



## State of the Science Review

## Risk factors for development of surgical site infections among liver transplantation recipients: An integrative literature review



Ramon Antônio Oliveira MSc, RN <sup>\*</sup>, Ruth Natália Teresa Turrini PhD, RN,  
Vanessa de Brito Poveda PhD, RN

School of Nursing, São Paulo University, Sao Paulo, Brazil

## Key Words:

Cross-infection  
Surgical wound infection  
Hepatic transplantation

**Background:** Surgical site infection (SSI) is an important complication in the postoperative period of recipients of liver transplantation. The purpose of this integrative literature review is to summarize the knowledge available about the risk factors contributing to the development SSI among adults undergoing liver transplantation.

**Methods:** We reviewed the Medical Literature Analysis and Retrieval System Online/PubMed, the Cumulative Index to Nursing and Allied Health Literature, the Latin American and Caribbean Health Sciences Literature, Scopus, and Web of Science databases.

**Results:** Two hundred sixteen articles were identified and the final sample of 9 articles was analyzed in full length. The SSI rate found in the investigations ranged between 9.6% and 35.5%. Risk factors for SSI were grouped into categories related to the preoperative period, such as Model for End-Stage Renal Disease score > 35 and ventilated support on day of transplant; to the intraoperative period activity, such as transfusion of packed red blood cells, extended surgical time, hyperglycemia >200 mg/dL, use of vasopressor drugs, and ascites flow >1 L; and to the donor/recipient relationship, such as age differences >10 years, ratio of donor liver mass to recipient body mass < 0.01. Additionally, centers that annually perform <50 transplants appear to have higher rates of SSI.

**Conclusions:** Few studies have addressed the subject of SSI in relation to liver transplantation in the scientific literature. Risk factors for SSI in patients who underwent liver transplantation vary between institutions.

© 2018 Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.

Health care-associated infections are currently a major problem related to hospitalization and result in increased costs related to increased length of stay and the use of antimicrobial agents, in addition to the direct affect on the lives of patients, leaving them out of work, generating psychological consequences from being isolated, separation from family, and other disorders related to the experience.<sup>1</sup>

Bacterial infections are among the most frequent complications during the postoperative period of liver transplantation and cause significant morbidity and mortality related to these infections, at rates of approximately 50% when accompanied by septic shock.<sup>2–4</sup>

Liver transplant recipients have a higher possibility of developing bacterial infections when compared with recipients of other types of transplants due to the complexity of the surgical procedure and the involvement and handling of the hepatobiliary tract. It is also worth noting the importance of the hospital environment as a carrier of infecting pathogens such as gram-negative and gram-positive bacteria.<sup>5,6</sup>

In addition to this scenario, there is a need for immunosuppression to prevent graft rejection. The presence of infections related to previous contact with the receiver or pathogens are common due to the acquisition of microorganisms during the transplant procedures.<sup>7</sup>

Among health care-associated infections, the surgical site infections (SSIs) that affect liver transplant recipients stand out because they are related to increased morbidity and mortality, to the need for new surgical procedures, to the use of a broad antimicrobial spectrum, and to extended hospital stays.<sup>8,9</sup>

Risk factors for SSI among patients undergoing surgery related to different specialties have been extensively studied; however, with

<sup>\*</sup> Address correspondence to Ramon Antônio Oliveira, MSc, RN, School of Nursing, São Paulo University, Av Dr Enéias de Carvalho Aguiar, 419 Cerqueira César, Sao Paulo, SP 05403-000, Brazil.

E-mail address: [oliveiraramon@yahoo.com.br](mailto:oliveiraramon@yahoo.com.br) (R.A. Oliveira).

Conflicts of interest: None to report.

the global growing demand for transplants, it is of great value to understand the risk factors specific to this population.

It is thus relevant to gather and synthesize information available in the scientific literature about the risk factors for SSI development among patients undergoing liver transplantation.

To this end, we aimed to summarize the knowledge about the risk factors that contribute to the development of SSIs among adult recipients of liver transplantation.

## MATERIAL AND METHODS

This was an integrative literature review (IR) guided by the question: What are the risk factors identified by the scientific literature that contribute to the development of SSI among adult recipients of liver transplantation?

The preparation and reporting of this review observed the principles of the Centre for Reviews and Dissemination, York University, guidance for undertaking reviews in health care.<sup>10</sup>

The following inclusion criteria were used: primary studies in which the sample patients were aged 18 years or older; liver transplant recipients of graft from a deceased donor; and published in English, Portuguese, or Spanish. We excluded scientific articles with samples composed of patients undergoing multiple-organ transplantation.

The search for articles was conducted in the following databases: the Medical Literature Analysis and Retrieval System Online, the Cumulative Index to Nursing and Allied Health Literature, Latin American and Caribbean Health Sciences, Scopus, and Web of Science. The initial period of search corresponded to the different index start dates until September 18, 2016.

For the selection of key words we used the constant Medical Subject Headings terms, the List of Topical Subheadings in CINAHL Information Systems, and descriptors in Health Sciences of the Virtual Health Library (Spanish and Portuguese).

The search of different databases was carried out using controlled and uncontrolled descriptors to ensure a sensitive search. To ensure the possibility of recovering all pertinent articles, we used combined strategies in different databases, using Boolean operators and additional strategies based on the searching terms in titles and abstracts (Supplementary Table S1).

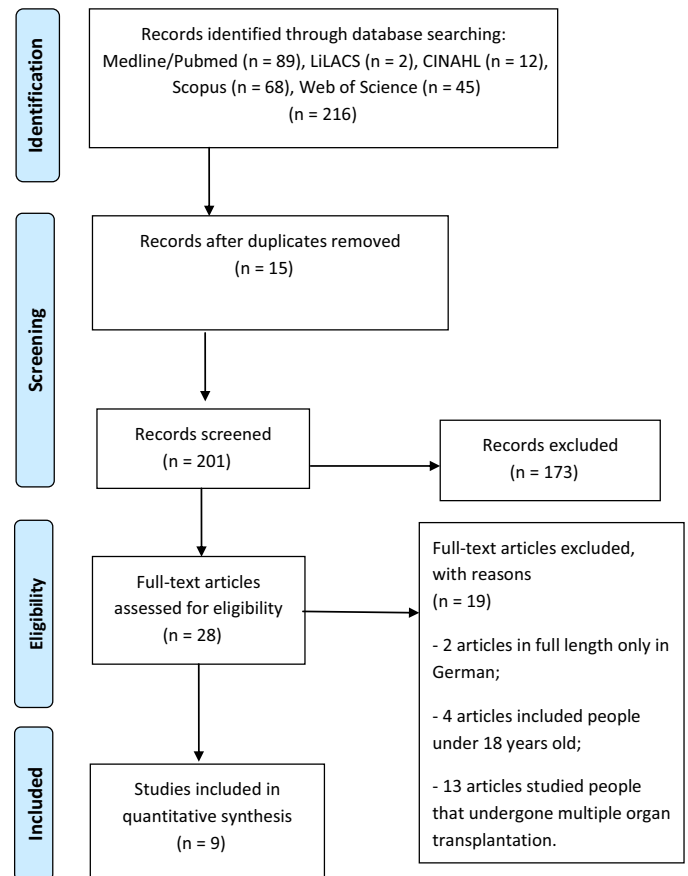
Using the aforementioned inclusion and exclusion criteria, 2 independent reviewers examined the titles and abstracts of the retrieved documents in the selected databases and discrepancies were later resolved through a third reviewer. The articles considered eligible were examined in full text.

The theoretical framework proposed by Melnyk and Fineout-Overholt<sup>11</sup> was used to assess the level of strength of the evidence concerning the prognosis or prediction of issues. Using this framework, the studies were stratified on a scale ranging from 1–5, in which 1 is evidence of higher strength, coming from synthesis of case studies control or cohort, and 5 indicates studies with a weaker level of evidence, such as expert opinions.

We extracted the following information from the included studies: data related to investigations (study design, purpose, year, and publication) and data on the variable of interest (predictive factors, comorbidities, and factors related to the donor). For this purpose, we created a tool built on the evaluation table proposed by Melnyk and Fineout-Overholt.<sup>11</sup>

Figure 1 describes the steps taken in the process of inclusion and exclusion of the studies. The authors used a unique nomenclature to identify the research designs included in this review.

To evaluate the methodologic quality and the risk of bias in the included articles, we used the Newcastle-Ottawa Scale. This scale is recommended by the Cochrane Collaboration as a tool for methodologic quality assessment in observational studies.<sup>12,13</sup> This



**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow-chart summarizing the search strategy using the Medical Literature Analysis and Retrieval System Online (Medline), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin American and Caribbean Health Sciences (LILACS), Scopus, and Web of Science.

instrument evaluates 3 areas, namely: selection of study groups, comparability of groups, and ascertainment of exposure or outcome. The articles are scored using stars, from 0–9, with 9 stars being the best score.<sup>12</sup>

## RESULTS

The final sample consisted of 9 articles published between 1999 and 2014, 33.3% of them published during 2009. Regarding the country in which the studies were carried out, 66.6% were produced in the United States,<sup>14–19</sup> 16.7% were conducted in Canada,<sup>20</sup> and 16.7% were conducted in Spain.<sup>21,22</sup> All of them were conducted by medical sciences professionals and published in English.

Regarding the definition of SSI, 3 studies (44.4%) used the Centers for Disease Control and Prevention concept as published in 1992,<sup>14,17,18,21</sup> 3 studies (33.3%) used the Centers for Disease Control and Prevention definition published in 1999,<sup>15,16,22</sup> and 2 studies did not cite which SSI definition was used.<sup>19,20</sup>

When analyzing the variable of interest of the IR—the risk factors for the development of SSI—it was found that the analyzed studies aimed to identify the risk factors for the development of SSI and its association with graft loss and death<sup>14,15,18,19</sup>; hyperglycemia during the intraoperative period, obesity, performing antibiotic prophylaxis,<sup>16,20,22</sup> and mortality of subjects affected by SSI.<sup>17</sup>

Regarding the level of evidence,<sup>11</sup> the 9 analyzed articles were classified as evidence level 2; that is, cohort studies. As for the

**Table 1**  
Presentation of synthesis of articles included in an integrative literature review addressing surgical site infections (SSI) and liver transplants (LTs), Sao Paulo, Brazil, 2016

Study	Design	n (SSI rate %)	Level of the evidence	Objective	Risk factors found
Sawyer et al, 1999 <sup>19</sup>	Retrospective cohort	302 (20)	2	To evaluate the effects of obesity in the outcomes of transplant and retransplant liver recipients	Preoperative body mass index >35 s
Hollenbeak et al, 2001 <sup>17</sup>	Retrospective cohort	777 (37.8)	2	To identify risk factors, estimate the effect of surgical risk infections, and mortality after 1 y of performing LT	Preoperative: - Low levels of serum albumin; Intraoperative: - No. of units of concentrate red blood cells received; - Surgical time >60 min; - Ascites fluid output >1,000 mL
Asensio et al, 2008 <sup>21</sup>	Retrospective cohort	1222 (10.4)	2	Define the incidence, timing, site, and risk factors, in particular antibiotic prophylaxis for SSI	Intra- and postoperative: - No. of units of concentrate red blood cells received; Low-volume hospitals: - Hospitals that perform fewer than 50 liver transplants/y
García-Prado et al, 2008 <sup>22</sup>	Prospective cohort	167 (35.5)	2	To research epidemiology, risk factors, and prognosis among LT and retransplant recipients with SSI	Preoperative: Antibiotic therapy 3 mo before LT
Hellinger et al, 2009 <sup>15</sup>	Retrospective cohort	370 (18)	2	To identify risk factors associated with SSI and analyze the association of such infections with graft loss or death within 1 y after LT	Intraoperative: - Surgical time >60 min Donor/recipient - Ratio of donor liver mass to recipient body mass < 0.01
Park et al, 2009 <sup>16</sup>	Retrospective cohort	680 (11.2)	2	Aimed to define if intraoperative hyperglycemia was associated to SSI after LT	Preoperative: - Model for End-Stage Liver Disease score > 35; - Mechanical ventilation used in the same day of transplantation; Intra- and postoperative: - No. of units of concentrate red blood cells received; - Hyperglycemia > 200 mg/dL; - Use of vasopressor drugs
Schaeffer et al, 2009 <sup>20</sup>	Retrospective cohort	167 (9.6)	2	Define the outputs in specific subgroups of LT recipients and evaluate morbidity and mortality in obese patients undergoing LT	Preoperative: Body mass index >35
Hellinger et al, 2011 <sup>14</sup>	Retrospective cohort	1036 (16)	2	To identify modifiable risk factors for SSI	Preoperative: - Model for End-Stage Liver Disease score > 35; Intraoperative: - No. of units of concentrate red blood cells received >5 units; - Surgical time > 60 min; Donor/recipient: - Sex incompatibility; - Age difference >10 y; - Ratio of donor liver mass to recipient body mass < 0.01
Shah et al, 2014 <sup>18</sup>	Retrospective cohort	152 (20.4)	2	To establish the incidence and risk factors of SSI among liver retransplant recipients	Risk factors for SSI after second LT were not readily apparent

research perspective, most of the investigations (88.8%) were retrospective.<sup>14–20</sup> Regarding assessment using the Newcastle-Ottawa Score, 4 studies (44.4%) got 7 stars,<sup>14,17,21,22</sup> whereas 11.2% got 6 stars,<sup>18</sup> and 22.2% got 5 stars,<sup>19,20</sup> showing from moderate to good methodologic quality, respectively. Investigations had lower performance on the items that assessed the comparability and representativeness of participants included in the cohorts.

The characteristics of the research included in this IR are described in Table 1.

With regard to the characterization of subjects, it was found that the average age ranged between 43 and 56 years, that most participants in all investigations were men,<sup>14–22</sup> and the average Model for End-Stage Liver Disease (MELD) score at transplantation varied from 16–25.<sup>14,15,18</sup> Hepatic cirrhosis caused by hepatitis C and alcoholic liver cirrhosis were the most common reasons for liver transplantation.<sup>14,15,18–22</sup> Related to the physical status immediately before carrying out the transplant, the American Society of Anesthesiologists (ASA) score quoted in 2 investigations was ASA IV,<sup>14,15,18</sup> representing subjects with severe organic life-threatening disorders.<sup>23</sup>

Risk factors for SSI were grouped into 4 categories related to the following periods: preoperative, intraoperative, donor/recipient mismatch, and the provider organization of health care.

Among risk factors related to the preoperative period, it was observed that MELD score > 35 was pointed out by 3 investigations, and in 2 of them<sup>14,16</sup> there was statistically significant difference when comparing the groups with and without SSI. Furthermore, a study<sup>14</sup> highlighted that MELD score > 35 almost doubles the chance of occurrence of SSI compared with participants whose MELD scores were lower (relative risk [RR], 1.81; 95% confidence interval [CI], 1.01–3.26;  $P = .047$ ). However, another study<sup>15</sup> showed no statistically significant difference for the same variable when comparing groups with and without SSI (RR, 1.00; 95% CI, 0.74–1.35;  $P = .99$ ).

A study observed that the use of mechanical ventilation on the day of the transplant increased by approximately three times the risk of developing SSI (RR 3.01; CI95% 1.70–5.33;  $P < .001$ ).<sup>16</sup> However, another research pointed to the absence of statistical significance (RR 1.44; CI95% 0.74–2.82;  $P = .29$ ).<sup>14</sup>

Malnutrition, as expressed by low levels of serum albumin, was addressed in a study showing an increase in the chances of occurrence of SSI by approximately 30%.<sup>17</sup> At the same time, body mass index > 35 was pointed out as an SSI predictor in 2 studies.<sup>19,20</sup> Despite this, 3 other articles did not show statistically significant differences between this variable and the occurrence of SSI.<sup>14,15,17</sup>

Moreover, the use of antimicrobial drugs during the 3 months before the liver transplantation procedure was associated with a

**Table 2**

Presentation of synthesis of risk factors for surgical site infection (SSI) by patients undergoing liver transplantation (LT) as shown in 6 studies, Sao Paulo, Brazil, 2016

Category	Risk factors	Sawyer et al, 1999 <sup>19</sup>	Hollenbeak et al, 2001 <sup>17</sup>	Asensio et al, 2008 <sup>21</sup>	García-Prado et al, 2008 <sup>22</sup>	Hellinger et al, 2009 <sup>15</sup>	Park et al, 2009 <sup>16</sup>	Schaeffer et al, 2009 <sup>20</sup>	Hellinger et al, 2011 <sup>14</sup>	Shah et al, 2014 <sup>18</sup>
Preoperative period	Antibiotic therapy during the 3 mo before liver transplantation	–	–	–	S	–	–	–	–	–
	Model for End-Stage Liver Disease score > 35	S	–	–	–	NS	S	–	S	–
	Body mass index > 35	–	NS	–	–	NS	–	S	NS	–
	Low levels of serum albumin (g/dL)	–	S	–	–	–	–	–	–	–
	Ventilated support on day of transplant	–	–	–	–	NS	S	–	–	–
Intraoperative period	Transfusion of packed red blood cells	–	S	S	–	NS	S	–	S	–
	Operative time (60-min increase)	–	S	–	–	S	NS	NS	S	NS
	Hyperglycemia >200 mg/dL	–	–	–	–	–	S	–	–	–
	Vasopressor	–	–	–	–	–	S	–	–	–
	Ascites (>1 L)	–	–	–	–	–	NS	–	–	–
Donor/recipient	Donor's age (10-y increase)	–	–	–	–	–	–	–	S	–
	Recipient–donor sex incompatibility	–	–	–	–	NS	–	–	S	–
	Ratio of donor liver mass to recipient body mass < 0.01	–	–	–	–	S	–	–	S	NS
Administrative	Fewer than 50 liver transplant procedures in the hospital per year	–	–	S	–	–	–	–	–	–

S, significant risk factor; NS, nonsignificant risk factor; –, risk factor not investigated.

2-fold increase in the chance of experiencing SSI (odds ratio, 2.02; 95% CI, 1.00–4.07;  $P = .049$ ).<sup>22</sup>

Analyzing the intraoperative period, it was found that 5 research reports addressed the surgery timing, showing an average procedure duration range between 241 and 414 minutes.<sup>14–17,21</sup> The results of 3 investigations suggest that every 60 minutes spent in surgery increases the risk of SSI between 14% and 19%. However, 2 other studies showed no statistically significant correlation between the duration of surgery and the occurrence of SSI.<sup>16,17,20</sup> The massive transfusion of concentrated red blood cell units was considered a predictor in 3 investigations, increasing approximately twice the chances of occurrence of SSI (RR, 1.9; 95% CI, 1.2–3.1;  $P = .004$ ). However, 2 research reports found no association between this variable and the development of SSI.<sup>14,15</sup>

An investigation showed that severe hyperglycemia (>200 mg/dL) increases the risk of SSI approximately by 2 and the use of vasopressor agents during surgery increases the risk of SSI more than 2 times, with an RR of 2.25 (95% CI, 1.26–4.03) and 3.14 (95% CI, 1.65–5.95), respectively.<sup>16</sup>

The volume of intraoperative ascites fluid output >1 L was addressed by 2 articles.<sup>16,17</sup> Patients with output values of ascites >1 L had an increased chance of developing SSI by 43% (RR, 1.43; 95% CI, 1.02–2.0;  $P = .037$ ).<sup>17</sup> Regarding donor and receiver mismatch, it was found that the incompatibility of sex was studied by 2 articles,<sup>14,15</sup> but only 1 showed an association (RR, 1.42; 95% CI, 1.05–1.93;  $P = .02$ ).<sup>14</sup> Age difference between donor and recipient >10 years appears to contribute to an increase by 10% of the risk for SSI and was singled out by an investigation,<sup>14</sup> reporting an RR of 1.10 (95% CI, 1.01–1.20;  $P = .02$ ). The ratio of donor liver mass to recipient body mass < 0.01 contributed to increased risk of being affected by SSI by approximately 2.5 times.<sup>14,15</sup>

As for the organization providing health care, a study pointed out that among liver transplant recipients undergoing the procedure in centers that perform fewer than 50 transplants a year, there is an increase in the risk of SSI when compared with patients undergoing transplant in centers performing more than 50 procedures annually (RR, 1.7; 95% CI, 1.2–2.4;  $P = .002$ ).<sup>21</sup>

Most studies used the 30-day period of observation for detecting SSI<sup>14–16,18,21,22</sup> and the observed number of subjects varied between 167<sup>20</sup> and 1,222<sup>21</sup> from the 4,873 participants analyzed in this review.

Regarding SSI, the rate ranged from 9.6%<sup>20</sup>–35.5%.<sup>22</sup> It is noteworthy that 1 specific investigation traced the SSI diagnosis for 1 year, obtaining a value of 37.6%.<sup>17</sup> Among the patients with SSI, the

deeper form was the most frequent.<sup>14,15,21</sup> It is noteworthy that there were no statistically significant differences among the SSI incidence rates among patients undergoing primary liver transplant and retransplant.<sup>14–22</sup>

Regarding the microorganisms isolated from the surgical site, the most frequent were: *Escherichia coli*, *Acinetobacter baumannii*, *Enterococcus*, *Staphylococcus*, and methicillin-resistant *Staphylococcus aureus*.<sup>14,15,17,18,21,22</sup>

Therefore, the risk factors describe patients as showing signs of worsening of the disease that led to transplantation (MELD score),<sup>14,16</sup> exhibiting low serum albumin,<sup>17</sup> being obese (body mass index > 35),<sup>19,20</sup> and needing mechanical ventilation before transplantation.<sup>16</sup> As contributing factors we found extended surgical time,<sup>14,15,17</sup> the need for transfusion of a considerable volume of red blood cells,<sup>14,16,17,21</sup> hyperglycemia >200 mg/dL, net ascites output >1 L, and use of vasopressors during the perioperative period.<sup>16</sup> They also call attention to disagreements between the donor and recipient such as sex mismatch<sup>14</sup>; differences in age of more than 10 years<sup>14</sup>; and ratio of donor liver mass to recipient body mass < 0.01, which translates into small-for-size grafts.<sup>14,15</sup> Regarding the institution providing the procedure, it can be inferred that those patients undergoing transplantation in centers performing fewer than 50 liver transplants per year are exposed to greater chance of developing SSI.<sup>21</sup>

To prepare an overview of the risk factors addressed by the studies in the sample, a summary table has been prepared that includes the risk factors according to statistical significance (Table 2).

## DISCUSSION

The results of our scientific literature review point to 4 groups of risk factors related to the preoperative and intraoperative periods, to mismatches between donor and recipient, and related to the health care facility. We did not identify additional risk factors among liver retransplant patients, probably due to the similarities between the surgical and clinical variables of those patients undergoing retransplant in the set of studies included in the present IR.<sup>18,19,22</sup>

The studies analyzed suggest the following as risk factors for SSI among liver transplant recipients: worsening of the disease causing the indication of transplant (MELD score),<sup>14,16</sup> antibiotic therapy during the 3 months before liver transplantation,<sup>22</sup> low levels of serum albumin,<sup>17</sup> obesity,<sup>19,20</sup> mechanical ventilation previous to transplantation,<sup>16</sup> extended surgical time,<sup>14,15,17</sup> high volumes of blood



transfusion,<sup>14,16,17,21</sup> glycemic levels >200 mg/dL, high volume of ascites output, and use of vasopressors during the intraoperative period.<sup>16</sup>

In addition to these, the review highlighted recipient and donor sex mismatch,<sup>14</sup> differences in age of more than 10 years,<sup>14</sup> and ratio of donor liver mass to recipient body mass < 0.01<sup>14,15</sup> as well as a low volume of procedures performed by the hospital.<sup>21</sup>

Well-known predictors of SSI are the presence of comorbidities with classification ASA III or higher, obesity, smoking, malnutrition with low albumin levels, use of immunosuppressive drugs, diabetes mellitus with glycemic peak >200 mg/dL during the perioperative period, and the complexity of the procedure involving an extensive surgical procedure<sup>24,25</sup> as well as prolonged hospital stay, colonization by *S aureus*, and transfusion of blood products during surgery.<sup>24</sup>

Thus, only a few of the risk factors highlighted by this review are present in those guidelines.<sup>25,26</sup> Therefore, this review shows that due to the specifics of the liver transplant, other predisposing factors arise in this category of patients.

During the preoperative period, MELD score > 35 presents itself as a risk factor.<sup>14,16</sup> Despite these results, there is no consensus in the literature regarding MELD scores that are associated with high risk of SSI; however, it seems to be agreed that values higher than 20 points indicate risk.<sup>27,28</sup> Thus, the higher the MELD score, the greater the deleterious effects of liver disease, so it appears that patients with higher MELD scores are subject to more hospitalizations and invasive procedures, followed by the use of antibiotic agents that contribute to colonization by microorganisms before performing a transplant.<sup>22</sup>

Similarly, it was observed that the use of mechanical ventilation before transplantation acted as a risk factor,<sup>16</sup> increasing risk by about 3 times compared with patients unexposed to mechanical ventilation. Still, in the research carried out by Hellinger et al<sup>15</sup> and Hellinger et al,<sup>14</sup> this variable did not appear to be significant.

It can be inferred that patients listed by Park et al<sup>16</sup> had respiratory failure due to more severe liver disease (MELD score = 32.65) among those who developed SSI, whereas a MELD score of 28.16 was found among those who did not develop an SSI.

In this sense, a multicenter study<sup>29</sup> evaluating whether hepatic dysfunction was associated with mortality among 805 patients who developed acute respiratory failure found that liver dysfunction during the first 48 hours of development of respiratory failure is associated with higher mortality rates.

As for the intraoperative period, the risk factors identified in this IR were extended surgical time, high-volume concentrates of transfused red blood cells, hyperglycemia, and use of vasopressors. Handling these factors becomes a real challenge for medical staff. Given the complexity of the surgical procedure and the severity of the patients who undergo them, these risk factors are expressed in the majority of transplants performed, and it is also noted that they are widely recognized as predictors of SSI.<sup>30</sup>

A new risk factor for SSI that appears during the intraoperative period is the volume of ascites output. Ascites are the most common complication of cirrhosis compared with jaundice, gastrointestinal bleeding, and even hepatic encephalopathy. Approximately (50%) of patients with chronic liver disease develop ascites.<sup>31</sup> Research that included 4,170 patients undergoing hepatectomy noted that those with hematocrit <35% presented a higher frequency of ascites, higher morbidity rate during the first 30 days after surgery, and more hospital readmissions.<sup>32</sup> Refractory ascites are related to events such as spontaneous bacterial peritonitis; abdominal hernia; hepatic hydrothorax; malnutrition; impaired renal function, which may lead to hepatorenal syndrome; and chronic ascites, which negatively influence quality of life and survival of 50% of patients with chronic liver disease in 2 years.<sup>33,34</sup> Despite these facts, there are still few studies that correlate the development of ascites to SSIs.

Another aspect that deserve to be investigated in depth are the differences between donor and recipient, highlighting the incompatibility of sex, age differences, and ratio of donor liver mass to body mass of recipient.

A study<sup>14</sup> suggested that the association between sex incompatibility between donor and recipient increases by approximately 42% the chance of SSI development.

This research is based on a retrospective cohort study<sup>35</sup> that followed 2,144 adults undergoing liver transplantation, and demonstrated that among male donors and female recipients, infection was the main complication, accounting for 17.2%; and from female donors and male recipients, SSI is the second leading cause of complications at 14.9%.

At the same time, intensification of the deleterious effects of high volume transfusion of concentrated red blood cell units and prolonged cold ischemia of the graft among female liver transplant recipients whose donor was a man has been observed. Thus, it is suggested that the incompatibility of sex between donors and recipients may aggravate the influence of these risk factors for SSI.<sup>36</sup>

Previous research has found that differences in age >10 years between liver transplant donors and recipients increased up to 10% the chance of being affected by SSI.<sup>14</sup> In addition, a study of 221 adults undergoing liver transplantation identified a shorter survival period among subjects who received an organ from donors whose ages were unpaired. Also there was greater frequency of graft loss in recipients of donors aged ≥60 years.<sup>37</sup> However, there is a paucity of research in the scientific literature that has addressed the effects of mismatch between the ages of donors and recipients on SSI.

Another SSI predictor indicated by 2 studies<sup>14,15</sup> is the ratio of donor liver mass to recipient body mass < 0.01. Small-for-size grafts increased the risk of SSI development about 2.5 times.

The effects of correspondence between the weight of the liver and the donor's weight were widely discussed in the arena of living donor liver transplant; the so-called small-for-size syndrome.<sup>38,39</sup> However, it seems that the effects of small-for-size syndrome are not widely discussed regarding deceased donors, especially when related to SSI.

Centers with low numbers of monthly procedures<sup>21,40,41</sup> constitute another aspect that can contribute as a risk factor for SSI and survival. In this sense, research that involved 5,130 patients undergoing liver transplantation in 63 hospitals in the United States during 2009 and 2010 found that patients assisted in centers that perform large volumes of this procedure (ie, >70 transplants/year) had lower mortality rates, lower average of length of stay in the intensive care unit, and shorter length of stay during the postoperative period, with a consequent reduction in direct costs compared with participants in transplant centers performing low volumes (ie, <47 transplants/year) for liver transplantation.<sup>40</sup>

A German study<sup>38</sup> showed that the survival rate during the first hours, during the first year, and after 3 years of transplantation is higher among patients assisted in large centers when compared with the results of small centers. However, these studies did not show the SSI rates in a way that could be compared.<sup>40,41</sup>

Despite the extended time of cold ischemia of the graft among patients undergoing transplantation and simultaneous kidney and liver transplantation<sup>27</sup> and accidental hypothermia during surgery<sup>41</sup> being identified as risk factors for SSI, no evidence was found pointing to transplant of the liver, so the risk factors listed in this IR plus the cold ischemia time and hypothermia during surgery should be subjects for future primary research.

Another aspect to be highlighted was the small number of publications available in the literature on this topic, in addition to the heterogeneity in the presentation of results that made it difficult to synthesize the data. Also, multiple investigations were conducted retrospectively, calling for the need to consider possible gaps

in the medical records of patients regarding SSIs, which could contribute to potential underreporting of the phenomenon.<sup>11,42</sup>

Finally, the IR is a first step in allowing care providers who deal with these patients to get familiar with information relevant to clinical practice and to let emerge new investigations conducive to optimizing the delivery of perioperative care.<sup>42</sup>

## CONCLUSIONS

In addition to traditional risk factors considered and mentioned by the literature as predisposing factors for SSI in any specialty, a few stood out as risk factors for SSI in liver transplant recipients. These factors can be categorized as those related to the preoperative period such as MELD score > 35 and using mechanical ventilation before transplantation; risk factors related to the intraoperative period such as net ascites output >1 L; factors related to the interrelationship between donor and recipient, such as differences in age >10 years, sex incompatibility and ratio of donor liver mass to recipient body mass < 0.01; and those related to centers performing fewer than 50 transplants per year.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ajic.2017.05.021>.

## References

- World Health Organization (WHO). Global guidelines for the prevention of surgical site infection. Geneva: World Health Organization; 2016. p. 186.
- Candel FJ, Grima E, Matesanz M, Cervera C, Soto G, Almela M, et al. Bacteremia and septic shock after solid-organ transplantation. *Transplant Proc* 2005;37:4097–9.
- Rubin RH. The direct and indirect effects of infection in liver transplantation: pathogenesis, impact, and clinical management. *Curr Clin Top Infect Dis* 2002;22:125–54.
- Xu L, Xu MQ, Yan LN, Li B, Wen TF, Wang WT. Causes of mortality after liver transplantation: a single center experience in mainland China. *Hepatogastroenterology* 2012;59:481–4.
- Sanclemente G, Moreno A, Navasa M, Lozano F, Cervera C. Genetic variants of innate immune receptors and infections after liver transplantation. *World J Gastroenterol* 2014;28:1116–30.
- Fishman JA. Infections in immunocompromised hosts and organ transplant recipients: essentials. *Liver Transpl* 2011;17(Suppl 3):S34–7.
- Green M. Introduction: infections in solid organ transplantation. *Am J Transplant* 2013;13(Suppl 4):3–8.
- Avkan-Oguz V, Ozkardesler S, Unek T, Ozbilgin M, Akan M, Firuzan E, et al. Risk factors for early bacterial infections in liver transplantation. *Transplant Proc* 2013;45:993–7.
- Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate Point-prevalence survey of health-care associated infections. *N Engl J Med* 2014;370:1198–208.
- Centre for Reviews and Dissemination—University of York. CRD's guidance for undertaking reviews in health care. New York: York Publishing Services Ltd; 2009.
- Melnik BM, Finout-Overholt E. Evidence-based practice in nursing & healthcare. 3rd ed. Philadelphia (PA): Wolters Kluwer; 2015.
- Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014.
- Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. 2011. Version 5.1.0 [updated March 2011].
- Hellinger WC, Heckman MG, Crook JE, Taner CB, Willingham DL, Diehl NN, et al. Association of surgeon with surgical site infection after liver transplantation. *Am J Transplant* 2011;11:1877–84.
- Hellinger WC, Crook JE, Heckman MG, Diehl NN, Shalev JA, Zubair AC, et al. Surgical site infection after liver transplantation: risk factors and association with graft loss or death. *Transplantation* 2009;87:1387–93.
- Park C, Hsu C, Neelakanta G, Nourmand H, Braunfeld M, Wray C, et al. Severe intraoperative hyperglycemia is independently associated with surgical site infection after liver transplantation. *Transplantation* 2009;87:1031–6.
- Hollenbeak CS, Alfrey EJ, Souba WW. The effect of surgical site infections on outcomes and resource utilization after liver transplantation. *Surgery* 2001;130:388–95.
- Shah H, Hellinger WC, Heckman MG, Diehl N, Shalev JA, Willingham DL, et al. Surgical site infections after liver retransplantation: incidence and risk factors. *Liver Transpl* 2014;20:930–6.
- Sawyer RG, Pelletier SJ, Pruett TL. Increased early morbidity and mortality with acceptable long-term function in severely obese patients undergoing liver transplantation. *Clin Transplant* 1999;13:126–30.
- Schaeffer DF, Yoshida EM, Buczkowski AK, Chung SW, Steinbrecher UP, Erb SE, et al. Surgical morbidity in severely obese liver transplant recipients—a single Canadian Centre Experience. *Ann Hepatol* 2009;8:38–40.
- Asensio A, Ramos A, Cuervas-Mons V, Cordero E, Sanchez-Turrión V, Blanes M, et al. Effect of antibiotic prophylaxis on the risk of surgical site infection in orthotopic liver transplant. *Liver Transpl* 2008;14:799–805.
- García-Prado ME, Matia EC, Ciuro FP, Diez-Canedo JS, Sousa Martin JM, Porras Lopez FM, et al. Surgical site infection in liver transplant recipients: impact of the type of perioperative prophylaxis. *Transplantation* 2008;85:1849–54.
- Dripps RD. New classification of physical status. *Anesthesiology* 1963;24:111.
- Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999;20:250–78.
- Leaper D, Burman-Roy S, Palanca A, Cullen K, Worster D, Gautam-Aitken E, et al. Prevention and treatment of surgical site infection: summary of NICE guidance. *BMJ* 2008;337:a1924.
- Freire MP, Soares ICO, Bonazzi PR, Guimarães T, Ramos Figueira ER, Bacchella T, et al. Surgical site infections in liver transplant recipients in the model for end-stage liver disease era: an analysis of the epidemiology, risk factors, and outcomes. *Liver Transpl* 2013;19:1011–9.
- Prieto J, Medina JC, Lopez M, Rando K, Iglesias C, Harguindeguy M, et al. Impact of a multimodal approach in prevention of surgical site infection in hepatic transplant recipients. *Transplant Proc* 2016;48:658–64.
- Dizier S, Forel JM, Ayzac L, Richard JC, Hraiech S, Lehingue S, et al. Early hepatic dysfunction is associated with a worse outcome in patients presenting with acute respiratory distress syndrome: a post-hoc analysis of the ACURASYS and PROSEVA studies. *PLoS ONE* 2015;10:e0144278.
- Anderson DJ, Podgorny K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;35:605–27.
- Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987;7:122–8.
- Tee MC, Shubert CR, Ubl DS, Habermann EB, Nagorney DM, Que FG. Preoperative anemia is associated with increased use of hospital resources in patients undergoing elective hepatectomy. *Surgery* 2015;158:1027–36.
- Singhal S, Baikati KK, Jabbour II, Anand S. Management of refractory ascites. *Am J Ther* 2012;19:121–32.
- Garcia N, Sanyal AJ. Ascites. *Curr Treat Options Gastroenterol* 2001;4:527–37.
- Schoening W, Helbig M, Buescher N, Andreou A, Bahra M, Schmitz V, et al. Gender matches in liver transplant allocation: matched and mismatched male-female donor-recipient combinations; long-term follow-up of more than 2000 patients at a single center. *Exp Clin Transplant* 2016;14:184–90.
- Grat M, Lewandowski Z, Patkowski W, Wronka K, Grat K, Krasnodebski M, et al. Relevance of male-to-female sex mismatch in liver transplantation for primary biliary cirrhosis. *Ann Transplant* 2015;20:116–23.
- Pagano D, Grosso G, Vizzini G, Spada M, Cintonaro D, Malaguarnera M, et al. Recipient-donor age matching in liver transplantation: a single-center experience. *Transplant Proc* 2013;45:2700–6.
- Kinaci E, Kayaalp C. Portosystemic shunts for “too small-for-size syndrome” after liver transplantation: a systematic review. *World J Surg* 2016;40:1932–40.
- Manas D, Burnapp L, Andrews PA. Summary of the British Transplantation Society UK guidelines for living donor liver transplantation. *Transplantation* 2016;100:1184–90.
- Macomber CW, Shaw JJ, Santry H, Saidi RF, Jabbour N, Tseng JF, et al. Centre volume and resource consumption in liver transplantation. *HPB (Oxford)* 2012;14:554–9.
- Nijboer A, Ulrich F, Bechstein WO, Schnitzbauer AA. Volume and outcome relation in German liver transplant centers: what lessons can be learned? *Transplant Res* 2014;3:3–5.
- John M, Ford J, Harper M. Peri-operative warming devices: performance and clinical application. *Anaesthesia* 2014;69:623–38.
- Melnik BM, Gallagher-Ford L, Long LE, Fineout-Overholt E. The establishment of evidence-based practice competencies for practicing registered nurses and advanced practice nurses in real-world clinical settings: proficiencies to improve healthcare quality, reliability, patient outcomes, and costs. *Worldviews Evid Based Nurs* 2014;11:5–15.