Non-anastomotic biliary strictures after liver transplantation part 2: Management, outcome and risk factors for disease progression

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NAS after liver transplantation: risk factors for disease progression

Abstract

Non-anastomotic biliary strictures (NAS) after orthotopic liver transplantation (OLT) are associated with high retransplant rates. The aim of the present study was to describe the treatment, and identify risk factors for radiological progression of bile duct abnormalities, recurrent cholangitis, biliary cirrhosis and retransplantation in patients with NAS. We retrospectively studied 81 cases of NAS. Strictures were classified according to severity and location. Management of strictures was recorded. Possible prognostic factors for bacterial cholangitis, radiological progression of strictures, development of severe fibrosis/cirrhosis and graft and patient survival were evaluated. Median follow up after OLT was 7.9 years. NAS were most prevalent in the extrahepatic bile duct. Twenty-eight patients (35%) underwent some kind of interventional treatment, leading to a significant improvement in biochemistry. Progression of disease was noted in 68% of cases with radiological follow-up. Radiological progression was more prevalent in patients with early NAS and one or more episodes of bacterial cholangitis. Recurrent bacterial cholangitis (> 3 episodes) was more prevalent in patients with a hepaticojejunostomy. Severe fibrosis or cirrhosis developed in 23 cases, especially in cases with biliary abnormalities in the periphery of the liver. Graft but not patient survival was influenced by the presence of NAS. Thirteen patients (16%) were re-transplanted for NAS. In conclusion, especially patients with a hepatico-jejunostomy, those with an early diagnosis of NAS, and those with NAS presenting at the level of the peripheral branches of the biliary tree, are at risk for progressive disease with severe outcome.
Introduction

Biliary complications are common after orthotopic liver transplantation (OLT). Biliary strictures and leakage of bile are most frequently encountered. Strictures are often referred to as anastomotic or non-anastomotic. Non-anastomotic strictures (NAS) are generally considered to be the most troublesome type of biliary complications after liver transplantation, with a graft loss rate of up to 46% after two years (1).

In a separate study we have analyzed the radiological characteristics of NAS at the time of diagnosis and risk factors for the development of NAS (2). In this study, we were able to identify significant differences in risk factors for the development of NAS depending on the time of initial presentation. In addition, large variations in anatomical localization and severity of NAS at the time of presentation were found, indicating that NAS is not a single disease, but rather a group of biliary abnormalities with different pathogenesis. It is unknown whether the different subtypes of NAS are also associated with difference in outcome and prognosis. Previous studies concerning the treatment and outcome of NAS have not considered different types of NAS as relevant subgroups and risk factors for radiological and clinical progression once the diagnosis has been established have not been identified so far.

The aim of the present work was to study NAS in a large cohort of liver transplant recipients with long-term follow up and to describe the results of treatment. In addition, we aimed to identify risk factors for radiological progression of bile duct abnormalities, recurrent cholangitis, biliary cirrhosis and re-transplantation.

Patients and Methods

Patients

Between January 1986 and May 2003 a total number of 717 liver transplants were performed in 639 patients at the University Medical Center Groningen. After exclusion of children (<18 years), and patients with NAS caused by hepatic artery thrombosis, 487 transplants in 428 adult patients were included in this study. Follow-up was until November 1st 2005, allowing a minimal follow up time after transplantation of 2.5 years. Eighty-one grafts with NAS were identified in 77 patients as described previously (2). In short, all post-transplant radiological material of the biliary tree was reviewed by a radiologist blinded to the clinical data (EJ). Anatomical extent
and severity of the biliary abnormalities were classified using a standardized scoring system. The scheme used to classify anatomical localization and extension of NAS is depicted in Figure 1. Severity was arbitrarily scored as mild, moderate or severe, according to the degree of narrowing, pre-stenotic dilatation, and mucosal irregularity. Patient characteristics as well as anatomical localization and severity of NAS are summarized in Table 1.

Figure 1. Schematic presentation of the anatomical zones of biliary tree used to define the localization of NAS after liver transplantation

**Study Endpoints**

Clinical variables. Clinical information was obtained from the original patient notes, operation notes and endoscopy reports. Records were reviewed for patient characteristics, indication for liver transplantation, type of biliary reconstruction and outcome. Laboratory values of alkaline phosphatase (APh), gamma glutamyltransferase (GGT), alanine-aminotransferase (ALT) and total bilirubin (bili) were studied for the following time points: at the time of presentation, at the beginning of treatment, and to study the effect of treatment, at a stable level within 3 months after the last intervention.
Management of NAS. Information about interventions was obtained from the patient notes. Endoscopic retrograde cholangiopancreaticography (ERCP), percutaneous transhepatic cholangiodrainage (PTCD), surgery, and medical therapies (ursodeoxycholic acid, antibiotics) were noted. When ERCP or PTCD with interventions had been performed, the number of sessions was registered, as well as technical details of the procedure. In case of surgical treatment, the type of surgical procedure was recorded. Complications of treatment were registered. Radiological progression. To study radiological progression of NAS all cholangiograms (drain cholangiography, PTCD, MRCP, ERCP) that were performed after transplantation were reviewed by a single radiologist (EJ), blinded to clinical information, and using the same scoring system as described above. Bacterial cholangitis. Bacterial cholangitis episodes were noted. Bacterial cholangitis was defined as an episode of liver test abnormalities combined with fever for which antibiotic treatment was given. Recurrent cholangitis was defined as three or more episodes of cholangitis.

Table 1. Patient Characteristics and Possible Prognostic Factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (% or range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of transplantation (median, range)</td>
<td>46 (18-66)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>40 / 37</td>
</tr>
<tr>
<td>Primary liver disease: PSC / Other</td>
<td>25 (31%) / 56 (69%)</td>
</tr>
<tr>
<td>Biliary reconstruction: Duct-to-duct / Roux-en-Y</td>
<td>62 (77%) / 19 (23%)</td>
</tr>
<tr>
<td>Re-transplant graft</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>IBD before OLT</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>IBD after OLT</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Early NAS (&lt;1 year after OLT)</td>
<td>50 (62%)</td>
</tr>
<tr>
<td><strong>Extent of NAS at presentation</strong>*</td>
<td></td>
</tr>
<tr>
<td>Zone A</td>
<td>66 (81%)</td>
</tr>
<tr>
<td>Zone B</td>
<td>52 (67%)</td>
</tr>
<tr>
<td>Zone C</td>
<td>33 (42%)</td>
</tr>
<tr>
<td>Zone D</td>
<td>15 (19%)</td>
</tr>
<tr>
<td><strong>Severity of NAS at presentation</strong>*</td>
<td></td>
</tr>
<tr>
<td>Mild / Moderate / Severe</td>
<td>43 / 28 / 7</td>
</tr>
<tr>
<td><strong>Type of immunosuppression</strong></td>
<td></td>
</tr>
<tr>
<td>Prednisone / azathioprine / cyclosporine</td>
<td>51 (63%)</td>
</tr>
<tr>
<td>Prednisone / tacrolimus</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Prednisone / tacrolimus / azathioprine</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (20%)</td>
</tr>
</tbody>
</table>

* Data on patients with radiological material available (n=78)
Pathology. To see whether NAS led to biliary fibrosis of cirrhosis, the most recent available pathology specimen of the liver of all patients was retrieved and scored by a liver pathologist (AG) blinded to the clinical context. Liver fibrosis was scored as absent, minimal, moderate or severe, with severe being either extensive bridging fibrosis or cirrhosis.

Survival. Graft and patient survival were analyzed by comparing patients with NAS to controls matched for age and period of transplantation. Controls also had to be alive at the time of diagnosis of NAS in the patients with NAS. Causes of death and graft failure were noted.

Prognostic factors. Possible prognostic factors for several outcome parameters are listed in Table 1. The definition of inflammatory bowel disease (IBD) after liver transplantation was an episode of abdominal pain and/or diarrhea, with inflammation seen during endoscopy, confirmed pathologically and after exclusion of infectious causes. In addition the following factors were included in the analysis: (type of) interventional treatment, the presence of radiological progression, the occurrence of bacterial cholangitis, the maintenance use of antibiotics, and the use of ursodeoxycholic acid.

Statistical Methods
Data were analyzed using SPSS 12.0 software. Comparison between groups was made using the Chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. When indicated, a risk estimate was made calculating the relative risk (RR) and confidence intervals using a Chi-Square test. Comparison of survival between groups was made using Kaplan-Meier statistics with a log-rank test. A p-value of 0.05 or less was considered to indicate statistical significance.

Ethical statement
Retrospective studies are approved by the institutional ethical committee.

Results
NAS were present in 81 grafts of 77 patients. In four patients NAS occurred in both a first and second graft. Apart from NAS, a concomitant anastomotic stricture was diagnosed at some point in the postoperative course in 21 patients. Median follow-up after the diagnosis of NAS was 6.0 years (1.0-17.0). Median follow-up after OLT was 7.9 years (range 1.0-17.1). The biliary reconstruction was duct-to-duct in 62 cases (77%), and a hepaticojejunostomy with Roux-en-Y deviation in 19 cases (23%).
Which Modalities Were Used for Treatment of NAS?

Interventions. Twenty eight patients (35%) were treated with ERCP, PTCD, surgery, or a combination of these. Thirteen patients underwent one or more sessions of ERCP. Dilatation was performed in all cases; in 12 also one or more stents were placed. Complications occurred in 7, mostly cholangitis. No severe complications were observed. The median number of therapeutic ERCP’s in these patients was 3 (range 1-11).

Seven patients underwent PTCD. Four patients underwent both ERCP and PTCD. In patients treated with PTCD dilatation and stenting was performed in all cases. In two cases an expandable metal stent was placed. The median number of therapeutic PTCD sessions in these patients was 3 (range 1-6). A minor complication occurred in 2 cases.

In the end, eight patients underwent surgery for NAS, four after previous ERCP or PTCD. The surgical procedure was conversion of duct-to-duct anastomosis to a hepatico-jejunostomy in five patients, and revision of a previous hepatico-jejunostomy in three. Patients with a dilated biliary tree were treated surgically more often than those without dilatation (20% vs. 2%, p=0.01). All concomitant anastomotic strictures were successfully treated with success by ERCP (n=13), PTCD (n=5), surgery (n=1) or a combination of these (n=2).

Ursodeoxycholic acid. Seventy-one patients (88%) were treated with long-term ursodeoxycholic acid, mostly at a dose of 600 mg b.i.d.

Biochemical response to interventions. When the biochemical response within 3 months after completion of interventional treatment was studied, significant improvements in serum ALT (median 65 U/l vs. 36 U/l, p=0.015), bilirubin (median 46 µmol/l vs. 23 µmol/l, p<0.000) and GGT (median 360 U/l vs. 125 U/l, p=0.014) was noted, compared to pretreatment values. No significant improvement in AP was seen. In 8 of the 28 patients no biochemical response to treatment was seen.

Is NAS a Progressive Disease?

Radiological progression. Material for retrospective radiological evaluation of NAS at presentation was available in 78 of the 81 transplants (96%). In 59 cases (80%) follow-up cholangiography was performed and available for determination of progression of the biliary abnormalities. The median time between the diagnostic and last cholangiography was 1.7 years (range 0.1 – 11.7). Progression of the severity of biliary abnormalities was observed in 28 (42%) of the 59 grafts with follow up cholangiography. At the time of diagnosis, the
severity of NAS was scored as mild in 32 (54%), moderate in 22 (37%) and severe in 5 (9%) cases. At the end of follow up the severity of NAS was scored as mild in 17 (29%), moderate in 22 (37%) and severe in 20 (34%) cases. Progression of the anatomical extent of the biliary abnormalities was seen in 36 (61%) of the patients with follow up cholangiography. The details are listed in Table 2. Progression was seen at all levels of the biliary tree.

Table 2. Radiological Progression of NAS in Patients With Follow-up Cholangiography (n=59)*

<table>
<thead>
<tr>
<th>Localization</th>
<th>Presentation N (%)</th>
<th>End of follow up N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrahepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone A</td>
<td>50 (58)</td>
<td>56 (97)</td>
</tr>
<tr>
<td>Intrahepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone B</td>
<td>5 (8.5)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>left</td>
<td>7 (11.9)</td>
<td>8 (13.6)</td>
</tr>
<tr>
<td>right</td>
<td>27 (45.8)</td>
<td>40 (67.8)</td>
</tr>
<tr>
<td>both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone C</td>
<td>5 (8.5)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>left</td>
<td>7 (11.9)</td>
<td>13 (22)</td>
</tr>
<tr>
<td>right</td>
<td>15 (25.4)</td>
<td>25 (42.4)</td>
</tr>
<tr>
<td>both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone D</td>
<td>1 (1.7)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>left</td>
<td>2 (3.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>right</td>
<td>7 (11.9)</td>
<td></td>
</tr>
<tr>
<td>both</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* More than one area could be involved in one patient.

Casts and sludge were seen at some time point after transplantation in 21 (27%) and 18 (23%) patients respectively. Cholangitis episodes. Thirty-nine subjects (48%) had at least one episode of cholangitis. Nineteen had to be admitted repeatedly for recurrent bacterial cholangitis (defined as three or more episodes). The median number of cholangitis episodes in these 19 was 5 (range 3-17). Thirty patients were put on maintenance use of antibiotics for some time, mostly ciprofloxacin.

Liver pathology. Pathology specimens were available from 63 livers. The mean time from transplantation to biopsy was 3.7 years (range 0.1-15.9). At the end of follow up, pathologically proven biliary cirrhosis or severe bridging fibrosis had developed in 17 cases (25%). In an additional six patients the diagnosis of cirrhosis was made on clinical grounds: these patients were known with severe NAS, and developed ascites, abnormal coagulation or varices with radiological evidence of cirrhosis while the portal vein was open. Thus, in the end severe fibrosis or cirrhosis developed in 23 (28%) of the livers with NAS.
Are Patient and Graft Survival Affected by NAS?

Graft survival. Graft survival of the patients with NAS after one, five and ten years was 91% (3.1), 73% (5.0) and 63% (6.1) respectively (standard error in parentheses). Graft survival was significantly lower in the patients with NAS, compared to matched controls without NAS (p=0.001, fig. 3).

Thirteen patients (16%) underwent re-transplantation of the liver for NAS after a median of 0.9 years (mean 3.9 years, range 0.2 – 12.3). At the end of this study, two patients were awaiting liver re-transplantation for NAS.

Patient survival. Compared to matched controls, patient survival was lower in patients with NAS, although this did not reach statistical significance (fig. 3).

At the end of the study 17 patients had died. In 5 cases, the cause of death was related to NAS. In four patients the cause of death was multi-organ failure after sepsis due to cholangitis, in one case liver failure due to biliary cirrhosis. Two patients had been offered a re-transplantation, but refused.

Which Factors Are Predictive for Progression of NAS?

An overview of the analyses of prognostic factors is presented in Table 3.

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Prognostic factor</th>
<th>RR (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological progression</td>
<td>Early NAS (&lt; 1 year)</td>
<td>1.9 (1.1-3.4), 0.004</td>
</tr>
<tr>
<td></td>
<td>One or more episodes of cholangitis</td>
<td>2.0 (1.0-4.2), 0.018</td>
</tr>
<tr>
<td>Recurrent cholangitis</td>
<td>Roux-en-Y hepaticojejunostomy</td>
<td>3.6 (1.7-7.6), 0.001</td>
</tr>
<tr>
<td>Biliary cirrhosis/bridging fibrosis</td>
<td>Abnormalities at Zone B*</td>
<td>1.5 (1.1-1.9), 0.021</td>
</tr>
<tr>
<td></td>
<td>Abnormalities at Zone C*</td>
<td>1.8 (1.2-2.8), 0.022</td>
</tr>
<tr>
<td>Severe outcome **</td>
<td>Abnormalities at Zone C*</td>
<td>1.7 (1.1-2.7), 0.029</td>
</tr>
<tr>
<td></td>
<td>Radiological progression during follow up</td>
<td>1.8 (1.1-3.0), 0.026</td>
</tr>
<tr>
<td>Asymptomatic course***</td>
<td>Mild abnormalities*</td>
<td>1.9 (1.3-2.7), 0.002</td>
</tr>
</tbody>
</table>

* at presentation

** defined as: death due to NAS, cirrhosis/fibrosis, retransplantation

*** defined as: no cholangitis, no fibrosis or cirrhosis, no re-transplantation, no need for treatment
Patients diagnosed with NAS (N=81)

Treatment N=28
- ERCP: 11
- PTCD: 5
- ERCP+PTCD: 4
- Surgery 4
- ERCP+Surgery: 2
- PTCD+Surgery: 2

No treatment N=53

FOLLOW UP

Outcome
- Rec. Cholangitis 5 (18%) *
- Cirrhosis 8 (29%)
- Re-transplantation 5 (18%)
- Death d/t NAS 2 (7%)

Outcome
- Rec. Cholangitis 5 (10%)
- Cirrhosis 13 (25%)
- Re-transplantation 8 (15%)
- Death d/t NAS 3 (6%)

Figure 2. Clinical course and outcome in patients with NAS. * A total of 14 patients experienced recurrent cholangitis (3 or more episodes). A total of 5 patients experienced recurrent cholangitis after treatment was finished.

Predictors of radiological progression. When patients with progression of radiological abnormalities were compared with patients in whom the severity and extent of abnormalities was not progressive, two risk factors for progression were identified: early NAS presenting within 1 year after transplantation and one or more episodes of cholangitis. Patients presenting with early NAS were also at increased risk for both casts (RR 1.6, 95%CI 1.2-2.2, p=0.008) and sludge (RR 1.8, 95%CI 1.4-2.4, p=0.001). Predictors of bacterial cholangitis. The only risk factor for recurrent cholangitis, defined as 3 or more episodes, was a biliary reconstruction with a Roux-en-Y hepatico-jejunostomy. Predictors of progression of fibrosis. Radiological abnormalities at the intrahepatic level were identified as risk factors for development to severe bridging fibrosis or cirrhosis. These concerned Zone B and Zone C.
Predictors of an asymptomatic course. In 23 cases (28%) the NAS were completely asymptomatic, defined as no episodes of cholangitis, no biliary fibrosis or cirrhosis, and no need for interventional treatment. When these patients were compared with the other 58 patients, the radiological findings at presentation were predictive of an asymptomatic course: patients with abnormalities that were scored as mild at the time of diagnosis had a significantly higher chance of an asymptomatic course (44% if mild vs. 11% not mild, p=0.002).

Predictors of severe outcome. To analyze risk factors for NAS with severe outcome, we identified three markers of severe outcome: death due to NAS, re-transplantation, and biliary cirrhosis or severe bridging fibrosis. Patients experiencing one or more of these were compared with the remaining group of patients. Two risk factors for severe outcome were identified: NAS presenting at the intrahepatic Zone C, and NAS that showed radiological progression during follow up. With respect to severe outcome there was no difference between the 28 patients who received interventional treatment (ERCP, PTCD, surgery) versus the 53 patients who did not (severe outcome 46% versus 37%, p=0.389).
Discussion

NAS or intrahepatic biliary strictures are a common and often troublesome complication after liver transplantation. Although previous studies on this subject differ markedly concerning methodology and results, a high incidence of retransplantation has been reported almost uniformly, as well as the need for frequent biliary interventions and admissions (3-5). In the present study, we found a relatively high incidence of NAS compared to previous reports. Whereas most large series report an incidence of NAS of 5-10% (6-8), we found that 17% of patients were diagnosed with NAS at some point after OLT. Most likely, this difference is due to the fact that we defined any type of biliary stricture other than anastomotic strictures as NAS. In addition, postoperative cholangiography via the biliary drain has been routine practice in our center. This allowed us to identify a large number of cases without any persisting clinical signs of biliary disease (23 cases, 28%). This is also reflected by the rather low number of retransplantations (16%) compared to previous reports from other centers. Another possible explanation is the large number of patients transplanted for PSC (17%) and relatively low number transplanted for viral disease (16%) in our center. PSC is a known risk factor for the development of NAS (9-12).

From the present material it becomes clear that NAS after liver transplantation is not just one disease, but a spectrum of abnormalities, ranging from slight, localized mucosal irregularity to extensive and diffuse biliary strictures. Possibly, not all areas of non-anastomotic bile duct narrowing are due to a fibrotic type of stricture (13). We thus aimed to identify from this diverse group of NAS those cases that would progress to a clinically relevant or progressive disease. We found radiological progression in 68% of our patients with cholangiographic follow-up. Most likely, this number is lower for the entire group of patients with NAS, since those patients without radiological follow-up probably did not have marked progression. Interestingly, NAS presenting early after transplantation had a higher risk of progression. Previous investigators have also mentioned a more severe course of disease in patients with NAS presenting early after transplantation (14-16). Besides a higher risk of radiological progression, these cases also showed a significantly higher risk for the development of casts and sludge. These differences are probably due to a different pathogenesis of NAS presenting early or late after transplantation, as has been described by Buis et al. earlier in this journal.

The most critical clinical consequences of NAS are recurrent cholangitis and biliary cirrhosis.
Both may necessitate re-transplantation. We found recurrent cholangitis (arbitrarily defined as three or more episodes) in 19 of our patients, despite treatment with maintenance therapy with antibiotics in most patients. The only risk factor for recurrent cholangitis that was identified was the presence of a hepaticojejunostomy instead of a duct-to-duct anastomosis. Most likely, this type of biliary reconstruction leads to reflux of bacteria into the biliary tree, as has been shown in animal models (17). In a patient that is immunosuppressed and has diminished flow of bile due to NAS, it is foreseeable that this situation will lead to bacterial colonization of the bile ducts and repeated episodes of cholangitis.

Biliary cirrhosis is the ‘end-point’ of long-standing NAS. We found biliary cirrhosis or severe fibrosis in 23 of our cases (28%). At the end of follow up, nine of these 23 (39%) were re-transplanted. Interestingly, the two risk factors for development of biliary cirrhosis were strictures at the level of the segmental (Zone B) and sub-segmental (Zone C) branches. Apparently, these strictures cause more long-term damage to the liver than more centrally located lesions. This may be due to a number of factors. Perhaps, this type of NAS has a different pathogenesis than the more ‘proximal’ type of NAS, leading to ongoing biliary damage. Another possible explanation is that these abnormalities are less amenable to treatment. Knowing that strictures at the site of the segmental and sub-segmental branches are a risk factor for biliary cirrhosis, one can make an estimate of the risk for progressive disease at the time of diagnosis.

When biliary cirrhosis, retransplantation and death due to NAS were combined to define serious disease, strictures at the level of the subsegmental branches (Zone C) and radiological progression of strictures were identified as significant risk factors. Thus, one can use these characteristics to define patients with a higher risk of serious disease in the future.

Although we did see NAS-related mortality in our series, overall patient survival was not significantly affected. This corresponds to previous studies on this subject (18-21). Graft survival however was impaired compared to matched controls (73% vs. 94% after five years). This is not a surprising finding. It is not possible from our results to conclude whether or not treatment for NAS prevented re-transplantation in a number of cases. Although the number of re-transplantations was similar in patients with and without endoscopic, percutaneous or surgical therapy; we do not know what these numbers would have been like without treatment. Previously, others have described successful treatment of NAS with a number of modalities (22-26).

We did not study the success of treatment in these patients, since the group of patients treated with ERCP, PTCD or surgery is rather small (28 cases), heterogeneous concerning
location and severity of abnormalities, and several types of treatment modalities were used. However, in the majority of patients an improvement in liver test was seen, although this is not synonymous with uneventful long-term outcome. To date, practically all studies on the treatment of NAS are retrospective and descriptive in nature. Definitive answer on the best treatment modality for NAS should come from a multi-center, prospective, randomized study. However, practical difficulties in such a study would be the large variability in the timing of presentation and the progression of the biliary abnormalities. Our study on risk factors for the occurrence of NAS (2), combined with the current study on outcome and prognostic risk factors for disease progression, facilitates in the identification of important subgroups and clinical variables that can be used for stratification in a prospective study (see also figure 4).

![Figure 4. Schematic representation of risk factors and prognostic factors for the development of early and late NAS, bacterial cholangitis, progressive radiological abnormalities and severe outcome. Each connection represents a statistical correlation (present study and work by Buis et al (2)). NAS: non-anastomotic strictures, PSC: primary sclerosing cholangitis.](image-url)
In conclusion, non-anastomotic biliary strictures are a common complication after orthotopic liver transplantation. The radiological and clinical picture of NAS shows a spectrum ranging from minor abnormalities without any symptoms to severe strictures eventually leading to re-transplantation. Graft survival is significantly reduced in patients suffering from NAS. Especially patients with a hepatico-jejunostomy, those with an early diagnosis of NAS, and those with NAS presenting at the level of the peripheral branches of the biliary tree, are at risk for the development of recurrent cholangitis, radiological progression, development of cirrhosis and eventually retransplantation.
References


