



## Cross-sectional Study

# Association of blood isolate's multi antibiotic resistance-index on laboratory-confirmed bloodstream infection: A cross-sectional study

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## ARTICLE INFO

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## ABSTRACT

**Background:** A not optimal way of the insertion of the intravenous catheter can be one of the factors that cause bloodstream infection (BSI) that should be confirmed with blood culture, and if positive it is called Laboratory-Confirmed Bloodstream Infection (LCBI). One of the surveillance methods of nosocomial infection that is commonly used is the Multi Antibiotic Resistance (MAR)-Index. The aimed of study was association of MAR-index from blood isolates on LCBI category.

**Method:** This study used a cross-sectional study with a consecutive sampling method. Data collection for this study includes identification of micromaterial profile, antimicrobial test, MAR-Index, and LCBI category. The analysis used is the Mann Whitney test with  $p < 0.05$ .

**Result:** There were 43 isolates of LCBI 1, 26 isolates of LCBI 2, and none of the LCBI 3. Microorganisms in the LCBI category 1 were *Staphylococcus aureus* (53.4%), *Acinetobacter baumannii* (20.9%), *Escherichia coli* (9.3%), *Klebsiella pneumonia* (7.0%), *Pseudomonas aeruginosa* (4.7%), and *Enterococcus faecalis* (4.7%) with the MAR-Index ranged from 0.22 to 0.91. Microorganisms in the LCBI category 2 were *Staphylococcus haemolyticus* (69.3%), *Staphylococcus epidermidis* (19.3%), *Staphylococcus hominis* (3.8%), *Streptococcus viridans* (3.8%), and *Corynebacterium jeikeium* (3.8%) with the MAR-Index ranging between 0.11 and 0.79. There is no significant difference of MAR-index between LCBI 1 and 2 ( $p = 0.424$ ) and no association of MAR-index on LCBI ( $p = 0.571$ ).

**Conclusion:** Most LCBI type 1 is *Staphylococcus aureus* and LCBI type 2 is *Staphylococcus haemolyticus* which there is no significant association of MAR-index on LCBI.

## 1. Introduction

Bloodstream Infection (BSI) is one of the factors that increase morbidity and mortality rates [1]. Based on the latest study, BSI in 2015–2019 increased by 31% [2]. Various studies have reported that the main factor of increasing length of stay (LOS) and hospital expenses are hospital-acquired bloodstream infections (HA-BSIs) [3]. In developing countries, hospital-acquired infections (HAI) become more complex and harder to overcome because of the lack of resources and the health worker's low compliance of hand washing, so the incidence of BSI can be 5 times higher than international's standard [4]. Diagnose BSI, further examination of blood culture is needed to determine the causative agent of the infection and antibiotic sensitivity test of the organism is also needed. BSI that is confirmed by the culture is called Laboratory-Confirmed Bloodstream Infection (LCBI) which is then

classified into 3 categories based on age, clinical manifestations, and isolated microorganisms [5]. Multiple Antibiotic Resistance (MAR) Index is one of the indicators used to analyze antibiotic resistance that is easy, effective, fast, and doesn't need particular training or expensive equipment [6].

In Indonesia, data related to the MAR index is still very limited, only reports related to the bacterium *Pseudomonas aeruginosa* have been reported in 2020 [7]. In addition, there are still not many studies that describe the MAR index. Based on this description, we are interested in analyzing the association of MAR-Index from blood isolates on LCBI categories.

## 2. Method

The subjects of this study were venous blood samples of patients

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diagnosed with BSI [8,9]. Inclusion criteria were positive blood culture by Disease Control and Prevention (CDC) and National Healthcare Safety Network (NHSN) 2020 criteria including LCBI 1, LCBI 2, LCBI 3 [10]. Tip culture and secondary BSI were excluded. Participants who are willing to take part in the study must first fill out an informed consent form.

This study used a cross-sectional study with a consecutive sampling method. The population in this study was bacterial isolate's data from blood specimens between January 1 – December 31, 2019. Data collection for this study includes identification of micromaterial profile, antimicrobial test, MAR-Index, and LCBI category. This study report uses strengthening the reporting of cohort studies in surgery (STROCSS) 2019 Guideline [11]. This study received ethical approval based on the Declaration of Helsinki and obtained the registry of research at the Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Identification of the isolates and susceptibility analyses were initially carried out in the automated BD Phoenix™ system (Becton Dickinson, New Jersey, USA) which also performed the antimicrobial test. Then, the identified microorganism was a pathogen, it was categorized as LCBI 1. Normal flora in patients aged  $\geq 1$  year was categorized as LCBI 2, meanwhile, if the age was  $< 1$  year then LCBI 3. After that, MAR-Index from the result of antibiotic sensitivity was calculated, then the difference between LCBI categories was analyzed.

The collected data were analyzed using the help of IBM SPSS Statistics software version 25.0 (IBM Corp., Armonk, NY, USA). The analysis is used in the independent *t*-test or Mann-Whitney test which data is first analyzed using the Shapiro Wilk test. While the analysis of the association between MAR-index and LCBI used the chi-square test. The results of statistical analysis were declared significant if the *p*-value  $< 0.05$ .

### 3. Results

#### 3.1. Characteristic of participant

Most of the participants were female as much as 55.1% and most of the participants aged in the range of 20–60 years as much as 59.4%. In addition, 73.9% of participants were found to be infected with gram-positive bacteria (Table 1).

#### 3.2. Profile of bacteria base on multiple antibiotic resistance index

Most of the bacteria identified were *Staphylococcus aureus* (53.5%) in LCBI type 1 while in LCBI type 2 *Staphylococcus haemolyticus* (69.2%) was the most common. In this study, several LCBI type 1 bacteria were identified, such as *Staphylococcus aureus* (53.5%), *Acinetobacter baumannii* (20.9%), *Escherichia coli* (9.3%), *Klebsiella pneumoniae* (7.0%), *Enterococcus faecalis* (4.6%), and *Pseudomonas aeruginosa* (4.6%). Meanwhile, LCBI type 2 consisted of *Staphylococcus haemolyticus* (69.2%), *Staphylococcus epidermidis* (19.2%), *Corynebacterium jeikeium*

(3.8%), *Staphylococcus hominis* (3.8%), and *Staphylococcus viridans* (3.8%; Fig. 1). LCBI type 3 was not found in all isolates.

Various types of bacteria have been tested for antibiotic sensitivity on LCBI types 1 and 2 which can be seen in detail in Table 2. There are several antibiotics that have sensitivity to gram positive bacteria based on LCBI types 1 and 2, including Ampicillin (4.0%), Ampicillin clavulanic acid (33.3%), Tetracycline (38.0%), Chloramphenicol (38.0%), Ciprofloxacin (38.0%), Erythromycin (44.0%), Clindamycin (63.0%), Gentamicin (66.7%), Cotrimoxazole (71.0%), levofloxacin (71.0%), Moxifloxacin (75.0%), Fosfomycin (85.0%), Linezolid (98.0%), and Vancomycin (100.0%). The sensitivity is divided into 3, namely red, yellow, and green which red is an antibiotic that has a sensitivity of  $< 30\%$ , yellow is an antibiotic that has a sensitivity of 30–60%, and green is an antibiotic that has a sensitivity of  $> 60\%$ .

The results of the MAR-index assessment on LCBI type 1 obtained the most results were *Staphylococcus aureus* as much as 53.49% with a MAR-index value of 0.22–0.44. The MAR-index values are categorized as 3, namely low, middle, and high which in LCBI type 1 there is no MAR-index category low in LCBI type 1. While in LCBI type 2, the highest MAR-index category middle value is 65.4% which *Staphylococcus haemolyticus* is the most common species with a MAR-index value of 0.26–0.58. The results of the statistical test showed that there was no significant comparison in the value of the MAR index on LCBI types 1 and 2 ( $p = 0.424$ ; Table 3). In addition, the results of the analysis show that there is no significant association between the MAR-Index on LCBI ( $p = 0.571$ ).

### 4. Discussion

The isolates causing infection in this study were Gram-positive, mostly from normal flora. *Staphylococcus aureus* is a normal flora that is commonly found on the skin and some cause self-limited to invasive and life-threatening disease [12]. *Staphylococcus aureus* is also found to be the most common cause of blood flow in the Asian region including the Philippines, Nepal, Thailand, Bangladesh, Sri Lanka, Pakistan, Vietnam, Papua New Guinea, India, Burma, Laos [13]. In addition, *Acinetobacter baumannii* is the second most common cause of blood flow in LCBI type 1 where *Acinetobacter baumannii* is commonly found in the environment but in the 1990s and above the incidence of infection caused by *Acinetobacter baumannii* increased. *Acinetobacter baumannii* was also found to be resistant to carbapenems [14].

Microorganisms belonging to the LCBI category 1 are a collection of microorganisms that are often reported as pathogenic agents with high resistance rates and have their acronym “ESKAPE” which stands for *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. ESKAPE pathogens are associated with nosocomial infections, which in turn result in increased case-fatality rates. Sepsis due to ESKAPE is reported more frequently than due to other pathogens. In a recent study, the infection caused by the ESKAPE pathogen was associated with high mortality and prolonged hospitalization, especially for immunocompromised patients. The cause of BSI due to ESKAPE is often associated with the inappropriate use of empirical antibiotics [15].

Based on their structure, Gram-negative bacteria are easier to become resistant so that they have the potential to significantly increase morbidity and mortality [16]. In Gram-negative bacteria, there is an outer membrane which is a major factor in antibiotic resistance. The majority of antibiotics must pass through the outer membrane to access the target of action and kill microorganisms, so changes in the outer membrane will have an impact on some antibiotics. Another resistance mechanism that can occur in Gram-negative bacteria is enzymatic and non-enzymatic processes that increase intrinsic resistance [17]. BSI caused by Gram-negative bacteria has a possible resistance mechanism, so WHO places Gram-negative bacteria as a priority for handling antibiotic-resistant bacteria [16,18].

Coagulase-negative staphylococci (CoNS) is a normal flora of human

**Table 1**  
Characteristic of participant.

Variable	n (%)
Gender	
Male	31 (44.9)
Female	38 (55.1)
Age	
0–1 years	3 (4.3)
2–10 years	4 (5.9)
11–19 years	8 (11.6)
20–60 years	41 (59.4)
>60 years	13 (18.8)
Microorganism	
Gram-positive	51 (73.9)
Gram negative	18 (26.1)

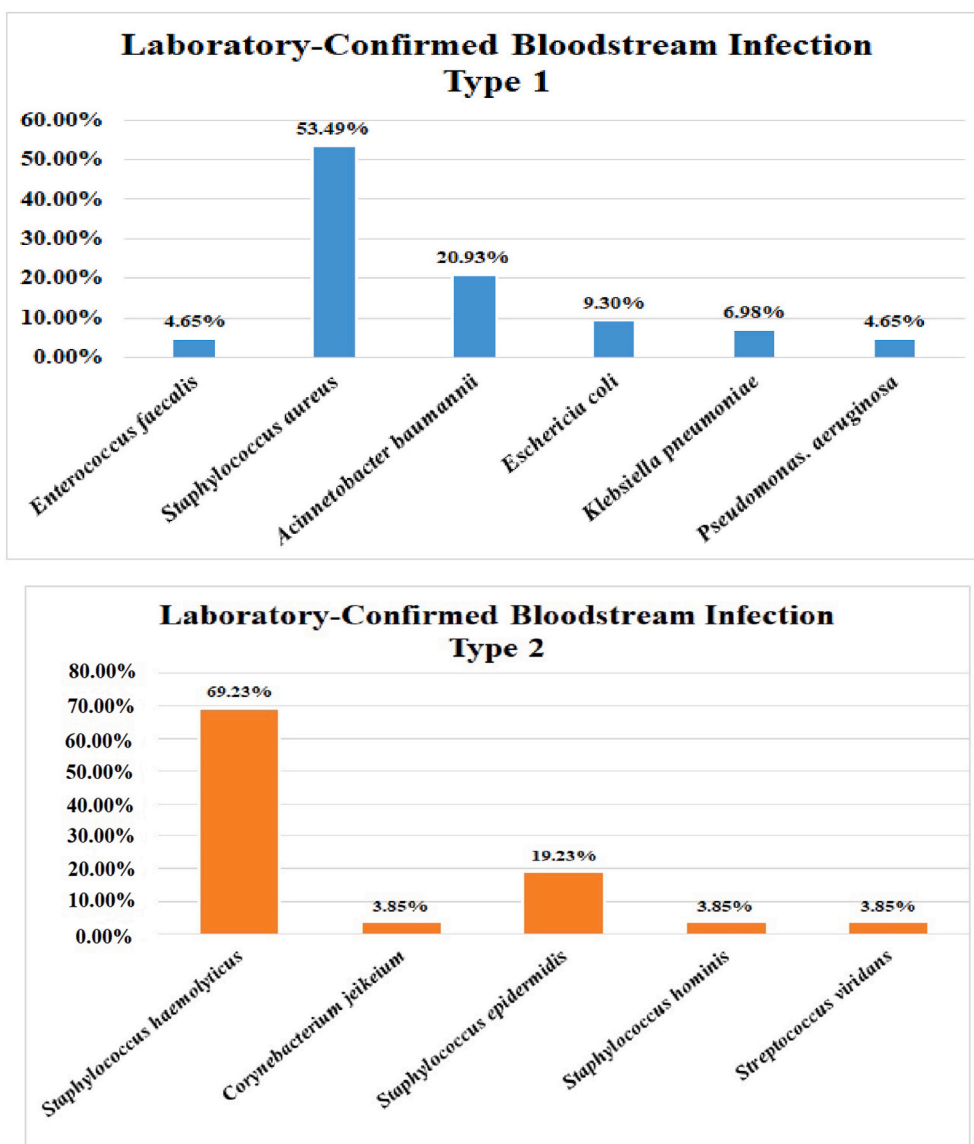


Fig. 1. A–B. Distribution of Microorganism based on Laboratory-Confirmed Bloodstream Infection (LCBI).

skin and mucosa. Risk factors for CoNS infection are patients with old age, patients with nutritionally malnourished status, patients taking immunosuppressant drugs, immunocompromised patients, there are wounds on the mucocutaneous layer, a history of long exposure to antibiotics, and the use of catheter tubes, especially intravenous catheters [19,20]. As a normal flora of human skin, CoNS is very easy to move and enter the bloodstream during medical procedures, this is due to medical procedures that are not well prepared [21]. The most common Gram-positive bacteria that cause bacteremia are bacteria belonging to CoNS, such as *Staphylococcus haemolyticus* (40%), *Staphylococcus hominis* (32%), *Staphylococcus epidermidis* (7%), *Staphylococcus wareri* (4%), but in this study CoNS isolates had a low level of resistance [22].

During this time CoNS is often considered as contamination, but over time CoNS infection has increased and is associated with nosocomial infections. Nearly 55–75% of infections by CoNS are caused by methicillin-resistant isolates. This infection is associated with high medical procedures and the insertion of catheters into the patient's body, especially intravenous catheters [23]. A similar study conducted in South Africa stated that the MAR-Index of CoNS causing bacteremia was between 0.05 and 0.80 and was dominated by *Staphylococcus epidermidis* [24]. There is a match between phenotypic and genotypic.

Methicillin-resistant isolates were continued with genotypic testing and found the *mecA* gene in 92.6% of MR-CoNS. In isolates that do not have the *mecA* gene, resistance traits are carried by the *mecC* gene, *mecB* and overproduction of  $\beta$ -lactamase [24,25]. ESKAPE and MR-Cons are the emerging pathogens causing nosocomial infections that become a particular challenge because of the need for specific attention to stop the spread that possibly happens and the limited antibiotics that can be selected which cause increased morbidity and mortality.

The limitations of the study were the smaller number of participants, the low resource setting, and the analysis predictors/determinants in the study have not been explored more deeply. Future research is expected to make comparisons between the MAR-index of microorganisms.

## 5. Conclusion

There were 43 isolates included in the LCBI category 1, which consisted of *Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli* with a MAR – Index range of 0.43–0.83. There were 26 isolates included in LCBI category 2, which consisted of *Staphylococcus haemolyticus*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Streptococcus viridans*,

**Table 2**  
Bacterial sensitivity to antibiotics based on LCBI type 1 and 2.

Antibiotic	LCBI	
	Type 1	Type 2
<b>Gram-positive</b>		
Gentamicin (GN)	88.0%	38.0%
Ampicillin (AMP)	0.0%	7.7%
Ampicillin clavulanic acid (AMC)	56.0%	7.7%
Penicillin (P)	0.0%	0.0%
Oxacillin (OX)	84.0%	12.0%
Cefoxitin (FOX)	84.0%	12.0%
Cotrimoxazole (SXT)	88.0%	46.0%
Tetracycline (TE)	36.0%	35.0%
Chloramphenicol (C)	16.0%	54.0%
Erythromycin (E)	44.0%	38.0%
Clindamycin (DA)	88.0%	31.0%
Quinopristine-dalfopristin (SYN)	92.0%	77.0%
Moxifloxacin (MXF)	84.0%	58.0%
Levofloxacin (LEV)	80.0%	54.0%
Ciprofloxacin (CIP)	44.0%	27.0%
Fosfomycin (FOS)	84.0%	77.0%
Teicoplanin (TEICO)	100.0%	76.9%
Vancomycin (VA)	100.0%	88.5%
Linezolid (LZD)	96.0%	88.5%
<b>Gram negative</b>		
Gentamicin (GN)	61.0%	-
Amikacin (AK)	67.0%	-
Aztreonam (ATM)	11.0%	-
Ampicillin (AMP)	0.0%	-
Ampicillin clavulanic acid (AMC)	0.0%	-
Ampicillin sulbactam (SAM)	39.0%	-
Piperacillin (PIPE)	17.0%	-
Piperacillin tazobactam (TZP)	67.0%	-
Cefazoline (KZ)	0.0%	-
Ceftazidime (CAZ)	22.0%	-
Ceftriaxone (CRO)	0.0%	-
Cefotaxime (CTX)	11.0%	-
Cefoperazone sulbactam (SCF)	67.0%	-
Cefepime (FEP)	17.0%	-
Cotrimoxazole (SXT)	44.0%	-
Tetracycline (TE)	28.0%	-
Chloramphenicol (C)	39.0%	-
Moxifloxacin (MXF)	50.0%	-
Levofloxacin (LEV)	50.0%	-
Ciprofloxacin (CIP)	39.0%	-
Fosfomycin (FOS)	28.0%	-
Imipenem (IPM)	89.0%	-
Meropenem (MEM)	89.0%	-

**Table 3**  
Comparison of multiple antibiotic resistance index in laboratory-confirmed bloodstream infection type 1 and 2.

MAR Index	Species	Value	p
<b>LCBI type 1</b>			
High	<i>Enterococcus faecalis</i>	0.83	0.424
	<i>Acinetobacter baumannii</i>	0.61–0.91	
	<i>Escherichia coli</i>	0.61–0.78	
	<i>Staphylococcus aureus</i>	0.22–0.44	
	<i>Acinetobacter baumannii</i>	0.30–0.57	
Moderate	<i>Escherichia coli</i>	0.48	
	<i>Klebsiella pneumoniae</i>	0.52–0.57	
	<i>Pseudomonas aeruginosa</i>	0.43	
	-	-	
<b>Low</b>			
<b>LCBI type 2</b>			
High	<i>Staphylococcus haemolyticus</i>	0.63–0.79	0.74
	<i>Corynebacterium jeikeium</i>	0.74	
	<i>Staphylococcus epidermidis</i>	0.74	
Moderate	<i>Staphylococcus haemolyticus</i>	0.26–0.58	0.58
	<i>Staphylococcus epidermidis</i>	0.26–0.58	
	<i>Staphylococcus hominis</i>	0.58	
Low	<i>Staphylococcus haemolyticus</i>	0.11	0.16
	<i>Staphylococcus viridans</i>	0.16	

Note: LCBI = laboratory-confirmed bloodstream infection; MAR index = multiple antibiotic resistance; High  $\geq 0.6$ ; Moderate = 0.21–0.59; Low  $\leq 0.2$ .

and *Corynebacterium jeikeium*. The highest number of isolates was *Staphylococcus haemolyticus* as many as 18 isolates (26.1%) with a range of MAR – Index 0.16–0.79. There is no significant difference between LCBI categories 1 and 2.

### Ethical statement

This research has been reviewed and approved by Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Consent for human subjects was acquired and patient-related data was kept in confidentiality.

### Sources of funding

None.

### Author contributions

MP and EBW designed the study. MP performed the experiments. EBW and LA supervised the experiments. MP and EBW analyzed the data. MP, EBW, and LA wrote the paper with input from all authors.

### Consent

Written informed consent was obtained from the patient.

### Registration of research studies

1. Name of the registry: Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
2. Unique Identifying number or registration ID: 0497/122/4/1/2021.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):-.

### Guarantor

Eddy Bagus Wasito is the person in charge for the publication of our manuscript.

### Provenance and peer review

Not commissioned, externally peer-reviewed.

### Declaration of competing interest

The authors declare that they have no conflict of interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.103086>.

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