

Prevalence of MRSA Bacteremia in Liver Transplant Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Backgrounds: Infection is one of the major threats to liver transplant patients and significantly affects associated mortality and morbidity. Serious infections are likely to occur a few months after transplantation, and most of them are bacterial. The aim of this study was to evaluate the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in liver transplant patients.

Materials & Methods: In this systematic review and meta-analysis, Preferred Reporting Items for systematic reviews and meta-analysis guidelines were used. International databases including PubMed, Scopus, Web of Sciences, Embase, and Cochrane were searched by related MeSH terms and keywords for studies published until July 26, 2020. The current study was registered by a pre-defined protocol in PROSPRO.

Findings: After a comprehensive literature search, 11 articles were selected for inclusion in the analysis. The prevalence of MRSA in liver transplant patients was 75% (95% CI: 58% - 89%); however, an evident heterogeneity was observed between the studies ($I^2=87.84\%$, $p<.001$).

Conclusion: In conclusion, this study results demonstrate that the prevalence of post-transplant MRSA colonization bacteremia is high among liver transplant patients. This should be considered seriously, and efforts should be made to prevent mortality in this group of patients.

Keywords: MRSA, Bacteremia, Liver transplant, Meta-analysis

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Introduction

Infection is one of the major threats to liver transplant patients and significantly affects associated mortality and morbidity. Liver transplant patients are susceptible to microbial colonization and infection due to complications of surgical procedures and frequent use of catheters [1]. Serious infections are likely to occur a few months after transplantation, and most of them are bacterial. Gram-positive bacteria are more prevalent than Gram-negative bacteria, including *Staphylococcus aureus* and *Enterococcus* species. *S. aureus* isolates have a high potential for pathogenicity since these strains harbor various virulence factors [2-4]. Various types of infections are observed after liver transplantation, but bacteremia, abdominal infections (especially cholangitis), and pneumonia cases are predominant.

Bacteremia or bloodstream infection is more common in patients undergoing liver transplantation than in patients undergoing other solid organ surgery [5]. In a previous study, of all pathogens isolated from liver transplant recipients, 26% were found to be *S. aureus*, and the morbidity rate related to *S. aureus* bacteremia in these patients ranged from 0.6 to 29% [6]. Extensive exposure to broad-spectrum antibiotics and the subsequent increase in antibiotic resistance is a fundamental risk factor for transplant patients and an additional concern for clinicians. This event occurs due to routine prophylaxis with quinolones against spontaneous bacterial peritonitis in cirrhotic patients [7, 8]. Methicillin-resistant *S. aureus* (MRSA) bacteremia accounts for 42–69% of all MRSA infections developed after liver transplantation, and the mortality

Table 1) Characteristics of the studies included in the analysis

Study	<i>S. aureus</i>	MRSA	Country	Sample Size (Patients)	Age	Sex	Study Period
Singh et al. (2000) [11]	26	26	USA	165	49		1990-1998
Bedini et al. (2007) [12]	5	5	Italy	205	12-70 (median=52)	145 m/ 60 f	2000-2006
Bert et al. (2010) [13]	56	28	France	704	Mean = 48		1997-2007
Lida et al. (2010) [14]	19	9	Japan	181	Median = 55 (16-89)	90 m/ 91 f	2006-2009
Shi et al. (2010) [15]	13	13	China	475	Mean=43	424 m/ 51 f	2003-2006
Lee et al. (2011) [16]	21	8	China	392			
Nafady et al. (2011) [17]	124	93	Egypt	345		151 m/ 194 f	1998-2009
Kim et al. (2013) [18]	14	13	Korea	222	Mean=49	168 m/ 54 f	2005-2011
Bordo et al. (2014) [19]	19	5	Spain	318		224 m/ 94 f	2007-2013
Jiandang Zhou (2015) [20]	20	16	China	275	42.7±14.5	19 m/ 1 f	
Hassan et al. (2017) [21]	12	9	Egypt	337	Mean=57	243 m/ 94 f	January 2016- June 2016

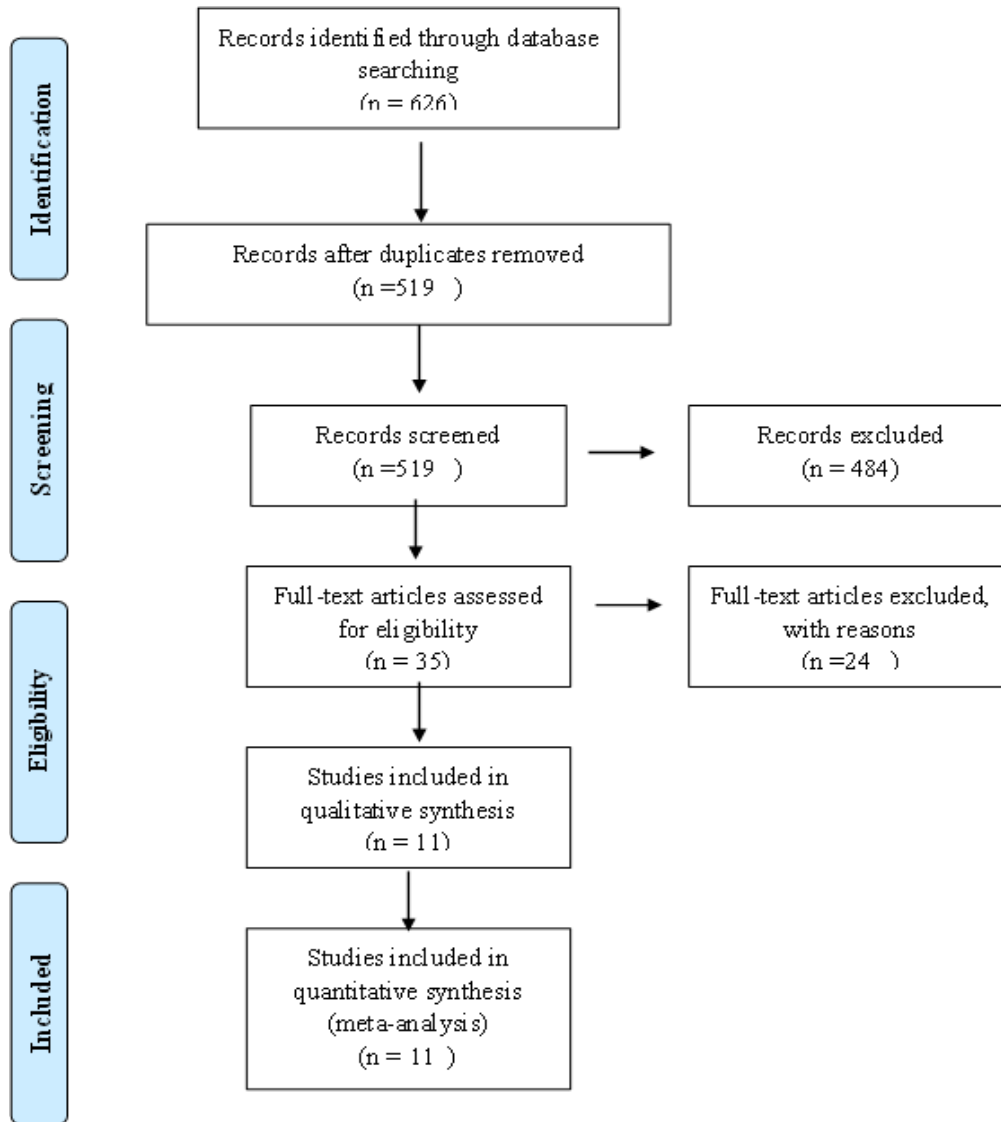


Figure 1) PRISMA flow chart of the systematic literature search review and article

rate is estimated to be 0.4–27.4% [9]. In recent years, the increasing incidence of extensive drug resistance has become a major public health challenge, especially for immunosuppressed patients.

Objectives: The current study aimed to evaluate the prevalence of MRSA bacteremia in liver transplant patients.

Materials and Methods

Search Strategy: Preferred Reporting Items for systematic reviews and meta-analysis (PRISMA) guidelines were used in the current systematic review and meta-analysis. International databases including PubMed,

Scopus, Web of Sciences, Embase, and Cochrane were searched for studies published until July 26, 2020. Search terms included “bloodstream infection”, “bacteremia”, “septicemia”, “infection”, “microbiology”, “*Staphylococcus aureus*”, “MRSA”, and “liver transplantation”. For further evaluations, reference lists of proper studies were also searched and reviewed. The current study was registered by a pre-defined protocol in PROSPERO (CRD42020153535).

Articles with clear objectives and methodology and any relevant studies, which reported the prevalence of MRSA isolates in liver transplant patients and the number

Table 2) Quality assessments of the studies included in the analysis

Study	Selection	Comparability	Exposure/Outcome	Total Score
Singh et al. (2000) ^[11]	*****	**	***	*****
Bedini et al. (2007) ^[12]	*****	*	***	*****
Bert et al. (2010) ^[13]	*****	**	***	*****
Shi et al. (2010) ^[15]	*****	*	***	*****
Lida et al. (2010) ^[14]	*****	**	***	*****
Nafady et al. (2011) ^[17]	*****	*	**	*****
Lee et al. (2011) ^[16]	****	**	***	*****
Kim et al. (2013) ^[18]	*****	**	***	*****
Bordo, et al. (2014) ^[19]	*****	**	***	*****
Jiandang Zhou (2015) ^[20]	****	**	***	*****
Hassan et al. (2017) ^[21]	*****	*	**	*****

of patients with MRSA, were considered as eligible for inclusion in the analysis. Case reports, congress abstracts, and reviewed articles were excluded. The literature search was restricted to articles published in English.

Data extraction and quality assessments:

Two authors (A.E and F.J) performed the screening and evaluation of articles. All the included articles were qualitatively assessed using the Newcastle-Ottawa Scale^[10]. The results of quality assessments and the characteristics of the included studies are provided in Table 2 and 1, respectively. The following information was extracted from the included original studies: first author name, age, sex, year, country, and study duration.

Statistical analysis: The inverse method was used to pool MRSA prevalence with a 95% confidence interval. Random or fixed model was used based on the possibility of

heterogeneity. The random effect model was used in case of considerable heterogeneity ($I^2 > 75\%$). Egger weighted regression method was used to evaluate the publication bias. Data analysis was performed by Stata13 statistical software package.

Findings

In a comprehensive search, a total of 626 studies were collected. After screening, 107 cases were excluded due to duplication, and 484 cases were excluded based on the evaluation of their titles and abstracts. After full-text evaluation, 11 articles were finally selected for inclusion in the analysis. Overall, 3619 patients with liver transplants were included in the reviewed studies. Among them 1464 were male, and the rest were female (Figure 1).

As presented in Figure 2, the prevalence of

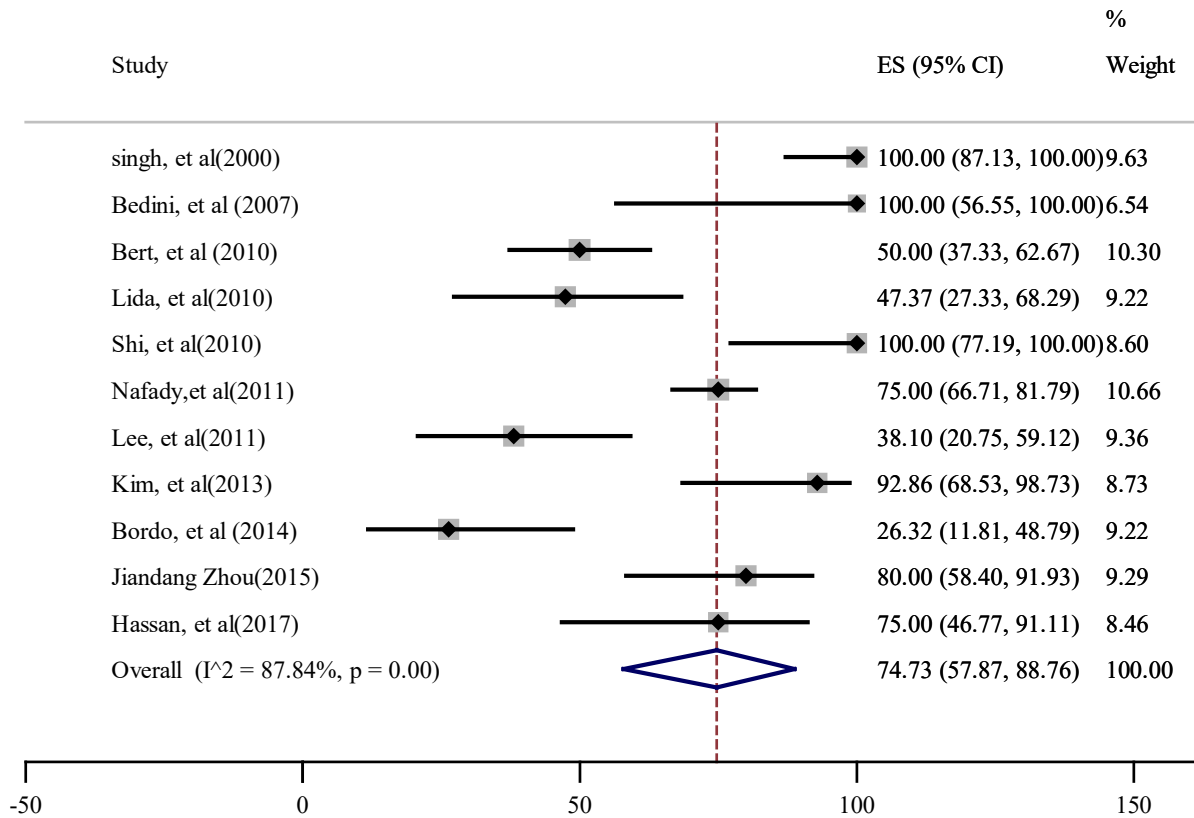


Figure 2) Forest plot of MRSA prevalence among liver transplant patients

MRSA in liver transplant patients was 74.73% (95% CI: 57.87% - 88.76%); however, an evident heterogeneity was observed between the studies based on Egger weighted regression ($I^2=87.84\%$, $p < .001$). Moreover, based on the funnel plot shown in Figure 3, no publication bias was observed.

Discussion

MRSA colonization is one of the serious threats to liver recipients. Based on various reports, prolonged hospitalization, postoperative bleeding at surgical sites, and the use of broad-spectrum antimicrobial agents are factors contributing to the development of drug resistance after liver transplantation. Furthermore, it has been found that Gram-positive bacteria are predominant among strains isolated within 30 days after surgery [13, 22, 23].

According to a recent analysis, the incidence of MRSA-induced bacteremia is high among patients with liver transplantation. Although this is an inevitable event, infection control measures could be effective in reducing colonization rates and thus mortality [24]. Catheter-related bacteremia due to MRSA would be prevented by accurate implementation of CDC management

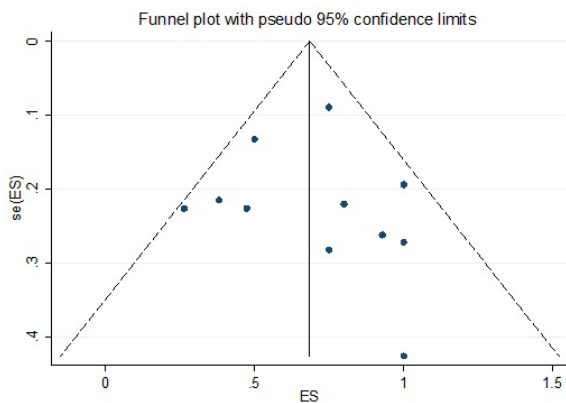


Figure 3) Funnel plot of publication bias evaluation

strategies [25]. Moreover, hygiene care and daily skin cleaning with chlorhexidine could control this type of bacteremia. To improve host reactivity, it is suggested to reduce the use of immunosuppressive drugs to prevent the onset of MRSA bacteremia in this group of patients [26]. Although a high heterogeneity was observed between the included studies, it could be attributed to the different geographical locations of the studies and the different criteria used for the inclusion of patients. Due to the small number of studies, subgroup analysis was not a good solution. Another effective infection control strategy that could reduce the incidence of *S. aureus* infection from 26 to 4% is mupirocin therapy, especially for nasal and rectal colonization that may occur before transplantation [27]. Moreover, in a meta-analysis, there was a relationship between mupirocin treatment and a reduction in preoperative MRSA nasal colonization and surgical infection rates [28]. However, Patereson et al. (2003) did not suggest the use of mupirocin for liver transplant patients since it had no effect on MRSA infection rates [29].

The choice of empirical antibiotic therapy for liver transplant patients is a major decision that could cause significant variations in the susceptibility pattern of MRSA. Recently, the standard treatment suggestion for MRSA is glycopeptide, while others have shown that no antibiotic is as effective against MRSA as vancomycin [30, 31]. According to the FDA, the two approved agents against MRSA are vancomycin and Da. Also, a review study recommended these two antibiotic agents as first-choice drugs for MRSA bacteremia. Moreover, in some case reports, telavancin has been suggested as a successful treatment for MRSA bacteremia [32, 33]. Besides antibiotic therapy, the implementation of infection control measures plays a critical role in reducing MRSA infection rates [27]. Preventing the infection transmission via

healthcare workers and performing hand hygiene procedures would be effective in managing MRSA colonization. Screening patients (transplant recipients) at the admission time in terms of MRSA carriage is another preventive measure. Improving surgical techniques to prevent postoperative bleeding is associated with eliminating bacteremia.

Considering the mortality and morbidity caused by MRSA in liver recipients, it is suggested that more clinical trials be conducted and more effective and antibiotic treatments be investigated.

This study has an inherent limitation. The majority of studies reported the number of patients with MRSA but not the number of isolates.

Conclusion

In conclusion, this study results demonstrate that the prevalence of post-transplant MRSA colonization bacteremia is high among liver transplant patients. This should be considered seriously, and efforts should be made to prevent mortality in this group of patients.

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Ethical permission: The protocol of this study was approved by the Research and Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.229) and pre-defined in PROSPERO (CRD42020153535).

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Authors Contribution: Conceptualization: AE ; formal analysis: FJ; methodology: FJ ; project administration: AE ; software: FJ; supervision: AE; writing of the original draft: AE; writing-review and editing: AR, NP.

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