# ACLF: Why G-CSF works for some, but fails others

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Acute-on-chronic liver failure (ACLF) carries a high mortality risk, driven by systemic inflammation and immune dysfunction. Granulocyte-colony stimulating factor (G-CSF) has emerged as a potential therapeutic agent, but its efficacy remains inconsistent across trials, leaving clinicians without clear guidance on patient selection. A recent sub-study of the GRAFT trial sought to identify immune biomarkers that could predict both overall prognosis and response to G-CSF treatment in this critically ill population.1

**KEY TAKEAWAYS**

- The Pivot: Specific immune cell populations, particularly monocytes and neutrophils, and inflammatory markers like IL-6, predict G-CSF response and mortality in ACLF.
- The Data: Patients with a G-CSF-induced increase in CD14+CD16+ monocytes had a 3-month survival rate of 80% compared to 33% in non-responders (HR 0.23; 95% CI, 0.08-0.65; P=.006).
- The Action: Monitoring changes in monocyte subsets and inflammatory cytokines after G-CSF initiation may help identify patients most likely to benefit, guiding treatment escalation or de-escalation.

Acute-on-chronic liver failure represents a severe decompensation of chronic liver disease, characterised by organ failure and high short-term mortality. The condition is often triggered by an acute insult, such as infection or alcoholic hepatitis, leading to a profound systemic inflammatory response and immune paralysis. This immune dysregulation is central to the pathogenesis, contributing to susceptibility to further infections and progression of organ failure. G-CSF, a cytokine that stimulates granulopoiesis and mobilises hematopoietic stem cells, has been investigated as a potential therapy to modulate this immune response and improve outcomes.1

The GRAFT trial (NCT02669680) was a prospective, randomised, controlled study designed to evaluate the efficacy and safety of G-CSF in patients with ACLF. This particular sub-study, published in Hepatology International, performed a secondary analysis of 50 patients with ACLF, all of whom received G-CSF treatment. The investigators aimed to identify baseline immune parameters and changes in these parameters after G-CSF administration that correlated with clinical outcomes, specifically 3-month survival and response to therapy. Patients were enrolled from multiple centres, ensuring a representative cohort of individuals with varying etiologies of ACLF.1

## Immune Cell Dynamics and Survival

Patients with ACLF exhibit significant alterations in their immune cell profiles, which this sub-study meticulously characterised. Baseline analysis revealed that patients with higher levels of circulating CD14+CD16+ monocytes, a pro-inflammatory subset, had a worse prognosis. Specifically, those with baseline CD14+CD16+ monocyte counts above the median experienced significantly lower 3-month survival rates compared to those below the median (38% vs 62%; HR 2.1; 95% CI, 1.05-4.2; P=.036). This finding highlights the role of specific monocyte subsets in driving the inflammatory

cascade that dictates ACLF severity and outcome.1

But the dynamic changes in these cells after G-CSF treatment proved even more important for patient survival. Patients whose CD14+CD16+ monocyte count increased by at least 20% from baseline after the first dose of G-CSF demonstrated a markedly improved 3-month survival. Their survival rate reached 80%, in stark contrast to the 33% survival observed in patients who did not show this increase (HR 0.23; 95% CI, 0.08-0.65; P=.006). This suggests that G-CSF's beneficial effects might be mediated through its ability to modulate these specific monocyte populations, potentially shifting them towards a more protective phenotype or enhancing their functional capacity. The ability to identify such a clear responder group based on an early immune response is a significant step forward in personalising ACLF treatment.1

The study also examined other immune cell populations. Neutrophil counts, as expected with G-CSF administration, increased in all patients. However, the magnitude of this increase did not independently predict survival. This indicates that while G-CSF stimulates granulopoiesis, the mere increase in neutrophil numbers may not be the sole mechanism of clinical benefit. Instead, the qualitative changes in immune cell function or the specific subsets mobilised appear to be more relevant. Lymphocyte counts, often suppressed in ACLF, did not show a consistent pattern of change that correlated with G-CSF response or survival in this cohort.1

These detailed immune phenotyping results provide a deeper understanding of the complex relationship between G-CSF and the host immune system in ACLF. The data moves beyond simply counting cells to identifying specific subsets that are mechanistically linked to patient outcomes. This level of granularity is essential for developing targeted therapies and predictive markers, especially in a condition as heterogeneous as ACLF. For a broader understanding of liver disease progression and management, clinicians might find Sherlock's Diseases of the Liver and Biliary System a valuable resource.

## Inflammatory Markers and Prognosis

Beyond cellular changes, the sub-study also investigated the role of inflammatory cytokines as prognostic and predictive biomarkers. Interleukin-6 (IL-6), a key pro-inflammatory cytokine, emerged as a strong independent predictor of mortality. Patients with baseline IL-6 levels above 100 pg/mL had a significantly lower 3-month survival rate (25%) compared to those with lower levels (75%; HR 3.5; 95% CI, 1.6-7.8; P=.001). This reinforces the established role of systemic inflammation in driving poor outcomes in ACLF, highlighting IL-6 as a critical mediator.1

The change in IL-6 levels following G-CSF treatment also held prognostic value. Patients who experienced a reduction in IL-6 levels by at least 30% from baseline after the first G-CSF dose had a significantly higher 3-month survival rate (70%) compared to those whose IL-6 levels remained elevated or increased (30%; HR 0.3; 95% CI, 0.1-0.8; P=.015). This suggests that G-CSF's efficacy might be partly attributed to its ability to attenuate the systemic inflammatory response, and that monitoring IL-6 could serve as an early indicator of treatment success. This aligns with a growing body of evidence linking inflammatory control to improved outcomes in critical illness.1

Other inflammatory markers, such as C-reactive protein (CRP) and tumour necrosis factor-alpha (TNF-alpha), were also measured. While elevated baseline levels of both CRP and TNF-alpha correlated with worse prognosis, their dynamic changes after G-CSF treatment did not reach statistical significance as independent predictors of survival in this cohort. This indicates a specific role for IL-6 in mediating G-CSF's effects or reflecting the overall inflammatory burden more accurately in this context. The study did not explore the full spectrum of inflammatory mediators, but the focus on IL-6 provides a clear, actionable target for monitoring.1

Understanding these inflammatory dynamics is essential for clinicians managing ACLF. Identifying patients with persistently high IL-6 despite G-CSF could prompt consideration of alternative or additional anti-inflammatory strategies. This also provides a potential mechanism for G-CSF's action, beyond just immune cell mobilisation. For more on the broader context of liver disease management and emerging diagnostics, our coverage of non-invasive diagnostics in liver disease staging offers additional insights.

## Predicting G-CSF Response

The core objective of this sub-study was to identify markers that predict response to G-CSF. The most compelling finding was the predictive power of the early change in CD14+CD16+ monocytes. An increase of at least 20% in these cells after the first G-CSF dose was the strongest independent predictor of 3-month survival among G-CSF treated patients (HR 0.23; 95% CI, 0.08-0.65; P=.006). This suggests that a rapid, favourable immune modulation is key to G-CSF's success. Clinicians could potentially use this early cellular response as a guide for continuing or discontinuing G-CSF therapy.1

But it was not just the monocytes. The study also found that baseline levels of IL-6, when combined with the monocyte response, offered an even more robust predictive model. Patients with low baseline IL-6 and a positive CD14+CD16+ monocyte response had the best prognosis, with a 3-month survival rate exceeding 85%. Conversely, patients with high baseline IL-6 and no monocyte response had a dismal survival rate of less than 20%. This stratification highlights the importance of considering both the pre-treatment inflammatory state and the early immune response to G-CSF.1

The study also explored the predictive value of other clinical parameters, such as MELD score and ACLF grade. While these scores are established prognostic indicators in ACLF, they did not independently predict response to G-CSF treatment in the same way the immune biomarkers did. This suggests that while MELD and ACLF grade reflect overall disease severity, they do not capture the specific immunological factors that determine G-CSF efficacy. This distinction is critical for moving towards precision medicine in ACLF. Our previous reporting on factors influencing liver disease outcomes also touches on the complexity of prognostic indicators.

The open-label design of the GRAFT trial is an obvious caveat for this sub-study, as all patients received G-CSF. This means the study could identify predictors of response among G-CSF recipients, but it could not compare outcomes to a placebo group to definitively prove G-CSF's overall efficacy in a biomarker-selected population. A future randomised controlled trial incorporating these biomarkers for patient selection would be necessary to validate this approach. The relatively small sample size of 50 patients also limits the generalisability of these findings, necessitating replication in larger, more diverse cohorts. Still, the consistency of the immune response data across multiple markers lends credibility to the observed associations.1

The trial was not powered to detect differences in rare subgroups, and that gap matters. ACLF is a heterogeneous condition with various etiologies, and the immune response to G-CSF might differ depending on the underlying cause. The study did not provide a detailed breakdown of how these biomarkers performed across different ACLF etiologies (e.g., alcoholic vs. viral hepatitis-induced ACLF). This is an area for future research, as a universal biomarker may not be applicable to all forms of the disease. The study focused on 3-month survival, which is a critical short-term outcome, but longer-term survival and quality of life endpoints were not extensively evaluated in this sub-study.1

The methodology involved flow cytometry for immune cell phenotyping and multiplex assays for cytokine measurement, which are sophisticated techniques not routinely available in all clinical settings. For these biomarkers to become clinically actionable, simpler, more accessible assays would be needed. The timing of biomarker measurement also

needs standardisation; this study focused on baseline and post-first-dose changes. Whether later measurements provide additional predictive value remains unclear. For clinicians seeking a comprehensive reference on internal medicine, the Harrison's Principles of Internal Medicine offers extensive coverage of complex conditions like ACLF.

The study provides a strong foundation for future research into personalised G-CSF therapy for ACLF. The next trial needs to show whether prospectively selecting patients based on these immune biomarkers can improve overall G-CSF efficacy and patient outcomes compared to unselected treatment. This would involve a randomised trial where patients are stratified by their predicted response, potentially leading to a more efficient and effective use of G-CSF in this challenging patient population. Our coverage of AATD-liver disease management also highlights the importance of tailored therapeutic approaches.

### CLINICAL IMPLICATIONS

The GRAFT sub-study offers a compelling argument for a more precise approach to G-CSF in acute-on-chronic liver failure. Simply administering the drug without understanding the underlying immune market appears to be a suboptimal strategy. Identifying patients who exhibit a favourable immune response, specifically an increase in CD14+CD16+ monocytes and a reduction in IL-6, could transform G-CSF from a controversial therapy into a targeted intervention.

For clinicians, this means moving beyond a one-size-fits-all approach. While the assays for these biomarkers are not yet standard practice, the data suggests that an early immune response to G-CSF is a critical determinant of survival. This should prompt a re-evaluation of how G-CSF trials are designed and how treatment decisions are made at the bedside. The current uncertainty surrounding G-CSF efficacy might stem from a failure to identify the true responders.

The pharmaceutical industry, particularly those developing immunomodulatory agents for liver disease, should take note. This study provides clear targets for companion diagnostics. Developing accessible, rapid assays for these monocyte subsets and inflammatory cytokines could unlock the full potential of G-CSF and similar therapies, ensuring they reach the patients most likely to benefit and avoiding futile treatment in non-responders. This precision medicine approach is long overdue in ACLF.

This research pushes the field towards a more sophisticated understanding of ACLF immunology. The next step is to validate these biomarkers in a prospective, randomised trial where patient selection is guided by these immune profiles. Only then can we definitively determine if G-CSF, when precisely targeted, can significantly alter the grim prognosis of ACLF.

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### REFERENCES

1. 1. Splith K, Berndt N, Haber PK. Immune biomarkers predicting response to G-CSF in acute-on-chronic liver failure: results from a GRAFT trial sub-study. Hepatol Int. 2026;20(1):123-132. PMID: 41793651.

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