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Original research

Biliary strictures after liver transplantation: Role of interleukin 28B genotypes in cyclosporine treated

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HIGHLIGHTS

- Biliary strictures after liver transplantation are frequent.
- The pathogenesis involves vascular, immunological and genetic factors.
- Role of IL-28B genotypes and cyclosporine in biliary strictures is presented.

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ABSTRACT

Introduction: The role of Interleukin 28B (IL-28B) genetic polymorphisms in influencing the occurrence of biliary complications after liver transplantation has never been evaluated. This study aimed to investigate whether IL-28B rs12979860C/T polymorphisms associate with the occurrence of biliary complications after liver transplantation and if these complications may influence survival. **Methods**: One hundred seventy one recipients (133 males) who underwent liver transplantation were recruited. To confirm the mechanical etiology of cholestasis, endoscopic cholangio pancreatography, percutaneous and/or trans-Kehr cholangiography or cholangio magnetic resonance were performed. Two main clinical pictures were identified: biliary strictures and biliary leakage. Immunosuppressive therapy was based on cyclosporine ($N = 54$) or tacrolimus ($N = 117$), in association with steroids during the first month after operation. IL-28B rs12979860C/T genotypes were detected by means of polymerase chain reaction. **Results**: Forty patients (23.4%) presented anastomotic strictures, 7 (4.1%) non-anastomotic strictures, 10 (5.8%) leakage, 8 (4.7%) leakage plus anastomotic strictures. IL-28B rs12979860C/C genotype in association with cyclosporin was found to be an independent predictor of anastomotic strictures occurrence ($p = 0.008$). A significant difference in 5 years survival was observed between patients with viral etiology of liver disease experiencing either anastomotic or non-anastomotic strictures (16/23) and the remaining patients (104/112, $p = 0.001$). **Conclusions**: In recipients carrying rs12979860 IL-28B C/C genotype the use of cyclosporine seems to contribute to enhance the probability of developing biliary complications which in hepatitis B and C positives appear to reduce patient survival. If confirmed in larger studies the use of cyclosporine in these patients could be revised.

1. Introduction

Biliary complications are probably the most frequent problem that transplant hepatologists and surgeons have to manage following liver transplantation (LT) [1–3]. They are generally classified according to their anatomical location into anastomotic and non-anastomotic complications, because of the different clinical presentation and management. Anastomotic complications comprise leakage and stricture. The overall reported incidence of anastomotic strictures (AS), that are by far the most frequent biliary complications, ranges between 13% and 19% after full size and living donor liver transplantation (LDLT) respectively [2,4]. Their incidence is increasing in the post MELD era, reaching 16.7% in some series, probably because of the use of marginal grafts from older

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donors [2,5,6]. These factors have also been linked to the occurrence of non-anastomotic strictures (NAS), in relationship to a suboptimal biliary blood supply or to an enhanced susceptibility of the biliary tree to ischemic damage [2,6]. The treatment of AS generally consists of endoscopic balloon dilatation with or without stents placement. This approach can solve up to 60–90% of AS and generally requires repeated sessions and progressive dilatation up to the complete resolution of the stricture [7].

Among the risk factors described for the occurrence of AS, most of them related to surgical and technical aspects [5,8], recent studies suggested an influence exerted by the cross-talk between donor and recipient immune responses and by the degree of inflammation. In fact, Jacob et al. [9] found that AS occurrence was associated with recipient fractalkine receptor (CX3CR1)-V249I polymorphism and with the presence of donor-specific anti-human leucocyte antigen (HLA) class II antibodies. In the same study, patients with AS exhibited higher serum levels of IFN-γ, IL-6 and IL-10. Therefore, a new scenario, where the innate immune response can play an important role in the occurrence of biliary complications, may be hypothesized.

Interleukin 28B (IL-28B) gene encodes for Interferon lambda 3 which is a cytokine involved in the innate immune response [10,11]. Both donor and recipient IL-28B rs12979860 genetic polymorphisms have been implicated in the severity of HCV recurrence and in response to antiviral treatment after LT [12]. The simultaneous carriage in donor and recipients of IL-28B CC genotype has been associated with a better response to antiviral therapy for HCV recurrence [13,14] but conflicting results have been published considering the effect of IL-28B genetic polymorphisms on graft survival both in HCV positive and HCV negative recipients [12,15]. Moreover, an association has been demonstrated between IL-28B polymorphisms and the occurrence of post LT diabetes mellitus and acute cellular rejection [16,17]. These data seem to support the evidence that this cytokine could play an important role in the modulation of immune response in liver transplanted patients. No data have been reported regarding the potential influence of IL-28B genetic polymorphisms on the occurrence of biliary complications after LT.

The aim of this retrospective study was to investigate whether IL-28B rs12979860C/T polymorphisms may be associated with the development of biliary complications after liver transplantation in HCV negative and positive recipients.

2. Patients and methods

Two hundred twenty five consecutive adult recipients who underwent liver transplant at the University of Udine from January, 1st 2004 to November, 30th 2010 were considered for the study. Thirty four patients were excluded because of HIV co-infection, 1 for having received an LDLT, 3 because died within 30 days after transplant and 16 since they were lost of follow-up (Fig. 1). The remaining 171 patients were enrolled in the study. The protocol for the research project has been approved by our Ethical Committee. The study conforms to the provision of the declaration of Helsinki; all patients gave an informed consent. All clinical and demographic data were recorded from the Transplant Center database and are reported in Table 1. Biliary-digestive anastomosis during LT was at discretion of the surgeon and generally reserved to patients transplanted for cholestatic liver diseases such as primary sclerosing cholangitis. In the remaining patients choledocho–choledocho terminal anastomosis was performed with or without the placement of Kehr T tube. In the former patients a trans-Kehr cholangiography was done within 10 days after LT or when clinically required. Kehr T tube was removed 3 months after transplant adopting the endoscopic retrograde cholangiopancreatography (ERCP) rendez-vous technique which was always associated with the placement of a biliary stent to prevent biliary leakage.

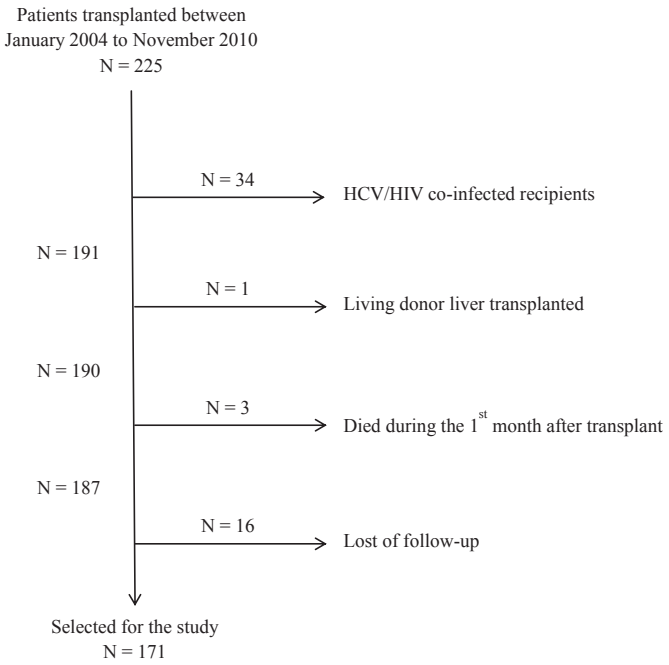

Fig. 1. Flow chart showing the selection of patients recruited in the study.

Table 1
Main demographic and clinical characteristics of studied population (N = 171). Continuous variables are presented as median (range) and categorical variables as frequencies (%).

Recipient age, years	56 (25–68)
Donor age, years	51 (11–81)
Recipient male gender	133 (77.8%)
Donor male gender	115 (67.3%)
Split liver	13 (7.6%)
MELD	14 (6–40)
D-MELD	670 (99–2479)
Recipient BMI at LT, kg/m^2	25 (15–35)
CMV reactivation	35 (20.5%)
Kehr T tube	23 (13.5%)
Viral etiology (HCV or HBV related)	85 (49.7%)
Presence of hepatocellular carcinoma before LT	61 (35.7%)
Total ischemia time, min	460 (128–955)
Use of University of Wisconsin solution	45 (26.3%)
Use of cyclosporine	54 (31.6%)
Presence of diabetes mellitus before LT	44 (25.7%)
Presence of systemic arterial hypertension before LT	50 (29.2%)
Patients with at least 1 moderate to severe ACR	36 (21.1%)
Hepatic artery resistance index 1 month after LT	0.67 (0.33–0.87)
Hepatic artery thrombosis	5 (2.9%)
Steroid treatment duration, days	137 (0–868)

MELD = Model of End Stage Liver Disease; BMI = body mass index; CMV = Cytomegalovirus; HCV = hepatitis C virus; HBV = hepatitis B virus; LT = liver transplantation; ACR = acute cellular rejection.

The suspicion of mechanical cholestatic syndrome derived from the increase in serum levels of alkaline phosphatase, bilirubin and gamma glutamyl transpeptidase, in conjunction with ultrasound evident dilatation of intra-hepatic biliary three with the patency of hepatic artery and portal vein. To confirm the mechanical etiology of cholestasis, ERCP, percutaneous and/or trans-Kehr cholangiography and magnetic resonance imaging (MRI) of biliary three were performed. Two main clinical pictures were identified: presence of biliary strictures (AS and NAS) and biliary leakage. Biliary strictures

were defined as the presence of an obstructive lesion in the biliary three needing a therapeutic intervention such as endoscopic ballooning and/or insertion or substitution of a previously placed biliary stent. Biliary leakage was defined by the presence of biloma.

Immunosuppressive therapy was based on cyclosporine (CSA, $N = 54$) or tacrolimus (TAC, $N = 117$), in association with steroids during the first month after LT. Dosage of CSA was based on pre-dose plasma concentrations, with targeted values from 250 to 350 μg/L within the first 6 weeks after transplant and from 50 to 150 μg/L thereafter. Dosage of TAC was based on pre-dose plasma concentrations, with targeted values from 10 to 15 μg/L during the first 6 weeks after transplantation and from 5 to 10 μg/L thereafter. In all patients both CSA and TAC serum concentrations were measured at the first day, after the starting loading dose, and thereafter at the following days: 15, 30, 60, 90, 120, 150, 180 and 360. The daily concentration of the immunosuppressive drugs was estimated calculating the area under the curve (AUC) adopting the trapezoid rule. Corticosteroid therapy was started during liver transplant with the administration of 500 mg of metilprednisolone i.v., followed by metilprednisolone 250 mg i.v. in the second and in the third day after the operation. Oral prednisone at a dosage of 40 mg daily was started at the fourth day after transplant. Corticosteroids were tapered and suspended within 4 months. Twenty four patients were treated with a steroid free immunosuppressive regimen.

2.1. Molecular biology

Identification of IL-28B genotype polymorphism rs12979860C/T was done as previously described [18]. In brief, a polymerase chain reaction-based restriction fragment length polymorphism assay technique was used. DNA was extracted from whole blood samples using QIAamp DNA Blood Mini Kit (Qiagen Milan, Italy). In a total volume of 10 μL an amplicon of 242-base pairs, using the 5′-GCTTATCGCATACGGCTAGG-3′ and 5′-AGGCTCAGGGTCAATCACAG-3′ primers, was obtained. The thermal profile adopted was 90° for 30″, 62 °C for 30″, 72 °C for 30″ repeated for 40 cycles in a Techne TC-5000 thermal cycler. The amplicons obtained were then digested overnight at 60 °C with one unit of BstU-I (New England Biolabs, Hitchin, UK) restriction enzyme. The fragments obtained were of 135 + 82 + 25 bp for the C allele and of 160 + 82 bp for the T allele variant respectively, stained with ethidium bromide and resolved in a 3.5% agarose gel electrophoresis.

2.2. Statistical analysis

Statistical analysis of data was performed using the BMDP dynamic statistical software package 7.0 (Statistical Solutions, Cork, Ireland). Categorical variables have been presented as frequencies and continuous variables as medians (range). Pearson chi-squared test and Chi-square test for linear trend, when appropriate, have been applied to detect associations between categorical variables. The chi-square G test “Goodness of Fit” was employed to verify whether the proportions of the polymorphism were distributed in accordance with the Hardy–Weinberg equation. Step-wise logistic regression analysis has been used to explore independent predictors of AS. Kaplan Mayer and Mantel Cox test were employed to evaluate predictors of survival. Cox proportional hazard model was used to identify independent predictors in survival analysis. Statistical significance has been considered for p values <0.05.

3. Results

3.1. Occurrence of biliary complications

Forty patients (23.4%) presented AS, 7 patients (4.1%) presented NAS, 10 patients (5.8%) leakage and 8 (4.7%) leakage plus AS. By means of One-Way ANOVA for linear trend, mean time for the occurrence of biliary complications significantly increased from biliary leakage (2.1 months) to NAS (8.4 months) to AS (10.9 months, $p = 0.015$ for linear trend).

3.2. Risk factors associated with the occurrence of AS

Table 2 illustrates the association between demographic and clinical variables and the occurrence of AS. At the univariate analysis, the only clinical feature strongly associated with AS was the use of Kehr T tube. Moreover, use of CSA as the main immunesuppressive agent was slightly associated with a higher probability to develop AS.

3.3. IL-28B rs12979860C/T polymorphism and the occurrence of AS

Recipient IL-28B genotypic frequencies were: $C/C = 71$ (41.5%), $C/T = 83$ (48.5%), $T/T = 17$ (10.0%). The allelic frequencies were: $C = 0.658$ and $T = 0.342$. The genotypic frequencies observed did not differ from what expected according to the Hardy–Weinberg formula ($p = 0.306$). A significant association was observed between recipient IL-28B rs12979860C/T polymorphism and occurrence of AS which was found in 22/71 (31.0%) patients carrying the *C/C* genotype, in 16/83 (19.3%) carrying the *C/T* genotype and in 2/17 (11.8%) carrying the T/T genotype ($p = 0.039$ for linear trend).

Table 2
Associations between demographic and clinical variables and occurrence of biliary anastomotic stricture following liver transplantation. The statistical analysis was performed by means of Pearson chi square test.

Biliary anastomotic stricture			
	Yes $N = 40$ (23.4%)	No $N = 131$ (76.6%)	p
Recipient age >55 years	24 (60.0%)	75 (57.3%)	0.758
Donor age >45 years	27 (67.5%)	75 (57.3%)	0.247
Recipient male gender	32 (80.0%)	101 (77.1%)	0.699
Donor male gender	31 (77.5%)	84 (64.1%)	0.115
MELD >14	17 (42.5%)	58 (44.3%)	0.843
D-MELD >750	15 (37.5%)	52 (39.7%)	0.803
Recipient BMI at LT > 25 kg/m^2	20 (50.0%)	52 (39.7%)	0.248
CMV reactivation	8 (20.0%)	27 (20.6%)	0.933
Kehr T tube	12 (30.0%)	11 (8.4%)	<0.001
HCV and/or HBV etiology	16 (40.0%)	69 (52.7%)	0.161
Total ischemia time >460 min	14 (35.0%)	54 (41.2%)	0.482
Use of University of Wisconsin solution	7 (17.5%)	38 (29.0%)	0.148
Use of cyclosporine	18 (45.0%)	36 (27.5%)	0.037
Presence of DM before LT	12 (30.0%)	32 (24.4%)	0.480
Steroid treatment duration >120 days	29 (72.5%)	82 (62.6%)	0.251
Occurrence of hepatic artery thrombosis	1 (2.5%)	4 (3.1%)	0.856
Hepatic artery RI > 0.67 1 month after LT	21 (52.5%)	58 (44.3%)	0.361
Occurrence of moderate to severe ACR	11 (27.5%)	25 (19.1%)	0.253

MELD = Model of End Stage Liver Disease; BMI = body mass index; CMV = Cytomegalovirus; HCV = hepatitis C virus; HBV = hepatitis B virus; LT = liver transplantation; ACR = acute cellular rejection.

3.4. IL-28B rs12979860C/T polymorphism, occurrence of AS in relationship with the immune suppressive regimen

Fig. 2 shows the relationship between IL-28B rs12979860C/T polymorphisms (*C*/*C* vs *T*/* genotypes) and the occurrence of AS. Data were presented considering all patients and dividing them on the basis of the type of immunosuppressive regimen adopted (CSA or TAC). The carriage of IL-28B C/C genotype was significantly associated with a more frequent development of AS (22/71 vs 18/100, $p = 0.048$); this was confirmed in patients treated with CSA (10/20 vs 8/34, $p = 0.046$) but not in patients treated with TAC (12/51 vs 10/66, $p = 0.250$). By logistic regression analysis the interaction between IL-28B polymorphism and CSA was found to be an independent predictor of AS occurrence, together with receiving a graft from a male donor and the use of a Kehr-T tube (Table 3).

3.5. Management of biliary complications

Biliary complications were managed as follows: 53 (81.5%) had subjected to ERCP and 12 (18.5%) to percutaneous-cholangio-pancreatography (PCCP); 9 (13.8%) of the latter underwent to both procedures. In patients who were subjected to ERCP, 13 performed the procedure once, 12 twice, 11 thrice, 5 fourfold, 9 fivefold, 4 sixfold, 4 sevenfold, 1 eightfold, 2 ninefold and 1 tenfold. In the 62 patients who underwent to ERCP a significant association was observed between carriage of C/C genotype plus CSA use and the need to be subjected to more than 3 procedures (7/10 vs 19/52, $p = 0.049$).

3.6. Biliary complications and survival

Five years survival among recipients who completed at least one year of follow-up after LT ($N = 135$) was found to be significantly worse in patients who experienced the occurrence of a biliary stricture, either AS or NAS (Mantel–Cox $p = 0.046$). In particular this was confirmed in patients with viral etiology of liver disease (HCV + HBV, $N = 64$, Fig. 3 panel A) while it was not observed in the remaining patients (others, $N = 71$, Fig. 3 panel B). Accordingly a highly significant difference in 5 years survival was observed between patients with a viral etiology of liver disease experiencing either AS or NAS (16/23) and the remaining patients (104/112, Mantel Cox $p = 0.001$). At Cox proportional hazard model, the interaction between the viral etiology of liver disease with the occurrence of biliary strictures was found to be an independent predictor of death within 5 years (O.R. = 3.76, 95% C.I. = 1.34–10.5, improvement of chi square $p = 0.005$) in conjunction with CSA use (O.R. = 3.52, 95% C.I. = 1.18–10.5, improvement of chi square $p = 0.026$).

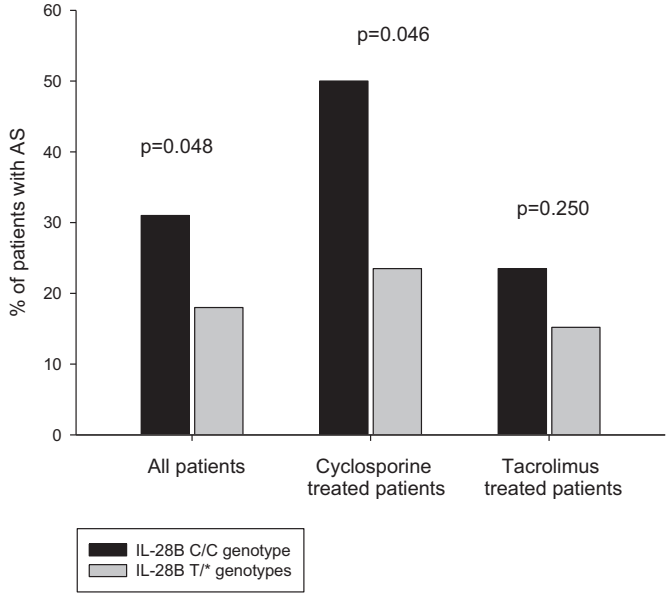

Fig. 2. Relationship between IL-28B rs12979860C/T polymorphisms (*C*/*C* vs *T*/* genotypes) and the occurrence of anastomotic strictures. Data were presented considering all patients and dividing them on the basis of the type of immunosuppressive regimen adopted (Cyclosporin or Tacrolimus).

Table 3
Summary of the results of stepwise logistic regression analysis in the prediction of biliary anastomotic strictures occurrence. Covariates were those reported in Table 2, IL-28B polymorphism (*C*/*C* Vs *T*/*) and the interaction between IL-28B polymorphism and type of immunosuppression (*C*/*C* plus cyclosporine use Vs the remaining patients).

	Coefficient	S.E.	O.R.	95% C.I.	*P*
Kehr T tube adoption	1.697	0.499	5.46	2.04–14.6	0.001
C/C genotype and cyclosporine use	1.435	0.516	4.20	1.52–11.6	0.008
Donor male gender	0.959	0.471	2.61	1.03–6.61	0.032

S.E. = standard error; O.R. = odds ratio; C.I. = confidence interval.

4. Discussion

Biliary complications are a major source of morbidity after LT. Classification systems are based mainly on the time of occurrence, etiology and localization. AS (stenosis or leak) develop later and are distinguished from NAS that typically occur earlier after LT [2,19]. Risk factors for AS occurrence include older donor age, use of Kehr T tube, marginal grafts, prolonged ischemia time and split liver transplantation [1,3].

The frequency of biliary strictures after LT has been reported to be quite variable. In the present paper the overall incidence of biliary strictures was about 32%, higher compared to what observed in other retrospective series [2,4]. This can be explained by the fact that in this study donors were older in comparison to what reported in the major series of liver transplantation performed in USA [20]. Moreover, about 14% of the recipients underwent biliary reconstruction with the insertion of a Kehr T tube. The relevance of this procedure in influencing AS occurrence in the present study was confirmed both in the univariate and in the multivariate analysis.

Although AS could be mainly considered as the final result of a fibrotic process elicited by mechanical or ischemic injuries [1], a role of the immunological response in modulating inflammation and scarring may be advocated. In fact, it has been shown that AS are more prevalent in recipients who present early and severe HCV recurrence compared to those with late and mild recurrence [21], suggesting that a stronger immune reaction may facilitate inflammation and scarring.

In HCV positives donor and recipient IL-28B rs12979860 genetic polymorphisms influence both the severity of HCV recurrence and the probability to achieve sustained viral response after interferon and ribavirin therapy [13]. In fact, these polymorphisms are in linkage disequilibrium with SS469415590 T/T or ΔG of Interferon-λ4 gene [22]. The carriage of IL-28B rs12979860C/C genotype was associated with the carriage of Interferon-λ4 SS469415590 T/T genotype. This genotype leads to a frame-shift that inactivates the gene and in turn determines HCV clearance and a positive treatment outcome [23]. IL-28B genetic polymorphisms have also been found to be associated with the development of acute cellular rejection (ACR) after LT [17], a condition strictly related to the

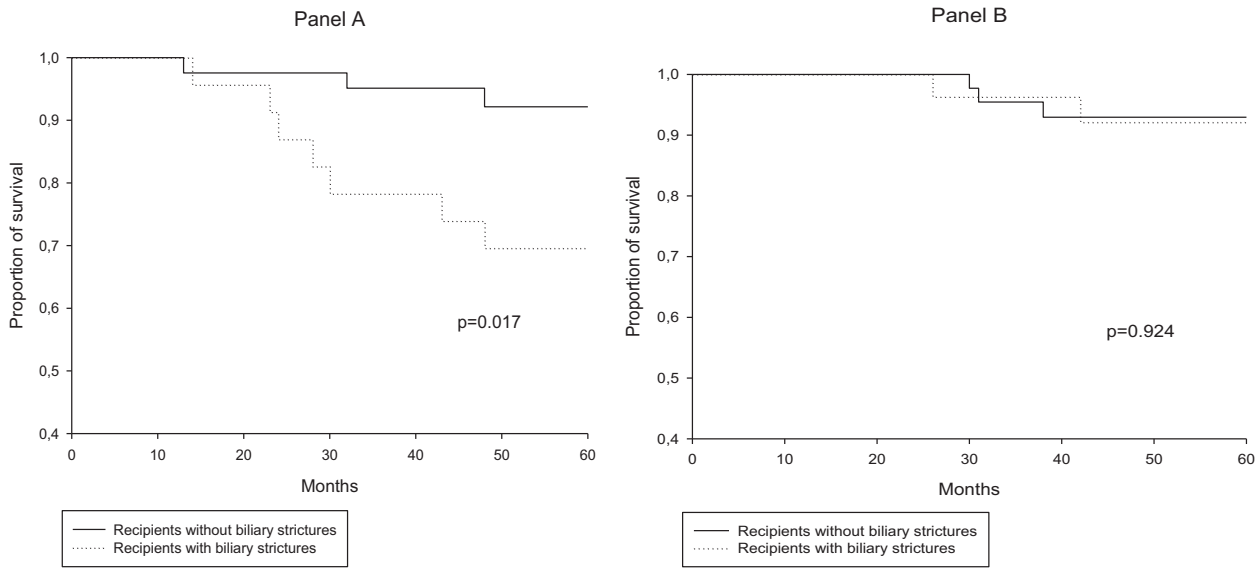

Fig. 3. Five years survival in recipients who completed at least one year of follow-up after liver transplantation ($N = 135$) according to the occurrence of biliary strictures either anastomotic or not anastomotic. Panel A refers to recipients with viral (HCV + HBV) etiology of liver disease ($N = 64$). Panel B refers to recipients with no viral etiologies of liver disease ($N = 71$).

intensity of innate immune response mechanisms. Recipients carrying the rs12979860C/C genotype experienced more severe ACR episodes compared to those carrying the T/* genotype [17].

Accordingly, AS were found to be more frequent in recipients carrying the rs12979860C/C compared to those carrying *C/T* or *T/T* genotypes. What appears more intriguing is the observation that the carriage of rs12979860C/C genotype exerts its maximal influence in determining AS in conjunction with the CSA use. A simple explanation for this novel result is unknown; nevertheless it should be pointed out that CSA alters hepato-biliary function by perturbing biliary flow and bile acid secretion [24]. Finally, the interaction observed between CSA and rs12979860C/C polymorphism parallels that found between the carriage of rs12979860C/C polymorphism and CSA use in conditioning a favorable antiviral response in recurrent hepatitis C [14].

Studies reporting the association between occurrence of biliary complications and worse graft and patient survival have been published [25,26]. Nevertheless, it must be emphasized that these results might be limited by the influence of different kinds of clinical management of biliary complications, i.e. conservative-endoscopic or invasive-surgical treatment. In this regard the series reported here were managed in all the cases with a conservative-endoscopic or percutaneous approach. Indeed, a worse effect on patient survival, determined by the presence of biliary complications, was confirmed in the present paper. The effect was maximally evident in recipients with the viral etiology of liver disease (HCV and HBV) and disappeared in those with non-viral etiologies. The data was reinforced by the result of multivariate analysis that highlighted the effect of biliary complications in conditioning a worse patient survival in HBV and HCV positive recipients.

In conclusion, despite the advances in both operative and therapeutic modalities biliary complications remain the Achille's heel of LT. In recipients carrying rs12979860 IL-28B C/C genotype the use of CSA seem to contribute to enhance the probability of developing biliary complications and in HBV and HCV positives to reduce patients survival. If confirmed in larger studies the use of CSA in these patients could be revised.

Ethical approval

The study has been approved by IRB and all patients gave a written consent form for participating in the study.

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None.

Author contribution

Pierluigi Toniutto, Edmondo Falleti, Davide Bitetto and Carlo Fabris are responsible for the study design and written the paper. Sara Cmet and Annarosa Cussigh performed the laboratory and genetic analyses. Milutin Buljiac, Salvatore vadalà and Maurizio Zilli performed the cholangiopancreatography procedures.

Conflicts of interest

None.

References

[1] R.C. Verdonk, C.I. Buis, R.J. Porte, E.B. Haagsma, Biliary complications after liver transplantation: a review, Scand. J. Gastroenterol. (Suppl.) (2006) 89–101.
[2] D. Seehofer, D. Eurich, W. Veltzke-Schlieker, P. Neuhaus, Biliary complications after liver transplantation: old problems and new challenges, Am. J. Transpl. 13 (2013) 253–265.
[3] W.S. Ayoub, C.O. Esquivel, P. Martin, Biliary complications following liver transplantation, Dig. Dis. Sci. 55 (2010) 1540–1546.
[4] N. Akamatsu, Y. Sugawara, D. Hashimoto, Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome, Transpl. Int. 24 (2011) 379–392.
[5] R.C. Verdonk, C.I. Buis, R.J. Porte, et al., Anastomotic biliary strictures after liver transplantation: causes and consequences, Liver Transpl. 12 (2006) 726–735.
[6] V. Sundaram, D.T. Jones, N.H. Shah, et al., Posttransplant biliary complications in the pre- and post-model for end-stage liver disease era, Liver Transpl. 17 (2011) 428–435.
[7] J.S. Park, M.H. Kim, S.K. Lee, et al., Efficacy of endoscopic and percutaneous treatments for biliary complications after cadaveric and living donor liver transplantation, Gastrointest. Endosc. 57 (2003) 78–85.
[8] G. Kochhar, J.M. Parungao, I.A. Hanouneh, M.A. Parsi, Biliary complications following liver transplantation, World J. Gastroenterol. 19 (2013) 2841–2846.

[9] S. Iacob, V.R. Cicinnati, A. Dechene, et al., Genetic, immunological and clinical risk factors for biliary strictures following liver transplantation, Liver Int. 32 (2012) 1253–1261.
[10] M.P. Morrow, P. Pankhong, D.J. Laddy, et al., Comparative ability of IL-12 and IL-28B to regulate Treg populations and enhance adaptive cellular immunity, Blood 113 (2009) 5868–5877.
[11] T. Urban, M.R. Charlton, D.B. Goldstein, Introduction to the genetics and biology of interleukin-28B, Hepatology 56 (2012) 361–366.
[12] A. Duarte-Rojo, B.J. Veldt, D.D. Goldstein, et al., The course of posttransplant hepatitis C infection: comparative impact of donor and recipient source of the favorable IL28B genotype and other variables, Transplantation 94 (2012) 197–203.
[13] M.R. Charlton, A. Thompson, B.J. Veldt, et al., Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection, Hepatology 53 (2011) 317–324.
[14] D. Bitetto, T. De Feo, M. Mantovani, et al., Interaction between calcineurin inhibitors and IL-28B rs12979860 C>T polymorphism and response to treatment for post-transplant recurrent hepatitis C, Dig. Liver Dis. 45 (2013) 927–932.
[15] S.R. Allam, B. Kruger, A. Mehrotra, T. Schiano, B. Schroppel, B. Murphy, The association of IL28B polymorphism and graft survival in patients with hepatitis C undergoing liver transplantation, PLoS One 8 (2013) e54854.
[16] A. Duarte-Rojo, M.G. Deneke, M.R. Charlton, Interleukin-28B polymorphism in hepatitis C and liver transplantation, Liver Transpl. 19 (2013) 49–58.
[17] D. Bitetto, C. Fabris, E. Falleti, et al., Recipient interleukin-28B Rs12979860 C/T polymorphism and acute cellular rejection after liver transplantation: role of the calcineurin inhibitor used, Transplantation 93 (2012) 1038–1044.
[18] C. Fabris, E. Falleti, A. Cussigh, et al., IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: role in the course of chronic viral hepatitis and the development of HCC, J. Hepatol. 54 (2011) 716–722.
[19] S. Sharma, A. Gurakar, N. Jabbour, Biliary strictures following liver transplantation: past, present and preventive strategies, Liver Transpl. 14 (2008) 759–769.
[20] A.W. Avolio, U. Cillo, M. Salizzoni, et al., Balancing donor and recipient risk factors in liver transplantation: the value of D-MELD with particular reference to HCV recipients, Am. J. Transpl. 11 (2011) 2724–2736.
[21] S. Horster, F.J. Bauerlein, P. Mandel, et al., Influence of hepatitis C virus infection and high virus serum load on biliary complications in liver transplantation, Transpl. Infect. Dis. 15 (2013) 306–313.
[22] L. Prokunina-Olsson, B. Muchmore, W. Tang, et al., A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus, Nat. Genet. 45 (2013) 164–171.
[23] S. Bibert, T. Roger, T. Calandra, et al., IL28B expression depends on a novel TT/-G polymorphism which improves HCV clearance prediction, J. Exp. Med. 210 (2013) 1109–1116.
[24] B.G. Stone, M. Udani, A. Sanghvi, et al., Cyclosporin A-induced cholestasis. The mechanism in a rat model, Gastroenterology 93 (1987) 344–351.
[25] C.K. Enestvedt, S. Malik, P.P. Reese, et al., Biliary complications adversely affect patient and graft survival after liver retransplantation, Liver Transpl. 19 (2013) 965–972.
[26] D.A. Axelrod, K.L. Lentine, H. Xiao, et al., National assessment of early biliary complications following liver transplantation: Incidence and outcomes, Liver Transpl. 20 (2014) 446–456.