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Serum Interleukin-6 Levels as a Prognostic Marker in Patients With Sepsis

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ABSTRACT

Interleukin-6 (IL-6) is one of the earliest and most abundant cytokines to rise in the blood of patients with sepsis, and many studies since the late 1980s have asked whether a single serum measurement can tell clinicians who is likely to do badly. This narrative review examines that question using published work on the biology of IL-6, the kinetics of the host response, and the design and reporting of prognostic marker studies. It reports no new data and no local cohort. Higher circulating IL-6 has repeatedly been associated with greater severity and with death, and the association is biologically coherent, because the cytokine is produced downstream of the first inflammatory signals and tracks the size of the insult. Yet the same literature shows why the marker has not become a bedside standard: concentrations change within hours, differ between assays and populations, overlap widely between survivors and non-survivors, and add uncertain value once severity scores are already known. Thresholds are rarely validated outside the cohort that produced them. Evidence that IL-6 can guide treatment is thinner still, and it is strongest where it is used to select patients with a hyperinflammatory picture instead of to predict outcome. The review concludes that IL-6 is a useful indicator of host response intensity, a modest prognostic aid at best when used alone, and a candidate for better-designed studies that report timing, calibration and added value over existing scores.

Keywords: Interleukin-6; Sepsis; Prognosis; Biomarker; Septic shock; Cytokines; Narrative review

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Article Class: Narrative Review

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (1). It remains a leading cause of death in hospitals around the world, and estimates of its burden,

although imperfect, point to many millions of cases each year (2, 3). Clinicians who treat it face an awkward fact: the diagnosis is made on clinical grounds, the course is hard to predict, and the patient who looks similar at the bedside on Monday may look very different on Wednesday (4, 5).



International guidelines emphasise early recognition, prompt antimicrobial therapy and supportive care, and they do not recommend treatment decisions on the basis of a cytokine level (6, 7).

A blood test that said early and reliably who is heading for trouble would be valuable. Interleukin-6 (IL-6) has been proposed for that role since the late 1980s, when it was found at high concentration in the serum of patients with septic shock (8, 9). It is easy to measure, it rises early, and its level often tracks how ill the patient is (10, 11). Those properties explain the enthusiasm. They do not by themselves show that the number improves care.

This article reviews what published work says about serum IL-6 as a prognostic marker in sepsis. The title may suggest a study of a particular group of patients; it is not one. No patients were recruited, no samples were analysed and no local data are reported. Instead we synthesise the literature on the biology of the cytokine, on how its concentration behaves in sepsis, and on how prognostic marker studies should be judged. The aim is to say plainly what is established, what is plausible and what is only repeated.

2. Literature Review

2.1 Biology of Interleukin-6

IL-6 was first characterised as a factor that drives B lymphocytes to produce antibody (12), and it has since turned out to act on far more than B cells. Reviews describe a pleiotropic cytokine that shapes acute inflammation, immune cell differentiation, metabolism and tissue repair (13, 14). It is produced by macrophages, endothelial cells, fibroblasts and many other cells, usually in response to earlier signals such as tumour necrosis factor and interleukin-1 (15). In the liver it drives the acute-phase response, including the rise in C-reactive protein (CRP) (13).

The cytokine is not simply a villain. It signals through a membrane receptor on a limited set of cells and through a soluble receptor on many more, and the two routes are linked to different effects, with the second more often tied to inflammation and the first to regenerative and protective functions (16, 17). A high serum level therefore says that the system is activated, but not which of its effects dominates in a given patient. Figure 1 sketches the sequence from infection to a measurable signal.

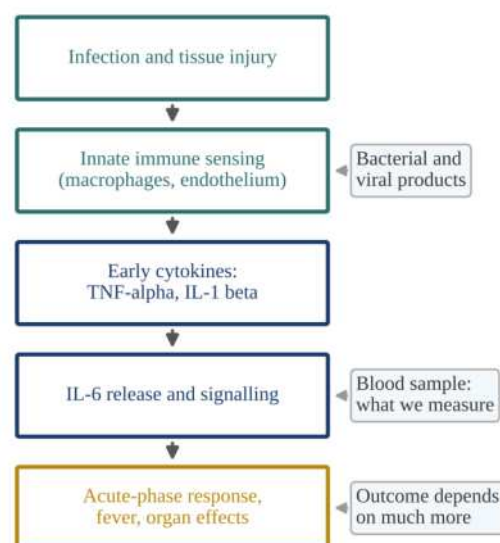


Figure 1. From infection to a measurable IL-6 signal (schematic, not data).

2.2 IL-6 in the Host Response to Sepsis

In sepsis, pathogen products and tissue damage stimulate innate immune cells to release an early burst of cytokines, among them TNF-alpha and IL-1 beta, followed by IL-6 (8, 18). The picture is more complicated than a simple surge. Reviews of the immunology of sepsis describe a response in which inflammatory and immunosuppressive features coexist from early on, with different patients showing different balances (19, 20). The term cytokine storm is common in the literature, but it is applied to a heterogeneous group of states, and its use can suggest more



uniformity than the evidence supports (21, 22).

Timing is a recurring theme. TNF-alpha tends to peak early and fall quickly, IL-6 rises somewhat later and stays up for longer, and CRP lags further behind (Figure 2). In meningococcal septic shock, one of the first clinical groups studied, serum cytokines showed a complex pattern in which high IL-6 accompanied the most severe disease (8). That the order of peaks is reasonably consistent does not mean the actual hours are, and any single blood draw captures a moving target. Timing matters in a disease that can change within hours.

2.3 Definitions and Severity Scores

Prognostic studies are only as comparable as the definition of the disease they enrol. Older work used the systemic inflammatory response criteria and the terms severe sepsis and septic shock (23), whereas current practice follows the Sepsis-3 definitions, which centre on organ dysfunction measured by the SOFA score (1, 24, 25). A study from the 1990s and one from the 2020s may not be describing the same patients even when both say sepsis. Severity scores such as APACHE II offer a competing way of estimating risk of death (26), and the bar a new marker must clear is therefore not zero: it has to say something that these scores do not.

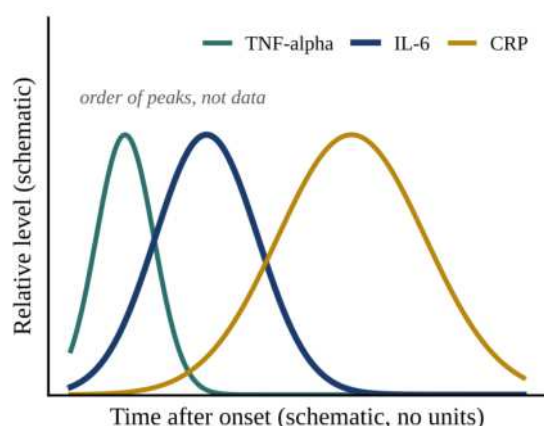


Figure 2. Expected relative timing of three markers after onset (schematic, not data).

2.4 Other Markers

IL-6 is one of many candidate markers. Reviews of sepsis biomarkers list well over a hundred, most of them studied in small groups and few adopted in routine care (27, 28). Procalcitonin is the best-known competitor; it has been evaluated mainly for diagnosing bacterial infection and for guiding the duration of antibiotics (29, 30), and its role in predicting outcome is less certain (31). Panels combining several markers have been tried, with the idea that a pattern may carry more information than any one value (32). Table 1 compares IL-6 with several of these.

Table 1. IL-6 compared with other markers discussed in sepsis research.

Marker	Time course	Main strength	Main limitation
IL-6	Rises within hours (8, 9)	Tracks response intensity (10, 33)	Assay and timing dependent
CRP	Slower, peaks later	Cheap, widely available	Slow; weak for prognosis
Procalcitonin	Rises in hours (29)	Bacterial infection and antibiotic stewardship (30)	Less clear for outcome (31)
Lactate	Rapid	Perfusion, in definitions (1)	Not specific to infection
SOFA / APACHE II	Scored daily	Established severity grading (25, 26)	Needs many variables

Note: Qualitative summary of the cited literature; no cut-off values are given because they differ by assay and population.

3. Materials and Methods

3.1 Scope and Question

The review asks one question in two parts: is a higher serum IL-6 concentration



associated with worse outcome in sepsis, and does measuring it add anything useful to what clinicians already know? We divided that into the sub-questions a good study would have to answer, namely how sepsis was defined, when blood was taken, how IL-6 was measured, how the analysis treated the number, and whether the marker was compared with a severity score.

3.2 Literature Assembly

The review draws on published work in four areas: the biology of IL-6; the immunology and epidemiology of sepsis; studies reporting IL-6 alongside outcome; and the methodological literature on prognostic research. Sources were chosen for relevance, influence in the field and clarity of methods, and studies of related conditions are used only for what they teach about mechanism or design.

We did not carry out a formal systematic search and we do not claim one. This is a narrative synthesis and the choice of sources reflects the judgement of the authors. In practice it means that the review is a better guide to what a sound study should contain than to the precise size of any reported association, and it deliberately avoids quoting effect sizes from individual studies that could not be checked against the primary papers for this article.

3.3 Appraisal Framework

To judge how far a study of IL-6 can be trusted, we asked six questions, summarised in [Table 2](#). They draw on guidance for assessing bias in prognostic factor studies ([34](#)), on the principles of prognostic model research ([35](#)), and on reporting statements for prediction and accuracy studies ([36](#), [37](#)). Each question was answered from what a paper reports, not from what we suspect it did.

Table 2. Questions used here to appraise a prognostic IL-6 study.

Domain	Question asked	Common problem
Population	Sepsis defined by which criteria (1 , 23)?	Definitions change over time
Timing	When after onset was blood drawn?	Single, unstated time point
Measurement	Which assay, sample and handling?	Not described
Analysis	Continuous or cut-off (38)?	Optimistic cut-offs
Added value	Better than severity score (39 , 40)?	Rarely tested
Reporting	Follows a checklist (36 , 37)?	Incomplete

Note: Framework drawn from the cited methodological literature; it is not attributed to any single study.

4. Results

4.1 IL-6 and Severity

The earliest studies were small and consistent in direction. Patients with septic shock had higher serum IL-6 than those with milder illness, and levels were higher in those who died ([9](#), [11](#)). A study of patients with severe sepsis proposed IL-6 as a marker of severity ([10](#)), and a multiplex analysis of a panel of cytokines later reached a similar conclusion, with IL-6 among the mediators that separated sicker from less sick patients ([33](#)). A large cohort of patients with pneumonia and sepsis found that higher early cytokine levels were associated with worse outcome, although the relationship was not simple and varied with the underlying illness ([41](#)).

More recent work using the Sepsis-3 definitions has compared IL-6 directly with procalcitonin and other markers, and has generally found that IL-6 carries prognostic information ([42](#), [43](#)). These are



single-centre cohorts of modest size, and their thresholds were derived in the same data in which they were tested. We therefore read them as supporting the existence of an association, and as silent on how reliably a threshold would perform elsewhere. Read this way, a weak association in a small cohort is neither proof of failure nor proof of promise.

4.2 Does IL-6 Add to Existing Scores?

The central practical question is whether a measured IL-6 adds anything to a patient's clinical picture. A marker can be strongly associated with death and still be of little use, because the information may already be contained in age, organ failure scores and lactate. Methodologists describe how added value should be shown: by comparing models with and without the marker, checking calibration as well as discrimination, and, where decisions are at stake, asking whether the model leads to better choices (39, 40).

Few IL-6 studies do this. Many report an area under a curve for IL-6 alone, with no comparison against a severity score and no check on calibration. Some of the studies that did compare markers found IL-6 to be useful but not clearly superior to existing measures (42, 43). The honest summary is that IL-6 has often been shown to predict outcome and rarely been shown to improve prediction. That is a modest claim, and it is the one the literature will bear.

4.3 Thresholds and Statistical Handling

Reports often convert IL-6 into a yes-or-no variable above or below a cut-off. This has a statistical cost: dichotomising a continuous variable discards information and tends to exaggerate apparent differences, especially when the cut-off is chosen to give the best result in the study sample (38). Cut-offs found this way seldom hold up in new patients, and published values differ widely between

studies, as one would expect given differences in assay, population and timing. Table 3 lists the sources of variation we found most often.

Distributions are heavily skewed, with a few very high values among many moderate ones, which makes means misleading and small studies unstable. Reporting the full distribution, with estimates and intervals instead of significance alone, would help readers judge what a number means. Individually such differences look small, yet together they decide whether a threshold travels.

Table 3. Why a serum IL-6 value is hard to interpret.

Source	Effect on the value	What helps
Sampling time	Value moves within hours (8)	Record hours from onset
Assay platform	Different scales and ranges	Report platform, range
Host factors	Age, comorbidity, source of infection	Describe cohort fully
Treatment	Steroids, source control, fluids	Note timing of therapy
Case mix	Surgical, medical, shock (41)	Stratify or adjust
Statistics	Skewed data, small cohorts (34)	Report estimates, intervals

Note: Sources of variation are those discussed in the cited work and in general laboratory practice.

4.4 From Prediction to Treatment

Prognosis and treatment guidance are different questions. A marker that predicts death does not tell you what to do about it. One trial of an anti-TNF antibody fragment in patients with severe sepsis and elevated IL-6 used the cytokine to select participants, a design that reflects the idea that treatment may work best in those with a stronger inflammatory response; the overall findings were modest and the question is still debated (44, 45). More broadly, trials of immune-modulating



drugs in unselected septic patients have disappointed, and heterogeneity of the patient population is a leading explanation (45, 46).

Work on clinical phenotypes in sepsis suggests that patients fall into groups with different patterns of inflammation and outcome (47). If so, a single IL-6 threshold applied to everyone is likely to be less informative than IL-6 interpreted within a phenotype. The most direct evidence that an IL-6 pathway can be a treatment target comes from outside classical bacterial sepsis: trials of IL-6 receptor antagonists in critically ill patients with severe COVID-19 (48). That setting differs from bacterial sepsis in important ways, and we cite it as evidence that the pathway matters, not as evidence about the marker in sepsis. A clinician reading a marker study needs to know whether the finding would survive on a different ward.

5. Discussion

5.1 Interpretation

Put plainly, the literature supports a cautious statement. Serum IL-6 is higher, on average, in sicker septic patients and in those who die, and the biology makes this unsurprising. The cytokine is better seen as a measure of how hard the host response is working than as a prognosis in itself (4, 14). Two patients with the same value may be at very different points in the illness, with different sources of infection, different comorbidities and different treatments in progress. This is one reason the same marker can look decisive in one report and unremarkable in the next.

The number is also shaped by every step between the bedside and the report, which is easy to forget when a result appears on a screen as a single figure (Figure 3). Sampling time, assay, patient context and the choice of threshold each add their own uncertainty, and a study that controls for

none of them can offer only a loose estimate of what the marker means. It is a habit worth keeping even when the answer seems obvious.

The overlap between survivors and non-survivors matters more than the difference in averages. A marker with a clear average difference but wide overlap will misclassify many individuals, and a clinician cannot act on an average. This is why a statistically significant association can sit alongside a poor performance as a decision aid (34, 39). The point is not that a study is poor, only that its result travels less far than its abstract suggests.

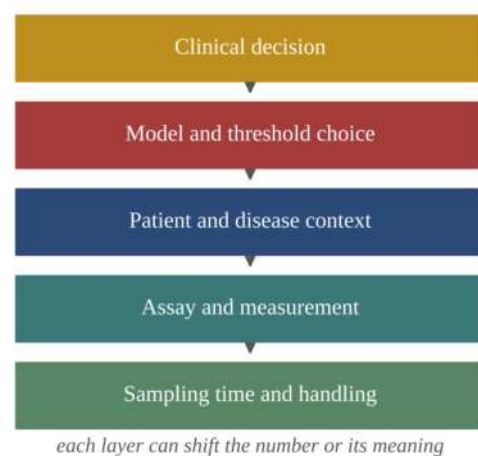


Figure 3. Layers between a blood draw and a clinical decision (schematic, not data).

5.2 Limitations

The limitations of the evidence base are the main finding of this review. Studies differ in definitions of sepsis, in sampling time, in assay platform and in how outcome was measured (24, 28). Cohorts are often small and recruited at one centre. Few follow reporting guidance, so readers cannot always tell when blood was drawn or how missing data were handled (36, 37). A number that cannot be reproduced on the next analyser is not yet a number a ward can use.



The limitations of this article should also be stated. It is a narrative review, with no systematic search, no quantitative synthesis and no formal risk-of-bias rating. The selection of studies is ours, and a different group might have chosen differently. We have avoided quoting numbers from individual studies for that reason, and the conclusions are correspondingly qualitative. Reviews are more useful when they say where the evidence stops than when they smooth it over.

5.3 Future Work

Better evidence would come from cohorts that define sepsis by current criteria, record the hours from onset to sampling, measure IL-6 repeatedly instead of once, state the platform, and report calibration and added value over a severity score (35, 36). Repeated measurement is particularly promising, because the trajectory of a marker over the first days may say more than a single value, and it matches the way clinicians actually watch patients. Studies should also test whether using IL-6 changes decisions or outcomes, since a marker that cannot do so has little claim to a place in practice (40).

A second line of work is to examine IL-6 within phenotypes and to learn whether combinations with other markers outperform any single marker (32, 47). A third is simple replication across settings with different case mix and different laboratory practice. Replication matters because a threshold that works in one intensive care unit may fail in another, where patients arrive earlier or later in the illness, where the infections differ, and where the laboratory uses a different analyser.

Methodological work in this area is also needed. Studies should state in advance which outcome they are predicting and over what period, handle patients who die

early or are discharged in a pre-specified way, and describe how many eligible patients were not sampled and why. These details look tedious, yet they decide whether a reader can tell a real signal from the by-product of who happened to be enrolled. Where several markers are tested, the number tested should be reported, so that a single favourable result among many can be recognised for what it is (27, 34).

Finally, patients and clinicians would benefit from studies that ask what an IL-6 result changes in practice. A marker might shorten uncertainty about who needs a higher level of care, it might help decide whom to enrol in a trial, or it might do neither. Those are testable questions, and answering them would be more valuable than another cohort reporting a further cut-off (40, 47).

6. Conclusion

Serum IL-6 is a biologically sensible and consistently informative indicator of the intensity of the host response in sepsis, and higher values are repeatedly associated with greater severity and with death. As a prognostic marker used alone it is more modest: thresholds are unstable, timing is rarely controlled, and added value over existing scores is seldom demonstrated. The marker may find its best use in combination with clinical data and in selecting patients for studies of immune-modulating treatment, rather than as a stand-alone predictor. The same caution applies to almost any single biomarker in critical illness.

For the researcher, the opportunity is a set of carefully designed and fully reported studies that measure IL-6 at defined times, compare it with severity scores, and test whether acting on it helps patients. For the clinician, the practical message is to treat a high value as one more sign that the patient is seriously ill, and not as an answer.



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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

D.A. conceived the review and wrote the sections on transfusion and clinical context. A.V. wrote the sections on cytokine biology and biomarkers. S.S. wrote the sections on microbiology of sepsis and on study design. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients or samples were involved and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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