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LETTER TO THE EDITOR

Interpreting the hazard zone: Factor V and lactate as critical indicators in severe early allograft injury

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Abstract

Graft failure is the worst complication of organ transplantation. Considering liver transplantation, aminotransferase levels have been demonstrated to be a precursor of severe graft failure, in particular when they exceed 5000 U/L in the immediate post-operation. However, some studies show that the outcome of the transplanted liver is not determinable by biochemistry alone. One of the most relevant studies is the one published by Lazzarotto-da-Silva *et al*. In this retrospective study, 341 transplanted livers are considered. In 25 cases, this severe biochemical insult has been reported. But despite this event, more than half had significant long-term survival. One of the most valuable elements that emerge from this work is the identification of two easily measurable markers - serum factor V and arterial lactate, which independently can indicate the graft's 90-day outcome. This finding provides a key clinical picture to distinguish patients who are most likely to recover from those destined for irreversible graft loss. In a time where organs are increasingly scarce, these discoveries could facilitate more prudent use of retransplantation, improving both individual outcomes and the overall distribution of resources. This study contributes significantly to a deeper understanding of early graft injury, although larger prospective studies are needed. It highlights the need to move beyond singular value thresholds and toward integrated, evidence-based decision making during the crucial early post-transplant period. This study not only captures risk but also provides a tool for intervention.

Key Words: Liver transplantation; Early allograft failure; Factor V; Arterial lactate; Biomarker-guided decision-making

Core Tip: In liver transplant recipients, quick identification of grafts susceptible to failure continues to be a clinical challenge, especially when aminotransferase levels exceed 5000 U/L during the early postoperative phase. Although generally considered concerning, these increases do not always indicate poor prognosis. For this reason, the use of functional biomarkers, such as serum factor V and arterial lactate levels, is highly considered to more accurately distinguish patients with a greater chance of recovery from those at risk of early transplant failure. Incorporating these elements into daily clinical practice can improve decision making, minimize retransplantations, optimizing patient outcomes and organ preservation.

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TO THE EDITOR

The early postoperative period in liver transplantation (LT) is a critical and delicate phase in which doctors have to evaluate graft function to closely predict possible organ failure. Traditionally, hepatologists have considered the peak of aminotransferase levels, in particular aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values greater than 5000 U/L within the first 48 hours, as signs of liver damage and criteria for early retransplantation. However, it has been highlighted that these biomarkers, even if altered, do not correspond in an absolute way to a transplant failure; this can be seen in the prolonged longevity observed in many patients with significant enzymatic elevations. This dichotomy demonstrates the need for more specific markers that assess the synthetic and metabolic capacities of the liver, rather than indicating only cellular damage[1-3].

The retrospective study by Lazzarotto-da-Silva *et al*[1] provides an important contribution in this field, systematically evaluating early determinants of graft survival in patients with severe postoperative elevation of aminotransferase. Considering 341 patients who underwent LT, the authors identified 25 cases where AST or ALT levels developed greater than 5000 U/L. No concomitant vascular thrombosis was seen. Early allograft failure (EAF) was developed in 44% of these 25 and was characterized by mortality or need for a new transplant within 90 days. Globally, more than 50% of these patients achieved durable transplant survival. The most important element that emerges from the study is the inadequacy of aminotransferase elevation alone as a catalyst for aggressive clinical intervention. It emphasizes the risks associated with overreliance on isolated markers of injury[4].

Another crucial element discovered by the authors was the recognition of serum factor V and arterial lactate levels assessed on first postoperative day as significant independent indicators of graft outcome. The receiver operating characteristic curve study revealed that serum factor V has an area under the curve (AUC) of 0.936, with an ideal cutoff of 26.2% (with 90% of sensitivity and 92.8% of specificity). Similarly, arterial lactate showed an AUC of 0.919, with a cutoff of 9 mmol/L and similar predictive efficacy. All patients presenting both low factor V levels and high lactate concentrations fulfilled the criteria for EAF, underlining a synergistic prognostic significance. The significance of these two indicators can be indicative of current liver function and systemic metabolic stress, thus providing a more physiologically coherent evaluation of transplant viability[5].

In the study, the predictive value of serum factor V and arterial lactate was measured with remarkable statistical accuracy[1]. On the first postoperative day, factor V exhibited an AUC of 0.936, signifying exceptional discriminating capability. The ideal cutoff determined was 26.2%, with a sensitivity of 90% and a specificity of 92.8%. Correspondingly, arterial lactate produced an AUC of 0.919, with a threshold value of 9 mmol/L, indicating strong predictive accuracy. The thresholds are both statistically significant and clinically actionable: Individuals below the factor V cutoff and over the lactate threshold consistently met the criteria for EAF. The interplay of biomarkers provides a real-time, physiology-based assessment of graft function, assisting doctors in differentiating between reversible graft damage and eventual failure with far better precision than aminotransferase levels alone.

The possibility of integrating these indicators into standard clinical assessments significantly influences decision-making in the early post-transplantation stage. This is very important because the prevailing standard of care often favors reassignment of patients with significant transaminase elevations, causing the risk of an unwarranted new transplantation. Talking about retransplantation, we must take into consideration a few critical aspects; however, it is lifesaving in specific cases: It has significant risks, increased perioperative mortality, suboptimal long-term outcomes, and high healthcare costs. Moreover, it depletes the valuable resource of vital donor organs that could otherwise serve patients on the primary waiting list. Consequently, the identification of patients who maintain synthetic and metabolic function despite elevations in aminotransferases allows physicians to delay or avoid retransplantation. This ensures prudent use of donor organs and patient outcomes[6-8].

It is crucial to evaluate the comparison between serum Factor V and arterial lactate with recognized scoring systems like early allograft dysfunction and the model for early allograft function. These models predominantly depend on conventional biochemical indicators such as bilirubin, international normalized ratio, and aminotransferase levels within the initial week following transplantation. Nevertheless, they may not completely reflect real-time hepatic function or metabolic stress. The incorporation of factor V and lactate may improve existing scoring systems by providing earlier and more physiologically pertinent markers of graft function. Incorporating these indicators into such frameworks may enhance prognostication and optimize the timing of healthcare treatments.

A change in focus can take place during the evaluation of transplant candidates, transitioning from a damage-centric to a function-centric approach. This may introduce an ethical dimension in transplant medicine. The criteria for organ distribution are based on equity, urgency, and efficacy. Starting a new transplant based solely on aminotransferase elevations may lead to overtreatment of patients who should recover, while disadvantaging others with more significant needs. The use of factor V and lactate in clinical decision-making frameworks respects ethical obligations for equitable and reasonable organ management. This strategy has multiple advantages: It could ease the burden on transplant programs, reduce intensive care admissions, and reduce exposure to immunosuppressants when the viability of the transplanted organ is scarce.

Despite the compelling data, we must recognize some limitations: (1) The study is retrospective and conducted in a single center with specific methods and laboratory capabilities. Access to serum factor V testing is not universally available in real time; (2) Lactate is more readily available, but it can be influenced by several systemic factors, as hemorrhagic shock, sepsis, and renal failure, which may obscure its interpretive significance; and (3) The sample size is appropriate for exploratory research, but inadequate to generalize the results across different transplant groups; it requires further validation[9].

Access to serum factor V testing is not universally available in real-time, as it frequently relies on specialized laboratory tests with protracted turnaround times. Recent advancements in hemostatic point-of-care devices and the growing interest in coagulation factor profiling have stimulated preliminary research into bedside or near-patient testing technology. Prototype systems utilizing microfluidic platforms or clot waveform analysis are now under investigation for their ability to fast and correctly assess Factor V. However, they are not yet widely used. The clinical integration of these technologies might facilitate the prompt implementation of findings from research such as that of Lazzarotto-da-Silva *et al* [1], hence broadening their significance beyond tertiary facilities.

To advance the field further, multicenter and prospective studies are needed. The key points of this research could confirm the predictive accuracy of factor V and lactate; assess serial biomarker trends; and study their integration into predictive models or scoring systems, comparing them with conventional measures. Point-of-care tests for factor V could facilitate its widespread adoption in transplant centers. Also, artificial intelligence and machine learning could enable the creation of a dynamic risk classification by integrating biochemical, hemodynamic, and radiographic data into personalized prognostic algorithms. Transplant programs should consider implementing experimental clinical guidelines that integrate early assessments of factor V and lactate in patients with significant aminotransferase elevations.

It is important to note that while the study offers persuasive findings, it is limited by certain methodological constraints. The retrospective methodology automatically predisposes the study to selection and information bias, thus compromising the generalizability of the findings. Confounding factors, such as simultaneous infections, perioperative problems, or inconsistencies in postoperative care protocols, may also affect lactate levels and graft outcomes, thus skewing the perceived prognostic value of the biomarkers. Moreover, serum Factor V testing exhibits a lack of uniformity among transplant centers, characterized by considerable diversity in assay methodologies, turnaround durations, and laboratory capabilities. This variability may provide difficulties in reproducing results or using standardized techniques across diverse therapeutic environments.

CONCLUSIONS

What emerges from the work of Lazzarotto-da-Silva *et al*[1] is a pertinent and therapeutically relevant statement: Aminotransferase levels greater than 5000 U/L, although concerning, cannot definitively indicate liver loss. What is proposed in the article is a paradigm shift toward a function-based assessment, using serum factor V and arterial lactate as primary markers. These biomarkers improve prognostic accuracy, facilitate personalized patient therapy, and maintain ethical organ stewardship in LT. Transplant teams should integrate these markers into early post-liver transplant assessment protocols. This can improve outcomes, minimize unnecessary retransplants, and preserve the limited supply of donor livers.

FOOTNOTES

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