The Impact of Donor Liver Fibrosis on the Outcomes of Patients Who Undergo Liver Transplant: A Cohort Study from Unos Database

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Article

The Impact of Donor Liver Fibrosis on the Outcomes of Patients Who Undergo Liver Transplant: A Cohort Study from UNOS Database

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Abstract: Background: The increasing prevalence of fibrosis in donor livers raises concerns about its impact on post-transplantation outcomes, though this relationship remains unclear. This study aims to assess the effect of donor liver fibrosis on patient and graft survival following liver transplantation. **Methods:** Data from the UNOS-STAR registry (1987–2024) were analyzed, focusing on patients who received liver transplants with biopsy-proven fibrosis. The cohort was stratified based on fibrosis grade, and outcomes were compared using Cox regression and Kaplan-Meier survival analysis. Competing risk models were applied to assess specific mortality causes, and subgroup analyses explored the sensitivity of fibrosis on transplant outcomes. **Results:** Of the 22,897 patients, 17,926 received non-fibrotic grafts, and 4,971 had grafts with varying fibrosis grades. Donor fibrosis was associated with donor age, steatosis, and portal infiltrate, generally affecting those in better overall condition. Significant differences were observed in patient survival (p=0.001) and graft survival (p=0.002) between the fibrosis and non-fibrosis groups. Further analysis revealed that fibrosis increased the risk of malignancy (p=0.028), cardiovascular disease (p=0.017), and respiratory failure (p=0.033), but showed lower rejection rates at six months and one year. Sensitivity analyses confirmed fibrosis as an independent risk factor, with varying effects in subgroups. **Conclusion:** Donor liver fibrosis significantly impacts post-transplant outcomes, notably increasing the risk of all-cause mortality and graft failure. Specific causes of death, such as malignancy and cardiovascular disease, were more prevalent in recipients of fibrotic grafts, highlighting the need for further research to refine donor selection criteria.

Keywords: liver transplantation; donor fibrosis; graft failure; transplant outcome

Introduction

Liver transplantation(LT) remains the most effective treatment for end-stage liver disease, offering patients a chance for long-term survival and improved quality of life[1], However, the success of this procedure heavily depends on the quality of the donor liver.[2] In recent years, the disparity between organ availability and demand has contributed significantly to waitlist mortality and has thereby led to increased utilization of marginal or extended criteria donor (ECD), with the increasing prevalence of liver fibrosis in donor organs, which now has been emerged as a significant challenge for transplantation[3,4]. Fibrosis, which results from chronic liver injury, leads to the accumulation of fibrotic tissue in the liver and has become more common due to various reasons, the elder donor population[5]and rising incidences of metabolic disorders such as obesity, diabetes, and metabolic dysfunction associated with steatohepatitis(MASH)[6–8], While liver, including patient survival and graft function, remains insufficiently studied.

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Previous studies have focused on various donor characteristics, such as age, body mass index (BMI)[9,10], and the presence of steatosis[11,12], but have largely overlooked the role of fibrosis itself. Fibrosis progression after transplant is often considered a negative prognostic factor[13,14], which leads to early graft loss and patient death. However, the impact of donor fibrosis is controversial, the lack of clear and solid evidence creates confusion when determining whether to use fibrotic livers and selecting appropriate patients. As the demand for donor organs continues to exceed supply, understanding the risks and outcomes associated with using fibrotic grafts is crucial for optimizing transplant success and ensuring better long-term outcomes for recipients.

The objective of this study is to evaluate the impact of donor liver fibrosis on post-transplant outcomes, specifically focusing on all-cause mortality and graft survival. Using data from the UNOS registry[15], this study aims to explore whether the presence and severity of fibrosis in donor livers are independent risk factors for adverse transplant outcomes for a long-term follow-up. Additionally, this study investigates the relationship between fibrosis and specific causes of mortality, such as malignancy and cardiovascular disease, while also assessing potential protective factors, such as lower rejection rates within the first year after transplantation.

To achieve these aims, this study analyzed a large cohort of liver transplant recipients using advanced statistical methods. Patients were stratified based on the histologic grade of fibrosis in the donor grafts, and outcomes were compared using Cox proportional hazards models and Kaplan-Meier survival analysis. Further analyses included competing risk models to assess specific causes of mortality, along with subgroup sensitivity analyses to evaluate the robustness of fibrosis as an independent risk factor. By leveraging the extensive data available from the UNOS-STAR registry, this study provides a comprehensive assessment of the risks associated with receiving fibrotic donor grafts and contributes to refining donor selection criteria.

To be short, this study seeks to clarify the role of donor liver fibrosis in influencing post-transplant outcomes. By identifying the specific risks and potential benefits associated with using fibrotic grafts, this research has the potential to instruct clinical decision-making and improve the allocation of donor organs. Ultimately, the findings will help guide transplant professionals in balancing the risks of fibrosis with the pressing need for donor organs, thereby optimizing outcomes for liver transplant recipients.

Methods

Patients selection

This study utilized data from the United Network for Organ Sharing (UNOS) Scientific Registry of Transplant Recipients (SRTR), which includes liver transplant recipients between September 30, 1987, and April 1, 2024. The primary focus was on deceased donor liver transplant cases. The initial dataset comprised 291,377 transplant cases, from which the study cohort was refined based on specific exclusion criteria. Patients were excluded if they had incomplete liver biopsy data for macrovascular and microvascular steatosis, missing liver fibrosis or portal vein infiltrates records, missing key variables such as Patient or Graft survival time, or if they were under the age of 18 or had undergone prior liver transplants or other organ transplantation. In order to assess the outcome more precisely we also exclude a follow-up time of less than one year. After applying these criteria, the final study cohort included 22,898 patients. This cohort was further stratified based on the histologic grade of fibrosis, with the aim of comparing post-transplant outcomes.

Outcomes

The primary outcomes of interest were all-cause mortality and graft survival. Secondary outcomes included specific causes of mortality, such as malignancy, cardiovascular disease, and respiratory failure, as well as early rejection rates within six months and one-year post-transplant. Historically variable factors, such as donor age, the presence of steatosis, and portal infiltrates, were also analyzed to assess their association with fibrosis and transplant outcomes. These factors provided context to better understand how donor conditions influenced the recipient's survival and graft function after the transplant.

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Statistical Analysis

Statistical analyses were conducted using Cox proportional hazards regression models to evaluate the impact of donor liver fibrosis on patient survival and graft survival. Kaplan–Meier(KM) survival and competing risk models were used to assess specific causes of mortality, such as malignancy and cardiovascular disease while accounting for the competing risk of death from other causes. Subgroup analyses were performed to explore the sensitivity of fibrosis as an independent risk factor across various recipient demographics and clinical conditions. All statistical analyses were conducted using statistical software, and a p-value of less than 0.05 was considered statistically significant.

Results

Baseline of donor and recipient characteristic

The study analyzed 22,897 liver transplant recipients, comparing those who received non-fibrotic grafts (n=17,926) with those who received fibrotic grafts (n=4,971). Donors' average age was higher in the fibrosis group (48.6 vs. 47.3 years, p<0.001), and gender differences were notable, with 59.9% male in the fibrosis group versus 55.6% in the non-fibrotic group (p<0.001). Macro-steatosis in the liver also differed significantly, averaging 10.5% fatty change in the fibrosis group versus 8.2% in the non-fibrotic group with p<0.001, the same trend observed in micro-steatosis with p<0.001. There were no differences in HCV and HBV infection between the two groups. About the recipient's characteristics, older age (57.0 vs. 56.2 years, p<0.001) and higher MELD scores (22.9 vs. 21.4, p<0.001) were seen in the fibrosis group. The liver function at transplant and other indicators like total bilirubin (6.37 vs. 7.68, p<0.001) and INR (1.80 vs. 1.93, p<0.001) showed significant disparities between the two groups. In terms of the outcome, notably, rejection rates within six months were lower in the survival group (7.13% vs. 9.02%, p<0.001), and one-year rejection rates were also lower (9.03% vs. 10.8%, p=0.001). The no-fibrosis group demonstrated longer patient survival times (1,305 vs. 1,222 days, p<0.001) and graft survival times (1,303 vs. 1,220 days, p<0.001). However, hospital stay length and rates of failure due to malignancy, cardiovascular disease, infection, and respiratory failure showed no significant differences. This data shows us the main features of donor and recipient characteristics in two groups. Providing insights for the reason of fibrosis and donor allocation in matching suitable recipients.

The KM survival analysis showed that recipients of fibrotic grafts had significantly worse patient survival (HR 1.42,95%CI:1.05-1.22, p=0.039) and graft survival (HR 1.36,95%CI:1.04-1.22 p=0.041). By competing risk model analysis we found more precise results. Fibrosis was linked to higher mortality from cancer (p=0.039), cardiovascular disease (p=0.041), and respiratory failure (p=0.020). Infection and liver-related graft failure rates were similar between groups, but non-liver-related graft failure-related deaths were significantly higher in the fibrosis group (p<0.001). These results indicate that donor liver fibrosis significantly impacts post-transplant outcomes.

The multivariate regression analysis revealed that donor liver fibrosis significantly impacts transplant outcomes. In a crude model (Model 1), recipients of fibrotic grafts had a 12-13% higher risk of death (HR 1.13,95%CI:1.05-1.22,p<0.001), which remained significant after adjusting for 10 covariates in Model 2 (HR 1.12,95%CI:1.04-1.21, p=0.003). The risk of all causes of graft failure showed similar increases (Model 1: HR 1.12,95%CI:1.04-1.20, p=0.002; Model 2: HR1.10, 95%CI:1.03-1.18,p=0.008). For special causes of graft failure, donor hepatic fibrosis was also associated with a higher risk of death from cardiovascular disease and respiratory failure. However, the latter was borderline significant in the adjusted model (p=0.054). Interestingly, fibrosis was linked to lower rejection rates at 6 months (HR 0.77,95%CI:0.68-0.88,p<0.001) and 1 year (HR 0.82,95%CI: 0.72-0.92,p=0.001) but with no different in early allograft failure. The 10 covariates added for adjustment included donor and recipient characteristics such as age, gender, cold ischemia time, and MELD score, which showed that fibrosis affects outcomes beyond these factors, particularly influencing survival and rejection rates.

The subgroup analysis explored the sensitivity of donor liver fibrosis on transplant outcomes across different recipient groups. Overall, fibrosis was associated with worse overall patients and

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graft survival, but its impact varied across subgroups. Recipients aged less than 65 experienced a significant increase in mortality risk, with HR 1.14(95%CI: 1.05-1.24, p=0.003) for patient survival and HR 1.12(95%CI: 1.03-1.21, p=0.007), while those over 65 did not been affected by fibrosis. Both genders showed higher risks, with males being more vulnerable for fibrosis, for patient and graft survival, with p=0.002 and p 0.015, respectively. HCV-positive recipients were more sensitive to fibrosis (HR 1.15,95%CI: p=0.019) compared to HCV-negative (HR 1.12, 95%CI: p=0.021). Additionally, patients with hepatocellular carcinoma (HCC) had increased risk (HR 1.15,95%CI: p=0.005), and those with MELD scores >30 were particularly affected (HR 1.16,95%CI: p=0.001). Also, we found that those who have a better status of pre-transplantation may be affected mostly by fibrosis, without life support, dialysis, grade I-II ascites, and grade I-II encephalopathy. There is no interaction among fibrosis and all subgroups with no significant p-value.

Discussion

This study demonstrates that donor liver fibrosis significantly impacts post-transplant prognosis, both short-term and long-term outcomes, particularly patient and graft survival. To our knowledge, this is the largest sample size of patients analyzing hepatic fibrosis about LT outcomes. Additionally, this study is novel in that it includes the application of a competing risk survival model and subgroup analysis to further analyze various causes of Mortality. This allows for the identification of particularly vulnerable LT recipients to better define parameters for recipients of fibrotic grafts. Additionally, the highlighted causes of mortality in our analysis can also be used to help guide management post-LT.

Our data revealed that recipients who received a graft with hepatic fibrosis had significantly lower survival in comparison to patients without fibrosis. Although liver fibrosis can be assessed by histological examination to help in the decision-making for organ viability, the impact of fibrosis on the recipient's outcome remains to be cleared. A recent paper by Wadhera et al. studied the role of graft fibrosis on recipients' outcomes, finding no impact on long-term survival[16], however in our study, recipients of fibrotic donor livers had a 12-13% higher risk of death and graft failure, even after adjusting for important covariates. These findings are equal to what D'Errico A reported that portal fibrosis and inflammation negative impact on a patient's prognosis after LT[17,18]. All these suggest that fibrosis independently diminishes transplant long-term survival, underscoring the importance of careful donor selection and vigilant monitoring of recipients receiving fibrotic grafts. Besides the comparison of all-cause mortality of patient death and graft failure, we furthered detail on the specific cause of graft failure, and fibrosis influences on short-term outcomes, including early allograft failure(EAF), and allograft rejection(AR) in half and one year. We see no difference in EAF incidence but a solid difference in allograft rejection with a lower incidence in the fibrosis group. The association between rejection and pre-exist fibrosis is not well recognized in previous studies, but there is emerging evidence that graft fibrosis progression could be driven by antibody mediated rejection in post-transplantation[19–22]. But on the other hand, whether there is the possibility of local immune environment formation due to higher portal inflammation making a major contribution is unknown, further exploration needs to be conducted for validation.

The subgroup analysis offers valuable insights into how recipient characteristics alter the effect of donor liver fibrosis on outcomes. Younger recipients (≤65 years) showed a 14% higher mortality risk, while older patients were not similarly affected. This indicates that younger patients might be more vulnerable to the adverse effects of fibrosis, potentially due to higher expectations for graft longevity and function. Thus, age should be a key consideration in determining the suitability of fibrotic grafts[23]. Additionally, gender differences were observed, with male recipients experiencing slightly higher risks than females, potentially reflecting physiological differences or underlying comorbidities[24]. HCV-positive recipients were more sensitive to the effects of fibrosis, experiencing greater risks than their HCV-negative counterparts. This aligns with the understanding that hepatitis C exacerbates liver graft complications, reinforcing the need for specialized post-transplant care in HCV-positive patients, which is consistent with the recurrence of HCV and will promote the progression of liver allograft fibrosis post-transplant [25,26]. Furthermore, patients with high MELD

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scores (>30) and those diagnosed with hepatocellular carcinoma (HCC) experienced worse outcomes with fibrotic grafts, indicating that fibrosis amplifies their pre-existing vulnerabilities. These findings highlight the importance of personalized donor-recipient matching, particularly for high-risk groups.

This study demonstrates that donor liver fibrosis significantly impacts post-transplant outcomes, increasing the risks of patient mortality and graft failure. Fibrosis independently influences survival, especially in younger, HCV-positive, and high-MELD recipients, who are more vulnerable to its effects. Additionally, fibrosis was associated with lower rejection rates at six months and one-year post-transplant. These findings emphasize the importance of personalized donor-recipient matching and targeted post-transplant care for high-risk patients. Future research should explore the underlying mechanisms of fibrosis and strategies to mitigate its impact on liver transplantation.

The identification of fibrosis as an independent risk factor highlights the need for cautious selection of donor grafts and emphasizes the importance of stratifying recipients based on their vulnerability to the adverse effects of fibrosis. The use of fibrosis reduced the number of deaths on the waiting list, besides the progression is not definitely to be worse, It reported that 30% of liver fibrosis alleviated,40% stayed stable and 30% elevated[16], these indicated the complexity of liver fibrosis and good post-transplantation make a difference[27]. Moreover, the observed reduction in rejection rates warrants further investigation into the immunological mechanisms involved, potentially offering new insights into managing fibrotic grafts more effectively.

This study highlights that donor liver fibrosis negatively influences post-transplant outcomes, particularly affecting survival rates for younger recipients, HCV-positive patients, and those with high MELD scores. However, limitations should be acknowledged. First, the study's retrospective design and reliance on registry data introduce the possibility of bias, particularly regarding incomplete or missing records. Variability in histologic grading across transplant centers could also impact data consistency, as fibrosis staging may differ by pathologist interpretation. Additionally, although lower rejection rates were observed in recipients of fibrotic grafts, the mechanisms behind this finding are not fully understood. One hypothesis is an altered immune response triggered by the fibrotic liver environment, which may merit further exploration. Despite these limitations, this study provides valuable clinical insights, underscoring the need for personalized donor-recipient matching and vigilant post-transplant management in high-risk patients. Future research should aim to identify the mechanisms through which fibrosis affects graft function and patient survival and develop strategies to mitigate these risks to improve outcomes in liver transplantation.

Conclusion

In conclusion, this study demonstrates that donor liver fibrosis significantly compromises transplant outcomes, particularly among specific high-risk groups. Future research should aim to explore the underlying mechanisms of fibrosis in the context of transplantation and develop strategies to mitigate its negative impact, ultimately improving long-term survival and graft function for liver transplant recipients.

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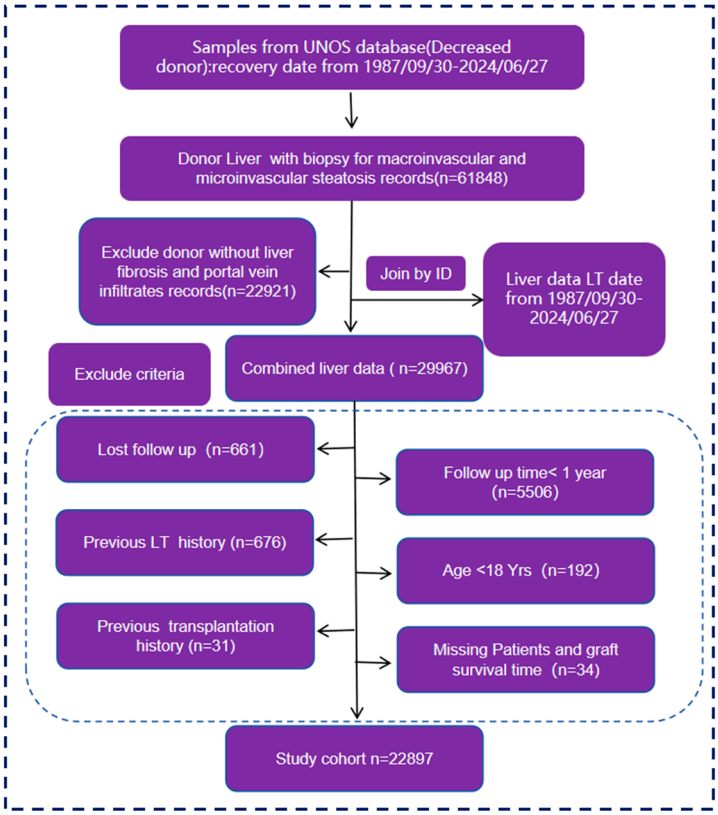

Figure 1. The flow chat of sample include and exclude criteria.

Table 1. Baseline characteristic of Donor and Recipients between fibrosis group.

Characteristics	All	N	Fibrosis group		P_Value
			No(n=17926)	Yes(n=4971)	
Donors					
Age_donor(Mean,SD,yrs)	47.6 (14.7)	22897	47.3 (14.9)	48.6 (13.9)	<0.001
Gender_donor(Male,%)	12946 (56.5%)	22897	9968 (55.6%)	2978 (59.9%)	<0.001
BMI_donor	30.1 (7.56)	22861	30.1 (7.58)	30.1 (7.50)	0.534
HCV(n,%)	2170 (9.49%)	22878	1683 (9.40%)	487 (9.80%)	0.406
CMV(n,%)	14950 (65.5%)	22820	11703 (65.5%)	3247 (65.5%)	1
HBV(n,%)			1343 (7.50%)	539 (10.8%)	<0.001
Portal inflammation		22897			<0.001
Mild	10596 (46.3%)		7688 (42.9%)	2908 (58.5%)	
Moderate_servere	1637 (7.15%)		844 (4.71%)	793 (16.0%)	
Macro_steatosis(mean,SD,%)	8.71 (11.9)	22897	8.20 (11.5)	10.5 (12.9)	<0.001
Micro_steatosis(mean,SD,%)	9.75 (15.7)	22897	9.36 (15.7)	11.1 (15.7)	<0.001
Cold_ischemia time (mean,SD,hrs)	6.24 (2.36)	22822	6.26 (2.38)	6.18 (2.30)	0.031
Recipients					
Age(Mean,SD,yrs)			56.2 (10.7)	57.0 (10.3)	<0.001
BMI(Mean,SD,Kg/m^2)			29.2 (5.94)	29.2 (5.82)	0.828
Ethnicity(n,%)		22897			<0.001
Non-Hispanic/Non-Latino	19408 (84.8%)		15094 (84.2%)	4314 (86.8%)	
Hispanic/Latino	3489 (15.2%)		2832 (15.8%)	657 (13.2%)	
Gender(Male,%)	15378 (67.2%)	22897	11980 (66.8%)	3398 (68.4%)	0.044
ABO incompatible match(n,%)	362 (1.58%)	22897	288 (1.61%)	74 (1.49%)	0.407
TIPS(n,%)	2425 (10.8%)	22443	1913 (10.9%)	512 (10.5%)	0.485
Portal vein thrombosis(n,%)	3230 (14.1%)	22837	2517 (14.1%)	713 (14.4%)	0.586

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Creatinine(mean,SD,mg/dl)	1.52 (1.37)	22897	1.53 (1.36)	1.49 (1.40)	0.113
Bilirubin(mean,SD,mg/dl)	7.40 (9.71)	22897	7.68 (9.94)	6.37 (8.78)	<0.001
INR(mean,SD)	1.90 (1.14)	22897	1.93 (1.19)	1.80 (0.91)	<0.001
Albumin(mean,SD,g/dl)	3.19 (0.69)	22897	3.19 (0.69)	3.18 (0.68)	0.463
Dialysis(n,%)	3030 (13.3%)	22773	2475 (13.9%)	555 (11.2%)	<0.001
Encephalopathy(n,%)		22897			0.701
I-II	20208 (88.3%)		15829 (88.3%)	4379 (88.1%)	
III-IV	2689 (11.7%)		2097 (11.7%)	592 (11.9%)	
Ascites(n,%)		22897			0.11
I-II	15309 (66.9%)		11938 (66.6%)	3371 (67.8%)	
III-IV	7588 (33.1%)		5988 (33.4%)	1600 (32.2%)	
MELD_score(mean,SD)	6945 (30.3%)	22897	22.9 (10.3)	21.4 (9.59)	<0.001
Diabetes(n,%)	6945 (30.3%)	22897	5359 (29.9%)	1586 (31.9%)	0.007
Life support(n,%)	1530 (6.68%)	22897	1245 (6.95%)	285 (5.73%)	0.003
HBV(n,%)	743 (3.24%)	22897	604 (3.37%)	139 (2.80%)	0.08
HCV(n,%)	5112 (22.7%)	22560	3901 (22.1%)	1211 (24.7%)	<0.001
HCC(n,%)	6591 (28.9%)	22823	5111 (28.6%)	1480 (29.8%)	0.097
Outcomes					
Hospital_stay after LT(mean,SD,days)	3230 (14.1%)	22837	15.7 (21.7)	15.7 (24.6)	0.974
Overall graft survival(n,%)	4532 (19.8%)	22897	3507 (19.6%)	1025 (20.6%)	0.102
Graft survival time(mean,SD,days)	1285 (857)	22897	1303 (864)	1220 (828)	<0.001
Patient survival(n,%)	4101 (17.9%)	22897	3169 (17.7%)	932 (18.7%)	0.085
Patient survival time(mean,SD,days)	1287 (857)	22897	1305 (865)	1222 (828)	<0.001
Graft failure from malignancy(n,%)	665 (2.90%)	22897	506 (2.82%)	159(3.20%)	0.178
Graft failure for CVD(n,%)	582 (2.54%)	22897	439 (2.45%)	143(2.88%)	0.100
Graft failure for infection(n,%)	599 (2.62%)	22897	471 (2.63%)	128 (2.57%)	0.877
Graft failure for respiratory failure(n,%)	249 (1.09%)	22897	182 (1.02%)	67 (1.35%)	0.054
Early allograft failure(EAF)(n,%)	1180 (5.15%)	22897	914 (5.10%)	266 (5.35%)	0.499
Re_transplantation(n,%)	565 (2.47%)	22897	445 (2.48%)	120 (2.41%)	0.823
Rejection in 6 months(n,%)	1579 (8.61%)	18346	1292 (9.02%)	287 (7.13%)	<0.001
Rejection in 1 year(n,%)	1854 (10.4%)	17784	1500 (10.8%)	354 (9.03%)	0.001
Liver related Graft Failure(n,%)	1063 (4.64%)	22897	837 (4.67%)	226 (4.55%)	0.747
Followup_time(mean,SD,days)	1285 (857)	22897	1303 (864)	1220 (828)	<0.001

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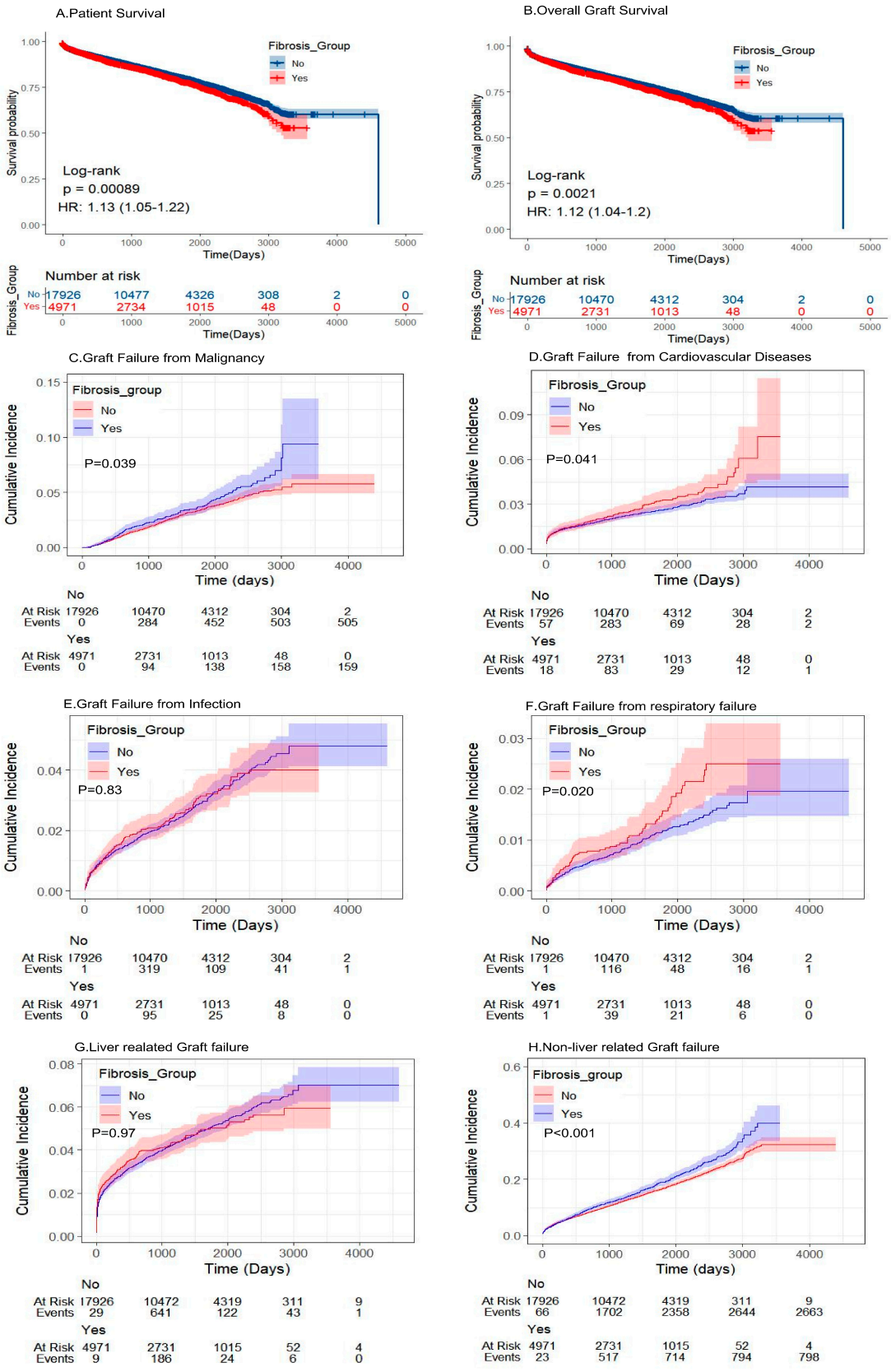

Figure 2. KM survival and competing risk model for liver transplantation outcomes.

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Figure 3. The association between fibrosis and LT outcomes. OR: Odds Ratio, CI: Confidence Interval. Model1: Crude. Model2: Adjust: Macro_steatosis, Micro_steatosis, Cold ischemia time, Age, Gender, Bilirubin, Dialysis, Encephalopathy, ASCITES, MELD_score, Diabetes, Life support, HCC.

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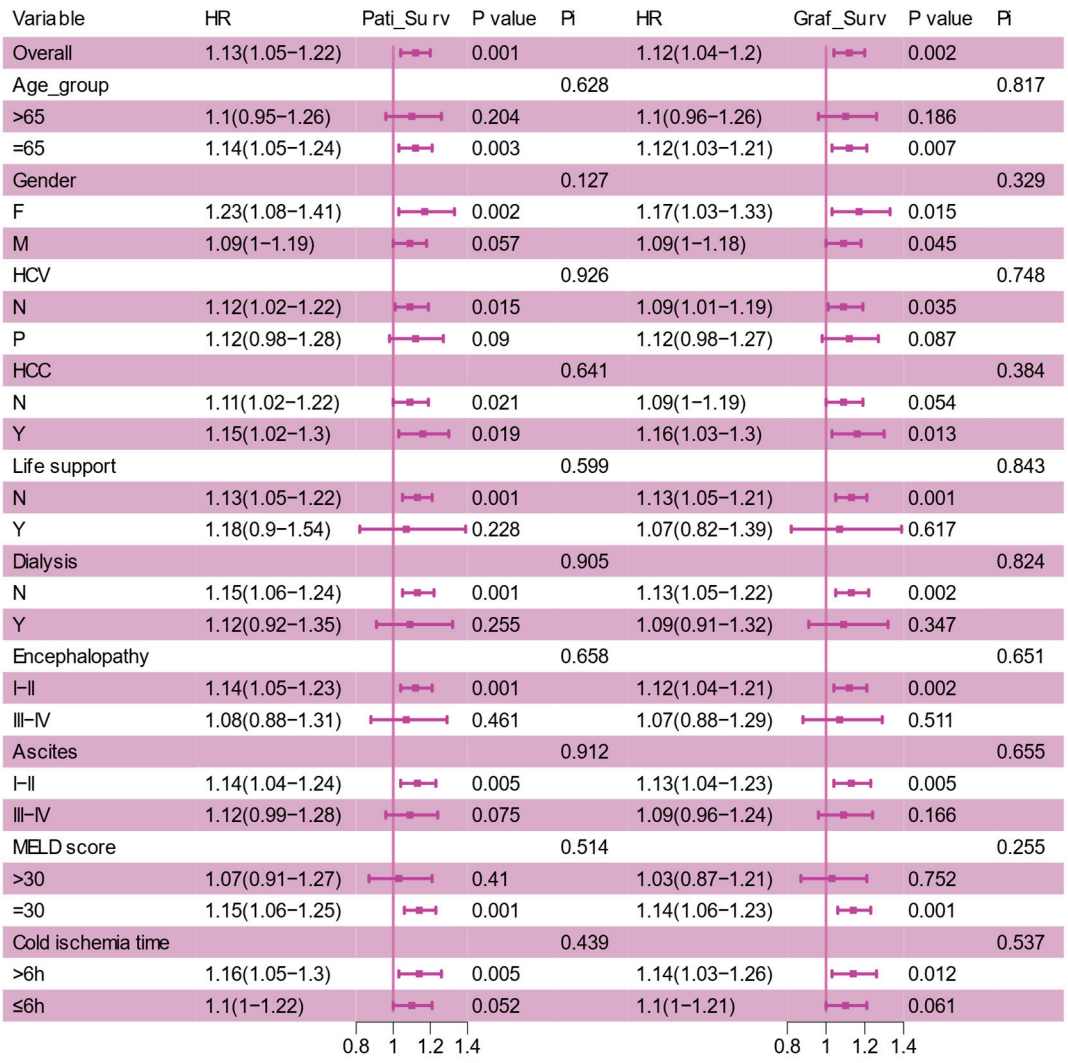

Figure 4. The subgroup analysis for fibrosis and recipients characteristics.

Data Availability Statement: Data for this analysis were obtained from the UNOS-SRTR database. The availability of these data is restricted and was permitted under a specific license for this study. Requests for UNOS data access can be directed to the National Health Insurance Sharing Service website (http://unos.org). Access requirements include a completed application form, a detailed research proposal, and an Institutional Review Board approval, all subject to review by the UNOS research support inquiry committee.

Ethics Statement: The study protocol was exempted by the Ethics Review Committee of The First Affiliated Hospital of Kunming Medical University for the OPTN database is deidentified and publicly available.

Author Contributions: All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures, and tables has not been previously published, and the manuscript is not under consideration elsewhere. All authors approve the final version of the manuscript, including the authorship list, and agree to be 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. Data collection and analysis –Congwen Bian, Supervision – Hanfei Huang, Zhong Zeng. Original draft - Congwen Bian, Review, and editing – Zhong Zeng, Hanfei Huang. All authors have read and approved the final version of the manuscript for submission.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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