Infection (2019) 47:77–85
https://doi.org/10.1007/s15010-018-1230-5

ORIGINAL PAPER

Risk factors of bloodstream infections in recipients after liver transplantation: a meta-analysis

Qiang He[1] · Pin Liu[1] · Xuan Li[1] · Kewen Su[1] · Dan Peng[1] · Zhongshuang Zhang[1] · Wei Xu[1] · Zhen Qin[1] · Shuai Chen[1] · Yingli Li[1] · Jingfu Qiu[1]

Received: 22 February 2018 / Accepted: 28 September 2018 / Published online: 28 October 2018

Abstract

Purpose Bloodstream infection (BSI) is an important cause of adverse outcomes for recipients with liver transplantation (LT). This meta-analysis aimed to identify risk factors associated with post-LT BSI.

Methods Relevant studies published up to June 2017 were searched from seven electronic databases. The studies were reviewed according to the inclusion and exclusion criteria. The *Z* test was used to determine the pooled odds ratio (OR) or standardized mean difference (SMD) of the risk factors. ORs and their corresponding 95% confidence intervals (CIs), or SMDs and their corresponding 95% CIs were used to identify the significant difference of risk factors.

Results Seventeen studies enrolling 4410 recipients were included. Eleven risk factors were identified to be associated with BSI after LT: male recipient (OR = 1.28), ascites (OR = 1.68), model for end-stage liver disease (MELD) score (SMD = 0.20), Child–Pugh class C (OR = 1.69), operation time (SMD = 0.18), incompatible blood type (OR = 2.87), operative blood loss (SMD = 0.33), rejection (OR = 1.72), biliary complications (OR = 1.91), hemodialysis (OR = 3.37), and retransplantation (OR = 2.86).

Conclusions Although some risk factors were identified as significant factors for BSI after LT, which may provide a basis for clinical prevention, well-designed prospective studies should be done to overcome the limitations of this study.

Keywords Bloodstream infection · Liver transplantation · Risk factors · Meta-analysis

Introduction

Liver transplantation (LT) has made great progress over the last 50 years, and it can be considered a true life-saving procedure for patients with end-stage liver disease (ESLD) [1]. LT is a complex surgery that is performed in the potentially contaminated abdominal cavity, and liver transplant recipients often also show nutritional deficiency and metabolic abnormalities. Although surgical techniques have improved and prophylactic strategies have been enhanced substantially over the last several years, infection, particularly bloodstream infection (BSI), is still a main cause of morbidity and mortality for patients with LT [2]. A previous multicenter study reported that BSIs were identified in 19–40% of liver transplant recipients [3]. Moreover, reported mortality associated with BSI ranges from 10 to 52% [4–6].

Due to the variations in regional pathogen epidemiology, the causative organisms of BSI are different between medical centers. The most frequent isolates are *Enterococcus, Klebsiella, Pseudomonas* and *Staphylococcus aureus* (*S. aureus*). Fungal infection is also an increasing cause of BSI after LT [7–9]. In addition, intra-abdominal sepsis or biliary tract infections with duodenal ascending colonization and hematogenous spread from the hepatic portal vein are the main causes of BSI. Other sources, such as catheter-related infections, urinary tract infections, pulmonary infections and wound infections are also important causes of BSI [10–12].

The main risk factors of infections after LT have been reported widely. These factors include recipient factors such as model for end-stage liver disease (MELD) score, age, malnutrition, and immunosuppression before surgery; donor factors such as type of donor, long stay in

✉ Yingli Li
liylyl@126.com

✉ Jingfu Qiu
jfqiu@126.com

[1] School of Public Health and Management, Chongqing Medical University, No.1 Yixueyuan Road, Yuzhong District, Chongqing 400016, China

the hospital and antibiotic therapy; and transplant factors such as intra-operative blood transfusion, type of biliary anastomosis, and longer ischemia time [13, 14]. However, the reported risk factors for BSI after LT are controversial. For example, two studies reported that hemodialysis was a risk factor of BSI after LT [25, 26], whereas two others reported hemodialysis was not related to BSI after LT [23, 30]. A well-designed meta-analysis measures the quantitative combined effect and increases the power of statistical analysis through integrating multiple independent studies with the same objective. Therefore, to address these inconsistent results, we performed this meta-analysis involving 17 studies. Our findings provide more solid evidence for the risk factors of BSI after LT.

Methods

Data source collection

A systematic search was performed in PubMed, the Cochrane Library, Web of Science, Embase, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Chinese Biological Medical Database to identify articles related to risk factors of BSI after LT that were published up to June 2017. The search terms were "liver transplantation or liver grafting or hepatic transplantation" and "bloodstream infection or BSI or bacteremia or sepsis" and "risk factors". All of the identified works were entered into a reference management software (EndNote, version X7).

Inclusion criteria

The initial screening of titles and abstracts was independently carried out by two reviewers (Q.H. and P.L.). A second screening was performed through a full-text review by the same reviewers. The two reviewers' lists of final included studies were compared by cross-checking. Inconsistencies were discussed and handled by a third reviewer (J.Q.) when necessary.

A study included in the meta-analysis had to satisfy the following criteria: (1) the study was related to the risk factors of BSI in recipients after LT. (2) BSI was defined as the isolates of a laboratory-confirmed pathogen from a single blood sample along with clinical symptoms, or the isolates of a pathogen of common skin bacteria from more than 1 set of blood cultures along with clinical symptoms [15]. (3) The study was designed as a case–control study or a cohort study. (4) The study was published in English or Chinese.

Exclusion criteria

Studies were excluded according to the following criteria: (1) duplicate articles describing the same study or publications from different databases. (2) No definition or no diagnostic criteria for BSI. (3) Studies were related to the risk factors of BSI after organ transplantation but did not provide information on the LT subgroup. (4) Did not provide sufficient data to calculate the pooled odds ratio (OR) and its 95% confidence interval (CI). (5) Case reports or reviews.

Data extraction

Relevant data were extracted by three reviewers (Q.H., D.P. and Z.Z.) independently, and the results were evaluated by other reviewers (P.L. and X.L.). The extracted data included the first author, year of publication, study time and country, study design, number of cases and controls and initial data of risk factors.

Quality assessment

The quality of each included article was evaluated by three reviewers (Y.L., K.S. and W.X.) according to the Newcastle–Ottawa Scale (NOS), which was designed especially for observational case–control and cohort studies. The NOS includes three separate categories and a total of nine points, consisting of 4 points for selection, 2 points for comparability, and 3 points for outcome and exposure. Studies with scores of 0–4 points were identified as low quality and 5–9 points as high quality [16]. Low-quality studies were excluded from the meta-analysis.

Statistical analysis

Statistical analysis of the data was carried out using Review Manager 5.0 (The Cochrane Collaboration, Copenhagen). Heterogeneity among the trials was assessed with the χ^2 test and the I^2 statistic. The pooled OR and standardized mean difference (SMD) were calculated to evaluate the risk factors of BSI in recipients after liver transplantation for dichotomous and continuous variables, respectively, and significance was determined by the Z test. The 95% CI of SMD was greater than 0 (upper and lower limits were both greater than 0), which is equivalent to the 95% CI of OR when it was greater than 1, and it indicated that the variables were significant risk factors. The fixed-effects model was used for calculating the pooled effect size and its 95% CI for the homogeneous data ($I^2 < 50\%$ or $P > 0.05$). Otherwise, the random-effects model was used. A sensitivity analysis was also conducted by omitting individual studies one by one

and exchanging the effects model. The results were identified reliably when the corresponding *P* value of pooled-effects size was not significantly different. Publication bias was examined using Egger's test in Stata 12.0 (StataCorp, College Station, TX). A *P* value < 0.05 suggested that there was publication bias in the study. The population-attributable risk proportion (PARP) was calculated as follows: $PARP = P_e\ (OR - 1)/[P_e\ (OR - 1) + 1]$, where P_e refers to the pooled exposure rate of controls, which substitutes as the overall population exposure rate.

Results

Study selection and characteristics

A total of 2525 potentially relevant citations were systematically identified through an electronic database search, 803 of which were excluded due to duplication. A further 1420 were excluded after screening of the titles and abstracts because they were reviews or case reports or were not relevant to the risk factors of BSI after LT. Then 285 were excluded after reviewing the full articles, mainly because they did not match the inclusion criteria. Finally, 17 studies enrolling a total of 4410 recipients (745 cases and 3665 controls) were included in the meta-analysis [17–33]. The process used for article selection is presented in Fig. 1.

These studies were published from 2004 to 2016. They were carried out in China [17, 30], Japan [21–24, 31–33], Korea [25, 26, 29], the USA [27], Italy [18], France [19], the UK [20], and Germany [28]. Eleven studies were case–control designs [17–19, 21, 22, 25–27, 29, 32, 33], while six studies were cohort study designs [20, 23, 24, 28, 30, 31]. The results of four case–control studies [17–19, 27] and three cohort studies [24, 28, 30] did not adjust for any potential confounders, whereas the remaining studies adjusted for one or more fundamental risk factors, such as encephalopathy, diabetes, Child–Pugh class C, operation time, incompatible blood type, rejection, biliary complications, hemodialysis and retransplantation. All of the included studies were assessed with 6–8 points (high quality) by NOS. The detailed characteristics of the 17 included articles are listed in Table 1.

Risk factors of BSI

The risk factors of BSI after LT are shown in Table 2. Several risk factors, including recipient age, donor age, MELD score, blood albumin concentration, operation time, graft volume/standard liver volume (GV/SLV) ratio, operative blood loss, graft recipient weight ratio (GRWR), cold ischemia time and warm ischemia time, were continuous variables, and the rest were count variables. Risk factors with a significant relationship with BSI after LT were as follows: male recipient (OR = 1.28, 95% CI 1.07–1.55), ascites (OR = 1.68, 95% CI 1.02–2.79), MELD score (SMD = 0.20, 95% CI 0.02–0.38), Child–Pugh class C (OR = 1.69, 95% CI 1.22–2.34), operation time (SMD = 0.18, 95% CI 0.07–0.30), incompatible blood type (OR = 2.87, 95% CI 2.00–4.11), operative blood loss (SMD = 0.33, 95% CI 0.15–0.50), rejection (OR = 1.72, 95% CI 1.18–2.52), biliary complications (OR = 1.91, 95% CI 1.40–2.62), hemodialysis (OR = 3.37, 95% CI 2.21–5.13), retransplantation (OR = 2.86, 95% CI

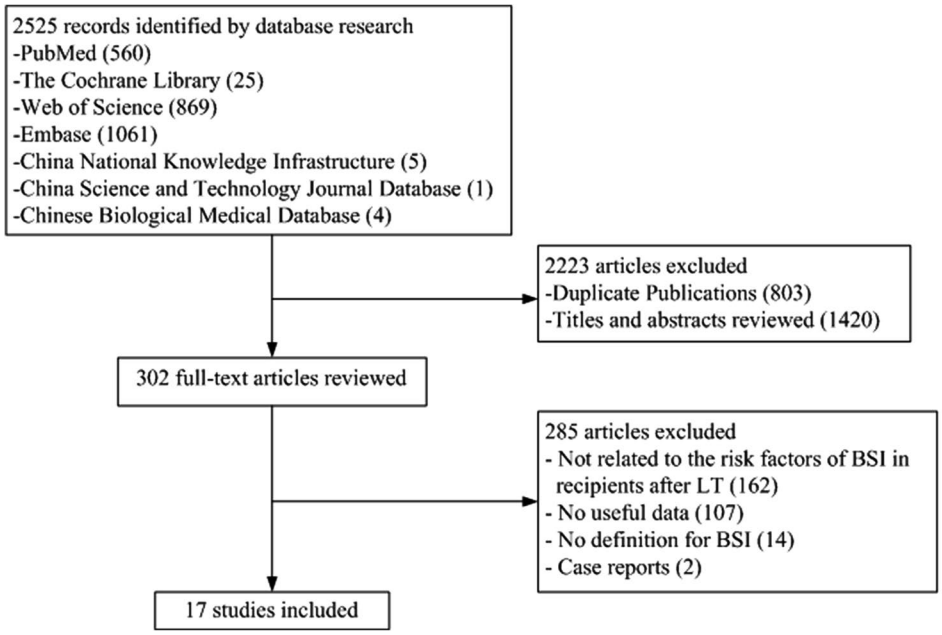

Fig. 1 Flowchart of the selection process. *BSI* bloodstream infection, *LT* liver transplantation

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Type of study	Country	Study period	Cases/controls	Quality assessment[a]	Adjusted variables
Tai et al. [17]	2011	Case–control	China	January 1993–May 2010	7/688	6 points	NA
Bedini et al. [18]	2007	Case–control	Italy	October 2000–September 2006	28/177	6 points	NA
Bert et al. [19]	2010	Case–control	France	January 1997–December 2007	205/499	6 points	NA
Karvellas et al. [20]	2011	Cohort	UK	January 2003–July 2005	15/203	6 points	Retransplantation
Hashimoto et al. [21]	2008	Case–control	Japan	January 1996–November 2004	21/221	8 points	Diabetes
Iida et al. [22]	2010	Case–control	Japan	April 2006–November 2009	62/119	6 points	Child–Pugh class C, incompatible blood type
Iinuma et al. [23]	2004	Cohort	Japan	April 2001–March 2002	19/94	6 points	Operation time, incompatible blood type
Ikegami et al. [24]	2012	Cohort	Japan	May 1997–July 2011	46/300	7 points	NA
Kim HK et al. [25]	2013	Case–control	Korea	February 2005–May 2011	64/158	8 points	Biliary complications
Kim SI et al. [26]	2009	Case–control	Korea	January 2005–September 2007	34/110	6 points	Hemodialysis
Munoz-Price et al. [27]	2004	Case–control	USA	January 1994–December 1999	29/163	8 points	NA
Oweira et al. [28]	2016	Cohort	Germany	January 2008–February 2011	45/117	6 points	NA
Rhee KW et al. [29]	2012	Case–control	Korea	1994–1998	32/117	7 points	Encephalopathy, incompatible blood type, rejection
Shi SH et al. [30]	2010	Cohort	China	January 2003–December 2006	39/436	7 points	NA
Shimizu et al. [31]	2016	Cohort	Japan	January 2006–December 2012	17/72	7 points	Incompatible blood type
Shoji et al. [32]	2015	Case–control	Japan	November 2005–February 2013	53/157	7 points	Incompatible blood type
Takeda et al. [33]	2016	Case–control	Japan	1992–2015	29/34	7 points	Incompatible blood type

NA not available

[a]Low-quality research, 0–4 points; high-quality research, 5–9 points

1.89–4.34). A forest plot describing the relationship between Child–Pugh class C and BSI after LT is provided in Fig. 2.

PARP of risk factors

PARP was used to estimate the percentage of cases in a population that is attributable to one kind of exposed factor. The PARP of risk factors such as male recipient, ascites, Child–Pugh class C, incompatible blood type, rejection, biliary complications, hemodialysis and retransplantation are shown in Table 3. The PARP ranged from 10.28 to 28.86%. Child–Pugh class C had the highest PARP, whereas retransplantation had the lowest PARP. The PARP of three other risk factors, MELD score, operation time and operative blood loss, are not listed in Table 3 because they are continuous variables and could not be used to calculate P_e.

Sensitivity analysis

Sensitivity analysis was conducted by eliminating individual studies one by one. Although most of the results did not change, some did. Ascites became statistically non-significant if we removed the study of Hashimoto or Iida. Similarly, male recipient or MELD score also became statistically non-significant if the study of Bert or Ikegami was removed, respectively.

Table 2 Meta-analysis of risk factors of bloodstream infections in recipients after liver transplantation

Risk factors	Combination studies	Cases/controls	OR (95% CI) or SMD (95% CI)	*Z*	*P*	Heterogeneity of study design			Analysis model	Egger's test
						χ^2	*P*	I^2		
Male recipient	16	713/3548	1.28 (1.07, 1.55)	2.62	0.009[b]	10.49	0.79	0	Fixed	0.242
Male donor	3	120/580	1.17 (0.77, 1.78)	0.74	0.46	0.02	0.99	0	Fixed	0.650
Recipient age	7	427/1659	0.08 (−0.10, 0.26)[a]	0.90	0.37	13.24	0.04	55	Random	0.560
Donor age	2	74/151	0.10 (−0.34, 0.55)[a]	0.46	0.65	2.22	0.14	55	Random	NA
Ascites	3	102/434	1.68 (1.02, 2.79)	2.02	0.04[b]	1.84	0.40	0	Fixed	0.667
Encephalopathy	4	116/1143	1.09 (0.66, 1.82)	0.34	0.74	2.35	0.50	0	Fixed	0.800
Diabetes	5	182/861	1.41 (0.93, 2.13)	1.62	0.11	5.24	0.26	24	Fixed	0.558
History of surgery	2	55/331	1.21 (0.59, 2.48)	0.52	0.60	0.05	0.83	0	Fixed	NA
MELD score	4	171/563	0.20 (0.02, 0.38)[a]	2.21	0.03[b]	4.22	0.24	29	Fixed	0.879
Child–Pugh class C	6	228/1138	1.69 (1.22, 2.34)	3.18	0.001[b]	5.70	0.34	12	Fixed	0.860
Albumin	2	63/144	0.05 (−0.26, 0.35)[a]	0.31	0.76	0.16	0.69	0	Fixed	NA
ICU status before LT	2	72/251	1.66 (0.90, 3.03)	1.63	0.10	0.51	0.48	0	Fixed	NA
Potal vein thrombosis	3	101/631	1.52 (0.76, 3.06)	1.18	0.24	1.87	0.39	0	Fixed	0.536
Operation time	6	395/1156	0.18 (0.07, 0.30)[a]	3.08	0.002[b]	9.44	0.09	47	Fixed	0.051
Incompatible blood type	8	322/1051	2.87 (2.00, 4.11)	5.75	0.000[b]	10.29	0.17	32	Fixed	0.885
GV/SLV ratio	2	75/334	0.10 (−0.16, 0.36)[a]	0.76	0.45	0.32	0.57	0	Fixed	NA
Operative blood loss	4	182/570	0.33 (0.15, 0.50)[a]	3.67	0.000[b]	1.51	0.68	0	Fixed	0.476
GRWR	2	75/334	0.05 (−0.21, 0.31)[a]	0.38	0,71	0.40	0.53	0	Fixed	NA
Cold ischemia time	3	137/453	−0.04 (−0.24, 0.16)[a]	0.38	0.71	0.38	0.83	0	Fixed	0.403
Warm ischemia time	3	137/453	0.12 (−0.08, 0.32)[a]	1.17	0.24	0.98	0.61	0	Fixed	0.237
Rejection	13	632/3141	1.72 (1.18, 2.52)	2.79	0.005[b]	34.43	0.000	65	Random	0.028
Biliary complications	6	384/1833	1.91 (1.40, 2.62)	4.04	0.000[b]	7.96	0.16	37	Fixed	0.093
Hemodialysis	4	156/798	3.37 (2.21, 5.13)	5.67	0.000[b]	5.17	0.16	42	Fixed	0.559
Retransplantation	7	393/2005	2.94 (1.97, 4.39)	5.27	0.000[b]	6.16	0.41	3	Fixed	0.724
Antibiotic use	3	124/815	2.36 (0.91, 6.09)	1.78	0.08	8.68	0.01	77	Random	0.943

OR odds ratio, *CI* confidence interval, *NA* not available, *MELD* model for end-stage liver disease, *ICU* intensive care unit, *GV* graft volume, *SLV* standard liver volume, *GRWR* graft recipient weight ratio

[b] $P < 0.05$ stands for significant

[a] Standardized mean difference (SMD)

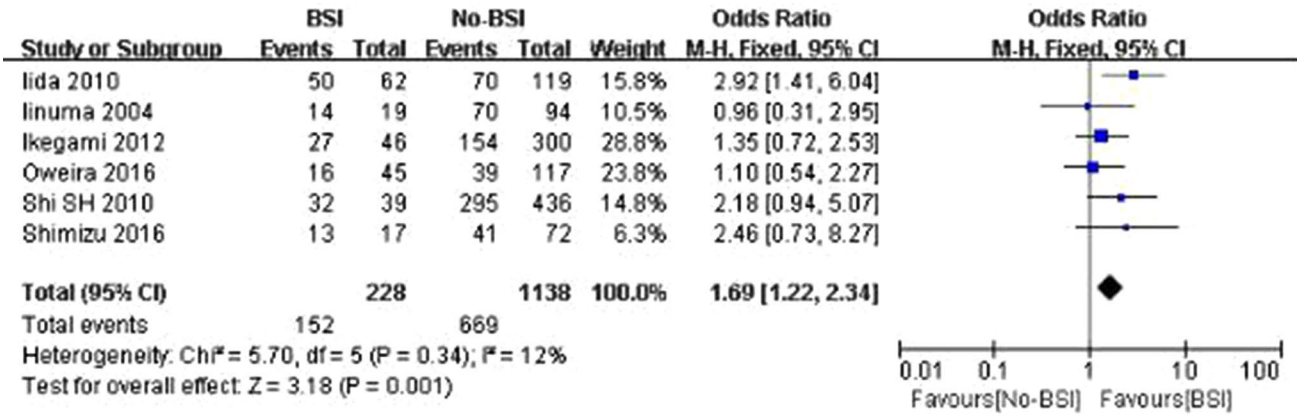

Fig. 2 Forest plot for the association between BSI after LT and Child–Pugh class C. The individual block squares denote the OR for each study of Child–Pugh class C, with an area proportional to the amount of statistical information in each study. The horizontal line denotes a 95% CI. The pooled estimate and its 95% CI are represented by a diamond. Diamonds plotted in the right half indicate increased BSI risk. *BSI* bloodstream infections, *LT* liver transplantation, *OR* odds ratio, *CI* confidence interval

Table 3 Population-attributable risk proportion of risk factors of bloodstream infections in recipients after liver transplantation

Risk factors	OR (95% CI)	P_e (%)	PARP (%)
Child–Pugh class C	1.69 (1.22, 2.34)	58.79	28.86
Ascites	1.68 (1.02, 2.79)	45.24	23.53
Hemodialysis	3.37 (2.21, 5.13)	12.16	22.37
Male recipient	1.28 (1.07, 1.55)	68.80	16.15
Incompatible blood type	2.87 (2.00, 4.11)	8.47	13.67
Rejection	1.72 (1.18, 2.52)	21.17	13.23
Biliary complications	1.91 (1.40, 2.62)	13.75	11.12
Retransplantation	2.94 (1.97, 4.39)	6.16	10.28

OR odds ratio, *CI* confidence interval, P_e pool exposure rate, *PARP* population-attributable risk proportion

Publication bias

We assessed the publication bias for the included studies with Egger's test, which is often used to assess the evidence of publication bias (Table 2). There were no obvious asymmetries of the risk factors, except rejection ($P = 0.028$), in this meta-analysis.

Discussion

The success of LT can be limited by infectious complications, and BSI is known to be a major factor for recipient morbidity and mortality after LT. To prevent BSI after LT, the identification of risk factors is necessary. A number of articles have reported the risk factors for BSI after LT. However, controversy about the risk factors persists, perhaps because individual studies have few subjects or because different studies use different selection criteria or study designs. Until now, no meta-analysis has been published on this issue. The aim of the present study was to determine the risk factors for BSI after LT using a meta-analysis to increase the sample size and to improve the power of the statistical analysis and provide the best evidence for clinical treatment.

According to the inclusion and exclusion criteria, a total of 17 studies including 4410 patients were brought into the present meta-analysis. Most eligible studies clearly defined the criteria for inclusion and exclusion of study subjects and the outcome indicators. Further, all of the included studies were rated as high quality by NOS. Thus, we conclude that the results based on the present evidence are convincing. Among these studies, three studies only focused on BSI caused by methicillin-resistant *S. aureus*, Gram-positive bacteria and multi-drug-resistant Gram-positive cocci, respectively [17, 18, 30]. The rest of the studies included recipients with BSI caused by various pathogenic microorganisms.

The results show that incompatible blood type and postoperative rejection are both important risk factors for BSI after LT. Rejection is one of the most usual causes of graft dysfunction, and it has been reported to increase the infection rate [17, 34]. Stronger immunosuppressive therapy is necessary to inhibit antibody-mediated rejection in ABO-incompatible LT patients compared with ABO-compatible LT patients. However, overuse of immunosuppressors could lead to cellular immune dysfunction, which is associated with a wide variety of infections [35]. Therefore, a good balance of immunosuppression is essential, and the choice of immune strategy must be cautious. In addition, incompatible blood type could be avoided by choosing donors with matched blood type before LT. It is noteworthy that a publication bias for rejection was observed using Egger's test.

This may have occurred because all of the articles in the study were published articles, and studies with statistically significant results are more likely to be published. Hence, further studies are needed to investigate the correlation between BSI after LT and rejection.

At present, LT is the only curative therapy with excellent long-term results in patients with ESLD [36]. The Child–Pugh class and the MELD score are two widely used prognostic models for ESLD [37]. We observed a significantly higher MELD score and a larger Child–Pugh class C ratio in the patients with postoperative BSI than those without BSI after LT. In addition, this meta-analysis showed that ascites was associated with postoperative BSI. Ascites is an index of Child–Pugh classification [38]. High MELD score, Child–Pugh class C and ascites reflect the severity of the underlying liver disease and its associated immune dysfunction, which contribute to the appearance of BSI. As these risk factors are part of the underlying disease and only limitedly modifiable, infectiological surveillance and prophylaxis should be intensified in LT recipients with higher MELD, Child–Pugh class C or ascites. Moreover, male recipients had a higher risk of BSI than female recipients. This result can be thought of as a consequence of differences in physical structure, immune response and lifestyle between the genders.

Long operation time was another risk factor for BSI. In general, tissue injury at the surgical site is aggravated as the operation time grows longer, which is bad for postoperative recovery. Moreover, the long-time operation is performed in the potentially contaminated abdominal cavity, increasing the chance of BSI. This risk factor could be modified by enhancing surgeon's surgical performance skill. The operative blood loss was significantly different between BSI and non-BSI cases. The reason for this effect is that massive blood loss results in massive transfusion and causes transfusion-related immune dysfunction. At the same time, patients undergoing LT are at risk of blood loss due to preexisting liver dysfunction and major intraoperative and postoperative coagulopathy [39]. To prevent massive operative blood loss, the key is a careful surgical technique during the hepatectomy and correction of coagulation abnormalities throughout the procedure [40]. In this meta-analysis, biliary complications, principally including biliary leakage and biliary stricture after LT, increased the incidence of BSIs. Kochhar et al. have reported that biliary complications were related to the type of biliary reconstruction performed at the time of LT. The choledochocholedochostomy with T tube and the choledochojejunostomy were the potential risk factors of biliary complications. However, the T tube and the choledochojejunostomy were unavoidable sometimes [41]. Therefore, the surgeon's choice is crucial when they perform a biliary reconstruction at the time of LT. Renal dysfunction is a common complication in patients with ESLD and is widespread in LT patients. Hemodialysis is a traditional treatment for patients with renal dysfunction requiring renal replacement therapy [42]. However, blood is drained into the dialyzer during hemodialysis, so the pollution of dialysis machines and the dialysate could increase the risk of BSI. Furthermore, a markedly different incidence of retransplantation was observed between the case group and the control group.

We found that Child–Pugh class C and ascites had the top two PARP. In our study, PARP was used to estimate the percentage of BSIs in LT recipients that is attributed to one kind of risk factor. From this, we infer that these risk factors were most important for BSI after LT.

In the present meta-analysis, strong evidence for male recipient, MELD score and ascites as risk factors for BSI was shown, but some of the results were unstable if we removed individual studies. The SMD and corresponding 95% CI for MELD score changed to SMD = 0.08 and 95% CI − 0.14–0.29, while the OR and 95% CI of male recipient changed to OR = 1.14 and 95% CI 0.92–1.42. Similarly, the OR and 95% CI of ascites changed to OR = 1.46 and 95% CI 0.80–2.67 or OR = 1.54 and 95% CI 0.78–3.07 upon removal of individual studies. It indicated that if we removed one of the included studies, male recipient, MELD and ascites would be no more statistically significant risk factors. The unstable results may have been caused by the small sample sizes of the included studies, so the pooled effect size was overstated and led to an inverse conclusion.

Some limitations that may have effects on the results of this meta-analysis should be considered. First, we just included English- and Chinese-language studies from seven databases. Thus, relevant articles published in other languages or databases or unpublished studies may have been missed. Second, significant heterogeneity was found in some risk factors. Although we used strict inclusion criteria, the basic conditions and accepted medical treatment levels of enrolled patients from different areas may have significantly varied. Finally, some studies were excluded from the meta-analysis because they lacked a definition and diagnostic criteria for BSI. Thus, we may have missed some relevant information, and the statistical power was limited.

In conclusion, this meta-analysis identified some perioperative risk factors for BSI after LT and may provide a basis for clinical prevention. However, well-designed prospective cohort studies should be done to further confirm our findings and take effective measures for hospital infection control.

Funding This work was supported by the National Natural Science Foundation of China (31200064, 31071093, and 31170129).

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Song AT, Avelino-Silva VI, Pecora RA, Pugliese V, D'Albuquerque LA, Abdala E. Liver transplantation: fifty years of experience. World J Gastroenterol. 2014;20:5363–74.
2. Lee SO, Kang SH, Abdel-Massih RC, Brown RA, Razonable RR. Spectrum of early-onset and late-onset bacteremias after liver transplantation: implications for management. Liver Transpl. 2011;17:733–41.
3. Santos CA, Hotchkiss RS, Chapman WC, Olsen MA. Epidemiology of bloodstream infections in a multicenter retrospective cohort of liver transplant recipients. Transpl Direct. 2016;2:e67.
4. Shao M, Wan Q, Xie W, Ye Q. Bloodstream infections among solid organ transplant recipients: epidemiology, microbiology, associated risk factors for morbility and mortality. Transpl Rev (Orlando Fla). 2014;28:176–81.
5. Wagener MM, Yu VL. Bacteremia in transplant recipients: a prospective study of demographics, etiologic agents, risk factors, and outcomes. Am J Infect Control. 1992;20:239–47.
6. Hsu J, Andes DR, Knasinski V, Pirsch J, Safdar N. Statins are associated with improved outcomes of bloodstream infection in solid-organ transplant recipients. Eur J Clin Microbiol Infect Dis. 2009;28:1343–51.
7. Sganga G, Spanu T, Bianco G, Fiori B, Nure E, Pepe G, et al. Bacterial bloodstream infections in liver transplantation: etiologic agents and antimicrobial susceptibility profiles. Transpl Proc. 2012;44:1973–6.
8. Kalpoe JS, Sonnenberg E, Factor SH, del Rio Martin J, Schiano T, Patel G, et al. Mortality associated with carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients. Liver Transpl. 2012;18:468–74.
9. Wan QQ, Ye QF, Ming YZ, Ma Y, Zhou JD, Qiao BB, et al. The risk factors for mortality in deceased donor liver transplant recipients with bloodstream infections. Transpl Proc. 2013;45:305–7.
10. Kritikos A, Manuel O. Bloodstream infections after solid-organ transplantation. Virulence. 2016;7:329–40.
11. Singh N, Gayowski T, Wagener MM, Marino I. Bloodstream infections in liver transplant recipients receiving tacrolimus. Clin Transpl. 1997;11:275–81.
12. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med. 1977;296:1305–9.
13. van Hoek B, de Rooij BJ, Verspaget HW. Risk factors for infection after liver transplantation. Best Pract Res Clin Gastroenterol. 2012;26:61–72.
14. Avkan-Oguz V, Ozkardesler S, Unek T, Ozbilgin M, Akan M, Firuzan E, et al. Risk factors for early bacterial infections in liver transplantation. Transpl Proc. 2013;45:993–7.
15. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16:128–40.
16. Margulis AV, Pladevall M, Riera-Guardia N, Varas-Lorenzo C, Hazell L, Berkman ND, et al. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle–Ottawa Scale and the RTI item bank. J Clin Epidemiol. 2014;6:359–68.
17. Tai Q, Wu WL, Ju WQ, Wang DP, Wang GD, Ma Y, et al. A 17-year retrospective study of the risk factor of bloodstream infection with MRSA after liver transplantation. J Trop Med 2011:1141–3.
18. Bedini A, Codeluppi M, Cocchi S, Guaraldi G, Di Benedetto F, Venturelli C, et al. Gram-positive bloodstream infections in liver transplant recipients: incidence, risk factors, and impact on survival. Transpl Proc. 2007;39:1947–9.
19. Bert F, Larroque B, Paugam-Burtz C, Janny S, Durand F, Dondero F, et al. Microbial epidemiology and outcome of bloodstream infections in liver transplant recipients: an analysis of 259 episodes. Liver Transpl. 2010;16:393–401.
20. Karvellas CJ, McPhail M, Pink F, Asthana S, Muiesan P, Heaton N, et al. Bloodstream infection after elective liver transplantation is associated with increased mortality in patients with cirrhosis. J Crit Care. 2011;26:468–74.
21. Hashimoto M, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Togashi J, et al. Bloodstream infection after living donor liver transplantation. Scand J Infect Dis. 2008;40:509–16.
22. Iida T, Kaido T, Yagi S, Yoshizawa A, Hata K, Mizumoto M, et al. Posttransplant bacteremia in adult living donor liver transplant recipients. Liver Transpl. 2010;16:1379–85.
23. Iinuma Y, Senda K, Fujihara N, Saito T, Takakura S, Kudo T, et al. Surgical site infection in living-donor liver transplant recipients: a prospective study. Transplantation. 2004;78:704–9.
24. Ikegami T, Shirabe K, Yoshiya S, Yoshizumi T, Ninomiya M, Uchiyama H, et al. Bacterial sepsis after living donor liver transplantation: the impact of early enteral nutrition. J Am Coll Surg. 2012;214:288–95.
25. Kim HK, Park YK, Wang HJ, Kim BW, Shin SY, Lim SK, et al. Epidemiology and clinical features of post-transplant bloodstream infection: an analysis of 222 consecutive liver transplant recipients. J Infect Chemother. 2013;45:315–24.
26. Kim SI, Kim YJ, Jun YH, Wie SH, Kim YR, Choi JY, et al. Epidemiology and risk factors for bacteremia in 144 consecutive living-donor liver transplant recipients. Yonsei Med J. 2009;50:112–21.
27. Munoz-Price LS, Slifkin M, Ruthazer R, Poutsiaka DD, Hadley S, Freeman R, et al. The clinical impact of ganciclovir prophylaxis on the occurrence of bacteremia in orthotopic liver transplant recipients. Clin Infect Dis. 2004;39:1293–9.
28. Oweira H, Lahdou I, Daniel V, Hofer S, Mieth M, Schmidt J, et al. Early post-transplant neopterin associated with one year survival and bacteremia in liver transplant recipients. Hum Immunol. 2016;77:115–20.
29. Rhee KW, Oh SH, Kim KM, Kim DY, Lee YJ, Kim T, et al. Early bloodstream infection after pediatric living donor living transplantation. Transpl Proc. 2012;44:794–6.
30. Shi SH, Kong HS, Jia CK, Xu J, Zhang WJ, Wang WL, et al. Coagulase-negative staphylococcus and enterococcus as predominant pathogens in liver transplant recipients with Gram-positive coccal bacteremia. Chin Med J (Engl). 2010;123:1983–8.
31. Shimizu S, Tanaka Y, Tazawa H, Verma S, Onoe T, Ishiyama K, et al. Fc-gamma receptor polymorphisms predispose patients to infectious complications after liver transplantation. Am J Transpl. 2016;16:625–33.
32. Shoji K, Funaki T, Kasahara M, Sakamoto S, Fukuda A, Vaida F, et al. Risk factors for bloodstream infection after living-donor liver transplantation in children. Pediatr Infect Dis J. 2015;34:1063–8.
33. Takeda K, Sawada Y, Kumamoto T, Tanaka K, Endo I. Severe sepsis after living donor liver transplantation: risk factors and outcomes. Transpl Proc. 2016;48:2124–9.
34. Banff Working G, Demetris AJ, Adeyi O, Bellamy CO, Clouston A, Charlotte F, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology. 2006;44:489–501.
35. Yan HM, Ji SH, Chen HR, Wang HX, Zhu PY, Xue M, et al. Immune-reconstitution following HLA haplotype related T-cell undepleted allogeneic bone marrow transplantation. J Clin Hematol. 2005;18:7–10.
36. Genda T, Ichida T, Sakisaka S, Tanaka E, Mochida S, Ueno Y, et al. Survival in patients with Child-Pugh class C cirrhosis: analysis of the liver transplant registry in Japan. Hepatol Res. 2017;47:1155–64.
37. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC, et al. A model to predict poor survival in patients undergoing

transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31:864–71.
38. Peng Y, Qi XS, Dai JN, Li HY, Guo XZ. Child-Pugh versus MELD score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis. Int J Clin Exp Med. 2015;8:751–7.
39. Tischer S, Miller JT. Pharmacologic strategies to prevent blood loss and transfusion in orthotopic liver transplantation. Crit Care Nurs Q. 2016;39:267–80.
40. Mor E, Jennings L, Gonwa TA, Holman MJ, Gibbs J, Solomon H, et al. The impact of operative bleeding on outcome in transplantation of the liver. Surg Gynecol Obstet. 1993;176:219–27.
41. Kochhar G, Parungao JM, Hanouneh IA, Parsi MA. Biliary complications following liver transplantation. World J Gastroenterol. 2013;19:2841–6.
42. Nadim MK, Annanthapanyasut W, Matsuoka L, Appachu K, Boyajian M, Ji L, et al. Intraoperative hemodialysis during liver transplantation: a decade of experience. Liver Transpl. 2014;20:756–64.