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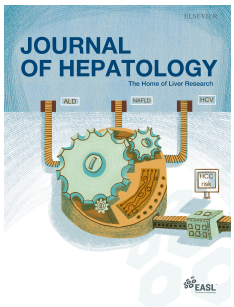

Prognostic Scores for Ursodeoxycholic Acid-Treated Patients Predict Graft Loss and Mortality in Recurrent Primary Biliary Cholangitis after Liver Transplantation

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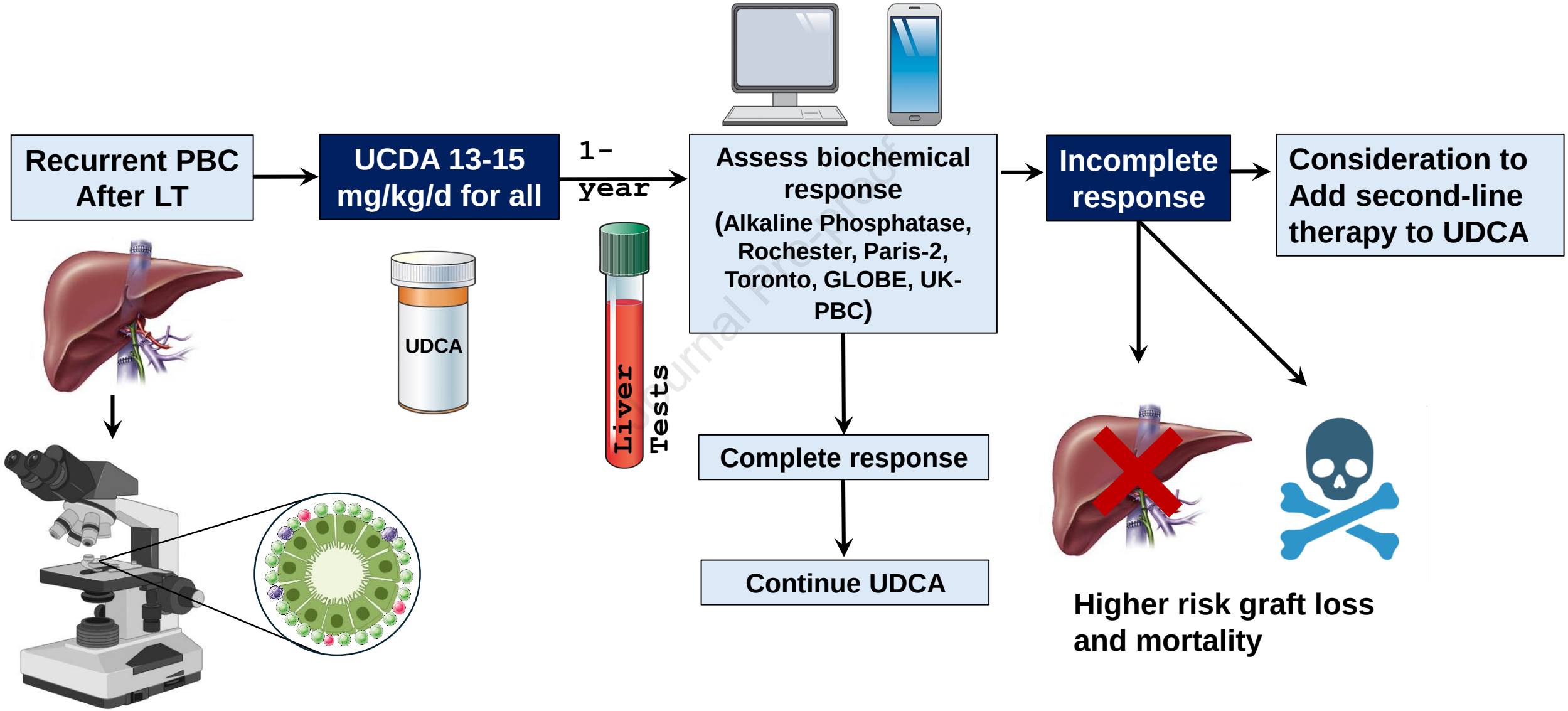

Prognostic Scores for Ursodeoxycholic Acid-Treated Patients Predict Graft Loss and Mortality in Recurrent Primary Biliary Cholangitis after Liver Transplantation

Short Title: Assessing Outcomes in Patients with PBC Recurrence After Liver Transplant

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Abbreviations:

ALT, alanine aminotransferase
AST, aspartate aminotransferase
ALP, alkaline phosphatase
HR, hazard ratio
INR, international normalised ratio
MELD, Model for End-stage Liver Disease
LT, liver transplantation
OCA, obeticholic acid
PBC, primary biliary cholangitis
*r*PBC, recurrent PBC
UDCA, ursodeoxycholic acid

Specific author contributions:

Aldo J. Montano-Loza, study design, analyses of the data, creation of the first draft of the manuscript and final version; Ellina Lytvyak, analyses of the data, creation of the first draft of the manuscript and final version and submitting the manuscript for review; Bettina E. Hansen, analyses of the data, creation of the first draft of the manuscript and final version; Gideon Hirschfield, analyses of the data, creation of the first draft of the manuscript and final version; Thierry Berney, critical revision of the manuscript for important intellectual content; Christian Toso, critical revision of the manuscript for important intellectual content; Giulia Magini, critical revision of the manuscript for important intellectual content; Alejandra Villamil, critical revision of the manuscript for important intellectual content; Frederik Nevens, critical revision of the manuscript for important intellectual content; Natalie Van den Ende, critical revision of the manuscript for important intellectual content; Albert Pares, critical revision of the manuscript for important intellectual content; Pablo Ruiz, critical revision of the manuscript for important intellectual content; Débora Terrabuio, critical revision of the manuscript for important intellectual content; Palak Trivedi, critical revision of the manuscript for important intellectual content; Nadir Abbas, critical revision of the manuscript for important intellectual content; Maria Francesca Donato, critical revision of the manuscript for important

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Conflicts of interest:

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Data availability statement:

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author at reasonable request.

ABSTRACT

Background/aim: Recurrent primary biliary cholangitis (*r*PBC) develops in approximately 30% of patients and negatively impacts graft and overall patient survival after liver transplantation (LT). There is a lack of data regarding the response rate to ursodeoxycholic acid (UDCA) in *r*PBC. We evaluated a large, international, multi-center cohort to assess the performance of scores for PBC to predict the risk of graft and overall survival after LT in patients with *r*PBC.

Methods: A total of 332 patients with *r*PBC after LT were evaluated from 28 centres across Europe, North and South America. The median age at the time of *r*PBC was 58.0 years [IQR 53.2 - 62.6], and 298 patients (90%) were females. The biochemical response was measured with serum levels of alkaline phosphatase (ALP) and bilirubin, and Paris-2, GLOBE and UK-PBC scores at 1 year after UDCA initiation.

Results: During a median follow-up of 8.7 years [IQR 4.3 - 12.9] after *r*PBC diagnosis, 52 patients (16%) had graft loss and 103 (31%) died. After 1 year of UDCA initiation the histological stage at *r*PBC (HR, 3.97, 95%CI 1.36-11.55, P=0.01), use of prednisone (HR 3.18, 95%CI 1.04-9.73, P=0.04), ALP xULN (HR 1.59, 95%CI 1.26-2.01, P<0.001), Paris-2 criteria (HR 4.14, 95%CI 1.57-10.92, P=0.004), GLOBE score (HR 2.82, 95%CI 1.71-4.66, P<0.001), and the UK-PBC score (HR 1.06, 95%CI 1.03-1.09, P<0.001) were associated with graft survival in the multivariate analysis. Similar results were found in the overall survival analysis.

Conclusion: Patients with *r*PBC and disease activity as indicated by standard PBC risk scores have impaired outcomes, supporting efforts to treat recurrent disease in similar ways to pre-transplant PBC.

Keywords: autoimmune liver disease, recurrent disease, survival, graft survival, liver transplantation.

IMPACT AND IMPLICATIONS

One in three people who have liver transplantation for primary biliary cholangitis develop recurrent disease in their new liver. Patients with recurrent primary biliary cholangitis and incomplete response to ursodeoxycholic acid according to conventional prognostic scores have worse clinical outcomes, with higher risk of graft loss and mortality in similar ways to the disease before liver transplantation. Our results emphasized supporting efforts to treat recurrent disease in similar ways to pre-transplant primary biliary cholangitis.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic cholestatic disease characterised by granulomatous destruction of intrahepatic bile ducts, and in some cases even when treated can remain a progressive disease [1]. Approximately five percent of patients who undergo liver transplantation (LT) in Europe and North America have PBC as an underlying liver disease [2, 3]. Even though there has been a decrease in PBC as an indication for LT in the last decades related to better disease awareness and widespread treatment with ursodeoxycholic acid (UDCA), the absolute annual number of LT for PBC has steadied.
The outcome after LT for patients with PBC is generally good, but recurrent PBC (*r*PBC) occurs in more than 20% of patients after 5 years and more than 35% after 10 years [4]. Several risk factors associated with *r*PBC have been reported, including young age at the time of diagnosis with PBC or at LT, use of tacrolimus as immunosuppression, and biochemical markers of cholestasis after LT. Importantly, *r*PBC has a negative impact on graft and patient survival; therefore, strategies to prevent recurrence after LT, such as preventive UDCA are imperative [5].
Liver function tests [6] and different binary [7-13] and dimensional scores [14, 15] have been used to evaluate prognosis in patients with PBC, mainly by assessing response to UDCA and helping clinical decisions for the addition of second-line treatments before LT [16]. However, there is a lack of data regarding their utility in patients with a diagnosis of *r*PBC after LT. We aimed to evaluate the utility of serum liver function tests and the GLOBE and UK-PBC scores to predict graft and overall survival after LT in patients with *r*PBC treated with UDCA.

METHODS

Study Population

Patients included in this study were selected from an international registry from the GLOBAL PBC study group, consisting of 947 patients with PBC who underwent LT from February 1983 until September 2019 from 28 centres across Asia, Europe, and North and South America, were evaluated (Supplementary Figure 1) [4, 5]. All patients had a diagnosis of PBC as an indication for LT according to the AASLD and European Association for the Study of the Liver (EASL) guidelines [1, 17]. In this study, 332 patients with histological diagnosis of *r*PBC [4] and at least one year of follow-up after diagnosis were included for analysis.

Clinical and Laboratory Assessments

The data extracted from the medical records included age at LT and *r*PBC, sex, type of LT (cadaveric, living donor), BMI, LT period (divided into 6-year periods), time from LT to *r*PBC, UDCA use and dose after *r*PBC, time from *r*PBC to UDCA start date, immunosuppression at *r*PBC, episodes of rejection after *r*PBC, and clinical outcomes. Liver tests including ALT, AST, ALP, bilirubin, and albumin were collected at the time of *r*PBC and 1 year after starting UDCA. The ULN for ALT ranged from 31 to 56 U/L, AST from 30 to 52 U/L, and bilirubin from 18 to 22 µmol/L between the different LT centres. The lower level of normal (LLN) for albumin was 35 g/L and for platelets 140 x10^9/L.

Diagnosis of Recurrent PBC

The diagnosis of recurrent disease was made histologically and defined by the presence of liver histology compatible with PBC in the absence of other biliary diseases including hepatic artery thrombosis, and anastomosis stricture [18]. All patients with cholestasis and suspicion of recurrence of PBC after LT had an ultrasound Doppler examination to rule out the presence of biliary duct dilation or stricture, and hepatic artery thrombosis as reported elsewhere [19].

In addition, allograft rejection, the presence of infections, and concomitant use of potentially hepatotoxic drugs were ruled out. Histologic features of *r*PBC were the presence of florid duct lesions or destructive lymphocytic cholangitis with significant portal infiltrate in the absence of endothelialitis [18]. Histological diagnosis of recurrence of PBC was made by liver pathologists in all cases. Histological recurrence of PBC was graded according to Ludwig and Scheuer classification [20]. Overlap syndrome with autoimmune hepatitis was ruled out in all patients with recurrence of PBC according to Paris criteria [21].

Response to UDCA

Response to UDCA was established at a fixed time point, 1 year after UDCA initiation, and determined by the Paris-2 criteria [12], GLOBE score [15], and the 5-year UK-PBC score [14] in those patients who received UDCA (94%). For patients who did not receive UDCA (6%), Paris-2 criteria, GLOBE and 5-year UK-PBC scores were calculated at 1 year after diagnosis of *r*PBC. Other treatments for PBC, such as obeticholic acid and fibrates were also recorded.

Statistical Analyses

The Fisher exact probability test was used to compare categorical variables, and the unpaired *t*-test was used to compare differences in means of continuous variables. Variables with a P-value equal to or less than 0.1 in the univariate analysis were included in the multivariate regression analysis.

To determine whether the response to UDCA in patients with *r*PBC was significantly associated with graft loss and overall survival, the impact of UDCA response versus no response on graft loss, and survival was assessed using univariate and multivariate Cox regression analyses. As some patients received preventive UDCA (n=28) or did not receive UDCA after *r*PBC diagnosis (n=20), we performed the analysis in two parts. The first part included all *r*PBC patients. The index date for this part was the date of diagnosis of *r*PBC; however, in this analysis, the time to start UDCA was modelled as a time-dependent covariate and the biochemical parameters at one year after UDCA initiation were not included. In the second part of the analysis, we included only patients who received UDCA after *r*PBC (also excluding patients who received preventive UDCA) to evaluate the utility of serum liver function tests and PBC scores to predict graft and overall survival after LT. Variables with a P-value equal to or less than 0.1 in the univariate analysis and other relevant variables were included in the Cox proportional hazard regression multivariate analysis. Patients who did not develop graft loss and died and those who were lost during follow-up were censored at the time of death or at the time of their last visit. Graft loss was defined using a death-censored definition of graft failure and therefore, graft loss did not include patients who died with a functioning graft. Graft loss only included deaths secondary to or associated with graft failure (*i.e.* cirrhosis development on the graft, recurrent disease, chronic ductopenic rejection, sepsis in patients with biliary or vascular complications, or re-transplantation). The cumulative incidence of graft loss and mortality after *r*PBC were calculated using the Kaplan-Meier method, and they were compared using the Log-Rank (Mantel-Cox) test [22]. Median survival probabilities were presented, unless 50% of the subjects developed the event of interest, in which case mean survival was presented. One limitation of Cox proportional hazard models is that assume competing events are absent and so, they may overestimate the risk. The Fine and Gray competing risks approach assesses the association between variables and outcomes in the presence of competing events. Competing-risk analysis is a more robust approach, compared to the conventional survival analysis, in the presence of competing events [23]. Therefore, as the next step competing risk analysis was conducted using the Fine-Gray subdistribution hazard model for graft survival considering non-graft-loss-related deaths as the competing event.
Lastly, a subanalysis for overall survival was done for cases classified as liver-related deaths. Data are presented as the medians and interquartile ranges [IQR 25th-75th] and categorical values as proportions (%) in tables and text. Statistical analyses were conducted using SPSS 26.0 and SATA 18.0. For handling the missing variables in the analysis, we used mean imputation for continuous variables and allocated a fixed number (99) for categorical variables.

RESULTS

Characteristics of Patients with Primary Biliary Cholangitis Recurrence

A total of 332 patients who had a liver biopsy-proven diagnosis of *r*PBC after LT from 28 centres across Europe, North and South America were evaluated. The median age at the time of *r*PBC was 58.0 years [IQR 53.2 - 62.6], and 298 patients (90%) were women (Table 1). Of all the LT,116 (35%) were performed from 1983 to 1999, and 216 (65%) in the period 2000-2020. The distribution of LT performed every 6 years is presented in Table 1. Twenty-eight patients (8%) received preventive UDCA before *r*PBC.

The median time from LT to *r*PBC was 5.0 years [IQR 1.8 - 10.1]. At the time of *r*PBC, 218 patients (66%) were receiving immunosuppression with tacrolimus alone or in combination either with mycophenolate mofetil, sirolimus, prednisone or azathioprine, and 95 (29%) were receiving immunosuppression with cyclosporine alone or in combination either with mycophenolate mofetil, sirolimus, prednisone or azathioprine. Other immunosuppression regimens are presented in Table 1.

The histological stage at the time of PBC recurrence was stage one in 227 patients (68%), stage two in 76 patients (23%), stage three in 21 patients (6%) and stage 4 in 8 patients (2%).

Clinical and Biochemical Features Associated with Graft Loss

A total of 312 patients (94%) received treatment with UDCA after *r*PBC diagnosis. The mean dose was 13 mg/kg/daily [IQR 10-15] and the time from *r*PBC to the UDCA initiation was 0.4 year [IQR 0 - 4.8].

During a median follow-up of 8.7 years [IQR 4.3 - 12.9], 52 patients (16%) had lost graft, 22 (7%) underwent re-transplantation, and 103 (31%) died. Graft failure was secondary to *r*PBC in 43 of the 52 patients (83%).

Graft survival after *r*PBC was 92% and 85% at 5-, and 10 years, respectively (Figure 1a). Overall survival was 85% and 75%, respectively (Figure 1b).

In the univariate Cox regression analysis, the LT period and the histological stage at diagnosis of *r*PBC were associated with a higher risk of graft loss. When we analysed the impact of immunosuppression at the time of *r*PBC, the use of tacrolimus was associated with a protective effect for graft survival; whereas patients who received cyclosporine at the time of *r*PBC had a higher risk of graft loss (Table 2).

Regarding biochemical parameters at one year after UDCA treatment by univariate Cox analysis, ALP xULN, AST xULN, ALT xULN, bilirubin xULN, and albumin xULN were associated with a higher risk of graft loss.

However, in the multivariate analysis, only the histological stage at diagnosis of *r*PBC (HR 2.45, 95%CI 1.18-5.09), P=0.01), the use of prednisone at the time of *r*PBC (HR 3.18, 95% CI 1.04-9.73, P=0.04), and ALP xULN (HR 1.59, 95% CI 1.26-2.01, P<0.001), at one year after UDCA initiation were independently associated with a higher risk of graft loss (Table 2, Figure 2a).

In Fine and Gray's competing risks analysis of graft survival considering non-graft-loss-related deaths as the competing event, the results were similar to the Cox analysis and are presented as supplementary material (Table S3).

Mean graft survival was lower in patients with ALP >2 ULN at one year after UDCA initiation, 18.02 years (95% CI 14.88-21.16) as compared to 23.08 years (95% CI 22.06-24.11) for patients with ALP ≤2 ULN (Log-rank, P=0.003, Figure 3a). Similarly, mean graft survival was significantly diminished in patients with bilirubin >1.0 ULN to 14.28 years (95% CI 9.51-19.06) as compared to 22.37 years (95% CI 21.11-23.62), for patients with ≤1.0 times the ULN (Log-rank, P=0.003, Figure 3b).

Scores to Evaluate UDCA Response and Impact on Graft Loss

All the risk scores evaluated at 1 year after UDCA including, Rochester-II (ALP >2 xULN), Toronto (ALP >1.67 xULN), Paris-2 (ALP ≥1.5 xULN or AST ≥1.5 xULN or bilirubin >1 mg/dL [17.1 μmol/L]), GLOBE and UK-PBC score were significantly associated with graft survival in the univariate and multivariate Cox regression analysis (Table 3).

In Fine and Gray's competing risks approach to evaluate graft survival considering non-graft-loss-related deaths as the competing event, the results were similar to the Cox analysis and are presented as supplementary material (Table S4).

Graft survival was lower in patients with ALP >1.67 xULN at one year after UDCA initiation, 17.99 years (95% CI 14.96-21.02) as compared to 23.19 years (95% CI 22.17-24.20) for patients with ALP ≤1.67 times the ULN (Log-rank, P=0.002, Figure 3c).

Similarly, graft survival was lower in patients who met the criteria for inadequate Paris-2 response, of 17.39 years (95% CI 14.49-20.28) as compared to 23.54 years (95% CI 22.63-24.45) with adequate Paris-2 response (Log-rank, P<0.001, Figure 3d).

In addition, graft survival was lower in patients with a GLOBE score >0.3, 19.46 years (95% CI 17.43-21.49) as compared to 23.10 years (95% CI 21.91-24.29), for patients with a GLOBE score ≤0.3 (Log-rank, P=0.03, Figure 3e).

Clinical and Biochemical Features Associated with Overall Mortality

In Cox regression analysis, age at LT, time from *r*PBC to starting UDCA, ALP xULN, bilirubin xULN, and albumin xULN at one year after UDCA initiation were associated with a higher risk

of mortality (Table 4). However, in the multivariate analysis only ALP xULN (HR 1.52, 95% CI 1.29-1.78, P<0.001), was associated with a higher risk of mortality (Table 4) (Figure 2b).
The subanalysis for cases classified as liver-related death (n=48), demonstrated relatively similar results and are presented as supplementary material in Tables S5 and S6.
Overall survival was lower in patients with ALP >2 xULN at one year after UDCA initiation, 11.63 years (95% CI 9.01-14.27) as compared to 20.35 years (95% CI 18.86-21.85) for patients with ALP <2 xULN (Log-rank, P<0.001, Figure 4a).
Similarly, overall survival was significantly lower in patients with bilirubin >1.0x ULN at 1 year after UDCA initiation, 9.73 years (95% CI 6.27-13.19) as compared to 18.22 years (95% CI 16.42-20.01), for patients with bilirubin ≤ xULN (Log-rank, P<0.001, Figure 4b).

Scores to Evaluate UDCA Response and Impact on Overall Mortality

All the risk scores evaluated at 1 year after UDCA including, Rochester-II (ALP >2 xULN), Toronto (ALP >1.67x ULN), Paris-2 (ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dL [17.1 μmol/L]), GLOBE and UK-PBC score were significantly associated with overall survival in the univariate and multivariate Cox regression analysis (Table 5).
Overall survival was significantly diminished in patients with ALP >1.67 xULN to 11.90 years (95% CI 9.41-14.40) as compared to 20.42 years (95% CI 18.91-21.93) for patients with ALP ≤1.67 xULN (Log-rank, P<0.001, Figure 4c).
Similarly, overall survival was significantly diminished in patients meeting the criteria for inadequate Paris-2 response of 11.89 years (95% CI 9.63-14.15) as compared to 20.82 years (95% CI 19.33-22.31), for patients with an adequate response (Log-rank, P<0.001, Figure 4d).
In addition, overall survival was significantly diminished in patients with a GLOBE score >0.3 to 14.77 years (95% CI 12.57-16.96) as compared to 20.41 years (95% CI 18.70-22.13), for patients with a GLOBE score. ≤0.3 (Log-rank, P<0.001, Figure 4e).

Discontinuation of UDCA and Use of Second-line Treatments in Patients with Incomplete Response

Twenty-one patients (6%), discontinue UDCA after a median follow-up of 57 months (IQR, 17-93 months). Ten patients discontinue UDCA due to intolerance, five for no response, and six for unknown reasons.
Only 22 patients (7%) patients were started on second-line treatments. Nineteen patients (6%) were started on fibrates (bezafibrate, fenofibrate), and three patients (1%) on obeticholic acid.

Of the patients who received second-line treatment, 12 (55%) had an ALP <2 times after one year of starting the second-line treatment. Similarly, 14 patients (64%) had bilirubin <1 time the ULN after one year of starting the second-line treatment. In addition, 11 patients (50%) had an adequate response according to Paris-2 criteria and 14 (64%) patients had a GLOBE score <0.3 after one year of starting the second-line treatment.
Of the patients who started second-line treatments, two patients (9%) lost their graft and three patients (14%) died during a mean time of 7.99 years [IQR 5.31-9.72].

DISCUSSION

In the largest cohort of patients with a diagnosis of *r*PBC after LT to date, we are the first to demonstrate that disease activity indicated by standard PBC risk scores is associated with impaired outcomes, supporting efforts to treat recurrent disease in similar ways to pre-transplant PBC.

To our knowledge, this is the first study to demonstrate the utility of conventional scores in patients with recurrent PBC after LT. Our study challenges current paradigms and perceptions emphasising the importance of stratification of risk in recurrent PBC, as even when treated with ursodeoxycholic acid, recurrent PBC can remain a progressive disease leading to graft loss and mortality. This study highlights the importance of individual assessments for the risk of developing progressive recurrent PBC, and consequently, the potential need for second-line treatments.

It is currently well established that PBC management is based on initiating UDCA for all patients and performing risk stratification according to both the characteristics at baseline and the response to treatment. However, this assessment could be overseen in patients with a diagnosis of *r*PBC, given the complexity of the management of LT patients, and sometimes the fallacious idea that recurrent disease does not have a negative impact on graft or patient survival [4].

In this study, we demonstrated that patients with histological diagnosis of *r*PBC and incomplete response to UDCA evaluated by different categorical or dimensional scores had from 2 to 3-fold-times higher risk for graft loss or mortality.

We consider our results to be important, as they shed light on the individualised care after LT for PBC. Along the same line, all patients who receive a LT for PBC should receive

preventive UDCA as this strategy reduces the risk of *r*PBC and improves graft and patient outcomes [5].

Our study underlines the definition and management of patients at risk and is a fundamental part of the evaluation of patients with recurrent PBC, similar to patients before LT [16]. The assessment of biochemical response to UDCA is typically performed at 12 months; however, a recent study showed that identification of patients for second-line therapy could be done at six months using an ALP threshold of 1.9 xULN, as approximately 90% of these patients are non-responders according to POISE criteria [24].

Interestingly, we found that bilirubin at one year after UDCA was associated with graft loss and mortality in the univariate analysis (Tables 2 and 4); however, the association was lost in the multivariate analysis. We recognize that bilirubin is an established predictor of prognosis in PBC [25]; however, we consider that only patients with relatively advanced disease are likely to show meaningful changes in bilirubin levels that will independently predict the risk of graft loss and mortality [6].

Our results suggest that response criteria to UDCA in recurrent PBC must include ALP and bilirubin levels (Paris-2, GLOBE, UK-score), and abnormal levels of total and conjugated bilirubin or ALP level >1.5 xULN should be the minimal thresholds above which second-line therapies should be considered. In addition, we demonstrated that many of the current scores/response definitions, including Paris-2, Toronto, Rochester II, GLOBE and UK-score can identify patients with a higher risk of graft loss and mortality after LT.

Patients with recurrent PBC and adequate biochemical response can be maintained on UDCA monotherapy. In contrast, patients with recurrent PBC and no or inadequate response to UDCA should be considered for second-line therapy, among which obeticholic acid (licensed) or fibrates (at present unlicensed), in addition to continued treatment with UDCA, are currently the main options.

Notably, as the prognostic scores for UDCA-treated patients with PBC include variables such as bilirubin and albumin, these might predict graft loss and mortality in LT recipients for different etiologies other than PBC. However, this should be evaluated in other studies.

It is important to emphasise that patients with cholestasis after LT should be evaluated for other potential etiologies, including hepatic arterial stenosis, ischemic cholangiopathy or chronic ductopenic rejection among others. All the patients evaluated in this study had a

histological diagnosis of recurrent PBC and had a clinical and radiological evaluation to rule out other etiologies of cholestasis.

Notably, in the univariate analysis, we found that the use of tacrolimus at the time of *r*PBC was associated with a lower risk of graft loss (HR 0.48, P=0.01), and cyclosporine was associated with a higher risk (HR 2.21, P=0.008). Interestingly, previous studies have demonstrated that tacrolimus is associated with a higher risk of *r*PBC after LT, whereas cyclosporine was associated with a protective effect for *r*PBC [4, 26]. However, in this cohort similar to other studies [27], the use of tacrolimus at that time or *r*PBC was associated with better graft survival, whereas cyclosporine was associated with worse graft survival. Overall tacrolimus is better immunosuppression and is considered the backbone of most anti-rejection regimens after LT [28].
The association of prednisone with graft loss is interesting. Previous randomized placebo-controlled trials with steroids as add-on therapy to UDCA in patients with early-stage PBC exhibited a significant reduction in serum ALP as well as improvement in liver histology [29]. In addition, a recent trial with budesonide add-on therapy was not associated with improved liver histology in patients with PBC and insufficient response to UDCA [30], but these trials did not demonstrate an association of steroids with worse clinical outcomes. We found that patients who had episodes of T-cell mediate rejections after *r*PBC had a higher frequency of prednisone use at the time of *r*PBC (16% versus 9.6%, P=0.02). This could explain at least partially the higher risk of graft loss (Table 2).

Recent experience has demonstrated that vibration-controlled transient elastography (VCTE) is a useful tool to predict clinical outcomes in patients with PBC [31]. In this study, we only had information for VTCE in 27 patients (8%) at the time of recurrent PBC. Despite the small number, increasing VCTE was associated with a higher risk of graft loss (HR 1.14, 95% CI 1.02-1.28). Therefore, future studies should evaluate the utility of VTCE in addition to biochemical response in patients with recurrent PBC.

We acknowledge there are limitations in this study, mainly related to its retrospective nature. For example, we did not have information regarding the management of PBC before LT, as this could had an impact on clinical outcomes in *r*PBC. In the same line, up to 25% of patients had missing data; however, the median percentage of missing data was 6.5% for all the variables (Range, 0-25%; Supplementary Table 2). In addition, the diagnosis of *r*PBC was based on liver biopsies in a non-protocol fashion. This could explain why more than 31% of patients had histological stages 2 to 4. However, we consider our results to emphasise the need for clinical trials to reduce the burden of *r*PBC, trying to minimise the risk of graft loss

related to *r*PBC. Combination therapy in patients with incomplete response to UDCA should be prospectively assessed and it will be important to evaluate the pharmacodynamics and the interaction of obeticholic acid and fibrates in patients with recurrent PBC and incomplete response to UDCA.

In conclusion, patients with *r*PBC and disease activity as indicated by standard PBC risk scores have impaired outcomes, supporting efforts to treat recurrent disease in similar ways to pre-transplant PBC. Future studies for patients with *r*PBC and incomplete response to UDCA, to evaluate the benefit of the addition of second-line treatment such as obeticholic acid, and fibrates are warranted.

FIGURE LEGENDS

Figure 1a. Graft survival in patients with recurrent PBC.
Graft survival after diagnosis of recurrent PBC at 5 years was 92%, and at 10 years was 85%.

Figure 1b. Overall survival in patients with recurrent PBC.
Overall survival after diagnosis of recurrent PBC at 5 years was 85% and at 10 years was 75%.

Figure 2a. Forrest plot showing variables associated with graft loss in the multivariate analysis.
The histological stage at rPBC, use of prednisone, and ALP at 1 year after UDCA initiation were associated with a higher risk of graft loss.

Figure 2b. Forrest plot showing variables associated with overall mortality in the multivariate analysis.
ALP at 1 year after UDCA initiation was associated with a higher risk of overall mortality.

Figure 3a. Graft survival in recurrent PBC after one year of UDCA treatment and response according to ALP levels.
Graft survival according to ALP at 1 year after UDCA was started. Patients who had an ALP ≤2 xULN after 1 year of treatment with UDCA are in the blue line, and ALP >2 xULN after one year of treatment with UDCA are in red. The 5-year probability was 96% and 86%, respectively (P=0.003, log-rank test).

Figure 3b. Graft survival in recurrent PBC after one year of UDCA treatment and response according to bilirubin levels.
Graft survival according to bilirubin at one year after UDCA was started. Patients who had bilirubin ≤1 x ULN after one year of treatment with UDCA are in the blue line, and bilirubin >1 x ULN after one year of treatment with UDCA are in red. The 5-year probability was 96% and 77%, respectively (P=0.003, log-rank test).

Figure 3c. Graft survival in recurrent PBC after one year of UDCA treatment and response according to Toronto score.
Graft survival according to ALP one year after UDCA was started. Patients who had an ALP ≤1.67 x ULN after one year of treatment with UDCA are in the blue line, and ALP >1.67 x

ULN after one year of treatment with UDCA are in red. The 5-year probability was 97% and 88%, respectively (P=0.002, log-rank test).

Figure 3d. Graft survival in recurrent PBC after one year of UDCA treatment and response according to Paris-2 score

Graft survival according to Paris-2 score at one year after UDCA was started. Patients with criteria for response according to Paris-2 after one year of treatment with UDCA are in the blue line, and non-responders after one year of treatment with UDCA are in red. The 5-year probability was 97% and 89%, respectively (P<0.001, log-rank test).

Figure 3e. Graft survival in recurrent PBC after one year of UDCA treatment and response according to GLOBE score.

Graft survival according to GLOBE score at one year after UDCA was started. Patients who had a GLOBE score ≤0.3 at one year of treatment with UDCA are in the blue line, and patients who had a GLOBE score >0.3 after one year of treatment with UDCA are in red. The 5-year probability was 97% and 91%, respectively (P=0.03, log-rank test).

Figure 4a. Overall survival in recurrent PBC after one year of UDCA treatment and response according to ALP levels.

Overall survival according to ALP at one year after UDCA was started. Patients who had an ALP ≤2 x ULN after 1 year of treatment with UDCA are in the blue line, and ALP >2 x ULN after one year of treatment with UDCA are in red. The 5-year probability was 93% and 85%, respectively (P<0.001, log-rank test).

Figure 4b. Overall survival in recurrent PBC after one year of UDCA treatment and response according to bilirubin levels.

Overall survival according to bilirubin at one year after UDCA was started. Patients who had bilirubin ≤1 x ULN after one year of treatment with UDCA are in the blue line, and bilirubin >1 x ULN after one year of treatment with UDCA are in red. The 5-year probability was 90% and 70%, respectively (P<0.001, log-rank test).

Figure 4c. Overall survival in recurrent PBC after one year of UDCA treatment and response according to Toronto score.

Overall survival according to ALP at one year after UDCA was started. Patients who had an ALP ≤1.67 x ULN after one year of treatment with UDCA are in the blue line, and ALP >1.67 x ULN after one year of treatment with UDCA are in red. The 5-year probability was 93% and 78%, respectively (P<0.001, log-rank test).

Figure 4d. Overall survival in recurrent PBC after one year of UDCA treatment and response according to Paris-2 score.

Overall survival according to Paris-2 score at one year after UDCA was started. Patients with criteria for response according to Paris-2 after one year of treatment with UDCA are in the blue line, and non-responders after one year of treatment with UDCA are in red. The 5-year probability was 92% and 80%, respectively (P<0.001, log-rank test).

Figure 4e. Overall survival in recurrent PBC after one year of UDCA treatment and response according to GLOBE score.

Overall survival according to GLOBE score at one year after UDCA was started. Patients who had a GLOBE score ≤0.3 at one year of treatment with UDCA are in the blue line, and patients who had a GLOBE score >0.3 after one year of treatment with UDCA are in red. The 5-year probability was 93% and 81%, respectively (P<0.001, log-rank test).

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Table 1. Baseline Features at the Time of Diagnosis of Recurrent PBC

Characteristics	**n = 332**
Sex, female	296 (90)
Age at PBC diagnosis	44.4 [37.7 - 52.3]
Age at LT	51.8 [44.9 - 58.9]
LT type	
• Cadaveric	297 (89)
• Living donor	35 (11)
BMI, kg/m^2	25.2 [22.5 - 28.4]
Age at *r*PBC (years)	58.0 [53.2 - 62.6]
Time diagnosis PBC to LT (years)	6.0 [2.9 - 10.2]
Time from LT to *r*PBC (years)	5.0 [1.8 - 10.1]
LT period (Six-year periods)	
• 1983-1989	19 (6)
• 1990-1995	50 (15)
• 1996-2001	75 (23)
• 2002-2007	79 (24)
• 2008-2013	67 (20)
• 2014-2020	42 (13)
Preventive UDCA	28 (8)
UDCA after *r*PBC	312 (94)
Time from *r*PBC to UDCA initiation (months)*	0.5 [0 - 4.71]
UDCA dose, mg/kg/day	13 [10-15]
Immunosuppression at *r*PBC	
• Tacrolimus monotherapy	77 (23)
• Cyclosporine monotherapy	16 (5)
• Prednisone monotherapy	5 (1.5)
• Mycophenolate mofetil monotherapy	5 (1.5)
• Azathioprine monotherapy	1 (0.5)
• Sirolimus/everolimus monotherapy	8 (2)
• Tacrolimus + Mycophenolate mofetil	61 (18)
• Tacrolimus + Sirolimus	7 (2)
• Tacrolimus + Prednisone	53 (16)
• Tacrolimus + Azathioprine	20 (6)
• Cyclosporine + Prednisone	32 (10)
• Cyclosporine + Mycophenolate mofetil	26 (8)
• Cyclosporine + Sirolimus	2 (0.5)
• Cyclosporine + Azathioprine	19 (6)
Histological stage at *r*PBC	
• Stage 1	227 (68)
• Stage 2	76 (23)
• Stage 3	21 (6)
• Stage 4	8 (2)

Biochemical parameters at *r*PBC • ALP (U/L) • AST (U/L) • ALT (U/L) • Bilirubin (µmol/L) • Albumin (g/dL) • Platelets (x10^9/L)	 282 [155 - 282] 58 [32 - 58] 44.0 [27.8 - 81.3] 16.0 [9.9 - 19.0] 39.0 [39.0 - 41.0] 193 [162 - 206]
Biochemical parameters at 1-year after UDCA initiation • ALP (U/L) • AST (U/L) • ALT (U/L) • Bilirubin (µmol/L) • Albumin (g/dL) • Platelets (x10^9/L)	 128 [88 - 240] 27 [20 - 42] 27 [17 - 43] 10 [8 - 15] 40 [38 - 43] 183 [143 - 234]
Rejection after *r*PBC	39 (12)
Graft failure • Related to *r*PBC	52 (16) 43 (13)
Retransplantation	22 (7)
Death	103 (31)
Follow-up	8.7 [4.3 - 12.9]

LT = liver transplant; PBC = primary biliary cholangitis; *r*PBC = recurrent PBC.
Continuous variables are summarised as medians [IQR 25th-75th] and categorical values as proportions (%).

Table 2. Clinical and Biochemical Features Associated with Graft Loss after Liver Transplantation in Patients with Recurrent PBC

Characteristics (n=332)	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at LT	1.01 (0.98-1.05)	0.51		
Age at *r*PBC	1.00 (0.97-1.03)	0.99		
Sex, male	1.51 (0.64-3.56)	0.35		
BMI (kg/m^2)	1.02 (0.96-1.09)	0.54		
LT type†	0.95 (0.34-2.67)	0.92		
LT period*	**0.75 (0.59-0.95)**	**0.02**	0.98 (0.70-1.38)	0.92
Time diagnosis PBC to LT (years)	0.96 (0.89-1.03)	0.23		
Time LT to *r*PBC (years)	1.05 (0.99-1.11)	0.13		
Time *r*PBC to starting UDCA (months)¶	0.97 (0.94-1.01)	0.11		
Histological - stage at *r*PBC (Reference - stage 1-2)	**2.45 (1.18-5.09)**	**0.02**	**3.97 (1.36-11.55)**	**0.01**
Immunosuppression at *r*PBC				
• Tacrolimus	**0.48 (0.27-0.86)**	**0.01**	0.82 (0.08-7.91)	0.86
• Cyclosporine	**2.21 (1.23-3.96)**	**0.008**	1.16 (0.12-11.59)	0.90
• Sirolimus/Everolimus	1.97 (0.78-4.99)	0.15		
• Prednisone	1.77 (0.96-3.27)	0.07	**3.18 (1.04-9.73)**	**0.04**
• Mycophenolate mofetil	0.54 (0.25-1.15)	0.11		
• Azathioprine	1.02 (0.43-2.40)	0.97		
Biochemical parameters at 1-year after UDCA initiation (n=284)**				
ALP xULN	**1.72 (1.42-2.09)**	**<0.001**	**1.59 (1.26-2.01)**	**<0.001**
AST xULN	**1.50 (1.22-1.84)**	**<0.001**	2.18 (0.54-8.70)	0.27
ALT xULN	**1.55 (1.22-1.99)**	**<0.001**	0.59 (0.14-2.49)	0.48
Bilirubin xULN	**1.40 (1.20-1.63)**	**<0.001**	1.08 (0.72-1.63)	0.70
Albumin xLLN	**0.01 (0.001-0.22)**	**0.005**	0.03 (0.001-1.16)	0.06
Platelets xLLN	0.43 (0.15-1.29)	0.13		

LT = liver transplant; PBC = primary biliary cholangitis; *r*PBC = recurrent PBC.
ULN, upper limit of normal; LLN, lower limit of normal.
Continuous variables are summarised as medians [IQR 25th-75th] and categorical values as proportions (%).
LT type† (Cadaveric vs. Living donor).
LT period*: six-year periods (1983-1989, 1990-1995, 1996-2001, 2002-2007, 2008-2013, 2014-2020).
¶These HRs were obtained by considering time from *r*PBC to starting UDCA as a time-dependent covariate in the analyses.
**Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC.

Table 3. Risks Scores Associated with Graft Loss after Liver Transplantation in Patients with Recurrent PBC

Scores for PBC (n=284) **	Univariate		*Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Rochester-II (ALP >2 xULN) at 1-year after UDCA initiation	**3.01 (1.32-6.89)**	**0.009**	**2.79 (1.09-7.15)**	**0.03**
Toronto (ALP >1.67x ULN) at 1-year after UDCA initiation	**3.90 (1.57-9.66)**	**0.003**	**2.85 (1.11-7.32)**	**0.03**
Paris-2 (ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dL [17.1 µmol/L]) at 1-year after UDCA initiation	**5.04 (1.98-12.85)**	**<0.001**	**4.14 (1.57-10.92)**	**0.004**
GLOBE score at 1-year after UDCA initiation	**2.64 (1.72-4.06)**	**<0.001**	**2.82 (1.71-4.66)**	**<0.001**
GLOBE score >0.3 at 1-year after UDCA initiation	**2.78 (1.09-76.76)**	**0.03**	**2.68 (1.04-6.92)**	**0.04**
UK-PBC score (5-years) at 1-year after UDCA initiation	**1.06 (1.03-1.09)**	**<0.001**	**1.06 (1.03-1.09)**	**<0.001**
UK-PBC score (10-years) at 1-year after UDCA initiation	**1.04 (1.02-1.06)**	**<0.001**	**1.04 (1.02-1.06)**	**<0.001**
UK-PBC score (15-years) at 1-year after UDCA initiation	**1.03 (1.02-1.05)**	**<0.001**	**1.03 (1.01-1.05)**	**<0.001**

HR = hazard ratio; CI = confidence interval.
*Adjusted for LT period (Sexennial periods: 1983-1989, 1990-1995, 1996-2001, 2002-2007, 2008-2013, 2014-2020), histological stage at *r*PBC (Stage 3-4), use of tacrolimus, cyclosporine or prednisone at the time for *r*PBC.
Biochemical parameters and PBC scores were not included in the same model to avoid collinearity.
**Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC.

Table 4. Clinical and Biochemical Features Associated with Overall Mortality after Liver Transplantation in Patients with Recurrent PBC

Characteristics (n=332)	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at LT	**1.04 (1.01-1.06)**	**0.006**	0.99 (0.94-1.06)	0.95
Age at *r*PBC	1.02 (0.99-1.05)	0.08	1.03 (0.97-1.09)	0.39
Sex, male	1.05 (0.54-2.03)	0.87		
BMI (kg/m^2)	1.03 (0.97-1.05)	0.89		
LT type†	1.62 (0.88-2.99)	0.12		
LT period*	0.98 (0.83-1.15)	0.80		
Time diagnosis PBC to LT	1.03 (0.99-1.07)	0.16		
Time LT to *r*PBC	1.05 (0.99-1.11)	0.13		
Time *r*PBC to starting UDCA (months)¶	**0.98 (0.97-0.99)**	**0.02**	0.97 (0.94-1.001)	0.06
Histological stage at *r*PBC (Stage 3-4)	1.08 (0.53-2.21)	0.84		
Immunosuppression at *r*PBC				
• Tacrolimus	0.93 (0.61-1.41)	0.72		
• Cyclosporine	1.16 (0.75-1.78)	0.51		
• Sirolimus/Everolimus	1.37 (0.55-3.45)	0.50		
• Prednisone	1.42 (0.91-2.22)	0.12		
• Mycophenolate mofetil	0.69 (0.41-1.14)	0.69		
• Azathioprine	0.96 (0.52-1.76)	0.89		
Biochemical parameters (n=284) **				
ALP xULN	**1.70 (1.47-1.96)**	**<0.001**	**1.52 (1.29-1.78)**	**<0.001**
AST xULN	1.13 (0.96-1.33)	0.15		
ALT xULN	1.09 (0.87-1.37)	0.44		
Bilirubin xULN	**1.14 (1.04-1.25)**	**0.007**	1.03 (0.85-1.25)	0.77
Albumin xLLN	**0.05 (0.005-0.48)**	**0.01**	0.13 (0.01-1.24)	0.08
Platelets xLLN	0.93 (0.65-1.32)	0.67		

LT = liver transplant; PBC = primary biliary cholangitis; *r*PBC = recurrent PBC.
ULN, upper limit of normal; LLN, lower limit of normal.
LT period*: sexennial periods (1983-1989, 1990-1995, 1996-2001, 2002-2007, 2008-2013, 2014-2020).
¶These HRs were obtained by considering time from *r*PBC to starting UDCA as a time-dependent covariate in the analyses.
**Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC.

Table 5. Risk Scores Associated with Overall Mortality after Liver Transplantation in Patients with Recurrent PBC

Scores for PBC (n=284) **	**Univariate**		***Multivariate**	
Rochester-II (ALP >2 xULN) at 1-year after UDCA initiation	**3.89 (2.22-6.82)**	**<0.001**	**3.47 (1.97-6.10)**	**<0.001**
Toronto (ALP >1.67x ULN) at 1-year after UDCA initiation	**3.69 (2.10-6.47)**	**0.002**	**3.28 (1.86-5.77)**	**<0.001**
Paris-2 (ALP ≥1.5x ULN or AST ≥1.5xULN or bilirubin >1 mg/dL [17.1 µmol/L]) at 1-year after UDCA initiation	**4.82 (2.71-8.57)**	**<0.001**	**3.35 (1.90-5.92)**	**<0.001**
GLOBE score at 1-year after UDCA initiation	**2.05 (1.52-2.76)**	**<0.001**	**2.04 (1.50-2.68)**	**<0.001**
GLOBE score >0.3 at 1-year after UDCA initiation	**2.61 (1.48-4.58)**	**<0.001**	**2.55 (1.41-4.63)**	**0.002**
UK-PBC score (5-years) at 1-year after UDCA initiation	**1.02 (1.01-1.04)**	**0.002**	**1.03 (1.01-1.04)**	**0.002**
UK-PBC score (10-years) at 1-year after UDCA initiation	**1.03 (1.01-1.04)**	**<0.001**	**1.03 (1.01-1.04)**	**<0.001**
UK-PBC score (15-years) at 1-year after UDCA initiation	**1.02 (1.12-1.04)**	**<0.001**	**1.02 (1.01-1.04)**	**<0.001**

HR = hazard ratio; CI = confidence interval.
*Adjusted for age at LT and *r*PBC, and time from *r*PBC to starting UDCA as a time-dependent covariate in the analysis. Biochemical parameters and PBC scores were not included in the same model to avoid collinearity.
**Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC.

Figure 1a.

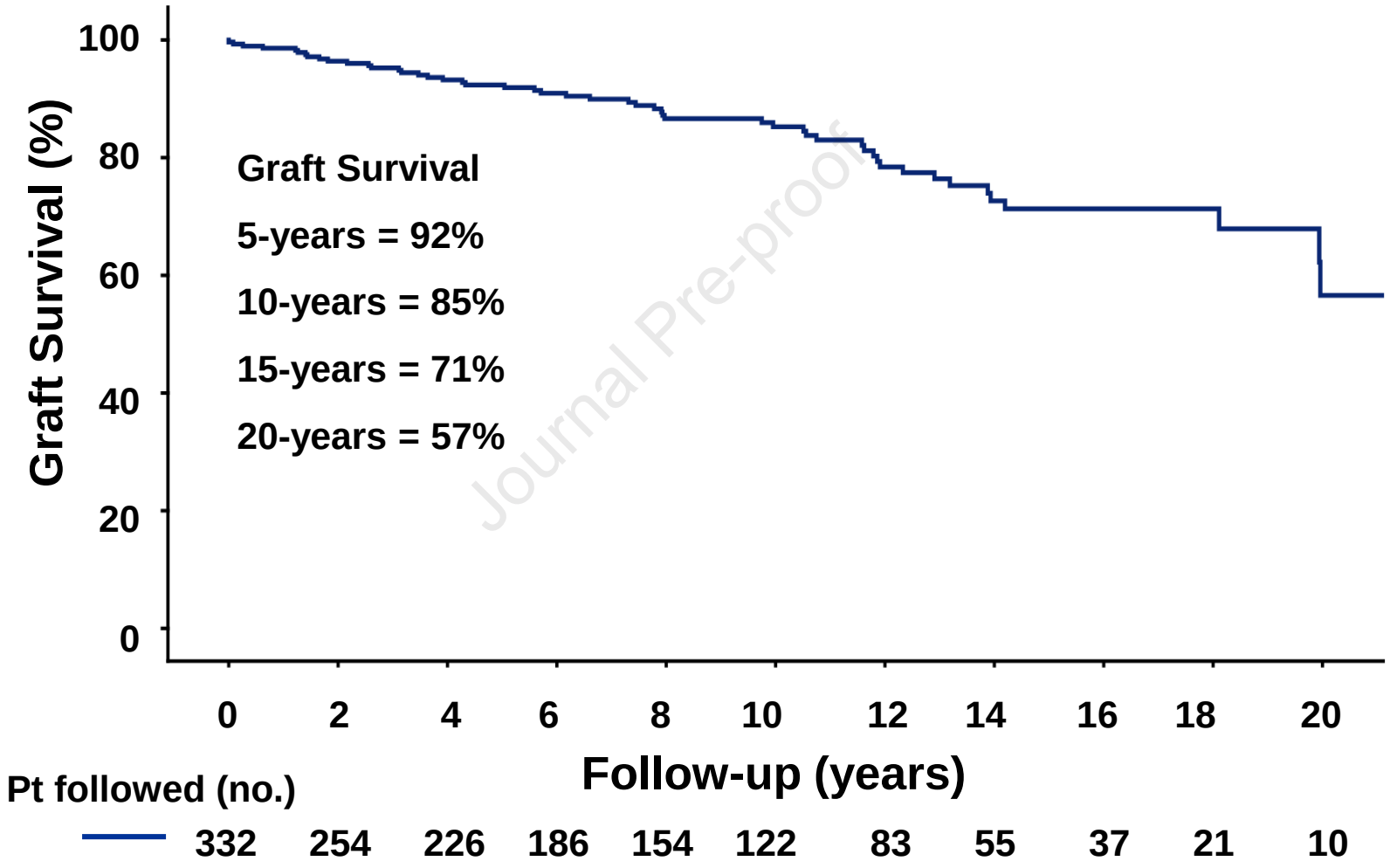


Figure 1b.

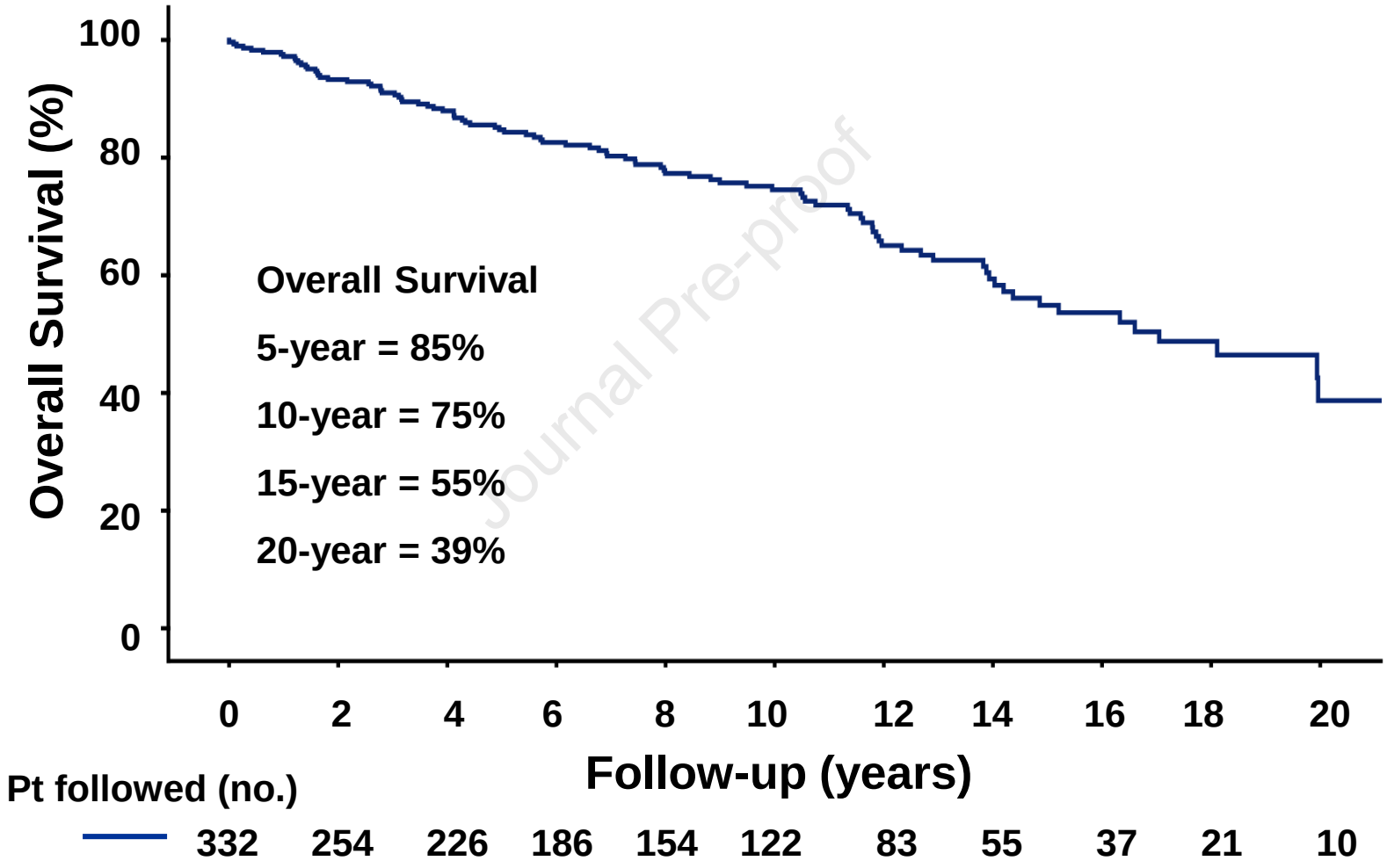


Figure 2a.

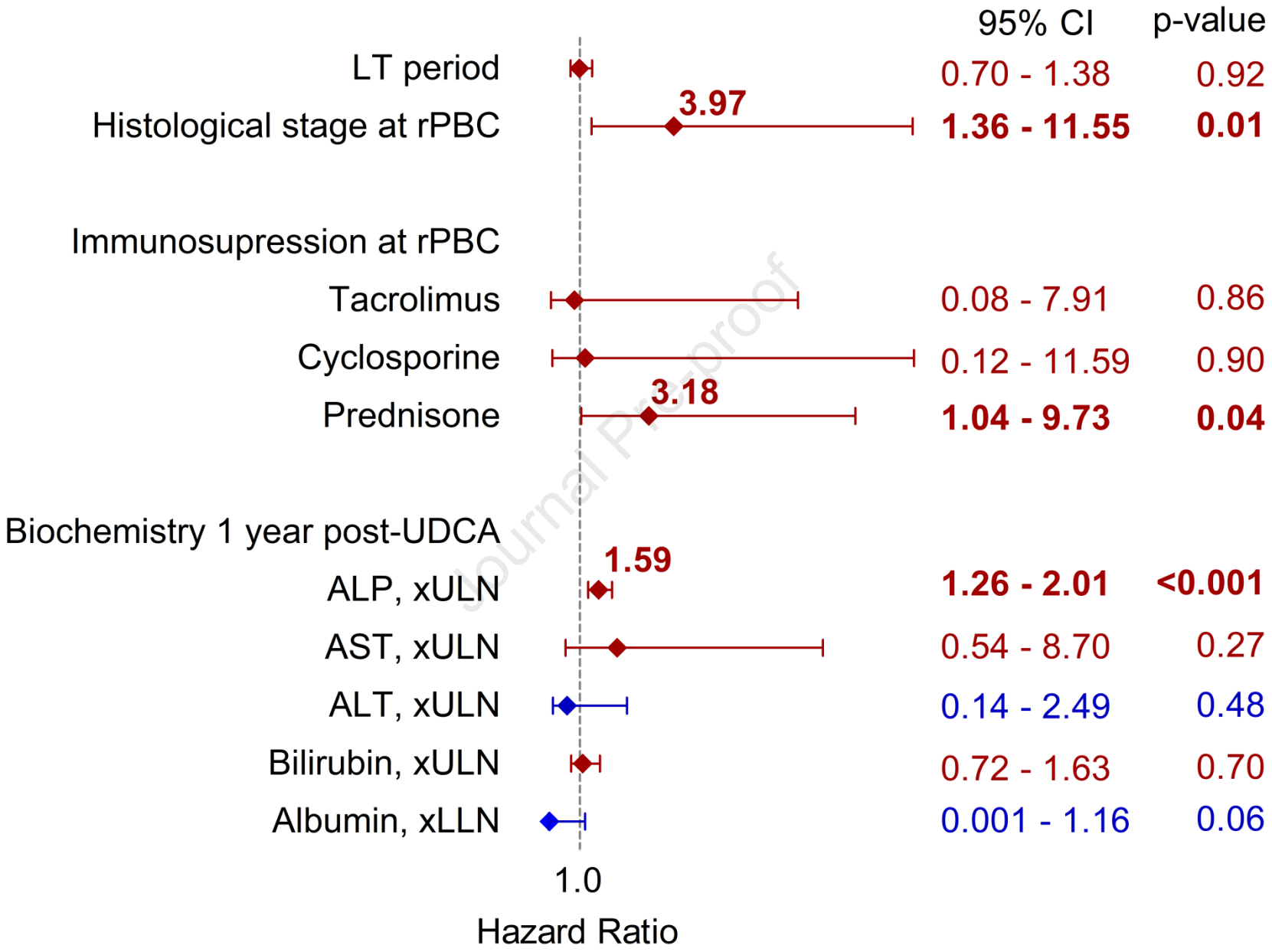


Figure 2b.

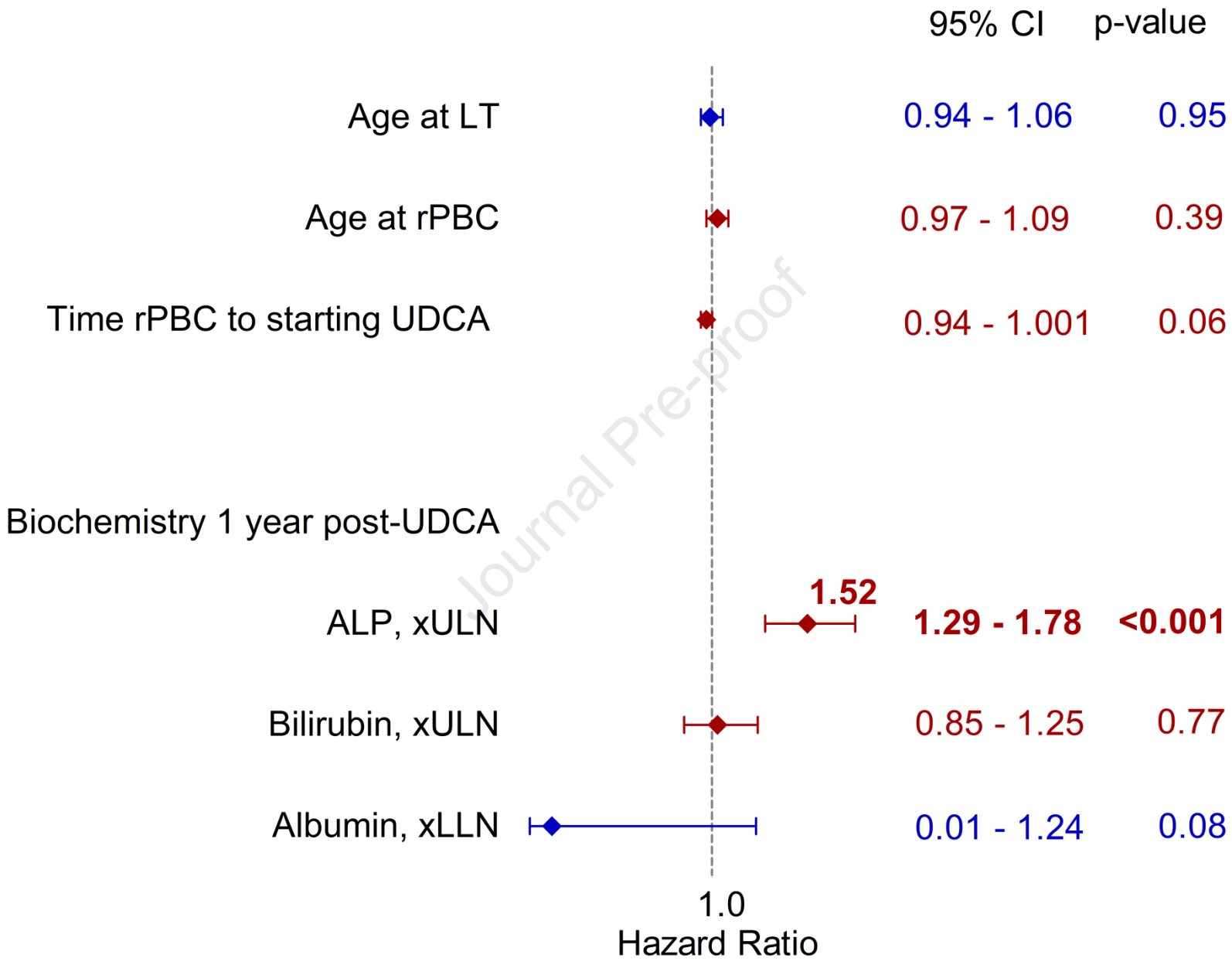
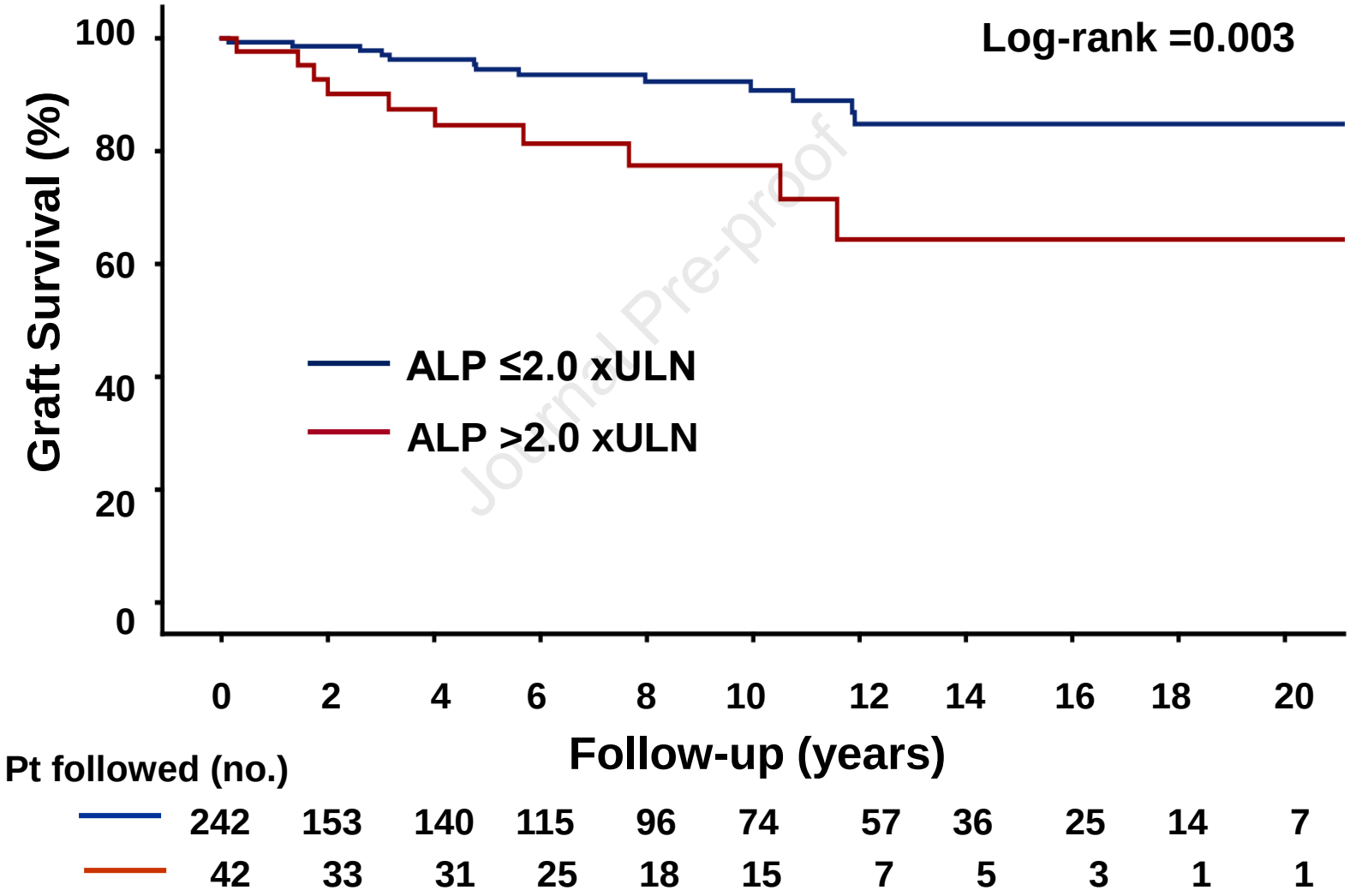


Figure 3a.



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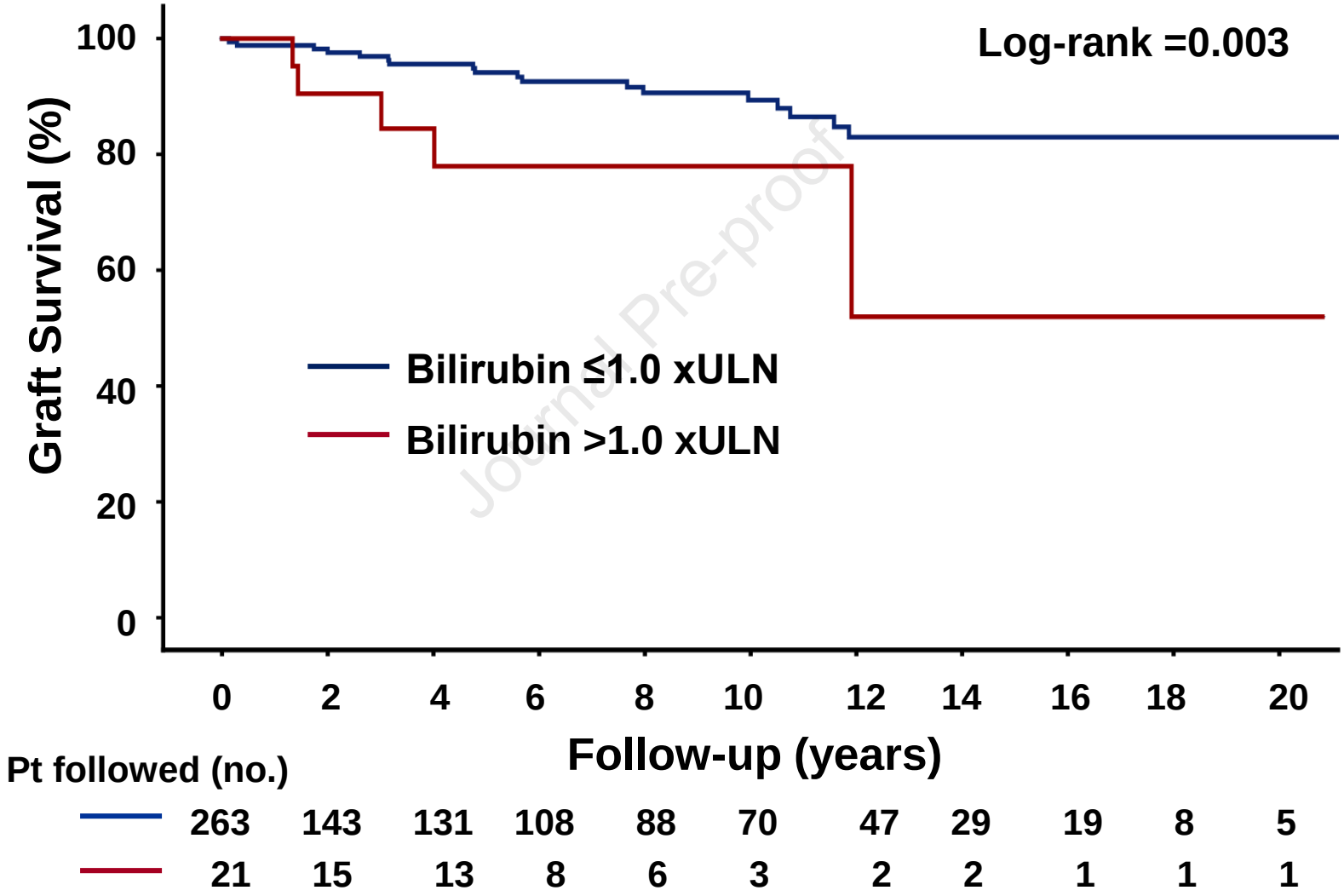
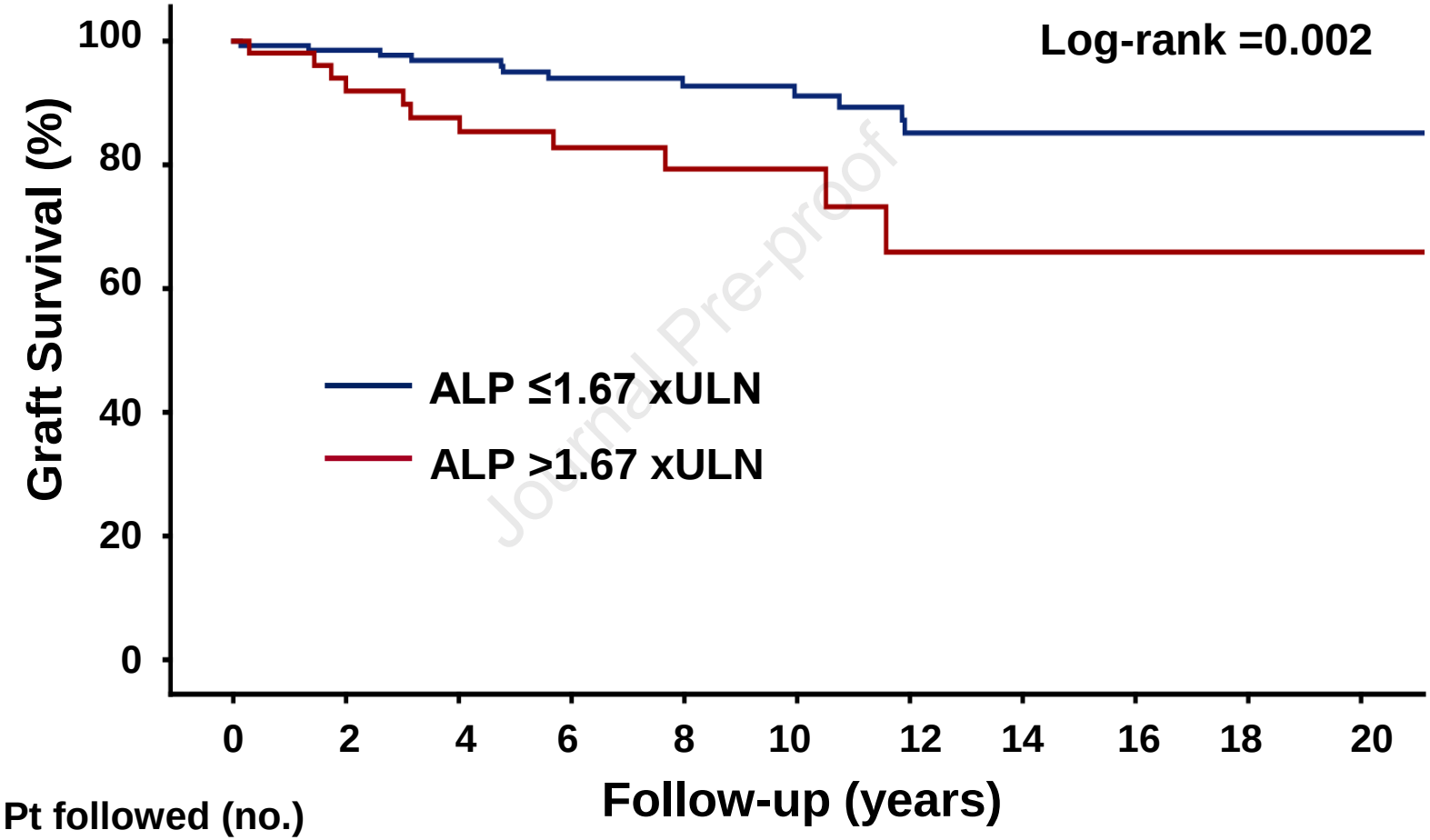


Figure 3c.



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48	39	28	21	15	7	5	3	2	2	1

Figure 3d.

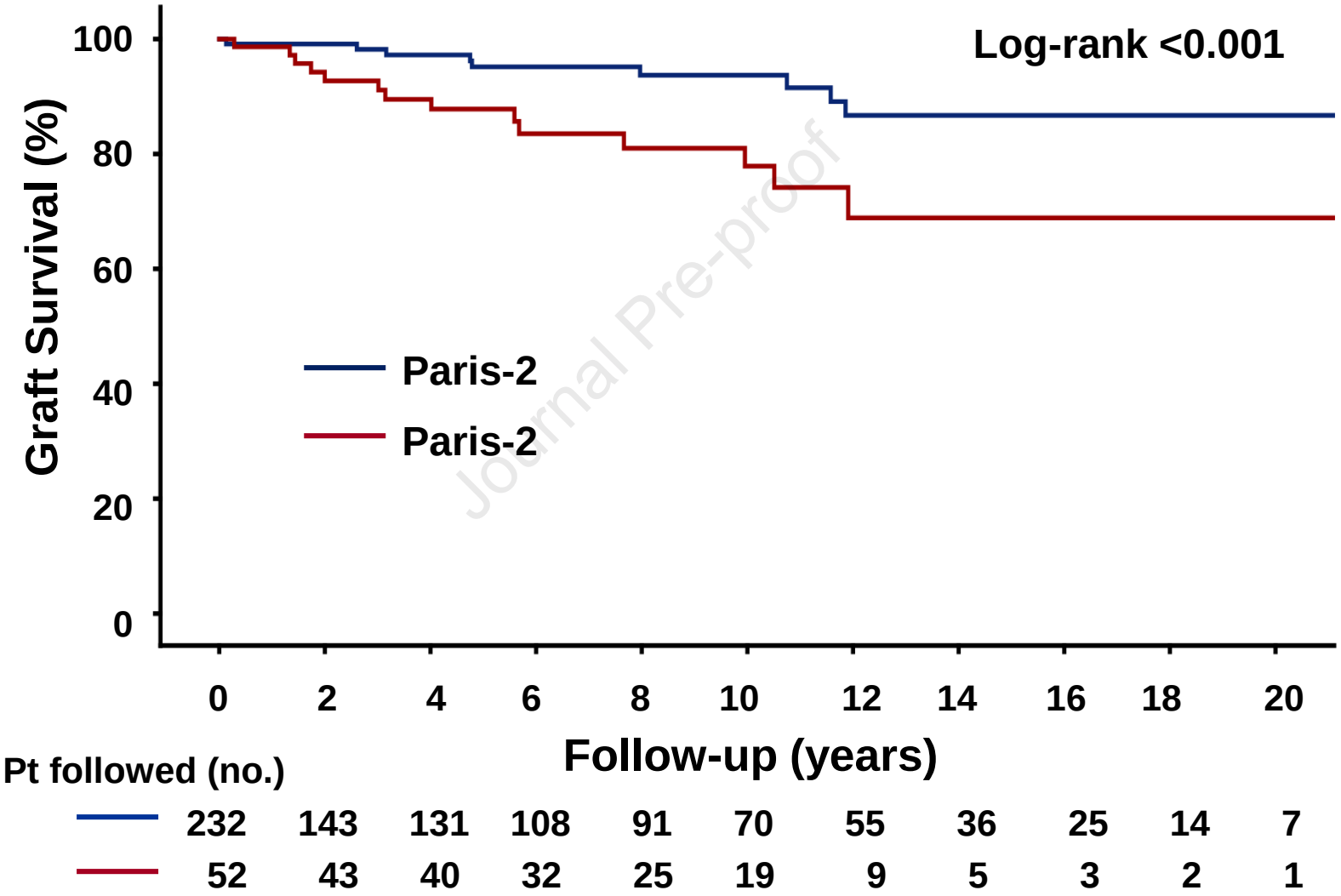


Figure 3e.

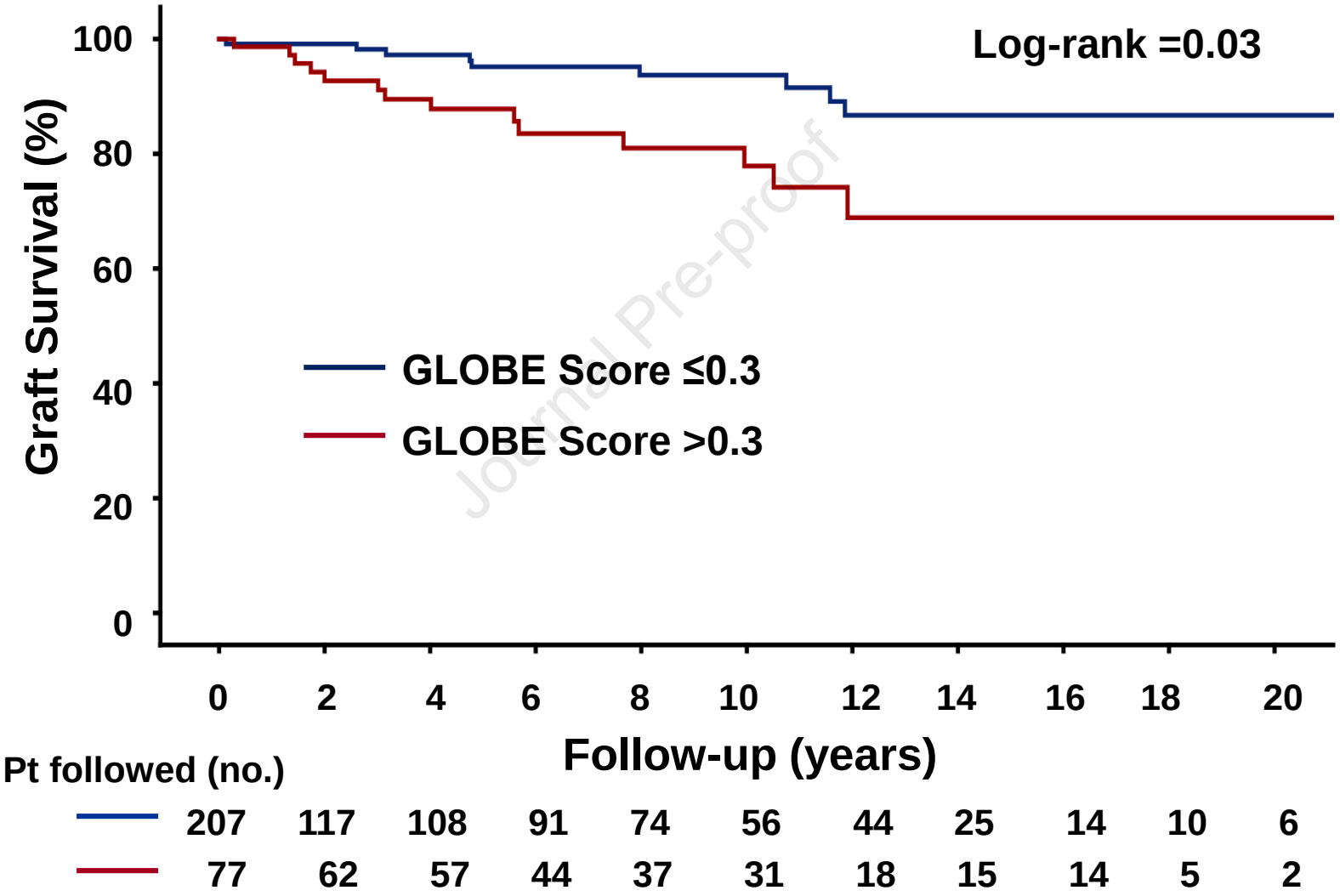
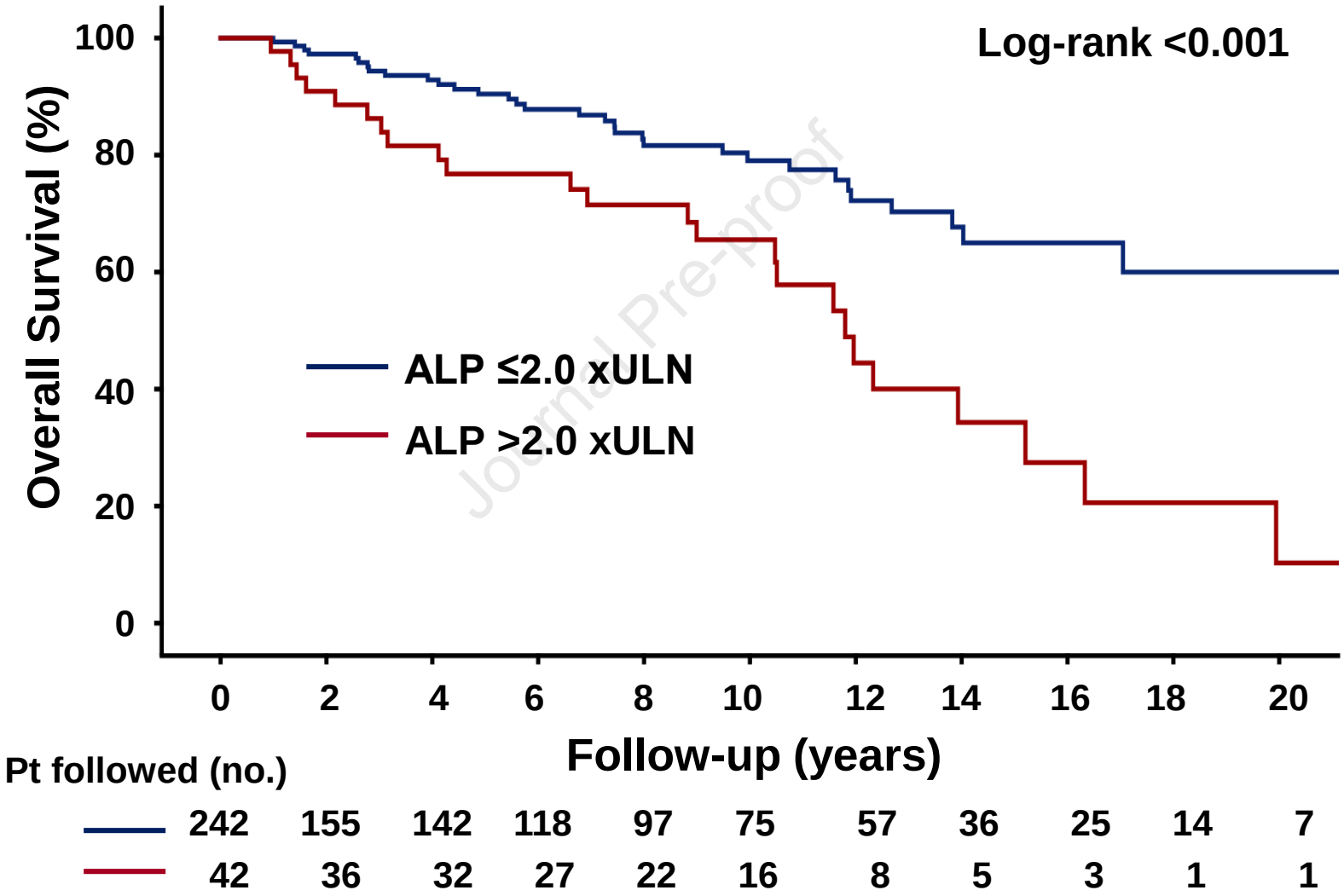


Figure 4a.



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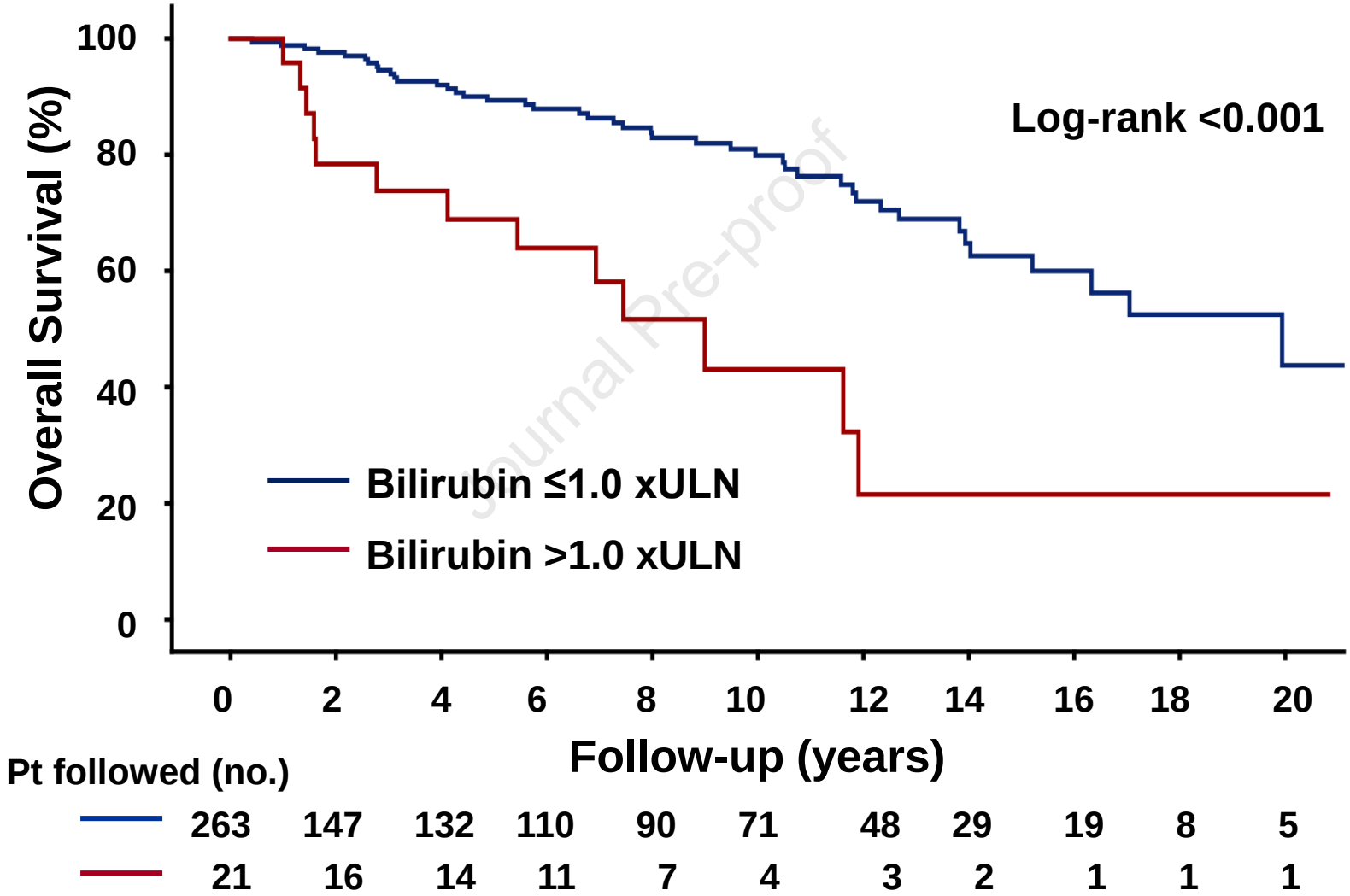

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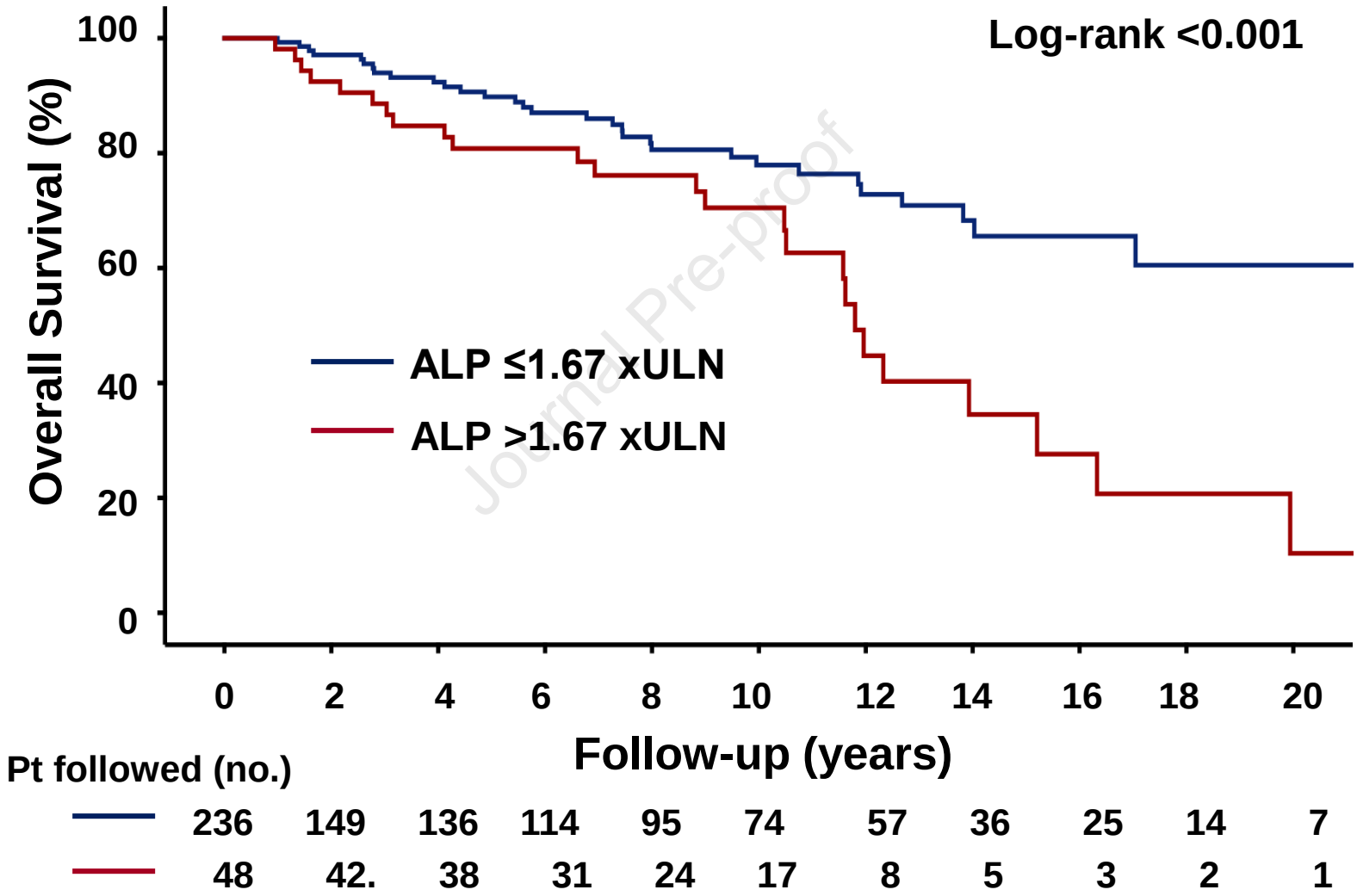
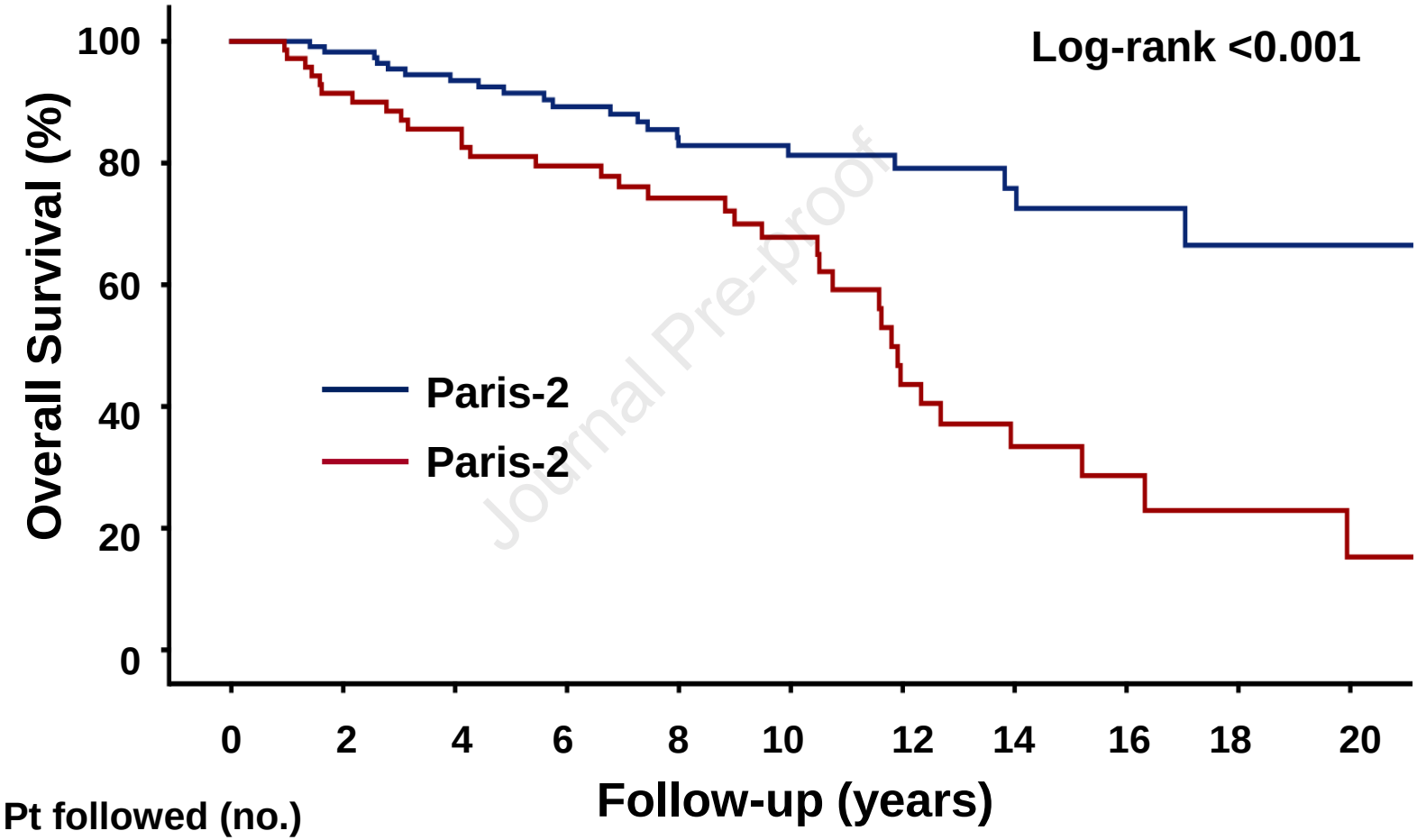


Figure 4d.



Pt followed (no.)										
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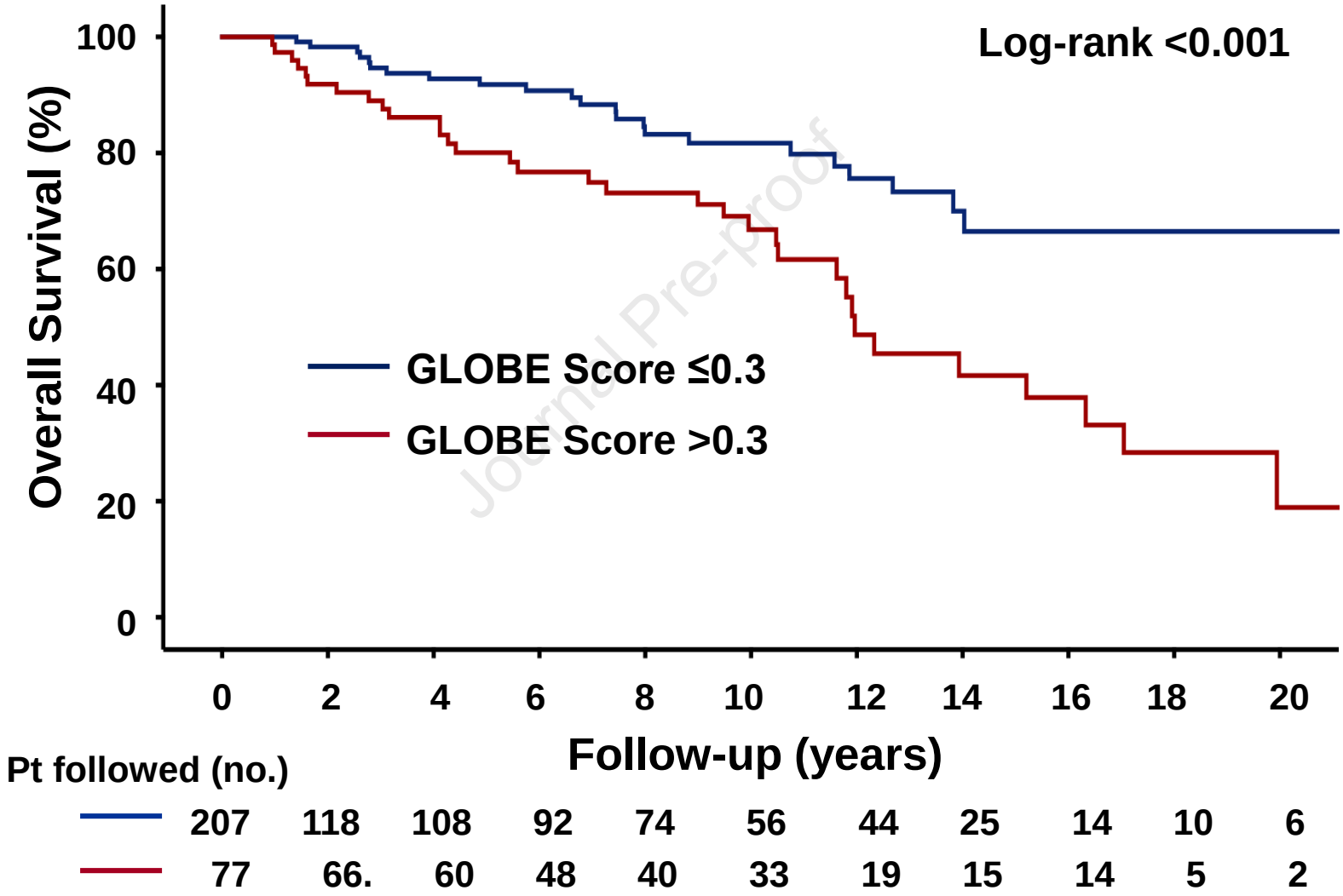
52	46	42	35	28	21	10	5	3	1	1

Figure 4e.



Highlights:

- Recurrent primary biliary cholangitis (*r*PBC) develops in approximately 30% of patients and negatively impacts graft and overall patient survival after liver transplantation (LT).

- Levels of alkaline phosphatase at one year of ursodeoxycholic treatment (UDCA) predict graft loss and mortality in patients with *r*PBC after LT.

- Prognostic Scores for UDCA-Treated Patients Predicts Graft Loss and Mortality in Patients with *r*PBC after LT.

- Future studies for patients with *r*PBC and incomplete response to UDCA, to evaluate the benefit of the addition of second-line treatment such as obeticholic acid, and fibrates are warranted.