ORIGINAL ARTICLE

The impact of infections on delisting patients from the liver transplantation waiting list

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SUMMARY

Approximately 20% of the patients listed for liver transplantation die before transplantation can be accomplished. Understanding risk factors for waiting list mortality may help to improve survival and organ allocation. Infections are very common in patients with cirrhosis and are associated with significant morbidity and mortality. This study analysed the frequency and characteristics of infections in patients awaiting liver transplantation, identified risk factors for withdrawal from the waiting list and evaluated the impact of infections on the clinical outcome. A retrospective analysis of consecutive patients listed for liver transplantation in Rotterdam, the Netherlands from 2007 to 2014 was conducted. Infections occurred in 144 of 327 studied patients (44%). In this cohort, 23.4% of the patients on the liver transplantation waiting list were delisted or died before transplantation. Patients with an infection were 5.2 times more likely to become delisted than noninfected patients. In the 30 days after the first infection, patients were 33.8 times more likely to become delisted compared to noninfected patients. High age, high MELD score, refractory ascites and inappropriate antibiotic therapy were independent predictors for delisting due to infection. Infections occur frequently in patients on the liver transplantation waiting list. Emphasis on appropriate and timely antimicrobial therapy is required.

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infection, liver transplantation, mortality, waiting list

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Introduction

Liver transplantation (LT) is a life-saving procedure for patients with sustained irreversible liver injury [1,2]. However, LT from deceased donors is limited by the scarcity of suitable donor organs. The accumulating incidence of liver disease worldwide increases donor organ shortage and leads to a prolonged time for patients on the LT waiting list [3]. The median pretransplant waiting time among active wait-listed adults was 9 months in 2015 in the United States and approximately 10 months in the Eurotransplant region [4,5]. In the United States, 19.8% of the listed patients died in 2015 before transplantation could be accomplished, which was comparable to the 18.4% mortality of listed patients in the Eurotransplant region [4,5].

During the time awaiting transplantation, patients are at risk for progressive liver failure [6]. Infections are an

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important precipitating factor for acute decompensation and acute-on-chronic liver failure [7,8].

Infections are present at admission or develop during hospitalization in 20–60% of patients with liver cirrhosis and are associated with fourfold increased mortality; up to 30% of patients has been reported to die within 1 month and another 30% within 1 year [9–11]. Intestinal bacterial overgrowth, increased bacterial translocation and an altered inflammatory response are considered major aetiological factors [12,13].

Knowledge about risk factors for waiting list mortality may help improve organ allocation and reduce waiting list mortality. A recent study found that hospitalized cirrhotic patients with infections complicated by extrahepatic organ failure are at higher risk for delisting and death before LT [14]. However, the frequency of infections in wait-listed patients and the subsequent risk of delisting and death after infection have not been clearly established.

This study aimed to (i) analyse the frequency and epidemiology of infections in patients awaiting LT, (ii) identify risk factors for infection-related removal from the waiting list and (iii) evaluate the impact of having an infection on the clinical outcome of listed patients.

Patients and methods

Patients

All consecutive patients on the LT waiting list from 2007 to 2014 at Erasmus MC, University Medical Center, Rotterdam, were studied retrospectively. Patients with acute liver failure or listed for a nonprimary liver graft were excluded. Patients delisted because of clinical improvement, intercurrent psychiatric disorders (mostly substance-related disorders), non-liver-related mortality or patients declining an offered organ were excluded.

Data collection

Demographic and clinical data, and information on the clinical course, including details of infectious complications, were retrieved from hospital medical records. Diagnosis of infection and the type of infection were made according to definitions formulated by the Centers for Disease Control (CDC) [15–18]. Episodes, clinically interpreted and treated as infection, without satisfying CDC criteria were reviewed by two clinicians (infectious disease specialist and research physician). Statistical sensitivity analyses were performed to assess whether this subgroup was comparable to the group meeting CDC criteria for infection. All infections of patients were evaluated; hospitalized and nonhospitalized infections in both our centre and in other centres. Infections taking place in other centres were communicated to physicians of our transplant centre. Additional information was requested if information regarding the infection in other centres was not sufficient. Multidrug-resistant (MDR) bacteria were defined as bacteria with nonsusceptibility to at least one agent in three or more antimicrobial categories, extended-spectrum β-lactamase (ESBL) or carbapenemase-producing Enterobacteriaceae [19]. Inappropriate antibiotic therapy was defined as: use of antimicrobial agents to which a pathogen was resistant *in vitro* or administration of antibiotic therapy with a delay of at least 24 h after diagnosis of infection. Multidrug resistance and inappropriate antibiotic therapy were determined in a subgroup of patients with available antimicrobial susceptibility patterns and sufficient information about the timing of antibiotic therapy. Renal failure was defined as increase in serum creatinine of >50% from baseline, or a rise in serum creatinine of ≥26.4 μmol/l (≥0.3 mg/dl) within 48 h [20]. Refractory ascites was defined as ascites that did not recede or that reoccurred shortly after therapeutic paracentesis, despite sodium restriction and diuretic treatment [21]. Data were collected from the time of waiting list placement until the follow-up was completed. The follow-up was complete when a clinical endpoint was reached: (i) liver transplantation, (ii) delisting or death due to infection, (iii) delisting or death for other reasons (e.g. unmet Milan criteria) or (iv) still registered on the waiting list on 1st May 2016. Delisting or death due to infection was defined as definite withdrawal from the list within 30 days after an infection was diagnosed due to clinical deterioration with suspicion of infection outside the liver. The endpoint 'becoming delisted from the liver transplantation waiting list due to infection' will be systematically used and will include: an inactive waiting list status without reactivation, delisting with infaust prognosis and death due to infection.

Statistical methods

A mean and standard deviation (SD) was computed for numerical variables, if normally distributed, and compared using the Student's *t*-test. Non-normal distributed continuous variables were summarized with a median and interquartile range (IQR), and compared using the Mann–Whitney rank-sum test. Categorical variables were expressed with percentages and compared using

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the chi-square test. A two-sided *P*-value <0.05 was considered significant. The probability for the occurrence of infection for the length of time after waiting list placement was presented using Kaplan–Meier. Patients were censored when a clinical endpoint was reached. Logistic regression modelling was employed to determine possible predictors for withdrawal from the waiting list due to infection, and each determinant was reported with an odds ratio (OR). The analysed variables were age, gender, aetiology, MELD score, medication use, type of infection, microorganism of infection, MDR bacteria, inappropriate antibiotic therapy, events of acute decompensation, intensive care unit (ICU) admission or an invasive procedure 30 days prior to infection. A time-dependent Cox proportional hazard model was used to study the nonproportional hazards effect of the first infection on the competing endpoints: liver transplantation, delisting or death due to infection, delisting or death with other reasons and waiting on the list. The hazard for delisting is presumably highest during and right after the infection, while the hazard for liver transplantation commences to increase after the recovery of the infection. Thus, infection could have a nonproportional hazard on the competing endpoints compared to noninfected patients. The landmark analysis method was used to study time intervals after infection, and the landmarks 30 and 180 days after infection were chosen. The model was adjusted for covariates age, gender, aetiology and MELD score at listing. The effect of the first infection on the various endpoints was assessed for the interval of 30 days following infection, and the interval between 30 and 180 days following infection and after 180 days. Furthermore, the likelihood on becoming delisted in relation to the number of infections was analysed using a multivariate Cox regression adjusted for age, gender, aetiology and MELD score at listing. The odds on clinical endpoints are reported as hazard ratio (HR) on liver transplantation and delisting. In the logistic regression model, as well as the Cox proportional hazard models, variables with a *P*-value of <0.20 in univariate analysis were included in a multivariate analysis and maintained in the multivariate model with a *P*-value <0.10. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patients

Four hundred and forty-five patients were registered on the national liver transplant waiting list between January 2007 and January 2014. Three hundred and twenty-seven patients were eligible for the present analysis (Fig. 1). The mean follow-up time was 208 days (IQR 56–406). The study cohort included 217 men and 110 women. At time of waiting list placement, patients were aged 54 (IQR 46–60) years and had a median MELD score of 16 (IQR 11–19). The baseline demographics and clinical characteristics of infected and noninfected

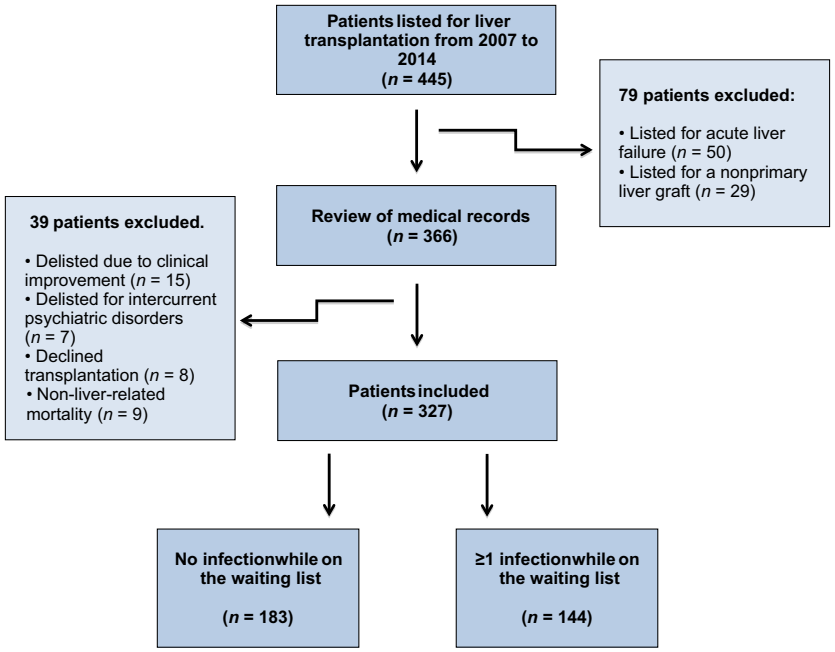

Figure 1 Flow diagram of study population.

listed patients at waiting list placement are shown in Table 1. Patients with infections had more frequent viral hepatitis or primary sclerosing cholangitis (PSC) as aetiology, and less frequent hepatocellular carcinoma (HCC) ($P < 0.001$). Furthermore, patients with infections had higher baseline MELD scores ($P = 0.003$), and more often used antibiotic prophylaxis ($P = 0.005$), diuretics ($P = 0.005$) and laxatives ($P = 0.026$).

Infections

In 144/327 (44%) of the listed patients, at least one infection occurred; the number of infections in these patients ranged from one to eleven. The actuarial percentage of patients with an infection was 23% at 3 months, 29% at 6 months, 33% at 9 months and 37% after 12 months (Fig. 2). The median duration on the waiting list for patients with an infection was 381 days (IQR 137–753) compared to 163 days (IQR 43–320) for patients without infection ($P < 0.001$). In total, 318 infections occurred. Sixty-five patients experienced a single infection, 39 patients two infections, 40 patients three or more infections. Cholangitis (24%) was the most common infection, followed by spontaneous bacterial peritonitis (SBP) (18%), urinary tract infection (12%), respiratory infection (9%), bloodstream infection (7%) and gastro-intestinal infection (6%). The majority (83%) of infections were met by CDC criteria.

In 78/318 (25%) of all infections, microbiological studies were negative. Gram-negative bacteria were cultured in 73 infections (22%) and Gram-positive bacteria in 58 infections (18%) (Table 2). The antimicrobial susceptibility patterns and sufficient information about the timing of antibiotic therapy were available in 190 infections. Of these infections, 25% were caused by

Table 1. Demographic and clinical characteristics of patients at the time of listing for liver transplantation with respect to development of infections.

Characteristics	All patients *n* = 327	Patients without infection *n* = 183	Patients with infection(s) *n* = 144	*P*-value
Age (years)*	54 (46–60)	54 (48–61)	52 (43–59)	0.239†
Male gender	217 (66%)	129 (70%)	88 (61%)	0.075
Blood group				
0	146 (45%)	79 (43%)	67 (47%)	0.136
A	117 (36%)	69 (38%)	48 (33%)	
B	44 (13%)	20 (11%)	24 (17%)	
AB	20 (6%)	15 (8%)	5 (3%)	
Aetiology of liver disease				
Alcohol	49 (15%)	28 (15%)	21 (15%)	**<0.001**
Viral	32 (10%)	7 (4%)	25 (17%)	
PSC	72 (22%)	28 (15%)	44 (31%)	
HCC	90 (27%)	76 (42%)	14 (10%)	
Auto-immune & PBC	23 (7%)	7 (4%)	16 (11%)	
Other	61 (19%)	37 (20%)	24 (17%)	
MELD score*	16 (11–19)	15 (10–18)	17 (14–20)	**0.003**†
Child-Pugh score	8 (6–10)	8 (5–10)	9 (8–10)	**<0.001**†
Medication use				
Antibiotic prophylaxis	86 (26%)	37 (20%)	49 (34%)	**0.005**
Diuretics	196 (60%)	97 (53%)	99 (69%)	**0.005**
PPI	160 (49%)	82 (45%)	78 (54%)	0.102
Corticosteroids	31 (10%)	11 (6%)	20 (14%)	**0.016**
Noncorticosteroid immunosuppressives	19 (6%)	5 (3%)	14 (10%)	**0.008**
NSBB	112 (34%)	66 (36%)	46 (32%)	0.436
Laxatives	110 (34%)	52 (29%)	58 (40%)	**0.026**

HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NSBB, nonselective beta-blocker; PBC, primary biliary cirrhosis; PPI, proton-pump inhibitor, PSC, primary sclerosing cholangitis.

*Data are displayed as median with interquartile range.

†Mann–Whitney rank-sum test. *P*-values illustrated in bold reflect significant findings below the cut-off of 0.05.

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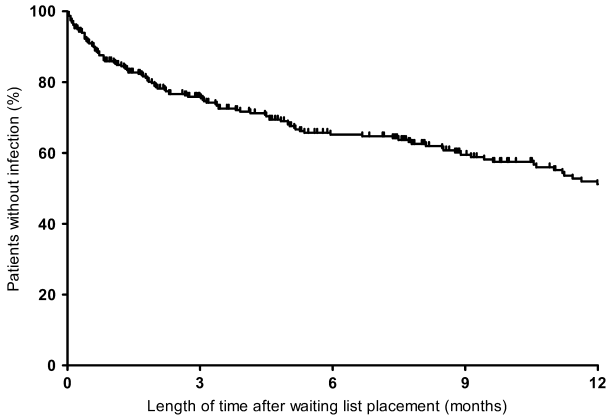

Figure 2 The actuarial percentage of patients without an infection in the first year after waiting list placement.

multidrug-resistant organisms. The majority of multidrug-resistant organisms were Enterococci spp. (48%), followed by Enterobacteria spp. (32%) and Staphylococci spp. (13%). The initial antibiotic therapy was considered inappropriate in 34% of the infections. The reasons for inappropriate therapy were as follows: microorganism not expected (Enterococcus $n = 20$, Candida $n = 11$, virus $n = 3$, Pseudomonas $n = 1$, Staphylococcus $n = 1$, Streptococcus $n = 1$), organism with acquired antibiotic resistance ($n = 14$), negative cultures and clinical improvement after antibiotic switch ($n = 6$) and administration of antibiotic therapy, according to guidelines, with a delay of at least 24 h after diagnosis of infection ($n = 7$).

Risk factors for delisting

In our study cohort, 245 (74.9%) patients underwent liver transplantation, 42 (12.8%) were delisted due to infection, 34 (10.4%) were delisted for other reasons, and 6 (1.8%) were still on the waiting list at the end of follow-up in the context of this study. The proportion of patients receiving a liver graft was higher in patients without infections (80.9%) as compared to patients with infections (67.4%) ($P = 0.012$).

In 13.2% (42/318) of all infections, patients were delisted in the 30 days following infection. In this time interval, no patients were delisted due to other reasons than infection. Risk factors associated with delisting due to infection were identified, and univariate analysis indicated 15 possible predictors (Table S1). Bloodstream infection, respiratory infection and SBP more often led to delisting compared to cholangitis, urinary tract infection and gastro-intestinal infection (Fig. 3a). In addition, delisting occurred more often after infections caused by multiple organisms or fungus in comparison with infection caused by single bacteria or when no microorganisms could be identified (Fig. 3b). Furthermore, an initial inappropriate antibiotic therapy and the presence of refractory ascites were significant predictors for delisting or death (Fig. 4).

Multivariate logistic regression analysis revealed four independent predictors for delisting after adjusting for gender: age (OR 1.1 per year; 95% CI 1.0–1.2; $P = 0.001$), MELD score (OR 1.3 per point; 95% CI 1.2–1.4; $P < 0.001$), inappropriate antibiotic therapy (OR 3.7; 95% CI 1.1–12.4; $P = 0.035$) and refractory ascites present within 30 days prior to infection (OR 3.3, 95% CI 0.9–12.0) (Table 3).

Sensitivity analyses were performed on the subgroups of CDC-validated infections and non-CDC-validated infections. The multivariate logistic regression model identified the same predictors for delisting within the 30 days following infection in both groups. There were no statistical significant differences between the subgroups and the complete study cohort (data not shown).

The risk for delisting in the first month, half year and afterwards

The Cox proportional hazard model showed that patients with one or more infections were more at risk

Table 2. Results of microbiological studies for the most common types of infection.

Type of infection	Gram-negative bacteria (%)	Gram-positive bacteria (%)	Fungus (%)	Multiple organisms (%)	Negative or no culture performed (%)
SBP ($n = 58$)	21 (36)	16 (28)	0	2 (3)	19 (33)
Cholangitis ($n = 75$)	11 (15)	10 (13)	0	3 (4)	51 (68)
Urinary tract ($n = 39$)	19 (49)	11 (28)	0	2 (5)	7 (18)
Respiratory ($n = 29$)	2 (7)	1 (3)	0	5 (17)	21 (73)
Bloodstream ($n = 22$)	9 (41)	8 (36)	1 (5)	4 (18)	0
Gastro-intestinal ($n = 19$)	4 (21)	2 (11)	2 (11)	0	11 (57)

SBP, spontaneous bacterial peritonitis.

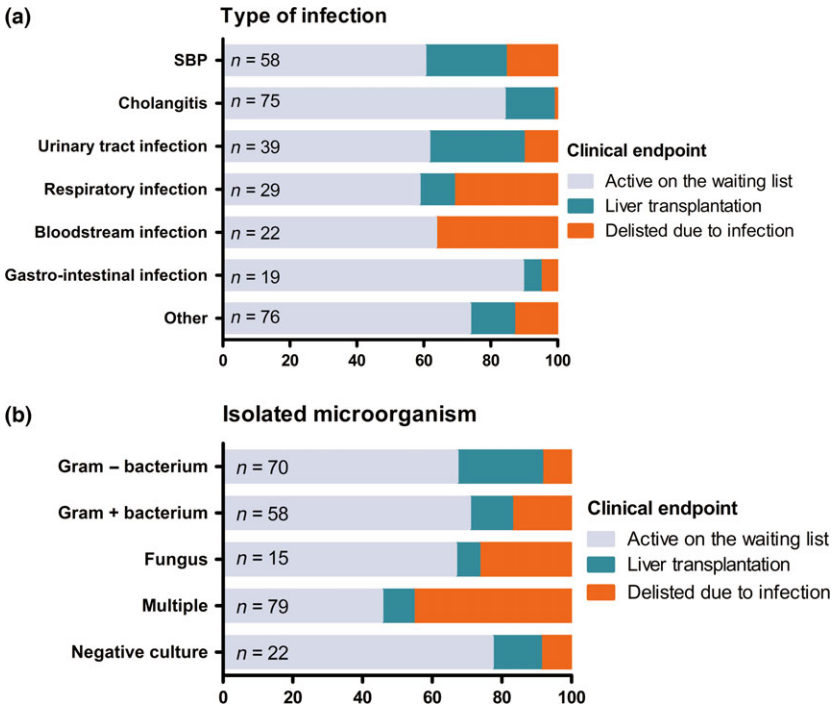

Figure 3 Clinical endpoint 30 days after infection shown in boxplots for group variables (a) type of infection ($P = 0.003$) and (b) isolated microorganism ($P = 0.001$).

of becoming delisted than patients without infections (HR 5.2; 95% CI 3.0–8.8; $P < 0.001$). There is a time-dependent hazard of becoming delisted or receiving a liver transplant following the first infection compared to wait-listed patients without infection. The hazard for delisting is highly increased in the first 30 days after infection (HR 33.8; 95% CI 7.2–157.9; $P < 0.001$), declines between 30 and 180 days (HR 5.7; 95% CI 2.6–12.3; $P < 0.001$) and further after 180 days (HR 2.2; 95% CI 1.1–4.5; $P = 0.036$).

Impact of the number of infections

The likelihood of delisting or death for patients with one infection ($n = 65$), two infections ($n = 39$) or ≥three or more infections ($n = 40$) was compared to patients without infection ($n = 183$) (Figure S1). The cumulative number of infections showed an increased risk for delisting after one and two infections (HR 12.1; 95% CI 6.8–21.7; $P < 0.001$ and HR 25.0; 95% CI 13.1–47.8; $P < 0.001$, respectively). This effect was attenuated in patients with three or more infections (HR 3.3; 95% CI 0.8–14.7; $P = 0.114$).

Discussion

This is the first study, to our knowledge, describing the impact of infection on liver transplantation waiting list dynamics. In this cohort, 23.4% of the patients became too sick or died before transplantation. Infection occurred in almost half of the patients (44%) and was the primary cause for delisting. Patients with an infection are 5.2 times more likely to become delisted than noninfected patients. In the 30 days after the first infection, patients are likely to migrate from the waiting list with a hazard of 33.8 to become delisted. High age, high MELD score, initial inappropriate antibiotic therapy and the presence of refractory ascites were significant predictors for delisting or death.

The results from our study indicate infection is the leading cause for delisting. This endorses the hypothesis that infection is the most important precipitating event for acute decompensation and acute-on-chronic liver failure resulting in (multi)organ failure [22]. Interestingly, the risk for death or delisting attenuates after three infections. Most of these patients were listed for PSC or auto-immune hepatitis and experienced recurrent cholangitis, which did not lead to delisting often. The high incidence of PSC could explain the relative high frequency of cholangitis compared to other studies [23,24]. Cholangitis lead to delisting infrequently as well (as shown in Fig. 3). We therefore postulate that PSC-related cholangitis lead to an increased burden of disease but did not affect the rate of delisting.

The observed epidemiological change that bacterial infections were more often caused by Gram-positive and MDR bacteria was confirmed in this study [11,25–28].

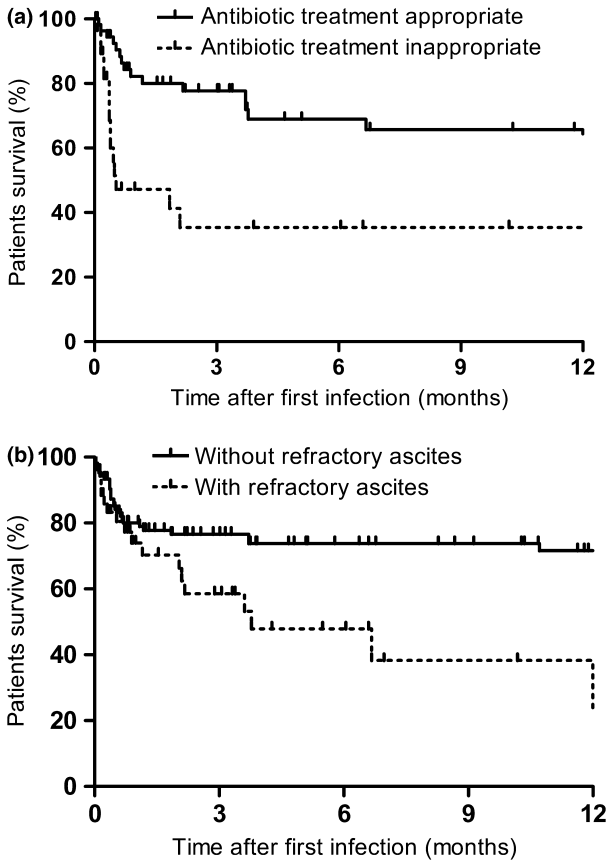

Figure 4 The survival of patients in the first year after the first infection. (a) Patients with an appropriate and inappropriate antibiotic treatment are shown in different curves. The solid line shows values for patients with an appropriate antibiotic treatment and the dotted line for patients with an inappropriate antibiotic treatment.
(b) Patients with and without refractory ascites are shown in different curves. The solid line shows values for patients without refractory ascites and the dotted line for patients with refractory ascites.

The rate of 25% MDR bacteria found in the study population was not expected from earlier studies in the Netherlands [29,30]. This can be explained mainly by the difference of international guidelines and the Dutch national guideline to define MDR organisms [19,31]. In particular, the definition for multidrug-resistant Enterococci spp. is much broader in international guidelines, which explains the majority of MDR organisms.

In contrast to earlier studies, the use of antibiotic prophylaxis did not significantly protect patients for delisting within 30 days following infection. In patients with advanced liver disease, long-term administration of norfloxacin reduces the incidence of SBP, prevents further decompensation and improves survival [32,33]. Several studies have already demonstrated that the current recommended antibiotic prophylaxis occasionally fails due to norfloxacin-resistant organisms [25,34,35].

In this cohort, 23.4% of the patients became too sick or died before transplantation, which is the unfortunate reality previously reported with data from transplant allocation programs [4,5,36,37]. A recent prospective study by Reddy *et al.* discusses the impact of infection in hospitalized patients listed for LT on clinical outcome. This study only included infected patients and did not contain a control cohort of patients without infections [14]. Our study population consisted of all patients registered for LT, including patients with cirrhosis as well as patients with HCC. Naturally, HCC patients follow different courses in progress of liver disease, featured by lower MELD score, less liver-related comorbidities and less infections.

Although the study was carefully prepared, this study entailed limitations arising from the study design and daily clinical practice. First, the retrospective design encompassed data from hospitalization episodes in other centres, which was occasionally unavailable. It was not feasible to differentiate between nosocomial, healthcare-acquired and community-acquired infections, because patients were not prospectively and systematically screened for infection on hospital admission. Secondly, 83% of infections were classified by the standardized CDC criteria, while an expert committee categorized the other proportion. This is inevitable in clinical practice when bacterial and fungal cultures are not standard performed or sometimes fail. Thirdly, the absence of predefined criteria for delisting patients is

Table 3. Multivariate regression analysis of risk factors for infection-related withdrawal from the waiting list.

Risk factors	Odds ratio	95% CI	*P*-value
Multivariate model (adjusted for gender)			
Age at time of infection (per year)	1.133	1.049–1.223	0.001
MELD score (per point) at time of infection	1.295	1.169–1.435	<0.001
Refractory ascites 30 days prior to infection (n = 83)	3.348	0.932–12.024	0.064
Inappropriate antibiotic therapy (n = 58)	3.683	1.096–12.376	0.035

MELD, model for end-stage liver disease.

leading to subjective decision-making based on an expert opinion of the transplant hepatologist, which is representative of what occurs in daily clinical practice. Fourthly, information about temporary delisting was unfortunately not at hand. This could have biased the results, because patients with a systemic infection acquire a temporarily inactive status on the waiting list and not in eligible for liver transplantation at that very moment. Lastly, we analysed patients and waiting list practices in the Netherlands. The Dutch population is presumably listed more often with PSC and with lower MELD scores compared to patients on the waiting list in the United States [4]. The results should be translated with care to other centres and geographical regions.

The results of this study underline the importance of appropriate and timely antimicrobial therapy once more. The clinical importance has been discussed in multiple cohort studies including cirrhotic patients with SBP or septic shock [38–41]. However, the significance of this issue has not yet been demonstrated for various infections in patients waiting for LT.

Emphasis should be directed on the prevention and treatment for infection by adequate antibiotic prophylaxis and immediate effective antibiotics, respectively. Knowledge about multidrug-resistant bacteria and geographical susceptibility patterns is crucial to address these issues. We hypothesize the implementation of periodically microbial colonization swabs in listed patients could support clinicians to prescribe effective antimicrobial prophylaxis and initiate immediate successful treatment. Improving clinical care regarding infection, prevention and treatment would hypothetically lower waiting list mortality and could positively influence the patient's pretransplantation and post-transplantation condition.

Future studies could focus on this window of opportunity for LT after the infection. It is necessary to gather more understanding when infection is likely to resolve or worsen, and which patients can benefit from early LT. Identifying biological and clinical parameters during the infection and the recovery could assist physicians in waiting list decision-making of re-activating patients' waiting list status or delisting. Additionally, prospective studies could benefit the knowledge about the pathophysiology of the clinical deterioration following the infection. Following this argument, research needs to be conducted whether infection might be considered as an exception in the transplantation priority algorithm, similar to patients with HCC and PSC. At last, outlining defined criteria for delisting could make the decision as objective and well considerate as the prioritization for LT.

In conclusion, this study demonstrates a large proportion of patients on the liver transplantation waiting list have infections. Infections have a negative effect on the outcome for patients, and therefore, antimicrobial schedules should be properly individual adapted for effective prophylaxis and treatment of infections.

Authorship

LJMA: performed the study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content and approval of the final article. RCO: involved in the acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis and finalizing the article. BEH: performed the analysis and interpretation of data, statistical analysis and approval of the final article. WGP: performed the critical revision of the manuscript for important intellectual content, and approval of the final article. HRB: performed the critical revision of the manuscript for important intellectual content and approval of the final article. RAM: performed the critical revision of the manuscript for important intellectual content and approval of the final article. CAMS: performed the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision and finalizing the article. HJM: performed the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision and finalizing the article.

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Conflict of interest

The authors declare that they have not anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Hazard ratios for liver transplantation or delisting from the liver transplantation list in patients with 1 infection, 2 infections, and ≥3 infections compared with patients without infection.

Table S1. Univariate regression analysis of risk factors for infection-related withdrawal from the waiting list.

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