Editorial

Advancing prognostic models in salvage liver transplantation

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Comment on: Wang K, Gao F, Dong S, *et al.* A novel nomogram for prognosis stratification in salvage liver transplantation: a national-wide study with propensity score matching analysis in China. Hepatobiliary Surg Nutr 2023;12:854-67.

Keywords: Hepatocellular carcinoma (HCC); transplantation; surgery

Submitted Jan 11, 2025. Accepted for publication Feb 20, 2025. Published online Mar 25, 2025.
doi: 10.21037/hbsn-2025-29
View this article at: https://dx.doi.org/10.21037/hbsn-2025-29

The relentless pursuit to optimize outcomes for hepatocellular carcinoma (HCC) patients currently drives extensive research in refining liver transplantation as a therapeutic option. The study "A novel nomogram for prognosis stratification in salvage liver transplantation: A nationwide study with propensity score matching analysis in China" provides a compelling argument for stratifying risks in patients undergoing salvage liver transplantation (SLT) to achieve better outcomes (1). Leveraging on a vast dataset from the China Liver Transplant Registry (CLTR), this study addresses the challenges of organ shortage and proposes an evidence-based, data driven framework in developing a pathway for SLT candidate selection to achieve better results, while appreciating that this group (SLT) in fact comprises two subsets; one with a high risk *vs.* another low risk with regards to disease recurrence and survival.

Bridging gaps in SLT evidence

SLT, as a treatment for recurrent HCC after liver resection (LR), has faced scrutiny due to varying outcomes and the lack of established selection criteria. This study not only highlights these disparities but also provides evidence-backed solutions. By utilizing propensity score matching (PSM), the authors addressed confounding factors and presented a balanced comparison between SLT and primary liver transplantation (PLT).

The authors examined 4,244 liver transplant cases performed between 2015 and 2019, applying PSM to balance demographic, clinical, and tumor-related factors between groups. This meticulous approach strengthens the study's validity, allowing for clearer insights into overall survival (OS) and disease-free survival (DFS) between SLT and PLT recipients under the Milan and Hangzhou criteria.

Key findings: risk stratification via nomograms

The study underscores the inherent differences in outcomes between SLT and PLT. SLT recipients meeting Milan (2) or Hangzhou (3) criteria exhibited significantly lower OS and DFS rates than their PLT counterparts. However, a subset of low-risk SLT recipients—classified using a novel nomogram—achieved outcomes comparable to PLT recipients who met Hangzhou criteria. The poorer long-term prognosis after SLT is consistent with that observed in previous studies (4,5). However, unlike previous studies this study also demonstrated no significant difference between SLT and PLT in terms of short-term perioperative outcomes such as operation time, blood loss and length of stay

The proposed nomogram in this study incorporated independent risk factors such as preoperative alpha-fetoprotein (AFP) levels, tumor size, and total tumor diameter and the use of preoperative transarterial chemoembolization (TACE) in offering a predictive tool for patient stratification. The ability to identify low- and high-

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risk SLT recipients has significant implications for clinical decision-making, particularly in resource-constrained settings like China, where organ shortages demand a judicious allocation of liver grafts and hence an LR would be the first choice in treatment of HCC where possible.

However, it is important to note that potentially important prognostic factors after SLT such as interval from LR to recurrence, number of prior treatments and histology of the HCC (grade, microvascular invasion) at the time of LR were not analyzed in the univariate analyses. Inclusion of these factors could potentially improve the robustness of the prognostic nomogram.

Propensity score matching: strengths and limitations

The study's reliance on PSM is a commendable effort to mitigate the inherent bias in retrospective analyses. By matching patients on key characteristics, the authors ensured that comparisons between SLT and PLT groups were more robust and less influenced by pre-existing disparities.

However, PSM (6,7) is not without its limitations. It can only account for measured variables included in the model, leaving unmeasured or unknown confounders unaddressed. Factors such as genetic predispositions, socioeconomic variables, or variations in surgical expertise might have influenced outcomes but were not included in the analysis. This residual bias underscores the importance of cautious interpretation when using PSM in clinical research.

Furthermore, while PSM enhances internal validity by creating well-matched groups, it can reduce generalizability. Unmatched cases are excluded, potentially omitting subpopulations that might be clinically significant. The study does acknowledge this limitation, emphasizing the need for complementary analyses or prospective studies to validate these findings in broader cohorts.

Another limitation of PSM lies in its dependence on observable data. If key prognostic factors are omitted, even the most rigorous matching process cannot eliminate confounding. For instance, tumor microenvironment characteristics or molecular markers—known to influence HCC prognosis—may not have been captured in this dataset.

To address these challenges, future research could incorporate sensitivity analyses to evaluate the impact of unmeasured confounders. Additionally, combining PSM with other methods, such as multivariate regression or instrumental variable analysis, could provide a more comprehensive adjustment for confounding variables (*Table 1*).

Clinical implications of the nomogram

The proposed nomogram represents a shift toward precision medicine in SLT. By integrating clinical, imaging, and biological factors, the model allows clinicians to make more informed decisions about transplant eligibility and risk stratification. This is particularly valuable in countries like China, where organ scarcity necessitates prioritizing patients with the highest likelihood of favorable outcomes.

The study's findings also challenge the applicability of existing Milan and Hangzhou criteria to SLT. While these criteria are well-established for PLT, they fail to account for the complexities of recurrent HCC following LR. The nomogram's ability to incorporate dynamic factors, such as preoperative TACE or AFP levels, reflects a more nuanced approach to candidate selection.

Notably, low-risk SLT recipients identified by the nomogram had comparable OS and DFS to PLT recipients meeting Hangzhou criteria. This suggests that SLT, when applied selectively, can be a viable alternative to PLT, potentially alleviating the burden on the transplant system without compromising outcomes.

Addressing resource constraints with evidence-based tools

The study highlights the potential of data-driven tools to optimize resource allocation in transplantation. As organ shortages persist worldwide, models like the proposed nomogram offer a pathway to maximize the utility of available grafts. By identifying patients likely to benefit most from SLT, transplant programs can enhance efficiency while maintaining equity (8,9).

Moreover, the study underscores the need for ongoing innovation in transplant selection criteria. Static thresholds, like those defined by the Milan or Hangzhou criteria, may no longer suffice in an era of personalized precision medicine. Dynamic models that account for tumor biology, preoperative interventions, and individual patient factors are better suited to address the complexities of transplantation.

Limitations and future directions

While the study represents a significant advancement, it is

Table 1 Propensity scoring considerations

Category	Variable	Potential impact on bias
Patient demographics	Socioeconomic status (income, education)	May affect access to healthcare, compliance with follow-ups, and overall health outcomes
	Geographic location (urban *vs.* rural)	Differences in access to advanced medical facilities and specialized care
	Lifestyle factors (smoking, alcohol use)	Could impact liver function and post-transplant recovery
Clinical factors	Genetic predispositions	May influence tumor progression, recurrence risk, and immune responses
	Nutritional status	Malnutrition or sarcopenia can affect post-surgical recovery and long-term survival
	Detailed comorbidities (e.g., cardiovascular)	Additional comorbidities can affect both perioperative and long-term outcomes
Tumor characteristics	Molecular and genetic markers	Markers like VEGF or HIF-1α may indicate aggressive tumor biology not captured by size or number alone
	Tumor microenvironment characteristics	Interactions with immune cells and stromal components could influence tumor behavior and recurrence
Preoperative factors	Psychosocial support	Lack of support could lead to poor compliance with immunosuppressive therapy and follow-up protocols
	Time from liver resection to SLT	May reflect tumor progression dynamics and patient stability over time
Postoperative factors	Surgical complications	These might independently impact survival outcomes beyond the immediate propensity score variables
	Adherence to immunosuppressive therapy	Non-adherence increases the risk of graft rejection and tumor recurrence
	Immunosuppressive regime	Low tacrolimus with or without everolimus/sirolimus
	Postoperative rehabilitation	Quality and duration of rehabilitation can influence recovery trajectories and survival outcomes
Health care variables	Surgical expertise of transplant team	Variations in skill levels can directly impact surgical success and complications
	Hospital resources and facilities	Differences in ICU capabilities, infection control, and post-operative care may affect patient outcomes

HIF-1α, hypoxia-inducible factor-1alpha; ICU, intensive care unit; SLT, salvage liver transplantation; VEGF, vascular endothelial growth factor.

not without its limitations. The retrospective design, though strengthened by PSM, remains susceptible to residual biases (8,10,11). The exclusion of unmatched cases further limits the generalizability of the findings. Additionally, the lack of longitudinal data from initial LR to SLT precludes an intention-to-treat analysis, which could provide deeper insights into patient trajectories.

Future research should focus on validating the nomogram in diverse populations through prospective, multicenter studies. Incorporating molecular and genetic markers could further refine its predictive accuracy. Additionally, studies examining the impact of preoperative interventions, such as TACE (10) or sorafenib, on long-term outcomes could inform more comprehensive risk models.

Conclusion: a new era in SLT management—a paradigm shift

This study marks a pivotal step forward in the management of recurrent HCC. By leveraging PSM and a novel

nomogram, the authors provide a robust framework for SLT candidate selection, addressing critical gaps in existing criteria. While PSM strengthens the validity of their findings, its limitations highlight the need for complementary approaches to account for unmeasured confounders.

The proposed risk stratification model offers a pragmatic solution to the challenges of organ allocation in transplantation. By identifying low-risk SLT candidates, it paves the way for more equitable and efficient use of resources. The fruits of this nomogram is clearly borne out by the survival benefits we see when the nomogram is applied (1). As the global transplant community embraces precision medicine, tools like this nomogram will play an increasingly central role in shaping the future of liver transplantation.

This study sets a high standard for future research in transplantation. The integration of rigorous statistical methods, large-scale data, and clinical insights underscores the importance of innovation and the use of data in improving patient outcomes. With continued validation and refinement, the findings of this study have the potential to reshape the landscape of SLT, offering new hope to patients with recurrent HCC.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *HepatoBiliary Surgery and Nutrition*. The article did not undergo external peer review.

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-2025-29/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Jeyaraj PR, Goh BKP. Advancing prognostic models in salvage liver transplantation. HepatoBiliary Surg Nutr 2025;14(2):332-336. doi: 10.21037/hbsn-2025-29