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ORIGINAL ARTICLE

SUSCEPTIBILITY PATTERN OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS BACTERIA IN DR. SOETOMO GENERAL ACADEMIC HOSPITAL SURABAYA

Pola Sensitivitas Bakteri Methicillin-Resistant Staphylococcus aureus di RSUD Dr. Soetomo Surabaya, Indonesia

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ABSTRACT

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-positive bacteria causing infection in hospital-acquired infection, has increased worldwide, including in Indonesia. Currently, the updated data on MRSA in Indonesia is limited. **Purpose:** This study aims to explore the prevalence and susceptibility pattern of MRSA in Dr. Soetomo General Academic Hospital Surabaya, Indonesia. **Methods:** This study was a descriptive-analytic study with a retrospective design. All clinical isolates of Methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA from January to December 2017 were included. All inpatients included one MSSA or MRSA, and colonized bacteria were excluded. Data were analyzed using Chi-Square or Fisher's Exact Test. **Results:** A total of 503 *Staphylococcus aureus* isolates were identified, of which 126 (25.05%) were MRSA. The highest prevalence of MRSA was from pus, wound swab, and tissue, 59 (28.37%) from 333, and the highest prevalence of the ward was in the intensive care unit (50%). MRSA were highly sensitive to daptomycin (n=95/95; 100%), linezolid (n=123/125; 98.40%), vancomycin (n=120/125; 96.00%), nitrofurantoin (n=43/45; 95.56%), quinupristin-dalfopristin (n=112/121; 92.56%), fosfomycin (n=87/97; 89.69%), and moxifloxacin (n=104/117; 88.89%). The susceptibility of the other

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antibiotics such as rifampicin, clindamycin, erythromycin, chloramphenicol, cotrimoxazole, levofloxacin, gentamicin, and tetracycline was less than 80%. **Conclusion:** The prevalence of MRSA among hospitalized patients in Dr. Soetomo General Academic Hospital, Surabaya, is 25.05% and tends to decrease from January to December 2017. Most MRSA was sensitive/intermediate to daptomycin, linezolid, vancomycin, nitrofurantoin, quinupristin-dalfopristin, fosfomycin, and moxifloxacin.

ABSTRAK

Latar Belakang: *MRSA (Methicillin-resistant Staphylococcus aureus), salah satu bakteri Gram positif utama penyebab infeksi pada manusia dan infeksi nosokomial. meningkat secara luas di dunia termasuk Indonesia. Belum banyak data terbaru yang tersedia mengenai MRSA di Indonesia.* ***Tujuan:*** *Penelitian ini dilakukan dengan tujuan untuk mengetahui prevalensi dan pola kepekaan bakteri MRSA di RSUD Dr. Soetomo Surabaya, Indonesia.* ***Metode:*** *Penelitian ini adalah deskriptif-analitik dengan desain retrospektif. Sampel penelitian merupakan isolat Staphylococcus aureus* (MSSA) *dan MRSA dari sampel klinik di Laboratorium Mikrobiologi Klinik RSUD Dr. Soetomo Surabaya, Indonesia, Januari–Desember 2017. Setiap pasien hanya diambil satu bakteri dan kolonisasi dikeluarkan dari penelitian. Data yang dianalisis dengan Chi-Square atau Fisher's Exact Test.* ***Hasil:*** *Sebanyak 503 isolat Staphylococcus aureus teridentifikasi, 126 (25.05%) diantaranya merupakan MRSA. Prevalensi MRSA tertinggi berasal dari pus, usap luka dan jaringan, 59 (28.37%) dari 333, dan prevalensi tertinggi di ruang rawat intensif (50%). MRSA sensitif terhadap daptomisin (n=95/95; 100.00%), linezolid (n=123/125; 98.40%), vankomisin (n=120/125; 96.00%), nitrofurantoin (n=43/45; 95.56%), quinupristin-dalfopristin (n=112/121; 92.56%), fosfomycin (n=87/97; 89.69%), dan moxifloxacin (n=104/117; 88.89%). Sensitivitas terhadap antibiotik lain seperti rifampisin, klindamisin, eritromisin, kloramfenikol, kotrimoksazol, levofloxacin, gentamisin, dan tetrasiklin kurang dari 80%.* ***Simpulan:*** *Prevalensi MRSA pada pasien rawat inap di RSUD Dr. Soetomo Surabaya, Indonesia, sebesar 25.05% dengan kecenderungan menurun sejak Januari sampai Desember 2017. Antibiotik yang memiliki sensitivitas baik untuk bakteri MRSA adalah daptomycin, linezolid, vancomycin, nitrofurantoin, quinupristin-dalfopristin, fosfomycin, dan moxifloxacin.*

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a specific strain of *Staphylococcus aureus* bacteria, resistant to beta-lactam antibiotics, including cephalosporin and carbapenem (Lee et al., 2018). MRSA is a Gram-positive bacteria that is a significant agent in nosocomial infection, causing a wide spectrum of infections to multiple organs, including skin infection, abscess, pneumonia, urinary tract infection, and bacteremia (Guo, Song, Sun, Wang, & Wang, 2020). Centers for Disease Control and Prevention has declared MRSA as one of the agents with a serious threat of drug resistance, meaning the resistance might aggravate and

become an urgent threat if uncontrolled with proper surveillance and prevention. Of an estimated 80,461 invasive MRSA infections in the USA, 11,285 ended with death (Centers for Disease Control and Prevention, 2019).

Since the discovery of MRSA in 1961, there has been an increase in MRSA prevalence world widely (Harkins et al., 2017), particularly in Asia (Lakhundi & Zhang, 2018). National Healthcare Safety Network (NHSN), a system used by CDC, recorded that the prevalence of CLABSI (Central Line-Associated Blood Stream Infections), CAUTI (Catheter-associated Urinary Tract Infections), and SSI (surgical site infection) caused by MRSA in 2014. These were 50.70%, 52.00%, and 42.60%, respectively (Weiner et al., 2019). A survey at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2014 showed out of 643 patients hospitalized in several wards, 52 (8.08%) were colonized by MRSA in their nose or throat. A survey from other tertiary hospitals in Indonesia revealed that 6.56 of 259 *Staphylococcus aureus* isolated between 2008-2010 were MRSA (Santosaningsih et al., 2016). An increase in MRSA prevalence in other countries might also indicate an increase in MRSA prevalence in Indonesia (Kuntaman et al., 2016).

MRSA possessed the *mecA* gene, encoding penicillin-binding protein 2a, facilitating resistance property to β-lactam antibiotics. Vancomycin was recognized as the last-line antibiotic against MRSA. However, vancomycin-resistant *Staphylococcus aureus* (VRSA) was reported in the USA in 2002 (McGuinness, Malachowa, & DeLeo, 2017). The discovery of the *Staphylococcus aureus* strain with resistance against vancomycin and other antibiotics highly increases the chance of MRSA becoming a *"Superbug" multiple-resistance* (Al-Zoubi, Al-Tayyar, Hussein, Al Jabali, & Khudairat, 2015).

The vast distribution of MRSA is not only restricted inside the hospital environment but is also found in a healthy community (Cameron, Hall, Tong, Paterson, & Halton, 2019; J. W. H. Wong et al., 2018). MRSA is recognized as a severe threat, and with the increase of antibiotic-resistant bacteria strains (Turner et al., 2020), further study into MRSA needs to be conducted. This study aims to assess the prevalence and resistance pattern of MRSA in Dr. Soetomo General Academic Hospital Surabaya, Indonesia.Chronic stress can take a toll on people's health. Moreover, stress can be considerably more unsafe for diabetics since the body obstructs its own delivery of insulin, a chemical that directs glucose levels (Ugwueze, Ezeokpo, & Nnolim, 2020).

Even the ordinary pressure of daily life can influence the patient's insulin and glucose function, which can worsen their diabetes. The previous study also stated that people with diabetes, hypertension, and extreme weight (BMI >40 kg/m^2) are bound to be affected and are at a higher risk of complications and death from COVID-19 (Yang et al., 2020). Additionally, COVID-19 could prompt extra pulmonary appearances like diabetes mellitus and hyperglycemia (Al-kuraishy, Al-Gareeb, Guerreiro, Cruz-Martins, & Batiha, 2021). It may raise the anxiety and fear of being infected with COVID-19 among diabetes patients. Furthermore, stress can put people with diabetes at risk of weight gain and elevated cholesterol, both of which can lead to hyperglycemia (H. Wong, Singh, Go, Ahluwalia, & Guerrero-go, 2019).

METHODS

This study was a descriptive-analytic with a retrospective design. The samples were all clinical isolates of *Staphylococcus aureus* and MRSA from inpatients from January to December 2017 identified in the Laboratory of Clinical Microbiology, Dr. Soetomo General Academic Hospital Surabaya, Indonesia. Duplicated clinical isolates were excluded. For example, if the patient has 2 MRSA results, only the first one result was included. Nasal, nasopharynx, and throat swab specimens were excluded from this study.

The susceptibility testing was conducted as a routine procedure in this laboratory. All bacteria and antibiotic susceptibility tests were diagnosed using the automatic microbiology diagnosis system BD Phoenix^{TM} M50 (Becton, Dickinson Diagnostics, Sparks, MD). An isolate is decided as MRSA or MSSA based on the susceptibility of oxacillin or cefoxitin. If the MIC of oxacillin is ≥4μg/ml or the MIC of cefoxitin ≥8 μg/ml, then the isolate was grouped as MRSA (Clinical and Laboratory Standards Institute, 2010). Antibiotics tested included clindamycin, erythromycin, gentamycin, levofloxacin, moxifloxacin), vancomycin, fosfomycin, linezolid, nitrofurantoin, rifampicin, and tetracycline, cotrimoxazole, Quinupristin-Dalfopristin, daptomycin, following our laboratory protocols.

The data were analyzed using Chi-Square or Fisher's Exact Test. The formula calculated the

prevalence of MRSA: total MRSA divided by all *Staphylococcus aureus* (total MRSA plus MSSA) referred to in a previous study (Pannewick, Baier, Schwab, & Vonberg, 2021). The sensitivity pattern of MRSA for each antibiotic was calculated based on the total sensitive and intermediate isolates from each antibiotic divided by the total isolates tested. This study was approved by the Health Research Ethical Committee of Dr. Soetomo Academic General Hospital Surabaya no. 537/Panke.KKE/IX/2017.

RESULTS

There were 503 Staphylococcus aureus (MSSA and MRSA) isolates from the various clinical specimens. The highest percentage of *Staphylococcus aureus* was identified from pus, wound swab, and tissue specimens (n=208/503; 41.35%), followed by blood specimens (n=150/503; 29.82%) and others in fewer numbers (Table 1). MRSA was detected among 126 patients (25.05%), whereas 377 (75%) were MSSA. The highest prevalence of MRSA was found in pus, wound swab, and tissue specimens, with a total number of 59 (28.37%) from the total isolates from pus, wound swab, and tissue specimens; from blood, 33 (22.00%) from the total isolates from blood; and sputum 26 (29.89%) from the total isolates from sputum. There were no significant differences between MRSA and MSSA among specimens (p = 0.29) (Table 1).

The MRSA prevalence had a declining trend from January to December 2017 (Figure 1), with the highest prevalence of MRSA found in January (37.21%) and then May (34.69%) (Table 2). The lowest MRSA prevalence was found in December (10.00%). Nevertheless, based on the absolute number, the highest number of MRSA was in May (n=17), and the lowest number was in December (n=3). There was no significant difference among months or per three-month period (Table 1). Based on Continuity Correction, there was a significant difference in MRSA prevalence between January and December (p = 0.02), May and December (p = 0.03), and data analysis was not shown.

The distribution of MRSA according to sex, age, and the ward was as follows: MRSA percentage was higher among male patients (65.08%; n=82/126), while the female patient was 34.92% (n=44/126) (p = 0.08). The highest MRSA frequency was found in the adult age group (n=79/290, 27.24%), followed by elderly group (n= 19/99, 19.19%) and children (n= 28/114, 24.56%). There was no significant difference in MRSA prevalence between the age group (p = 0.28).

The highest prevalence of MRSA patients was found in the intensive care unit (50%), followed by the medical ward (27.89%) and the emergency department (24.82%). There was no significant difference in MRSA prevalence between wards (p = 0.87). Still, based on the absolute number, the highest number of MRSA was in the medical ward (n=58), and the lowest number was in the obstetric-gynecology ward (n=0) (Table 1).

More than 80% of the MRSA isolates were susceptible to daptomycin (n=95/95; 100%), linezolid (n=123/125; 98.40%), vancomycin (n=120/125; 96.00%), nitrofurantoin (n=43/45; 95.56%), quinupristin-dalfopristin (n=112/121; 92.56%), fosfomycin (n=87/97; 89.69%), and moxifloxacin (n=104/117; 88.89%). The isolates were less sensitive (less than 60%) against chloramphenicol (n=49/119; 41.18%), cotrimoxazole (n=34/122; 27.87%), levofloxacin (n=25/125; 20.00%), gentamicin (n=22/126; 17.46%), and tetracycline (n=15/122; 12.30%) (Table 2).

Table 1
Distribution of *Staphylococcus aureus* (MSSA) and MRSA based on Clinical Specimens, Month, Three-month period, Gender, Age Group, Age Range, and the Ward

Variable	*S. aureus*						*p-value*
	MSSA		MRSA		Total		
	N	%	N	%	N	%	
Clinical specimen							
Pus, swab, tissue	149	71.63	59	28.37	208	41.35	0.29[a]
Blood	117	78.00	33	22.00	150	29.82	
Sputum	61	70.11	26	29.89	87	17.30	
Urine	38	86.36	6	13.64	44	8.75	
Cerebrospinal fluid	3	n.a[d]	2	n.a[d]	5	0.99	
Other body fluid	9	n.a[d]	0	n.a[d]	9	1.79	
Month							
January	27	62.79	16	37.21	43		0.15[b]
February	31	73.81	11	26.19	42		
March	40	80.00	10	20.00	50		
April	31	77.50	9	22.50	40		
May	32	65.31	17	34.69	49		
June	22	88.00	3	12.00	25		
July	28	68.29	13	31.71	41		
August	40	74.07	14	25.93	54		
September	38	77.55	11	22.45	49		
October	30	69.77	13	30.23	43		
November	31	83.78	6	16.22	37		
December	27	90.00	3	10.00	30		
Three-month Period							
January-March	98	72.59	37	27.41	135		0.56[b]
April-June	85	74.56	29	25.44	114		
July-September	106	73.61	38	26.39	144		
October-December	88	80.00	22	20.00	110		
Gender							
Male	210	71.92	82	28.08	292		0.08[c]
Female	167	79.15	44	20.85	211		
Age Group (years old)							
Children (< 18)	86	75.44	28	24.56	114		0.28[b]
Adult (18-60)	211	72.76	79	27.24	290		
Elderly (>60)	80	80.81	19	19.19	99		
Ward							
Emergency department	103	75.18	34	24.82	137		0.87[a]
Intensive Care Unit	9	50.00	9	50.00	18		
Pediatric ward	53	82.81	11	17.19	64		
Surgery ward	46	79.31	12	20.69	58		
Private wing	8	n.a[d]	2	n.a[d]	10		
Medical ward	150	72.12	58	27.88	208		
Obstetrics-Gynecology ward	8	n.a[d]	0	n.a[d]	8		
Total	377		126		503	100.00	

a = Mann-Whitney Test; b = Chi-square or Fisher's Exact Test;
c = Continuity Correction; d = Not applicable (result too small)

Table 2
The result of the antibiotic susceptibility test of MRSA isolates against varied antibiotics that are commonly used

Antibiotic	Isolates (n)	Sensitive		Intermediate		Sensitive + Intermediate	
		n	%	N	%	n	%
Daptomycin	95	95	100.00	0	0.00	95	100.00
Linezolid	125	123	98.40	0	0.00	123	98.40
Vancomycin	125	118	94.40	2	1.60	120	96.00
Nitrofurantoin	45	43	95.56	0	0.00	43	95.56
Quinupristin-Dalfopristin	121	110	90.91	2	1.65	112	92.56
Fosfomycin	97	85	87.62	2	2.06	87	89.69
Moxifloxacin	117	83	70.94	21	17.94	104	88.89
Rifampicin	117	86	73.50	0	0.00	86	73.50
Clindamycin	119	80	67.23	0	0.00	80	67.23
Erythromycin	120	79	65.83	1	0.83	80	66.67
Chloramphenicol	119	44	36.97	5	4.20	49	41.18
Cotrimoxazole	122	34	27.87	0	0.00	34	27.87
Levofloxacin	125	16	12.80	9	7.20	25	20.00
Gentamicin	126	20	15.87	2	1.59	22	17.46
Tetracycline	122	15	12.30	0	0.00	15	12.30

DISCUSSION

The prevalence of MRSA among all *Staphylococcus aureus* in this study was 25.05% (n=126/503). This number is consistent with the prevalence of MRSA in all hospitals in Kenya, Africa, from January 2014 until February 2016 (Gitau, Masika, Musyoki, Museve, & Mutwiri, 2018). This prevalence was lower than a report from a hospital in *Sub-Himalayan Center*, India, from July 2014 until June 2016, with a prevalence of 30.7% (n=198/644) (Husain, Rawat, Umesh, Kumar, & Verma, 2018). The result of this study showed that MRSA prevalence had a declining trend from January to December 2017, with significant differences in MRSA prevalence between January and December (p = 0.02), May and December (p = 0.03); data analysis was not shown. The same result was shown in a study in Finland (Jokinen et al., 2018). The declining trend of MRSA prevalence was probably due to the properly conducted PPRA (Program Pengendalian Resistensi Antimikroba or Antimicrobial resistance control program) policy in Dr. Soetomo General Academic Hospital Surabaya.

MRSA was mostly identified in pus, wound, and clinical tissue specimens (28.37%), followed by blood specimens (22.00%), without a significant difference among all specimens (p = 0.29) (Table 1). The higher prevalence of MRSA in pus specimens, was also shown in other studies such as in Kenya (65.98%; n=153/232) (Gitau et al., 2018), India (67.58%; n=638/944) (Husain et al., 2018), and in a similar study in Indonesia (87,00%; n=47/54) (Thirafi, Bramantono, & Kuntaman, 2018). However, other studies in teaching and referral hospitals in Malaysia showed that MRSA prevalence was highest in blood specimens (n=91/209; 43.54%) (Sit et al., 2017).

Since the higher MRSA prevalence in this study was isolated from pus specimens, we suggested the MRSA isolated were obtained from skin and tissue infection. Similar to a study by Garoy et al. in 2019 that *Staphylococcus aureus* mostly infects the skin and soft tissue. The risk factors for MRSA infection are open wounds, hemodialysis, prolonged hospital stay, prolonged infusion line, urinary catheter application, and other invasive medical procedures (Lee et al., 2018). Besides, contact with an infected environment (Thapaliya et al., 2019) and infected or colonized animals were also risk factors for MRSA infections (Boswihi & Udo, 2018).

In this study, patients with MRSA were mostly male (n=82/126; 65.08%) without a significant difference in prevalence against female patients (p = 0.08) (Table 1).This study was consistent with a Malaysian referral hospital study, which showed that MRSA prevalence was higher in males (n=132/209; 63.16%).Stress stimulates the release of various hormones, which can result in elevated blood glucose levels (McAllister et al., 2015). Severe mental depression can cause sufficient stress for the body to produce abnormally high blood sugar levels, even in people without diagnosed diabetes. However, when there is a major physical threat such as diabetes, stress

hinders the body from delivering insulin, and that allows glucose to accumulate in the blood (Khalfallah, Abdelmageed, Elgendy, & Hafez, 2020). Subsequently, elevated glucose levels can cause long-term complications such as diabetes.

The MRSA percentage was highest in the 18-60 age group (n=79/290; 27.24%), followed by the elderly (n=19/99, 19.19%), without a significant difference in MRSA prevalence between age groups (p = 0.28) (Table 1). Similarly, a study also found that most MRSA patients were older than 50 years old (n=138/209; 66.03%) and were associated with male patients older than 50 years old (Sit et al., 2017). However, a study found that elderly age and MRSA infection are unlikely (Peters, Dulon, Kleinmüller, Nienhaus, & Schablon, 2017). The highest percentage of MRSA infection in adult groups, especially the elderly, is because the elderly have a higher risk of being treated as an inpatient, increasing the risk of nosocomial infection caused by MRSA.

MRSA infection prevalence in this study was mostly in the intensive care unit (50.00%), followed by the medical ward (27.89%) and emergency department (24.82%), without a significant difference among all wards (p = 0.87) (Table 1). Frequent physical contact between medical staff and patients also bad self-hygiene increase the chance of MRSA spreading (Legese et al., 2018). MRSA from patients with severe medical conditions and risk factors was found more in the intensive care unit than in the medical ward (Djuric et al., 2017). From this, we could consider staying in the intensive care unit as a risk factor for MRSA infection or colonization.

Vancomycin remains the drug of choice for treating MRSA infection. Other therapy available for MRSA infection includes daptomycin, telavancin, oritavancin, linezolid, tedizolid, ceftaroline, and ceftobiprole (Boswihi & Udo, 2018). In the USA, vancomycin and daptomycin remain the first line of therapy for MRSA infection (Ortwine & Bhavan, 2018).

According to the Indonesia Ministry of Health Regulation number 8/2015 about the Antimicrobial Resistance Control Program in Hospitals, the limit for adequate sensitivity rate for therapeutic use was 80% or above (Indonesia Ministry of Health, 2015). Since ≥ 80.00% of MRSA isolates in this study were susceptible to daptomycin, linezolid, vancomycin, nitrofurantoin, quinupristin-dalfopristin, fosfomycin, and moxifloxacin, thenvancomycin can be used as a drug of choice for MRSA infection in RSUD Dr. Soetomo hospital. Daptomycin, linezolid, nitrofurantoin, quinupristin-dalfopristin, fosfomycin, and moxifloxacin, can also be used if there is contraindication or vancomycin is not available.

The consideration of choosing empirical therapy is not only based on the antibiotic sensitivity test but also drug availability, side effect profile, and the patient's profile (Kavanagh, Abusalem, & Calderon, 2018; Lewis, Heil, Covert, & Cluck, 2018). This study found that the susceptibility for gentamicin, chloramphenicol, cotrimoxazole, levofloxacin, and tetracycline was less than 60.00%. Like Lin et al. (2017) and Gitau et al. (2018), MRSA was quite sensitive toward tigecycline, nitrofurantoin, vancomycin, fosfomycin, clindamycin, and rifampicin. The frequently used oral antibiotics in the community and primary health facilities, such as erythromycin, chloramphenicol, cotrimoxazole, tetracycline, and gentamycin, showed very low efficacy with sensitivity < 60.00%. Therefore, these antibiotics can no longer be used as MRSA empirical therapy in hospitals.

A study about MRSA prevalence and antibiotics sensitivity patterns is essential because MRSA is one of the major causes of nosocomial infection (Weiner et al., 2019). If it is neglected, it can cause more morbidity and mortality for patients (Turner et al., 2020). This study must be done regularly in every healthcare facility because it impacts the hospital policy maker to formulate the antimicrobial resistance control program so that the clinicians can use the antibiotics rationally and other antibiotics resistance can be avoided.

Research Limitations

The limitation of this study includes the lack of a molecular study to detect the *mecA* gene as the gold standard for MRSA detection and *SCCmec* type to identify MRSA grouping.

CONCLUSION

The prevalence of MRSA in Dr. Soetomo General Academic Hospital Surabaya was quite high, with a declining trend from January to December 2017. The highest prevalence of MRSA was from pus, wound, and tissue samples, and the highest prevalence was in the intensive care unit. Antibiotics with good sensitivity for MRSA in Dr. Soetomo Hospital Surabaya were daptomycin, linezolid, vancomycin, nitrofurantoin, quinupristin-dalfopristin, fosfomycin, and

moxifloxacin. These antibiotic sensitivity patterns can be considered a guideline of the hospital's antimicrobial resistance control program policy.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

AUTHOR CONTRIBUTIONS

SZTT, RS, BB, KK: Author, conceptualization, methodology. SZTT, RS: Data curation, writing- Original draft preparation. SZTT: Visualization, investigation. BB, KK: conceptor and supervisor. SZTT, RS: Software. KK: Writing-Reviewing.

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