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Evaluation of Methicillin Resistant Staphylococcus aureus (MRSA) Diagnostic Test: A Systematic Review Study Evaluating Antibiotic Disc, Chromogenic Media, and Polymerase Chain Reaction Methods

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ABSTRACT

The infection caused by Staphylococcus aureus that is resistant to beta lactam antibiotic known as methicillin-resistant S. aureus (MRSA). This bacteria less the choice of effective antibiotic, increase hospital stay and cost, and mortality. Because of these problems, MRSA diagnostic testing must be done accurately. The gold standard of MRSA diagnostic testing PCR. Other that PCR, some methods that can be used for MRSA detection are antibiotic disc and chromogenic media. The three of them have diverse sensitivity, specificity, and turnaround time. Evaluating the diagnostic testing accuracy can be done by using sensitivity, specificity, and turnaround time. Based on the description above, this study has been carried out to evaluate the MRSA diagnostic test using antibiotic discs, chromogenic media, and PCR with a systematic review method. This research used Preferred Reporting Items for Systematic Review and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) for extracting and synthesizing data. 2,239 articles yielded and 59 of them fit the eligibility criteria used in this systematic review. Quadas-2 tool was used for risk of bias analysis. The sensitivity and specificity of MRSA diagnostic methods using antibiotic disc, chromogenic media and PCR were: 47,3-100% and 66,2-100%; 70-100% and 30-100%, 57,69-100% and 78,6-100% respectively. The incubation time is 16-48 hours for antibiotic disc, 18-48 hours for chromogenic media. The turnaround time is 36-48 hours for disc antibiotic and 58 minutes-6,5 hours for PCR. High resource laboratories can use PCR as a diagnostic method for MRSA, while limited resources laboratories can use antibiotic disc and chromogenic media. We conclude that MRSA diagnostic method using PCR has higher specificity and faster turnaround time than antibiotic disc, while chromogenic media has higher sensitivity than those two methods.

1. INTRODUCTION

Methicillin-resistant Staphylococcus aureus (MRSA) is a type of Staphylococcus aureus that is resistant to beta lactam antibiotics. In some cases, this bacteria are resistant to several classes of antibiotics at once. This resistance results in fewer effective antibiotic options, increasing length of hospital stay, treatment costs, and morbidity [1]. Therefore, diagnosis of MRSA should be done appropriately. The gold standard for diagnosing MRSA is the Polymerase Chain Reaction (PCR) method [2]. Other than PCR, antibiotic disc and chromogenic media can be used for the diagnostic test of MRSA. These methods have a different specificity, sensitivity, and turnaround time. The evaluation of the accuracy of a diagnostic test can be done by sensitivity, specificity, and turnaround time. Sensitivity is the ability of a test to differentiate between the infected and uninfected individuals. Specificity is the ability of a test to see that it is likely that an infected individual's test result will be positive on that test [3]. Turnaround time is the amount of time needed from the process of receiving samples to reporting [4]. Based on the description above, the authors did this research to evaluate the MRSA diagnostic test using antibiotic disks, chromogenic media, and PCR. However, because there had been many studies related to the diagnostic MRSA test using the antibiotic disc method, chromogenic media, and PCR in the past, the authors wanted to carry out their research using a systematic review method, to systematically summarize existing studies. The results of this study are expected to be a supporting material for medics to determine the method of MRSA diagnostic test.

2. MATERIALS AND METHODS

The authors use the PRISMA-DTA (Preferred Reporting Items for Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies) guide statements in this systematic review. Literature search was done on several journal databases: PubMed, Science Direct, and Google Scholar, using the keywords “methicillin resistant Staphylococcus aureus”, “MRSA”, “antibiotic disc”, “cefoxitin disc”, “oxacillin disc”, “CHROMagar”, “chromogenic media”, “PCR” “molecular detection”, “specificity”, “spesifisitas”, “sensitivity”, “sensitivitas”, “waktu penyelesaian”, dan “turnaround time” using Boolean logic. All articles obtained was checked for duplication and screened for titles and abstracts using the EndNote X8 and Microsoft Excel programs. Full-text reads were performed on the remaining articles. Articles that meet the inclusion criteria are articles published in January 2011-July 2020, cross-sectional and experimental diagnostic test research articles performed in the world (not limited to certain areas), which evaluate and include the specificity sensitivity, or turnaround time. The population under study was humans (either patients or carriers of MRSA infection). Studies analyzing MRSA using antibiotic disc and chromohenic media should use PCR as the reference standard. The types of publications that meet the inclusion criteria are international and national journals written in English and Indonesian. We excluded the articles that are published other than in English and Indonesian, articles without the full text, and type of other than journals and research articles (for example, theses, dissertations, books, parts of books, posters in conferences, literature reviews, systematic reviews, and brief reviews).

3. RESULT

2,239 journals yielded from three databeses (1,921 from Google Scholar, 15 from Pubmed, and 303 from Science Direct). Figure 1 summarizes the study selection process. The duplication and screening of titles and abstracts was done using EndNote X8 and Microsoft Excel. Only 59 articles involved in this systematic review because there were 406 articles that were not fit for eligibility criteria.

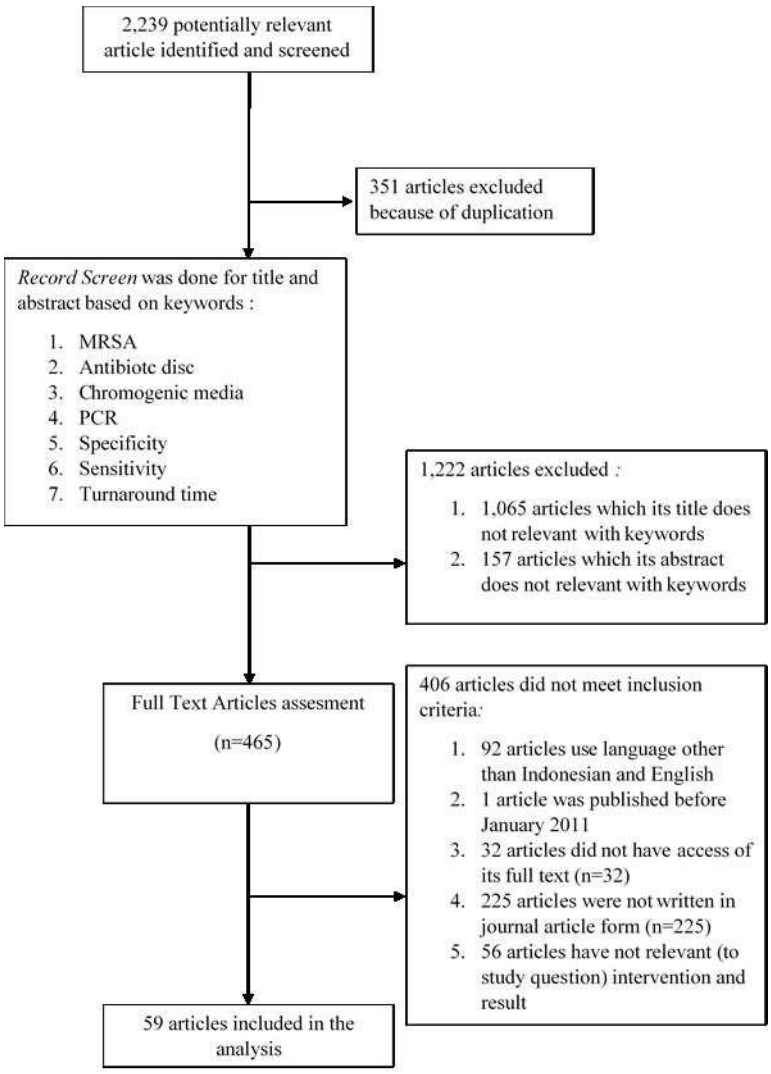

Figure 1. PRISMA flow chart

3.1 Risk of bias assesment

Risk of bias assesment was done using QUADAS-2 tool and is showed in figure 2. The assessment of risk of bias and concern of the applicability were carried out by categorizing them as "low", "high", or "unclear". Overall, the included studied showed a predominance of "low" risk of bias and concern of applicability. However, there are only 23 out of 59 journals with a low risk of bias and concern of applicability in all domains

3.2 Sensitivity of MRSA Diagnostic Test

The lowest and highest sensitivity of the MRSA diagnostic test using disc antibiotic was cefemtazole disc diffusion (47.3%), and oxacillin and cefoxitin disc diffusion (100%) respectively [12-24]. The sensitivity of chromogenic media ranges from 70% (BD CHROMagar MRSA II) - 100% (Brilliance MRSA Chrome Agar, ChromID MRSA, and Colorex MRSA). The sensitivity of conventional PCR and Real-Time PCR ranged from 57.69-100%. The Detect-Ready MRSA Panel Kit has a sensitivity of 57.69%, while the LightCycler MRSA Advanced Test, Xpert MRSA assay, GenoType MRSA Direct assay (Hain Life-science, Nehren, Germany), GenomEra MRSA / SA Diagnose, Real-Time PCR (TaqMan hydrolysis probe based on MERSA real time PCR detection kit), BD GeneOhm MRSA ACP assay, In-house PCR, and FluoroType MRSA assay have 100% sensitivity.

3.3 Specificity of MRSA Diagnostic Test

The specificity of the MRSA diagnostic test using an antibiotic disc ranges from 66.2% -100%. The lowest yield (66.2%) was the specificity of the Oxacillin disc diffusion presented in the study of Sultana et al. (2019) [8]. The highest specificity (100%) was obtained from Oxacillin and Cefoxitin disc diffusion which presented by several studies. The specificity of the chromogenic media ranges from 30% to 100%. MeReSa agar has a specificity of 30%, while CHROMagar MRSA and MRSASelect have a specificity of 100%. The specificity of both conventional and real-time PCR is 78.6% (LightCycler MRSA Advanced test)-100% (Xpert MRSA Gen 3, GenoType MRSA Direct assay (Hain Life-science, Nehren, Germany), GenomEra MRSA / SA Diagnose, and Real-Time PCR (TaqMan hydrolysis probe based MERSA real time PCR detection kit)).

3.4 Turnaround time of MRSA Diagnostic Test

Most of the studies that evaluate antibiotic disc and chromogenic media for MRSA diagnostic test only included the incubation time, not the turnaround time. The incubation time is 16-48 hours for antibiotic disc, 18-48 hours for chromogenic media. The turnaround time is 36-48 hours for disc antibiotic and 58 minutes-6,5 hours for PCR.

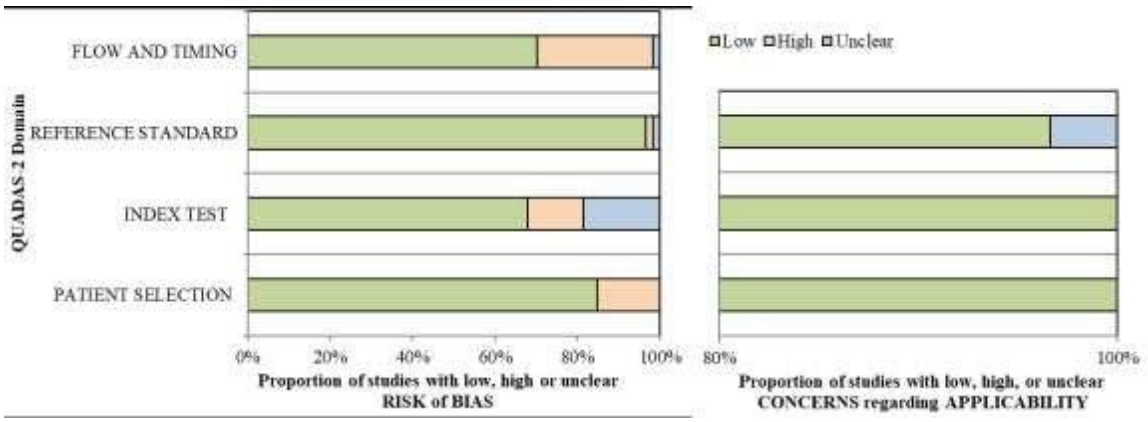

Figure 2. Studi Quality Assesment Using QUADAS-2.
Green: low risk of bias and concern of applicability
Pink: high risk of bias and concern of applicability
Blue: unclear risk of bias and concern of applicability

Table 1. Summary of Sensitivity, Specificity, and Study Completion Time

Author, Year of Publication	Index test	Reference Standard	Positivity threshold	Sensitivity (%)	Specificity (%)	Study Completion Time
Demir et al., 2016 [42]	Oxacillin disc diffusion	PCR (mecA)	Based on CLSI	98.7	96.9	-
	Cefoxitin disc diffusion		Based on CLSI	98.7	97.5	-
Sandle et al., 2014 [6]	Oxacillin disc diffusion	PCR	Inhibition zone ≤ 10 mm: resistant	95.83	100	Incubation time: 24 hours
	Cefoxitin disc diffusion		Inhibition zone ≤ 21 mm: resistant	83.33	100	Incubation time: 18-24 hours
Arici and Bayraktar, 2019 [7]	Cefoxitin disc diffusion	PCR (mecA (162 bp)/mecC 138 bp)	Based on CLSI guideline	100	100	-
Iraz et al., 2012 [43]	Oxacillin disc diffusion	PCR	Based on CLSI 2011	95.3	95.3	Incubation time:
	Cefoxitin disc diffusion		Based on CLSI 2011	96.5	98.4	24-48 hours
Chowdhury et al., 2013 [22]	Oxacillin disc diffusion	PCR (mecA 533 bp)	Inhibition zone ≤ 13 mm: resistant	100	94.31	Incubation time: 24 hours
	Cefoxitin disc diffusion		Inhibition zone ≤ 21 mm: resistant	96.42	95.45	Incubation time: 24 hours

Sultana et al., 2019 [8]	Oxacillin disc diffusion	PCR (gen mecA dengan 309 bp)	Inhibition zone ≤ 10 mm: resistant ≥ 13 mm: sensitive	84.2	66.2	Incubation time: 16-18 hours
	Cefoxitin disc diffusion		Inhibition zone ≤ 19 mm: resistant ≥ 20 mm: sensitive	100	100	Incubation time: 16-18 hours
Farahani et al., 2013 [9]	Oxacillin disc diffusion	PCR (gen mecA)	Based on 2007 CLSI guideline	73.6	100	-
	Cefoxitin disc diffusion			98.9	94.7	-
	Methicillin disc diffusion			87.9	92.6	-
	Cefotetan disc diffusion			98.5	91.4	-
	Cefemtazole disc diffusion			47.3	100	-
Pourmand et al., 2014 [10]	Oxacillin disc diffusion	PCR (gen mecA 162 bp)	Based on CLSI guideline	80	100	Incubation time:
	Cefoxitin disc diffusion			100	100	24 hours
Rostami et al. 2013 [11]	Oxacillin disc diffusion	PCR (gen mecA 310 bp)	Based on 2007 CLSI guideline	100	92.8	Incubation time:
	Cefoxitin disc diffusion			100	100	24 hour
Thampi et al., 2019 [12]	Oxacillin disc diffusion	PCR (gen mecA 533 bp)	Inhibition zone ≤ 10 mm: resistant, 11-12 mm: intermediately resistant, ≥13 mm: sensitive	81.96	97.89	-
	Cefoxitin disc diffusion		Inhibition zone ≤ 21 mm: methicillin resistant, ≥22 mm: methicillin sensitive	100s	100	-
	ChromID MRSA SMART (biomerieuc) (chromogenic media)		-	95.08	97.89	-
Buchan et al., 2015 [34]	Xpert MRSA/SABC (Xpert) assay (RT-PCR)	5% sheep blood agar and Mueller Hinton Agar with cefoxitin disc diffusion	MRSA: Positive for mecA gene, spa, and SCCmec-orfX junction MSSA: positive for spa gene with or without SCCmec-orfX	99.6	99.5	-
	GeneOhm StaphSR assay (RT-PCR)		MRSA: positive for SCCmec-orfX gene	99.2	96.5	-
Ahmad, 2013 [13]	Oxacillin disc diffusion	PCR (gen mecA 533 bp)	Inhibition zone < 10 mm: resistant strain, >13 mm: susceptible strain	91	99	Incubation time: 18-24 hours
	Cefoxitin disc diffusion		Inhibition zone < 21 mm: resistant, >22 mm: sensitive	100	100	
Diwakar et al., 2018 [14]	Oxacillin disc diffusion	PCR (gen mecA 310 bp)	Inhibition zone ≤ 10 mm: resistant strain, ≥13 mm: susceptible strain	76.19 (95 % CI: 52.83-91.78)	98.37 (95 % CI: 94.25-99.80)	-
	Cefoxitin disc diffusion		≤19 mm: MRSA, ≥ 22 mm: MSSA	100 (95 % CI: 83.89-100)	100 (95 % CI: 97.05-100)	Incubation time: 18-24 hours
Pillai et al., 2012 [44]	Oxacillin disc diffusion	PCR (gen mecA 310 bp)	Inhibition zone 10 mm: resistant (MRSA), 11-12 mm: intermediately resistant, 13 mm: susceptible (MSSA)	93.5 (95% CI: 86.4-97.3)	83.5 (95% CI: 79.2-85.8)	Incubation time: 24-48 hours
Kim et al., 2013 [45]	LightCycler MRSA Advanced Test	Conventional culture with MRSA confirmation using Cefoxitin disc diffusion	MRSA: based on strain ATCC33591	100	91	-
Koupahi et. al., 2016 [15]	Oxacillin disc diffusion	PCR (gen mecA 162 bp)	Based on CLSI guideline	100	100	Incubation time: 24 hours
	Cefoxitin disc diffusion			100	100	Incubation time: 18 hours
	CHROMagar MRSA		Mauve colony color: MRSA	98.13	100	Incubation time: 18-24 hours
Sultana et al., 2019 [8]	Oxacillin disc diffusion	PCR (gen mecA 309 bp)	Inhibition zone ≤ 10 mm: resistant (MRSA):	84.2	66.2	Incubation time: 24 hours
Mohajeri et al., 2015 [16]	Oxacillin disc diffusion	PCR (gen mecA)	Bsed on 2008 CLSI guideline	73.6	100	-
	Cefoxitin disc diffusion			98.9	94.7	-
	Methicillin disc diffusion			87.9	92.6	-
	Cefotetan disc diffusion			98.5	91.4	-
	Cefemetazole disc diffusion			47.3	100	-
Patil and Ghorpade, 2015 [17]	Oxacillin disc diffusion	PCR (gen mecA 310 bp)	Inhibition zone ≤ 10 mm: resistant strain (MRSA), ≥13 mm: susceptible strain (MSSA)	100	95.10	-
	Cefoxitin disc diffusion		Inhibition zone ≤19 mm: MRSA, ≥ 22 mm: MSSA	100	100	Incubation time: 18-24 hours
Bhutia et. al., 2012 [46]	Oxacillin disc diffusion	PCR (gen mecA 162 bp)	Inhibition zone ≤ 10 mm: resistant (MRSA), 11-12 mm: moderately sensitive, ≥13 mm: sensitive (MSSA)	70.58	75.75	Incubation time: 24 hours
	Cefoxitin disc diffusion		Inhibition zone ≤21 mm: resistant (MRSA), ≥ 22 mm: sensitive (MSSA)	86.27	83.33	Incubation time: 16-18 hours
Datta et al., 2011 [18]	Oxacillin disc diffusion	PCR (gen mecA 533 bp)	Inhibition zone ≤ 10 mm: resistant (MRSA), 11-12 mm: *intermediate*, ≥13 mm: sensitive (MSSA)	91.4	99.2	Incubation time: 24 hours

	Cefoxitin disc diffusion		Inhibition zone ≤21 mm: resistant (MRSA), ≥ 22 mm: sensitive (MSSA)	98.5	100	Incubation time: 16-18 hours
	CHROMagar MRSA (Hi-media)		Green colored colony	97.1	99.2	-
Kali et al., 2013 [47]	MeReSa agar (Hi-media, Mumbai, India) (media chromogenic)	PCR (gen mecA 533 bp)	-	97.82	30	-
Durmaz et al., 2015 [41]	Oxacillin disc diffusion	BD GeneOhm MRSA (BD Diganostic, Sparks, USA) (RT-PCR)	Sesuai dengan panduan CLSI	98	99.6	36-48 hours
	Cefoxitin disc diffusion			98	99.6	36-48 hours
	Chrom ID MRSA agar (bioMerieux, Marcy l'Etoile, Frnace)		Koloni berwarna hijau	98	99.6	18-24 hours
Huh et al., 2012 [40]	LightCycler MRSA Advanced test	Enrichment culture method and oxacillin disc diffusion. If there is a result difference, then mecA gene PCR kit test will be done.	Detected MRSA DNA	98.5	78.6	-
Khawaja et al., 2019 [21]	Oxacillin disc diffusion	PCR (gen mecA 310 bp)	Inhibition zone ≤ 10 mm: MRSA	94.3	73.33	Incubation time: 24 hours
	Cefoxitin disc diffusion		Inhibition zone ≤ 21 mm: resistant (MRSA), ≥ 22 mm: sensitive (MSSA)	96.73	76.92	Incubation time: 24 hours
Peterson et al., 2017 [48]	Cobas MRSA/SA Test	Direct and enrichment culture (HardyCHROM MRSA, cefoxitin disc diffusion)	Not mentioned in the study	93.9	97.5	-
Bashir et al., 2019 [27]	Cefoxitin disc diffusion	PCR (gen mecA 189 bp)	Inhibition zone ≤ 19 mm: resistant (MRSA), ≥ 20 mm: sensitive (MSSA)	98.8	99.1	Incubation time: 24 hours
	MRSA chromagar (Hichrome Me Re Sa agar, M1674, Himedia, Mumbai, India)		Bluish green colony color	81.6	97.3	Incubation time: 18-24 hours
Ho et al., 2011 [35]	BD GeneOhm assay (RT-PCR)	Coventional culture and broth enrichment (trypticase soy agar with 5% sheep blood agar plate (TSA II 5% SB) (Becton, Dickinson and Comapany, Sparks, MD, USA) with oxacillin disc diffusion)		95.9	85.3	-
Arcenas et. al., 2012 [49]	LightCycler MRSA Advanced Test	MRSASelect medium (culture)	Not mentioned in the study	95.2 (95% CI: 89.2-98.4)	95.5 (95% CI: 89.1-98.4)	< 2 hours (8-16 sample each batch)
	Xpert MRSA assay		Not mentioned in the study	99 (95% CI: 94.8-100)	95.5 (95% CI: 89.1-98.4)	
Patel et al., 2014 [50]	Cepheid Xpert SA Nasal Complete PCR Assay	Culture (CHROMagar SA dengan enrichment pada tryptic soy broth (TSB) and Roche LightCycler Real-Time PCR)	Not mentioned in the study	89.3 (95% CI: 80,2-94.7)	97.9 (95% CI: 96.6-98.7)	-
Oh et al., 2013 [51]	Xpert MRSA assay	Kultur (blood agar, Vitek 2 gram-positive identification card (bioMerieux, MarcyI'Etoile, France) untuk mendeteksi *S. aureus* and Vitek Broth Culture System (bioMerieux) untuk mengetahui resistantsi methicillin (MRSA))	SCC*mec* (Ct (*cycle treshold*): 30)	100	90.7	-
Ayebare et al., 2019 [26]	BD CHROMagar MRSA II	Composite Refeence Standard (CRS)	Mauve colored colony	70 (50-86)		18-48 hours
	Hain GenoQuick MRSA		Following instructions from producer	96 (81-100)		3.5 hours
	Xpert SA nasal complete		*S. aureus:* gen *spa* (Ct: 35) detected above upper threshold level MRSA: gen *spa*, *mecA*, and SCC*mec* (Ct: 35, 46, and 38) detected above upper threshold level Ct minimum for every gene: 10	52 (23-71)		1.25 hours

Lee et al., 2013 [32]	Xpert MRSA assay	Culture	MRSA: Ct ≤ 36	92.6 (95% CI: 86.4-98.8)	96.7 (95% CI: 84.7-98.6)	-
Hos, N. J., et al.; 2016 [52]	QIAGEN artus MRSA/SA QS-RGQ	MRSA culture enrichment (5% sheep blood agar and plate agar chromogenic. *S. aureus* detected tiwh MALDI-TOF, MRSA detected with latex agglutination test)	MRSA: detection of *mecA* and *mecC* gene	80.0	95.8	3.5 hours
	BD MAX MRSA assay		MRSA; detection of *mecA* gene	80.0	90.0	3.5 hours
Lepainteur et al., 2015 [53]	Xpert MRSA Gen 3	Enriched culture (enriched ChromID MRSA)	MRSA: target *mecA*/C gene found and no amplification of MREJ (*mec right extremity junction*) gene	95.7	100	58 minute
	BD MAX MRSA XT			87.5	97.1	120 minute
Al-Mohana et al., 2016 [24]	Oxacillin disc diffusion	PCR (*S. aureus*: coa 810 bp, MRSA: mecA 533 bp)	-	100	93.0	Incubation time: 24 hours
	Cefoxitin disc diffusion		-	100	95.8	Incubation time: 18 hours
	BBL CHROMagar MRSA		Pinkish to mauve colored colony.	95.3	98.6	Incubation time: 24 hours
	HiChrom Me Re Sa agar		Blueish to green colored colony.	96.9	97.2	Incubation time: 48 hours
Gupta et al., 2015 [54]	Cefoxitin disc diffusion	PCR (mecA 310 bp)	MSSA (*susceptible*): ≥ 22 mm. MRSA (resistant): ≤ 21 mm	94.8	90.5	Incubation time: 16-18 hours
	CHROMagar (Hi-media)		Koloni berwarna biru	89.7	90.5	Incubation time: 24 hours
Dalpke et al., 2012 [55]	BD MAX MRSA assay	Direct and enrichment culture (BBL CHROMagar MRSA plate (BD))	Not mentioned in the study.	93.9	99.2	140 minute
	BD GeneOhm MRSA ACP		Not mentioned in the study.	93.8	98.3	110 minute (8 samples)
Aydiner et al., 2012 [31]	LightCycler MRSA Advanced Test	BBL CHROMagar MRSA II (BD, Heidelberg, Germany)	MRSA: detection of SCCmec:orfX junction gene	84.3	98.52	< 2hours
	Detect-Ready MRSA Panel Kit		MRSA: detection of mecA, nuc, and Sccmec:orfX	57.69	99.59	5 hours
Kelley et al., 2013 [36]	ddPCR (bio-Rad QX100 dropletdigital PCR system)	Cepheid MRSA GeneXpert assay	Ct untuk mecA: 19,4 (genomic equivalent 106), 26,4 (genomic equivalent 104), 33, 7 (genomic equivalent 102)	96.8 (95% CI: 93.1-98.5)	91,0 (95% CI: 86.4-94.2)	-
	qPCR (Roche Light Cycler 480)			96.8 (95% CI: 93.1-98.5)	91.9 (95% CI:86.4-94.2)	-
Silbert et al., 2015 [56]	BD Max StaphSR assay	Combined direct and enriched culture (CHROMagar Staph aureus, CHROMagar MRSA II, TSA II plate)	Not mentioned in the study.	94.3 (95% CI: 81.4-98.4)	97.7 (95% CI: 94.8-99.0)	-
	BD Max MRSAXT assay			94.3 (95% CI: 81.4-98.4)	97.7 (95% CI: 94.8-99.0)	-
	First generation BD MAX MRSA			88.6 (95% CI: 74.0-95.5)	95.9 (95% CI: 92.4-97.8)	-
Brennan et al., 2015 [23]	Colorex MRSA	Data sample (MRSA and MSSA isolate)	-	100	85	-
	MRSA Select II		-	99	73	-
	ChromID MRSA		-	100	85	-
	MRSA Brilliance 2		-	98	82	-
Chowdury et al., 2013 [25]	Oxacillin disc diffusion	PCR (gen mecA 533 bp)	Inhibition zone (based on National Committee for Clinical Laboratory Standard) ≤ 13mm: MRSA (resistant)	100	94.31	Incubation time: 24 hours
	Brilliance MRSA Chrome Agar (Oxoid, UK)		Blue denim colored colony	100	After 24 hours incubation : 98.86 After 48 hours: 94.31	Incubation time: 24-48 hours
Manickam et al., 2013 [28]	MRSASelect	Routine identification	Pink colored colony	98	100	24 hours (18-28 hours)
Patel et. al., 2015 [57]	LightCycler MRSA Advanced Test (Roche Molecular Diagnostic, Pleasanton, CA)	Evidence of MRSA growth from nasal swab combined with positive result from Real-Time	-	98.3 (95% CI: 96.3-99.2)	98.9 (95% CI: 98,6-99.1)	-
	BD MAX MRSA assay (Becton Dickinson, Franklin Lakes, NJ)	PCR and positive culture of MRSA in the past 24 months. Reference	-	96.0 (95% CI: 88.9-98.6)	96.5 (95% CI: 94,9-97,5)	-
	Xpert MRSA assay (Cepheid, Sunnyvale, CA)	standard to determine the sensitivity in BD MAS MRSA assay is based on the current package insert.	-	95.7 (95% CI: 87.2-98.9)	98.8 (95% CI: 97.9-99.3)	-

Kang et al., 2012 [30]	Slan Real-Time PCR	Cefoxitin Disc Diffusion	MRSA: Ct <35 or Ct between 35 and 40 with S shaped curve in a repeated test.	96.4	96.6	-
Dalpke et al., 2015 [58]	BD Max StaphSR	Combined direct and enriched culture (DNAse plate testing, BBL CHROMagarMRSA II medium/ Oxoid Brilliance MRSA 2 agar, latex agglutination testing/Microgen Staph testing, MALDI-TOF), and susceiptibility testing with Vitek-2 and in-house PCR assay system to test mecA and femB)	MRSA: positive if MREJ (Ct: 36) and mecA/mecC (Ct: 37.9) gene was found.	96.4	93.6	2.5 hours
Sener et al., 2013 [29]	GenoType MRSA Direct assay (Hain Life-science, nehren, Germany)	PCR (mecA 310 bp)	Conjugate control and amplification control was present to determine sample positive treshold.	100	100	4 hours
Nielsen et al., 2016 [59]	Xpert MRSA Gen 3 PCR (GX MRSA)	Selective enrichment in tryptic soy broth followed by inoculation in MRSA CHROMagar and 5% Danish blood agar.	mecA/mecC gene was found.	88.2	97.9	2.9 hours (1-6 hours)
	BD MAX MRSA XT PCR (MAX MRSA)			88.2	97.4	49.6 hours (42-122 hours)
Elshabrawy et al., 2017 [60]	Media chromogenic MRSA-ID	Multiplex PCR detecting Locus A (495 bp), B(284 bp), and E(243 bp) in mecA gene.	Green colored colony	92.9	84	Incubation time: 24 hours
Jonckheere, S., et al.; 2015 [37]	Xpert MRSA	Culture after enrichment (BBL CHROMagar MRSA II)	MRSA: Positive for SCCmec-orfX junction gene with Ct<36 and mecA/C gene	94.9 (95% CI: 72.7-99.9)	97.9 (95% CI: 92.8-99.8)	-
	Xpert MRSA Gen 3		MRSA: Positive for SCCmec-orfX gene with Ct<38 mecA/C gene	94.9 (95% CI: 72.7-99.9)	91.8 (95% CI: 84.4-96.4)	-
Mehta et al., 2014 [38]	StaphSR assay BD GeneOhm assay	Culture (Colistin-Nalixidic acid agar with 5% sheep blood agar, Staphaurex (*S. aureus*), in-house developed Real-Time PCR (MRSA))	-	92.5 92.5	98.8 96.3	- -
Mendes et al., 2016 [61]	BD Max Staph SR	Antimicrobial susceptibility testing using disc diffusion and broth dilution.	MRSA: positive for nuc, mecA/C, and MREJ gene MRSA negative: no MREJ gene detected	99.7	99.8	-
Seki et al., 2015 [62]	BD GeneOhm MRSA assay	Mannitol Salt Agar culture with Oxacillin microdilution on Mueller-Hinton Agar	Target DNA SCCmec and regio orfX	75.9	96.4	-
Hirvonen, et al., 2012 [33]	GenomEra MRSA/SA Diagnose	Data sampel (berupa isolat MRSA and MSSA)	Not mentioned in the study.	100	100	<1hours/ sampel
Zobydi et al., 2013 [39]	BD GeneOhm MRSA ACP assay	Kultur (agar darah, Mannitol-Salt Agar, and Oxacillin disc diffusion)	Based on the positive and negative controls provided in the kit.	88.4	98.6	-
Abbadi et al., 2013 [63]	Real-Time PCR (TaqMan hydrolysis probe based MERSA real time PCR detection kit)	Oxacillin Disc Diffusion	Not mentioned in the study.	100	100	90 menit
Brukner et al., 2013 [64]	BD GeneOhm MRSA ACP assay	Culture (blood agar, mannitol salt agar, oxacillin and cefoxitin diisc diffusion)	Not mentioned in the study.	100 (95% CI: >83.2)	95.4 (95% CI: 93,5-96.9)	-
	In-house PCR		Saturation (Cp values less than 31) and corelation (Cp values that did not deviate more than eight cycles between mecA and the signal from *S. aureus* specific genes *nuc* and *coa*)	100 (95% CI: >83,2)	99,2 (95% CI: 98,2-99,8)	-
Eigner et al., 2014 [65]	FluoroType MRSA assay	Culture (CHROMagar, CNAagar, and thioglycollate broth, MALDI Biotyper, and GenoType MRSA (PCR))	Positive if SCCmec and orfX genes were found	100 100	99,2 96,1	2, 5 hours

"-" : information was not found in the study

4. DISCUSSION

4.1 Study Quality Assesment

The study quality assessment has given various results, with a dominant risk of bias and low risk of concern of applicability. This means that the overall risk of bias is not influential on the studies used and can represent those studies accurately. A study can be declared as having a "low" risk of bias or a "low" concern of applicability if all of its domains are declaring a "low" risk of bias, or "low" concern of applicability. The "high" risk of bias is mostly found in the flow and timing domain, namely 16 articles. Some of the studies used in this systematic review did not include all samples in the analysis of result for various reasons. The most common one is because of the invalid result or errors in the tools used. Other things in all domain that caused “high” risk of bias are the study used a case-control design, did not use consecutive or random sample methods in patient (sample) selection, did not specify the threshold used, and interpretation of reference standard by finding out the result of index test. The “unclear” risk of bias was mostly found in index test domain, namely 11 articles. This is because the interpretation and positivity threshold of the corresponding index test are not explained in several studies. In reference standard domain, it was caused since the study did not explain further about the reference standard used. In the flow and timing domain, the “unclear” risk of bias was because the study did not explain the sample included in the index test, reference standard, or in the analysis of result. 9 of 30 study about PCR as MRSA diagnostic test show that the study has at least one domain with “high” risk of bias. All of these studies have sensitivity or specificity less than 90%.

4.2 The Evaluation of MRSA Diagnostic Test

MRSA diagnosis using PCR (detection of mecA gene), which is the reference standard, is not always available in laboratory. Moreover, the price is often not affordable. Therefore, detection of MRSA by phenotype-based method is required for a laboratory [19]. There are various phenotype-based MRSA detection methods, including antibiotic disc diffusion and chromogenic media. The result of the phenotype-based MRSA test will depend on the standardization of the culture conditions such as temperature, incubation time, salt concentration, inoculation size, as well as pH of the medium. The result of antibiotic susceptibility testing for MRSA is also influenced by the heteroresistance and induced resistance seen in different isolates. These isolates are often misdiagnosed as methicillin-sensitive S. aureus (MSSA). Over time, there is a change in the PBP2a in MRSA, which is known as moderately resistant S. aureus (MODSA) and the strain with excess penicillinase production, namely borderline-oxacillin resistant S. aureus (BORSA). Apart from the mecA gene, a homologous property of mecA gene (the mecC gene) has also been reported to cause MRSA in human and bovine populations in both UK and Denmark. This isolate gives negative PCR result on mecA, but it is resistant to Oxacillin Disc Diffusion Testing [20]. Cefoxitin Disc Diffusion is considered to be the most sensitive test for routine use in laboratory with limited resources [21]. Several studies such as [7], [8], [10], [11], [12], [13], [15], dan Patil dan Ghorpade [17] have reported cefoxitin disc diffusion with 100% sensitivity and specificity with conventional PCR reference standard. Compared to oxacillin, cefoxite has also been reported to be a better predictor of heteroresistence in MRSA - since it is a strong inducer of PBP2a. Cefoxitin has limitations, that it can only detect MRSA with the mecA gene resistance mechanism. However, cefoxitin disc diffusion is easier to read than oxacillin, since there is often a blur in the zone of inhibition of oxacillin which causes errors in the interpretation of the result (interpreted as resistance to oxacillin). Cefoxitin Disc Diffusion also does not require special conditions for sample testing as required by Oxacillin Disc Diffusion (low incubation temperature and NaCl supplementation in the test medium) [22]. MRSA identification by using chromogenic media allows the specimen to be directly inoculated, so that the detection of MRSA can be conducted early and directly [12].

Chromogenic media has both good sensitivity and specificity, as well as having a relatively low price compared to PCR [19]. However, its result can easily be influenced by the specificity source, inoculation concentration, examiner, and incubation time [5]. In a study written by Brennan et al. [23], Colorex media and ChromID are able to detect the entire collection of MRSA isolates, whereas MRSA Select II and Brilliance MRSA are unable to detect some isolates showing resistance to oxacillin MIC. The sensitivity of chromogenic media will decrease if the media is used to test heterogeneous resistant strains. The false negatives in MRSA are found to occur due to the over-expression of mecR and mecI genes which are co-repressors of the gene [24]. The sensitivity of Brilliance MRSA Chrome Agar [25], ChromID MRSA [23], and Colorex MRSA [23] are able to reach 100%, while the sensitivity of BD CHROMagar MRSA II [26], can only reach 70%. [20] stated that Me Re Sa has a specificity of 30%. One limitation of the study is its small sample size. Inversely related to the specificity of Me Re Sa according to [20], the specificity of Me Re Sa according to [27] can be considered high; namely 97.3%. The specificity of CHROMagar MRSA and MRSASelect according to [15], [28] are also have a high (100%). Early and specific diagnosis of MRSA infection can significantly prevent the spread of MRSA. On the other hand, delays in the detection of MRSA can lead to the increase of transmission of MRSA among patients, a higher number of MRSA infections, as well as increased hospital costs [29]. [30] explained that MRSA screening on recently admitted patients is an essential part of effective control measures. Several studies have suggested that rapid identification of MRSA colonization in patients can reduce the incidence of MRSA from 13.89 / 1000 to 4 / 1000 per day. The identification of MRSA in patients with infection or carriers must be done quickly and accurately. Several rapid MRSA detection methods such as chromogenic media, latex agglutination test, and PCR require pure colonies; which means that it will take at least two days. On the other hand, Real-time PCR can detect MRSA directly from the clinical swab of the specimen [30].

The type of PCR evaluated by the studies used in the systematic review is real-time PCR. Its evaluated sensitivity ranged from 57.69% (Detect-Ready MRSA Panel Kit) to 100%. According to [31] this low sensitivity is thought to be caused by the problem of cutting off the software used to interpret the examination result. This software will automatically calculate if MRSA or other mixed populations of Staphylococci are present in the sample. False negatives result on the Detect-Ready MRSA Panel Kit can be caused by MRSA strain which lacks mecA gene. This strain will display a mecA gene homologue diverging with a different organization from other SCC elements. The specific SCCmec clones which are commonly found and cannot be detected using MRSA examination can also be the cause. According to [29], incompatibility result on Xpert MRSA assay with culture methods could occur due to low bacterial density. The value of Ct on PCR correlates with the density of bacteria in the sample. This could explain the reason of the false negatives, other than the absence of mecA gene in the SCC element [32]. The discovery of MRSA variation containing novel homologs of mecA gene LGA251 and SCCmec type XI in UK, Denmark, and Germany may also lead to false negatives [33]. [34] stated that the false negatives in GeneOhm assay are due to mutations in the junction region of SCCmec-orfX, which is the target of GeneOhm assay - or because of the variations in SCCmec type (including type Iva). In Xpert MRSA / SA BC assay, false negatives may be due to the contamination of reference culture with MRSA after molecular testing, as well as the variations of SCCmec cassette [34]. The false negatives on BD GeneOhm StaphSR assay can be caused by a low colonization level, an incorrect sampling method, as well as the quantity of MRSA / MSSA on the swab is below the limit of the detection of BD GeneOhm StaphSR assay but still sufficient to grow on culture media [35]. The false positives on MRSA examination can be caused by the presence of orfX gene on the Coagusalase- negative Staphylococci (CoNS), which is a homolog of S. aureus or SCCmec cassettes that do not contain mecA gene [31]. In the GeneXpert MRSA and GeneOhm assays, false positives are found due to strains with deletion of mecA gene [36].

According to a study by [37], the false positives of Xpert MRSA Gen3 [37] may occur due to the fact that the samples containing MSSA are more susceptible to non- specific amplification - resulting in a positive detection of SCCmec-orfX. Increasing the cut off Ct from SCCmec-orfX on Xpert MRSA Gen3 can also decrease the specificity of Xpert MRSA Gen3 [37]. [38], [35] described that false positives on real-time PCR using culture reference standard can be caused by the use of antibiotic regimens in patients. The use of these antibiotics can inhibit bacterial growth on culture media; however, the result is still positive on real-time PCR [41, 44]. Other causes are the absence of viable bacteria which can grow on culture media, but still had DNA residues which can be amplified by PCR (this situation may occur after exposure to antibiotics or decolonization therapy), and the samples obtained from anterior nares are scaled from a polymicrobial colonizing environment [35]. [39], Huh et al. [40], and Ho et al. [35] stated that the false positives on GeneOhm MRSA assay, MRSA gene assay, or BD GeneOhm StaphSR assay may occur in the absence of mecA gene in strains which have residual SCCmec right extremity fragments. Zobydi et al. [39] explained that several other researchers have stated that BD GeneOhm MRSA assay is also less sensitive when it comes to detect isolates type IVa SCCmec. In LightCycler MRSA, the traces of SCCmec in strains of MSSA, methicillin- resistant coagulase-negative Staphylococcus (MRCNS), or dead MRSA bacteria can also create false positives [40]. The main problem in evaluating the molecular testing in the detection of MRSA from clinical specimen is determining the specimens' true positive and true negative. In general, MRSA culture method is used as the reference standard of MRSA testing by using PCR. However, if the culture method result is negative while the PCR result is positive; the result of the sample tested by using this PCR will be considered as false positive on PCR. Some of the disadvantages of this are that various culture media have limited sensitivity, negative result on culture but positive result on MRSA which indicate growth of MRSA in additional broth enrichment procedures, as well as some patients with false positives on PCR have a history of MRSA infection / colonization [39].

4.3 Turnaround Time

Most of the studies evaluating antibiotic disc and chromogenic media in this systematic review did not evaluate its turnaround time, but only recorded the required incubation time. Of 28 studies evaluating the MRSA testing by using antibiotic disc; only 22 included incubation time and one included turnaround time. The incubation times, according to these studies, ranged from 16-48 hours; while the turnaround time ranged from 36-48 hours. The incubation time of the chromogenic media, according to the study pool used in this systematic review, ranged from 18-48 hours. The result of this systematic review also shows that PCR (real-time PCR) turnaround time ranges from 58 minutes-6.5 hours, depending on which type being used. According to [41]. The average PCR turnaround time is 14.5 hours, whereas the culture- based MRSA screening test takes 24-72 hours after sample collection. The time lag for culture-based methods can lead to cross-transmission in MRSA. Molecular MRSA detection can identify MRSA carrier status early in critical patients [41]. A shorter PCR turnaround time can save the cost of prevention and infection control measures [26].

4.4 Antibiotic Disc, Chromogenic Media, and PCR

PCR has high specificity and fast turnaround time, and chromogenic media has high sensitivity, if it is compared to two other media. Although it is faster, MRSA examination using PCR has several disadvantages, such as it requires expensive equipment, expertise in use (technical) and consumables which are difficult to find in laboratory with less resources [27]. The widespread use of MRSA detection method by using PCR (which has a high cost) in a patient population with low endemic MRSA rate is not cost-effective [29]. On the other hand, although culture-based methods have a longer turnaround time and lower sensitivity (if compared to PCR); they are easier to be applied in environments with limited resources, costs, technical expertise and human resources [26].

5. CONCLUSSION

MRSA diagnostic method using PCR has higher specificity and faster turnaround time than antibiotic disc, while chromogenic media has higher sensitivity than those two methods.

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