· Review ·

Progress in research on risk factors and prediction models for alcohol consumption after liver transplantation in patients with alcoholic liver disease

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Abstract

Patients with alcoholic liver disease who resume alcohol consumption after liver transplantation are at risk of graft dysfunction, which poses a serious threat to their survival. This review summarizes the definitions and classifications of alcohol relapse, risk factors for alcohol relapse after liver transplantation for alcoholic liver disease, and models that predict alcohol relapse. The aim is to provide a theoretical basis for identifying high-risk patients and optimizing nursing management strategies for this patient population.

Keywords: Alcoholic liver disease, liver transplantation, relapse drinking, influencing factors, predictive models

Alcoholic liver disease (ALD) refers to liver diseases caused by long-term heavy alcohol consumption. In the early stage, it usually manifests as simple fatty liver, which can then progress to alcoholic hepatitis, liver fibrosis, and cirrhosis, and may even lead to liver failure [1]. Liver transplantation (LT) is the most effective treatment for end-stage liver disease related to ALD [2], and the proportion of patients with alcoholic cirrhosis who undergo LT is increasing year by year [3]. Although LT is effective in treating end-stage ALD, it cannot eliminate the primary cause. Approximately 20.4% of patients will resume drinking after surgery, and this proportion gradually increases with the extension of postoperative time [4]. This phenomenon can lead to graft steatosis in patients, increase the risk of alcoholic hepatitis and cirrhosis, and significantly increase the risk of patient death [4, 5]. Therefore, resuming drinking has become a key issue affecting the long-term prognosis of ALD patients after LT. Identifying the influencing factors of postoperative resumption of drinking and establishing a predictive model is crucial for optimizing patient management and improving clinical outcomes. There have been numerous studies abroad [6, 7], but there are relatively few domestic reports. The following is a

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review of the definition and classification of resuming drinking, the influencing factors of the postoperative resumption of drinking status in ALD patients after LT, and the predictive model.

Definition and classification of resuming drinking

There is no unified standard for the definition of resuming drinking in existing research. In foreign countries, most studies [4, 6] define resuming drinking as the consumption of any alcohol after LT. There are also some studies that define resuming drinking based on the amount of alcohol consumed, such as the WHO's "more than 20 g of alcohol per day for women, more than 30 g of alcohol per day for men" [7], or consuming ≥5 alcohol units per day for more than 2 consecutive days, or having a total weekly alcohol consumption of ≥14 cups for at least 4 weeks [8]. In addition, some studies [4, 6] divide resuming drinking into two categories, namely "occasional" drinking and harmful drinking. Harmful resuming drinking generally refers to any continuous, heavy drinking or binge drinking events, including any reports of alcohol-related emergency visits and hospitalizations, or drinking events that cause social harm. There are also researchers and scholars [9] who further subdivide resuming drinking into the following five situations: death due to liver decompensation during alcoholic hepatitis, heavy drinking without attempting abstinence and increasing continuously, heavy drinking and attempting abstinence followed by admission to a psychiatric hospital, uncommon repeated drinking events, and single drinking occasions. The incidence of resuming drinking abroad ranges from 4% to 95% [10]. A meta-analysis study [10] showed that the incidence of postoperative resuming drinking was 22%. In China, the incidence of postoperative resuming drinking in ALD patients after LT ranges from 2.8% to 46.15% [11, 12]. These studies mainly identify whether patients have resumed drinking behavior through reports from patients and their families, or through the detection results of patients' body fluids and hair.

Influencing factors of postoperative resuming drinking status in ALD patients after LT

Patient factors

Demographic characteristics: Age, gender, employment status, and having first-degree relatives with alcoholism are influencing factors for postoperative resuming drinking in ALD patients, among which age and gender are immutable. Age is an important factor affecting postoperative resuming drinking in ALD patients. The average age of resuming drinkers is nearly 8 years younger than that of abstainers, and young people are more likely to drink excessively. Young people with alcohol use disorders are more inclined to binge drink to get drunk quickly [13-15]. In addition, younger patients, due to their "immaturity," have a lower sense of responsibility to their family and society and lack self-discipline, which is also an important reason for resuming drinking. Some research results [8, 16] show that women are a high-risk group for postoperative resuming drinking. However, due to the high incidence of anxiety and depression in the female population, it may to some extent confuse the judgment of women as a risk factor. On the contrary, some research results [17] show that men have a higher probability of resuming drinking. This difference in results may be due to the basic characteristics of the research subjects and the different definitions of resuming drinking, so the specific influence of gender still needs further verification. Some research results [7] show that the probability of postoperative resuming drinking in retired ALD patients is 2.9 times that of employed patients, which may be related to the fact that retired patients have a lot of spare time,

increasing the possibility of drinking. In addition, patients with first-degree relatives such as parents and siblings who have alcoholism are more likely to relapse after surgery [18], which may be related to genetic factors. Therefore, it is necessary to accurately assess the demographic characteristics of patients to provide effective clinical information for subsequent interventions.

Lifestyle: Smoking and preoperative drinking status are influencing factors for postoperative resuming drinking in ALD patients. Some research results [19] show that patients who smoke are more likely to resume drinking after surgery. Smoking and drinking have common reward pathways, and at the same time, smoking and drinking can reinforce each other. Tobacco and nicotine can increase the craving for alcohol, reduce the subjective effects of alcohol, and thus increase alcohol consumption [20]. The preoperative drinking status of LT is closely related to the patient's postoperative resuming drinking. The daily alcohol intake before surgery, whether there is alcohol dependence and alcohol withdrawal syndrome, whether to abstain from alcohol before surgery and whether to relapse after abstinence are all influencing factors [7, 8, 21, 22]. The duration of preoperative abstinence is the most concerned and controversial factor in the preoperative drinking status. Some research results [23] show that for every additional month of alcohol abstinence before LT, the recurrence rate of postoperative resuming drinking decreases by 5%. Some research results [24] show that patients with a pre-transplant abstinence period of less than 6 months are more likely to resume drinking after surgery. Previously, various transplant centers strictly required ALD patients to have a 6-month alcohol abstinence period before liver function and portal hypertension could potentially improve, and proposed that this could potentially reduce the possibility of alcohol relapse and ensure long-term alcohol abstinence. However, this conclusion has been questioned by many subsequent studies. Some research results [25, 26] show that there is no significant difference in the risk of death and resuming drinking after LT between patients with an abstinence period of less than 6 months and those with an abstinence period of 6 months or more, which is consistent with the previous research results in China [11-12]. In view of this, some countries no longer require end-stage ALD patients to abstain from alcohol for 6 months before LT [27]. In view of the above results, medical staff should fully understand the patient's lifestyle when assessing the patient, identify the risk of postoperative resuming drinking in ALD patients in time, and take effective intervention measures in time to reduce the incidence of patient resuming drinking.

Disease and treatment related factors

Chronic complications after transplantation: If patients have chronic complications such as biliary tract diseases, incisional hernia or umbilical hernia, intra-abdominal infection, cardiovascular and cerebrovascular diseases after LT, the risk of alcohol relapse will increase. The probability of alcohol relapse at 1 year and 3 years after transplantation is 7% and 13.3% respectively, and having chronic complications can increase the incidence of resuming drinking in low-risk groups by 23.92 times [28]. This suggests that high-risk groups for resuming drinking should be closely followed up, and medium and low-risk groups should also be monitored under the support of multidisciplinary teams and social support, so as to carry out individualized interventions when patients have chronic complications in the early stage to reduce the probability of alcohol relapse.

Treatment compliance: Previous research results [29, 30] show that the patient's treatment-related compliance is

related to the risk of postoperative resuming drinking. Patients who do not comply with outpatient follow-up have a significantly increased probability of alcohol relapse, and non-compliance with treatment is a risk factor for alcohol relapse. Stopping drinking at the initial diagnosis of liver disease, participating in preoperative intensive outpatient treatment under clinical advice, and having a high compliance with immunosuppressants are also positively correlated with patients' postoperative resuming drinking [21, 30]. The clinical medical team can provide systematic and professional support and regularly follow up high-risk groups to improve patients' understanding of disease treatment, thereby improving patients' treatment compliance.

Psychological factors: Previous research results [28, 31] show that patients with comorbid mental disorders (such as anxiety or depression) have a risk of postoperative resuming drinking that is 3.93 times that of patients without comorbid mental disorders. More than 1/3 of patients with alcohol use disorders have anxiety and other emotional disorders, and there is a strong bidirectional relationship between drinking and depressive or anxiety symptoms. On the one hand, alcohol can act as a "drug" to alleviate mental symptoms; on the other hand, long-term use of alcohol may lead to the development and exacerbation of these symptoms, which may be related to the destruction of social relationships by alcohol or its direct impact on the brain. This suggests that in addition to disease treatment for patients, it is recommended to use psychological support, such as improving self-efficacy, carrying out cognitive restructuring, balancing lifestyle and addictive behaviors, stimulus control techniques, and impulse management skills and other measures [32].

Factors related to social support system

Family and social support: The social support system is an important protective factor for preventing resuming drinking in ALD patients after LT. Social support includes recognition and help from family members, friends or others, especially in terms of transportation, drug supervision and daily life activities, which are crucial for patients to smoothly transition to independent living [14]. Among them, family support, especially support from spouses, is particularly concerned. Previous research results [6, 21] show that ALD patients without a life partner, or those who are single, divorced, or widowed, are more likely to resume drinking after surgery. However, some research results [33] show that compared with single patients, married patients are more likely to experience harmful relapse, which may be related to the fact that spouses are more likely to report and disclose relapse situations to the transplant team. Previous research results [21] show that spouse donation or accompaniment is an alternative factor for good family support, which can reduce the risk of alcohol relapse. The recurrence rate of patients with donors from spouses and first-degree relatives is lower than that of patients with donors from second-degree relatives. Existing research is increasingly emphasizing the inclusion of social support, especially increasing family support in alcohol rehabilitation programs, to strengthen alcohol management after LT. In nursing work, special attention should be paid to ALD patients with the above characteristics, and personalized intervention measures should be taken to prevent the occurrence of postoperative resuming drinking.

Multidisciplinary support: Receiving a multidisciplinary support (MS) program before LT is helpful in preventing alcohol relapse in ALD patients. The MS project effectively prevents alcohol relapse by identifying high-risk patients early and incorporating them into a close follow-up and intensive support system of nursing staff and family members [8]. However, research on the procedures and practices of providing support to

patients before and after LT to prevent alcohol relapse is relatively limited. Although there is a general consensus that patients undergoing LT should be assessed by a professional rehabilitation team, there is still a lack of clear standards when building an effective support system [34]. In addition, the current guidelines [35] also fail to provide specific guidance on how to achieve the best cooperation among multidisciplinary teams, and further research and standardization are needed.

Predictive model of postoperative resuming drinking atatus in ALD patients after LT

In the early stage of research, due to factors such as donor shortage, the starting point for researchers to build predictive models was to screen patients who were prone to resuming drinking on the transplant list. Nowadays, the important significance of the predictive model lies in the early identification of high-risk patients and the implementation of active interventions. The basic characteristics of the existing postoperative resuming drinking risk prediction models for ALD patients after LT at home and abroad are shown in Table 1.

High-risk alcohol relapse

High-risk alcohol relapse (HRAR) scale was developed in 1991 [36] using a Cox proportional hazards model in a study that included 255 male veterans from eight Veterans Affairs medical centers in the US and aimed to predict the risk of rehospitalization for alcohol relapse after treatment. The HRAR scale consists of three components: duration of heavy drinking (≤11 years, 0 points; 11–25 years, 1 point; ≥25 years, 2 points), daily alcohol consumption (≤9 drinks, 0 points; 9–17

Table 1. Four models for prediction of risk of alcohol relapse after liver transplantation in patients with alcoholic liver disease (n=4).

Studies included	Research subjects	Sample size, n	Age, years	Sex	Study design	Predicted outcome/ diagnostic basis	Statistical modeling	Evaluation of model	Verification of model
Booth et al. [36] (1991)	Veterans receiving treatment at a medical center	255	43.4 (21–70)[1]	Male, n=255 Female, n=0	Retrospective	Risk of readmission for alcohol use disorder after LT	Cox proportional hazards regression	Sensitivity of 0.55, specificity of 0.77	External validation
Rodrigue et al. [37] (2013)	Patients with liver and kidney transplantation	118	54.7 ± 8.2[2]	Male, n=101 Female, n=17	Retrospective	Any alcohol consumption after LT	Multivariate logistic regression	AUC of 0.892	No data
Lee et al.[38] (2019)	Patients with severe alcoholic hepatitis undergoing LT	129	42 [34, 51][3]	Male, n=96 Female, n=33	Retrospective	Continued alcohol consumption after LT	LASSO logistic regression, multivariate logistic regression, classification and regression trees	Specificity of 0.84, C-statistic of 0.76	Internal cross-validation
Satapathy et al. [39] (2020)	Patients with ALD undergoing LT	241	53.19 ± 8.42[2]	Male, n=196 Female, n=45	Retrospective	Harmful alcohol consumption after LT	Multivariate logistic regression	AUC of 0.79	Internal cross-validation

Notes: [1]Age is shown as the mean (range), [2]the mean ± standard deviation, and [3]as the median [interquartile range].
Abbreviations: ALD, alcoholic liver disease; AUC, area under the curve; LASSO, Least Absolute Shrinkage and Selection Operator; LT, liver transplantation.

drinks, 1 point; ≥17 drinks, 2 points), and number of previous alcohol dependence-related hospitalizations (0, 0 points; 1, 1 point; ≥1, 2 points). Each component can score 0–2 points, with the total score ranging from 0 to 6 points. Scores of 0–3 are considered low-risk, and scores of 4–6 are considered high-risk. In 1992, researchers validated this model in an independent sample, showing a rehospitalization rate within 6 months of 61% in the high-risk group and 28% in the low-risk group, indicating that the model had good discriminatory ability [37]. The HRAR scale was subsequently introduced for prediction of alcohol relapse in the LT population [38] and is now the tool most commonly used for prediction of post-LT alcohol relapse or harmful alcohol consumption. However, some studies have found that its predictive power is not ideal [39, 40]. For example, its C-statistic is only 0.59, with a sensitivity of 0.13/0.17 and a specificity of 0.87, possibly because of differences in the operational definitions of outcome variables between studies and the model not being sufficiently adapted when used in the LT population, reducing its accuracy. Moreover, the study population used for development of the HRAR scale was entirely male, and the model's prediction performance may be different in studies that include female patients [41]. Further research is needed for re-evaluation and adjustment of the parameters in the HRAR model by collecting data from relevant populations to ensure its predictive accuracy and reliability in new settings.

Alcohol relapse risk assessment

Alcohol relapse risk assessment (ARRA) scoring system was developed in a study published in 2013 [42]. The outcome variable was any alcohol consumption after LT, which occurred in 34% of cases. The researchers identified 25 dichotomous candidate predictors from a literature review, expert advice, and clinical experience, and retrospectively investigated 118 patients with alcohol dependence or abuse, including 106 patients who had undergone LT and 12 who had received a liver–kidney transplant. They screened the candidate variables in univariate analysis and constructed a scoring system using logistic regression, ultimately retaining nine predictors (hepatocellular carcinoma, tobacco dependence, continued alcohol consumption after diagnosis of liver disease, low motivation for treatment to prevent relapse, poor stress management skills, lack of rehabilitation relationships, limited social support, lack of consequences for non-medical behaviors, and continued participation in social activities that involve alcohol). The study did not use regression coefficients but assigned 1 point to each factor, with the total score being the sum. The ARRA categorizes scores into four groups: very low-risk (0 points, 0% risk of relapse), low-risk (1–3 points, 8% risk of relapse), moderate-risk (4–6 points, 57% risk of relapse), and high-risk (7–9 points, 75% risk of relapse). The simplified ARRA had an area under the curve of 0.892. Seven of the nine factors in the model are modifiable, which is advantageous when implementing nursing interventions, suggesting that intervening on these factors before LT can reduce the risk of postoperative alcohol relapse. However, the model needs to be evaluated by professionals, and the operational definition of some factors is not provided in the original study, which limits the popularization and application of the model to some extent.

Sustained alcohol use post-liver transplant

Sustained alcohol use post-liver transplant (SALT) was developed based on data from 129 patients with severe alcoholic hepatitis who were recruited from 12 medical centers in the US [43]. Sustained alcohol use was defined as consumption for ≥100 days and had an incidence rate of 10%. This study was the first to apply a machine learning algorithm to predict alcohol relapse

and used multiple methods, including LASSO (least absolute shrinkage and selection operator) logistic regression, logistic regression, and classification and regression trees to construct the SALT scale. This scoring system essentially includes four variables: consuming >10 alcoholic drinks/day during the first hospitalization (4 points), history of illegal drug use (1 point), an alcohol-related criminal record (2 points), and multiple attempts at cessation of alcohol consumption (4 points), with a score range of 0–11 points. The cut-off score for SALT is 5 points, which has a positive predictive value of 25% (95% confidence interval [CI] 10–47), a negative predictive value of 95% (95% CI 89–98), a specificity of 84% (95% CI 76–90), and a C-index of 0.76. The study used ten-fold cross-validation for internal validation; the average C-index was 0.74, indicating good prediction performance. However, the model has not undergone external validation and may be impacted by overfitting, limiting its generalizability to other datasets. Therefore, in subsequent studies, the prediction performance of the SALT scoring system has been unstable [24, 40, 44]. Furthermore, although alcohol-related crimes are increasing year by year in China [44], the overall incidence is much lower than in other countries. Whether factors such as a history of illegal drug use and an alcohol-related criminal record included in this scoring system are applicable to the local context in China requires further research and discussion.

Harmful alcohol relapse after liver transplant

Harmful alcohol relapse after liver transplant (HALT) score was developed in a study from 2020 that included 241 patients with ALD who underwent LT, with 18 patients also receiving a kidney transplant [45]. Factors were selected using forward, backward, stepwise, least absolute shrinkage, and LASSO regression methods. Finally, a harmful drinking risk assessment model was established using logistic regression as follows:

$$P = \{\exp[0.8155 + (-0.0817) \times \text{age at LT} + 0.8845 \times \text{abstinence period before LT} + 1.1172 \times \text{daily alcohol consumption} + 1.3277 \times \text{history of alcohol-related crimes}]\} / \{1 + \exp[0.8155 + (-0.0817) \times \text{age at LT} + 0.8845 \times \text{abstinence period before LT} + 1.1172 \times \text{daily alcohol consumption} + 1.3277 \times \text{history of alcohol-related crimes}]\}$$ [8].

Harmful alcohol consumption was defined as drinking ≥3 times per week, alcohol-related medical visits, or engaging in alcohol-related social harm events. In this study, alcohol relapse was determined primarily by urine testing. The incidence of harmful alcohol consumption was 10%. Age at the time of LT is a continuous variable in HALT, while the remaining three variables are dichotomous: history of alcohol-related criminal activity (1, yes; 0, no), whether or not the pre-LT abstinence period was ≤6 months (1, yes; 0, no); and whether the number of alcoholic drinks consumed per day was ≥10 (1, yes; 0, no). The HALT score can provide an estimate of the probability of a harmful alcohol relapse. The area under the receiver-operating characteristic curve for HALT is 0.79, and with a 2 to 1 ratio for internal cross-validation and 100 iterations, the average C-index is 0.74 and the mean accuracy is 0.90. This model was developed relatively recently and has not yet been investigated in other studies.

Comparison of prediction models

Construction methods: The Prediction Model Risk of Bias Assessment Tool (PROBAST) prioritizes prospective cohort studies, case-cohort studies, randomized controlled trials, and registry data as data sources [46]. However, the four studies in which the prediction models discussed in this report were developed had a retrospective design [36, 42, 45], increasing the risk of bias in their data sources. This shortcoming might be explained by sample size limitations that restricted the ability

to perform a prospective cohort study. Furthermore, the study populations in the SALT [43] and HRAR [36] studies were derived from multiple centers, while the others were from single centers [42, 45], meaning that the samples were insufficiently representative. In terms of outcome determination, two studies had or potentially had a risk of inconsistency in judgment methods. The outcome determination in ARRA [42] was based on reports from patients, their family members, or a review of medical records. Although all patients in the SALT study [43] self-reported, objective testing was conducted on all patients from seven centers, whereas only selected patients from the remaining three centers underwent testing. The HALT [45] and HRAR [36] studies used urine testing and structured interviews, respectively, to determine outcomes. The ARRA [42] and HRAR [36] studies selected predictors based on the results of univariate analysis, which increased the risk of bias. In contrast, the SALT [43]and HALT [45] studies used methods such as LASSO regression to screen for predictors, avoiding the risk of bias. In addition, the sample size calculation for prediction models often adopts the 10 events per variable rule, meaning that there should be 10 positive events for each variable. All the prediction models [36, 42, 43, 45] identified in this study have the drawback of including a large number of predictors but few positive events, which can lead to overfitting of the model.

Comparison of validation methods and clinical applications: In terms of model validation, the HALT study [45] used random splitting for internal validation, the SALT study [43] used 10-fold cross-validation, and the other two models [36, 42] reported results that were based on internal validation. All four studies [36, 42, 43, 45] reported on model calibration; however, the ARRA, SALT, and HALT studies [42, 43, 45] did not subject their model to external validation. In terms of clinical application, the SALT [43], HALT [45], and HRAR [36] scales are accurate and easy to use, allowing nurses to identify high-risk patients by history-taking, whereas the ARRA scale [42] contains a greater number of items and often requires administration by professionals such as addiction experts.

Other prediction tools: Rather than constructing prediction models, some studies have used previously established scales or scores to predict alcohol relapse. For example, the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) was originally designed for psychosocial assessment of transplant patients but was then used to predict alcohol relapse after surgery in patients with ALD [30]. The researchers found that a SIPAT score of ≥21 was associated with alcohol relapse (hazard ratio 6.40, 95% CI1.36–30.18, p=0.019). There is some research indicating that a SIPAT score of 30 has the best sensitivity and specificity (0.78 and of 0.51, respectively) [39]. Other researchers used the simplified Barrett Impulsiveness Scale and found that a cut-off score of 12 predicted alcohol relapse with an area under the receiver-operating characteristic curve of 83.3% [47]. Another group used a psychosocial score to predict harmful drinking after surgery and reported an area under the curve of 0.930 and acceptable external validation results [48]. There are additional tools, such as the Hopkins Psychosocial Scale [49] and the Michigan Alcoholism Prognosis Score [50], both of which have shortcomings in terms of the source of study participants, sample size, evaluation of model performance, and validation. Future studies should include larger sample sizes, conduct high-quality research, and validate and evaluate the scales to provide assessment tools that are suitable for clinical decision-making.

Outlook and Summary

Alcohol relapse in patients who have undergone LT

for ALD is influenced by various factors, but local research remains limited. Given the differences in drinking culture, social environment, and healthcare systems between China and Western countries, exploring specific risk factors for Chinese patients will provide better guidance for local clinical nursing practice. Future research on prediction models should consider the following: introduction of factors that align with the characteristics of the Chinese population in combination with China's cultural characteristics and everyday living situations; use of advanced machine learning algorithms to enhance the predictive power and clinical guidance value of a prediction model through visualization tools; and construction of a model in strict accordance with the PROBAST evaluation criteria to ensure methodological rigor and reduce the risk of bias, thereby optimizing the reliability and effectiveness of the model. Using these measures, future research will provide more precise guidance on how to improve postoperative management of patients with ALD in China.

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Author Contributions

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Conflicts of Interests

The author declares no conflict of interest.

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