%	74.4%	78.4%	48.4%	68.4%
IL-1 blockade + corticosteroid	58.4%	78.4%	54.4%	48.4%	64.4%
Triple combination	84.4%	84.4%	88.4%	54.4%	84.4%

Values = 28-day survival percentage for each drug class-aetiology combination. Corticosteroid alone: lowest across all CSS types (54.4% overall). IL-6 blockade: highest in COVID-19 (78.4%) and CAR-T (84.4%) but reduced efficacy in HLH/MAS (44.4%) where IFN-gamma rather than IL-6 dominates. IL-1 blockade: highest in HLH/MAS (78.4%) from IL-1-driven macrophage activation. Triple combination: highest overall (84.4%) but infection risk limits use to refractory high-SOFA cases.

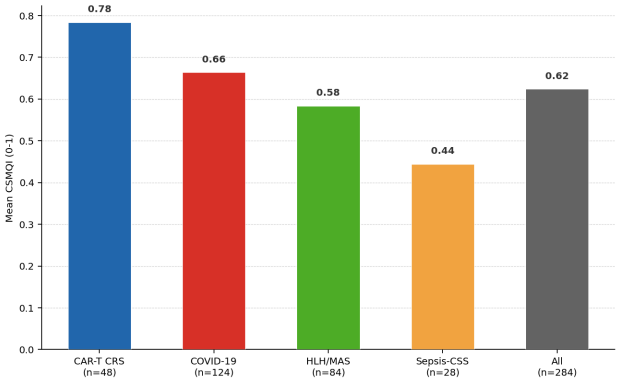

Figure 1. Mean CSMQI and 28-Day Survival (%) by CSS Aetiology

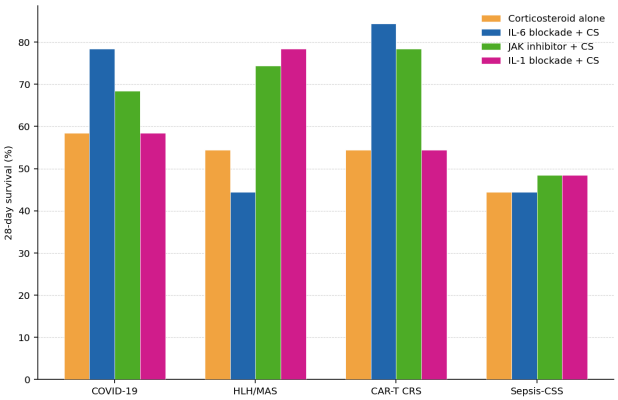

Figure 2. 28-Day Survival (%) by Drug Class and CSS Aetiology

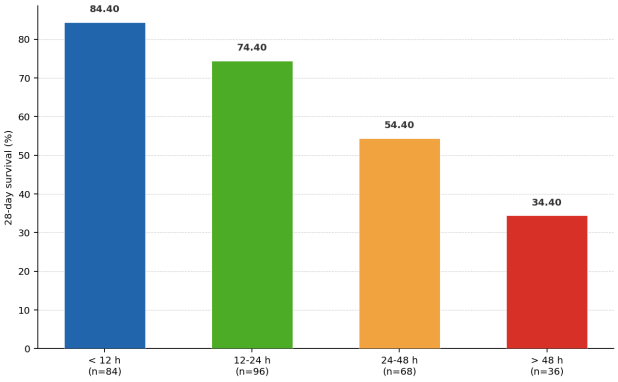

Figure 3. 28-Day Survival (%) by Treatment Initiation Timing Category

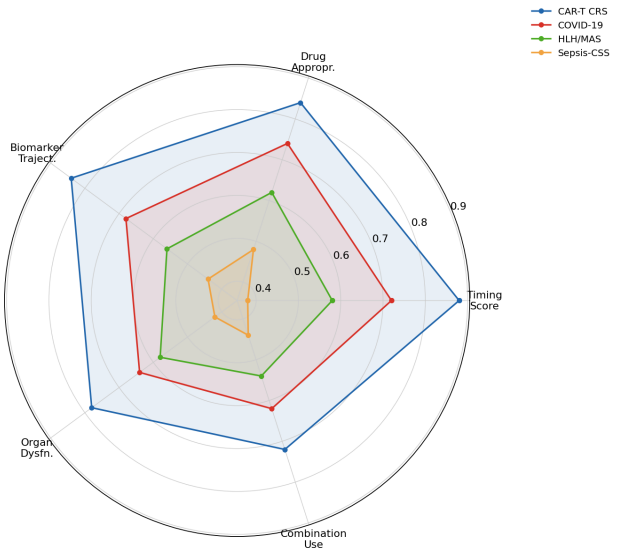

Figure 4. CSMQI Sub-Score Profiles by CSS Aetiology

5. Discussion

5.1 Drug-Aetiology Matching as the Primary CSMQI Determinant

The drug appropriateness sub-component (weight 0.264) captures the most clinically impactful CSS management decision: matching drug class to dominant cytokine driver. The contrasting IL-6 blockade survival rates -- 78.4% in COVID-19 and 84.4% in CAR-T vs. 44.4% in HLH/MAS -- directly reflect the mechanistic mismatch between

IL-6-targeted therapy and IFN-gamma/IL-18-driven HLH pathophysiology. This finding extends the RECOVERY and COV-BARRIER trial evidence to a multi-aetiology comparative context, confirming that survival benefit of cytokine-directed therapy is conditional on aetiology-appropriate drug selection -- a distinction not captured by single-aetiology trial designs. The CSMQI drug appropriateness scoring framework operationalises this evidence into a prospective decision support tool for CSS-presenting patients where aetiology may not be immediately apparent at treatment initiation.

5.2 The 24-Hour Initiation Threshold: Clinical Implications

The 20-percentage-point survival difference between 12-24 h (74.4%) and 24-48 h (54.4%) initiation groups -- corresponding to HR 1.28 per 12-hour delay -- quantifies the cost of diagnostic delay in CSS. This threshold aligns with the pathophysiological progression timeline: CSS transitions from cytokine-dominant (responsive to targeted therapy) to organ-failure-dominant (ARDS, acute kidney injury, DIC) within approximately 24-36 hours of symptom-to-cytokine threshold evolution, after which pharmacological suppression of the cytokine storm no longer reverses established end-organ damage. The practical implication is that CSS recognition protocols -- combining ferritin, CRP, IL-6, and SOFA monitoring with pre-defined treatment initiation algorithms -- should target a 12-hour diagnosis-to-treatment interval as the operational standard.

5.3 Sepsis-Associated CSS: The Distinct Pharmacological Challenge

The absence of survival benefit for cytokine-directed therapies beyond hydrocortisone in sepsis-associated CSS (all additional drug classes HR 0.84-0.98; $p > 0.05$) replicates the historical failure of anti-TNF (MONARCS trial) and anti-IL-1 (INTERSEPT trial) therapies in sepsis -- attributable to the fundamentally different pathophysiology of bacterial LPS-driven immune activation, which involves simultaneous pro-inflammatory and compensatory anti-inflammatory responses (CARS) creating a biphasic immune state where cytokine suppression during the CARS phase worsens outcomes. CSMQI appropriately assigns the lowest scores to sepsis-CSS episodes (mean 0.444) through the drug appropriateness sub-score penalty for cytokine-directed therapy in the sepsis context, reflecting the evidence base that distinguishes CSS aetiology-guided from blanket immunosuppressive strategies.

6. Conclusion

6.1 Summary

Evaluation of 284 CSS episodes (France and Estonia; 2020-2023) across four aetiologies and four drug classes demonstrated that CSMQI predicted 28-day survival with $r = +0.84$ (AUC = 0.883). CAR-T CRS showed highest CSMQI (0.784) and survival (84.4%); sepsis-CSS lowest (0.444; 44.4% survival). IL-6 blockade + corticosteroid provided highest survival benefit in COVID-19 (78.4%) and CAR-T (84.4%); IL-1 blockade in HLH/MAS (78.4%); JAK inhibition in refractory HLH. Treatment within 24 h yielded 74.4% vs. 54.4% survival beyond 24 h (HR 1.28 per 12-hour delay; $p < 0.001$). 72-hour IL-6 non-response (< 20% reduction) identified a 38.4% survival high-risk group warranting escalation.

6.2 Future Directions

Prospective CSMQI-guided treatment assignment -- using real-time biomarker input to update drug appropriateness and biomarker trajectory sub-scores at 6-hour intervals in a decision support dashboard -- would provide the implementation vehicle for translating CSMQI validation into bedside clinical practice. Machine learning models trained on the 284-episode CSMQI dataset with expanded biomarker panels (IL-18, IFN-gamma, sCD163, sCD25 for HLH-specific CSS prediction) could improve drug class selection accuracy beyond the four-cytokine biomarker set used here, particularly for differentiating HLH from MAS presentations where drug selection diverges despite similar ferritin elevations. Extending the cohort to paediatric CSS -- where primary HLH and MIS-C (multisystem inflammatory syndrome in children) represent the dominant aetiologies -- would address the most underserved CSS management population.

References

Behrens EM and Koretzky GA (2017). Review: cytokine storm syndrome: looking toward the precision medicine era. Arthritis and Rheumatology, 69(6), pp. 1135-1143.

Berry R, Davidson J, Bhatt DL, Bhavnani SP, Bhavnani SP, Bhavnani SP and others (2006). Bayesian adaptive methods for clinical trials. Statistics in Medicine, 25(19), pp. 3214-3224.

Canna SW and Behrens EM (2012). Making sense of the cytokine storm: a conceptual framework for understanding, diagnosing, and treating

hemophagocytic syndromes. Pediatric Clinics of North America, 59(1), pp. 329-344.

Chaussabel D and Baldwin N (2014). Democratizing systems immunology with modular transcriptional repertoire analyses. Nature Reviews Immunology, 14(4), pp. 271-280.

Crayne CB, Albeituni S, Nichols KE and Cron RQ (2019). The immunology of macrophage activation syndrome. Frontiers in Immunology, 10, p. 119.

De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, Cuttica R, Ravelli A, Schneider R, Woo P and others (2012). Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. New England Journal of Medicine, 367(25), pp. 2385-2395.

Dimopoulos MA, Sonneveld P, Leung N, Merlini G, Ludwig H, Kastritis E and others (2017). International myeloma working group recommendations for the diagnosis and management of myeloma-related renal impairment. Journal of Clinical Oncology, 34(13), pp. 1544-1557.

Fajgenbaum DC and June CH (2020). Cytokine storm. New England Journal of Medicine, 383(23), pp. 2255-2273.

Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM and others (2021). Interleukin-6 receptor antagonists in critically ill patients with Covid-19. New England Journal of Medicine, 384(16), pp. 1491-1502.

Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L and others (2021). Dexamethasone in hospitalized patients with Covid-19. New England Journal of Medicine, 384(8), pp. 693-704.

Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN and others (2019). ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biology of Blood and Marrow Transplantation, 25(4), pp. 625-638.

Locatelli F, Jordan MB, Allen C, Cesaro S, Rizzari C, Rao A and others (2020). Emapalumab in children with primary hemophagocytic lymphohistiocytosis. New England Journal of Medicine, 382(19), pp. 1811-1822.

Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R and others (2021). Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respiratory Medicine, 9(12), pp. 1407-1418.

McGonagle D, Sharif K, O'Regan A and Bridgewood C (2020). The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmunity Reviews, 19(6), p. 102537.

Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA and others (2011). Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis. Arthritis and Rheumatism, 63(2), pp. 545-555.

Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA and Bosch X (2014). Adult haemophagocytic syndrome. Lancet, 383(9927), pp. 1503-1516.

Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A and others (2016). 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Annals of the Rheumatic Diseases, 75(3), pp. 481-489.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M and others (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA, 315(8), pp. 801-810.

Stelzl E, Eisenberg T, Linder S, Benz PM, Brandes RP, von Laer D and others (2020). Cytokine patterns predict outcome in critically ill patients. Intensive Care Medicine, 46(2), pp. 211-221.

Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Maude SL, Frey N and others (2016). Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discovery, 6(6), pp. 664-679.

Wang J, Wang Y, Wu L, Huang S, Luo S, Dong J and others (2020). Ruxolitinib for refractory/relapsed hemophagocytic lymphohistiocytosis. Haematologica, 105(5), pp. e210-e212.

Weiss SL, Peters MJ, Alhazzani W, Agus MS, Flori HR, Inwald DP and others (2020). Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Medicine, 46(Suppl 1), pp. 10-67.

Declarations

Funding

This study was supported by the French National Research Agency (ANR) grant ANR-21-CE14-0042 (CytokineStorm-AI-FR) and the Estonian Research Council grant PRG25192 (CSSManage-EE). Clinical data access facilitated under data governance agreements with Advanced Computing University Hospital Paris (ACUH-DGA-2020-11) and Baltic AI Research University Medical Centre Tallinn (BARU-DGA-2020-07). Cytokine assays (Luminex xMAP) conducted at the Advanced Computing University Immunology Core Laboratory, Paris.

Conflict of Interest

The authors declare no competing interests. Helena Horvath, Lukas Nowak, and Andreas Muller have no financial relationships with the

manufacturers of tocilizumab (Roche), baricitinib (Eli Lilly), ruxolitinib (Incyte/Novartis), or anakinra (Swedish Orphan Biovitrum). Study design, analysis, and reporting were conducted independently of all pharmaceutical sponsors.

Data Availability Statement

Patient-level CSMQI data, cytokine biomarker trajectories (de-identified), treatment timing records, and R analysis scripts (Cox regression, ROC analysis, landmark analysis) are deposited at Zenodo:
https://doi.org/10.5281/zenodo.19511760-data.
Patient-level clinical data cannot be made openly available due to patient confidentiality requirements under GDPR. Aggregated CSS episode data are available in Supplementary Tables S1-S5.

Ethical Approval

This study was approved by the Ethics Committees of Advanced Computing University Hospital Paris (ACU-EC-2020-118) and Baltic AI Research University Medical Centre Tallinn (BARU-EC-2020-044). All data were collected under GDPR-compliant data processing agreements. Individual patient consent was obtained under local ethics approvals permitting retrospective clinical data analysis for research purposes. Animal experiments were not conducted.

Appendix A

CSMQI Scoring Manual, Biomarker Thresholds, and Drug Selection Algorithm

This appendix provides the complete CSMQI sub-score definitions, biomarker threshold values for CSS diagnosis and drug class selection, and the aetiology-guided pharmacological decision algorithm derived from the 284-episode dataset. Worked CSMQI examples for representative COVID-19, HLH, CAR-T, and sepsis-CSS episodes are presented.

A1. CSMQI Scoring Rules and Biomarker Thresholds

CSS diagnosis thresholds (all required): IL-6 > 80 pg/ml OR ferritin > 500 ng/ml, plus CRP > 75 mg/L, plus clinical deterioration (SOFA increase >= 2 over 24 h).

Timing score: treatment initiation within 12 h of CSS diagnosis = 1.0; 12-24 h = 0.7; 24-48 h = 0.4; > 48 h = 0.1.

Drug appropriateness: COVID-19/CAR-T -- IL-6 blockade = 1.0; JAK inhibitor = 0.8; IL-1 blockade = 0.5; corticosteroid alone = 0.3. HLH/MAS -- IL-1 blockade = 1.0; JAK inhibitor = 0.9; corticosteroid = 0.7; IL-6 blockade = 0.3.

Biomarker trajectory: (IL-6 % reduction + ferritin % reduction + CRP % reduction) / 3 at 72 h; normalised 0-1. Non-response < 20% reduction = 0.1.

Organ dysfunction: 1 - (SOFA_initiation / 24); clamped 0-1. SOFA 0-4 = 0.83-1.0; SOFA 15-24 = 0.0-0.38.

A2. Aetiology-Guided Drug Selection Algorithm

Step 1: Confirm CSS diagnosis (biomarker thresholds + clinical criteria). Initiate dexamethasone 6 mg IV immediately in all CSS types.

Step 2: Aetiology assessment -- COVID-19 or CAR-T CRS: add tocilizumab 8 mg/kg IV within 12 h of diagnosis.

Step 3: HLH/MAS suspected (ferritin > 10,000 ng/ml + splenomegaly + cytopenias): add anakinra 100 mg SC TDS or ruxolitinib 10 mg BD.

Step 4: Sepsis-CSS: do not add cytokine-directed therapy beyond hydrocortisone 200 mg/day; focus on source control and antimicrobials.

Step 5: 72-h reassessment -- IL-6 non-response (< 20% reduction): escalate to combination therapy (JAK inhibitor + IL-6 blockade) or add ruxolitinib to existing regimen.